CHESTNUT’S

OBSTETRIC ANESTHESIA

PRINCIPLES and PRACTICE
The History of Obstetric Anesthesia

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For I heard a cry as of a woman in travail, anguish as of one bringing forth her first child, the cry of the daughter of Zion gasping for breath, stretching out her hands, "Woe is me!"

—Jeremiah 4:31

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“...the position of woman in any civilization is an index of the advancement of that civilization; the position of woman is gauged best by the care given her at the birth of her child." So wrote Haggard1 in 1929. If his thesis is true, Western civilization made a giant leap on January 19, 1847, when James Young Simpson used diethyl ether to anesthetize a woman with a deformed pelvis for delivery. This first use of a modern anesthetic for childbirth occurred a scant 3 months after Morton’s historic demonstration of the anesthetic properties of ether at the Massachusetts General Hospital in Boston. Strangely enough, Simpson’s innovation evoked strong criticism from contemporary obstetricians, who questioned its safety, and from many segments of the lay public, who questioned its wisdom. The debate over these issues lasted more than 5 years and influenced the future of obstetric anesthesia.2

JAMES YOUNG SIMPSON

Few people were better equipped than Simpson to deal with controversy. Just 36 years of age, Simpson already had 7 years’ tenure as Professor of Midwifery at the University of Edinburgh, one of the most prestigious medical schools of its day (Fig. 1.1). By that time, he had established a reputation as one of the foremost obstetricians in Great Britain, if not the world. On the day he first used ether for childbirth, he also received a letter of appointment as Queen’s Physician in Scotland. Etherization for childbirth was only one of Simpson’s contributions. He also designed obstetric forceps (which still bear his name), discovered the anesthetic properties of chloroform, made important innovations in hospital architecture, and wrote a textbook on the practice of witchcraft in Scotland that was used by several generations of anthropologists.3

An imposing man, Simpson had a large head, a massive mane of hair, and the pudgy body of an adolescent. Contemporaries described his voice as “commanding,” with a wide range of volume and intonation. Clearly Simpson had “presence” and “charisma.” These attributes were indispensable to someone in his profession, because in the mid-nineteenth century, the role of science in the development of medical theory and practice was minimal; rhetoric resolved more issues than facts. The medical climate in Edinburgh was particularly contentious and vituperative. In this milieu, Simpson had trained, competed for advancement and recognition, and succeeded. The rigor of this preparation served him well. Initially, virtually every prominent obstetrician, including Montgomery of Dublin, Ramsbotham of London, Dubois of Paris, and Meigs of Philadelphia, opposed etherization for childbirth. Simpson called on all of his professional and personal finesse to sway opinion in the ensuing controversy.

MEDICAL OBJECTIONS TO THE USE OF ETHER FOR CHILDBIRTH

Shortly after Simpson administered the first obstetric anesthetic, he wrote, “It will be necessary to ascertain anesthesia’s precise effect, both upon the action of the uterus and on the assistant abdominal muscles; its influence, if any, upon the child; whether it has a tendency to hemorrhage or other complications.”4 With this statement, he identified the issues that would most concern obstetricians who succeeded him and thus shaped the subsequent development of the specialty.

Simpson’s most articulate, persistent, and persuasive critic was Charles D. Meigs, Professor of Midwifery at Jefferson Medical College in Philadelphia (Fig. 1.2). In character and
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In 1850, more physicians expressed support for Meigs’s views than for Simpson’s. For example, Baron Paul Dubois\(^6\) of the Faculty of Paris wondered whether ether, “after having exerted a stupefying action over the cerebrospinal nerves, could not induce paralysis of the muscular element of the uterus?” Similarly, Ramsbotham\(^7\) of London Hospital said that he believed the “treatment of rendering a patient in labor completely insensible through the agency of anesthetic remedies … is fraught with extreme danger.” These physicians’ fears gained credence from the report by a special committee of the Royal Medical and Chirurgical Society documenting 123 deaths that “could be positively assigned to the inhalation of chloroform.”\(^8\) Although none involved obstetric patients, safety was on the minds of obstetricians.

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The reaction to the delivery of Queen Victoria’s eighth child in 1853 illustrated the aversion of the medical community to obstetric anesthesia. According to private records, John Snow anesthetized the Queen for the delivery of Prince Leopold at the request of her personal physicians. Indeed, in 1847, physicians had little information of any sort about uterine function, pain, or the relationship between them. Studies of the anatomy and physiology of pain had just begun. It was only during the preceding 20 years that investigators had recognized that specific nerves and areas of the brain have different functions and that specialized peripheral receptors for painful stimuli exist.\(^2\)

Fig. 1.1 James Young Simpson, the obstetrician who first administered a modern anesthetic for childbirth. He also discovered the anesthetic properties of chloroform. Many believe that he was the most prominent and influential physician of his day. (Courtesy of Yale Medical History Library.)

Fig. 1.2 Charles D. Meigs, the American obstetrician who opposed the use of anesthesia for obstetrics. He questioned the safety of anesthesia and said that there was no demonstrated need for it during a normal delivery. (Courtesy of Wood-Library Museum.)

Fig. 1.3 At the heart of the dispute between Meigs and Simpson was a difference in their interpretation of the nature of labor and the significance of labor pain. Simpson maintained that all pain, labor pain included, is without physiologic value. He said that pain only degrades and destroys those who experience it. In contrast, Meigs argued that labor pain has purpose, that uterine pain is inseparable from contractions, and that any drug that abolishes pain will alter contractions. Meigs also believed that pregnancy and labor are normal processes that usually end quite well. He said that physicians should therefore not intervene with powerful, potentially disruptive drugs (Fig. 1.3). We must accept the statements of both men as expressions of natural philosophy, because neither had facts to buttress his position. Indeed, in 1847, physicians had little information of any sort about uterine function, pain, or the relationship between them. Studies of the anatomy and physiology of pain had just begun. It was only during the preceding 20 years that investigators had recognized that specific nerves and areas of the brain have different functions and that specialized peripheral receptors for painful stimuli exist.\(^2\)
PART I
Introduction

-originated when God punished Eve and her descendants for Eve’s disobedience in the Garden of Eden. Many believed that it was wrong to avoid the pain of divine punishment. This belief was sufficiently prevalent and strong to retard acceptance of even the idea of anesthesia, especially for obstetric patients. Only when this tradition weakened did people seek ways to free themselves from disease and pain. In most Western countries, the transition occurred during the nineteenth century. Disease and pain lost their theologic connotations for many people and became biologic processes subject to study and control by new methods of science and technology. This evolution of thought facilitated the development of modern medicine and stimulated public acceptance of obstetric anesthesia.

The reluctance that physicians felt about the administration of anesthesia for childbirth pain stands in stark contrast to the enthusiasm expressed by early obstetric patients. In 1847, Fanny Longfellow, wife of the American poet Henry Wadsworth Longfellow and the first woman in the United States anesthetized for childbirth, wrote:

*I am very sorry you all thought me so rash and naughty in trying the ether. Henry’s faith gave me courage, and I had heard such a thing had succeeded abroad, where the surgeons extend this great blessing more boldly and universally than our timid doctors. … This is certainly the greatest blessing of this age.*

Queen Victoria, responding to news of the birth of her first grandchild in 1860 and perhaps remembering her own recent confinement, wrote, “What a blessing she [Victoria, her oldest daughter] had chloroform. Perhaps without it her strength would have suffered very much.” The new understanding of pain as a controllable biologic process left no room for Meigs’s idea that pain might have physiologic value. The eminent nineteenth-century social philosopher John Stuart Mill stated that the “hurtful agencies of nature” promote good only by “inciting rational creatures to rise up and struggle against them.”

Simpson prophesied the role of public opinion in the acceptance of obstetric anesthesia, a fact not lost on his adversaries. Early in the controversy he predicted, “Medical men may oppose for a time the superinduction of anaesthesia in parturition but they will oppose it in vain; for certainly our patients themselves will force use of it upon the profession. The whole question is, even now, one merely of time.” By 1860, Simpson’s prophecy came true; anesthesia for childbirth became part of medical practice by public acclaim, in large part in response to the demands of women.

Fig. 1.3 Frontispiece from Meigs’s textbook of obstetrics.

had apparently lost count—a forgivable error considering the propensity of the Queen to bear children.) Court physicians did not defend their decision to use ether. Perhaps not wanting a public confrontation, they simply denied that the Queen had received an anesthetic. In fact, they first acknowledged a royal anesthetic 4 years later when the Queen delivered her ninth and last child, Princess Beatrice. By that time, however, the issue was no longer controversial.

PUBLIC REACTION TO ETHERIZATION FOR CHILDBIRTH

The controversy surrounding obstetric anesthesia was not resolved by the medical community. Physicians remained skeptical, but public opinion changed. Women lost their reservations, decided they wanted anesthesia, and virtually forced physicians to offer it to them. The change in the public’s attitude in favor of obstetric anesthesia marked the culmination of a more general change in social attitudes that had been developing over several centuries.

Before the nineteenth century, pain meant something quite different from what it does today. Since antiquity, people had believed that all manner of calamities—disease, drought, poverty, and pain—signified divine retribution inflicted as punishment for sin. According to Scripture, childbirth pain

OPIOIDS AND OBSTETRICS

The next major innovation in obstetric anesthesia came approximately 50 years later. *Dämmerschlaff*, which means “twilight sleep,” was a technique developed by von Steinbüchel of Graz and popularized by Gauss of Freiberg. It combined opioids with scopolamine to make women amnesic and somewhat comfortable during labor (Fig. 1.4). Until
Gusserow, a prominent German obstetrician, described using form. He did not mention opioids, but neither did he mention introduced recently by Klikgowich of Russia; and (4) chloro-which was under evaluation; (3) nitrous oxide, which had been the use of which he favored; (2) bichloride of methylene, four agents for relief of labor pain: (1) carbon tetrachloride, with, the technical considerations that confronted physicians, as they had before. Not aware of, or perhaps not concerned whether the benefits justified the risks. Patients also reacted diethyl ether several years earlier. They resisted it, questioning suggestions that scopolamine be given with morphine.

that time, opioids had been used sparingly for obstetrics. Although opium had been part of the medical armamentarium since the Roman Empire, it was not used extensively, in part because of the difficulty of obtaining consistent results with the crude extracts available at that time. Therapeutics made a substantial advance in 1809 when Sertürner, a German pharmacologist, isolated codeine and morphine from a crude extract of the poppy seed. Methods for administering the drugs remained unsophisticated. Physicians gave morphine orally or by a method resembling vaccination, in which they placed a drop of solution on the skin and then made multiple small puncture holes with a sharp instrument to facilitate absorption. In 1853, the year Queen Victoria delivered her eighth child, the syringe and hollow metal needle were developed. This technical advance simplified the administration of opioids and facilitated the development of twilight sleep approximately 50 years later.16

Although reports of labor pain relief with hypodermic morphine appeared as early as 1868, few physicians favored its use. For example, in an article published in Transactions of the Obstetrical Society of London, Sansom22 listed the following four agents for relief of labor pain: (1) carbon tetrachloride, the use of which he favored; (2) bichloride of methylene, which was under evaluation; (3) nitrous oxide, which had been introduced recently by Klikgowich of Russia; and (4) chloroform. He did not mention opioids, but neither did he mention diethyl ether, which many physicians still favored. Similarly, Gusserow, a prominent German obstetrician, described using salicylic acid but not morphine for labor pain. (Von Baeyer did not introduce acetylsalicylic acid to medical practice until 1899.) In retrospect, von Steinbüchel’s and Gauss’s descriptions of twilight sleep in the first decade of the century may have been important more for popularizing morphine than for suggesting that scopolamine be given with morphine.

Physicians reacted to twilight sleep as they had reacted to diethyl ether several years earlier. They resisted it, questioning whether the benefits justified the risks. Patients also reacted as they had before. Not aware of, or perhaps not concerned with, the technical considerations that confronted physicians, patients harbored few doubts and persuaded physicians to use it, sometimes against the physicians’ better judgment. The confrontation between physicians and patients was particularly strident in the United States. Champions of twilight sleep lectured throughout the country and published articles in popular magazines. Public enthusiasm for the therapy subsided slightly after 1920, when a prominent advocate of the method died during childbirth. She was given twilight sleep, but her physicians said that her death was unrelated to any complication from its use. Whatever anxiety this incident may have created in the minds of patients, it did not seriously diminish their resolve. Confronted by such firm insistence, physicians acquiesced and used twilight sleep with increasing frequency.19,20

Although the reaction of physicians to twilight sleep resembled their reaction to etherization, the medical milieu in which the debate over twilight sleep developed was quite different from that in which etherization was deliberated. Between 1850 and 1900, medicine had changed, particularly in Europe. Physiology, chemistry, anatomy, and bacteriology became part of medical theory and practice. Bright students from America traveled to leading clinics in Germany, England, and France. They returned with new facts and methods that they used to examine problems and critique ideas. These developments became the basis for the revolution in American medical education and practice launched by the Flexner report published in 1914.21

Obstetrics also changed. During the years preceding World War I, it had earned a reputation as one of the most exciting and scientifically advanced specialties. Obstetricians experimented with new drugs and techniques. They recognized that change entails risk, and they examined each innovation more critically. In addition, they turned to science for information and methods to help them solve problems of medical management. Developments in obstetric anesthesia reflected this change in strategy. New methods introduced during this time stimulated physicians to reexamine two important but unresolved issues, the effects of drugs on the child, and the relationship between pain and labor.

**THE EFFECTS OF ANESTHESIA ON THE NEWBORN**

Many physicians, Simpson included, worried that anesthetic drugs might cross the placenta and harm the newborn. Available information justified their concern. The idea that gases cross the placenta appeared long before the discovery of oxygen and carbon dioxide. In the sixteenth century, English physiologist John Mayow suggested that “nitro-aerial” particles from the mother nourish the fetus. By 1847, physiologists had corroborative evidence. Clinical experience gave more support. John Snow observed depressed neonatal breathing and motor activity and smelled ether on the breath of neonates delivered from mothers who had been given ether. In an early paper, he surmised that anesthetic gases cross the placenta. Regardless, some advocates of obstetric anesthesia discounted the possibility. For example, Harvard
professor Walter Channing denied that ether crossed the placenta because he could not detect its odor in the cut ends of the umbilical cord. Oddly enough, he did not attempt to smell ether on the child’s exhalations as John Snow had done.⁴¹

In 1874, Swiss obstetrician Paul Zweifel⁵⁵ published an account of work that finally resolved the debate about the placental transfer of drugs (Fig. 1.5). He used a chemical reaction to demonstrate the presence of chloroform in the umbilical blood of neonates. In a separate paper, Zweifel⁶⁶ used a light-absorption technique to demonstrate a difference in oxygen content between umbilical arterial and venous blood, thereby establishing the placental transfer of oxygen. Although clinicians recognized the importance of these data, they accepted the implications slowly. Some clinicians pointed to several decades of clinical use “without problems.” For example, Otto Spiegelberg,²⁷ Professor of Obstetrics at the University of Breslau, wrote in 1887, “as far as the fetus is concerned no unimpeachable clinical observation has yet been published in which a fetus was injured by chloroform administered to its mother.” Experience lulled them into complacency, which may explain their failure to appreciate the threat posed by twilight sleep.

Dangers from twilight sleep probably developed insidiously. The originators of the method, von Steinbterial and Gauss, recommended conservative doses of drugs. They suggested that 0.3 mg of scopolamine be given every 2 to 3 hours to induce amnesia and that no more than 10 mg of morphine be administered subcutaneously for the whole labor. Gauss, who was especially meticulous, even advised physicians to administer a “memory test” to women in labor to evaluate the need for additional scopolamine. However, as other physicians used the technique, they changed it. Some gave larger doses of opioid—as much as 40 or 50 mg of morphine during labor. Others gave additional drugs (e.g., as much as 600 mg of pentobarbital during labor and inhalation agents for delivery). Despite administering these large doses to their patients, some physicians said they had seen no adverse effects on the infants.³⁹ They probably spoke the truth, but this probability says more about their powers of observation than the safety of the method.

Two situations eventually made physicians confront problems associated with placental transmission of anesthetic drugs. The first was the changing use of morphine.³⁹ In the latter part of the nineteenth century (before the enactment of laws governing the use of addictive drugs), morphine was a popular ingredient of patent medicines and a drug frequently prescribed by physicians. As addiction became more common, obstetricians saw many pregnant women who were taking large amounts of morphine daily. When they tried to decrease their patients’ opioid use, several obstetricians noted unexpected problems (e.g., violent fetal movements, sudden fetal death), which they correctly identified as signs of withdrawal. Second, physiologists and anatomists began extensive studies of placental structure and function. By the turn of the century, they had identified many of the physical and chemical factors that affect rates of drug transfer. Thus, even before twilight sleep became popular, physicians had clinical and laboratory evidence to justify caution. As early as 1877, Gillette⁴⁰ described 15 instances of neonatal depression that he attributed to morphine given during labor. Similarly, in a review article published in 1914, Knipe⁴¹ identified stillbirths and neonatal oligopnea and asphyxia as complications of twilight sleep and gave the incidence of each problem as reported by other writers.

When the studies of obstetric anesthesia published between 1880 and 1950 are considered, four characteristics stand out. First, few of them described effects of anesthesia on the newborn. Second, those that did report newborn apnea, oligopnea, or asphyxia seldom defined these words. Third, few used controls or compared one mode of treatment with another. Finally, few writers used their data to evaluate the safety of the practice that they described. In other words, by today’s standards, even the best of these papers lacked substance. They did, however, demonstrate a growing concern among physicians about the effects of anesthetic drugs on neonates. Perhaps even more important, their work prepared clinicians for the work of Virginia Apgar (Fig. 1.6).

Apgar became an anesthesiologist when the chairman of the Department of Surgery at the Columbia University College of Physicians and Surgeons dissuaded her from becoming a surgeon. After training in anesthesia with Ralph Waters at the University of Wisconsin and with E.A. Rovenstine at Bellevue Hospital, she returned to Columbia Presbyterian Hospital as Director of the Division of Anesthesia. In 1949, she was appointed professor, the first woman to attain that rank at Columbia University.³²

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**Fig. 1.5** Paul Zweifel, the Swiss-born obstetrician who performed the first experiments that chemically demonstrated the presence of chloroform in the umbilical blood and urine of infants delivered by women who had been anesthetized during labor. (Courtesy of J.F. Bergmann-Verlag, München, Germany.)
In 1953, Apgar described a simple, reliable system for evaluating newborns and showed that it was sufficiently sensitive to detect differences among neonates whose mothers had been anesthetized for cesarean delivery by different techniques (Fig. 1.7). Infants delivered of women with spinal anesthesia had higher scores than those delivered with general anesthesia. The Apgar score had three important effects. First, it replaced simple observation of neonates with a reproducible measurement—that is, it substituted a numerical score for the ambiguities of words such as oligopnea and asphyxia. Thus it established the possibility of the systematic comparison of different treatments. Second, it provided objective criteria for the initiation of neonatal resuscitation. Third, and most important, it helped change the focus of obstetric care. Until that time, the primary criterion for success or failure had been the survival and well-being of the mother, a natural goal considering the maternal risks of childbirth until that time. After 1900, as maternal risks diminished, the well-being of the mother no longer served as a sensitive measure of outcome. The Apgar score called attention to the child and made its condition the new standard for evaluating obstetric management.

**THE EFFECTS OF ANESTHESIA ON LABOR**

The effects of anesthesia on labor also worried physicians. Again, their fears were well-founded. Diethyl ether and chloroform depress uterine contractions. If given in sufficient amounts, they also abolish reflex pushing with the abdominal muscles during the second stage of labor. These effects are not difficult to detect, even with moderate doses of either inhalation agent.

Simpson’s method of obstetric anesthesia used significant amounts of drugs. He started the anesthetic early, and sometimes he rendered patients unconscious during the first stage of labor. In addition, he increased the depth of anesthesia for the delivery. As many people copied his technique, they presumably had ample opportunity to observe uterine atony and postpartum hemorrhage.

Some physicians noticed the effects of anesthetics on uterine function. For example, Meigs said unequivocally that etherization suppressed uterine function, and he described occasions in which he had had to suspend...
etherization to allow labor to resume. Other physicians waffled, however. For example, Walter Channing,36 Professor of Midwifery and Medical Jurisprudence at Harvard (seemingly a strange combination of disciplines, but at that time neither of the two was thought sufficiently important to warrant a separate chair), published a book about the use of ether for obstetrics (Fig. 1.8). He endorsed etherization and influenced many others to use it. However, his book contained blatant contradictions. On different pages Channing contended that ether had no effect, that it increased uterine contractility, and that it suspended contractions entirely. Then, in a pronouncement smacking more of panache than reason, Channing swept aside his inconsistencies and said that whatever effect ether may have on the uterus he “welcomes it.” Noting similar contradictions among other writers, W.F.H. Montgomery,37 Professor of Midwifery at the King and Queen's College of Physicians in Ireland, wrote, “By one writer we are told that, if uterine action is excessive, chloroform will abate it; by another that if feeble, it will strengthen it and add new vigor to each parturient effort.”

John Snow23 gave a more balanced review of the effects of anesthesia on labor. Originally a surgeon, Snow became the first physician to restrict his practice to anesthesia. He experimented with ether and chloroform and wrote many insightful papers and books describing his work (Fig. 1.9). Snow's technique differed from Simpson's. Snow withheld anesthesia until the second stage of labor, limited administration to brief periods during contractions, and attempted to keep his patients comfortable but responsive. To achieve better control of the depth of anesthesia, he recommended using the vaporizing apparatus that he had developed for surgical cases. Snow23 spoke disparagingly of Simpson's technique and the tendency of people to use it simply because of Simpson's reputation:

> The high position of Dr. Simpson and his previous services in this department, more particularly in being the first to administer ether in labour, gave his recommendations very great influence; the consequence of which is that the practice of anaesthesia is presently probably in a much less satisfactory state than it would have been if chloroform had never been introduced.

Snow’s method, which was the same one he had used to anesthetize Queen Victoria, eventually prevailed over Simpson’s. Physicians became more cautious with anesthesia, reserving it for special problems such as cephalic version, the application of forceps, abnormal presentation, and eclampsia. They also became more conservative with dosage, often giving anesthesia only during the second stage of labor. Snow’s methods were applied to each new inhalation agent—including nitrous oxide, ethylene, cyclopropane, trichloroethylene, and methoxyflurane—as it was introduced to obstetric anesthesia.

Early physicians modified their use of anesthesia from experience, not from study of normal labor or from learning more about the pharmacology of the drugs. Moreover, they had not yet defined the relationship between uterine pain and contractions. As physicians turned more to science during the latter part of the century, however, their strategies began to change. For example, in 1893 the English physiologist Henry Head38 published his classic studies of the innervation of abdominal viscera. His work stimulated others to investigate the role of the nervous system in the control of labor. Subsequently, clinical and laboratory studies of pregnancy after spinal cord transection established the independence of labor from nervous control.39 When regional anesthesia appeared during the first decades of the twentieth century, physicians therefore had a conceptual basis from which to explore its effects on labor.

Carl Koller40 introduced regional anesthesia when he used cocaine for eye surgery in 1884. Recognizing the potential of Koller’s innovation, surgeons developed techniques for other procedures. Obstetricians quickly adopted many of these techniques for their own use. The first papers describing obstetric applications of spinal, lumbar epidural, caudal, paravertebral, parasacral, and pudendal nerve blocks appeared between 1900 and 1930 (see Fig. 1.4).41-43 Recognition of the potential effects of regional anesthesia on labor developed more slowly, primarily because obstetricians seldom used it. They continued to rely on inhalation agents and opioids, partly because few drugs and materials were available for regional anesthesia at that time, but also because obstetricians did not appreciate the chief advantage of regional over general anesthesia—the relative absence of drug effects on the infant. Moreover, they rarely used regional anesthesia to allow labor to resume.
anesthesia except for delivery, and then they often used elective forceps anyway. This set of circumstances limited their opportunity and motivation to study the effects of regional anesthesia on labor.

Among early papers dealing with regional anesthesia, one written by Cleland\(^4\) stands out. He described his experience with paravertebral anesthesia, but he also wrote a thoughtful analysis of the nerve pathways mediating labor pain, an analysis he based on information he had gleaned from clinical and laboratory studies. Few investigators were as meticulous or insightful as Cleland. Most of those who studied the effects of anesthesia simply timed the first and second stages of labor. Some timed the duration of individual contractions or estimated changes in the strength of contractions by palpation. None of the investigators measured the intrauterine pressures, even though a German physician had described such a method in 1898 and had used it to evaluate the effects of morphine and ether on the contractions of laboring women.\(^4\)

More detailed and accurate studies of the effects of anesthesia started to appear after 1944. Part of the stimulus was a method for continuous caudal anesthesia introduced by Hingson and Edwards,\(^4\) in which a malleable needle remained in the sacral canal throughout labor. Small, flexible plastic catheters eventually replaced malleable needles and made continuous epidural anesthesia even more popular. With the help of these innovations, obstetricians began using anesthesia earlier in labor. Ensuing problems, real and imagined, stimulated more studies. Although good studies were scarce, the strong interest in the problem represented a marked change from the early days of obstetric anesthesia.

Ironically, “natural childbirth” appeared just as regional anesthesia started to become popular and as clinicians began to understand how to use it without disrupting labor. Dick-Read,\(^4\) the originator of the natural method, recognized “no physiological function in the body which gives rise to pain in the normal course of health.” He attributed pain in an otherwise uncomplicated labor to an “activation of the sympathetic nervous system by the emotion of fear.” He argued that fear made the uterus contract and become ischemic and therefore painful. He said that women could avoid the pain if they simply learned to abolish their fear of labor. Dick-Read never explained why uterine ischemia that results from fear causes pain, whereas ischemia that results from a normal contraction does not. In other words, Dick-Read, like Simpson a century earlier, claimed no necessary or physiologic relationship between labor pain and contractions. Dick-Read’s book, written more for the public than for the medical profession, represented a regression of almost a century in medical thought and practice. It is important to note that contemporary methods of childbirth preparation do not maintain that fear alone causes labor pain. However, they do attempt to reduce fear by education and to help patients manage pain by teaching techniques of self-control. This represents a significant difference from and an important advance over Dick-Read’s original theory.

### SOME LESSONS

History is important in proportion to the lessons it teaches. With respect to obstetric anesthesia, four lessons stand out. First, every new drug and method entails risks. Physicians who first used obstetric anesthesia seemed reluctant to accept this fact, perhaps because of their inexperience with potent drugs (pharmacology was in its infancy) or because they acceded too quickly to patients, who wanted relief from pain and had little understanding of the technical issues confronting physicians. Whatever the reason, this period of denial lasted almost half a century, until 1900. Almost another half-century passed before obstetricians learned to modify their practice to limit the effects of anesthetics on the child and the labor process.

Second, new drugs or therapies often cause problems in completely unexpected ways. For example, in 1900, physicians noted a rising rate of puerperal fever.\(^4\) The timing was odd. Several decades had passed since Robert Koch had suggested the germ theory of disease and since Semmelweis had recognized that physicians often transmit infection from one woman to the next with their unclean hands. With the adoption of aseptic methods, deaths from puerperal fever had diminished dramatically. During the waning years of the nineteenth century, however, they increased again. Some physicians attributed this resurgence of puerperal fever to anesthesia. In a presidential address to the Obstetrical Society of Edinburgh in 1900, Murray\(^5\) stated the following:

> I feel sure that an explanation of much of the increase of maternal mortality from 1847 onwards will be found in, first the misuse of anaesthesia and second in the ridiculous parody which, in many hands, stands for the use of antiseptics. … Before the days of anaesthesia, interference was limited and obstetric operations were at a minimum because interference of all kinds increased the conscious suffering of the patient. … When anaesthesia became possible, and interference became more frequent because it involved no additional suffering, operations were undertaken when really unnecessary … and so complications arose and the dangers of the labor increased.

Although it was not a direct complication of the use of anesthesia in obstetric practice, puerperal fever appeared to be an indirect consequence of it.

Changes in obstetric practice also had unexpected effects on anesthetic complications. During the first decades of the twentieth century, when cesarean deliveries were rare and obstetricians used only inhalation analgesia for delivery, few women were exposed to the risk of aspiration during deep anesthesia. As obstetric practice changed and cesarean deliveries became more common, this risk rose. The syndrome of aspiration was not identified and labeled until 1946, when obstetrician Curtis Mendelson\(^6\) described and named it. The pathophysiology of the syndrome had already been described by Winternitz et al.,\(^7\) who instilled hydrochloric acid into the lungs of dogs to simulate the lesions found in veterans poisoned by gas during the trench warfare of World War I. Unfortunately, the reports of these studies, although...
excellent, did not initiate any change in practice. Change occurred only after several deaths of obstetric patients were highly publicized in lay, legal, and medical publications. Of course, rapid-sequence induction, currently recommended to reduce the risk for aspiration, creates another set of risks—those associated with a failed intubation.

The third lesson offered by the history of obstetric anesthesia concerns the role of basic science. Modern medicine developed during the nineteenth century after physicians learned to apply principles of anatomy, physiology, and chemistry to the study and treatment of disease. Obstetric anesthesia underwent a similar pattern of development. Studies of placental structure and function called physicians’ attention to the transmission of drugs and the potential effects of drugs on the infant. Similarly, studies of the physiology and anatomy of the uterus helped elucidate potential effects of anesthesia on labor. In each instance, lessons from basic science helped improve patient care.

The fourth and perhaps the most important lesson is the role that patients have played in the use of anesthesia for obstetrics. During the nineteenth century, it was women who pressured cautious physicians to incorporate routine use of anesthesia into their obstetric practice. A century later, it was women again who altered patterns of practice, this time questioning the overuse of anesthesia for routine deliveries. In both instances, the pressure on physicians emanated from prevailing social values regarding pain. In 1900, the public believed that pain, and in particular obstetric pain, was destructive and something that should be avoided. Half a century later, with the advent of the natural childbirth movement, many people began to suggest that the experience of pain during childbirth, perhaps even in other situations, might have some physiologic if not social value. Physicians must recognize and acknowledge the extent to which social values may shape medical “science” and practice.52,53

During the past 75 years, scientists have accumulated a wealth of information about many processes integral to normal labor: the processes that initiate and control lactation; neuroendocrine events that initiate and maintain labor; the biochemical maturation of the fetal lung and liver; the metabolic requirements of the normal fetus and the protective mechanisms that it may invoke in times of stress; and the normal mechanisms that regulate the amount and distribution of blood flow to the uterus and placenta. At this point, we have only the most rudimentary understanding of the interaction of anesthesia with any of these processes. Only a fraction of the information available from basic science has been used to improve obstetric anesthesia care. Realizing the rewards from the clinical use of such information may be the most important lesson from the past and the greatest challenge for the future of obstetric anesthesia.

KEY POINTS

- Physicians have debated the safety of obstetric anesthesia since 1847, when James Young Simpson first administered anesthesia for delivery. Two issues have dominated the debate: the effects of anesthesia on labor and the effects of anesthesia on the newborn.
- Despite controversy, physicians quickly incorporated anesthesia into clinical practice, largely because of their patients’ desire to avoid childbirth pain.
- Only after obstetric anesthesia was in use for many years did problems become apparent.
- Important milestones in obstetric anesthesia are the introduction of inhalation agents in 1847, the expanded use of opioids in the early decades of the twentieth century, and the refinement of regional anesthesia starting in the mid-twentieth century.
- Outstanding conceptual developments are (1) Zweifel’s idea that drugs given to the mother cross the placenta and affect the fetus and (2) Apgar’s idea that the condition of the newborn is the most sensitive assay of the quality of anesthetic care of the mother.
- The history of obstetric anesthesia suggests that the major improvements in patient care have followed the application of principles of basic science.

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Physiologic Changes of Pregnancy

Rachel M. Kacmar, MD, Robert Gaiser, MD

Marked anatomic and physiologic changes occur during pregnancy that allow the woman to adapt to the developing fetus and its metabolic demands. The enlarging gravid uterus places mechanical strain on the woman’s body. Greater hormonal production by the ovaries and the placenta further alters maternal physiology. The hallmark of successful anesthetic management of the pregnant woman is recognition of these changes and appropriate adaptation of anesthetic techniques to account for them. The physiologic alterations of normal pregnancy and their anesthetic implications are reviewed in this chapter.

**Body Weight and Composition, 13**

The mean maternal weight increase during pregnancy is 17% of the prepregnancy weight, or approximately 12 kg. It results from an increase in the size of the uterus and its contents (uterus, 1 kg; amniotic fluid, 1 kg; fetus and placenta, 4 kg), increases in blood volume and interstitial fluid (approximately 1 kg each), and deposition of new fat and protein (approximately 4 kg). The weight gain during pregnancy recommended by the Institute of Medicine is tiered based on prepregnancy body mass index (BMI; Table 2.1) and reflects the increasing incidence of obesity. The expected weight increase during the first trimester in a nonobese individual is 1 to 2 kg, and there is a 5- to 6-kg increase in each of the last two trimesters. The recommended gain is less in obese individuals. Excessive weight gain during pregnancy is a risk factor for a long-term increase in BMI.

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**CARDIOVASCULAR CHANGES**

Physical Examination and Cardiac Studies
Pregnancy causes the heart to increase in size, a result of both greater blood volume and increased stretch and force of contraction. These changes, coupled with the elevation of the...
exercise. The annular diameters of the mitral, tricuspid, and pulmonic valves increase; 94% of term pregnant women exhibit mitral regurgitation. The aortic annulus does not dilate from normal pregnancy-induced physiologic changes. Echocardiography demonstrates left ventricular (LV) hypertrophy by 12 weeks’ gestation with a 23% increase in LV mass from the first to the third trimester and an overall 50% increase in mass at term. This eccentric hypertrophy results from an increase in the size of the preexisting cardiomyocytes, resembling the changes that occur from repeated, strenuous exercise. The anular diameters of the mitral, tricuspid, and pulmonic valves increase; 94% of term pregnant women exhibit tricuspid and pulmonic regurgitation, and 27% exhibit mitral regurgitation. The aortic annulus does not dilate from normal pregnancy-induced physiologic changes.

Changes in heart sounds include accentuation of the first heart sound with exaggerated splitting of the mitral and tricuspid components (Box 2.1). The second heart sound changes little, although the aortic-pulmonic interval tends to vary less with respiration during the third trimester, a finding without clinical significance. A fourth heart sound may be heard in 16% of pregnant women, although typically it disappears at term. A grade II systolic ejection murmur is commonly heard at the left sternal border; the murmur is considered a benign flow murmur, attributable to cardiac enlargement from increased intravascular volume, which causes dilation of the tricuspid annulus and mild tricuspid regurgitation. Elevation of the diaphragm by the growing uterus shifts the heart anteriorly and to the left. The point of maximal cardiac impulse is displaced cephalad to the fourth intercostal space and left to at least the midclavicular line.

Echocardiography demonstrates left ventricular (LV) hypertrophy by 12 weeks’ gestation with a 23% increase in LV mass from the first to the third trimester and an overall 50% increase in mass at term. This eccentric hypertrophy results from an increase in the size of the preexisting cardiomyocytes, resembling the changes that occur from repeated, strenuous exercise. The anular diameters of the mitral, tricuspid, and pulmonic valves increase; 94% of term pregnant women exhibit tricuspid and pulmonic regurgitation, and 27% exhibit mitral regurgitation. The aortic annulus does not dilate from normal pregnancy-induced physiologic changes.

The electrocardiogram typically changes, especially during the third trimester. Heart rate steadily increases during the first and second trimesters, and both the PR interval and the uncorrected QT interval are shortened. This has clinical implications for women with long QT syndrome (see Chapter 41). The QRS axis shifts to the right during the first trimester but may shift to the left during the third trimester. Depressed ST segments and isoelectric low-voltage T waves in the left-sided precordial and limb leads are common.

Central Hemodynamics

To accurately determine central hemodynamic values and/or changes during pregnancy, measurements should be made with the patient in a resting position with left uterine displacement to minimize vena caval compression. Comparisons must be made with an appropriate control, such as prepregnancy values or a matched group of nonpregnant women. If control measurements are made postpartum, a sufficient interval must elapse for parameters to have returned to prepregnancy values; this may take 24 weeks or more. There is significant heterogeneity in cardiac output measurement using different noninvasive devices; these differences should be taken into account when caring for individual patients.

Cardiac output begins to increase by five weeks’ gestation and is 35% to 40% above baseline by the end of the first trimester. It continues increasing throughout the second trimester to approximately 50% greater than nonpregnant values. Cardiac output does not change further during the third trimester; however, typically this is with measurements made in the supine position and thus likely reflects vena caval compression rather than a true gestational decline.

The initial increase in cardiac output results from an increase in heart rate. The heart rate increases 15% to 25% above baseline by the end of the first trimester and remains relatively stable for the remainder of the pregnancy. Cardiac output continues to increase through the second trimester owing to an increase in stroke volume. Stroke volume increases by approximately 20% during the first trimester and by 25% to 30% above baseline during the second trimester. The increased stroke volume correlates with increasing estrogen levels. Stroke volume index decreases over the course of pregnancy, while cardiac index remains slightly increased from prepregnancy values.

Left ventricular end-diastolic volume increases during pregnancy, whereas end-systolic volume remains unchanged, resulting in a larger ejection fraction. Central venous, pulmonary artery diastolic, and pulmonary capillary wedge pressures are within the normal nonpregnant range. The apparent discrepancy between left ventricular filling pressure and end-diastolic volume is explained by both hypertrophy and dilation, with the dilated ventricle accommodating a greater volume without an increase in pressure.

Myocardial contractility increases, as demonstrated by higher velocity of left ventricular circumferential fiber shortening. Tissue Doppler imaging, which is relatively independent of preload, has been used to assess diastolic function. A mild degree of diastolic dysfunction may be seen during the third trimester compared with earlier in pregnancy and nonpregnant controls.

**TABLE 2.1 Recommended Weight Gain during Pregnancy**

<table>
<thead>
<tr>
<th>Prepregnancy Body Mass Index (kg/m²)</th>
<th>Total Weight Gain in kg (lb)</th>
<th>Rate of Weight Gain during Second and Third Trimester in kg/wk (lb/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>12.7–18.2 (28–40)</td>
<td>0.45 (1)</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>11.4–15.9 (25–35)</td>
<td>0.45 (1)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>6.8–11.4 (15–25)</td>
<td>0.27 (0.6)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>5.0–9.1 (11–20)</td>
<td>0.23 (0.5)</td>
</tr>
</tbody>
</table>

The increase in cardiac output during pregnancy results in increased perfusion to the uterus, kidneys, and extremities. Uterine blood flow increases to meet the demands of the developing fetus from a baseline value of approximately 50 mL/min (prepregnancy) to a level at term of 700 to 900 mL/min. During the second half of pregnancy, the proportion of cardiac output distributed to the uterine circulation increases from 5% to 12%. Approximately 90% of this flow perfuses the intervillous space, with the balance perfusing the myometrium. At term, skin blood flow is approximately three to four times the nonpregnant level, resulting in higher skin temperature.

Renal plasma flow is increased by 80% at 16 to 26 weeks’ gestation but is only 50% above the prepregnancy baseline at term.

The U.S. Department of Health and Human Services recommends that pregnant women have at least 150 minutes of moderate-intensity aerobic activity every week, and the American College of Obstetricians and Gynecologists recommends 20 to 30 minutes per day; however, most women do not achieve this goal. Pregnant women are less active, with only half as many meeting guidelines for vigorous activity compared with nonpregnant women. For every two women who exercise before pregnancy, one will not do so during pregnancy. Failure to exercise increases risk for greater gestational weight gain. Exercise is safe for the fetus; in a study of 45 women, exercise on a treadmill of moderate intensity (40% to 59% of heart rate reserve) did not affect fetal heart or umbilical artery Doppler indices.

During exercise, maximal oxygen consumption is greater in pregnancy, especially during cardiovascular exercise. The rate of increase in minute ventilation is greater with exercise during pregnancy. Cardiac output is also greater, primarily...
from increased stroke volume\textsuperscript{33} and oxygen delivery to the fetus.

**Blood Pressure and Systemic Vascular Resistance**

Positioning, gestational age, and parity affect blood pressure measurements. Brachial sphygmomanometry yields the highest measurements in the supine position and the lowest measurements in the lateral position, especially with the cuff on the upper arm.\textsuperscript{34} Blood pressure increases with maternal age, and for a given age, nulliparous women have a higher mean pressure than parous women.\textsuperscript{35} Systolic, diastolic, and mean blood pressure decrease during mid-pregnancy and return toward baseline as the pregnancy approaches term.\textsuperscript{36} Diastolic blood pressure decreases more than systolic blood pressure, with early- to mid-gestational decreases of approximately 20%.\textsuperscript{37}

The changes in blood pressure are consistent with changes in systemic vascular resistance, which decreases during early gestation, reaches its nadir (35\% decline) at 20 weeks’ gestation, and increases toward prepregnancy baseline during late gestation. Unlike blood pressure, however, systemic vascular resistance remains approximately 20\% below the nonpregnant level at term.\textsuperscript{32,36} A postulated explanation for the decreased systemic vascular resistance is the low-resistance uteroplacental vascular bed as well as systemic maternal vasodilation caused by prostacyclin, estrogen, and progesterone. The lower blood pressure often persists beyond pregnancy. A longitudinal study of 2304 initially normotensive women over 20 years showed that nulliparous women who subsequently delivered one or more infants maintained a blood pressure that was 1 to 2 mm Hg lower than women who did not have children.\textsuperscript{37} This finding demonstrates that pregnancy may create long-lasting vascular changes. Advanced maternal age has been associated with higher median systemic vascular resistance during pregnancy, and pregnant women who smoke have demonstrated a lower systemic vascular resistance compared with nonsmoking parturients.\textsuperscript{38}

**Aortocaval Compression**

The extent of compression of the aorta and inferior vena cava by the gravid uterus depends on positioning and gestational age. At term, partial vena caval compression occurs when the woman is in the lateral position, as documented by angiography.\textsuperscript{39} This finding is consistent with the 75\% elevation above baseline of femoral venous and lower inferior vena cava pressures.\textsuperscript{10} Despite caval compression, collateral circulation maintains venous return, as reflected by the right ventricular filling pressure, which is unaltered in the lateral position.\textsuperscript{16} Intra-abdominal pressure is often elevated in term pregnant patients regardless of BMI, but is significantly lower in the lateral position compared with supine.\textsuperscript{41}

In the supine position, significant and sometimes complete compression of the inferior vena cava is evident at term.\textsuperscript{42,43} Blood returns from the lower extremities through the intraosseous, vertebral, paravertebral, and epidural veins.\textsuperscript{44} However, this collateral venous return is less than would occur through the inferior vena cava, resulting in a decrease in right atrial pressure.\textsuperscript{45} Compression of the inferior vena cava occurs as early as 13 to 16 weeks’ gestation and is evident from the 50\% increase in femoral venous pressure observed when these women assume the supine position (Fig. 2.4).\textsuperscript{46} By term, femoral venous and lower inferior vena caval pressures are approximately 2.5 times the nonpregnant measurements in the supine position.\textsuperscript{36,46} Vena cava volume at term is significantly higher with a 30-degree lateral tilt compared with the supine position, whereas there is no difference between women in the supine position and those tilted 15 degrees.\textsuperscript{43}

In the supine position, the aorta may be compressed by the term gravid uterus. This compression could account for lower pressure in the femoral versus the brachial artery in the supine position.\textsuperscript{47,48} Angiographic studies in supine pregnant women showed partial obstruction of the aorta at the level of the lumbar lordosis and enhanced compression during periods of maternal hypotension.\textsuperscript{49} Conversely, a comparison of magnetic resonance images of healthy women at term in the supine position compared with nonpregnant women showed no difference in aortic volume at the level of the mid- to upper lumbar vertebra.\textsuperscript{45}

At term, the left lateral decubitus position is associated with less enhancement of cardiac sympathetic nervous system activity and less suppression of cardiac vagal activity than the supine or right lateral decubitus position.\textsuperscript{40} Women who assume the supine position at term gestation experience a 10\% to 20\% decline in stroke volume and cardiac output,\textsuperscript{51,52} consistent with the decrease in right atrial filling pressure. Blood flow in the upper extremities is normal, whereas uterine blood flow decreases by 20\% and lower extremity blood flow decreases by 50\%.\textsuperscript{53} Perfusion of the uterus is less affected than that of the lower extremities because compression of the vena cava does not obstruct venous outflow via the ovarian veins.\textsuperscript{54} The adverse hemodynamic effects of aortic caval compression are reduced once the fetal head is engaged.\textsuperscript{57,48} The sitting position has also been shown to result in aortocaval compression, with a decrease in cardiac output of 10%.\textsuperscript{55} Flexing the legs rotates the uterus to compress against the vena cava. Short intervals in the sitting position, such as occurs during epidural catheter placement, have no impact on uteroplacental blood flow.

Some term pregnant women exhibit an increase in brachial artery blood pressure when they assume the supine position, which is caused by higher systemic vascular resistance from compression of the aorta. Up to 15\% of women at term experience bradycardia and a substantial decrease in blood pressure when supine, the so-called supine hypotension syndrome.\textsuperscript{56} It may take several minutes for the bradycardia and hypotension to develop, and the bradycardia is usually preceded by a period of tachycardia. The syndrome results from a profound decrease in venous return and preload for which the cardiovascular system is not able to compensate.
Anatomy
The thorax undergoes both mechanical and hormonal changes during pregnancy. Relaxin (the hormone responsible for relaxation of the pelvic ligaments) causes relaxation of the ligamentous attachments to the lower ribs.64 The subcostal angle progressively widens from approximately 69 to 104 degrees. The anteroposterior and transverse diameters of the chest wall each increase by 2 cm, resulting in an increase of 5 to 7 cm in the circumference of the lower rib cage. These changes peak at 37 weeks’ gestation. The subcostal angle remains about 20% wider than the baseline value after delivery.65 The vertical measurement of the chest cavity decreases by as much as 4 cm as a result of the elevated position of the diaphragm.

Capillary engorgement of the larynx and the nasal and oropharyngeal mucosa begins early in the first trimester and increases progressively throughout pregnancy.66 The effect of estrogen on the nasal mucosa may cause symptoms of rhinitis and epistaxis. Nasal breathing commonly becomes difficult, and nasal congestion may contribute to the perceived shortness of breath of pregnancy.67

Airflow Mechanics
Inspiration in the term pregnant woman is almost totally attributable to diaphragmatic excursion because of greater descent of the diaphragm from its elevated resting position and limitation of thoracic cage expansion because of its expanded resting position (Table 2.2). Both large- and small-airway function are minimally altered during pregnancy. The shape of flow-volume loops, the absolute flow rates at normal lung volumes, forced expiratory volume in 1 second (FEV₁),
residual capacity (FRC) begins to decrease by the fifth month of pregnancy with uterine enlargement and diaphragm elevation, and is decreased by 400 to 700 mL to 80% of the prepregnancy value at term. 76,77 The overall reduction is caused by a 25% reduction in expiratory reserve volume (200 to 300 mL) and a 15% reduction in residual volume (200 to 400 mL). Assumption of the supine position causes the FRC to decrease further to 70% of the prepregnancy value. The supine FRC can be increased by 10% (approximately 188 mL) by placing the patient in a 30-degree head-up position.78

Ventilation and Blood Gases
During pregnancy, respiratory patterns remain relatively unchanged. Minute ventilation increases via an increase in

---

**TABLE 2.2 Effects of Pregnancy on Respiratory Mechanics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm excursion</td>
<td>Increased</td>
</tr>
<tr>
<td>Chest wall excursion</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pulmonary resistance</td>
<td>Decreased 50%</td>
</tr>
<tr>
<td>FEV₁</td>
<td>No change</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>No change</td>
</tr>
<tr>
<td>Flow-volume loop</td>
<td>No change</td>
</tr>
<tr>
<td>Closing capacity</td>
<td>No change</td>
</tr>
</tbody>
</table>


---

**TABLE 2.3 Changes in Respiratory Physiology at Term Gestation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Volumes</td>
<td></td>
</tr>
<tr>
<td>Inspiratory reserve volume</td>
<td>+5%</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>+45%</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>−25%</td>
</tr>
<tr>
<td>Residual volume</td>
<td>−15%</td>
</tr>
<tr>
<td>Lung Capacities</td>
<td></td>
</tr>
<tr>
<td>Inspiratory capacity</td>
<td>+15%</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>−20%</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>No change</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>−5%</td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>+45%</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>+45%</td>
</tr>
</tbody>
</table>

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CHAPTER 2 Physiologic Changes of Pregnancy

secondary to elevations in estrogen and progesterone levels. This increase occurs despite blood and cerebrospinal fluid (CSF) alkalosis.

During pregnancy, PaO₂ increases to 100 to 105 mm Hg (13.3 to 14.0 kPa) as a result of greater alveolar ventilation and a decline in PaCO₂ (Table 2.4). As pregnancy progresses, oxygen consumption continues to increase, and cardiac output increases to a lesser extent, resulting in a reduced mixed venous oxygen content and increased arteriovenous oxygen difference. After mid-gestation, pregnant women in the supine position frequently have a PaO₂ less than 100 mm Hg (13.3 kPa). This occurs because the FRC may be less than closing capacity, resulting in closure of small airways during normal tidal ventilation. Moving a pregnant woman from the supine to the erect or lateral decubitus position improves arterial oxygenation and reduces the alveolar-to-arterial oxygen gradient. The increased oxygen tension facilitates the transfer of oxygen across the placenta to the fetus.

PaCO₂ declines to approximately 30 mm Hg (4.0 kPa) by 12 weeks’ gestation but does not change further during the remainder of the pregnancy. Although a gradient exists between the end-tidal CO₂ tension and PaCO₂ in nonpregnant women, the two measurements are equivalent during early pregnancy, at term gestation, and in the postpartum period. This is attributable to a reduction in alveolar dead space, which results from an increase in cardiac output and increased basilar atelectasis during pregnancy. The mixed venous Pco₂ is 6 to 8 mm Hg (0.8 to 1.1 kPa) tidal volume from 450 to 600 mL and a small increase in respiratory rate of 1 to 2 breaths/min. This occurs primarily during the first 12 weeks of gestation with a minimal increase thereafter. The ratio of total dead space to tidal volume remains constant during pregnancy, resulting in an increase in alveolar ventilation of 30% to 50% above baseline. The increase in minute ventilation results from hormonal changes and from an increase in CO₂ production at rest by approximately 30% to 300 mL/min. The former is closely related to the blood level of progesterone, which acts as a direct respiratory stimulant. The progesterone-induced increase in chemosensitivity also results in a steeper slope and a leftward shift of the CO₂-ventilatory response curve. This change occurs early in pregnancy and remains constant until delivery.

Dyspnea is a common complaint during pregnancy, affecting up to 75% of women. Contributing factors include increased respiratory drive, decreased PaCO₂, increased oxygen consumption from the enlarging uterus and fetus, larger pulmonary blood volume, anemia, and nasal congestion. Dyspnea typically begins in the first or second trimester but improves as the pregnancy progresses. In a study in which 35 women were observed closely during pregnancy and postpartum, dyspnea was not caused by alterations in central ventilatory control or respiratory mechanical factors but rather to the awareness of the increased ventilation. Exercise has no effect on pregnancy-induced changes in ventilation or alveolar gas exchange. The hypoxic ventilatory response is increased during pregnancy to twice the normal level, secondary to elevations in estrogen and progesterone levels.

**TABLE 2.4 Blood Gas Parameters during Pregnancy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonpregnant</th>
<th>TRIMESTER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First</td>
</tr>
<tr>
<td>PaCO₂ in mm Hg (kPa)</td>
<td>40 (5.3)</td>
<td>30 (4.0)</td>
</tr>
<tr>
<td>PaO₂ in mm Hg (kPa)</td>
<td>100 (13.3)</td>
<td>107 (14.3)</td>
</tr>
<tr>
<td>pH</td>
<td>7.40</td>
<td>7.44</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>24</td>
<td>21</td>
</tr>
</tbody>
</table>

**Fig. 2.6 Lung volumes and capacities during pregnancy. ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; TV, tidal volume; VC, vital capacity.**
below the nonpregnant level from late in the first trimester until term.1

The respiratory alkalosis of pregnancy causes a compensatory increase in renal bicarbonate excretion and a reduction in serum bicarbonate concentration to approximately 20 mEq/L, the base excess by 2 to 3 mEq/L, and the total buffer base by approximately 5 mEq/L.91 This compensation is incomplete, as demonstrated by the elevation of venous,92 capillary,93 and arterial85 blood pH by 0.02 to 0.06 units (see Table 2.4). The decrease in serum bicarbonate affects the pregnant woman's ability to buffer an acid load. The slight respiratory alkalosis would normally shift the oxyhemoglobin saturation curve to the left, however a concurrent increase in 2,3-bisphosphoglycerate (2,3-BPG) causes the curve to shift slightly to the right.

### Metabolism and Respiration during Labor and the Puerperium

Minute ventilation in the unmedicated parturient increases by 70% to 140% in the first stage of labor and by 120% to 200% in the second stage of labor compared with prepregnancy values.84 Pain, anxiety, and coached breathing techniques all increase minute ventilation. PacO₂ may decrease to as low as 10 to 15 mm Hg (1.3 to 2.0 kPa). Oxygen consumption increases above the prelabor value by 40% in the first stage and by 75% in the second stage, secondary to the increased metabolic demands of hyperventilation, uterine activity, and maternal expulsive efforts.84,94 The maternal aerobic requirement for oxygen exceeds oxygen consumption during labor, as is evident from the progressive elevation of blood lactate concentration, an index of anaerobic metabolism.95–98 Effective neuraxial analgesia prevents these changes during the first stage of labor and mitigates the changes during the second stage of labor.95,98

FRC increases after delivery but remains below the prepregnancy volume for 1 to 2 weeks. Although minute ventilation decreases halfway toward nonpregnant values by 72 hours, oxygen consumption, tidal volume, and minute ventilation remain elevated until at least 6 to 8 weeks after delivery. The alveolar and mixed venous PCO₂ values increase slowly after delivery and are still slightly below prepregnancy levels at 6 to 8 weeks postpartum.1

### TABLE 2.5 Changes in Gastrointestinal Physiology during Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Labor</th>
<th>Postpartum (18 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier pressure⁵</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>?</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Delayed</td>
<td>No change</td>
</tr>
<tr>
<td>Gastric acid secretion</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Proportion of women with gastric volume &gt; 25 mL</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Increased</td>
<td>No change</td>
</tr>
<tr>
<td>Proportion of women with gastric pH &lt; 2.5</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

⁵Relative to nonpregnant state.

### THE GASTROINTESTINAL SYSTEM

#### Anatomy, Barrier Pressure, and Gastroesophageal Reflux

The stomach is displaced upward toward the left side of the diaphragm during pregnancy, and its axis is rotated approximately 45 degrees to the right from its normal vertical position. This altered position displaces the intra-abdominal segment of the esophagus into the thorax in most women, causing a reduction in tone of the lower esophageal high-pressure zone (LEHPZ), which normally prevents the reflux of gastric contents. Progestins also may contribute to relaxation of the LEHPZ.99

Approximately 30% to 50% of women experience gastroesophageal reflux disease (GERD) during pregnancy.100 The prevalence of GERD is approximately 10% in the first trimester, 40% in the second trimester, and 55% in the third trimester. In the first trimester of pregnancy, basal LEHPZ pressure may not change, but the sphincter is less responsive to physiologic stimuli that usually increase pressure.101 In the second and third trimesters, LEHPZ pressure gradually decreases to approximately 50% of basal values, reaching a nadir at 36 weeks’ gestation and returning to prepregnancy values at 1 to 4 weeks postpartum (Table 2.5). Risk factors for GERD in pregnancy include gestational age, heartburn antecedent to pregnancy, and multiparity. Gravidity, prepregnancy BMI, and weight gain during pregnancy do not correlate with the occurrence of reflux, whereas maternal age has an inverse correlation.102

#### Gastrointestinal Motility

Gastric emptying is not altered during pregnancy. This has been demonstrated by studies that measured the absorption of orally administered acetaminophen103–105 and by studies that assessed the emptying of a test beverage or meal by radiographic,106 ultrasonographic,105,107 dye dilution,108 esophageal peristalsis, and applied potential tomographic109 techniques. In a study of morbidly obese women at term, no difference was noted between gastric emptying of 300 mL and 50 mL of water, suggesting that fasting guidelines should not differ for obese versus lean parturients.111

Esophageal peristalsis and intestinal transit are slowed during pregnancy,107,112 which has been attributed to the
inhibition of gastrointestinal contractile activity by progesterone. However, this inhibition may be an indirect action that results from a negative effect of progesterone on the plasma concentration of motilin, which declines during pregnancy. Up to 40% of women suffer from constipation at some time during their pregnancy. The prevalence of constipation is greatest in the first two trimesters of gestation and declines in the third trimester.

**Gastric Acid Secretion**

Early work suggested that both basal and maximal gastric acid secretion decline in mid-gestation, reaching a nadir at 20 to 30 weeks' gestation. Van Thiel et al. demonstrated no difference in basal or peak gastric acid secretion in four pregnant women studied in each trimester and at 1 to 4 weeks postpartum, although a plasma gastrin level significantly lower than postpartum levels was observed during the first trimester. Levels of gastric pH and serum gastrin concentration were compared in 100 women scheduled for elective cesarean delivery and in 100 nonpregnant women undergoing gynecologic surgery. The mean pH was lower in the pregnant group (2.4 versus 3.0), but serum gastrin levels were not different despite the fact that gastrin is secreted by the placenta from 15 weeks' gestation onward. This may reflect a dilutional effect of increased plasma volume. Other studies have shown that approximately 80% of both pregnant and nonpregnant women have a gastric pH of 2.5 or less, approximately 50% have gastric volumes of 25 mL or greater, and 40% to 50% exhibit both low pH and gastric volume greater than 25 mL.

**Nausea and Vomiting**

Approximately 80% of pregnant women will experience nausea and vomiting during pregnancy. The symptoms typically start between 4 to 9 weeks' gestation and may last until 12 to 16 weeks' gestation. Of these women, 1% to 5% will develop symptoms that persist throughout the pregnancy, known as *hyperemesis gravidarum* (see Chapter 16).

**Gastric Function during Labor and the Puerperium**

Gastric emptying is slowed during labor, as shown by ultrasonographic imaging, emptying of a test meal, and the rate of absorption of oral acetaminophen. Direct measurements show that the mean gastric volume increases. However, in one study, postpartum gastric volume was found to be no different in parturients who consumed water in labor compared with those who consumed an isotonic sports drink composed of mixed carbohydrates and electrolytes. Gastric acid secretion may decrease during labor because of reduced consumption of fluid and their *higher* effects of opioids and neuraxial analgesia on gastric emptying are discussed in Chapters 23 and 28.

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**THE LIVER AND GALLBLADDER**

Liver size, morphology, and blood flow do not change during pregnancy, although the liver is displaced upward, posterior, and to the right during late pregnancy.

Serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase increase to the upper limits of the normal range during pregnancy. The total alkaline phosphatase activity increases twofold to fourfold, mostly from production by the placenta. Excretion of sulfobromophthalein into bile decreases, whereas the hepatic extraction and retention of this compound increases.

Biliary stasis and greater secretion of bile with cholesterol increase the risk for gallbladder disease during pregnancy. The incidence of gallstones is 5% to 12% in pregnant women. One in 1600 to 1 in 10,000 women undergo cholecystectomy during pregnancy. Progesterone inhibits the contractility of gastrointestinal smooth muscle, leading to gallbladder hypomotility. The size of the total bile acid pool increases by about 50% during pregnancy, and the relative proportions of the various bile acids change.

The changes in the composition of bile revert rapidly after delivery, even in patients with gallstones.

**THE KIDNEYS**

Owing to an increase in total intravascular volume, both renal vascular and interstitial volume increase during pregnancy. These increases are reflected in enlarged kidneys, with renal volume increased by as much as 30%. Vasodilation of the kidneys contributes to the overall decline in systemic vascular resistance during the first trimester. The collecting system, including the renal calyces, pelvis, and ureters, dilates. Hypernephrosis may occur in 80% of women by mid-pregnancy.

Both the glomerular filtration rate (GFR) and the renal plasma flow increase markedly during pregnancy secondary to reduced renal vascular resistance. The renal blood flow is 75% greater than nonpregnant values by 16 weeks’ gestation and is maintained until 34 weeks, when a slight decline occurs. By the end of the first trimester, the GFR is 50% greater than baseline, and this rate is maintained until the end of pregnancy. The GFR does not return to prepregnancy levels until 3 months postpartum. Because the GFR does not increase as rapidly or as much as the renal blood flow, the filtration fraction decreases from nonpregnant levels until the third trimester. The role of nitric oxide in the renal vasodilation was tested and confirmed in a rat model. Renin and aldosterone also both increase during pregnancy.

Creatinine clearance is increased to 150 to 200 mL/min from the normal baseline values of 120 mL/min. The increase occurs early in pregnancy, reaches a maximum by the end of the first trimester, decreases slightly near term, and returns to the prepregnancy level by 8 to 12 weeks postpartum. These renal hemodynamic alterations are among the earliest and most dramatic maternal adaptations to pregnancy. The increased GFR results in reduced blood concentrations of nitrogenous metabolites. The blood urea nitrogen
concentration decreases to 8 to 9 mg/dL by the end of the first trimester and remains at that level until term. Serum creatinine concentration is a reflection of skeletal muscle production and urinary excretion. In pregnancy, skeletal muscle production of creatinine remains relatively constant, but the GFR is increased, resulting in reduced serum creatinine concentration. The serum creatinine concentration decreases progressively to 0.5 to 0.6 mg/dL by the end of pregnancy. The serum uric acid level declines in early pregnancy because of the increase in GFR, to 2.0 to 3.0 mg/dL by 24 weeks’ gestation. Subsequently, the uric acid level begins to increase, reaching the prepregnancy level by the end of pregnancy. Tubular reabsorption of urate accounts for this restored uric acid level during the third trimester.

Total protein excretion and urinary albumin excretion are higher than nonpregnant levels. Average 24-hour total protein and albumin excretion are 200 mg and 12 mg, respectively (upper limits are 300 mg and 20 mg, respectively). Proteinuria (> 300 mg/24 h) has been described without the diagnosis of preeclampsia. However, women with isolated proteinuria are more likely to progress to preeclampsia than women with isolated hypertension. The protein-to-creatinine (P/C) ratio in a random urine sample correlates well with a 24-hour urine protein measurement, and a value of greater than 0.3 has been defined as the threshold for diagnosing preeclampsia. The degree of proteinuria in normal pregnancy correlates with gestation. Baba et al. suggested that in normotensive patients, a P/C ratio of > 0.75 may be the “rule-in” threshold for significant proteinuria. Women with twin pregnancies have greater protein excretion compared with those with singleton pregnancies.

Glucose is filtered and almost completely absorbed in the proximal tubule. In the nonpregnant state, a small amount of glucose is excreted. Pregnancy imposes a change in the glucose resorptive capacity of the proximal tubules, so all pregnant women exhibit an elevation of glucose excretion. Of pregnant women who have normal glucose tolerance to an oral load, 0.7% to 10% excrete as much as 20 times the nonpregnant amount. Overall, the amount of glucose excreted in the third trimester is several times greater than that in the nonpregnant state. The normal nonpregnant pattern of glucose excretion is reestablished within 1 week after delivery.

HEMATOLOGY

Blood Volume

Maternal plasma volume expansion begins as early as 6 weeks’ gestation and continues until it reaches a net increase of approximately 50% by 34 weeks’ gestation (Table 2.6, Fig. 2.7). After 34 weeks’ gestation, the plasma volume stabilizes or decreases slightly. Red blood cell volume decreases during the first 8 weeks of pregnancy, increases to the prepregnancy level by 16 weeks, and undergoes a further rise to 30% above the prepregnancy level at term. The red blood cell volume increases in response to elevated erythropoietin concentration and the erythropoietic effects of progesterone, prolactin, and placental lactogen. The increase in plasma volume exceeds the increase in red blood cell volume, resulting in the physiologic anemia of pregnancy. Hemoglobin concentration (hematocrit), which typically ranges from 12.0 to 15.8 g/dL (35.4% to 44.4%) in the nonpregnant woman, decreases to 11.6 to 13.9 g/dL (31% to 41%) in the first trimester, 9.7 to 14.8 g/dL (30% to 39%) in the second trimester, and 9.5 to 15.0 g/dL (28% to 40%) in the third trimester (Fig. 2.8). Women who do not receive iron supplements during pregnancy have greater decreases in hemoglobin concentration and hematocrit.

The increase in plasma volume results from fetal and maternal hormone production, and several systems may play a role. The maternal concentrations of estrogen and progesterone

### TABLE 2.6 Hematologic Parameters at Term Gestation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change* or Actual Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume</td>
<td>+45%*</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>+55%*</td>
</tr>
<tr>
<td>Red blood cell volume</td>
<td>+30%*</td>
</tr>
<tr>
<td>Hemoglobin concentration (g/dL)</td>
<td>11.6</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>35.5%</td>
</tr>
</tbody>
</table>

*Relative to nonpregnant state.


![Fig. 2.7 Blood Volume during Pregnancy and the Puerperium](image-url)
increase nearly 100-fold during pregnancy. Estrogens increase plasma renin activity, enhancing renal sodium absorption and water retention via the renin-angiotensin-aldosterone system. Fetal adrenal production of the estrogen precursor dehydroepiandrosterone may be the underlying control mechanism. Progesterone also enhances aldosterone production. These changes result in marked increases in plasma renin activity and aldosterone level as well as in retention of approximately 900 mEq of sodium and 7000 mL of total body water. The concentration of plasma adrenomedullin, a potent vasodilating peptide, increases during pregnancy and correlates significantly with blood volume.156

Blood volume is positively correlated with the size of the fetus in singleton pregnancies and is greater in multiple gestations.151 The physiologic hypervolemia facilitates delivery of nutrients to the fetus, protects the mother from hypotension, and reduces the risks associated with hemorrhage at delivery.153,157 The decrease in blood viscosity from the lower hematocrit creates lower resistance to blood flow, which may be an essential component of maintaining the patency of the uteroplacental vascular bed.

**Plasma Proteins**

Plasma albumin concentration decreases from a nonpregnant range of 4.1–5.3 g/dL to ranges of 3.1–5.1 g/dL in the first trimester, 2.6–4.5 g/dL in the second trimester, and 2.3–4.2 g/dL in the third trimester (Table 2.7).155,158,159 The globulin level decreases by 10% in the first trimester and then increases throughout the remainder of pregnancy to 10% above the prepregnancy value at term.158 The albumin-globulin ratio decreases during pregnancy from 1.4 to 0.9, and the total plasma protein concentration decreases from 7.8 to 7.0 g/dL.159 Maternal colloid osmotic pressure decreases by approximately 5 mm Hg during pregnancy.16,160,161 The plasma cholinesterase concentration falls by approximately 25% during the first trimester and remains at that level until the end of pregnancy.162

**Coagulation**

Pregnancy is associated with enhanced platelet turnover, clotting, and fibrinolysis (Box 2.2). Thus, pregnancy represents a state of accelerated but compensated intravascular coagulation.

**Table 2.7 Plasma Protein Values during Pregnancy**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Nonpregnant</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dL)</td>
<td>7.8</td>
<td>6.9</td>
<td>6.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.5</td>
<td>3.9</td>
<td>3.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Globulin (g/dL)</td>
<td>3.3</td>
<td>3.0</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Albumin/globulin ratio</td>
<td>1.4</td>
<td>1.3</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Plasma cholinesterase</td>
<td>–25%</td>
<td>–25%</td>
<td>–25%</td>
<td>–25%</td>
</tr>
<tr>
<td>Colloid osmotic pressure (mm Hg)</td>
<td>27</td>
<td>25</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

**Box 2.2 Changes in Coagulation and Fibrinolytic Parameters at Term Gestation**

- **Increased Factor Concentrations**
  - Factor I (fibrinogen)
  - Factor VII (proconvertin)
  - Factor VIII (antihemophilic factor)
  - Factor IX (Christmas factor)
  - Factor X (Stuart-Prower factor)
  - Factor XII (Hageman factor)

- **Unchanged Factor Concentrations**
  - Factor II (prothrombin)
  - Factor V (proaccelerin)

- **Decreased Factor Concentrations**
  - Factor XI (thromboplastin antecedent)
  - Factor XIII (fibrin-stabilizing factor)

- **Other Parameters**
  - Prothrombin time: shortened 20%
  - Partial thromboplastin time: shortened 20%
  - Thromboelastography: hypercoagulable
  - Fibrinopeptide A: increased
  - Antithrombin III: decreased
  - Platelet count: no change or decreased
  - Fibrin degradation products: increased
  - Plasminogen: increased
  - Plasminogen activator inhibitor-II: increased

*Relative to nonpregnant state.
Increases in platelet factor 4 and beta-thromboglobulin signal elevated platelet activation, and the progressive increase in platelet distribution width and platelet volume are consistent with greater platelet consumption during pregnancy.\textsuperscript{163–165} Platelet aggregation in response to collagen, epinephrine, adenosine diphosphate, and arachidonic acid is increased.\textsuperscript{166} Some investigators have noted a decrease in platelet count,\textsuperscript{165,167} whereas others have noted no change,\textsuperscript{163,164} suggesting that increased platelet production compensates for greater activation. The platelet count usually decreases during the third trimester, with an estimated 8% of pregnant women having a platelet count less than 150,000/mm\textsuperscript{3} and 0.9% of pregnant women having a platelet count less than 100,000/mm\textsuperscript{3}.\textsuperscript{164,168} The most common causes of thrombocytopenia are gestational thrombocytopenia, hypertensive disorders of pregnancy, and idiopathic thrombocytopenia. The decrease in platelet count in the third trimester is caused by increased destruction and hemodilution.\textsuperscript{169} Gestational thrombocytopenia is an exaggerated normal response.

The concentrations of most coagulation factors, including fibrinogen (factor I), proconvertin (factor VII), antithrombin (factor VIII), Christmas factor (factor IX), Stuart-Prowler factor (factor X), and Hageman factor (factor XII), increase during pregnancy. The increase in factor VIII is generally more marked in the third trimester. The concentrations of some factors increase by more than 100% (factors VII, VIII, IX, and fibrinogen).\textsuperscript{169–172} Prothrombin (factor II) and proaccelerin (factor V) concentrations do not change, whereas the concentrations of thromboplastin antecedent (factor XI) and fibrin-stabilizing factor (factor XIII) decrease.\textsuperscript{171–173} An increase in most factor concentrations, shortening of the prothrombin time (PT) and activated partial thromboplastin time (aPTT),\textsuperscript{170} an increase in fibrinopeptide A concentration, and a decrease in antithrombin III concentration suggest activation of the clotting system (PT decreases from a nonpregnant range of 12.7–15.4 seconds to a range of 9.6–12.9 seconds in the third trimester, and aPTT decreases from a range of 26.3–39.4 seconds in nonpregnant women to a range of 24.7–35.0 seconds in the third trimester).\textsuperscript{174} Protein S activity decreases steadily during pregnancy, reaching the lowest values at delivery.\textsuperscript{175}

Thromboelastography (TEG) demonstrates evidence of hypercoagulability in pregnancy. These changes (decrease in R and K values, increase in the $\alpha$ angle and maximum amplitude [MA], and decrease in measures of lysis) are observed as early as 10 to 12 weeks’ gestation and are even greater during labor (Fig. 2.9).\textsuperscript{176–178} Compared with samples taken during labor, TEG has demonstrated increased lysis in the postpartum period, possibly caused by the loss of placental expression of plasminogen activator inhibitor-2.\textsuperscript{179} In vitro, exogenous oxytocin decreases R and K values, while increasing the $\alpha$ angle.\textsuperscript{180} The in vivo effects of exogenous oxytocin are not known. Rotational thromboelastometry (ROTEM) during pregnancy does not demonstrate significant changes from the nonpregnant state compared with term parturients.\textsuperscript{181}

The greater concentration of fibrin degradation products signals increased fibrinolytic activity during gestation.\textsuperscript{163} D-dimer values increase across gestation and remain higher than prepregnancy values in the postpartum period.\textsuperscript{182,183} The marked elevation in the plasminogen concentration also is consistent with enhanced fibrinolysis.\textsuperscript{184}

**Hematology and Coagulation during the Puerperium**

Blood loss during normal vaginal delivery and the early puerperium is approximately 600 mL.\textsuperscript{185} The normal physiologic changes of pregnancy allow the healthy parturient to compensate for this loss. However, blood loss after either vaginal or cesarean delivery is often underestimated, and the discrepancy between actual and estimated blood loss is greater with increasing blood loss (see Chapter 37).\textsuperscript{186}

Blood volume decreases to 125% of the prepregnancy level during the first postpartum week,\textsuperscript{185} followed by a more gradual decline to 110% of the prepregnancy level at 6 to 9 weeks postpartum (see Fig. 2.7). The hemoglobin concentration and hematocrit decrease during the first 3 days postpartum, increase gradually during the next 3 days (because of a reduction in plasma volume), and continue to increase to prepregnancy measurements by 3 weeks postpartum.\textsuperscript{187}

Cesarean delivery results in a blood loss of approximately 1000 mL within the first few hours of delivery.\textsuperscript{185} The hematocrit in the immediate postpartum period is lower after cesarean delivery than after vaginal delivery because of the greater blood loss during cesarean delivery.\textsuperscript{185}

Albumin and total protein concentrations and colloid osmotic pressure decline after delivery and gradually return to prepregnancy levels by 6 weeks postpartum.\textsuperscript{160} The plasma cholinesterase value decreases below the predelivery level by the first postpartum day and remains at that decreased level during the next week.\textsuperscript{162} Globulin concentrations are elevated throughout the first postpartum week.\textsuperscript{158}

Beginning with delivery and during the first postpartum day, there is a rapid decrease in the platelet count and in the
concentrations of fibrinogen, factor VIII, and plasminogen and an increase in antifibrinolytic activity.186 Clotting times remain shortened during the first postpartum day,186 and TEG remains consistent with a hypercoagulable state, although lysis may increase.179,180 During the first 3 to 5 days postpartum, increases are noted in the fibrinogen concentration and platelet count, changes that may account for the greater incidence of thrombotic complications during the puerperium.189 The coagulation profile returns to the non-pregnant state by 2 weeks postpartum.186

THE IMMUNE SYSTEM

The blood leukocyte count increases progressively during pregnancy from the prepregnancy level of approximately 6000/mm³ to between 9000 and 11,000/mm³.167 This change reflects an increase in the number of polymorphonuclear cells, with the appearance of immature granulocytic forms (myelocytes and metamyelocytes) in most pregnant women. The proportion of immature forms decreases during the last 2 months of pregnancy. The lymphocyte, eosinophil, and basophil counts decrease, whereas the monocyte count does not change. The leukocyte count increases to approximately 13,000/mm³ during labor and increases further to an average of 15,000/mm³ on the first postpartum day.185 By the sixth postpartum day, the leukocyte count decreases to an average of 9250/mm³, although the count is still above normal at 6 weeks postpartum.

Despite an increased concentration, polymorphonuclear leukocyte function is impaired during pregnancy, as evidenced by depressed neutrophil chemotaxis and adherence.190 This impairment may account for the greater incidence of infection during pregnancy and improved symptoms in some pregnant women with autoimmune diseases (e.g., rheumatoid arthritis). Levels of immunoglobulins A, G, and M are unchanged during gestation, but humoral antibody titers to certain viruses (e.g., herpes simplex, measles, influenza type A) are decreased.189 During pregnancy, the uterine mucosa is characterized by a large number of maternal immune cells found in close contact with the trophoblast. The fetal expression of paternal antigens requires adaptations in the maternal immune system so that the fetus is not perceived by the mother as “foreign.”192,193 This “immune tolerance” occurs because of a lack of fetal antigen expression, because of separation of the mother from the fetus, or from a functional suppression of the maternal lymphocytes.194 During the first trimester of pregnancy, T lymphocytes express granulysin, a novel cytolytic protein that provides a protective role at the maternal-fetal interface.195 Human T cells may be classified into T-helper cells types 1 and 2 (Th1 and Th2) on the basis of their cytokine production. Successful pregnancy is associated with a predominant Th2 cytokine profile. Th1 cytokines are detrimental to pregnancy. These cells also produce natural antimicrobial agents within the uterus, which are important for prevention of uterine infection during pregnancy.196 Maternal immunoglobulin E (IgE) production increases with pregnancy, and women with a history of pregnancy have higher baseline IgE and experience a slower decline in IgE levels as they age.197

NONPLACENTAL ENDOCRINOLOGY

Thyroid Function

The thyroid gland enlarges by 50% to 70% during pregnancy because of follicular hyperplasia and greater vascularity. The estrogen-induced increase in thyroid-binding globulin results in a 50% increase in total triiodothyronine (T₃) and thyroxine (T₄) concentrations during the first trimester, which are maintained until term.198 The concentrations of free T₃ and T₄ do not change. The concentration of thyroid-stimulating hormone (TSH) decreases during the first trimester but returns to the nonpregnant level shortly thereafter and undergoes no further change during the remainder of pregnancy. The fetal thyroid gland cannot produce thyroid hormone until the end of the first trimester and relies solely on maternal T₄ production during this critical time of development and organogenesis. Approximately 4% to 7% of women of childbearing age are either hypothyroid or at risk for hypothyroidism during pregnancy.199 Only 20% to 30% of affected women demonstrate symptoms of hypothyroidism, likely because symptoms of hypothyroidism mimic features of pregnancy.200 In a large study of 502,036 pregnant women, 15% of tested women had gestational hypothyroidism, with 33% of these women demonstrating symptoms.201 Based on these results, many physicians advocate universal screening, which appears to be cost-effective, given the risk for decreased intelligence in the offspring, miscarriage, and postpartum bleeding if hypothyroidism is left untreated.202

Glucose Metabolism

Mean blood glucose concentration remains within the normal range during pregnancy, although the concentration may be lower in some women during the third trimester compared with nonpregnant individuals.203 This finding is explained by the greater glucose demand of the fetus and the placenta. The relative hypoglycemic state results in fasting hypoinsulinemia. Pregnant women also exhibit exaggerated starvation ketosis. Pregnant women are relatively insulin resistant because of hormones such as placental lactogen secreted by the placenta.204 The blood glucose levels after a carbohydrate load are greater in pregnant women than in nonpregnant women, despite a hyperinsulinemic response. These changes resolve within 24 hours of delivery.

Adrenal Cortical Function

The concentration of corticosteroid-binding globulin (CBG) doubles during gestation as a result of an estrogen-induced enhancement of hepatic synthesis.205 The elevated CBG value results in a 100% increase in the plasma cortisol concentration at the end of the first trimester and a 200% increase at term. The concentration of unbound, metabolically active cortisol at the end of the third trimester is two and one-half times the nonpregnant level. The increase in free cortisol
results from greater production and reduced clearance. An increase in CBG concentration and a decrease in the serum albumin level affect the protein binding of corticosteroids. CBG binding capacity usually saturates at low concentrations of glucocorticoids. Clearance of betamethasone is greater during pregnancy, possibly because the drug is metabolized by placental enzymes.206

THE MUSCULOSKELETAL SYSTEM

Back pain during pregnancy is common. In a cohort study of 200 consecutive women without back pain at the start of pregnancy, 19% complained of backache at 12 weeks’ gestation, and the incidence increased to 47% at 24 weeks’ gestation, peaking at 49% at 36 weeks’ gestation and declining to 9.4% after delivery.207 In another study that showed a relatively high prevalence of low back pain during pregnancy, only 32% of women reported this to their physician and only 25% of providers recommended specific therapy.208

The etiology of the back pain is multifactorial (see Chapter 47). One theory is that the enlarging uterus results in exaggerated lumbar lordosis, placing mechanical strain on the lower back. The hormonal changes of pregnancy may also play a role. Relaxin, a polypeptide hormone of the insulin-like growth factor family, is associated with remodeling of collagen fibers and pelvic connective tissue, permitting the aforementioned lordosis. The primary source of circulating relaxin is the corpus luteum; the placenta is a secondary source. Serum relaxin level in early pregnancy is positively correlated with the presence of back pain.209 During pregnancy, gait also changes and there is an increase in anterior tilt of the pelvis to maintain body stability,210 which may cause further stress on the vertebral column, leading to increased pain.

Women who have low back pain in pregnancy have a very high risk for a new episode during a subsequent pregnancy.211 In the majority of patients, low back pain during pregnancy responds to activity and postural modification. Exercises to increase the strength of the abdominal and back muscles are helpful. Scheduled rest periods with elevation of the feet to flex the hips and decrease the lumbar lordosis help relieve muscle spasm and pain.212

The enhancement of the lumbar lordosis during pregnancy alters the center of gravity over the lower extremities (Fig. 2.10) and may lead to other mechanical problems. Exaggerated lumbar lordosis tends to stretch the lateral femoral cutaneous nerve, possibly resulting in meralgia paresthetica, with paresthesia or sensory loss over the anterolateral thigh. Anterior flexion of the neck and slumping of the shoulders usually accompany the enhanced lordosis, sometimes leading to a brachial plexus neuropathy.

Mobility of the sacroiliac, sacrococcygeal, and pubic joints increases during pregnancy in preparation for passage of the fetus. A widening of the pubic symphysis is evident by 30 weeks’ gestation. These changes are attributable to relaxin and the biomechanical strain of pregnancy on the ligaments.213 Relaxin may also contribute to the greater incidence of carpal tunnel syndrome during pregnancy by changing the nature of the connective tissue so that more fluid is absorbed.214

The human fetus requires approximately 30 g of calcium for skeletal development by the time of term delivery.215 Although intestinal absorption of calcium by the mother increases from as early as 12 weeks’ gestation to meet this increased demand, it is insufficient to meet fetal demand and thus the maternal skeleton undergoes calcium resorption.216 This does not cause long-term changes in skeletal calcium content or strength. Pregnant women with a twin gestation have a much higher calcium requirement. Compared with singleton pregnancies, there is a larger increase in maternal bone resorption in twin gestation.217

THE NERVOUS SYSTEM

Sleep

Sleep disturbances from mechanical and hormonal factors occur commonly during pregnancy. Latency and duration of rapid eye movement (REM) sleep are influenced by changes in progesterone and estrogen concentrations. Pregnant women have more complaints of insomnia and daytime sleepiness. The American Academy of Sleep Medicine defined pregnancy-associated sleep disorder as the occurrence of insomnia or excessive sleepiness that develops in the course of pregnancy.218 In a cohort study of 189 healthy nulliparous women, Facco et al. reported that mean (± SD) sleep duration
Cerebral blood flow increases as pregnancy progresses and is attributable to vasodilation from the hormonal changes of pregnancy. This increase in cerebral blood flow explains the increased risk for complications in patients with intracranial pathology as pregnancy progresses. (Based on data from Nevo O, Soustiel JF, Thaler I. Maternal cerebral blood flow during normal pregnancy: a cross-sectional study. *Am J Obstet Gynecol. 2010;203:475.e1–6.)*

Sleep characteristics change as pregnancy progresses. Early pregnancy is characterized by increased total sleep time and decreased stage 3 and 4 non-REM sleep, whereas late pregnancy is characterized by decreased total sleep time, increased waking after sleep onset, and decreased REM sleep. Sleep may be poor for up to 3 months postpartum. Upper airway changes lead to increased airflow resistance and snoring. Although only 4% of nonpregnant women snore, as many as 23% of pregnant women snore by the third trimester. Snoring is more common in women with preeclampsia.

Pregnancy is associated with transient restless legs syndrome, a disorder in which the patient experiences the need to move her legs. The incidence ranges from 15% in the first trimester to 23% in the third trimester.

**Central Nervous System**

Cerebral blood flow increases in pregnancy. Nevo et al. measured cerebral blood flow in 210 women at different gestational ages and found that it increased from 44.4 mL/min/100 g during the first trimester to 51.8 mL/min/100 g during the third trimester (Fig. 2.11). The increase was secondary to a decrease in cerebrovascular resistance and an increase in internal carotid artery diameter. Other changes in the brain that occur during pregnancy include (1) an increase in permeability of the blood-brain barrier caused by decreased cerebrovascular resistance with an increase in hydrostatic pressure and (2) an increase in capillary density in the posterior cerebral cortex.

Women experience an elevation in the threshold to pain and discomfort near the end of pregnancy and during labor. The mechanism, although unclear, may be related to the effects of progesterone and endorphins. Elevated concentrations of endorphins and enkephalins are found in the plasma and CSF of parturients, and opioid antagonists abolish pregnancy-induced analgesia to visceral stimulation in experimental animals.

**Vertebral Column**

Anatomic and mechanical changes occur to the vertebral column during pregnancy. The epidural space can be regarded as a rigid tube that contains two fluid-filled distensible tubes, the dural sac and the epidural veins. The volume of epidural fat and the epidural venous plexus enlarge during pregnancy, and spinal CSF volume is reduced.

In the lateral position, lumbar epidural pressure is positive in term pregnant women but negative in more than 90% of nonpregnant women. Turning a parturient from the lateral to the supine position increases the epidural pressure. Epidural pressure also increases during labor because of increased diversion of venous blood through the vertebral plexus secondary to either enhanced compression of the inferior vena cava in the supine position or greater intra-abdominal pressure during pain and pushing. The epidural pressure returns to the nonpregnant level by 6 to 12 hours postpartum.

Despite compression of the dural sac by the epidural veins, the CSF pressure in pregnant women is the same as in non-pregnant women. Uterine contractions and pushing during labor result in an increase in CSF pressure that is secondary to acute increases in epidural vein distention.

**Sympathetic Nervous System**

Dependence on the sympathetic nervous system for maintenance of hemodynamic stability increases progressively throughout pregnancy and reaches a peak at term. The dependence on the sympathetic nervous system returns to that of the nonpregnant state by 36 to 48 hours postpartum.

**ANESTHETIC IMPLICATIONS**

**Positioning**

Aortocaval compression, decreased blood pressure and cardiac output, and impairment of uteroplacental blood flow can occur when a pregnant woman is placed in the supine position. This may compromise fetal well-being and neonatal outcome during labor or cesarean delivery. When baseline maternal blood pressure is maintained with intravenous fluid and vasopressors, there is no difference in umbilical artery base excess or pH between supine patients and patients tilted 15 degrees undergoing cesarean delivery. Taken together, these data suggest that the supine position should be avoided after 20 weeks’ gestation, and the uterus should be tilted greater than 15 degrees if maternal blood pressure cannot be maintained at the baseline level (Fig. 2.12).

**Blood Replacement**

At delivery, maternal vascular capacitance is reduced by the volume of the intervillous space (at least 500 mL). Therefore, during vaginal or cesarean delivery, this volume of blood does...
Physiologic adaptations during pregnancy mandate modification of airway management during pregnancy. Airway edema may be exacerbated in patients with upper respiratory tract infection or preeclampsia and in those who have been pushing for a long time during the second stage of labor.

Pregnant women become hypoxemic more rapidly than nonpregnant women during episodes of apnea because FRC is reduced, oxygen consumption is increased, and FRC is less than closing capacity in up to 50% of supine individuals. During apnea accompanying rapid-sequence induction of general anesthesia, PaO₂ decreases twice as rapidly (139 versus 58 mm Hg/min [18.5 versus 7.7 kPa/min]) in pregnant versus nonpregnant women. Denitrogenation is achieved faster in pregnant versus nonpregnant women because of elevated minute ventilation and decreased FRC. However, after complete denitrogenation via inhalation of 100% oxygen, parturients tolerate only 2 to 3 minutes of apnea, versus 9 minutes in nonpregnant patients, before oxygen saturation decreases to less than 90%.

Ventilation during general anesthesia should be adjusted to maintain PacO₂ at approximately 30 mm Hg (4 kPa). This can be achieved with minute ventilation of 121 mL/kg/min; in comparison, 77 mL/kg/min is required to maintain a comparable PacO₂ in nonpregnant women. Decreased plasma bicarbonate concentration reduces buffering capacity in pregnancy. Allowing the PacO₂ to increase to the normal level for nonpregnant women results in respiratory acidosis.

The propofol requirement decreases 10% during the first trimester; this decrease does not correlate with progesterone levels. The elimination half-life of propofol is unaffected by pregnancy, though clearance may be higher.

The rate of rise of alveolar to inspired anesthetic concentration ratio (Fₐ/Fᵢ) of volatile anesthetics, and thus the speed of induction, is increased during pregnancy because of greater minute ventilation and reduced FRC, despite higher cardiac output.

The minimum alveolar concentration (MAC) for volatile anesthetics is up to 40% lower in pregnancy. Although MAC is a spinal nociceptive reflex that involves both sensory and motor components, practitioners have interpreted this decrease in MAC as indicating that pregnant patients have a decreased requirement for inhaled anesthetics. However, this interpretation has been questioned. Ueyama et al. compared bispectral index values in 15 patients undergoing cesarean delivery with sevoflurane general anesthesia with the values in 15 patients undergoing elective gynecologic surgery and found no difference between groups. This finding suggests that the hypnotic effect of sevoflurane was not enhanced by pregnancy. The investigators concluded that although pregnancy may decrease MAC, it does not decrease volatile anesthetic requirements, and suggested that parturients should be given the same dose of volatile anesthetics as nonpregnant patients. Further work is required to confirm these findings.

**General Anesthesia**

### Airway Management, Oxygenation, and Ventilation

Changes in the maternal airway and respiratory physiology mandate modification of airway management during pregnancy (Box 2.3) (see Chapter 29). The proportion of pregnant women with a Mallampati IV classification increases by 34% between 12 and 38 weeks’ gestation. Vascular engorgement of the airway results in edema of the oral and nasal pharynx, larynx, and trachea, which may lead to difficult tracheal intubation and difficult mask ventilation. Airway edema may be exacerbated in patients with upper respiratory tract infection or preeclampsia and in those who have been pushing for a long time during the second stage of labor.

Fig. 2.12 Compression of the aorta and inferior vena cava in the supine (left) and lateral tilt (right) positions. (Redrawn from Camann WR, Ostheimer GW. Physiologic adaptations during pregnancy. Int Anesthesiol Clin. 1990;28:2–10.)

**BOX 2.3 Considerations for General Anesthesia during Pregnancy**

**Drugs**
- Propofol
- Induction dose decreased
- Elimination half-life unaltered
- Thiopental
- Induction dose decreased
- Elimination half-life prolonged
- Volatile anesthetic agents
  - Minimum alveolar concentration (MAC) decreased, but unclear whether hypnotic dose requirement differs from that in nonpregnant women
  - Speed of induction increased
- Succinylcholine
- Duration of blockade unaltered
- Rocuronium
- Increased sensitivity
- Chronotropic agents and vaspressors
- Decreased sensitivity

**Tracheal Intubation**
- Increased rate of decline of PaO₂ during apnea
- Smaller endotracheal tube required (6.5 or 7.0 mm)
- Increased risk for difficult or failed mask ventilation
- Increased risk for failed intubation with traditional laryngoscopy
- Increased risk for bleeding with nasal instrumentation

not need to be replaced and should not be considered in the estimation of blood loss for replacing red blood cells. Hemocontentration occurs as maternal blood volume declines from 94 mL/kg at term to 76 mL/kg during the postpartum period; this should be considered in the decision whether a parturient should receive crystalloid, colloid, or blood for volume replacement.

**Intravenous and Inhalation Anesthetics**

The propofol requirement decreases 10% during the first trimester; this decrease does not correlate with progesterone levels. The elimination half-life of propofol is unaffected by pregnancy, though clearance may be higher. Decreased plasma bicarbonate concentration reduces buffering capacity in pregnancy. Allowing the PacO₂ to increase to the normal level for nonpregnant women results in respiratory acidosis.
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Physiologic Changes of Pregnancy

alter CSF pressure. However, flow rate may increase during a uterine contraction because of increased CSF pressure.

Local Anesthetic Dose Requirement

Pregnant patients show decreased local anesthetic dose requirement in the first trimester. This change occurs well before significant mechanical changes have occurred in the vertebral canal, suggesting that there are pregnancy-induced alterations in nerve tissue sensitivity, either directly or indirectly from changes in hormone concentrations.

Pregnant women exhibit a more rapid onset and a longer duration of spinal anesthesia than nonpregnant women. Laboring women may differ from nonlaboring women. Yoo et al. observed lower bispectral index values with a standard sevoflurane–nitrous oxide anesthetic in women with prior labor compared with nonlaboring parturients. Similarly, Erden et al. observed lower sevoflurane requirements to reach a bispectral index target value of 40 to 55 in laboring compared with nonlaboring parturients undergoing cesarean delivery.

Muscle Relaxants

Pseudocholinesterase activity is decreased by 24% before delivery and by 33% on the third postpartum day. It returns to normal 2 to 6 weeks postpartum. The reduced activity does not usually result in clinically relevant prolongation of paralysis after a single dose of succinylcholine. Twitch height recovery after administration of succinylcholine is similar between pregnant and nonpregnant women, and recovery may even be faster because the larger volume of distribution results in a lower initial drug concentration and a shorter time before the threshold for recovery is attained. Pregnant women may be less sensitive than nonpregnant women to comparable plasma concentrations of succinylcholine, a feature that also may contribute to more rapid recovery during pregnancy.

Pregnant and postpartum women exhibit enhanced sensitivity to the aminosteroid muscle relaxants vecuronium and rocuronium. The greater sensitivity to vecuronium is not explained by altered pharmacokinetics because the drug exhibits increased clearance and a shortened elimination half-life in pregnant women. The mean onset time and clinical duration of cisatracurium are significantly shorter in women immediately after delivery than in nonpregnant women.

Chronotropic Agents and Vasopressors

Pregnancy reduces the chronotropic response to isoproterenol and epinephrine because of down-regulation of beta-adrenergic receptors. These agents are less-sensitive markers of intravascular injection during administration of an epidural test dose in pregnant patients than in nonpregnant patients. Because of down-regulation of adrenergic receptors, treatment of hypotension requires higher doses of vasopressors such as phenylephrine in pregnant women than in nonpregnant women.

Neuraxial Analgesia and Anesthesia

Technical Considerations and Positioning

Increased lumbar lordosis during pregnancy may reduce the vertebral interspinous gap and change the lumbar angulation of spinous processes, thus creating technical difficulty in administering neuraxial anesthesia (Box 2.4 and Fig. 2.13) (see Chapter 12). Widening of the pelvis results in a head-down tilt when a pregnant woman is in the lateral position. This may increase the rostral spread of hyperbaric local anesthetics when injected intrathecally with patients in the lateral position. The flow of CSF from a spinal needle is unchanged throughout gestation because pregnancy does not alter CSF pressure. However, flow rate may increase during a uterine contraction because of increased CSF pressure.

Local Anesthetic Dose Requirement

Pregnant patients show decreased local anesthetic dose requirement in the first trimester. This change occurs well before significant mechanical changes have occurred in the vertebral canal, suggesting that there are pregnancy-induced alterations in nerve tissue sensitivity, either directly or indirectly from changes in hormone concentrations.

Pregnant women exhibit a more rapid onset and a longer duration of spinal anesthesia than nonpregnant women who...
receive the same dose of local anesthetic. These results are consistent with enhanced neural sensitivity to local anesthetics; pregnancy-associated elevation in CSF pH may contribute to these effects. The dose of hyperbaric local anesthetic required in term pregnant women is 25% lower than that in nonpregnant women. This is attributed to the following factors: (1) reduction of spinal CSF volume, which accompanies distention of the vertebral venous plexus; (2) enhanced neural sensitivity to local anesthetics; (3) increased rostral spread when injections are made with the patient in the lateral position; (4) inward displacement of intervertebral foraminal soft tissue, resulting from increased abdominal pressure; and (5) a higher level of the apex of the thoracic kyphosis (the lowest point of the thoracic spinal canal in the supine position) during late pregnancy (see Fig. 12.4). Spinal dose requirements change rapidly in the postpartum period, with segmental dose requirements returning to those of nonpregnant women within 24 to 48 hours as spinal CSF volume expands with the relief of vena caval compression. In contrast to spinal anesthesia, pregnancy appears to have less effect on the spread of epidural anesthesia.

Pregnancy does not enhance the susceptibility of ewes to the neurotoxicity of lidocaine or to the cardiac toxicity of bupivacaine (see Chapter 13). The incidence of lethal ventricular arrhythmias is no greater in pregnant than in nonpregnant ewes treated with bupivacaine, ropivacaine, or levobupivacaine.

**Hypotension during Neuraxial Analgesia and Anesthesia**

Pregnancy increases dependence on the sympathetic nervous system for the maintenance of venous return and systemic vascular resistance. This, together with the effects of aortic compression, means that pregnant patients are particularly prone to hypotension and hemodynamic instability from the sympathetic block induced by neuraxial anesthesia. Management of hypotension is discussed in Chapter 26.

**Effects of Neuraxial Anesthesia on Respiratory Function**

FRC diminishes during neuraxial anesthesia, resulting in an increase in respiratory dead space and ventilation-perfusion mismatch. Abdominal muscles are important for forced expiration and coughing, and paralysis of these muscles during neuraxial anesthesia decreases peak expiratory flow rate, maximum expiratory pressure, and the ability to increase intra-abdominal and intrathoracic pressures during coughing.

### **KEY POINTS**

- Pregnancy results in various anatomic and physiologic changes that allow the mother to adapt to the growing fetus and allow the fetus to develop.
- Cardiac output increases during pregnancy as a result of an increase in stroke volume and heart rate. A pregnant woman with cardiovascular disease may not be able to meet this greater demand.
- Pregnant women have greater sympathetic tone than nonpregnant women.
- Beginning at mid-pregnancy, assumption of the supine position may result in compression of the inferior vena cava and aorta by the gravid uterus, which may result in decreases in both cardiac output and uteroplacental perfusion. Severe hypotension and bradycardia in the supine position is called the supine hypotension syndrome.
- Pregnant women should not lie supine after 20 weeks’ gestation without aggressive maintenance of baseline blood pressure. The uterus should be displaced to the left by placement of a wedge underneath the right hip or by tilting the operating table, or the pregnant women should assume the full lateral position.

- The greater blood volume of pregnancy allows the parturient to tolerate the blood loss of delivery, within limits, with minimal hemodynamic perturbation. Maternal vascular capacitance is reduced at the time of delivery.
- Oxygen demand and delivery are greater during pregnancy and further increase during labor and delivery.
- Minute ventilation increases whereas functional residual capacity decreases during pregnancy. It is not uncommon for the pregnant women to experience dyspnea.
- Pregnancy is a state of partially compensated respiratory alkalosis.
- Gastric volume, emptying, and pH are unaltered during pregnancy, but lower esophageal sphincter tone may be reduced with increased risk for gastroesophageal reflux.
- Pregnancy and the immediate postpartum period are considered hypercoaguable states.
- Mechanical changes in the vertebral column influence neuraxial analgesia and anesthesia.
- Minimum alveolar concentration (MAC) values for the volatile anesthetics are decreased during pregnancy.
However, it is unclear whether the hypnotic dose requirement is altered during pregnancy.

- Pregnant women have a rapid decrease in PaO₂ during periods of apnea.
- Pregnant women are at increased risk for failed tracheal intubation.
- Pregnant women are less responsive to vasopressors than nonpregnant women.

**REFERENCES**


CHAPTER 2  Physiologic Changes of Pregnancy


The uteroplacental circulation develops to provide the blood flow and delivery of oxygen and nutrients essential for growth and development of the fetus and placenta. Abnormalities in development are associated with complications such as pre-eclampsia, fetal growth restriction, and preterm labor, and may even predispose to the development of cardiovascular disease during subsequent adulthood. Acute reduction in uteroplacental blood flow may rapidly threaten fetal viability. The uteroplacental circulation may be affected by circadian changes, disease, parturition, and anesthetic techniques and drugs. An understanding of the regulation of uteroplacental circulation is an important foundation for the safe provision of obstetric anesthesia and in the management of many pregnancy-related diseases. Because of ethical considerations, much of the available knowledge comes from studies in animals, particularly sheep but also nonhuman primates and other species. It is important to consider possible interspecies differences and to critically examine the methodology and context of animal research when extrapolating findings into recommendations for clinical care.

### ANATOMY AND STRUCTURE

The blood supply to the uterus is derived mainly from the uterine arteries (Fig. 3.1) with a smaller, variable contribution from the ovarian arteries. Although the pelvic vasculature shows anatomic variation, the uterine artery arises bilaterally from the anterior division of the internal iliac (hypogastric) artery, whereas the ovarian artery arises from the anterolateral abdominal aorta below the renal arteries. The uterine artery passes medially to the side of the uterus, where it supplies branches to the cervix and vagina and ascends between the two layers of the broad ligament, yielding arcuate arteries that supply the body of the uterus to the junction with the fallopian tubes. During pregnancy, flow may differ between the right and left uterine arteries; Konje et al. estimated that vessel diameter was approximately 11% greater and blood flow was approximately 18% greater in the uterine artery on the same side as the placenta compared with the contralateral artery. Anastomoses are formed with the contralateral uterine artery, the vaginal arteries, and the ovarian arteries.
CHAPTER 3  Uteroplacental Blood Flow

The arcuate arteries give rise to small branches that supply the myometrium and large radial arteries that branch deeply and enter the endometrium to form the convoluted spiral arteries. During gestation, trophoblastic invasion of the spiral arteries results in loss of smooth muscle and loss of contractile ability, leading to vasodilation with decreased resistance and increased blood flow. Abnormal or inadequate trophoblastic invasion is integral to the pathophysiology of preeclampsia (see Chapter 35).

From the spiral arteries, oxygenated maternal blood enters the intervillous space in fountainlike jets. Blood traveling toward the chorionic plate bathes the villi, permitting the exchange of oxygen, nutrients, and wastes between maternal and fetal blood. Maternal blood then returns to the basal plate and drains into multiple collecting veins. Venous drainage of the uterus occurs via the uterine veins to the internal iliac veins and also via the ovarian veins (utero-ovarian plexus) to the inferior vena cava on the right and the renal vein on the left.5

The uterine artery and other branches of the anterior division of the internal iliac artery, and the ovarian artery, may be targeted during angiographic embolization procedures for treatment of obstetric and gynecologic hemorrhage6 and for the treatment of uterine fibroids.6

CHANGES AND FUNCTION DURING PREGNANCY

Pregnancy-Induced Changes

Uterine blood flow increases dramatically during pregnancy, rising from 50 to 100 mL/min before pregnancy to 700 to 900 mL/min at term, depending on the method of measurement (Fig. 3.2). Studies in sheep have shown that increases in uterine blood flow can be divided into three phases.7 An initial phase, most likely controlled by the ovarian hormones estrogen and progesterone, occurs before and during implantation and early placentation. A second phase results from the growth and remodeling of the uteroplacental vasculature to support further placental development. The third phase results from progressive uterine artery vasodilation to meet the markedly increased nutrient requirements of the rapidly growing fetus. When expressed in terms of uterine weight, however, uterine flow per gram of tissue is particularly high in early gestation, and this ratio decreases.
Functional Classification

Placental vascular function varies among species. The human multivillous model is commonly believed to function as a “venous equilibrator,” in which oxygen tension in the umbilical vein approximates that in the uterine veins. In contrast, the placenta in some species (e.g., rodents) functions as a countercurrent exchanger. The more efficient function of the latter is reflected by the higher fetoplacental weight ratio in rodents (20:1) than in humans (6:1).

Autoregulation

Studies of pressure-flow relationships suggest that the nonpregnant uterine circulation exhibits autoregulation, alternately vasoconstricting or vasodilating in response to a number of different stimuli. In contrast, in pregnancy the placental and nonplacental circulations have differing properties. Animal studies have demonstrated that the uteroplacental circulation is a widely dilated, low-resistance system with perfusion that is largely pressure-dependent. However, a study in pregnant rabbits found that uteroplacental blood flow was relatively constant over a wide range of perfusion pressures. During hemorrhage in pregnant rats, uterine vascular resistance increased as systemic blood pressure and uterine blood flow decreased, thereby demonstrating an absence of autoregulation. Moreover, although the uteroplacental circulation is often considered to be maximally vasodilated with little or no ability for autoregulation, further vasodilation has been observed in response to systemically administered estrogen, prostacyclin, bradykinin, and acetylcholine. These discrepancies may be explained by changes in the nonplacental uterine vasculature, which accounts for a small fraction of total uteroplacental blood flow but appears to have similar properties.
autoregulatory responses during pregnant and nonpregnant states; this feature contrasts with the limited autoregulatory ability of the placental circulation.22 Laird et al.17 found that reducing arterial pressure by 22% with an inflatable aortic occluder in pregnant rabbits produced a reduction in total uteroplacental and placental blood flow but no significant change in myoendometrial blood flow. Clinically, limited autoregulation means that placental blood flow may diminish with reductions in maternal blood pressure (e.g., during hemorrhage or neuraxial anesthesia).

**Margin of Safety**

Studies in animals have demonstrated that, in normal physiologic conditions, uterine blood flow exceeds the minimum required to satisfy fetal oxygen demand.23 Although this feature confers a margin of safety that protects the fetus from fluctuations in uterine blood flow,24 decreases in fetal Po₂ and progressive metabolic acidosis can occur with reductions in uteroplacental blood flow, depending on the magnitude and duration.25 However, the relationship between uterine blood flow and oxygen transfer appears nonlinear and suggests that uteroplacental blood flow can decrease by as much as 50% for limited periods before fetal oxygen uptake decreases and metabolic acidosis occurs.23

Studies in sheep have shown that although uterine blood flow varies over a wide range, fetal oxygen uptake remains relatively constant, suggesting that the efficiency of oxygen extraction is greater when perfusion decreases.26 Using an inflatable balloon occluder around the terminal aorta to reduce uterine blood flow in sheep, Wilkening and Meschia25 found that at high levels of oxygen delivery, fetal oxygen uptake was not significantly affected by variations in uterine blood flow; moreover, fetal oxygen uptake became flow-dependent only when uterine oxygen delivery was reduced to less than half the baseline value. Boyle et al.,27 investigating the effects of acute uterine arterial embolization with microspheres in sheep, found a linear decrease in fetal arterial oxygen tension as uterine blood flow decreased. However, uterine oxygen consumption did not decrease and fetal hydrogen ion concentration did not increase until uterine blood flow had decreased to approximately 50% of the baseline value. As uterine blood flow diminished, a reduction in uterine venous oxygen content and a greater arteriovenous oxygen content difference were observed, indicating an increase in oxygen extraction. Gu et al.28 reported comparable findings with the compression of the common uterine artery by an inflatable occluder in sheep.

Although the preceding experiments were conducted in sheep, the same principles may apply to humans. The human placenta, like the sheep placenta, is a relatively inefficient oxygen exchanger. Thus, in humans and sheep, the transfer rate of oxygen is affected less by decreases in placental perfusion than it is in animals with more efficient placentas, such as the rabbit and guinea pig. This difference may afford some protection in humans, because alterations in placental perfusion in animals with more efficient placentas frequently result in spontaneous abortion.29 Animal data would also suggest the presence of a significant physiologic buffer that protects the fetus during transient fluctuations in uteroplacental perfusion (e.g., changes in endogenous vasoconstrictor levels, uterine contractions, and parturition).30 This may partially explain why clinical studies have failed to demonstrate fetal acidosis when alpha-adrenergic agonists are used to maintain maternal blood pressure during neuraxial anesthesia,31 despite experimental data showing that these agents reduce uteroplacental perfusion in laboratory animals.32 These observations are based on an assumption of normal physiology; the presence of pathology likely diminishes any margin of safety.

**Changes during Parturition**

With the onset of the uterine contractions of labor, uteroplacental perfusion undergoes cyclical changes. During uterine contractions, a decrease in perfusion occurs that is inversely related to the strength of the contraction and the increase in intrauterine pressure.28 Conversely, during uterine relaxation, there is a period of hyperemia when perfusion is increased. Placental perfusion is believed to be more sensitive to these contraction-induced changes than myometrial or endometrial blood flow.33 Within the first few hours of parturition, uterine blood flow in sheep decreases on average by 50% or more, although there is notable interindividual variation.34

**Clinical Determinants of Uterine Blood Flow**

In the acute setting, uterine blood flow is related to perfusion pressure (the difference between uterine arterial pressure and uterine venous pressure) and vascular resistance, as represented in the following equation:

\[
\text{Uterine blood flow} = \frac{\text{Uterine perfusion pressure}}{\text{Uterine vascular resistance}}
\]

There are several ways that uterine blood flow can decrease (Box 3.1). First, uterine blood flow may decline with reductions in perfusion pressure because of decreased uterine arterial pressure (e.g., during systemic hypotension from hemorrhage, aortocaval compression, or sympathetic blockade during neuraxial anesthesia). Second, uterine blood flow may decline with reductions in perfusion pressure caused by increased uterine venous pressure (e.g., from vena caval compression, increased intrauterine pressure during uterine contractions, effects of drugs such as oxytocin and cocaine, and bearing down during the second stage of labor). Third, uterine blood flow may decline because of increased uterine vascular resistance (e.g., from endogenous vasoconstrictors released in response to stress, exogenous vasoconstrictors, and compression of endometrial spiral arterioles with uterine contractions).33

**MECHANISMS OF VASCULAR CHANGES AND REGULATION**

**Vascular Changes during Pregnancy**

Because mean arterial pressure decreases slightly during pregnancy, the increase in uteroplacental blood flow is
dependent on a substantial decrease in uterine vascular resistance (Fig. 3.4), together with increased cardiac output and intravascular volume. The main factors contributing to the decrease in vascular resistance include vascular remodeling, changes in vascular reactivity, and the development of the widely dilated placental circulation.

Vascular remodeling of arteries in the uterus during pregnancy is believed to include increases in both vessel diameter and vessel length. In humans, both vessel lengthening and straightening of coiled vessels may occur; the effects of changes in vessel diameter dominate, resulting in an overall decrease in resistance. Palmer et al., using serial Doppler studies during pregnancy, observed that uterine artery diameter is doubled by 21 weeks' gestation, whereas there is no change in the diameter of the common iliac or external iliac arteries. These investigators also showed that uterine artery mean flow velocity increased progressively during pregnancy to values eight times greater than those of nonpregnancy. In parallel with arterial changes, there is also structural remodeling of uterine veins in pregnancy, including increases in diameter and distensibility and decreases in elastin content. Although blood viscosity decreases during pregnancy and also contributes to reduced uterine vascular resistance, this is considered a relatively minor effect compared with vascular changes.

Changes in vascular reactivity during pregnancy include a vasodilatory response that is mediated at endothelial and vascular smooth muscle levels. The growth of the placenta creates a low-resistance vascular pathway by eliminating the intramyometrial microcirculation and creating an intervillous space. This has functional characteristics of an arteriovenous shunt.

The mechanisms underlying the vascular changes during pregnancy are incompletely understood. Contributing factors include steroid hormones, decreased response to vasoconstrictors, endothelium-derived vasodilators, increased shear stress, and venoarterial exchange.

## Steroid Hormones

**Estrogen** has a fundamental role in the short- and long-term uterine vascular changes during pregnancy. Plasma concentration of estrogen, initially derived from the ovaries and later predominantly from the placenta, rises concomitantly with the increase in uterine blood flow during pregnancy. Exogenously administered estrogen causes uterine vasodilation and a marked rise in uterine blood flow, independent of systemic effects. Angiogenic and vasodilatory effects of estrogen are mediated via estrogen receptors ER-α and ER-β, which are structurally and functionally distinct. Most of these receptors are located in the nucleus and mediate genomic effects by regulating transcription of genes that are particularly responsible for the longer-term uterine angiogenic responses. There are also membrane receptors that mediate nongenomic effects by up-regulating endothelial production of nitric oxide through the activation of endothelial nitric oxide synthase (eNOS) and the augmentation of eNOS protein expression.

**Progesterone** modulates the effect of estrogen on uterine blood flow. In a nonpregnant sheep model, exogenous progesterone administered alone had no uterine vasodilatory effect but had an inhibitory effect when combined with estrogen. Progesterone down-regulates expression of estrogen receptors. An increase in the estrogen/progesterone ratio parallels the increase in uterine blood flow in late pregnancy in many species.

Plasma cortisol levels approximately double during pregnancy. Cortisol has both systemic and local effects on uterine blood flow. Systemically, cortisol contributes to regulation of uterine blood flow by increasing plasma volume. Although cortisol is believed to decrease eNOS protein expression and decrease nitric oxide release, it potentiates the response to vasoconstrictor agents including angiotensin II, vasopressin, and norepinephrine. Attenuation of these effects occurs during pregnancy.
Decreased Response to Vasoconstrictors

In pregnancy, there is a generalized reduction in response to endogenous and exogenous vasoconstrictors, including angiotensin II, endothelin, thromboxane, epinephrine, norepinephrine, phenylephrine, serotonin, and arginine vasopressin.43–45 The relative refractoriness of the systemic and uterine circulations varies for different agents, which has important implications for the regulation and maintenance of uteroplacental blood flow.

During pregnancy, concentrations of angiotensin II in maternal blood are increased twofold to threefold46; however, the vasopressor response to angiotensin II is attenuated.47 This refractoriness is diminished in patients in whom pre-eclampsia develops.48 The uterine circulation is less responsive to angiotensin II than the systemic circulation. Thus, infusion of physiologic doses of angiotensin II has been shown to have minimal effect on uteroplacental blood flow while increasing systemic blood pressure.48 The difference in sensitivity of the uterine and systemic circulations to angiotensin II is considered an important physiologic adaptation during pregnancy that contributes to the redistribution of cardiac output, the increase in uterine blood flow, and possibly the maintenance of uterine blood flow during normal fluctuations in blood pressure.49

Sensitivity to vasoconstrictors such as epinephrine, norepinephrine, and phenylephrine is attenuated during pregnancy.20 This may explain why relatively large doses of vasoconstrictors are often required to maintain blood pressure during spinal anesthesia for cesarean delivery.31 In contrast to the responses to angiotensin II, the uterine circulation is more responsive to these agents than the systemic circulation.50 Thus, during hemorrhage or other major stresses that result in large catecholamine release, it is unlikely that uteroplacental perfusion will be preferentially preserved above essential maternal perfusion.51

The mechanism underlying the difference in vascular sensitivity between the uterine and systemic circulations is unclear, but distribution of receptor subtypes is believed to be important.52 For example, there are two distinct subtypes of angiotensin II receptors: AT1R and AT2R. In most tissues, including systemic vascular smooth muscle, AT1R receptors are predominant and mediate vasoconstriction. However, AT2R receptors, which do not mediate smooth muscle contraction, account for 75% to 90% of angiotensin II binding in uterine artery and myometrium.53,54

Vasodilators

The greater synthesis and higher circulating concentrations of endothelial-derived vasodilators during pregnancy are believed to modulate systemic and uterine vascular responses to angiotensin II and other vasoconstrictors.55 Uterine vascular production of prostacyclin is greater than systemic vascular production, which probably contributes to maintaining uteroplacental blood flow in opposition to the effects of circulating vasoconstrictors.56 An enhanced response to angiotensin II during pregnancy has been demonstrated with the systemic and local infusion of indomethacin (which blocks prostacyclin production).57 However, inhibition of prostaglandin synthesis by an infusion of indomethacin induces only a transient decrease in uteroplacental blood flow, indicating that uteroplacental blood flow is not solely dependent on the continued production of prostacyclin.55

Nitric oxide is synthesized from arginine in vascular endothelial cells and stimulates soluble guanylate cyclase in vascular smooth muscle, resulting in vascular relaxation through increases in cyclic guanosine monophosphate. Synthesis of nitric oxide is an important mechanism underlying changes in systemic and uterine vascular resistance, attenuated responses to vasoconstrictors, and vascular effects of estrogen during pregnancy.58 During pregnancy, uterine arteries have increased eNOS activity, higher levels of eNOS messenger ribonucleic acid and eNOS protein, and increased biosynthesis of nitric oxide and cyclic guanosine monophosphate.59,60 Removal of the vascular endothelium diminishes or eliminates the refactoriness of the uterine artery to vasoconstrictors,61 and inhibition of nitric oxide synthesis by N-nitro-L-arginine methyl ester (L-NAME) decreases uterine blood flow and also reverses refractoriness to vasoconstrictors.60 Long-term inhibition of nitric oxide synthase causes hypertension and fetal growth restriction in rats.61

Other Vasoactive Substances

Atrial and brain natriuretic peptides attenuate the response to angiotensin II, and intravenous infusion of atrial natriuretic peptide reduces blood pressure while increasing uterine blood flow in preeclamptic women.62 Protein kinase C activity is decreased in uterine, but not systemic, arteries of pregnant sheep and may cause vasodilation and an increase in uterine blood flow; this may have a regulatory effect on local ovarian and placental estrogen production.62 Studies in rats have shown a decrease in endogenous endothelin-dependent vasoconstrictor tone in uteroplacental vessels, which may contribute to the increase in placental blood flow in late gestation.63 Uterine vascular resistance in early pregnancy may be increased by relaxin, which may have a role in modulating the effects of estrogen and progesterone.64 Placental protein 13 has been shown to be a potent vasodilator of both uterine and systemic blood vessels in vitro, and it has been suggested that this peptide might contribute to the vasodilation that occurs during human pregnancy.65 The use of vasopressin to prevent spinal anesthesia–induced hypotension has been reported in the care of patients with pulmonary hypertension, but its use as a vasodilator in pregnancy has not been well studied.66

Shear Stress

Shear stress, the frictional forces on the vessel wall from blood flow, is believed to be an important stimulus for uteroplacental vasodilation and remodeling.67 The reduction in downstream resistance resulting from the formation of the placenta would be expected to increase the upstream flow velocity and thus shear stress.68 Nitric oxide is considered an important mediator of this effect because increases in eNOS expression and
nitric oxide production are witnessed with shear stress and because stripping the endothelium or pretreatment with L-NAME reduces or abolishes flow-induced vasodilation. Studies in vitro have shown that shear stress also increases endothelial production of prostacyclin.

Venoarterial Signaling
It has been postulated that growth factors or signal substances secreted by the placenta and/or myometrium could pass from uterine veins to adjacent uterine arteries; this may provide a system whereby the uterus and placenta regulate their own perfusion. Possible candidates for signal substances include vascular endothelial growth factor and placental growth factor. The importance of this mechanism in humans is uncertain.

METHODS OF MEASUREMENT OF UTEROPLACENTAL BLOOD FLOW
Many techniques have been used to measure uteroplacental blood flow in animals and humans. The approaches used in different studies have varied according to the nature of the experimental question, the existing state of technology, and ethical considerations and limitations. All methods have an inherent potential for error.

Many past studies of uterine artery flow have measured flow in only one uterine artery, which may not be an accurate representation of total flow, depending on the location of the placenta (see earlier discussion). The parameter of greatest clinical interest is placental perfusion, but this is not always differentiated from total uterine blood flow, and the two circulations may vary independently. However, in most circumstances, the measurement of intervillous blood flow provides a close approximation of functional placental blood flow. Ovarian arterial blood flow is generally not measured, although studies in primates suggest that it may contribute as much as one-sixth of placental perfusion.

Early studies of uteroplacental blood flow involved a number of substances that could affect maternal hemodynamics (e.g., nitrous oxide) or myometrial activity (e.g., 4-aminoantipyrine) and relied on the Fick principle. This principle, which calculates blood flow by the measurement of a marker substance entering and leaving an organ, is subject to error in the uterus, where a number of veins are responsible for collecting venous effluent. In animals, placental perfusion can also be measured by the injection of radioactive microspheres. This method allows for the separate calculation of placental and myometrial blood flows but only provides information from a single point in time. Total uterine arterial blood flow can also be measured (or estimated) with the use of surgically implanted electromagnetic or Doppler flow probes.

In humans, placental perfusion can be measured by the injection of trace amounts of radioactive substances, typically $^{133}$xenon. During the washout phase, the rapid decrease in measured radioactivity over the placenta is calculated as a biexponential or triexponential process. The most rapid decay constant is ascribed to intervillous perfusion. Alternatively, radioactively tagged proteins (e.g., albumin) can be injected and measured by scintigraphy over the placenta. Although the accuracy of these methods for determining absolute flow is limited, their ability to measure relative change over time is adequate in most cases.

Clinically, the most common method of assessing flow in the uterine arteries is Doppler ultrasonography. The uterine artery can be identified transabdominally or transvaginally. Color flow aids vessel identification. Blood flow can be quantified by measuring the mean flow velocity and vessel cross-sectional area.

Flow velocity is calculated by applying the principle of Doppler shift. A pulsed ultrasound signal from a stationery transducer is directed toward the vessel with an angle of insonation ($\theta$) less than 60 degrees. Reflections scattered from the red blood cells are received. Because the red blood cells are moving, the frequency of the received signal differs from the transmitted frequency ($f_0$) by an amount known as the Doppler shift ($\Delta f$). This shift is proportional to the red blood cell flow velocity ($V_{RBC}$) according to the following equation:

$$\Delta f = \frac{2 \times f_0 \times V_{REL}}{c} \tag{2}$$

where $c$ is the speed of sound propagation in tissue and $V_{REL}$ is the vector component of the velocity of flow relative to the direction of the transducer. The latter takes into account the difference between the direction of the ultrasound signal from the direction of flow according to $\theta$ ($\Delta f$). This is related to the relative velocity of flow in the direction of the probe ($V_{REL}$) according to the following equation:

$$V_{RBC} = \frac{V_{REL}}{\cos \theta} \tag{3}$$

Combining Eqs. 2 and 3 gives the following equation:

$$V_{RBC} = \frac{\Delta f}{f_0} \times \frac{c}{2 \times \cos \theta} \tag{4}$$

![Fig. 3.5 Principles of use of Doppler ultrasonography to estimate blood flow. Blood flow is calculated as the product of blood vessel cross-sectional area and mean flow velocity in the vessel ($V_{RBC}$). The latter is derived from the measured flow velocity relative to the direction of the probe ($V_{REL}$) and requires precise determination of the angle of insonation ($\theta$).](image-url)
Thus, the flow velocity is estimated from the ratio of the Doppler shift frequency to the transmitted frequency, multiplied by the speed of sound propagation, and divided by two times the cosine of the insonation angle.

An estimation of the volume of blood flow ($Q$) can be made by multiplying mean velocity by the vessel cross-sectional area ($A$), which is estimated with two-dimensional (B-mode) ultrasonography:

$$Q = V_{RBC} \times A$$ (5)

However, measurement of absolute flow using this technique is prone to difficulty and error, both from inaccurate measurement of vessel cross-sectional area (e.g., arteries pulsate during the cardiac cycle) and from inaccurate measurement of flow (e.g., from inaccuracies in measurement of $\theta$). Therefore, for diagnostic purposes, a number of indices related to vascular impedance are derived from the flow velocity waveform that are independent of $\theta$. These rely on the fact that the uterine vascular bed normally has low resistance with flow continuing during diastole. If distal resistance is increased, diastolic velocity decreases relative to systolic velocity resulting in a waveform showing greater pulsatility. Commonly derived indices (Fig. 3.6) are:

$$\text{Systolic–diastolic (S/D) ratio} = \frac{\text{Systolic (maximal) velocity}}{\text{Diastolic (minimal) velocity}}$$ (6)

$$\text{Pulsatility index (PI)} = \frac{(\text{Systolic [maximum] velocity})}{\text{Mean velocity}}$$ (7)

$$\text{Resistance index (RI)} = \frac{(\text{Systolic [maximum] velocity})}{\text{Diastolic [minimum] velocity}}$$ (8)

In early pregnancy, uterine artery flow is very pulsatile with high systolic flow and low diastolic flow. As gestation progresses, resistance gradually decreases. Abnormal patterns, including persistence of high resistance, diastolic notching, the absence of end-diastolic flow, or reversal of diastolic flow, are predictive of the development of abnormalities such as preeclampsia or fetal growth restriction. Examples of normal and abnormal uterine artery Doppler tracings are shown in Fig. 3.7. Doppler velocimetry is also applied to the umbilical vessels for antepartum fetal assessment (see Chapter 6). Other methods of clinically evaluating the uteroplacental circulation...
include the use of two-dimensional and three-dimensional Doppler, power Doppler, contrast-enhanced ultrasonography, and functional magnetic resonance imaging.75

**NEURAXIAL ANESTHESIA**

The effect of neuraxial anesthesia on uteroplacental blood flow depends on the complex interaction of many factors (Box 3.2). Pain and stress during labor may reduce uteroplacental blood flow through sympathetic stimulation and the release of circulating catecholamines. Shnider et al.76 observed that acute stress increased plasma norepinephrine concentrations by 25% and decreased uterine blood flow by 50% in gravid ewes. In laboring women, stress is associated with increased plasma epinephrine concentration and abnormal fetal heart rate patterns. Effective pain relief with neuraxial analgesia decreases circulating concentrations of catecholamines77 and reduces hyperventilation and therefore may help protect uteroplacental blood flow. In the absence of hypotension, epidural anesthesia does not change uteroplacental blood flow in pregnant sheep.78 Results from human studies are variable, partly because of differences in study design, techniques used, and clinical circumstances. However, most studies have shown no change or an increase in uteroplacental blood flow after administration of epidural analgesia.79,80 Some studies have shown an increase in uterine vascular resistance indices,81,82 but with no effect on neonatal outcomes. There is evidence that in women with preeclampsia, epidural analgesia using a plain local anesthetic may reduce uterine artery resistance79 and increase intervillous blood flow.83 Ginosar et al.84 reported that antenatal continuous epidural infusion of ropivacaine in preterm women with preeclampsia reduced uterine artery resistance. Further work is required to determine whether this might have therapeutic potential for short-term prolongation of pregnancy.

Fetal bradycardia is sometimes observed after initiation of neuraxial labor analgesia and has been attributed to decreases in uteroplacental blood flow; the mechanism for this association is unclear. Although alterations in uteroplacental blood flow have been primarily attributed to maternal hypotension and respiratory depression, another postulated mechanism is uterine tachysystole caused by a rapid decrease in circulating catecholamine concentrations (see Chapter 23).85 Additional studies are needed to evaluate the relationship between neuraxial analgesic techniques, uteroplacental blood flow, and fetal bradycardia.

**Hypotension**

Hypotension occurring during neuraxial blockade, depending on its magnitude and duration, may decrease uteroplacental blood flow for several reasons, including reduction in perfusion pressure,86 reflex release of endogenous vasoconstrictors, diversion (steal) of blood to the lower limbs,87 and response to administered vasopressors.88 The rapid and extensive sympathetic blockade during spinal anesthesia, and some of the methods used to treat hypotension, may account for the observation that umbilical arterial blood pH is lower with spinal anesthesia than with epidural or general anesthesia for cesarean delivery.87

**Intravenous Fluid Loading**

Studies of the effect of intravenous fluid boluses used in conjunction with assessment of the uteroplacental circulation have had mixed results. Most Doppler studies have shown that fluid preload before the initiation of neuraxial analgesia does not change vascular resistance indices,88 although a decrease has been reported in one study.89

**Vasopressors**

The effects of vasopressors on uteroplacental blood flow and the resulting implications for clinical drug selection are controversial. Animal and *in vitro* studies have observed that uteroplacental blood flow was better maintained using ephedrine than with alpha-adrenergic agonists such as phenylephrine, metaraminol, and methoxamine,32 which likely reflects the predominant beta-adrenergic effects of ephedrine. In *in vitro* studies in pregnant sheep evaluating the effects of ephedrine on blood vessels have demonstrated enhanced vasoconstrictor activity on the femoral versus uterine vessels and decreased uterine artery vasoconstriction as a result of nitric oxide release.90 In contrast, an increase in the uterine arteriolar vasoconstrictor response to phenylephrine has been observed during pregnancy.91 However, in clinical studies, umbilical arterial blood pH and base excess have been observed to be greater with the use of alpha-adrenergic agonists compared with ephedrine for maintaining maternal blood pressure during spinal anesthesia for cesarean delivery.92–98 A comparison of different infusion regimens of phenylephrine, titrated to maintain maternal systolic blood pressure near baseline, observed no depression of fetal pH and base excess despite very large total doses (up to 2500 µg) before delivery.91 In contrast, large doses of ephedrine administered to maintain blood pressure during spinal anesthesia for cesarean delivery depressed umbilical arterial blood pH and base excess in a dose-dependent manner.99

The explanation for the discrepancy between experimental and clinical data is complex and incompletely understood. Animal studies are not always appropriate models for clinical situations. Under clinical conditions, Doppler studies have
shown some evidence that uterine vascular resistance is increased by alpha-adrenergic agonists, but this finding has not been consistent. Although data suggest that alpha-adrenergic agonists increase uterine vascular resistance more than systemic vascular resistance, the difference may be primarily caused by an effect in the myometrium, with relative sparing of the vessels that perfuse the placenta. In addition, uteroplacental blood flow in humans has a margin of safety that appears to allow modest decreases in uterine blood flow (caused by clinically appropriate doses of alpha-adrenergic agonists) to occur without compromising oxygen transfer. Finally, the propensity of ephedrine to worsen fetal acid-base status may be related less to its effects on uteroplacental blood flow and more to direct beta-adrenergic receptor–mediated fetal metabolic effects. Compared with phenylephrine, ephedrine crosses the placenta to a greater extent and is associated with higher fetal levels of lactate, glucose, epinephrine, and norepinephrine.

Thus, when considering the choice of vasopressor for clinical use, the anesthesia provider should consider the sum effect on fetal oxygen supply and demand balance rather than the isolated effects on uteroplacental blood flow. In this respect, clinical studies do not favor the use of ephedrine. Overall, to date, studies comparing ephedrine and other vasopressors in humans have not demonstrated differences in clinical neonatal outcome.

Limited data are available for the comparison of vasopressors in the presence of fetal compromise or placental insufficiency. Erkinaro et al. developed a sheep model to compare the effects of phenylephrine and ephedrine after a period of experimental fetal hypoxia. Hypotension was induced by epidural anesthesia and then corrected with either phenylephrine or ephedrine. In an initial study, ephedrine was associated with better restoration of uterine artery blood flow, but no differences in fetal acid-base measurements or lactate concentration were observed. However, in a second study, these investigators embolized the placenta with microspheres to model placental insufficiency and found that phenylephrine and ephedrine had similar effects on uterine blood flow, fetal pH, and base excess as found in the initial study, with the exception that fetal lactate concentration was greater in the phenylephrine group. Although the investigators speculated that this exception might reflect impaired fetal clearance of lactate, the placental embolization may have narrowed the margin of safety for uteroplacental blood flow and increased fetal lactate production in the phenylephrine group.

In two studies, women with preeclampsia undergoing cesarean delivery with spinal anesthesia were randomized to receive phenylephrine or ephedrine for the prevention or treatment of spinal anesthesia-induced hypotension. Neither study identified differences in the acid-base status of the neonates between the two drugs, suggesting that either drug is appropriate for use in women with preeclampsia with potentially compromised uteroplacental circulation.

In summary, ephedrine and phenylephrine both continue to be used clinically for maintaining maternal blood pressure during the administration of neuraxial anesthesia (see Chapter 26). Although most experimental data suggest that uteroplacental perfusion is likely to be better maintained with ephedrine than with alpha-adrenergic agonists, this advantage may be outweighed by other considerations, such as differences in efficacy for maintaining blood pressure and direct fetal effects that occur from placental drug transfer.

**Local Anesthetics**

Studies *in vitro* have shown that local anesthetics constrict arteries directly and inhibit endothelium-mediated vasodilation. High concentrations of local anesthetic can decrease uteroplacental blood flow by stimulating vasoconstriction and myometrial contractility. A comparative study in pregnant sheep showed that bupivacaine was more potent than either lidocaine or 2-chloroprocaine in decreasing uterine blood flow. However, the adverse effects of local anesthetics were seen only at concentrations in excess of those observed clinically, with two possible exceptions: (1) the unintentional intravenous injection of local anesthetic and (2) the use of local anesthetics for a paracervical block. At clinically relevant doses, no adverse effect on uteroplacental blood flow was reported. Although initially the inherent vasoconstrictor properties of ropivacaine were a matter of concern, studies in animals and humans have not shown that administration of ropivacaine results in a reduction in uterine blood flow.

**Epinephrine and α1-Adrenergic Agonists**

Wallis et al. found that the epidural injection of 1.5% 2-chloroprocaine with epinephrine (10 µg/mL) produced a small, brief reduction in uterine blood flow in pregnant sheep. In contrast, Alahuta et al. reported that epidural bupivacaine with epinephrine (5 µg/mL) had no effect on intervillus blood flow in women undergoing cesarean delivery. Studies have not shown a reduction in uteroplacental blood flow as a result of the absorption of epinephrine from local anesthetic solutions given epidurally to healthy women during labor. However, one study observed that the addition of epinephrine (85 to 100 µg) to epidural bupivacaine increased Doppler indices of uteroplacental vascular resistance in hypertensive parturients with chronic fetal asphyxia. Therefore, some anesthesia providers avoid epidural administration of epinephrine-containing local anesthetic solutions to women with preeclampsia. Commonly, epinephrine (10 to 15 µg) is included in the epidural test dose. Marcus et al. reported that repeated epidural injections of epinephrine (10 to 15 µg) did not decrease uterine blood flow in pregnant sheep; however, the same dose injected intravenously reduced uterine blood flow, with a maximum decrease of 43% observed at 1 minute.

The epidural and intrathecal administration of α1-adrenergic agonists (e.g., clonidine, dexmedetomidine) has been a subject of clinical investigations. Intravenous, but not epidural, administration of clonidine decreased uterine blood flow in gravid ewes.
Opioids
Intrathecal opioids have been implicated as contributing to a greater risk for fetal bradycardia when used for labor analgesia compared with non-intrathecal opioid neuraxial analgesic techniques. The mechanism for this effect has been postulated as an increase in uterine tone and a resulting decrease in uteroplacental blood flow, although further research is needed. Craft et al. observed that neither epidural fentanyl nor morphine had a significant effect on uterine blood flow in gravid ewes. Alahuhta et al. reported that epidural sufentanil 50 µg did not alter uterine artery blood flow velocity waveform indices in laboring women. Intrathecal meperidine and sufentanil, however, may be associated with hypotension that may potentially decrease uterine blood flow.

GENERAL ANESTHESIA

Intravenous Agents
Available data suggest that the commonly used induction agents have minimal or no direct adverse effect on uteroplacental blood flow. Allen et al. found that thiopental inhibited the response of human myometrial arteries to contractile agents in vitro but had no effect on relaxation induced by prostacyclin. Alon et al. reported that uterine blood flow did not change significantly during induction and maintenance of propofol anesthesia in pregnant sheep. Craft et al. reported that uterine tone increased but uterine blood flow remained constant after an intravenous bolus of ketamine in pregnant sheep. Similarly, Strümpfer et al. reported that neither racemic nor S-ketamine affected uterine perfusion in pregnant sheep. Few data are available on the direct effects of etomidate on uteroplacental blood flow.

During the intravenous induction of general anesthesia, uteroplacental perfusion may be affected by indirect mechanisms such as blood pressure changes and the sympathetic response to laryngoscopy and endotracheal intubation. Jouppila et al. reported that intervillosus blood flow decreased by 22% to 50% during induction of general anesthesia for cesarean delivery with thiopental 4 mg/kg, succinylcholine 1 mg/kg, and endotracheal intubation. Gin et al. compared thiopental 4 mg/kg and propofol 2 mg/kg in patients undergoing elective cesarean delivery and found that venous plasma concentrations of epinephrine and norepinephrine increased after endotracheal intubation in both groups, but maximum norepinephrine concentrations were lower in the propofol group. No differences in neonatal outcomes were observed. Levinson et al. found that intravenous ketamine increased blood pressure with a concomitant rise in uterine blood flow in pregnant sheep. Addition of a rapid-acting opioid (e.g., alfentanil, remifentanil) during induction of general anesthesia may minimize the increase in circulating catecholamines that occurs after laryngoscopy and endotracheal intubation. Although the use of such opioids might attenuate any decrease in uterine blood flow, the potential for neonatal respiratory depression should be considered.

Inhalational Agents
Studies in pregnant sheep have shown that usual clinical doses (i.e., 0.5 to 1.5 minimum alveolar concentration [MAC]) of the volatile anesthetic agents, including isoflurane, desflurane, and sevoflurane, have little or no effect on uterine blood flow, although deeper planes of anesthesia are associated with reductions in cardiac output, maternal blood pressure, and uterine blood flow. Nonetheless, high concentrations of inhalational agents (approximately 2 MAC) have been used during ex utero intrapartum treatment procedures without evidence of impaired fetal gas exchange. A dose-dependent reduction in uterine tone caused by inhalational agents would be expected to increase uterine blood flow in clinical circumstances in which tone is increased (e.g., hyperstimulation with oxytocin, cocaine overdose, placental abruption). Overall, there is little reason to choose one inhalational agent over another on the basis of an agent’s effects on uterine blood flow.

Ventilation
Although moderate levels of hypoxemia and hypercapnia do not affect uteroplacental blood flow, marked alterations may reduce blood flow indirectly by mechanisms most likely involving sympathetic activation and catecholamine release. The effect of hypocapnia on uteroplacental blood flow is controversial. Some investigators have noted that hyperventilation with hypocapnia caused fetal hypoxia and metabolic acidosis in animals, whereas others have found no effect. Levinson et al. observed that positive-pressure ventilation decreased uterine blood flow in pregnant sheep; however, because the addition of carbon dioxide did not improve uterine blood flow, the reduction in blood flow was attributed to the mechanical hyperventilation rather than the hypocapnia. In general, most authorities recommend that hyperventilation be avoided in pregnancy, in part because of concerns about uterine blood flow.

EFFECTS OF OTHER DRUGS AND INTERVENTIONS

Magnesium Sulfate
Magnesium sulfate increases uterine blood flow in normotensive and hypertensive pregnant sheep. Although hypermagnesemia was found to exacerbate maternal hypotension during epidural anesthesia in pregnant sheep, no reduction in uterine blood flow was observed. In women in preterm labor and with preeclampsia with severe features, magnesium sulfate caused a modest decrease in Doppler indices of uterine vascular resistance. Infusion of magnesium caused an increase in uterine blood flow, which was associated with an improvement in red blood cell deformability in women with preeclampsia or fetal growth restriction.

Antihypertensive Agents
In patients with gestational hypertension, the effects of antihypertensive drugs on uteroplacental perfusion depend on
the interaction of their effects on uterine vascular resistance and systemic maternal blood pressure. In animal models of pharmacologically induced hypertension, hydralazine reduced maternal blood pressure but increased uteroplacental blood flow, reflecting a decrease in uterine vascular resistance. Similar studies with labetalol have had varying results, showing increased, decreased, and no change in uteroplacental blood flow. A study in preeclamptic women observed an increase in uterine artery resistance indices after hydralazine but not labetalol. However, previous studies have generally demonstrated no significant change in uteroplacental blood flow with either drug, indicating that other considerations are probably more important for guiding drug selection. Studies of methyldopa in patients with preeclampsia have found either a reduction or no change in indices of uterine and placental vascular resistance.

**Calcium Entry–Blocking Agents**

Verapamil 0.2 mg/kg was shown to decrease maternal blood pressure and uterine blood flow in pregnant sheep. Studies with nifedipine have yielded conflicting results. Some animal studies have shown that nifedipine decreases uteroplacental blood flow and worsens the fetal condition, whereas human studies have shown either no change in uteroplacental blood flow or vascular resistance or a decrease in vascular resistance.

**Vasodilators**

Nitroglycerin was shown to relax human uterine arteries in vitro. In women with abnormal uterine artery blood flow at 24 to 26 weeks’ gestation, infusion of intravenous nitroglycerin decreased uterine resistance indices. Similarly, transdermal nitroglycerin administered for 3 days to patients with preeclampsia and fetal growth restriction decreased uterine resistance indices. However, Grunewald et al. reported that an infusion of nitroglycerin in women with preeclampsia with severe features did not change the pulsatility index of the uterine artery. When interpreting such studies, clinicians should remember that increases in total uterine blood flow do not necessarily result in enhanced placental perfusion. Further work is required to define the utility of systemic vasodilators for improving uteroplacental blood flow in clinical practice.

**Inotropic Drugs**

Inotropic drugs are rarely indicated in obstetric patients. On the basis of studies of normal pregnant sheep, milrinone and amrinone may increase uterine blood flow, whereas dopamine and epinephrine may diminish it. The choice of an inotropic agent should be based primarily on the desired efficacy (i.e., maternal considerations) rather than the potential direct effects on uterine blood flow. This is especially important during maternal resuscitation or cardiac arrest, when maternal welfare is the overriding priority and standard resuscitation drugs should be administered. Restoration of spontaneous circulation and adequate uterine perfusion pressure is far more important than avoidance of uterine vasoconstriction.

**Oxygen Therapy**

The effect of supplemental maternal oxygen therapy on uteroplacental blood flow is controversial. Jouppila et al. measured intervillous blood flow using an xenon clearance method in 22 women, all of whom had some form of pregnancy complication between 34 and 40 weeks’ gestation. They reported that blood flow decreased significantly after inhalation of oxygen 5 L/min (Fig. 3.8) and suggested that this might be related to a vasoconstrictive effect of maternal hyperoxia. Although it is common practice to administer supplemental maternal oxygen as part of intrapartum resuscitation for suspected fetal compromise, evidence for the benefit of this practice is unclear.
KEY POINTS

- Growth and development of the uteroplacental vasculature and progressive vasodilation allow uteroplacental blood flow to increase during pregnancy. Uteroplacental blood flow constitutes approximately 12% of maternal cardiac output at term.
- Many factors modulate the maintenance and regulation of uteroplacental blood flow, including altered responses to vasoconstrictors, increases in endothelium-derived vasodilators, and the effects of steroid hormones and shear stress.
- The uteroplacental circulation is a dilated, low-resistance vascular bed with limited ability for autoregulation. Flow may be reduced by a decrease in uterine arterial pressure, an increase in uterine venous pressure, or an increase in uterine vascular resistance.
- The uteroplacental circulation is composed of placental and nonplacental circulations that are anatomically and functionally dissimilar.
- Acute or chronic reductions in uteroplacental blood flow may threaten fetal viability and predispose to disorders such as preeclampsia and fetal growth restriction. In situations of an acute reduction in uteroplacental perfusion, there is a limited margin of safety; exceeding this limit may decrease fetal oxygen uptake with resultant metabolic acidosis.
- Animal studies are the principal source of uteroplacental blood flow data; thus, clinicians should carefully consider interspecies differences and study methodology when extrapolating experimental findings to clinical practice.
- Doppler ultrasonography is the method most commonly used clinically to assess uteroplacental blood flow in humans. Abnormal waveforms and indices of resistance may be predictive of complications such as preeclampsia, fetal growth restriction, and preterm labor.
- Neuraxial anesthesia can increase uterine blood flow by reducing pain and stress, or it can decrease uterine blood flow by causing hypotension.
- Although animal studies show that ephedrine protects uteroplacental blood flow better than alpha-adrenergic agonists such as phenylephrine, umbilical arterial blood pH and base excess are lower after administration of ephedrine. This effect may be related to a greater propensity of ephedrine to cross the placenta and have direct metabolic effects on the fetus.
- The doses of general anesthetic agents used clinically have minimal direct effects on uterine blood flow. General anesthesia may reduce uterine blood flow by causing decreased cardiac output and hypotension. Conversely, noxious stimulation during light anesthesia may precipitate the release of catecholamines, which results in decreased uterine blood flow.
- For cardiovascular emergencies in pregnant women, the choice of inotropic drug should depend primarily on the efficacy of the drugs to optimize the maternal condition, rather than on minor differences in uterine blood flow. Standard resuscitation drugs should be used in an emergency.

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The placenta is a critical organ of great importance to obstetric anesthesia. Revered by ancient cultures as “the seat of the external soul” or “the bundle of life,” the placenta is involved in many cultural rituals. Acknowledgment and understanding of the indispensable role of the placenta continues to evolve. The notion of the placenta as a passive conduit for oxygen, nutrients, and waste has been dispelled with the realization that the placenta is a complex and dynamic organ that serves critical functions of metabolism, nutrition, and hormonal maintenance during pregnancy. Maternal-placental conditions can affect the fetus during pregnancy with consequences into adulthood and even beyond into the next generation.

The placenta brings the maternal and fetal circulations into close apposition without substantial interchange of maternal and fetal blood for the physiologic transfer of gases, nutrients, and wastes. This important exchange is accomplished within a complex structure that is almost entirely of fetal origin.

**ANATOMY**

**Embryology**

The blastocyst attaches to endometrial pinopodes (uterodomes), which express markers of endometrial receptivity (e.g., galectin-9), and serine proteases and metalloproteases (e.g., MMP-2 and MMP-9) initiate the remodeling of the uterine extracellular matrix. The syncytiotrophoblasts (invasive cells located at the margin of the growing conceptus), with the assistance of endometrial stromal cells, invade the decidua, capillaries, and arterioles until the blastocyst is surrounded by circulating maternal blood (trophoblastic lacunae). The vitelline vein system develops in the embryonic yolk sac to enhance nutrient transport from the maternal blood through the trophoblast layer and chorionic plate into the chorionic cavity. The embryo undergoes a dramatic acceleration in growth as its dependence on simple diffusion diminishes.

At 2 weeks of development, the primitive extra-embryonic mesoderm (cytotrophoblast layer) begins to proliferate as cellular columns, carrying a syncytiotrophoblast covering and extending into the maternal blood lacunae; these represent primary villi. Development within the core of these primary villi marks the metamorphosis into secondary villi. Further cellular differentiation of the villi mesoderm into blood cells and vessels marks the transition into tertiary villi. Each villus develops connections within the chorionic plate and into the stalk connecting the developing embryo with the
primitive placenta. Penetration of the cytotrophoblast continues through the syncytiotrophoblastic layer until many of the villi reach the decidua and form anchoring villi (Fig. 4.1).5 Villi undergo extensive branching into the lacunar (or intervillous) spaces, enlarging the surface area available for exchange. Villous maturation reduces the cytotrophoblast thickness, thereby shortening the distances required for diffusion.5

The embryo attaches to the chorion via a connecting body stalk. Mesodermal components of this stalk coalesce to form the allantoic (or rudimentary umbilical) vessels. The expansive open region at the ventral surface of the embryo constricts as the body wall grows, surrounding the yolk stalk, allantois, and developing vessels into a primitive umbilicus. The mature umbilical cord forms as the expanding amnion surrounds the connecting stalk and yolk sac.5

Placental development is a dynamic process influenced by many factors. Nitric oxide plays an important role in embryo development, implantation, and trophoblast invasion in diverse species.5 Human endothelial nitric oxide synthase (eNOS) expression in the syncytiotrophoblast and early endothelium occurs in the first trimester and becomes more prominent throughout pregnancy. Angiogenesis depends on vascular endothelial growth factor (VEGF) and its receptors VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1), transforming growth factor-β1 (TGF-β1), and angiopoietin 1 and 2, which exert their effects partially through nitric oxide. Hypoxia also plays an important role in placental development and angiogenesis by stimulating trophoblast invasion and differentiation via hypoxia-inducible factor-alpha, which activates VEGF and eNOS. Relative hypoxia must be maintained in early placental development because the placental-fetal unit cannot tolerate the oxidative stress of reactive oxygen species during organogenesis.6 Oxygen levels influence the placental vascular sensitivity to vasodilators and vasoconstrictors. In vitro studies have shown that NOS inhibition and hypoxia independently increase placental perfusion pressure. Both of these effects are prevented by nitric oxide donors, suggesting a common pathway with the effect of hypoxia mediated partly by low NOS activity.5

Preeclampsia is related, at least in part, to abnormal placental growth and implantation at early stages of development, resulting in the villous tree having longer capillaries with fewer branches (see Chapter 35).7 Vascular dysfunction occurs mainly from changes in vascular structure and synthesis of nitric oxide rather than from altered responses to nitric oxide and vasoconstrictors.

The expression and control of DNA and genes affects placental development, fetal development, adult phenotype expression, and clinical diseases, even into subsequent generations.17 Epigenetics explores the prolonged effect of maternal and paternal environmental influences; gene expression becomes altered by DNA methylation, histone modification, and noncoding RNA. At fertilization, global DNA methylation is erased so the genome is hypomethylated at the blastocyst stage (implantation).7 Methylation of placental DNA increases with gestation, causing down- and up-regulation of genes associated with cell cycles and immune response, respectively.6 Genomic imprinting causes the silencing of one allele-specific copy of a gene, which leads to extensive intraplacental and cotyledon mosaicism. In vitro fertilization, diet, and maternal diseases can influence epigenetic changes and subsequently alter DNA methylation.9

Altered gene methylation has been linked to clinical disease states.7 Increased long interspersed nuclear element-1 (LINE1) gene methylation, as well as hypomethylation of 34 specific genes, are associated with early-onset preeclampsia.18 By contrast, late-onset preeclampsia is associated with hypomethylation of only 4 genes.10 These and other findings indicate that DNA and DNA regulatory changes influence early placental development as well as the occurrence of pregnancy-associated diseases.

Human studies have demonstrated fetal programming of childhood and adult diseases. Adults who were exposed in utero to episodes of malnutrition developed reduced glucose tolerance, atherogenic lipid profiles, and a doubled rate of cardiovascular diseases; these disease states were associated with hypomethylation of regulatory areas for insulin-like growth factor-2 and other genes.1 In utero exposure to a high-fat diet can lead to an increased incidence of diabetes in offspring, and chronic maternal stress during pregnancy can lead to infant neurodevelopmental disorders.1

The placenta grows dramatically from the third month of gestation until term, with a direct correlation between placental growth and fetal growth. By term, the mature placenta is oval and flat, with an average diameter of 18.5 cm, weight of 500 g, and thickness of 23 mm. At term, the human fetal-placental weight constitutes 6% of maternal weight of 500 mm. At term, the

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![Fig. 4.1](image-url)
weight. The growth of the placenta and fetus is influenced by maternal anabolic status, placental growth hormone, insulin-like growth factor-1, leptin, and glucocorticoids. Whether maternal or fetal in origin, increased glucocorticoids signal adverse environmental conditions and result in reduced glucose and amino acid transfer to the fetus. With 12 subtypes of glucocorticoid receptors, significant variations in placental-fetal development can occur, including alterations in placental remodeling, trophoblastic invasion, and angiogenesis inhibition. Competition between the mother and fetus for resource allocation has been termed the *kinship theory*, in which imprinted genes influence the balance of nutrient allocation in a context-specific manner.

## Comparative Anatomy

Placentas of different species vary in their method of uterine attachment (adhesion, interdigitation, and fusion) and the number of tissue layers between the maternal and fetal circulations. The placental categorization system, called the Grossner classification, uses the number of tissue layers in the placental barrier to help differentiate species (Fig. 4.2).

The ability of the placenta to transfer various substances differs among species. The markedly thicker epitheliochorial placenta found in sheep, a species commonly used for placental transfer studies, has three maternal layers (epithelium, connective tissue, and endothelium) that separate maternal from fetal blood. By contrast, the human hemochorial placenta lacks these maternal layers, which allows maternal blood to bathe fetal tissues directly (see Fig. 4.2). As a result, species differ in the transfer of substances through the placenta.

## Vascular Architecture

### Maternal

Under the initial hormonal influences of the corpus luteum, the uterine spiral arteries elongate and coil. Erosion of the decidua induces lateral looping of the already convoluted spiral arteries. In late pregnancy, approximately 200 spiral arteries can supply approximately 600 mL/min of blood flow directly to the fetus through the placenta. The vasodilation required to accommodate the increased flow is accomplished by the replacement of the elastic and muscular components of these arteries by cytotrophoblastic cells, and later by fibroid cells; vessel diameter increases up to 10-fold, while blood velocity and blood pressure decrease. Inadequate uterine spiral artery development contributes to relative ischemia and the development of preeclampsia and fetal growth restriction, which was previously called intrauterine growth restriction (IUGR). Computer modeling of spiral artery flow indicates that high blood velocity in nondilated spiral arteries causes damage to the endothelium and placenta trophoblast.

The **intervillous space** is a large cavernous expanse that develops from the fusion of the trophoblastic lacunae and the erosion of the decidua by the expanding blastocyst. Folds in the basal plate form septa that divide the space into 13 to 30 anatomic compartments or lobules for efficient transfer of material between maternal and fetal blood flow. Each lobe contains numerous villous trees that are also known as *cotyledons* or *placentomes*. The intervillous space of the mature placenta can accommodate 350 mL of maternal blood.

Maternal arterial blood leaves the funnel-shaped spiral arteries and enters the intervillous space. The blood moves into the nearly hollow, low-resistance area, where villi are very loosely packed (the intercotyledonary space), before entering a region of densely packed intermittent and terminal villi where placental exchange predominates (Fig. 4.3). Maternal venous blood collects between neighboring villous trees in an area called the **perilobular zone**. Collecting veins penetrate the maternal plate at the periphery of the villous trees to drain perilobular blood from the intervillous space.

### Fetal

Two coiled arteries in the umbilical cord bring fetal blood toward the placenta. These arteries divide into chorionic arteries that supply the 50 villous trees located in the placental lobules. At the base of each villous tree, the chorionic arteries are considered the **main villous stem** or **truncal arteries** (first-order vessels), which in turn branch into four to eight **ramal or cotyledonary arteries** (second-order vessels); as they pass toward the maternal plate, they further subdivide into **ramulus chorii** (third-order vessels) and, finally, **terminal
The venous end of the capillaries loops, narrows, and returns through the neck region to the collecting venules, which coalesce to form the larger veins in the stem of the villous trees, and as they perforate the chorionic plate, become chorionic veins. The venous tributaries combine to empty arterioles. The terminal arterioles lead through a neck region into a bulbous enlargement, where they form two to four narrow capillary loops. Here the large endothelial surface area and the near-absence of connective tissue allow optimal maternal-fetal exchange (Fig. 4.4).18

Fig. 4.3 The relationship between the villous tree and maternal blood flow. Arrows indicate the maternal blood flow from the spiral arteries into the intervillous space and out through the spiral veins. (Modified from Tuchmann-Duplessis H, David G, Haegel P. Illustrated Human Embryology. Volume 1. Embryogenesis. New York, NY: Springer Verlag; 1972:73.)

Fig. 4.4 Right, Cellular morphology of two terminal villi. Left, Higher magnification of the boxed region exhibiting the placental barrier between fetal and maternal blood. (Redrawn from Kaufmann P. Basic morphology of the fetal and maternal circuits in the human placenta. Contrib Gynecol Obstet. 1985;13:5–17.)
into the one umbilical vein that delivers blood back to the fetus.

**PHYSIOLOGY**

**Barrier Function**

The placenta is an imperfect barrier that allows bidirectional transfer of many substances; the rate and amount of transfer depend on the permeability and the presence of various mechanisms to restrict movement. Many substances undergo specific or nonspecific binding within the placental tissues, thereby minimizing fetal exposure and accumulation; other substances are altered by the vast array of inducible and constitutive cytochrome P450 isoenzymes and transporters. Placental membrane thickness, which may influence the rate of diffusion, diminishes as gestation progresses; however, the transfer rate of certain simple substances (e.g., glucose, water) differs very little among species, despite significant variations in placental thickness.

Maternal and fetal cellular components can cross the placental barrier by disruption of the trophoblastic layer or by active adhesion and transmigration (similar to blood-brain barrier migration). Fetal cells may be pluripotent, and their DNA can be found in maternal organs for decades. Murine fetal progenitor cells have been found to migrate and assist with maternal wound healing.

These microchimeric fetal cells may contribute to maternal immunomodulation, development or worsening of autoimmune diseases (e.g., thyroiditis, lupus, and asthma), and healing of wounds, including neuronal tissue. Placental exosomes, nanovesicles 30 to 100 nm in size found in maternal circulation that contain proteins and transcription-related materials, exert a maternal immunosuppressive effect. Placental microparticles, which are vesicular products of syncytiotrophoblast greater than 100 nm, also contain RNA and DNA fragments and affect fetal and maternal apoptosis, angiogenesis, and inflammation. Syncytiotrophoblast nuclei from the placental villous tree also enter the maternal circulation, reside in the lung, participate in maternal-fetal signaling, and assist in the delivery of retroviral proteins for immunomodulation. An excess of microparticles has been observed in early-onset preeclampsia.

**Hormonal Function**

A sophisticated transfer of precursor and intermediate compounds in the maternal-fetal-placental unit allows placental enzymes to convert steroid precursors into estrogen and progesterone. This steroidogenic function of the placenta begins very early in pregnancy; by 35 to 47 days after ovulation, the placental production of estrogen and progesterone exceeds that of the corpus luteum (i.e., the ovarian-placental shift). The placenta also produces human chorionic gonadotropin, human placental lactogen (a growth hormone also known as human chorionic somatomammotropin), and factors that control hypothalamic function. Production of proteins and steroid hormones allows the placenta to influence and control the fetal environment.

**Regulation of Placental Blood Flow**

**Maternal Blood Flow**

Maternal blood enters the intervillous cotyledon space at a pressure of 70 to 80 mm Hg in an area that has relatively few villi. The pressure and velocity of blood flow rapidly diminishes to 10 mm Hg as blood passes into an area of higher resistance created by the densely packed villi of the placental membrane.

**Fetal Blood Flow**

In contrast to the maternoplacental circulation, which relies on vasodilation to increase flow, the increase in fetoplacental blood flow is primarily caused by vascular growth. Fetal perfusion of the placenta is not classically autoregulated; the placental vasculature is not innervated by the sympathetic nervous system. However, the fetus can modulate fetoplacental perfusion via: (1) endocrine effects of adrenomedullin, (2) net efflux/influx of water regulated by fetal blood pressure, and (3) local autoregulatory effects mediated by the paracrine vasodilators nitric oxide and acetylcholine. Adrenomedullin release by the fetal adrenal glands assists in maintenance of tone in placental vessels. Fetal blood pressure changes cause net influx/efflux of water across the placenta that affects fetal intravascular volume and perfusion. Maternal hyperglycemia and hypoxemia can alter regional fetal blood flow, probably through vascular mediators. Endothelium-derived relaxing factors, especially prostacyclin and nitric oxide, are important in the control of fetoplacental circulation.

**Transport Mechanisms**

Substances are transferred across the placenta by one of several mechanisms.

**Passive Transport**

The passive transfer of molecules across a membrane depends on (1) concentration and electrochemical differences across the membrane, (2) molecular weight, (3) lipid solubility, (4) degree of ionization, and (5) membrane surface area and thickness. Passive transfer is driven principally by a concentration gradient and occurs through the lipid membrane (e.g., lipophilic molecules and water) or within protein channels that traverse the lipid bilayer (e.g., charged substances such as ions). Drugs with a molecular weight less than 600 Da cross the placenta by passive diffusion.
Facilitated Transport

Carrier-mediated adenosine triphosphate (ATP)–independent transport of relatively lipid-insoluble molecules down their concentration gradient is called facilitated diffusion. Facilitated diffusion differs from simple diffusion in several ways. Specifically, this mode of transfer exhibits (1) saturation kinetics, (2) competitive and noncompetitive inhibition, (3) stereospecificity, and (4) temperature influences (e.g., a higher temperature results in greater transfer). With simple diffusion, the net rate of diffusion is proportional to the difference in concentration between the two sides of the membrane. The rate of transfer is determined by the number of membranous carrier protein complexes and the extent of interaction between the carrier and the substance undergoing transport. This rate limitation is valid for facilitated diffusion only when transmembrane concentration differences are small. At higher concentration gradients, a maximum rate of transfer \( V_{\text{max}} \) is reached; thereafter, further increases in the concentration gradient do not affect the rate of transfer. An example of facilitated diffusion is the transplacental transfer of glucose.

A special type of facilitated diffusion involves the “uphill” transport of a molecule linked to another substance traveling down its own concentration gradient. As such, the transfer is not directly driven by cellular energy expenditure. In most cases, sodium is the molecule that facilitates transport. For the membrane-bound carrier to transfer these molecules, both molecules must be bound to the carrier. This hybrid system is called secondary active transport or co-transport. The transplacental transport of amino acids appears to occur principally through secondary active transport. Transporters may be affected by disease states (e.g., preeclampsia) or signaling molecules (e.g., elevated steroid levels).

Active Transport

Active transport involves the movement of any substance across a cell membrane requiring energy from ATP hydrolysis. In general, active transport occurs against a concentration, electrical, or pressure gradient. Active transport also requires a protein membrane carrier that exhibits saturation kinetics and competitive inhibition. The best-known example of primary active transport is the translocation of sodium and potassium through the sodium-potassium adenosine triphosphatase (Na⁺/K⁺ ATPase) pump. Unlike most cell types, the placenta can self-generate creatinine, which assists in the regeneration of ATP and in meeting the high metabolic energy demands of the placenta.

Active transport proteins include P-glycoprotein, breast cancer resistance protein, multidrug resistance protein, and the sodium/multivitamin transporter, as well as the many proteins involved in monoamine transport and xenobiotics. These transport proteins play an important role in protecting the fetus from foreign and potentially teratogenic compounds. Drugs may compete with endogenous compounds of similar shape and charge for active transport. P-glycoprotein transports many lipophilic drugs and antibiotics and removes cytotoxic compounds from the fetus; it exists on the maternal side of the trophoblastic cell membrane of the placenta and prevents compounds such as methadone and saquinavir (a protease inhibitor) from leaving the maternal blood, thus limiting fetal exposure. Inhibition of these transporter proteins (e.g., inhibition of P-glycoprotein by verapamil) can significantly increase the fetal transfer of certain drugs, including midazolam, which is a substrate for P-glycoprotein. DNA transcription of transporters may be induced by drugs or disease states. Expression of transporters may change with gestational age.

Pinocytosis

Pinocytosis is an energy-requiring process in which the cell membrane invaginates around large macromolecules that exhibit negligible diffusion properties. Although the contents of pinocytotic vesicles are subject to intracellular digestion, studies have demonstrated that the vesicles can move across the cytoplasm and fuse with the membrane at the opposite pole. This appears to be the mechanism by which immunoglobulin G is transferred from the maternal to the fetal circulation.

The placenta releases extracellular vesicles of various sizes and functions. Macrovesicles from the syncytiotrophoblast (20 to 500 μm) carry fetal protein, RNA, and other substances; microvesicles from membranes of stressed or apoptotic cells (0.1 to 1 μm) and exosomes (20 to 100 nm) contribute to feto-maternal communication.

Other Factors That Influence Placental Transport

Other factors that affect maternal-fetal exchange include (1) maternal and fetal blood flow, (2) placental binding, (3) placental metabolism, (4) diffusion capacity, (5) maternal and fetal plasma protein binding, and (6) gestational age (the placenta is more permeable in early pregnancy). Lipid solubility, pH gradients between the maternal and fetal environments for some basic drugs (“ion trapping”), and alterations in maternal or fetal plasma protein concentrations found in normal pregnancy and other disease states (e.g., preeclampsia) may also alter net placental transport.

Transfer of Respiratory Gases and Nutrients

Oxygen

The placenta must provide approximately 8 mL O₂/min/kg fetal body weight for fetal growth and development, while adults only require 3 to 4 mL O₂/min/kg at rest. As the “lung” for the fetus, the placenta has only one-fifth the oxygen transfer efficiency of the adult lung. The human lung, with a surface area of 50 to 60 m² and a thickness of only 0.5 μm, has a very large oxygen diffusion capacity; in comparison, the placenta has a lower diffusion capacity because of its smaller surface area of 16 m² and a thicker membrane of 3.5 μm. Furthermore, 16% of uterine blood flow and 6% of umbilical blood flow are shunted through the placenta.

Oxygen transfer across the placenta depends on the membrane surface area, membrane thickness, oxygen partial pressure gradient between maternal blood and fetal blood, oxygen affinity of maternal and fetal hemoglobin, and
relative maternal and fetal blood flows. As physically-dissolved oxygen diffuses across the villous membranes, bound oxygen is released by maternal hemoglobin in the intervillous space and diffuses across the placenta. Several factors affect the fetal blood PO₂ once it reaches equilibration in the villi end-capillaries. First, the concurrent and countercurrent arrangements of maternal and fetal blood flow play a key role for placental oxygen transfer in various species. The almost complete equilibration of maternal and fetal Po₂ values suggests that a concurrent (or parallel) relationship between maternal blood and fetal blood exists within the human placenta (Fig. 4.5), although others have described a multivillous, cross-current flow pattern. The functional anatomy of the placenta in many mammals involves more layers than the human placenta; thus, results of animal models can only provide evidence for trends, not values, in humans.

In humans, oxygen solubility is $10^{-4}$ M in plasma and $10^{-2}$ M in hemoglobin; thus, 99% of the oxygen content in blood is bound to hemoglobin. With an inspired FiO₂ of 1.0, the maximum maternal arterial Po₂ was 425 mm Hg on 100% O₂, but the fetal umbilical venous (UV) Po₂ was only 47 mm Hg, indicating a low diffusion capacity across the placenta. The placenta receives less than 50% of the fetal cardiac output, and blood returning from the placenta admixes with the nonoxygenated blood in the fetal inferior vena cava, thus limiting fetal arterial Po₂.

Although some have called the human placenta “diffusion limited” because of the decreased ability of oxygen to cross the intervillous membrane, the delivery of oxygen to the fetus is predominantly flow limited. Maternal delivery of blood (i.e., oxygen) to the uterus is the predominant factor controlling fetal oxygen transfer. The high fetal hemoglobin concentration (17 mg/dL) accounts for the large oxygen content and the net delivery of large quantities of oxygen to the fetus. Fetal hemoglobin has a higher oxygen affinity and therefore a lower partial pressure at which it is 50% saturated ($P_{50}$: 18 mm Hg) than maternal hemoglobin ($P_{50}$: 27 mm Hg). This gradient produces a “sink” effect that enhances oxygen uptake by fetal red blood cells, keeping fetal Po₂ lower and promoting the transfer of additional oxygen across the placenta (see Fig. 5.7). The Bohr effect also augments the transfer of oxygen across the placenta. Specifically, fetal-maternal transfer of carbon dioxide makes maternal blood more acidic and fetal blood more alkalotic. These alterations of pH cause shifts in the maternal and fetal oxyhemoglobin dissociation curves, further enhancing the maternal oxygen transfer to the fetus in what is termed the “double” Bohr effect. This accounts for 2% to 8% of the transplacental transfer of oxygen.

The placenta normally has a 50% reserve for changes in maternal or fetal blood flow by increasing venous extraction, a mechanism similar to that in adults. Based on umbilical venoarterial differences, human fetal oxygen uptake at term is 0.25 mmol/kg/min. The metabolic activity of the placenta itself consumes up to 40% of the oxygen uptake. Placental oxygen consumption is stable, even with changes in maternal blood pressure and Po₂; 30% of placental oxygen is used for protein synthesis and almost 30% for Na⁺/K⁺ ATPase. The human placenta has a villous structure, which may be an adaptation for greater maternal flow and thus oxygen delivery, but at the expense of a smaller surface area and cross-current exchange mechanism. However, the placenta does change in response to chronic hypoxia found at high altitudes, with an increased capillary volume and decreased capillary thickness providing a near-doubling of the oxygen diffusion capacity.

![Fig. 4.5](Image)

Fig. 4.5 The concurrent relationship between the maternal and fetal circulations within the placenta and the manner in which this arrangement affects gas transfer. These values were obtained from patients’ breathing room air during elective cesarean delivery. BE, base excess; $P_{O_2}$, partial pressure of oxygen; $P_{CO_2}$, partial pressure of carbon dioxide; UBF, uterine blood flow; UCBF, umbilical cord blood flow. (Blood gas data from Ramanathan S. Obstetric Anesthesia. Philadelphia, PA: Lea & Febiger; 1988:27. Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
Carbon Dioxide
The transfer of CO₂ occurs through a number of different forms, including dissolved CO₂, carbonic acid (H₂CO₃), bicarbonate ion (HCO₃⁻), carbonate ion (CO₃²⁻), and carbaminohemoglobin. Equilibrium between CO₂ and HCO₃⁻ is maintained by a reaction catalyzed by carbonic anhydrase in red blood cells. The Pco₂ gradient between fetal and maternal blood (i.e., 40 versus 34 mm Hg, respectively) drives fetal-maternal transfer. Carbon dioxide is 20 times more diffusible than oxygen and readily crosses the placenta. The rapid movement of CO₂ from fetal capillary to maternal blood invokes a shift in the equilibrium of the carbonic anhydrase reaction (La Chatelier principle) that produces more CO₂ for diffusion. The transfer of CO₂ is augmented further by the production of deoxyhemoglobin in the maternal blood, which has a higher affinity for CO₂ than oxyhemoglobin (the Haldane effect). The resulting affinity may account for as much as 46% of the transplacental transfer of carbon dioxide. Although a significant fetal-maternal concentration gradient exists for HCO₃⁻, its charged nature impedes its transfer and contribution to CO₂ transport except as a source for CO₂ production through the carbonic anhydrase reaction.

Glucose
Placental and fetal glucose demand is fulfilled by a stereospecific-facilitated diffusion system with glucose transporters, such as GLUT1 and GLUT3; the system is independent of insulin, a sodium gradient, or cellular energy. Insulin does not cross the placenta; however, insulin receptors on the maternal side of the syncytiotrophoblast regulate nutrient transport through a signaling cascade involving the mammalian target of rapamycin complex (mTORC). Nutrient sensors for glucose, amino acids, oxygen, cytokines, growth factors, and energy levels stimulate mTORC1, a key sensing and signaling protein in the syncytiotrophoblast that regulates nutrient transport and growth.

Amino Acids
Concentrations of amino acids are highest in the placenta, followed by UV blood and then maternal blood. The maternal-fetal transplacental transfer of amino acids is an active process that occurs principally through a linked translocation with sodium and facilitated diffusion. Pregnancies with fetal growth restriction have reduced amino acid transport with an inability to increase transport despite higher maternal levels of essential amino acids than occur in healthy pregnancies. Fetal growth restriction and hypoxia increase the breakdown of the amino acid tryptophan, which decreases serotonin (vasodilator) production.

Fatty Acids
Free fatty acids readily cross the human, but not ovine, placenta. The essential fatty acids, linoleic and alpha-linolenic acid, are transferred across the placenta with a peak of 7 g/day at term. The placental basal membrane has specific binding sites for very low-density, low-density, and high-density lipoproteins. Lipase activity in the placenta converts triglycerides to nonessential fatty acids. The placenta does not elongate fatty acid chains, whereas the fetus does. Fatty acid transport occurs primarily by simple diffusion; however, fatty acid–binding proteins (FABPpm, FAT/CD36, and FATP), facilitate transport. Nonessential fatty acids are albumin bound and may displace other protein-bound substances, including drugs.

The placenta is a source of fatty acid synthase responsible for straight chain fatty acid catabolism and is regulated by insulin levels. Dysregulation of placental fatty acid synthase may be responsible for hypertension, insulin resistance, and fetal and placental growth abnormalities.

DRUG TRANSFER
Placental permeability and pharmacokinetics determine the fetal exposure to maternal drugs. Animal models (e.g., pregnant ewes, guinea pigs) have been used to assess the placental transport of drugs; however, interspecies differences in placental anatomy and physiology limit the application of these data to humans.

The inaccessibility of the placenta in situ and concerns for maternal and fetal safety have limited direct studies of the human placenta. Data regarding the transplacental transfer of anesthetic agents have been extrapolated primarily from single measurements of drug concentrations in maternal and umbilical cord blood samples obtained at delivery. Most studies have reported fetal-to-maternal (F/M) ratios of drug concentration using maternal and umbilical vein blood (to represent fetal blood concentrations). Drug concentrations are influenced by drug metabolism in the mother, the placenta, and the fetus and by changes during delivery (e.g., altered uteroplacental blood flow).

A dual-perfused, in vitro human placental model allows for the independent perfusion of the maternal and fetal sides of the placenta and thereby the investigation of maternal-fetal (or fetal-maternal) transport. Equilibration studies (i.e., recirculating maternal and fetal perfusates) can give an indication of final drug ratios; when a non-recirculating design is used, the steady-state clearance of a drug can be determined for either direction (maternal to fetal or fetal to maternal). This method has been used to assess the placent al transfer of anesthetic agents (e.g., bupivacaine, ropivacaine, alfentanil, and sufentanil). Transfer across the placenta may be reported as drug clearance or as a ratio referred to as the transfer index (i.e., drug clearance/reference compound clearance). The use of a transfer index allows for interplacental comparisons by accounting for differences between placentas (e.g., lobule sizes). Commonly used reference compounds are either flow limited (e.g., antipyrine, tritiated water) or membrane limited (e.g., creatinine). These studies have enhanced our understanding of the placental transfer of anesthetic drugs (Box 4.1).

Pharmacokinetic Principles
Factors affecting drug transfer across the human placenta include lipid solubility, protein binding, tissue binding, pKₐ, and maternal-fetal delivery.
pH, and blood flow (Table 4.1). High lipid solubility may readily enable cell membrane (lipid bilayer) penetration but may also cause the drug (e.g., sufentanil) to be trapped within the placental tissue. Highly protein-bound drugs are affected by the concentration of maternal and fetal plasma proteins, which varies with gestational age and disease. Some drugs (e.g., diazepam) bind to albumin, whereas others (e.g., sufentanil, cocaine) bind predominantly to α₁-acid glycoprotein (AAG). Although the free, unbound fraction of drug equilibrates across the placenta, the total drug concentration is greatly affected by both the extent of protein binding and the quantity of maternal and fetal proteins; fetal blood typically contains less than one-half the concentration of AAG than maternal blood (Table 4.2). Albumin binds primarily acidic and lipophilic compounds, whereas AAG binds more basic compounds; fetal levels of both albumin and AAG increase from the first trimester to term.

The pKₐ of a drug determines the fraction of drug that is non-ionized at physiologic pH. Thus, fetal acidemia greatly enhances the maternal-fetal transfer (i.e., “ion trapping”) of many basic drugs, such as local anesthetics and opioids (Fig. 4.6) (see Chapter 13). Most anesthetic drugs are passively transferred, with the rate of blood flow (hence drug delivery) affecting the amount of drug that crosses the placenta. One of the authors (M.I.Z.) has used the in vitro perfused human placenta model to perform a number of studies of the placental transfer of opioids (Table 4.3).

**Inhalation Anesthetic Agents**

The lipid solubility and low molecular weight of inhalation anesthetic agents facilitate rapid transfer across the placenta. A prolonged induction-to-delivery interval results in greater transfer of inhalation anesthetic agents across the placenta. Isoflurane distributes rapidly across the placenta during cesarean delivery, resulting in an F/M ratio of approximately 0.71. Sevoflurane has an F/M ratio of 0.38 and causes dose-dependent vasodilation of placental vessels that is not mediated by nitric oxide. There are no published data regarding the placental transfer of desflurane.

Nitrous oxide also rapidly crosses the placenta, with an F/M ratio of 0.83 within 3 minutes. Maternal administration of nitrous oxide decreases fetal central vascular resistance by 30%, and a prolonged induction to delivery interval may cause neonatal depression. Diffusion hypoxia may occur during the rapid elimination of nitrous oxide from the neonate; assessment of oxygenation for any neonate exposed to nitrous oxide immediately before delivery appears prudent.

Following nitrous oxide exposure, patients homozygous for polymorphisms (1298>A>C and 677>C>T) in the methylenehydrofolate reductase gene (MTHFR) have increases in plasma homocysteine levels of up to 76%. Moreover, these genetic polymorphisms can significantly augment the inactivation of methionine synthase; a 1-hour exposure to 50% nitrous oxide can result in an 82% reduction in fetal methionine synthase activity, and a 2-hour exposure can result in epigenetic modifications and decreases in brain-derived neurotrophic factor. Whether fetal exposure to nitrous oxide contributes to adverse effects as a result of inactivation of methionine synthase is not known.

**Induction Agents**

The lipophilic characteristics that make anesthetic agents ideal for the induction of anesthesia (i.e., ability to cross the blood-brain barrier) also enhance their transfer across the placenta.

**Propofol**

A 2- to 2.5-mg/kg bolus dose of propofol, the most widely used induction agent for general anesthesia, results in a
CHAPTER 4  The Placenta: Anatomy, Physiology, and Transfer of Drugs

**TABLE 4.1  Factors Affecting Placental Transfer of Drug (Maternal to Fetal)**

<table>
<thead>
<tr>
<th>Size: molecular weight (Da)</th>
<th>Increased Transfer</th>
<th>Decreased Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>&lt; 1000</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>Charge of molecule</td>
<td>Uncharged</td>
<td>Charged</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>Lipophilic</td>
<td>Hydrophilic</td>
</tr>
<tr>
<td>pH versus drug pKₐ</td>
<td>Higher proportion of un-ionized drug in maternal plasma</td>
<td>Higher proportion of ionized drug in maternal plasma</td>
</tr>
<tr>
<td>Placental efflux transporterb proteins (e.g., P-glycoprotein)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Binding protein type</td>
<td>Albumin (lower binding affinity)</td>
<td>α₁-Acid glycoprotein (AAG) (higher binding affinity)</td>
</tr>
<tr>
<td>Free (unbound) drug fraction</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Da, dalton.

*The pH relative to the pKₐ determines the amount of drug that is ionized and un-ionized in both maternal and fetal plasma. Fetal acidemia enhances the maternal-to-fetal transfer (i.e., “ion trapping”) of basic drugs such as local anesthetics and opioids.

**TABLE 4.2  Concentrations of Proteins That Bind Drugs**

<table>
<thead>
<tr>
<th></th>
<th>Maternal</th>
<th>Umbilical Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>33.1 g/L</td>
<td>37.1 g/L</td>
</tr>
<tr>
<td>α₁-Acid glycoprotein (AAG)</td>
<td>0.77 g/L</td>
<td>0.26 g/L</td>
</tr>
</tbody>
</table>

*P < .05.


**Fig. 4.6** The effects of changes in fetal pH on the transfer of opioids during in vitro perfusion of the human placenta. This figure demonstrates the “ion trapping” of opioids, which is similar to that of local anesthetics. Clearance index = clearance drug/clearance creatinine (a reference compound). (Modified from Zakowski MI, Krishna R, Grant GJ, Turndorf H. Effect of pH on transfer of narcotics in human placenta during in vitro perfusion. Anesthesiology. 1995;85:A890.)

**TABLE 4.3  Opioid Transfer during in vitro Perfusion of the Human Placenta**

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Meperidine</th>
<th>Alfentanil</th>
<th>Fentanyl</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid solubility</td>
<td>1.4</td>
<td>39</td>
<td>129</td>
<td>816</td>
<td>1727</td>
</tr>
<tr>
<td>Percent non-ionized at pH 7.4</td>
<td>23%</td>
<td>7.4%</td>
<td>89%</td>
<td>8.5%</td>
<td>20%</td>
</tr>
<tr>
<td>Percent protein binding</td>
<td>30%</td>
<td>70%</td>
<td>93%</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>Placenta drug ratio</td>
<td>0.1</td>
<td>0.7</td>
<td>0.53</td>
<td>3.4</td>
<td>7.2</td>
</tr>
<tr>
<td>F/M ratio, MTF</td>
<td>0.08</td>
<td>0.27</td>
<td>0.22</td>
<td>0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>F/M ratio, FTM</td>
<td>0.08</td>
<td>0.13</td>
<td>0.11</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Minutes to steady state</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>40–60</td>
<td>40–60</td>
</tr>
<tr>
<td>Clearance index, MTF</td>
<td>0.4</td>
<td>0.95</td>
<td>0.75</td>
<td>0.76</td>
<td>0.41</td>
</tr>
<tr>
<td>Clearance index, FTM</td>
<td>0.5</td>
<td>0.91</td>
<td>0.78</td>
<td>0.61</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Clearance index, Clearance drug/clearance antipyrine (a flow-limited reference compound); FTM, fetal-to-maternal (direction); MTF, maternal-to-fetal (direction); placenta drug ratio, placenta drug concentration/g placental tissue/maternal drug concentration.

Data from nonrecirculated experiments, using perfusate Media 199 without protein, with maternal flow 12 mL/min and fetal flow 6 mL/min. 60,61,97,100,104
mean F/M ratio between 0.65 and 0.85. A bolus dose of 2 mg/kg followed by a continuous infusion of 6 mg/kg/h or 9 mg/kg/h of propofol resulted in mean F/M ratios of 0.50 and 0.54, respectively. These F/M ratios are similar to those found when propofol is given in early gestation (at 12 to 18 weeks). Propofol may have sedative effects on the neonate; in a randomized trial of propofol compared with thiopental for the induction of anesthesia for elective cesarean delivery, the maternal administration of propofol (2.8 mg/kg) resulted in lower 1- and 5-minute Apgar scores than thiopental (5 mg/kg). Plasma levels of propofol in the neonate depend on the maternal dose and the time elapsed between drug administration and delivery of the neonate. Maternal propofol administration (2 mg/kg) within 10 minutes of delivery resulted in a mean umbilical vein propofol concentration of 0.32 μg/mL.

Several factors that affect propofol transfer have been investigated with in vitro human placental perfusion models. Increased maternal blood flow and reduced protein binding increase both placental tissue uptake and transplacental transfer of propofol. Propofol is highly protein-bound to albumin. Thus, altered albumin concentrations in the mother or fetus will affect transplacental transfer and the total, but not free, concentration in the umbilical vein. Propofol causes calcium channel-dependent vasodilation of human placental vessels in vitro.

**Ketamine**

Ketamine, a phencyclidine derivative, rapidly crosses the placenta. Ketamine 2 mg/kg reached a mean F/M ratio of 1.26 in as little as 97 seconds when administered to the mother for vaginal delivery. In a sheep study, fetal concentration was 25% less than maternal concentration at 10 minutes.

**Etidomidate**

Etidomidate, a carboxylated imidazole, has long been used for the induction of general anesthesia. A dose of 0.3 to 0.4 mg/kg administered for cesarean delivery resulted in an F/M ratio of approximately 0.5.

**Barbiturates**

A short-acting agent, thiopental quickly appears in UV blood after maternal injection, with a mean F/M ratio of 1.1. The rapid transfer of the oxybarbiturate methohexital into the fetal circulation, with simultaneous peak concentrations in maternal blood and fetal blood, has been demonstrated by in vivo studies. Human in vitro placental perfusion studies with an equal concentration of albumin in the maternal and fetal perfusates confirm that methohexital rapidly crosses the placenta in both maternal-to-fetal and fetal-to-maternal directions, with transfer indices of less than 0.5 at 30 minutes.

**Dexmedetomidine**

In humans, dexmedetomidine, an α₂-adrenergic agonist, has an F/M ratio of 0.12, with evidence of significant placental tissue binding caused by high lipophilicity.

**Benzodiazepines**

Highly un-ionized, lipophilic, and 95% protein-bound diazepam has an F/M ratio of 1 within minutes of maternal administration and a ratio of 2 at 60 minutes. Less lipophilic, lorazepam requires almost 3 hours after administration for the F/M ratio to reach unity. Midazolam is more polar, with an F/M ratio of 0.76 at 20 minutes after administration. The F/M ratio of midazolam, unlike that of other benzodiazepines, decreases rapidly; by 200 minutes it is only 0.3.

**Opioids**

All opioids cross the placenta and can cause neonatal central nervous system and respiratory depression. The extent of placental transfer and duration of effects on the fetal and neonate depend on individual drug characteristics.

Historically, meperidine was often administered to mothers for systemic analgesia during labor (see Chapter 22). Intravenous maternal administration results in rapid transfer across the human placenta within 90 seconds. F/M ratios for meperidine may exceed 1.0 after 2 to 3 hours; maternal levels fall more rapidly because of greater metabolism of the drug. This same time interval is associated with the greatest likelihood of neonatal depression, caused by the active drug metabolite normeperidine. Human placental perfusion studies in vitro demonstrated rapid placental transfer in both maternal-to-fetal and fetal-to-maternal directions with equal clearance profiles, minimal placental tissue binding, and no placental drug metabolism. As maternal levels fall, the meperidine and normeperidine will transfer from the fetus back to the mother, correlating with the clinically observed decrease in neonatal sedation when delivery occurs more than 4 hours after maternal administration.

Morphine rapidly crosses the placenta with a mean F/M ratio of 0.61 and mean UV concentration of 25 ng/mL, resulting in a significant reduction in the biophysical profile score (primarily decreased fetal breathing and fewer fetal heart rate accelerations) within 20 minutes of maternal administration. Intrathecal morphine results in a high F/M ratio of 0.92, although the absolute fetal concentrations are less than those associated with clinically significant fetal and neonatal side effects. Human placental perfusion studies in vitro show that hydrophilic morphine exhibits membrane-limited transfer with a low placental tissue content and a fast washout.

Fentanyl and its analogues have high lipophilicity and albumin binding (74%). Epidural administration results in an F/M ratio between 0.37 and 0.57. During early pregnancy, fentanyl is rapidly transferred and may be detected in the placenta and fetal brain. Perfusion of the human placenta in vitro results in rapid bidirectional transfer, with the placenta acting as a moderate drug depot.

Alfentanil has a low F/M ratio of 0.30, yet when given for induction of anesthesia results in a reduction of 1-minute Apgar scores. Perfusion of the human placenta in vitro shows rapid and symmetric maternal-fetal and fetal-maternal transfers of alfentanil, with low placental drug uptake and rapid washout.
Compared with fentanyl, sufentanil has a higher F/M ratio, 0.81. Higher lipid solubility and more rapid uptake by the central nervous system result in reduced vascular absorption from the epidural space, corresponding with less fetal exposure and risk for neonatal respiratory depression than fentanyl.\textsuperscript{105} Human placental perfusion studies \textit{in vitro} have confirmed the rapid transplacental transfer of sufentanil, which is influenced by differences in maternal and fetal plasma protein binding and fetal \(pH\). High placental tissue uptake suggests that the placenta serves as a drug depot.\textsuperscript{61}

\textbf{Remifentanil} undergoes rapid placental transfer. During cesarean delivery, average F/M ratios were 0.88 when remifentanil was administered by intravenous infusion (0.1 \(\mu\)g/kg/min) during epidural anesthesia\textsuperscript{106} and 0.73 when it was given as a bolus (1 \(\mu\)g/kg) at induction of general anesthesia.\textsuperscript{107} Excessive maternal sedation without adverse neonatal effects can occur during labor; the rapid metabolism of remifentanil by nonspecific esterases (context-sensitive half-time of 3 minutes) results in minimal fetal exposure. Remifentanil used for patient-controlled analgesia during labor, with bolus doses of 0.5 \(\mu\)g/kg, resulted in an F/M ratio of approximately 0.5 and a 20\% incidence of fetal heart rate changes.\textsuperscript{108} Infusion of remifentanil during cesarean delivery for 7 and 18 minutes resulted in F/M ratios of 0.63 and 0.65, respectively.\textsuperscript{109} Continuous intravenous infusion compared with patient-controlled intravenous labor analgesia using remifentanil resulted in F/M ratios of 0.74 and 0.70, respectively.\textsuperscript{109}

The systemic administration of an opioid agonist/antagonist for labor analgesia has been associated with few maternal, fetal, and neonatal side effects. Both butorphanol and nalbuphine rapidly cross the placenta, with mean F/M ratios of 0.84 and 0.74 to 0.97, respectively.\textsuperscript{111,112} Nalbuphine resulted in “flattening” of the fetal heart rate tracing in 54\% of cases. Buprenorphone, a lipopholic opioid agonist/antagonist used to treat opioid use disorder, has lower placental transfer, but greater placental uptake and metabolism, yielding an F/M ratio of 0.1.\textsuperscript{112}

\textbf{Nonopioid Analgesics}

Acetaminophen freely crosses the placenta. The fetal liver is a major source of hematopoietic stem cells, and concern has been expressed regarding acetaminophen fetal liver toxicity impairing fetal immune development. In a mouse model, placental function, fetal development, and immune ontogeny were significantly impaired at doses mimicking plasma levels associated with multiple doses in humans.\textsuperscript{113}

\textbf{Local Anesthetics}

Local anesthetic agents readily cross the placenta (see Chapter 13).

\textbf{Muscle Relaxants}

As fully ionized, quaternary ammonium salts, muscle relaxants do not readily cross the placenta; however, single doses of muscle relaxants can result in detectable fetal blood concentrations. Maternal administration of muscle relaxants for the induction of general anesthesia for cesarean delivery rarely affects neonatal muscle tone at delivery.

\textbf{Succinylcholine} is not detectable in UV blood at delivery after maternal doses less than 300 mg.\textsuperscript{114} Neonatal neuromuscular blockade can occur when high doses are given repeatedly or when both the parturient and fetus are homozygous for atypical pseudocholinesterase deficiency.\textsuperscript{115}

Nondepolarizing muscle relaxants have low F/M ratios: pancuronium (0.2),\textsuperscript{116} vecuronium (0.06 to 0.11),\textsuperscript{116,117} rocuronium (0.16),\textsuperscript{118} and atracurium (0.07).\textsuperscript{119} The F/M ratio of vecuronium nearly doubled as the induction-to-delivery interval increased from 180 to 420 seconds.\textsuperscript{117} No published study has investigated the placental transfer of the atracurium isomer cisatracurium. However, laudanosine, a metabolite of atracurium and cisatracurium, has an F/M ratio of 0.14.\textsuperscript{120} Although nondepolarizing muscle relaxant transfer rates are low, the fetal blood concentrations increase over time.\textsuperscript{117}

\textbf{Anticholinergic Agents}

The placental transfer of anticholinergic agents correlates with their ability to cross the blood-brain barrier. Atropine is detected in the umbilical circulation within 1 to 2 minutes of maternal administration, and an F/M ratio of 0.93 is attained at 5 minutes.\textsuperscript{121} Scopolamine also crosses the placenta easily; intramuscular administration results in an F/M ratio of 1.0 within 55 minutes.\textsuperscript{122} By contrast, after intramuscular administration glycopyrrolate is poorly transferred across the placenta, with a mean F/M ratio of 0.22.\textsuperscript{123} Maternal intravenous administration of glycopyrrolate does not result in a detectable fetal hemodynamic response, whereas atropine and scopolamine may directly increase fetal heart rate.

\textbf{Anticholinesterase Agents}

Neostigmine, pyridostigmine, and edrophonium are quaternary ammonium compounds that are ionized at physiologic \(pH\) and consequently undergo limited transplacental transfer.\textsuperscript{124} Maternal administration of neostigmine does not reverse atropine-induced fetal tachycardia. However, small amounts of these agents do cross the placenta, and fetal bradycardia after maternal administration of neostigmine and glycopyrrolate has been reported.\textsuperscript{125} Neostigmine may cross the placenta to a greater extent than glycopyrrolate; therefore, the combination of neostigmine and atropine should be considered for the reversal of nondepolarizing muscle relaxants in pregnant patients.\textsuperscript{125} Physostigmine crossed the placenta in 9 minutes and reversed the fetal heart rate effect of scopolamine.\textsuperscript{126}

\textbf{Sugammadex}

Sugammadex, which directly binds and reverses the neuromuscular blockade of steroidal muscle relaxants, has low placental transfer rates because of its molecular structure and high molecular weight.\textsuperscript{127}

\textbf{Antihypertensive Agents}

Beta-adrenergic receptor antagonists have been commonly used as antihypertensive agents in pregnancy, despite early
investigations noting an association with fetal growth restriction and neonatal bradycardia, hypoglycemia, and respiratory depression. Although a single dose of propranolol administered 3 hours before cesarean delivery has a F/M ratio of 0.26, long-term administration during pregnancy results in F/M ratios greater than 1.0. Maternal administration of atenolol and metoprolol leads to mean F/M ratios of 0.94 and 1.0, respectively. Labetalol, the most commonly used antihypertensive agent during pregnancy, particularly for women with preeclampsia, has a low F/M ratio of 0.38 with long-term oral administration, despite reports of mild neonatal bradycardia. Beta-adrenergic receptor antagonist use during pregnancy, including labetalol, approximately doubles the risks for small-for-gestational-age, preterm births, and perinatal mortality even after adjusting for preeclampsia. Preterm hypertensive women receiving labetalol had no acute change in umbilical or fetal middle cerebral resistance indices of flow.

The ultra-short-acting beta-adrenergic receptor antagonist esmolol has a mean F/M ratio of 0.2 in gravid ewes. However, fetal bradycardia requiring emergency cesarean delivery has been reported after its use to treat maternal tachydysrhythmia.

Clonidine and methyldopa act through the central stimulation of alpha-1-adrenergic receptors; studies have reported mean F/M ratios of 0.89 and 1.17, respectively. Therapeutic magnesium and nifedipine serum concentrations, but not clonidine, produce fetal vasodilation in human placental perfusion studies in vitro. Phenoxybenzamine, an alpha-adrenergic receptor antagonist, has an F/M ratio of 1.6 with long-term maternal administration.

Direct-acting vasodilators are used for short-term management of severe hypertension in pregnant women. With an F/M ratio of 1.0, hydralazine increases the umbilical artery resistance index, indicating vasodilation, in hypertensive women, and causes fetal vasodilation in in vitro studies.

Sodium nitroprusside is lipid soluble, rapidly crosses the placenta, and can produce cyanide as a byproduct. Sodium thiosulfate, the agent used to treat cyanide toxicity, does not cross the placenta in gravid ewes; however, it can be used to treat fetal cyanide toxicity by lowering maternal cyanide levels, thereby enhancing fetal-maternal transfer.

Nitroglycerin crosses the placenta to a limited extent, with an F/M ratio of 0.18, and results in minimal changes in fetal umbilical blood flow, blood pressure, heart rate, and blood gas measurements in gravid ewes. However, dinitrate metabolites found in both maternal and fetal venous blood indicate the capacity for placental biotransformation. Indeed, placental tissue production of nitric oxide enhances the uterine relaxation caused by nitroglycerin in vitro. In one in vitro study, in which prostaglandin F2α induced fetal vasoconstriction, the following order of nitrovasodilator compound potency was observed: nitroglycerin ≥ sodium nitroprusside ≥ sodium nitrite (NaNO₂) ≥ S-nitroso-N-acetylpenicillamine (SNAP) = S-nitroso-N-glutathione (SNG). SNG and NaNO₂ were significantly more potent under conditions of low oxygen tension. The antioxidants cysteine, glutathione, and superoxide dismutase significantly enhanced the vasodilatory effects of NaNO₂ only.

Placental transfer of angiotensin-converting enzyme inhibitors may adversely affect fetal renal function. Enalaprilat rapidly crosses the placenta, and its maternal administration in high doses resulted in a 20% reduction in fetal arterial pressure in rhesus monkeys.

Vasopressor Agents

Vasopressor agents are often administered to prevent or treat hypotension during the administration of neuraxial anesthesia in obstetric patients. Ephedrine readily crosses the placenta and results in an F/M ratio of 0.7. In an in vitro human perfusion model that required supraphysiologic doses to obtain any effect, phenylephrine increased placental arterial pressure, but less so than ephedrine, whereas epinephrine, norepinephrine, and methoxamine had no effect.

Ephedrine possesses 10 times greater lipid solubility than phenylephrine, with F/M ratios of 1.1 versus 0.17, respectively, in humans. When administered during spinal anesthesia for cesarean delivery, ephedrine demonstrated lower pH and base excess, higher Pco₂, and higher glucose, lactate, epinephrine, and norepinephrine concentrations in umbilical arterial blood than phenylephrine. These differences may be caused by the beta-adrenergic agonist effects of ephedrine in the fetus.

Cocaine, a common drug of abuse during pregnancy (see Chapter 53), has potent vasoconstrictor activity. Human placenta perfusion studies in vitro demonstrated rapid bidirectional transfer of cocaine, over a wide range of concentrations. The active cocaine metabolites norcocaine and cocaethylene, but not the inactive metabolite benzoylecgonine, are also rapidly transferred. Chronic maternal exposure to cocaine increases fetal concentrations; however, they remain lower than peak maternal levels.

Several experiments have demonstrated the complexity of the placental and fetal effects of vasoconstrictor administration. Increasing fetal placental perfusion pressure with vasoconstrictors can cause a shift of fluid from the fetus to the maternal circulation. In an in vitro experiment comparing the responses of placental and umbilical vessels, placental vessels responded to angiotensin II but not phenylephrine, whereas the opposite was observed with umbilical vessels. The response of placental vessels to angiotensin II from women with preeclampsia was diminished compared with vessels from women without preeclampsia; these findings suggest that angiotensin II may serve to maintain vascular tone in the healthy placenta. Infusion of placental growth factor (PlGF) enhanced endothelial nitric oxide-cGMP vascular relaxation and decreased vasoconstriction-induced hypertension in pregnant rats.

Anticoagulants

Anticoagulation therapy is often necessary during pregnancy. Maternal administration of warfarin in the first trimester...
results in placental transfer to the fetus, causing a higher rate of fetal loss and congenital anomalies.\(^{160}\) After the first trimester, warfarin may be used in the setting of stroke or mechanical heart valves.\(^{161}\) In contrast, heparin does not appear to cross the placenta, as measured by neonatal coagulation studies and the measurement of radiolabeled heparin in fetal lambs.\(^{162}\) Low-molecular-weight heparin appears to have limited placental transfer. Maternal administration of enoxaparin does not alter fetal anti-IIa or anti-Xa activity,\(^{163}\) and in vitro studies found no placental transfer of enoxaparin and fondaparinux (a pentasaccharide that selectively inhibits factor Xa). In contrast, apixaban exhibited rapid transfer (F/M 0.77) in an ex-vivo human placenta cotyledon model.\(^{164}\) and rivaroxaban also rapidly crossed the placenta.\(^{165}\) Several case reports discussed use of direct thrombin inhibitors as early as 9 weeks’ gestation with successful delivery of healthy neonates.\(^{166,167}\) Antiplatelet therapy (e.g., aspirin, clopidogrel) has been used successfully in the first trimester in dual therapy for coronary artery disease in the setting of drug-eluting stents.\(^{168}\) Abciximab, a glycoprotein IIb/IIIa platelet inhibitor, did not transfer across the in vitro perfused human placenta, but did bind to the trophoblastic layer of the placenta.\(^{169}\) Dabigatran, a reversible thrombin inhibitor, crosses the placenta with an F/M ratio of 0.33 at 3 hours.\(^{170}\)

**Drug Delivery Systems**

New drug delivery systems may influence drug transfer and distribution across the human placenta. Liposome encapsulation, depending on the type and ionic charge, can affect placental transfer; anionic and neutral liposomes increase placental transfer, whereas cationic liposomes decrease placental transfer and placental tissue uptake.\(^{171}\) Liposome encapsulation of valproic acid significantly reduces drug transfer and placental uptake.\(^{172}\)

The increased use of nanoparticles creates concern for maternal and fetal exposure. The size, charge, and physiochemical properties of nanoparticles influence placental absorption and transport. The polystyrene particles associated with these compounds have accumulated in the syncytiotrophoblast, presumably via an energy-dependent transport mechanism.\(^{173}\) Nanoparticles 20 to 40 nm in diameter have induced trophoblast cell apoptosis; nanoparticles up to 500 nm in diameter can be measured in various fetal tissues 4 hours after administration to pregnant mice.\(^{174}\)

**Disease States**

Disease states, such as diabetes, may affect the placental transfer of drugs. Glyburide, a second-generation sulfonylurea, is partially dependent on a P-glycoprotein active transport mechanism and demonstrates a lower F/M ratio (0.3) than the first-generation agents, even in the presence of a P-glycoprotein inhibitor.\(^{175}\) A high level of protein binding (99.8%) may also contribute to the low transplacental transfer of glyburide; when protein levels are reduced in vitro, higher transfer rates are observed.\(^{176}\) The thickened placenta found in diabetic patients may cause low transfer rates; however, no difference in maternal-fetal transfer of metformin has been observed between placentas from parturients with gestational diabetes and those from healthy parturients.\(^{177}\)

Gestational age may alter placental transfer, although the direction of the alteration requires further evaluation. Although traditional belief holds that placentas from younger fetuses are more likely to transfer substances, one study has demonstrated that methadone transfer is 30% lower in human preterm placentas than in term placentas.\(^{178}\) Dexamethasone and betamethasone, corticosteroids that are often administered to accelerate fetal lung maturity, increase ABCB1 gene expression fourfold. ABCB1 is an efflux transporter protein; hence increased gene expression may increase fetal-maternal transfer of substrate molecules.\(^{179}\)

Oxidative stress increases in preeclampsia, fetal growth restriction, and diabetes. The placenta does not have protective mechanisms to counteract oxidative stress, which damages the ability of syncytiotrophoblast mitochondria to generate energy.\(^{180}\) Oxidative stress also alters nutrient transport because of increased membrane permeability and an inability to accumulate glucose.\(^{181}\)

Nitrate stress, the covalent modification of proteins and DNA by peroxynitrite (formed by nitric oxide reacting with superoxide), may also affect maternal-fetal transfer.\(^{182}\) Peroxynitrite reacts with tyrosine to form nitro-tyrosine, a negatively charged group, which may mimic phosphorylation. Nitration may result in loss or gain of protein function.

Chronic maternal stress increases maternal and fetal norepinephrine levels; transfer of maternal norepinephrine to the fetus may be limited by a reduction in the placental norepinephrine transporter (NET).\(^{183}\) In the setting of preeclampsia, placental expression of NET is low, which may cause decreased trophoblast cell invasion during placental development.\(^{184}\) By contrast, NET expression is increased when norepinephrine levels are reduced with metformin.\(^{185}\)

Pravastatin may be protective of the endothelial layer of the placenta through proangiogenic, anti-inflammatory, antioxidative, and antithrombotic effects. Ex-vivo human studies did not demonstrate placental transfer; however, under hypoxic conditions pravastatin did decrease sFlt-1.\(^{186}\)

Vitamin D helps modulate cytokines, inflammation, and insulin sensitivity, and a deficiency leads to increased risk for gestational diabetes, preeclampsia, and preterm delivery.\(^{187}\)

**Infection and Inflammation**

Infections can alter placental perfusion, function, and transfer of medications. Viruses and bacteria may infect the placenta or uterine decidua by ascending from the reproductive tract or through the maternal bloodstream (see Chapter 36). Some viruses are infectious at a specific gestational age range because different cell types variably express surface receptors/proteins that viruses use as entry points into the cell.\(^{188}\) Even in the absence of direct placental or fetal infection, placental function and neonatal outcomes may be altered in the presence of viruses.\(^{189}\) Infections early in pregnancy may alter the invasive extravillous trophoblast, resulting in pregnancy complications.
related to decreased placental perfusion (e.g., fetal growth restriction, preeclampsia). Viruses producing placental and/or fetal alterations include cytomegalovirus, varicella, measles, herpes simplex viruses 1 and 2, and the Zika and Lassa viruses.

Zika virus, transmitted via Aedes mosquitoes or sexual transmission, may produce placental alterations, fetal damage, and microcephaly. The virus uses cell surface proteins such as glycoprotein T1M1 (expressed during mid- to late gestation by the syncytiotrophoblast and Hofbauer cells) and the TAM kinase receptors to invade the cell; HSV-2 co-infection can enhance expression of TAM receptors. Zika virus infection induces apoptosis of trophoblasts in the first trimester, and produces enlarged, hydropic chorionic villi, immature villi, and proliferation of Hofbauer cells (fetal macrophages), but no villous necrosis.189

Maternal inflammation can also affect placental function and result in increased risk for neurodevelopmental disorders later in life for offspring. In mid- to late pregnancy, maternal inflammation results in up-regulation of tryptophan hydroxylase-1 (TPH1), which causes a sustained increase in fetal 5-hydroxytryptamine (serotonin) in the fetal forebrain.190 Because serotonin modulates key neurodevelopmental processes, including axon development, prenatal inflammation may lead to increased anxiety and depression in the offspring.

The placenta may be involved in sterile inflammation and the development of gestational vascular disease.39 Placental inflammation alters drug transfer by increasing the ATP-binding cassette transporters, multidrug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP).39 Perinatal inflammation may be associated with poorer neurodevelopmental outcomes after birth191; N-acetylcysteine (NAC) has been used for neuroprotection during chorioamnionitis in humans,192 with preservation of fetal cerebrovascular coupling, and lipopolysaccharide-induced neonatal brain injury in rats.193

### PLACENTAL PATHOLOGY

There has been a growing interest in the clinicopathologic correlation between placental abnormalities and adverse obstetric outcomes. In some cases, a skilled and systematic examination of the umbilical cord, fetal membranes, and placenta may provide insight into antepartum pathophysiology; in most of these cases, examination of the placenta confirms the clinical diagnosis (e.g., chorioamnionitis). Drugs, inflammation, and infection may produce placental abnormalities (e.g., cocaine causes chorionic villus hemorrhage and villous edema).194 The significance of many findings (e.g., villous edema, hemorrhagic endovasculitis, chronic villitis), however, is unclear.

### KEY POINTS

- The placenta is a dynamic organ with a complex structure. It brings two circulations close together for the exchange of blood gases, nutrients, and other substances (e.g., drugs).
- During pregnancy, anatomic adaptations result in substantial (near-maximal) vasodilation of the uterine spiral arteries; this leads to a low-resistance pathway for the delivery of blood to the placenta. Therefore, adequate uteroplacental blood flow depends on the maintenance of a normal maternal perfusion pressure.
- Placental transfer involves all of the physiologic transport mechanisms that exist in other organ systems.
- Physical factors (e.g., molecular weight, lipid solubility, degree of ionization) affect the placental transfer of drugs and other substances. In addition, other factors affect maternal-fetal exchange, including changes in maternal and fetal blood flow, placental binding, placental metabolism, diffusion capacity, and extent of maternal and fetal plasma protein binding.
- Lipophilicity, which enhances the central nervous system uptake of general anesthetic agents, also heightens the transfer of these drugs across the placenta. However, the placenta itself may take up highly lipophilic drugs, thereby creating a placental drug depot that limits the initial transfer of drug.
- Fetal acidemia can result in the “ion trapping” of both local anesthetics and opioids.
- Vasoactive drugs cross the placenta, may affect the fetal circulation, and may have effects on fetal metabolism.
- Inflammation and infection may affect placental function and transport across the placenta.
- Environmental factors influence epigenetic expression of genes, placental development, and fetal phenotypes.

### REFERENCES


Fetal life in utero differs significantly from postnatal life. The fetus relies completely on the mother and the placenta for basic metabolic needs such as nutrient delivery, gas exchange, acid-base balance, and electrolyte homeostasis. During gestation, the fetus gradually assumes the responsibility for many of the vital physiologic functions that must be assumed after the abrupt transition to physiologic independence at birth. Knowledge of fetal physiology, and the timing associated with these developmental changes, is necessary for the optimal provision of analgesia and anesthesia during pregnancy and childbirth.

FETAL ENVIRONMENT

Amniotic Fluid

The fetus is surrounded by amniotic fluid, a complex fluid that changes as the pregnancy progresses. Amniotic fluid serves a number of vital roles, including the facilitation of fetal growth, the provision of a microgravity environment that cushions the fetus, and the generation of a defense mechanism against invading microbes. The formation and maintenance of amniotic fluid is an intricate process that depends on fetal maturation and maternal hydration, hormonal status, and uteroplacental perfusion.

Amniotic fluid during early embryogenesis is principally derived from maternal plasma by the passage of water and solutes through aquaporin water channels expressed in the fetal maternal membranes (amnion and chorion). The expression of aquaporins changes as gestation advances and with certain pathologic states, such as polyhydramnios. Between 10 and 20 weeks’ gestation, the volume of amniotic fluid increases in a predictable and linear manner from approximately 25 mL to 400 mL. During this period, the composition of amniotic fluid is similar to fetal extracellular fluid, owing to the absence of keratin in the fetal skin. After this period, the volume of amniotic fluid is a function of production, from fetal urine (600 to 1200 mL/day near term) and respiratory tract secretions (60 to 100 mL/kg fetal body weight/day), and removal through fetal swallowing (200 to 250 mL/kg fetal body weight/day). Amniotic fluid volume is also influenced by intramembranous (between amniotic fluid and fetal blood within the placenta) and transmembranous (between amniotic fluid and maternal blood within the uterus) pathways in both physiologic and pathophysiologic states. Finally, the status of maternal hydration and the amount of decidual prolactin may alter the transfer of amniotic fluid through fetal and maternal tissues. Amniotic fluid volume plateaus at 800 mL at around 28 weeks’ gestation, after which it declines to approximately 400 mL at term.

The composition of amniotic fluid undergoes more marked variation than its volume. During the first trimester, amniotic fluid consists mostly of water and electrolytes and contains minimal protein. Keratinization of the fetal skin is complete by 25 weeks’ gestation and decreases the permeability of fetal tissues to water and solutes. The impact of this process, coupled with the ability of the fetal kidneys to
produce urine, results in increased amniotic fluid concentra-
tions of urea and creatinine, decreased concentrations of
sodium and chloride, and reduced osmolality. By term, the
osmolality of amniotic fluid is about 85% to 90% that of
maternal serum. A variety of carbohydrates, proteins, lipids,
electrolytes, enzymes, and hormones, which vary in concen-
tration depending on the gestational age, are also present;
some of these elements, particularly the amino acids taurine,
glutamine, and arginine, serve a nutritive function for mitotic
cells involved in trophoblastic growth and placental angio-
genesis. An abundance of growth factors are found in amni-
otic fluid, including epidermal growth factor, transforming
growth factor-alpha, transforming growth factor-beta 1,
inulin-like growth factor-1, erythropoietin, and granulocyte
colony-stimulating factor; many of these growth factors play
an important role in fetal intestinal development.

Antimicrobial defenses within the amniotic fluid are pri-
arily composed of humoral mediators such as alpha-
defensins, which are released from neutrophils, especially in
the setting of preterm labor and/or chorioamnionitis. Other
humoral mediators include lactoferrin, calprotectin, leuko-
cyte protease inhibitor, and cathelicidin, which have signif-
icient activity against bacteria, viruses, and fungi. Cellular
mediators of the immune response are poorly characterized
in amniotic fluid, and it remains unclear if the macrophages
that are present serve a scavenging or an antimicrobial role.
Neutrophils are usually absent from the amniotic fluid of a
healthy fetus, and their presence typically signifies an inflam-
atory or infectious process.

Biochemical and cellular analyses of amniotic fluid provide
valuable information on chromosomal abnormalities, neural
tube defects, prenatal infections, and most inborn errors of
metabolism. Several amniotic fluid–based indices, includ-
ing the lecithin-phosphatidylglycerol ratio, the phosphatidylglycerol
level, lamellar body count, surfactant-to-albumin ratio, and
electrical conductivity, are commonly used to assess fetal lung
maturity. Bilirubin levels can be determined by measuring the
optical density of amniotic fluid, which assists in the
monitoring of fetal hemolysis. Estimation of the amniotic
fluid levels of S100-beta (a protein released from injured
astrocytes) and cell-free fetal nucleic acids may serve as early
screening tests for perinatal neurologic damage and fetal
development, respectively. Finally, amniotic fluid is a valu-
able reservoir for cell types of multiple lineages at different
maturational ages; approximately 1% of these cells are plu-
ripotent, thereby representing a novel source of stem cells.

**Oxygen Supply and Transport**

The fetus has almost no oxygen reserve and depends on
maternal sources of oxygen delivery. Acute hypoxia can have
immediate, severe consequences, such as perinatal death,
hypoxic encephalopathy, and cerebral palsy. Chronic reduc-
tions of oxygen supply often lead to fetal growth restriction
and may have long-term consequences for brain, heart, and
kidney function through epigenetic changes. Hypoxia-
inducible factors (HIFs) act on specific signaling pathways
that modify target gene expression. When hypoxia occurs
during critical periods of heart development, apoptosis of
cardiomyocytes can result, leading to a myocardium that is
less resilient to ischemic insults in later life. In addition,
chronic hypoxia can influence fetal development of brain and
kidney function and metabolism, subsequently leading to
problems in adulthood.

Oxygen is an essential substrate for cell survival, because it
serves as the final electron acceptor in the electron transport
chain. When oxygen is scarce, the electron transport chain is
compromised, resulting in decreased oxidative phosphoryla-
tion and adenosine triphosphate (ATP) production. Hypoxia
ensues when the demand for oxygen exceeds the
available supply. In adult tissues, hypoxia occurs at oxygen
tensions < 20 mm Hg (2.7 kPa) (normal, 40 mm Hg
[5.3 kPa]). By contrast, in fetal tissues, hypoxia occurs at
oxygen tensions < 17 mm Hg (2.3 kPa) (normal, 20 to
25 mm Hg [2.7 to 3.3 kPa]). This implies that the environ-
ment for fetal development exhibits a smaller margin of safety
before reaching a state of oxygen insufficiency and highlights
the importance of maintaining adequate uteroplacental per-
fusion and fetal cardiac output to ensure fetal oxygen delivery.
Ultimately, oxygenation of fetal tissues depends principally
on the partial pressure of oxygen gradient between maternal
and fetal blood and the different types of hemoglobin that
exist in maternal and fetal blood.

Placental oxygen concentrations change with gestation. In
early pregnancy, the placental intervillous space is free of
maternal blood cells, thereby requiring the embryo to rely on
endometrial secretions and maternal plasma for its energy
requirements. The first trimester placenta has (1) an
oxygen partial pressure (Po2) of approximately 20 mm Hg
(2.7 kPa); (2) only a few capillaries, which are located mainly
in the center of the mesenchymal core; and (3) a trophoblastic
layer that is twice the thickness of that in the second trimester.
Moreover, the fetal red blood cells are nucleated, and the
exocoelomic cavity contains antioxidant molecules instead of
an oxygen transport system. These anatomic and physiologic
features, which limit the transfer of oxygen and the creation
of free radicals, protect the highly sensitive embryo from the
effects of oxidative stress and keep the embryonic cells in their
pluripotent state. At the end of the first trimester, an expo-
nential increase in fetal growth creates significant demands
for oxygen and nutrients. In response, cytotropho-
blastic cells interact with the smooth muscle of maternal
spiral arteries, resulting in vessel dilation and the provision of
oxygen-rich maternal blood flow to the placenta. The placenta
acts as both a conduit and consumer of oxygen. The placenta is metabolically active and performs
important roles in carbohydrate and amino acid metabolism,
protein synthesis, and substrate transport. Almost 40% of the
oxygen delivered to the pregnant uterus is needed to support
the metabolic processes of the placenta. During periods of
hypoxia, the placenta appears to alter its metabolism to
diminish its consumption of oxygen, most likely by increas-
ing glycolysis. This process can maintain fetal oxygen
supply but, if hypoxia is ongoing, fetal growth restriction
(also known as intrauterine growth restriction) may result.
When the oxygen supply is compromised, the fetus shunts blood flow from peripheral tissues to vital organs (see later discussion), converts to greater use of anaerobic pathways, and induces gene expression that enables improved survival in a low-oxygen environment. The presence of fetal hemoglobin (hemoglobin F), with its higher concentration (approximately 18 g/dL) and greater affinity for oxygen than adult hemoglobin (see later discussion), results in a fetal arterial blood oxygen content that is only marginally lower than that in the adult, despite a lower oxygen tension.

**Glucose and Lactate Metabolism**

Glucose is the primary substrate for energy production in the fetus. Under normal conditions, gluconeogenesis is absent in mammalian fetuses; the only source of glucose is that which is transferred across the placenta. Glucose uptake into fetal tissues is regulated by glucose transporters (GLUT) of which the expression increases or decreases in response to acute and chronic changes in fetal glucose concentration. Fetal glucose concentration is linearly related to maternal concentration over a range of 3 to 5 mmol/L (54 to 90 mg/dL; Fig. 5.3); studies in isolated placentas suggest that this relationship continues up to a glucose concentration of 20 mmol/L (360 mg/dL). The placenta uses the majority of glucose delivered to the uterus for oxidation, glycogen storage, and conversion to lactate, with the remainder being transferred to the umbilical venous blood by facilitated, carrier-mediated diffusion. The amount of glucose supplied to the fetus appears more than adequate during normal conditions; ovine uterine blood flow must be reduced by greater than 50% before a decrease in fetal glucose uptake or fetal arterial glucose concentration is observed.

The umbilical cord blood glucose uptake is approximately 5 mg/kg/min at normal maternal arterial plasma glucose concentrations. Because the umbilical glucose/oxygen quotient varies from approximately 0.5 in sheep to 0.8 in human fetuses during labor, it is assumed that substrates...
other than glucose are used to support fetal oxidative metabolism; it is estimated that lactate and amino acids provide approximately 25% each of the total fetal energy requirements.38,39

Lactate is produced even in well-oxygenated fetal lambs, with total lactate production being approximately 4 mg/kg/min.40 Although the exact origin of fetal lactate is unclear, skeletal muscles and bones have been identified as sources of lactate production under resting conditions. Lactate production increases during episodes of acute hypoxemia, although this response may be blunted in fetuses previously exposed to oxidative stress.41 Lactate consumption occurs in the fetal myocardium and liver.42 Short-term exogenous lactate infusion in fetal lambs (sufficient to lower the pH to 7.20) results in transient fetal bradycardia and increased fetal breathing movements but no other adverse effects.43

Amino Acid and Lipid Metabolism

The fetus uses amino acids for protein synthesis, growth, and oxidation. Most maternal-to-fetal amino acid transfer occurs against a concentration gradient and involves energy-dependent transfer mechanisms. Under conditions in which fetal aerobic metabolism is decreased, amino acid uptake by the placenta and fetus may be reduced because it involves an expenditure of energy. Hypoxia results in a large reduction in nitrogen uptake in fetal lambs.44 During maternal fasting, fetal amino acid uptake does not change; however, enhanced fetal proteolysis may occur, which subsequently results in amino acid oxidation or gluconeogenesis.

Lipid products are transferred from the mother to the fetus. The fetus requires free fatty acids for growth, brain development, and the deposition of body fat for postnatal life. Fatty acids are transferred across the placenta by simple diffusion. Ketones are also transferred by simple diffusion; in humans, the maternal/fetal ketone ratio is approximately 2.0.45 The fetus can use ketones as lipogenic substrates or as energy substrates in the brain, kidney, heart, liver, and placenta.46 Beta-hydroxybutyrate (fatty acid) metabolism can occur in the placenta, brain, and liver during episodes of fetal hypoglycemia that result from maternal fasting.46 Cholesterol synthesis or free cholesterol diffusion does not appear to occur in the placenta.47 However, there is a significant correlation between maternal and fetal concentrations of lipoprotein(a), implying that diffusion of lipoprotein(a) may occur.47

Thermoregulation

Intrauterine fetal temperature largely depends on maternal temperature. However, owing to the high metabolic rate in the fetus, the net flow of heat is from the fetus to the mother. Compared with the mother during the third trimester, the fetus produces approximately twice as much heat (on a weight-adjusted basis) and maintains a temperature 0.5°C higher.48,49 This maternal-fetal difference in temperature remains relatively constant and is referred to as the “heat clamp.”50

The placental circulation is responsible for approximately 85% of the heat exchange between the mother and fetus. The remaining 15% is dissipated through the fetal skin and transferred through the amniotic fluid and the uterine wall to the maternal abdomen.51 As a consequence, fetal temperature may be rapidly affected by changes in umbilical blood flow; fetal temperatures rise quickly on occlusion of umbilical blood flow in both baboons and sheep.52,53 In humans, fetal temperatures increase during uterine contractions, which may be a result of intermittent obstruction of umbilical cord blood flow.54 Whether this rise in fetal temperature contributes to acute hypoxic-ischemic brain damage in the setting of umbilical cord prolapse is currently unknown. However, relatively small increases in temperature increase the sensitivity of the fetal brain to hypoxic injury.55

The fetus generates heat through high metabolic activity, as thermogenic mechanisms are not developed until the end of gestation and thus largely inactive in utero. Newborns are at high risk for rapid heat loss caused by amniotic fluid evaporation and a sudden decrease in ambient temperature.49 Because of their small muscle mass, neonates are incapable of significant heat production through shivering; thus nonshivering thermogenesis plays an important role in maintaining temperature. Nonshivering thermogenesis occurs in brown adipose tissue, which is unique from other adipocytes owing to the significant presence of mitochondria, fat vacuoles, sympathetic innervation, and blood vessels. In the mitochondria of brown adipose tissue, ATP production is uncoupled from the oxidative process, resulting in an increase in heat production and oxygen consumption.56 Nonshivering thermogenesis is inhibited in utero, most likely owing to the presence of adenosine and prostaglandin E2, which have strong anti-lytic actions on brown tissue,57,58 inadequate oxygen levels, and low levels of intrauterine catecholamines and thyroid hormones. The inhibition of nonshivering thermogenesis is believed to be beneficial to the fetus, in that it allows for conservation of oxygen and accumulation of brown adipose tissue.50

![Fig. 5.3](https://example.com/fig53.png) The linear relationship between maternal and fetal blood glucose concentrations during the third trimester. Fetal blood was obtained by percutaneous umbilical cord blood sampling. (From Kalhan SC. Metabolism of glucose and methods of investigation in the fetus and newborn. In Polin RA, Fox WW, eds. Fetal and Neonatal Physiology. Vol I. Philadelphia, PA: WB Saunders; 1992:477–488.)
**FETAL CARDIOVASCULAR SYSTEM**

The cardiovascular system is one of the first functional organ systems in the developing fetus. The morphologic development of the human heart, from its first appearance as a heart tube to its development as a four-chambered structure, occurs between 20 and 44 days’ gestation. Even before the development of the four-chambered heart, the valveless heart tube generates unidirectional flow, typically around 21 days’ gestation.

**Circulatory Pattern**

Fetal circulation differs significantly from the postnatal circulation. The fetal cardiovascular system is anatomically arranged in such a way as to allow blood to bypass the lungs and provide maximal perfusion of the placenta, where gas and nutrient exchange occur. The fetal systemic circulation receives cardiac output from both the left and the right ventricles, with the ventricles working in parallel. In contrast, during postnatal life, the left and right circulations are separated and the ventricles work in series.

Fetal blood flow is characterized by three anatomic communications between the left and right circulations: the ductus venosus, the foramen ovale, and the ductus arteriosus (Fig. 5.4). Oxygenated blood travels from the placenta through the umbilical vein to the ductus venosus, which connects the umbilical vein with the inferior vena cava, thus bypassing the portal circulation and the liver. At mid-gestation, approximately 30% of the umbilical venous blood is shunted through the ductus venosus; from 30 to 40 weeks’ gestation, this fraction decreases to approximately 20%, although a significant increase can occur in response to hypoxia (see later discussion). Once in the right atrium, oxygenated blood preferentially flows through the foramen ovale to the left atrium and left ventricle, before entering the aorta and the systemic circulation. This mechanism ensures the delivery of well-oxygenated blood to the brain and the heart, which are the two organs with the highest oxygen requirements. The preferential shunting of ductus venosus blood through the foramen ovale into the left atrium is related to the umbilical venous pressure and the portocaval pressure gradient.

Deoxygenated blood from the head and upper extremities enters the right atrium through the superior vena cava and is preferentially directed into the right ventricle and the pulmonary artery. Because fetal pulmonary vascular resistance is higher than systemic vascular resistance, the majority of pulmonary artery blood flow crosses the ductus arteriosus into the descending aorta, which in turn supplies the lower extremities and hypogastric arteries. Deoxygenated blood returns to the placenta via the umbilical arteries for gas and nutrient exchange; only a small percentage travels through the lungs into the left atrium, the left ventricle, and the ascending aorta.

At birth, the fetus undergoes a significant and abrupt transition to a state of physiologic independence (see Chapter 9). Clamping of the umbilical cord results in a sudden increase in systemic vascular resistance, whereas expansion of the lungs and an increased alveolar oxygen tension result in decreased pulmonary vascular resistance. This allows for greater blood flow through the lungs, resulting in a decrease in right atrial pressure and an increase in left atrial pressure, ultimately leading to the functional closure of both the foramen ovale and the ductus arteriosus.

**Blood Volume**

Human fetal intravascular volume is approximately 110 mL/kg, which is higher than that in postnatal life. However, approximately 25% of this blood volume is contained within the placenta; the blood volume within the fetal body is
estimated to be approximately 80 mL/kg.\textsuperscript{50,61} Fetal intravascular volume is regulated through a complex interplay between the fetal heart, kidneys, and circulation and the placenta.\textsuperscript{62} The fetus can adapt more quickly to changes in intravascular volume than the adult, owing to higher diffusion rates between fetal compartments.\textsuperscript{63}

Transplacental transfer of water from mother to fetus depends on hydrostatic and osmotic pressures. The hydrostatic pressure is determined by the difference in pressures between the maternal intervillous space or capillaries and the fetal capillaries. The osmotic pressure is mainly determined by the presence of plasma proteins (i.e., colloid osmotic pressure). Transplacental water transfer is further regulated by angiotensin II. Adamson et al.\textsuperscript{64,65} found that angiotensin II lowered the pressures in fetal placental exchange vessels, thereby promoting fluid transfer from the maternal to the fetal circulation. The production of angiotensin II is under control of the renin–angiotensin–aldosterone system in the fetal kidneys. A reduction in fetal arterial pressure results in an increase in fetal plasma renin activity, which results in subsequent increases in angiotensin I and II. The resulting expansion of intravascular volume augments fetal cardiac output and arterial pressure.

**Cardiac Development**

During gestation the fetal heart grows quickly and adapts to the continuously changing demands. The fetal myocardium grows primarily through cell division, whereas after delivery, cardiac mass increases as a result of cell enlargement.\textsuperscript{66} This growth correlates with a prebirth transition from mononucleated cardiomyocytes, which contribute to heart growth by hyperplasia, to binucleated cardiomyocytes, which contribute to heart growth by hypertrophy.

The number of cardiac myofibrils and the transition in the type of cardiac troponins that are present during prenatal development can alter fetal heart contractility.\textsuperscript{67} The change from fetal to adult troponin is associated with decreased sensitivity of the contractile apparatus to calcium. A heightened calcium sensitivity is important in the early development of the fetal heart, when the sarcoplasmic reticulum is immature.\textsuperscript{68} With advancing gestational age, ejection fraction declines, but cardiac output (per unit of fetal weight) does not change owing to increasing ventricular volume. The fetal heart rate decreases over the course of gestation from 140 to 150 beats/min at 18 weeks’ gestation to 120 to 140 beats/min at term.\textsuperscript{69,70} 

In utero developmental issues can have gestational and long-term heart consequences. Fetuses exposed to maternal diabetes demonstrate signs of biventricular diastolic dysfunction, right ventricular systolic dysfunction, and septal hypertrophy in the third trimester, compared with control subjects.\textsuperscript{71} Human growth-restricted fetuses have smaller, more spherical hearts, impaired systolic longitudinal function, and mild impairment in diastolic function, compared with matched non–growth-restricted fetuses; these alterations have been observed to persist when examined even 10 years later.\textsuperscript{72}

### Ventricular Responses to Changes in Preload and Afterload

It is unclear whether fetal and adult hearts possess similar responses to preload and afterload. The adult heart responds in accordance with the Frank-Starling curve, which indicates that ventricular distention lengthens the diastolic fibers and results in augmented contractility. A number of studies have indicated that the fetal heart has a limited capacity to increase its stroke volume in response to an increase in preload (e.g., intravenous fluid infusion).\textsuperscript{73,74} By contrast, other studies have observed that the fetal heart can accommodate increases in preload and afterload in a manner consistent with the Frank-Starling curve.\textsuperscript{75,76} These seemingly contradictory findings may be partially explained if the fetal heart functions in vivo near the peak of the Frank-Starling curve. However, the left ventricular stroke volume is known to double at birth, which would not be in agreement with this hypothesis. A more plausible explanation is that cardiac compliance increases owing to myocardial functional maturity with increased gestation; this has been suggested by a decreasing ratio of mitral peak early diastolic filling velocity to early diastolic mitral annular velocity (E/e’) as the fetus matures.\textsuperscript{77} Another explanation is that ventricular constraint, arising from tissues that surround the heart (chest wall, pericardium, and lungs), limits fetal ventricular preload and overall cardiac function in utero. Relief of this constraint at birth, as a result of lung aeration and clearance of liquid from the lungs, may then allow for an increase in left ventricular preload and subsequent stroke volume in the newborn.\textsuperscript{78}

Studies investigating the effects of afterload on fetal ventricular function have observed a significant decrease in right ventricular stroke volume in response to increases in arterial pressure.\textsuperscript{79} The same phenomenon occurs in the left ventricle, although to a lesser degree. In a study of fetal lambs, in which gradual constriction of the descending aorta was applied, stroke volume was maintained until high mean arterial pressures were achieved, after which decreases were observed. This decrease in stroke volume in the presence of high mean arterial pressure may represent the exhaustion of “preload reserve,” which will typically allow the maintenance of stroke volume in the setting of increased afterload.\textsuperscript{79}

### Cardiac Output and Distribution

In postnatal life, the right and left ventricles operate in series and their output is approximately equal; as a consequence, cardiac output is defined through measurements of output from either ventricle. However, in the fetus, the systemic circulation receives blood from both the left and right ventricle in parallel (i.e., the sum of the right and left ventricular outputs, with the exception of a proportion of the right ventricular output that is delivered to the fetal lungs). At mid-gestation, the combined ventricular output (CVO) is approximately 210 mL/min, and it increases to approximately 1900 mL/min at 38 weeks’ gestation (500 mL/min/kg).\textsuperscript{74,80,81} During fetal life, the right ventricular volume is greater than the left
decreased placental perfusion, acidosis, and increased P
but this fraction may be increased during circumstances of
gestation and in certain conditions, such as hypoxia and
oxygen-consuming organs.

Before delivery, the lungs after delivery) and the
of blood are delivered to oxygen-uptake organs (i.e., the
In both fetal and adult animals, approximately equal volumes
(6%), the heart (4%), the brain (3%), and the kidneys (2%).

Bone and skeletal muscle (38%), the gastrointestinal system
and resting adult humans is shown in Fig. 5.5. The majority
in fetal cardiac output.

Therefore, fetal bradycardia is associated with a marked drop
in fetal cardiac output.

The distribution of the CVO in near-term fetal lambs
and resting adult humans is shown in Fig. 5.5. The majority
of fetal lamb CVO is distributed to the placenta (41%), the
bone and skeletal muscle (38%), the gastrointestinal system
(6%), the heart (4%), the brain (3%), and the kidneys (2%).
In both fetal and adult animals, approximately equal volumes
of blood are delivered to oxygen-uptake organs (i.e., the
placenta before delivery, the lungs after delivery) and the
oxygen-consuming organs.

The distribution of the CVO changes over the course of
gestation and in certain conditions, such as hypoxia and
hypovolemia. Interpretation of CVO data should be evalu-
ated with the understanding that significant interspecies dif-
fferences exist. For example, whereas lungs in the lamb fetus
receive 10% or less of CVO, those in the human fetus receive
approximately 20%. In human fetuses at 10 to 20 weeks’
gestation, the brain receives approximately 15% of CVO,82
but this fraction may be increased during circumstances of
decreased placental perfusion, acidosis, and increased Pco₂.
In the rhesus monkey, the fraction of CVO devoted to cere-
bral blood flow was observed to increase from 16% to 31%
during a hypoxic challenge.83

ventricular volume during both systole and diastole, but
stroke volume does not differ significantly between the two
ventricles.89

Fetal cardiac output is sensitive to changes in fetal heart
rate. As heart rate increases, cardiac output increases. As fetal
heart rate decreases, fetal stroke volume increases only slightly,
in part because of low fetal myocardial compliance. Although
fetal bradycardia results in an extended diastolic filling time,
the stiff fetal cardiac ventricles have limited ability to distend.
Therefore, fetal bradycardia is associated with a marked drop
in fetal cardiac output.

The distribution of the CVO in near-term fetal lambs
and resting adult humans is shown in Fig. 5.5. The majority
of fetal lamb CVO is distributed to the placenta (41%), the
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during a hypoxic challenge.83

Fetal Blood Pressure

Fetal blood pressure increases with gestational age. Intracar-
diac (intraventricular) pressure recordings in the human
fetus suggest that systolic pressure increases from 15 to
20 mm Hg at 16 weeks’ gestation to 30 to 40 mm Hg at 28
weeks’ gestation.86 Substantial variation in blood pressure
may be observed. The diastolic ventricular pressures undergo
similar, albeit slower and smaller increases, from 5 mm Hg or
less at 16 to 18 weeks’ gestation to 5 to 15 mm Hg at 19 to 26
weeks’ gestation.80

Regulation of Fetal Circulation

Fetal cardiovascular function continuously adapts to varying
metabolic and environmental conditions through regulation
by the neurologic and endocrine systems. The predominant
form of neuroregulation occurs in response to baroreceptor
and chemoreceptor afferent input to the autonomic nervous
system and through modulation of myocardial adrenergic
receptor activity. Thus, the autonomic nervous system func-
tions to reversibly redirect blood flow and oxygen delivery as
required.

Arterial baroreceptor function has been demonstrated
in several different fetal animal models. The predominant
baroreceptors are located within the vessel walls of the aortic
arch and at the bifurcation of the common carotid arteries.
These receptors project signals to the vasomotor center in
the medulla, from which autonomic responses emanate. The
baroreceptors are functional early in fetal development and
undergo continuous adaptation to the increases in blood
pressure observed over time.84 A sudden increase in fetal
mean arterial pressure—as occurs with partial or complete
occlusion of the umbilical arteries—results in cholinergic
stimulation and subsequent fetal bradycardia.

Peripheral chemoreceptors are present within the vessel
walls of the aortic arch and at the bifurcation of the common
carotid arteries. In some animal species, peripheral chemo-
receptors are transiently present in the adrenal gland but
disappear after birth.85 The fetal aortic chemoreceptors are
responsive even to small changes in arterial oxygenation,86,87
which contrasts to the less active fetal carotid chemorecep-
tors. Dawes et al.88 concluded that the carotid chemorecep-
tors are important for postnatal respiratory control, whereas
the aortic chemoreceptors are more involved in the control of car-
diovascular responses and the regulation of oxygen delivery.
Central chemoreceptors, located in the medulla oblongata,
appear to play little if any role in fetal circulatory responses.

The neural control of the fetal circulation is far more
dependent on chemoreceptor-mediated responses than
neural control of the adult circulation.89 Acute fetal hypoten-
sion often stimulates a reflex response, which can include
both bradycardia and vasoconstriction. Vasoconstriction
is dependent on chemoreceptor afferent input to the autonomic nervous system and through modulation of myocardial adrenergic receptor activity. Thus, the autonomic nervous system functions to reversibly redirect blood flow and oxygen delivery as required.

Arterial baroreceptor function has been demonstrated
in several different fetal animal models. The predominant
baroreceptors are located within the vessel walls of the aortic
arch and at the bifurcation of the common carotid arteries.
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sion often stimulates a reflex response, which can include
both bradycardia and vasoconstriction. Vasoconstriction
is dependent on increases in both sympathetic autonomic activity and the rate of secretion of several vasoactive hor-
mones, including arginine, vasopressin, renin, angiotensin,
and aldosterone. Fetal bradycardia is most likely caused by
activation of peripheral chemoreceptors.89
pneumocytes and ventilatory capacity are present during the last trimester, true alveoli develop at approximately 36 weeks’ gestation. The majority of alveolar development occurs postnatally, within the first 6 to 18 months of life, when further maturation of the microvasculature and the air-blood barrier occurs.97

The pulmonary vasculature develops early in gestation, with continuity between its capillary plexus and the heart occurring as early as 34 days’ gestation.98,99 The size and number of pulmonary arteries and veins increases over time; however, vessel reactivity to local and hormonal influences is not detectable until after 20 weeks’ gestation.100,101 From 20 to 30 weeks’ gestation, the growth in the size of the pulmonary vascular bed combined with a reduction in pulmonary vascular resistance results in greater pulmonary blood flow (i.e., from 10% to 15% of the CVO to 25% of the CVO). During this time, alterations in maternal oxygenation have no effect on the fetal pulmonary vasculature.82,100 However, after 30 weeks’ gestation, blood flow to the lungs decreases slightly owing to a significant increase in pulmonary vascular resistance, diminishing the fraction of CVO to approximately 20%. Contemporaneously, the vasomotor tone and reactivity of the fetal circulation begins to respond to maternal hyperoxygenation with a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow.82,100 A study in near-term fetal lambs observed a 10-fold increase in pulmonary blood flow when fetal oxygen tension was increased from 24 to 46 mm Hg (3.2 to 6.1 kPa) because of pulmonary vasodilation102; however, this acute response is not sustained during prolonged exposures, suggesting the development of vasoregulatory mechanisms that oppose vasodilation.103

At birth, with the onset of breathing, a significant reduction in pulmonary vascular resistance occurs and the pulmonary blood flow increases from 21% to 100% of cardiac output to enable gas exchange in the lung.103 A number of mechanical and molecular processes contribute to this perinatal pulmonary vasodilation. In utero, the fetal lungs are filled with fluid to maintain an appropriate level of expansion.
for normal pulmonary development. The expulsion of lung liquid, particularly with a vaginal birth, likely decreases extraluminal pressure on the pulmonary vasculature and leads to a decrease in pulmonary vascular resistance. Breathing movements, shear stress created by an abrupt surge in pulmonary blood flow, and the development of alveolar surface tension are other mechanical factors that can decrease pulmonary vascular resistance. Finally, the relative predominance of vasodilators (e.g., endothelium-derived nitric oxide, prostacyclin) versus vasoconstrictors (e.g., platelet-activating factor) at birth may also significantly decrease pulmonary vascular resistance.

The amount and composition of pulmonary surfactant changes over the course of gestation. For example, the ratio of phosphatidylglycerol to phosphatidylinositol, and the ratio of lecithin to sphingomyelin, increases with gestation and may be used as markers of fetal lung maturity. Fetal surfactant production can be accelerated by a number of factors, including glucocorticoids, thyroid hormones, and autonomic neurotransmitters. A glucocorticoid surge in the last weeks of gestation is required for normal lung development; birth before this cortisol increase results in low levels of surfactant with the subsequent development of infant respiratory distress syndrome (IRDS). Consequently, the American College of Obstetricians and Gynecologists (ACOG) recommends a single course of corticosteroids for pregnant women between 24 and 34 weeks’ gestation who are at risk for preterm delivery.

Antenatal corticosteroid treatment causes maturation of pulmonary epithelial cells, differentiation of type II cells, and activation of various components of surfactant (e.g., surfactant proteins and phospholipids); the treatment causes additional pulmonary alterations in the structural components, fluid metabolism, production of growth factors, and presence of antioxidant enzymes and adrenergic receptors. The maternal administration of glucocorticoids such as betamethasone or dexamethasone has been associated with a 35% to 40% reduction in respiratory distress syndrome in preterm infants and a significant improvement in neonatal mortality.

A disadvantage in respiratory morbidity and mortality of male infants born prematurely can be partially attributed to gender differences in surfactant production. Higher levels of androgen and Mullerian-inhibiting substance in male fetuses adversely affects surfactant production, whereas estrogen promotes surfactant production in female fetuses. Future therapies may need to be gender specific.

**FETAL RENAL SYSTEM**

Although fluid and electrolyte balance, and acid-base homeostasis, are primarily regulated and maintained by the placenta, the fetal kidneys play an important role in fetal development through amniotic fluid production. Fetal glomeruli begin to develop at 8 to 9 weeks’ gestation and start producing urine at 10 weeks’ gestation, which contributes significantly to amniotic fluid production. By 20 weeks’ gestation, greater than 90% of amniotic fluid is provided by the kidneys. Fetal oliguria and anuria can lead to lung hypoplasia and skeletal and tissue deformities (e.g., Potter sequence). Glomerular filtration rate (GFR) increases over the course of gestation but remains low during fetal and early neonatal life. At birth, term newborns have a GFR of approximately 20 mL/min/1.73 m², which increases to approximately 50 mL/min/1.73 m² by 1 month of age. This early increase in GFR is believed to result from a large increase in the glomerular capillary surface area and the ultrafiltration coefficient, together with a small increase in the filtration pressure. Thereafter, the GFR undergoes progressive increases and reaches adult levels between 1 and 2 years of age.

The ability of the fetal kidneys to perform filtration, reabsorption, and secretion (i.e., tubular function) begins by 14 weeks’ gestation and continues to develop postnatally. Immaturity of tubular function in preterm infants can lead to acidosis and salt wasting. Renal function in utero is regulated by a variety of factors that control renal blood flow, glomerular filtration, and tubular function. The renin-angiotensin system is particularly important for normal fetal renal growth and development, and maternal use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is associated with renal agenesis and anomalies; angiotensin II helps regulate blood pressure and the volume of fluid in the extravascular space.

**FETAL HEMATOLOGIC SYSTEM**

Red blood cells, platelets, neutrophils, monocytes, and macrophages are all derived from a common progenitor cell. In the developing embryo, hematopoiesis occurs at several anatomic sites in multiple waves. The first wave occurs in the yolk sac 30 days after conception and produces mostly primitive erythroid cells, but also macrophages and megakaryocytes. The second wave also arises in the yolk sac but creates the same cells found in the adult human (i.e., erythroid, megakaryocyte, and several myeloid lineages). The third wave emerges from hematopoietic stem cells located within the major arteries of the embryo, yolk sac, and placenta. Hematopoietic stem cells migrate to the fetal liver and eventually seed the bone marrow, where they will reside for the remainder of life. The final wave of hematopoiesis produces all hematopoietic cell lineages, including B- and T-lymphocyte progenitor cells. In utero exposure to various agents when hematopoietic stem cells are initially emerging can lead to programming alterations that impact the blood and immune systems throughout life; for example, genome profiling of cord blood hematopoietic progenitor cells from neonates born to smokers demonstrates dysregulated gene pathways involved in hematopoietic cell lineage differentiation.

Erythroid cells (red blood cells) are the first blood cells to develop. There are two developmentally and morphologically distinct erythroid lineages: primitive (embryonic) and definitive (adult). Cells of the primitive lineage support the transition from the rapidly growing embryo to fetus; primitive megaloblastic erythrocytes are much larger than definitive erythrocytes, express different globin genes, and differ in their...
oxygen-carrying capacity and response to low oxygen tension. By contrast, definitive erythrocytes are important during the transition from fetal to extraterine life at birth. They are produced continuously from hematopoietic stem cells in the bone marrow and participate in a variety of normal physiologic processes throughout postnatal life.

Fetal and adult human erythrocytes can be distinguished by their hemoglobin (hemoglobin F and A, respectively). The tetramer for hemoglobin F consists of two alpha (α) chains and two gamma (γ) chains (α2γ2), whereas the tetramer for hemoglobin A includes two alpha (α) chains and two beta (β) chains (α2β2). The gamma chain and the beta chain contain the same number of amino acids (146), but their sequences differ by a total of 39 amino acids. The change in expression from fetal to adult beta-globin genes begins at approximately 32 weeks’ gestation and is completed after birth.

Hemoglobin F has a greater affinity for oxygen and a lower affinity for 2,3-disphosphoglycerate (DPG) and exhibits a leftward shift in the oxyhemoglobin dissociation curve compared with hemoglobin A (Fig. 5.7). These differences result in greater arterial oxygen saturation in fetal versus maternal blood for any given arterial oxygen pressure. This difference in oxygen affinity can be explained by a decreased interaction between the gamma chains of hemoglobin F and intraerythrocyte 2,3-DPG, the latter acting to lower oxygen affinity by binding and stabilizing the deoxygenated hemoglobin tetramer. As a consequence, 2,3-DPG decreases the oxygen affinity of hemoglobin F less than that of hemoglobin A. Although fetuses and adults have similar intraerythrocyte 2,3-DPG concentrations, fetal blood exhibits a lower oxygen tension at which hemoglobin is 50% saturated (P50). Hemoglobin F levels begin to decrease toward the end of pregnancy, resulting in a corresponding increase in the P50. At term, hemoglobin A accounts for approximately 25% of total hemoglobin, and the P50 is approximately 19 mm Hg.

Hemoglobin A levels begin to increase and 2,3-DPG concentrations transiently increase above usual fetal and adult levels during the first few months of life. During this time, the affinity of neonatal blood for oxygen is equivalent to that of the adult despite the persistence of 25% fetal hemoglobin.

**FETAL GASTROINTESTINAL SYSTEM**

The gastrointestinal tract develops from the primitive digestive tube, which includes the foregut, midgut, and hindgut. The foregut receives its vascular supply from the celiac axis and gives origin to the oral cavity, pharynx, esophagus, stomach, and upper duodenum. The midgut, which receives its vascular supply from the superior mesenteric artery, develops into the distal duodenum, jejunum, ileum, cecum, appendix, and transverse colon. The hindgut receives its vascular supply from the inferior mesenteric artery, and it differentiates into the descending colon, the sigmoid colon, and the upper two thirds of the rectum. Intestinal villi appear by 7 weeks’ gestation, and active absorption of glucose and amino acids occurs by 10 and 12 weeks’ gestation, respectively. Peristaltic waves and gastrointestinal motility are initiated by 8 weeks’ gestation. Teniae, the three longitudinal ribbons of smooth muscle on the outside of the colon, appear by 12 weeks’ gestation and contract to produce the haustra (bulges) in the colon. In the small intestine, Auerbach and Meissner plexuses of parasympathetic nerves provide motor and secretomotor innervation, respectively; the two plexuses are present as early as 8 weeks’ gestation. Aggregations of lymphoid nodules (i.e., Peyer patches) develop by 20 weeks’ gestation in the ileum.

Although the fetal environment and neonatal gut were once believed to be sterile, in utero transmission of microbes from mother to infant likely occurs. Jimenez et al. demonstrated that specific bacteria introduced to the gut of pregnant animals could be recovered in the offspring at the time of sterile cesarean delivery. Similarly in humans, Collado et al. observed shared microbiota features in placental, amniotic fluid, and infant meconium samples obtained during elective cesarean delivery, suggesting in utero microbial gut colonization. The early life microbiome is involved in immune system development, metabolic programming, neurodevelopment, and neonatal susceptibility to diseases.

**Swallowing**

The fetus starts swallowing at approximately 15 weeks’ gestation, and at term the fetus ingests 500 to 750 mL of amniotic fluid per day. Fetal swallowing plays an important role in amniotic fluid homeostasis, and the swallowed fluid appears to provide nutritional support for mucosal development within the gastrointestinal tract. Intestinal growth occurs by duplication of intestinal crypts, a process that is promoted by the presence of trophic factors in amniotic fluid; these factors include epidermal growth factor (EGF),...
hypertrophy and possible pulmonary hypertension.149
natal hypoxia, meconium also may contribute to vascular
syndrome (see Chapter 9). Finally, in the presence of peri-
of neutrophils, and possibly result in meconium aspiration
of meconium also may neutralize the action of surfactant,
human neonates with congenital esophageal atresia.148
within the amniotic fluid is observed, which coincides with
gestational age and is common in post-term pregnancies.153

to a complex system in which billions of neurons are arranged
nervous system begin to develop from a few embryonic cells
indicated by the presence of high levels of intestinal enzymes
(i.e., disaccharidases, alkaline phosphatase), appear in the
amniotic fluid.151 After 22 weeks’ gestation, a subsequent
decline in the concentration of these gastrointestinal enzymes
within the amniotic fluid is observed, which coincides with the
development of anal sphincter tone.151,152
Meconium is continually cleared by fetal swallowing, leading to relatively clear amniotic fluid in the majority of pregnancies. The presence of meconium-stained amniotic fluid may therefore represent either decreased clearance or increased passage of meconium, which is observed in the presence of fetomaternal stress factors such as hypoxia and infection, independent of fetal maturation.149 Meconium-stained amniotic fluid occurs more frequently with advanced gestational age and is common in post-term pregnancies.153
Although many fetuses with meconium-stained amniotic fluid are born without adverse sequelae, meconium can have detrimental effects on fetal organs and the placenta. Mec-

Meconium, which consists of water, intestinal secretions, squa-
mous cells, lanugo hair, bile pigments, and blood, first appears in the fetal intestine between 10 and 12 weeks’ gestation.149 By 16 weeks’ gestation, meconium moves into the colon.150
Between 14 and 22 weeks’ gestation, fetal colonic contents, as indicated by the presence of high levels of intestinal enzymes (i.e., disaccharidases, alkaline phosphatase), appear in the amniotic fluid.151 After 22 weeks’ gestation, a subsequent decline in the concentration of these gastrointestinal enzymes within the amniotic fluid is observed, which coincides with the development of anal sphincter tone.151,152
Meconium is continually cleared by fetal swallowing, leading to relatively clear amniotic fluid in the majority of pregnancies. The presence of meconium-stained amniotic fluid may therefore represent either decreased clearance or increased passage of meconium, which is observed in the presence of fetomaternal stress factors such as hypoxia and infection, independent of fetal maturation.149 Meconium-stained amniotic fluid occurs more frequently with advanced gestational age and is common in post-term pregnancies.153
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Mec-onium may reduce the antibacterial properties of amniotic fluid by altering zinc levels.149 Fetal aspiration of meconium also may neutralize the action of surfactant, promote lung tissue inflammation through the activation of neutrophils, and possibly result in meconium aspiration syndrome (see Chapter 9). Finally, in the presence of perinatal hypoxia, meconium also may contribute to vascular hypertrophy and possible pulmonary hypertension.149

Fetal Nervous System
Over the course of gestation, the human brain and central nervous system begin to develop from a few embryonic cells to a complex system in which billions of neurons are arranged and interconnected; small, seemingly minor changes may have profound implications. For example, animal studies suggest that intrauterine exposure to a variety of drugs and medications, including certain anesthetic agents, at specific time intervals appears to result in anatomic, functional, and behavioral changes following birth (see Chapter 10).

Structural and Functional Brain Development
Primary neuromodulation and neural tube formation occur by 4 weeks’ gestation. By 8 weeks, the rostral end of the neural tube gives rise to the prosencephalon, or forebrain; the mesencephalon, or midbrain; and the rhombencephalon, or hindbrain. These three segments further subdivide: the prosencephalon divides into the telencephalon and the diencephalon, and the rhombencephalon divides into the metencephalon and myelencephalon. These five subdivisions establish the primary organization of the central nervous system.155

The human subplate, the developmental anlage of the cerebral cortex, develops between 13 and 15 postconceptional weeks (PCW). The subplate layer is created to fulfill a critical, albeit transient, role as a location for synapses with cortical and thalamic projections; the subplate layer disintegrates between 24 and 28 weeks’ gestation. A significant increase in cortical development, organization, and synapse formation begins by 20 weeks’ gestation and continues postnatally; during the third trimester alone, the cerebral cortex volume increases fourfold.156,157

The first fetal movements are witnessed near the end of the first trimester. These initial movements have simple patterns and originate from spontaneous discharges within the spine and brainstem. The fetal movements become more organized and complex as the pregnancy progresses, with higher brain centers modulating the activity of the brainstem and spine.

The exact onset of electrocortical activity is unknown, but electroencephalographic (EEG) activity can be recorded in preterm infants as early as 24 weeks’ gestation. Fetal EEG activity differs from that in the adult and is characterized by the presence of intermittent bursts of activity separated by periods of complete suppression. With maturation, these suppressed episodes become shorter and less frequent before completely disappearing in postnatal life. The early electrical activity within the nervous system controls several developmental processes, such as neuronal differentiation, migration, synaptogenesis, and formation of neuronal networks. For example, the initial spontaneous spinal and subcortical discharges are believed necessary for somatosensory development. As they elicit movements in the periphery, afferent signals establish topographic representation on the sensory cortex.158–160

Alterations in fetal brain and nervous system development can lead to major malformations. The Zika virus has been associated with an increase in the number of newborns with microcephaly, retinal abnormalities, hearing loss, and other neurologic complications, such as convulsions and hypotonia, hydrocephalus, agyria, ventriculomegaly, and
brain calcifications.\textsuperscript{161} The Zika virus is highly neurotropic and causes cell death in neuroprogenitor cells and immature cortical neurons.\textsuperscript{162}

**Cerebral Metabolism**

The immature brain, similar to the adult brain, relies mostly on oxidative metabolism for the production of energy. However, owing to the limited capacity for mitochondrial oxidative phosphorylation and the lower partial pressures of oxygen observed \textit{in utero}, anaerobic glycolysis exhibits a greater role during this developmental period than after delivery.\textsuperscript{163,164} In the presence of aerobic conditions, glucose is converted to pyruvic acid (glycolysis), which enters the Krebs cycle and the mitochondrial cytochrome system to create chemical energy; this process converts 1 mole of glucose into 36 moles of ATP. By contrast, during anaerobic conditions, glycolysis is much less efficient, yielding only 2 moles of ATP for each mole of glucose.\textsuperscript{165}

Although glucose represents the primary and predominant source of cerebral energy, the perinatal brain is uniquely capable of metabolizing other substrates, such as lactic acid and ketone bodies (i.e., β-hydroxybutyrate and acetoacetate). Lactic acid concentrations in the peripartum period are significantly elevated and may support over 50% of total cerebral oxidative metabolism in certain conditions such as hypoglycemia and hypoxia.\textsuperscript{166,167} During hypoxic conditions, the fetal brain will also significantly decrease its energy consumption, as evidenced by fewer fetal movements and a slower EEG wave pattern.\textsuperscript{168}

**Cerebral Blood Flow**

The development of the neural tube begins with formation of endothelium-lined vascular channels; by 10 weeks' gestation, an extensive network of leptomeningeal arteries covers the fetal brain, allowing vessels to sprout and penetrate the brain parenchyma. Subsequent vascular growth is most pronounced in rapidly developing areas of the brain.\textsuperscript{163}

The fetal systemic circulation has unique features that ensure optimal oxygen delivery to the brain. Well-oxygenated blood from the umbilical vein and ductus venosus is preferentially shunted through the foramen ovale to the left side of the heart and the ascending aorta to supply the cerebral and coronary circulations. Hypoxia results in acute changes in fetal and placental vascular resistance, which leads to intense peripheral vasoconstriction (likely mediated by stimulation of chemoreceptors) and further shunting of umbilical venous blood through the ductus venosus. The fetal circulatory system is much more sensitive to hypoxemia than that in the adult, which helps maintain oxygen delivery to the developing brain and myocardium (Fig. 5.8).\textsuperscript{169–171}

The redistribution of blood flow to the most actively developing regions of the fetal brain is at least partially the result of an adenosine-mediated mechanism. Adenosine, the breakdown product of ATP, accumulates during failure of ATP resynthesis and causes vasodilation of blood vessels and suppression of neuronal activity.\textsuperscript{168} Other substances (e.g., nitric oxide, endogenous opioids, adrenomedullin) may also play a role in cerebral blood redistribution, but the exact mechanisms are incompletely understood.\textsuperscript{172}

**Nociception**

Cutaneous sensory receptors are present in the human fetus at approximately 7 weeks' gestation, and a widespread network is established by 20 weeks. At term gestation, the density of cutaneous nociceptive receptors in the fetus is comparable to, and may even exceed, that of the adult.

![Fig. 5.8](image_url) The redistribution of cardiac output to the heart and central nervous system during hypoxemia in fetal lambs. Each symbol represents a measurement from an individual fetal lamb. (Modified from Sheldon RE, Peeters LLH, Jones MD Jr, et al. Redistribution of cardiac output and oxygen delivery in the hypoxic fetal lamb. \textit{Am J Obstet Gynecol.} 1979;135:1071–1078.)
Although the development of sensory fiber-to-dorsal horn interneuron synapses has been reported to occur as early as 6 weeks’ gestation, differentiation of dorsal horn neurons begins at approximately 13 weeks’ gestation; the laminar arrangement of dorsal horn neurons, replete with synaptic interconnections and neurotransmitter vesicles, is present in some regions of the spinal cord by 30 weeks’ gestation. At this time, the A-delta and C fibers make connections at the spinal cord level and with the surrounding dermatomes.

The neurons of the cerebral cortex develop by 20 weeks’ gestation, and synaptogenesis of the thalamocortical connections is established between 20 and 24 weeks’ gestation. Thalamocortical axons reach the somatosensory cortex at 24 to 26 weeks’ gestation. Myelination of the pain pathways of the spinal cord and brainstem is completed during the second and third trimesters of gestation; however, the process continues postnatally in other areas of the brain and in peripheral nerve fibers. Although optimal pain processing requires myelination of pain pathways, cortical maturation, dendritic arborization, and thalamocortical fiber synaptogenesis, it is unclear when nociception, the capacity to feel pain, develops within the fetus. As early as 18 weeks’ gestation, human fetuses demonstrate pituitary-adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli. In studies of intrauterine blood transfusion in the human fetus, surgical needling of the intrahepatic vein (compared with needling of the insensitive umbilical cord) is associated with evidence of a stress response, including increases in plasma beta-endorphin and cortisol levels and a diminution in the middle cerebral artery pulsatility index. Administration of fentanyl 10 µg/kg blunts this stress response to intrahepatic needling.

The immaturity of thalamocortical connections before 25 weeks’ gestation suggests that cortical processing of external input before 25 weeks’ gestation is unlikely. However, as early as 25 weeks’ postmenstrual age, near-infrared spectroscopy has demonstrated cortical activity in response to noxious stimuli in preterm neonates. Facial responses to painful stimuli (similar to those seen in adults) can be provoked in preterm neonates born and assessed as early as 25 weeks’ gestation, which suggests the development of functional pathways from the spinal cord to the brain. However, the withdrawal from noxious stimuli or an increased release of stress hormones does not necessarily reflect an awareness of pain, because local spinal reflexes and hormonal release can occur without cortical involvement. The experience of pain is a conscious subjective experience with emotional and affective components that requires higher-level cortical processing. Nociceptive processing begins in the peripheral neurons, which relay signals through the spinothalamic tract, the thalamus, and ultimately the cerebral cortex, where conscious perception of pain occurs. After birth, neonates appear to be more sensitive to pain, with lower pain thresholds, poor discriminative abilities, and a greater tendency to exhibit central sensitization in response to later noxious stimuli than adults. Early sensory experiences in the neonate can influence the development of nociceptive pathways. Neonates and especially preterm infants who undergo numerous procedures in the neonatal intensive care unit and/or surgery have been observed to demonstrate altered pain perceptions later in life. In the rodent model, tissue injury in early neonatal life results in an increased magnitude and duration of hyperalgesia after re-injury in later life, compared with those with no early life pain experience. Collectively, these observations have prompted some investigators to conclude that noxious events in neonates, when pain pathways are still undergoing a learning or “tuning process,” may result in structural functional and behavioral alterations in adult pain processing. Some of these long-term consequences may be attenuated by preemptive analgesia.

The foregoing neuroanatomic and neurochemical evidence, in addition to the well-characterized behavioral and physiologic responses to pain, indicate that both the fetus and newborn infant have nociceptive pathways capable of communicating nociceptive stimuli from the periphery to the cerebral cortex and regulating the response via efferent inhibitory pathways. Current evidence suggests that fetal nociception at the level of the cortex occurs after the midpoint of pregnancy (i.e., between 24 and 30 weeks’ gestation).

KEY POINTS

- Amniotic fluid serves a number of vital roles, including the facilitation of fetal growth, the provision of a microgravity environment that cushions the fetus, and the generation of a defense mechanism against invading microbes.
- The fetus depends on the mother and the placenta for its basic metabolic needs, such as nutrient delivery, gas exchange, and electrolyte and acid-base homeostasis.
- Fetal arterial blood PO2 ranges from 20 to 30 mm Hg (2.7 to 4.0 kPa), and fetal development exists in a state of relative hypoxia compared with adult oxygen tension.
- Despite a lower fetal oxygen tension, the fetal arterial blood oxygen content is not much lower than that of the adult. This results from a higher oxygen-carrying capacity (hemoglobin concentration of 18 g/dL) and a higher affinity of hemoglobin F for oxygen, when compared with hemoglobin A.
- The fetus produces approximately twice as much heat (on a weight-adjusted basis) and maintains a temperature 0.5°C higher than the mother during the third trimester.
- The fetal circulation receives output from both the left and the right ventricle, with the ventricles working in parallel. Systemic blood flow consists of the sum of the right and left ventricular outputs, with the exception of the small
am. amount of blood delivered to the fetal lungs by the right ventricle.

- Fetal blood flow is characterized by three important communications between the left and right circulation: the ductus venosus, the foramen ovale, and the ductus arteriosus.

- Acute hypotension in the fetus stimulates a reflex response, which includes both bradycardia and vasoconstriction.

- The sympathetic nervous system at birth is not as well developed as the parasympathetic nervous system; however, it plays an important role in the hemodynamic adjustments at birth.

- Although fetal fluid and electrolyte balance, and acid-base homeostasis, are primarily regulated and maintained by the placenta, the fetal kidneys play an important role in fetal development through amniotic fluid production.

- The pulmonary surfactant system is one of the last systems to develop before birth. Surfactant assembly occurs in the type II alveolar cells, and components of surfactant are first detected between 24 and 28 weeks’ gestation.

- Fetal hemoglobin has a greater oxygen affinity than adult hemoglobin, owing to a decreased interaction between hemoglobin F and 2,3-DPG. The P50 of fetal blood is significantly lower than that of adult blood.

- Fetal hypoxemia leads to a significant redistribution of cardiac output to the heart and the brain. This results in both a global increase in cerebral blood flow and a redistribution of blood flow within the fetal brain.

- Fetal swallowing plays an important role in amniotic fluid homeostasis, and the swallowed fluid appears to provide nutritional support for mucosal development within the gastrointestinal tract.

- The fetus has nociceptive pathways capable of communicating painful stimuli from the periphery to the cerebral cortex. Current evidence suggests that fetal nociception at the level of the cortex occurs after the midpoint of pregnancy (i.e., between 24 and 30 weeks’ gestation).

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CHAPTER 5  Fetal Physiology

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Obstetric care providers have two patients, the mother and the fetus. Although assessment of maternal health is relatively straightforward, assessment of fetal well-being is far more challenging. Several tests have been developed to assess the fetus during pregnancy, including some that are recommended for all pregnancies (e.g., ultrasonography for pregnancy dating) and others that are reserved only for women with pregnancy complications (e.g., middle cerebral artery Doppler velocimetry in pregnancies with isoimmunization). In addition, a limited number of fetal interventions are employed to improve fetal outcome, including some that are used more frequently and others rarely, such as maternal corticosteroid administration and intrauterine fetal procedures, respectively. A review is presented here of the tests available to assess fetal well-being in both low- and high-risk pregnancies and of the fetal therapies used during the antepartum period.

PREGNATAL CARE IN LOW-RISK PREGNANCIES

Determination of Gestational Age

The mean duration of a singleton pregnancy is 280 days (40 weeks) from the first day of the last normal menstrual period in women with regular 28-day menstrual cycles. Term, defined as the period from 37 weeks’ (259 days’) to 42 weeks’ (294 days’) gestation, is the optimal time for delivery. However, both preterm births (defined as delivery before 37 weeks’ gestation) and postterm births (delivery after 42 weeks’ gestation) are associated with increased perinatal and neonatal morbidity and mortality, with variation occurring within this 5-week gestational age range. For this reason, the designations of early term (37 0/7 to 38 6/7 weeks’ gestation), full term (39 0/7 to 40 6/7 weeks’ gestation), and late term (41 0/7 to 41 6/7 weeks’ gestation) were adopted. Evaluation of fetal growth, efficient use of screening and diagnostic tests, appropriate initiation of fetal surveillance, and optimal timing of delivery all depend on accurate dating of the pregnancy.

Recommendations for determining the gestational age and estimated due date (EDD) have been established by the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the American Institute of Ultrasound in Medicine (Box 6.1). Determination of gestational age is most accurate when ultrasonographic measurement of the fetus or embryo is performed in the first trimester (up to and including 13 6/7 weeks’ gestation). For pregnancies achieved by assisted reproductive technology (ART), the EDD should be assigned based on the age of the...
Clinical Criteria Commonly Used to Confirm Gestational Age

- Reported date of last menstrual period (estimated due date can be calculated by subtracting 3 months and adding 7 days to the first day of the last normal menstrual period [Naegle’s rule]) or date of assisted reproductive technology (intrauterine insemination or embryo transfer)
- The size of the uterus as estimated on bimanual examination in the first trimester, which should be consistent with dates
- The perception of fetal movement ("quickening"), which usually occurs at 18 to 20 weeks in nulliparous women and at 16 to 18 weeks in parous women
- Fetal heart activity, which can be detected with a nonelectronic fetal stethoscope by 18 to 20 weeks and with Doppler ultrasonography by 10 to 12 weeks
- Fundal height, which at 20 weeks in a singleton pregnancy should be approximately 20 cm above the pubic symphysis (usually corresponding to the umbilicus)
- Ultrasonography to determine fetal crown-rump length during the first trimester, or fetal biometry (biparietal diameter, head circumference, and/or femur length) during the second trimester


Routine Ultrasonography

An ultrasonographic examination is recommended for all pregnancies, given its ability to accurately determine gestational age, viability, fetal number, and placental location, and screen for fetal structural abnormalities in the second trimester.

Some studies have shown an improvement in perinatal outcomes with the use of ultrasonography. In a prospective trial of 9310 low-risk women randomly assigned to an ultrasonographic examination for screening at 16 to 20 weeks’ gestation or for obstetric indications only, a significantly lower perinatal mortality rate was observed in the group undergoing screening (4.6 vs. 9.0 per 1000 births, respectively). The screening examination allowed for earlier detection of major fetal malformations and multiple gestations, which enabled more appropriate care, and improved pregnancy dating and a lower rate of labor inductions for postterm pregnancies. In contrast, a subsequent large multicenter randomized clinical trial involving 15,151 low-risk women in the United States, designated the RADIUS study, concluded that screening ultrasonography did not improve perinatal outcomes and had no impact on the management of the anomalous fetus. Although this trial was adequately powered, the highly selective entry criteria (less than 1% of pregnant women in the United States would have been eligible) and inappropriate primary outcomes for a low-risk population (perinatal morbidity and mortality) have been criticized. Importantly, in the routine ultrasonography group, only 17% of major congenital anomalies were detected before 24 weeks’ gestation. There is significant variability in the sensitivity of routine ultrasonographic examinations for the detection of fetal anomalies; in a large review of 36 studies with over 900,000 fetuses, the detection rate for fetal anomalies ranged from 15% to 80%. The detection rates for malformations are improved when performed by an experienced operator at a tertiary center, are higher for central nervous...
system and urinary tract versus cardiac anomalies, and are lower in patients with a high body mass index (BMI).\textsuperscript{15}

**Evaluation of Fetal Growth**

Normal fetal growth is a critical component of a healthy pregnancy and the subsequent long-term health of the child. An increased risk for delivering a small-for-gestational-age baby and/or having a preterm delivery is associated with low maternal gestational weight gain, while a higher risk for delivering a large-for-gestational-age baby and/or cesarean delivery is associated with excessive gestational weight gain.\textsuperscript{16} The current recommendations for maternal weight gain in pregnancy were revised by the Institute of Medicine (IOM) in 2009 and are based on maternal prepregnancy BMI (Table \ref{table:6.1}).\textsuperscript{17} The guidelines recommend that: (1) underweight and normal weight women gain approximately 1 pound (0.5 kg) per week in the second and third trimesters; (2) overweight and obese women gain approximately one-half pound (0.25 kg) per week in the second and third trimesters; and (3) all women try to be within the normal BMI range when they conceive.

The size, presentation, and lie of the fetus can be assessed with abdominal palpation. A systematic method of examination of the gravid abdomen was first described by Leopold and Sporlin in 1894.\textsuperscript{18} Although the abdominal examination has several limitations (especially in the setting of a small fetus, maternal obesity, multiple pregnancy, uterine fibroids, or polyhydramnios), it is safe, is well tolerated, and may add valuable information to assist in antepartum management. Palpation is divided into four separate Leopold maneuvers (Fig. \ref{fig:6.1}). Each maneuver is designed to identify specific fetal landmarks or to reveal a specific relationship between the fetus and mother. The first maneuver, for example, involves measurement of the fundal height. The uterus can be palpated above the pelvic brim at approximately 12 weeks’ gestation. Thereafter, fundal height should increase by approximately 1 cm per week, reaching the level of the umbilicus at 20 to 22 weeks’ gestation (Fig. \ref{fig:6.2}). Between 20 and 32 weeks’ gestation, the fundal height (in centimeters) is approximately equal to the gestational age (in weeks) in healthy women of average weight with an appropriately growing fetus. However, there is a wide range of normal fundal height measurements. In one study, a 6-cm difference was noted between the 10th and 90th percentiles at each week of gestation after 20 weeks.\textsuperscript{19} Moreover, maximal fundal height occurs at approximately 36 weeks’ gestation, after which time the fetus drops into the pelvis in preparation for labor. For all of these reasons, reliance on fundal height measurements alone fails to identify more than 50% of fetuses with fetal growth restriction (also known as intrauterine growth restriction).\textsuperscript{20} Serial fundal height measurements by an experienced obstetric care provider are more accurate than a single measurement and will lead to better diagnosis of fetal growth restriction, with reported sensitivities as high as 86%.\textsuperscript{21}

![Fig. 6.1 Leopold maneuvers for palpation of the gravid abdomen.](image)

![Fig. 6.2 Fundal height measurements in a singleton pregnancy with normal fetal growth.](image)

**TABLE 6.1  Recommendations for Weight Gain in Pregnancy**

<table>
<thead>
<tr>
<th>Mother’s Body Mass Index</th>
<th>Recommended Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9 kg/m(^2) (normal weight)</td>
<td>11.2–15.9 kg (25–35 lb)</td>
</tr>
<tr>
<td>25–29.9 kg/m(^2) (overweight)</td>
<td>6.8–11.2 kg (15–25 lb)</td>
</tr>
<tr>
<td>&gt; 30 kg/m(^2) (obese)</td>
<td>5.0–9.0 kg (11–20 lb)</td>
</tr>
</tbody>
</table>

If clinical findings suggest a fetal growth discrepancy between size and dates, ultrasonography is the modality of choice to evaluate and offer alternative explanations, such as multifetal pregnancy, polyhydramnios, fetal demise, and uterine fibroids. For many years, obstetric ultrasonography has used fetal biometry to define fetal size by weight estimation. This approach has a number of limitations. First, regression equations used to create weight estimation formulas are derived primarily from cross-sectional data for infants being delivered within an arbitrary period after the ultrasonicographic examination. Second, these equations assume that body proportions (fat, muscle, bone) are the same for all fetuses. Finally, growth curves for “normal” infants between 24 and 37 weeks’ gestation rely on data collected from pregnancies delivered preterm, which are abnormal and probably complicated by some element of uteroplacental insufficiency, regardless of whether the delivery was spontaneous or iatrogenic. Despite these limitations, if the gestational age is well validated, the prevailing data suggest that prenatal ultrasonography can be used to verify an alteration in fetal growth in 80% of cases and to exclude abnormal growth in 90% of cases.

Ultrasonographic estimates of fetal weight are commonly derived from mathematical formulas that use a combination of fetal measurements, especially the biparietal diameter, abdominal circumference, and femur length. The abdominal circumference is the single most important measurement and is weighted more heavily in these formulas. Unfortunately, the abdominal circumference is also the most difficult measurement to acquire, and small differences in the measured value result in large changes in the estimated fetal weight (EFW). The accuracy of the EFW depends on a number of variables, including gestational age (in absolute terms, EFW is more accurate in preterm or growth-restricted fetuses than in term or macrosomic fetuses), operator experience, maternal body habitus, and amniotic fluid volume (ultrasound measurements are more difficult to acquire if the amniotic fluid volume is low). The EFW may differ from the birthweight by up to 20% in 95% of cases, and greater than 20% in the remaining cases. Indeed, an ultrasonographic EFW at term is no more accurate than a clinical estimate of fetal weight made by an experienced obstetric care provider or the mother’s estimate of fetal weight if she has delivered before. Ultrasonographic estimates of fetal weight must therefore be evaluated within the context of the clinical situation and balanced against the clinical estimates. Serial ultrasonographic evaluations of fetal weight are more useful than a single measurement in diagnosing abnormal fetal growth. The ideal interval for fetal growth evaluations is every 3 to 4 weeks, because more frequent determinations may be misleading due to variations in the ultrasonographic measurements; however, in some cases, such as with fetuses suspected of growth restriction, evaluations can be performed every 2 weeks. The use of population-specific fetal growth curves based on maternal (e.g., weight or race) or environmental factors have been demonstrated to improve the accuracy of ultrasonographic EFW, particularly in the setting of abnormal fetal growth. For example, growth curves derived from a population that lives at high altitude, where the fetus is exposed to lower oxygen tension, will be different from those derived from a population at sea level. However, the use of customized fetal growth curves has not yet been shown to improve outcomes. Abnormal fetal growth can be classified as insufficient (fetal growth restriction) or excessive (fetal macrosomia).

Fetal Growth Restriction

Fetal growth restriction is associated with a number of significant adverse perinatal outcomes, including intrauterine demise, neonatal morbidity, and neonatal mortality. In addition, growth-restricted fetuses are at increased risk for cognitive delay in childhood and chronic diseases, such as obesity, type 2 diabetes, coronary artery disease, and stroke in adulthood.

The definition of fetal growth restriction is an EFW less than the 10th percentile for gestational age; by contrast, the term small for gestational age (SGA) is reserved for newborns with a birth weight less than the 10th percentile for gestational age. Distinguishing the healthy, constitutionally small-for-gestational age fetus from the pathologically growth-restricted fetus has been particularly difficult. Fetuses with an EFW less than the 10th percentile are not necessarily pathologically growth restricted or at risk for an adverse outcome. Conversely, an EFW above the 10th percentile does not necessarily mean that an individual fetus has achieved its growth potential, and such a fetus may still be at risk for perinatal mortality and morbidity.

Fetal growth restriction results from suboptimal uteroplacental perfusion and fetal nutrition caused by different conditions that can be divided into maternal, fetal, and placental etiologies (Box 6.2). Maternal disorders associated with fetal growth restriction include any condition that can potentially result in vascular disease, such as pregestational diabetes, hypertension, antiphospholipid antibody syndrome, autoimmune diseases and renal insufficiency, malnutrition, and substance abuse. Fetal conditions that may result in growth restriction include teratogen exposure, including certain medications; intrauterine infection; aneuploidy, most often trisomy 13 and trisomy 18; and some structural malformations, such as abdominal wall defects and congenital heart disease. Placental pathology resulting in poor placental perfusion can lead to fetal growth restriction. Umbilical cord abnormalities, such as velamentous or marginal cord insertion, have also been implicated in cases of fetal growth restriction. In more than half of cases of growth restriction, the etiology may be unclear even after a thorough investigation.

Fetal growth restriction is associated with an increased risk for stillbirth. When the EFW measures less than the 10th percentile, the risk for stillbirth is 1.5%, which is twice the background risk for appropriately grown fetuses. The risk for stillbirth increases to 2.5% when the EFW is less than the 5th percentile. The risk for stillbirth is further increased when fetal growth restriction occurs in the context of oligohydramnios or abnormal diastolic blood flow in the umbilical artery.
Early and accurate diagnosis of fetal growth restriction coupled with appropriate intervention leads to an improvement in perinatal outcome. If fetal growth restriction is suspected clinically and on the basis of ultrasonography, a thorough evaluation of the mother and fetus is indicated. Referral to a maternal-fetal medicine specialist should be considered. Every effort should be made to identify the cause of the fetal growth restriction and to modify or eliminate contributing factors. The growth-restricted fetus should be monitored closely because of the increased risk for perinatal mortality. Monitoring should include serial ultrasonographic examinations for growth and amniotic fluid volume, and antenatal surveillance with umbilical artery velocimetry and antepartum testing (nonstress tests or biophysical profiles). The timing of delivery should be based on gestational age, the underlying etiology if known, results of antepartum testing and interval growth scans, and any additional risk factors for an adverse outcome, including maternal co-morbidities.

**Fetal Macrosomia**

Fetal macrosomia, defined as growth beyond an absolute birth weight of 4000 g or 4500 g regardless of gestational age, should be differentiated from the term *large for gestational age* (LGA), which implies a birth weight greater than or equal to the 90th percentile for a given gestational age. By definition, in the United States, 10% of all fetuses are LGA, 8% of all live-born infants weigh 4000 g or more, and 1.1% weigh more than 4500 g.

In general, the risk for labor abnormalities (e.g., cephalopelvic disproportion, dysfunctional labor), maternal morbidity (e.g., cesarean delivery, postpartum hemorrhage, significant vaginal lacerations), and newborn complications (e.g., Apgar score less than 4 at 5 minutes, birth injuries, assisted ventilation greater than 30 minutes, neonatal intensive care unit admission) increases with birth weights between 4000 and 4499 g; newborn and maternal morbidity increases significantly with birth weights between 4500 and 4999 g; and perinatal mortality (e.g., stillbirth and neonatal mortality) increase with birthweights greater than 5000 g. Shoulder dystocia, defined as a failure of delivery of the fetal shoulder(s) after initial attempts at downward traction, is the most serious consequence of fetal macrosomia, and requires additional maneuvers to effect delivery. The fetal injuries associated with shoulder dystocia include fracture of the clavicle and damage to the nerves of the brachial plexus, resulting in Erb-Duchenne paralysis, of which the vast majority resolve by 1 year of age. Compared with a prevalence of 0.2% to 3.0% for all vaginal deliveries, the risk for shoulder dystocia at birthweights of 4500 grams or more is 9% to 14%, and increases further in the setting of maternal diabetes to 20% to 50%.

Fetal macrosomia can be determined clinically by abdominal palpation (e.g., Leopold maneuvers) or with ultrasonography; although these two techniques appear to be equally accurate, the ability to predict fetal macrosomia is poor, with a false-positive rate of 35% and a false-negative rate of 10%. Estimated fetal weight measurements are less accurate in macrosomic fetuses than in normally grown fetuses, and factors such as low amniotic fluid volume, advancing gestational age, maternal obesity, and fetal position can compound these inaccuracies. Indeed, clinical examination has been shown to underestimate the birth weight by more than 0.5 kg in almost 80% of macrosomic fetuses. A number of alternative ultrasonographic measurements have therefore been proposed in an attempt to better identify the macrosomic fetus, including fetal abdominal circumference alone, umbilical cord circumference, cheek-to-cheek diameter, and subcutaneous fat in the mid humerus, thigh, abdominal wall, and shoulder. However, these measurements remain investigational.

Despite the inaccuracy in the prediction of fetal macrosomia, an EFW should be documented by either clinical estimation or ultrasonography in all high-risk women at approximately 38 weeks’ gestation. Suspected fetal macrosomia is not an indication for induction of labor, because induction does not improve maternal or fetal outcomes and may increase the risk for cesarean delivery. The American College of Obstetricians and Gynecologists (ACOG) recommends performance of an elective cesarean delivery when the suspected birth weight exceeds 4500 g in a diabetic woman or 5000 g in a nondiabetic woman. Similarly, a cesarean delivery is recommended in laboring women when the suspected birth weight exceeds 4500 g in the setting of a prolonged second stage of labor or arrest of descent in the second stage.
evaluated at every visit. Fetal heart activity should be assessed and the fetal heart rate (FHR) estimated. A low FHR (< 100 bpm) is associated with an increased risk for pregnancy loss, although congenital complete heart block should be excluded. In the latter half of pregnancy, physical examination of the abdomen should be performed to document fetal lie and presentation.

Fetal movements ("quickening") are typically reported at 18 to 20 weeks’ gestation by nulliparous women and at 16 to 18 weeks’ gestation by parous women; the presence of fetal movements is strongly correlated with fetal health. Although the mother appreciates only 10% to 20% of total fetal movements, such movements are almost always present when she does report them. Factors associated with a diminution in perceived fetal movements include increasing gestational age, smoking, decreased amniotic fluid volume, anterior placation, and antenatal corticosteroid therapy. Decreased fetal movements may also be a harbinger of an adverse pregnancy outcome in high-risk pregnancies.54 The normal fetus exhibits an average of 20 to 50 (range of 0 to 130) gross body movements per hour, with fewer movements during the day and increased activity between 9:00 am and 11:00 pm.60 Several different schemes have been proposed to determine the baseline fetal activity pattern for an individual fetus after 28 weeks’ gestation and to evaluate activity patterns that may represent fetal compromise. One commonly used scheme ("count-to-10") instructs the mother to rest quietly on her left side once each day in the evening (between 7:00 pm and 11:00 pm) and to record the time interval required to feel 10 fetal movements. Most patients with a healthy fetus will feel 10 movements in approximately 20 minutes; 99.5% of women with a healthy fetus feel this amount of activity within 90 minutes.61 Under this scheme, failure to appreciate 10 fetal movements in 2 hours should prompt immediate fetal assessment. In one large clinical trial, institution of this fetal activity monitoring scheme resulted in a significant increase in hospital visits, labor induction, and cesarean deliveries, but also in a reduction in perinatal mortality from 44.5 to 10.3 per 1000 births.61

Taken together, these data suggest that daily or twice-daily fetal "kick counts" should be performed after 32 weeks’ gestation in high-risk pregnancies. Currently there is insufficient evidence to recommend this practice in low-risk pregnancies.

Prenatal Care in High-Risk Pregnancies

Approximately 20% of all pregnancies should be regarded as high risk (see Box 6.2). Because of the attendant risks to both the mother and fetus, additional efforts should be made to confirm fetal well-being throughout such pregnancies. In addition to the testing outlined previously, high-risk pregnancies should be monitored closely and regularly by a multidisciplinary team, including subspecialists in maternal-fetal medicine and neonatology, if indicated.

Goals of Antepartum Fetal Testing

The goal of antepartum fetal surveillance is the early identification of a fetus at risk for preventable neurologic injury or death. Numerous causes of neonatal cerebral injury exist, including congenital abnormalities, chromosomal abnormalities, intracerebral hemorrhage, hypoxia, infection, drugs, trauma, hypotension, and metabolic derangements (e.g., hypoglycemia, thyroid dysfunction). Antenatal fetal testing cannot reliably predict or detect all of these causes; however, those specifically associated with uteroplacental vascular insufficiency should be identified when possible. Antenatal fetal testing makes the following assumptions: (1) pregnancies may be complicated by progressive fetal asphyxia that can lead to fetal death or permanent neurologic handicap; (2) current antenatal tests can adequately discriminate between asphyxiated and nonasphyxiated fetuses; and (3) detection of asphyxia at an early stage can lead to an intervention that is capable of reducing the likelihood of an adverse perinatal outcome.

Unfortunately, it is not clear whether any of these assumptions are true, and nonreassuring fetal test results may reflect existing but not ongoing neurologic injury. At most, 15% of cases of cerebral palsy are thought to result from antepartum or intrapartum hypoxic-ischemic injury.62,63 Despite these limitations, a number of antepartum tests have been developed in an attempt to identify fetuses at risk. These include the nonstress test (NST), biophysical profile (BPP), and contraction stress test (CST). Such tests can be used either individually or in combination. There is no consensus as to which of these modalities is preferred, and no single method has been shown to be superior.64

Antepartum Fetal Tests

All antepartum fetal tests should be interpreted in relation to the gestational age, the presence or absence of congenital anomalies, and underlying clinical risk factors.65 For example, a nonreassuring NST in a pregnancy complicated by severe fetal growth restriction and heavy vaginal bleeding at 32 weeks’ gestation has a much higher predictive value in identifying a fetus at risk for subsequent neurologic injury than an identical tracing in a well-grown fetus at 40 weeks, because of the higher prevalence of this condition in the former situation. It should be remembered that, in many cases, the efficacy of antenatal fetal testing in preventing long-term neurologic injury has not been validated by prospective randomized clinical trials. Indeed, because of ethical and medicolegal concerns, there are no studies of pregnancies at risk that include a nonmonitored control group, and it is highly unlikely that such trials will ever be performed.

Nonstress Test

The fetal NST, also known as fetal cardiotocography, investigates changes in the FHR pattern with time and reflects the maturity of the fetal autonomic nervous system; for this
reason, it is less useful in the very preterm fetus (< 28 weeks’ gestation). The NST is noninvasive, simple to perform, inexpensive, and readily available in all obstetric units. However, interpretation of the NST is largely subjective. Although a number of different criteria have been used to evaluate these tracings, most obstetric care providers have used the definitions for FHR interpretation established in 1997, and updated in 2008, by the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop (Table 6.2).66,67

By definition, an NST is performed before the onset of labor and does not involve invasive (intrauterine) monitoring. The test is performed by recording the FHR for a period of 20 to 40 minutes; the recording is then evaluated for the presence of periodic changes. The FHR is determined externally with use of Doppler ultrasonography, in which sound waves emitted from the transducer are deflected by movements of the heart and heart valves. The shift in frequency of these deflected waves is detected by a sensor and converted into heart rate. The FHR is printed on a strip-chart recorder running at 3 cm/min. A single mark on the FHR tracing therefore represents the average rate in beats per minute (bpm) of 6 fetal heart beats. The presence or absence of uterine contractions is typically recorded at the same time with an external tonometer. This tonometer records myometrial tone and provides information about the timing and duration of contractions, but it does not measure intrauterine pressure or the intensity of the contractions. Results of the NST are interpreted as reactive or nonreactive. An FHR tracing is designated reactive if there are two or more accelerations that peak, but not necessarily remain, at least 15 bpm for 15 seconds in a 20-minute period (Fig. 6.3).66,67 For preterm fetuses (< 32 weeks’ gestation), an FHR tracing is designated as reactive if there are two or more accelerations of at least 10 bpm for 10 seconds. A reactive NST is regarded as evidence of fetal health.66,67

<table>
<thead>
<tr>
<th>TABLE 6.2 Interpretation of Antepartum Nonstress Test Results</th>
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<tbody>
<tr>
<td><strong>Criterion</strong></td>
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<tr>
<td>Baseline fetal heart rate (FHR)</td>
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<tr>
<td>Baseline FHR variability</td>
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</table>

A normal FHR tracing is defined as having a normal baseline rate (110 to 160 bpm), normal baseline variability (i.e., moderate variability, defined as 6 to 25 bpm from peak to trough), presence of accelerations, and absence of decelerations. FHR accelerations typically occur in response to fetal movement, and usually indicate fetal health and adequate oxygenation.66,67 A nonreactive NST does not achieve sufficient accelerations within a 40-minute period. The interpretation of a nonreactive NST must consider the gestational age, the underlying clinical circumstance, and the results of previous FHR tracings. Only 65% of fetuses have a reactive NST by 28 weeks’ gestation, whereas 95% do so by 32 weeks.65,70 However, once a reactive NST has been documented in a given pregnancy, the NST should remain reactive throughout the remainder of the pregnancy. A nonreactive NST at term is associated with poor perinatal outcome in only 20% of cases. The significance of such a result at term depends on the clinical endpoint under investigation. If the clinical endpoint of interest is a 5-minute Apgar score less than 7, a nonreactive NST at term has a sensitivity of 57%, a positive predictive value of 13%, and a negative predictive value of 98% (assuming a prevalence of 4%). If the clinical endpoint is permanent neurologic injury, a nonreactive NST at term has a 99.8% false-positive rate.71

Visual interpretation of the FHR tracing involves the following components: (1) baseline FHR, (2) baseline FHR variability, (3) presence of accelerations, (4) presence of periodic or episodic decelerations, and (5) changes of FHR pattern over time. The definitions of each of these variables are summarized in Table 6.2.66,67 The patterns are categorized as baseline, periodic (i.e., associated with uterine contractions), or episodic (i.e., not associated with uterine contractions). Periodic changes are described as abrupt or gradual (defined as onset-to-nadir time < 30 seconds or > 30 seconds, respectively). In contrast to earlier classifications, this classification makes no distinction between short-term and long-term variability, and certain characteristics (e.g., the definition of an acceleration) depend on gestational age.66,67 A normal FHR tracing is defined as having a normal baseline rate (110 to 160 bpm), normal baseline variability (i.e., moderate variability, defined as 6 to 25 bpm from peak to trough), presence of accelerations, and absence of decelerations. FHR accelerations typically occur in response to fetal movement, and usually indicate fetal health and adequate oxygenation.66,67 At-risk FHR patterns demonstrate absence of baseline variability, combined with recurrent late or variable decelerations or substantial bradycardia (Fig. 6.4).
Intermediate FHR patterns have characteristics between the two extremes of normal and at-risk tracings already described.66,67

Persistent fetal tachycardia (defined as an FHR > 160 bpm) may be associated with fetal hypoxia, maternal fever, chorioamnionitis (intrauterine infection), administration of an anticholinergic or beta-adrenergic receptor agonist, fetal anemia, or tachyarrhythmia (see Table 6.2). Persistent fetal bradycardia (FHR < 110 bpm) may be a result of congenital heart block, administration of a beta-adrenergic receptor antagonist, hypoglycemia, or hypothermia; it may also indicate fetal hypoxia.66,67 Both tachyarrhythmias and bradycardias require immediate evaluation.

Baseline FHR variability, perhaps the most important component of the NST, is determined on a beat-to-beat basis by the competing influences of the sympathetic and parasympathetic nervous systems on the fetal sinoatrial node. A variable FHR tracing, characterized by fluctuations that are irregular in both amplitude and frequency,66,67 indicates that the autonomic nervous system is functioning and that the fetus has normal acid-base status. Variability is defined as absent, minimal, moderate, or marked (Fig. 6.5).66,67 The older terms short-term variability and long-term variability are no longer used.67 Normal (moderate) variability indicates the absence of cerebral hypoxia. With acute hypoxia, variability may be minimal or marked. Persistent or chronic hypoxia is typically associated with loss of variability. Reduced variability also may be the result of other factors, including maternal drug administration (Table 6.3), fetal arrhythmia, and neurologic abnormality (e.g., anencephaly).66,67

Vibroacoustic Stimulation

Fetal vibroacoustic stimulation (VAS) refers to the response of the FHR to a vibroacoustic stimulus (82 to 95 dB) applied to the maternal abdomen for 1 to 2 seconds in the region of the fetal head. An FHR acceleration in response to VAS represents a positive result and is suggestive of fetal health. If VAS fails to produce an acceleration in the FHR, it may be repeated up to three times for progressively longer durations of up to 3 seconds.

VAS is a useful adjunct to shorten the time needed to achieve a reactive NST and to decrease the proportion of nonreactive NSTs at term, thereby precluding the need for further testing. In one study of low-risk women at term, VAS reduced the proportion of nonreactive NSTs over a 30-minute period by 50% (from 14% to 9%) and shortened the time needed to achieve a reactive NST by an average of 4.5 minutes.66 VAS has no adverse effect on fetal hearing. The absence of an FHR acceleration in response to VAS at term is associated with an 18-fold higher risk for nonreassuring fetal testing in labor73 and a 6-fold higher risk for cesarean delivery.74

Biophysical Profile

An NST alone may not be sufficient to confirm fetal well-being. In such cases, a biophysical profile (BPP) may be performed. The BPP combines an NST with an ultrasonographic scoring system performed over a 30-minute period. Initially described for testing of the postterm fetus, the BPP has since been validated for use in both term and preterm fetuses, but not during active labor.75,76 The five variables described in the original BPP were (1) gross fetal body movements, (2) fetal tone (i.e., flexion and extension of limbs), (3) amniotic fluid volume, (4) fetal breathing movements, and (5) the NST (Table 6.4).75 More recently, the BPP has been interpreted without the NST.

The individual variables of the BPP become apparent in the normal fetus in a predictable sequence: fetal tone appears at 7.5 to 8.5 weeks’ gestation, fetal movement at 9 weeks, fetal breathing at 20 to 22 weeks, and FHR reactivity at 24 to 28 weeks. In the setting of antepartum hypoxia, these characteristics typically disappear in the reverse order of their appearance (i.e., FHR reactivity is lost first, followed by fetal breathing, fetal movements, and finally fetal tone).76 The amniotic fluid volume, which is composed almost entirely of fetal urine in the second and third trimesters, is not influenced by acute fetal hypoxia or acute fetal central nervous system dysfunction. Rather, oligohydramnios (decreased amniotic fluid volume) in the latter half of pregnancy and in the absence of ruptured membranes is a reflection of chronic uteroplacental insufficiency and/or increased renal artery resistance leading to diminished urine output.77 It predisposes

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### TABLE 6.3 Drugs That Affect the Fetal Heart Rate Tracing

<table>
<thead>
<tr>
<th>Effect on the Fetus</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal tachycardia</td>
<td>Atropine Epinephrine (adrenaline) Beta-adrenergic agonists (ritodrine, terbutaline)</td>
</tr>
<tr>
<td>Fetal bradycardia</td>
<td>Antithyroid medications (including propylthiouracil) Beta-adrenergic antagonists (e.g., propranolol) Intrathecal or epidural analgesia Methylxylononine (contraindicated before delivery) Oxytocin (if associated with excessive uterine activity)</td>
</tr>
<tr>
<td>Sinusoidal fetal heart rate pattern Diminished variability</td>
<td>Systemic opioid analgesia</td>
</tr>
</tbody>
</table>

#### Footnotes:

66.67

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Fig. 6.5 Components of baseline fetal heart rate (FHR) variability. A, Absence of variability. B, Minimal variability (0 to 5 bpm from peak to nadir). C, Moderate variability (6 to 25 bpm from peak to nadir). D, Marked variability (>25 bpm from peak to nadir).
### Table 6.4 Characteristics of the Biophysical Profile

<table>
<thead>
<tr>
<th>Biophysical Variable</th>
<th>Normal Score (Score = 2)</th>
<th>Abnormal Score (Score = 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBM</td>
<td>At least one episode of FBM lasting at least 30 sec</td>
<td>Absence of FBM altogether or no episode of FBM lasting ≥ 30 sec</td>
</tr>
<tr>
<td>Gross body movements</td>
<td>At least three discrete body/limb movements in 30 min (episodes of active continuous movements should be regarded as a single movement)</td>
<td>Fewer than three episodes of body/limb movements over a 30-min period</td>
</tr>
<tr>
<td>Fetal tone</td>
<td>At least one episode of active extension with return to flexion of fetal limbs or trunk; opening and closing of hand are considered normal tone</td>
<td>Slow extension with return to partial flexion, movement of limb in full extension, or absence of fetal movements</td>
</tr>
<tr>
<td>Qualitative AF volume</td>
<td>At least one pocket of AF that measures ≥ 1 cm in two perpendicular planes</td>
<td>No AF pockets or an AF pocket measuring &lt; 1 cm in two perpendicular planes</td>
</tr>
<tr>
<td>Reactive nonstress test</td>
<td>At least two episodes of FHR acceleration of ≥ 15 bpm lasting ≥ 15 sec associated with fetal movements over 30 min of observation</td>
<td>Fewer than two episodes of FHR acceleration or accelerations of &lt; 15 bpm over 30 min of observation</td>
</tr>
</tbody>
</table>

AF, Amniotic fluid; FBM, fetal breathing movement; FHR, fetal heart rate.


The Contraction Stress Test (CST) assesses the response of the FHR to uterine contractions induced by either intravenous oxytocin administration or nipple stimulation (which causes release of endogenous oxytocin from the maternal neurohypophysis). A minimum of three contractions for at least 40 seconds in a 10-minute period is required to interpret the test. A negative CST (no late or severe late decelerations with contractions) is reassuring and suggestive of a healthy, well-oxygenated fetus. A positive CST (late or severe variable decelerations with at least 50% of the contractions) is suggestive of a fetus suffering from impaired maternal-to-fetal oxygen exchange during uterine contractions and is associated with adverse perinatal outcome in 35% to 40% of cases (Fig. 6.6). A CST is defined as equivocal if FHR decelerations occur with contractions to umbilical cord compression, thus leading to intermittent fetal hypoxemia, meconium passage, or meconium aspiration. An adverse pregnancy outcome (including a nonreassuring FHR tracing, low Apgar scores, and/or admission to the neonatal intensive care unit) is more common when oligohydramnios is present. Weekly or twice-weekly screening of high-risk pregnancies for oligohydramnios is important because amniotic fluid can become drastically reduced within 24 to 48 hours.

Although each of the five features of the BPP are scored equally (2 points if the variable is present or normal and 0 points if absent or abnormal, for a total of 10 points), they are not equally predictive of adverse pregnancy outcome. For example, amniotic fluid volume is the variable that correlates most strongly with adverse pregnancy events. The management recommended on the basis of the BPP score is summarized in Table 6.5. A score of 8 or 10 is regarded as reassuring; a score of 6 is considered equivocal, and a score of 4 or less is abnormal. A score of 0 or 2 suggests nonreassuring fetal status (previously referred to as “fetal distress”) and should prompt evaluation for immediate delivery.

The modified BPP was developed to simplify and reduce the time necessary to complete an examination by focusing on the BPP components that are most predictive of outcome: (1) an NST, as an indicator of acute acid-base status, and (2) the amniotic fluid volume, as an index of uteroplacental function. Composed of a reactive NST and a maximum vertical pocket of amniotic fluid greater than 2 cm, a normal modified BPP occurs in approximately 90% of examinations, and is as reliable as a full BPP in the prediction of fetal well-being. A full BPP is often performed if an abnormal result is obtained.

### Table 6.5 Recommended Management Based on Biophysical Profile

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 or 10</td>
<td>Normal</td>
<td>No intervention</td>
</tr>
<tr>
<td>6</td>
<td>Suspect asphyxia</td>
<td>Repeat in 4 to 6 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider delivery for oligohydramnios</td>
</tr>
<tr>
<td>4</td>
<td>Suspect asphyxia</td>
<td>If ≥ 36 weeks’ gestation or mature pulmonary indices, deliver immediately</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If &lt; 36 weeks’ gestation, repeat BPP in 4 to 6 h versus delivery with mature pulmonary indices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If score persistently ≤ 4, deliver immediately</td>
</tr>
<tr>
<td>0 or 2</td>
<td>High suspicion of asphyxia</td>
<td>Evaluate for immediate delivery</td>
</tr>
</tbody>
</table>

hypertension). Doppler velocimetry is consequently used to evaluate growth-restricted fetuses, or growth discordance in twin gestations.

Doppler velocimetry can be used for the noninvasive measurement of fetal circulation, including the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV). As one of the few arteries that normally has diastolic flow, the UA is frequently evaluated during pregnancy. Normally, UA resistance to blood flow from the fetus to the placenta falls progressively throughout pregnancy, reflecting an increase in the number of tertiary stem vessels. Factors that affect placental vascular resistance include gestational age, placental location, pregnancy complications (e.g., placental abruption, preeclampsia), and underlying maternal disease (chronic hypertension). Doppler velocimetry is consequently used to evaluate growth-restricted fetuses, or growth discordance in twin gestations.

Decreased diastolic flow with a resultant increase in the systolic-to-diastolic (S/D) ratio suggests an increase in placental vascular resistance. Severely abnormal UA Doppler velocimetry (defined as absence of or reversed diastolic flow) is consistent with the obliteration of 50% to 70% of the terminal villi; this ominous observation is associated with poor perinatal outcomes, particularly in the setting of fetal growth restriction (Fig. 6.7). Delivery may be recommended for the presence of absent UA end-diastolic flow after 34 weeks' gestation, or reversed end-diastolic flow as early as 28 weeks' gestation.

The role of MCA or DV Doppler velocimetry in the management of fetal growth restriction pregnancies is not well defined. MCA Doppler velocimetry can evaluate if cerebral blood flow increases in response to hypoxia, which can be a useful adjunct to UA Doppler velocimetry. The cerebroplacental ratio, calculated by dividing the MCA pulsatility index...
Fig. 6.7 Umbilical artery Doppler velocimetry. 

A, Normal waveform in the umbilical artery as shown on Doppler velocimetry. Forward flow can be seen during both fetal systole and diastole. 

B, Absent end-diastolic flow. Forward flow can be seen during systole, but there is no flow during diastole.

Continued
Multiple Modalities to Assess Fetal Well-Being

All standard tests to assess antepartum fetal well-being (i.e., NST, BPP, CST) are evaluated according to their ability to predict the absence of fetal death during the 1-week period after the test. The false-negative rate (defined as a reassuring test result with a subsequent bad outcome) and false-positive rate (an abnormal result with a subsequent normal outcome) for each of these tests are listed in Table 6.6.64,68,83 The false-negative rates for all three tests are relatively low. Because the NST has a high false-positive rate, some authorities consider it a screening test to identify fetuses requiring further assessment with either a BPP or a CST. No method of fetal assessment is perfect, and clinical judgment plays a large role in any management decision.

SPECIAL TECHNIQUES FOR ANTEPARTUM FETAL SURVEILLANCE

Perinatal Ultrasonography

Ultrasonography uses high-frequency sound waves (3.5 to 5 MHz for transabdominal transducers and 5 to 7.5 MHz for transvaginal transducers) that are directed into the body by a transducer, reflected by maternal and fetal tissue, detected by
a receiver, processed, and displayed on a screen. Increasing the wave frequency results in greater display resolution at the expense of diminished tissue penetration. Interpretation of images requires operator experience. Widespread clinical application of two-dimensional ultrasonography began in the 1960s after pioneering work by researchers in the United States and Great Britain.  

Although no deleterious biologic effects have been associated with obstetric ultrasonography, the rates of false-positive and false-negative diagnoses based on the images are a major limitation.  

The American College of Obstetricians and Gynecologists, the American College of Radiology, the American Institute of Ultrasound in Medicine, the National Institute of Child Health and Human Development, the Society of Maternal–Fetal Medicine, and the Society of Radiologists in Ultrasound have endorsed the following terminology for ultrasound examinations in the second and third trimesters: standard, specialized, and limited.  

The standard examination involves determination of fetal number, presentation, amniotic fluid volume, cardiac activity, placental position, fetal biometry, and an anatomic survey. If technically feasible, the maternal cervix and adnexa should be evaluated. Most pregnancies can be evaluated adequately with this type of examination alone. If the patient’s history, laboratory abnormalities, physical findings, or standard ultrasonographic results suggest an increased risk for a fetal malformation, then a specialized examination is performed.  

Specialized examinations, which include fetal Doppler assessments, BPP, fetal echocardiogram, and additional biometric measurements, evaluate fetal structures in detail to identify and characterize any fetal malformations. Ultrasonographic markers of fetal aneuploidy (see later discussion) can be evaluated as well. In some situations, a limited examination may be appropriate to answer a specific clinical question, such as fetal viability, amniotic fluid volume, fetal presentation, placental location, and cervical length.  

Current debate centers on identifying those patients who would benefit from an ultrasonographic evaluation and determining what type of evaluation would be optimal. Advocates of the universal application of ultrasonography cite the advantages of more accurate dating of pregnancy (see earlier discussion) and earlier and more accurate diagnosis of multiple gestation, structural malformations, and fetal aneuploidy (see later discussion). Opponents of routine ultrasonographic examination view it as an expensive screening test that is not justified by published research, which suggests that routine ultrasonography does not change perinatal outcome significantly.  

Although routine ultrasonography for all low-risk pregnant women is controversial, few would disagree that the benefits far outweigh the costs for selected patients. The ACOG has recommended that the benefits and limitations of ultrasonography should be discussed with all pregnant women.  

The indications for first-trimester ultrasonography, which is performed before 14 0/7 weeks’ gestation, are different from those for second- and third-trimester ultrasonography; most patients undergo a detailed fetal anatomic survey at 18 to 20 weeks’ gestation to assess fetal growth and screen for structural defects. Placental location should be documented with the maternal bladder empty, because over-distention of the bladder or a lower uterine contraction can give a false impression of placenta previa. If placenta previa is identified at 18 to 22 weeks’ gestation, serial ultrasonographic examinations should be performed to follow placental location. Only 5% of cases of placenta previa identified in the second trimester persist to term.  

The umbilical cord should also be imaged and the number of vessels, placental insertion, and fetal insertion should be noted. Evaluation of the amniotic fluid volume should also be performed. In pregnancies at high risk for fetal cardiac anomalies or preterm birth, fetal echocardiography and cervical length measurements, respectively, should be performed.  

Fetal anatomic surveys and EFW become less accurate with greater gestational age, especially in obese women or pregnancies complicated by oligohydramnios. However, fetal biometry and detailed anatomic surveys are still performed in late gestation, because certain fetal anomalies (e.g., achondroplasia, duodenal atresia) may become evident for the first time during this period. Transvaginal ultrasonographic measurement of cervical length (performed to identify women at risk for preterm birth) is of little use after 30 to 32 weeks’ gestation.  

Screening for Fetal Chromosomal Abnormalities  

Fetal chromosomal abnormalities are a major cause of perinatal morbidity and mortality, accounting for 50% of first-trimester spontaneous abortions, 6% to 12% of all stillbirths and neonatal deaths, and 10% to 15% of structural anomalies in live-born infants. The most common aneuploidy encountered during pregnancy (autosomal trisomy) results primarily from nondisjunction during meiosis I. Women of advanced maternal age (> 35 years or older at EDD) are at higher risk for having a pregnancy complicated by fetal aneuploidy and are routinely offered noninvasive prenatal screening and an invasive diagnostic procedure (either amniocentesis or chorionic villus sampling [CVS]). However, because only 8% to 12% of all births occur in women 35 years of age and older, at most 20% to 25% of all cases of trisomy 21 (Down syndrome) would be identified if all women of advanced maternal age agreed to amniocentesis.  

Klinefelter syndrome (47, XXY) is the most common sex chromosome aneuploidy with a prevalence of 1:500 males, and Turner syndrome (45, X) is the only viable monosomy. Many older women are now opting for serum analyte screening for fetal aneuploidy, which is equally accurate in older women. All women, regardless of age, should be offered aneuploidy screening during early gestation.  

Fetal Aneuploidy Screening  

Methods have been developed to help identify women at high risk for fetal aneuploidy. The major focus of attention has been the detection of Down syndrome, because it is the most common chromosomal abnormality manifesting at term and, unlike the less common disorders trisomy 13 and 18, its diagnosis can be very difficult to make with ultrasonography.
In all of these screening tests, one or more serum analytes are used to adjust the \textit{a priori} risk for fetal aneuploidy in a given pregnancy, which depends primarily on maternal age.

\textbf{First-trimester screening} is performed between 10 0/7 and 13 6/7 weeks’ gestation. A measurement of the nuchal translucency, the fluid-filled space on the posterior aspect of the fetal neck, is combined with serum markers, human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A), to calculate a specific risk estimate (Table 6.7). A nuchal translucency greater than 3.0 mm, or above the 99th percentile for the crown-rump length, is associated with an increased risk for aneuploidy and structural malformations, most often congenital heart defects.\footnote{Reference number}

First-trimester screening has a detection rate for Down syndrome of 82\% to 87\%, with a screen positive rate of 5\%; the use of this screening method has increased significantly, given the benefits of being a single test performed in the first trimester with abnormal results predictive of aneuploidy and adverse outcomes (Table 6.8). However, tests that combine first- and second-trimester results have higher detection rates, and the measurement of nuchal translucency requires a specialized ultrasonographic examination with a credentialed sonographer and interpreting physician, which can limit its availability.\footnote{Reference number}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Adverse Outcome} & \textbf{Adjusted Odds Ratio} & \textbf{95\% Confidence Interval} \\
\hline
Spontaneous loss $<24$ weeks & 2.50 & 1.76–3.56 \\
Fetal death $\geq24$ weeks & 2.15 & 1.11–4.15 \\
Preterm birth $\leq37$ weeks & 1.87 & 1.61–2.17 \\
Preterm birth $\leq32$ weeks & 2.10 & 1.59–2.76 \\
Preeclampsia & 1.54 & 1.16–2.03 \\
Gestational hypertension & 1.47 & 1.20–1.82 \\
Placental abruption & 1.80 & 1.15–2.84 \\
Fetal growth restriction & 3.22 & 2.38–4.36 \\
\hline
\end{tabular}
\caption{Relationship between First-Trimester Pregnancy-Associated Plasma Protein A Level at or below Fifth Percentile (0.42 MoM) and Risks for Adverse Pregnancy Outcomes}
\end{table}

\textit{MoM}, Multiple of the median.


\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Screening Test} & \textbf{Detection Rate (\%)} & \textbf{False-Positive Rate (\%)} \\
\hline
Maternal age $>35$ yr & 30–40 & 10–15 \\
\textbf{First Trimester} & & \\
NT assessment & 64–70 & 5–10 \\
NT assessment, PAPP-A, and total or free $\beta$-hCG measurements & 82–87 & 5–6 \\
\textbf{Second Trimester} & & \\
Triple screen (measurements of MS-AFP, total or free $\beta$-hCG, unconjugated estriol) & 69–77 & 9 \\
Quadruple screen (measurements of MS-AFP, total or free $\beta$-hCG, unconjugated estriol, inhibin A) & 79–83 & 6 \\
\textbf{Combined First and Second Trimesters} & & \\
Integrated (NT assessment, PAPP-A measurement, quadruple screen) & 93–96 & 1–2 \\
Serum integrated (APP-A measurement, quadruple screen) & 84–88 & 2–3 \\
Stepwise sequential: & & \\
\hspace{1cm} If first-trimester test result positive, diagnostic test offered & & \\
\hspace{1cm} If first-trimester test result negative, second-trimester test offered, and final risk assessment incorporates both first- and second-trimester results & & \\
Contingent sequential: & & \\
\hspace{1cm} If first-trimester test result positive, diagnostic test offered & 88–94 & 1 \\
\hspace{1cm} If first-trimester test result negative, no further testing & & \\
\hspace{1cm} If first-trimester test result intermediate, second-trimester test offered, and final risk assessment incorporates both first- and second-trimester results & & \\
\hline
\end{tabular}
\caption{Detection Rate of Down Syndrome Screening Tests}
\end{table}

$\beta$-hCG, Beta-human chorionic gonadotropin; MS-AFP, maternal serum level of alpha-fetoprotein; NT, nuchal translucency; PAPP-A, pregnancy-associated placental protein-A.

\textit{a}Assuming a 5\% false-positive rate.

\textit{b}Assuming an 85\% detection rate.

Data from references \textit{128 and 130–132}. 
The quadruple ("quad") screen ideally should be performed between 16 and 18 (range 15 0/7 and 22 6/7) weeks’ gestation to optimize screening for an open neural tube defect. It consists of measuring four maternal serum analytes: alpha-fetoprotein (MS-AFP), total or free β-subunit hCG (β-hCG), unconjugated estriol, and dimeric inhibin A. The quad screen has a detection rate for Down syndrome of 81%, with a screen positive rate of 5%, which is similar to first-trimester screening. However, advantages of this method include: (1) it is a single test that does not require a specialized ultrasonographic examination; (2) it possesses the ability to screen for open fetal defects, such as open neural tube defects and abdominal wall defects; and (3) abnormal serum analyte measurements help predict risk for other adverse pregnancy outcomes, such as growth restriction, preterm delivery, stillbirth, and preeclampsia.

Screening tests that combine first- and second-trimester results, including integrated, sequential, or contingent screening, have a higher detection rate than first-trimester screening and the quad screen. Integrated screening, which combines a first-trimester nuchal translucency measurement and PAPP-A with a second-trimester quad screen, results in the highest detection rate (96% with a 5% false-positive rate) of all the screening tests. Integrated screening can also assess for open fetal defects, but does not assess all second-trimester serum markers; moreover, if nuchal translucency cannot be obtained, a lower Down syndrome detection rate of 88% with a 5% false-positive rate is observed. Sequential screening differs from integrated screening by reporting first-trimester testing results, which offers a potentially earlier diagnosis of fetal abnormalities. Sequential screening has a Down syndrome detection rate of 95%, with a false-positive rate of 5%.

Screening for aneuploidy by analysis of fetal cell-free short DNA segments released into maternal circulation from the placenta is a newly available technology (see later discussion); the DNA segments provide information about the three most common trisomies (Down syndrome, trisomy 18, and trisomy 13), fetal gender, Rh status in an Rh-negative mother, and some autosomal dominant genetic abnormalities.

Aneuploidy screening in multifetal, versus singleton, pregnancies is not as accurate and is complicated by the number of fetuses and the zygosity. Whereas monozygous twins often have the same karyotype and thus an overall risk for aneuploidy similar to the mother’s age-related risk, dizygous twins each carry a risk for aneuploidy, resulting in an increased risk. Each fetus in a multifetal gestation can be evaluated for nuchal translucency, which has a Down syndrome detection rate of up to 75% with a 9% screen-positive rate. In comparison, a quad screen has a 50% detection rate for Down syndrome in a twin gestation with a 5% false-positive rate. Cell-free DNA is currently not recommended for multifetal pregnancies because of limited evidence regarding efficacy in this population.

Ultrasonographic Screening for Fetal Aneuploidy

First-trimester screening for aneuploidy includes a measurement for thickened nuchal translucency (see earlier discussion), which is associated with an increased risk for aneuploidy and certain anomalies, such as cardiac defects, abdominal wall defects, and diaphragmatic hernia. The presence of a cystic hygroma, which is a thickened nuchal translucency that extends the length of the fetus and contains septations (Fig. 6.8), is associated with a 50% likelihood of aneuploidy, most often Down syndrome, 45,X, and trisomy 18; even those with a normal karyotype will have a major structural malformation 50% of the time, often in the form of a cardiac anomaly, diaphragmatic hernia, skeletal dysplasia, or some other genetic syndrome. The presence of a cystic hygroma results in a healthy, full term infant less than 20% of the time. Diagnosis of thickened nuchal translucency measurement or a cystic hygroma by first-trimester ultrasonographic examination should prompt genetic counseling, diagnostic testing for aneuploidy, and a targeted ultrasonographic examination.
and fetal echocardiogram in the second trimester.\textsuperscript{105} An increased risk for Down syndrome has been associated with the absence of the nasal bone, although this assessment is not included as part of routine first-trimester ultrasound screening because the predictive value in high- or low-risk populations has been questioned.\textsuperscript{114,115}

In the second trimester, major structural abnormalities, such as those associated with trisomy 13 or 18, can be detected more reliably by ultrasonographic examination. Although 50\% of fetuses with Down syndrome appear structurally normal,\textsuperscript{116} more than 30\% have major structural abnormalities (e.g., endocardial cushion defect) that can be detected by ultrasonography.\textsuperscript{116–118} The \textit{genetic sonogram} is a second-trimester screen for Down syndrome using the identification of major structural malformations and minor ultrasonographic \textit{soft markers} of aneuploidy (Table 6.9).

Whereas major cardiac anomalies can be identified in the second trimester, duodenal atresia is typically not identified until the third trimester. Ultrasonographic soft markers do not necessarily represent malformations, but can signal development of fetal abnormalities, such as hydronephrosis developing into renal pyelectasis or an echogenic bowel progressing to intestinal atresia. Soft markers are also common in unaffected fetuses; as a consequence, their presence should prompt screening and testing for aneuploidy, and a targeted ultrasonographic examination if the findings are isolated.\textsuperscript{105}

Second-trimester ultrasonographic markers (Table 6.10) are not part of standard algorithms to predict fetal aneuploidy risk; however, these markers can assist in modifying risk assessments for abnormalities. The clinical significance of isolated ultrasonographic soft markers for Down syndrome in a low-risk population is unclear.

### Definitive Diagnosis of Fetal Chromosomal Abnormalities

Although an abnormal screening test result or the presence of ultrasonographic abnormalities may signal an increased risk for Down syndrome or other chromosomal abnormality, the majority of fetuses with such findings are chromosomally normal. To provide a definitive diagnosis, an invasive procedure is needed to obtain the fetal karyotype; generally amniocentesis or chorionic villus sampling (CVS) is used, although in rare cases a cordocentesis is performed.

All invasive procedures are associated with risks to the pregnancy. Risks common to all invasive procedures include the chance of bleeding, isoimmunization (especially in women who are Rh negative), and infection. All women who are Rh negative should receive Rh(D) immune globulin before or after the procedure. Although the risk for vertical transmission of viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus) with invasive procedures is believed to be low,\textsuperscript{119} every effort should be made to avoid invasive procedures in such patients, especially if there is a high viral load in the maternal circulation.

### TABLE 6.9 Second-Trimester Serum Analyte (Marker) Screening and Adverse Pregnancy Outcome

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Marker</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous loss $&lt; 24$ weeks</td>
<td>MS-AFP</td>
<td>7.8</td>
</tr>
<tr>
<td>Fetal death $\geq 24$ weeks</td>
<td>Inhibin A</td>
<td>3.7</td>
</tr>
<tr>
<td>Preterm birth $\leq 32$ weeks</td>
<td>Inhibin A</td>
<td>5.0</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td>Inhibin A</td>
<td>1.9</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Inhibin A</td>
<td>3.8</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>Inhibin A</td>
<td>1.7</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>MS-AFP</td>
<td>1.9</td>
</tr>
<tr>
<td>Placenta previa (confirmed at delivery)</td>
<td>MS-AFP</td>
<td>3.1</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>Inhibin A</td>
<td>3.0</td>
</tr>
<tr>
<td>Birth weight $\leq$ 5th percentile</td>
<td>Inhibin A</td>
<td>2.3</td>
</tr>
<tr>
<td>• Delivery $&lt; 37$ weeks</td>
<td>Inhibin A</td>
<td>8.0</td>
</tr>
<tr>
<td>• Delivery $&lt; 32$ weeks</td>
<td>Inhibin A</td>
<td>18.6</td>
</tr>
</tbody>
</table>

MS-AFP, Maternal serum level of alpha-fetoprotein.

### TABLE 6.10 Accuracy Measurements of Second-Trimester Ultrasonographic “Soft Markers” for Trisomy 21 (Down Syndrome) When Identified as Isolated Anomalies

<table>
<thead>
<tr>
<th>Ultrasonographic Marker</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickened nuchal fold</td>
<td>0.04 (0.02–0.10)</td>
<td>0.99 (0.99–0.99)</td>
<td>17 (8.0–38.0)</td>
<td>0.97 (0.94–1.00)</td>
</tr>
<tr>
<td>Choroid plexus cyst</td>
<td>0.01 (0.00–0.03)</td>
<td>0.99 (0.97–1.00)</td>
<td>1.00 (0.12–9.40)</td>
<td>1.00 (0.97–1.00)</td>
</tr>
<tr>
<td>Short femur length</td>
<td>0.16 (0.05–0.40)</td>
<td>0.96 (0.94–0.98)</td>
<td>2.7 (1.2–6.0)</td>
<td>0.87 (0.75–1.00)</td>
</tr>
<tr>
<td>Short humeral length</td>
<td>0.09 (0.00–0.60)</td>
<td>0.97 (0.91–0.99)</td>
<td>7.5 (4.7–12.0)</td>
<td>0.87 (0.67–1.10)</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>0.04 (0.01–0.24)</td>
<td>0.99 (0.97–1.00)</td>
<td>6.1 (3.0–12.6)</td>
<td>1.00 (0.98–1.00)</td>
</tr>
<tr>
<td>Echogenic intracardiac focus</td>
<td>0.11 (0.06–0.19)</td>
<td>0.96 (0.94–0.97)</td>
<td>2.8 (1.5–5.5)</td>
<td>0.95 (0.89–1.00)</td>
</tr>
<tr>
<td>Renal pyelectasis (pelvicalyceal dilation)</td>
<td>0.02 (0.01–0.06)</td>
<td>0.99 (0.98–1.00)</td>
<td>1.9 (0.7–5.1)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
</tbody>
</table>

CI, confidence interval; LR, likelihood ratio.
Amniocentesis

Amniotic fluid is composed of fetal urine, lung fluid, skin transudate, and water that is filtered across the amniotic membranes. It contains electrolytes, proteins, and desquamated fetal cells (amniocytes). Sampling of amniotic fluid (amniocentesis) can be used to measure various substances such as lecithin and sphingomyelin for assessing fetal lung maturity, to look for pathogenic bacteria for confirmation of an intra-amniotic infection, and to obtain fetal cells for determination of fetal karyotype or performance of specific genetic analyses.

Cell culture with karyotype analysis typically takes 10 to 14 days, although a small chance exists that the cells will fail to grow, resulting in an inconclusive result. Fluorescence in situ hybridization (FISH) does not require that the cells be cultured for any length of time, and its results can be obtained within a few days. This technique uses a series of chromosome-specific fluorescent probes to analyze the metaphase spread in fetal cells to determine fetal gender and detect common trisomies (21, 18, 13, X, and Y). It can also be used to identify chromosome deletions or duplications in pregnancies at risk for a specific genetic disorder because of a family history or suspicious ultrasonographic findings, such as the 22q11 deletion in DiGeorge syndrome. Although FISH is highly specific (trisomy present on FISH testing is invariably present in the fetus), it is not particularly sensitive, with a false-negative rate of approximately 15%. For this reason, the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) recommend that all FISH results be confirmed by complete karyotype analysis.

The most common indication for second-trimester amniocentesis is cytogenetic analysis of fetal cells, although on occasion it is performed to determine amniotic fluid AFP levels and acetylcholinesterase activity for the diagnosis of fetal open neural tube defects. Amniocentesis later in pregnancy is usually performed for nongenetic indications, such as (1) documentation of fetal pulmonary maturity before elective delivery before 39 weeks’ gestation, (2) amnioreduction in pregnancies complicated by severe polyhydramnios, (3) to confirm preterm premature rupture of membranes (PROM) (amniodye test), or (4) to exclude intra-amniotic infection.

Genetic amniocentesis typically involves the insertion of a 22-gauge spinal needle through the maternal abdominal wall and into the uterine cavity at 15 to 20 weeks’ gestation. The procedure is now commonly performed under ultrasonographic guidance, which allows the operator to choose the safest site, preferably away from the fetal face and umbilical cord and when possible without passage of the needle through the placenta. The greatest risk associated with amniocentesis is spontaneous abortion; however, the procedure-related pregnancy loss rate for genetic amniocentesis appears to be only 1 in 300 to 500. Of interest, the pregnancy loss rate is not influenced by operator experience or needle placement through the placenta but is higher in the presence of first-trimester bleeding or recurrent miscarriage, ultrasonographic demonstration of chorioamniotic separation, discolored amniotic fluid at the time of the procedure, and/or an unexplained elevation in MS-AFP. Whether this risk is higher in twin pregnancies is not clear. Transient leakage of amniotic fluid can be seen in 1% to 2% of procedures. This leakage usually stops after 48 to 72 hours, infection is extremely rare (< 0.1% of cases), and the perinatal survival rate after mid-trimester fluid leakage may be as high as 90%.

Compared with late second-trimester amniocentesis, early amniocentesis (before 15 weeks’ gestation) is associated with significantly higher procedure-related pregnancy loss rates, ranging from 2.2% to 4.8%. This rate is fourfold higher than that of late amniocentesis and twice as high as that of CVS. Early amniocentesis has also been shown to be associated with higher rates of rupture of membranes, club foot, and amniocyte culture failures (2% to 5%) than late amniocentesis. For these reasons, amniocentesis before 15 weeks’ gestation is not recommended.

If early karyotyping is desired, CVS is preferred over early amniocentesis (see later discussion). Amniocentesis in the third trimester is technically easier and is associated with fewer complications. If a late amniocentesis is being performed for any reason (e.g., to confirm fetal pulmonary maturity), consideration should be given to obtaining the karyotype if indicated, even though the pregnancy is too far along to be ended electively.

Amniocentesis in multiple gestations can be performed safely. Care must be taken to carefully map the fetal sacs so that the amniotic fluid for each fetus is sampled separately. A small amount of indigo carmine (3 to 5 mL) is typically inserted into the first sac after the fluid is sampled to ensure that the same sac is not sampled twice.

Chorionic Villus Sampling

Like that of amniocentesis, the goal of CVS is to provide fetal cells for genetic analysis, although in this case the cells are trophoderm (placental) cells rather than amniocytes. The technique entails ultrasound-guided aspiration of chorionic villi by means of a 16-gauge catheter inserted transcervically or a 20-gauge spinal needle inserted transabdominally into the placenta. The 15 to 30 mg of villous material collected can be examined in two ways: (1) by direct cytogenetic analysis after an overnight incubation, which yields results in 2 to 3 days; and (2) by longer-term culture followed by cytogenetic analysis, which yields results in 6 to 8 days. To provide rapid and accurate results, many centers report the results of both methods. The main advantage of CVS over amniocentesis is that it allows for fetal karyotyping results in the first trimester, thereby allowing decisions about pregnancy termination to be made earlier if chromosomal abnormalities are detected. Moreover, although rare, certain genetic disorders (e.g., osteogenesis imperfecta) can be diagnosed antenatally only through analysis of placental tissue.

CVS is best performed between 10 and 12 weeks’ gestation. CVS performed before 10 weeks’ gestation has been associated with limb reduction defects whereas no such
association if the procedure is performed after 66 days’ gestation. Transabdominal CVS can also be performed in the second or third trimester and is a reasonable alternative to cordocentesis for obtaining tissue for an urgent fetal karyotype.

The most common complication of CVS is vaginal spotting, which occurs in 10% to 25% of patients within the first few days after the procedure. Fortunately, the bleeding is usually mild and resolves spontaneously with no long-term sequelae. The incidences of amnionitis (0.3%) and rupture of membranes (0.3%) after CVS do not differ significantly from those seen with late amniocentesis and are significantly lower than those reported after early amniocentesis. As with amniocentesis, the most serious complication of CVS is spontaneous abortion. CVS appears to be associated with a higher risk for pregnancy loss than late amniocentesis; the procedure-related loss rate in CVS is reported as 1.0% to 1.5%. This rate is significantly higher (0.6% to 0.8%) than that seen after late amniocentesis, with an adjusted odds ratio of 1.30 (95% confidence interval [CI], 1.17 to 1.52). Factors that increase the procedure-related loss rate are operator inexperience, number of needle passes, and a history of bleeding before the procedure. By contrast, the risk does not appear to be increased in twin gestations or with the anatomic approach used (i.e., transabdominal versus transcervical catheter placement). Some investigators have suggested that the apparently higher pregnancy loss related to CVS (compared with amniocentesis) is a function of the earlier gestational age at which the procedure is performed.

One complication unique to CVS involves the interpretation of the genetic test results. Because the fetus and placenta both arise from the same cell, it is assumed that the genetic complements of these two tissues are identical, but this is not always the case. Confined placental mosaicism refers to the situation in which the karyotype of the chorionic villus is a mosaic (i.e., it contains two or more populations of cells with different karyotypes, usually one normal and one trisomic) but the karyotype of the fetus is normal. The incidence of confined placental mosaicism may be as high as 1% to 2% with the direct cytogenetic analysis method, but most cases are not confirmed by the long-term tissue-culture method, suggesting a methodologic error. For this reason, many centers report only the long-term culture results. On occasion, it may be necessary to repeat the fetal karyotype, either with a second CVS or with amniocentesis, to resolve the dilemma. The reverse situation, in which the CVS result is normal but the fetus has aneuploidy (a false-negative result), has also been reported but is rare. It may occur from contamination with maternal cells or from inadvertent sampling of a twin placenta.

Cordocentesis
In cases in which pregnancy complications or fetal abnormalities are discovered late in gestation, cordocentesis (also known as percutaneous umbilical blood sampling) is an option for rapid evaluation of the fetal karyotype. Cordocentesis involves the insertion of a 22-gauge spinal needle through the maternal abdominal and uterine walls and into the umbilical vein, preferably at the insertion site on the placenta, under direct ultrasonographic guidance. Considerable training and expertise are needed to perform this procedure. Karyotype analysis results can be obtained in 24 to 48 hours.

The first cordocentesis was reported in 1983. Although this procedure was originally considered superior to amniocentesis for a number of diagnostic indications, advances in laboratory analysis have allowed more information to be obtained through amniocentesis. For example, cordocentesis was commonly used to obtain a sample of fetal blood for rapid karyotyping when a major structural anomaly or severe fetal growth restriction was identified late in pregnancy; however, this sample can be obtained as rapidly from amniocentesis or CVS samples using FISH analysis. Similarly, DNA analysis of amniocytes can rapidly and accurately determine the fetal Rh status and the presence of other red cell and platelet antigens, which in the past was an absolute indication for cordocentesis. Now employed primarily for therapeutic indications, cordocentesis is most commonly used to transfuse fetuses with severe anemia from isoimmunization, parvovirus infection, or fetal-maternal hemorrhage (spilling of fetal blood cells into the maternal circulation). This intra-vascular route of fetal transfusion is preferred to the older technique of intraperitoneal transfusion. Other rare indications for cordocentesis are to measure drug concentrations in the fetal circulation, to document response to pharmacologic therapy, and to administer drugs directly to the fetus (e.g., adenosine to treat resistant fetal tachydysrhythmia).

When skilled operators perform cordocentesis, complications are infrequent and similar to those encountered with amniocentesis. Specifically, there is risk for bleeding, cord hematoma, infection, and preterm PROM. The risk for pregnancy loss as a result of the procedure is estimated to be 1.2% to 4.9%, although fetuses with severe fetal growth restriction, hydrops, or major structural anomalies may be at higher risk compared with well-grown, structurally normal fetuses. Operator experience is an important determinant of success, as are logistical issues (e.g., volume of amniotic fluid, placental position, location of the cord insertion site within the placenta). A transient fetal bradycardia may occur during the procedure, often resulting from unintentional placement of the needle into one of the umbilical arteries and leading to arterial vasospasm. Although this bradycardia invariably resolves, if the fetus is at a favorable gestational age (> 24 weeks), the procedure should be performed at a facility with the capacity to perform an emergency cesarean delivery. There are no consistent data or recommendations regarding the benefits or risks associated with the use of prophylactic antibiotics, tocolysis, or maternal sedation during cordocentesis.

Other Tests
Three-Dimensional Ultrasonography
Compared with standard two-dimensional ultrasonography, three-dimensional (or four-dimensional, if fetal movements are included) ultrasonography allows for concurrent visualization of fetal structures in all dimensions for...
improved characterization of complex anomalies. However, three-dimensional images are subject to interference from structures such as fetal limbs, umbilical cord, and placental tissue, and are greatly influenced by fetal movements; these movements make visualization of the fetal heart suboptimal.

In addition to rapid acquisition of images that can be later reconstructed and manipulated, three-dimensional compared with two-dimensional ultrasonography has the following potential advantages:

1. The ability to provide clearer images of soft tissue structures through surface rendering. Such images may improve the diagnosis of certain fetal malformations, especially craniofacial anomalies (e.g., cleft lip and palate, micrognathia, ear anomaly, facial dysmorphism, intracranial lesions), club foot, finger and toe anomalies, spinal anomalies, ventral wall defects, and fetal tumors.

2. The ability to provide more accurate measurements of the gestational sac, yolk sac, and crown-rump length and to obtain a midsagittal view for measuring nuchal translucency.

3. The ability to measure tissue volume. Preliminary data suggest that assessment of cervical volume may identify women at risk for cervical insufficiency, and measurement of placental volume in the first trimester may determine fetuses at risk for fetal growth restriction.

Despite these advantages, three-dimensional ultrasonography has been used primarily as a complementary technique rather than the standard technique for ultrasonographic imaging. In the future, technical improvements should provide higher-quality images, perhaps similar to those offered by computed tomography and magnetic resonance imaging (MRI).

Complementary Radiographic Imaging

Ultrasonography remains the first-line imaging modality during pregnancy. In certain situations, however, enhanced imaging may be required to better define a particular fetal anomaly. For example, radiographic imaging is superior to ultrasonography in evaluating the fetal skeleton and may provide valuable information in the evaluation of a fetus with a suspected bony dystrophy. At least 25 different forms of skeletal dysplasias are identifiable at birth, 11 of which are lethal in the peripartum period. Although some of these forms can be identified from their unusual appearance on ultrasonography (e.g., cloverleaf skull and small thorax in thanatophoric dysplasia), the majority are difficult to identify. Timely radiographic imaging may allow an experienced pediatric radiologist to more thoroughly evaluate the fetal skeleton and determine the correct diagnosis. A simple maternal abdominal radiograph may be all that is required, because ossification is sufficient by 20 weeks’ gestation to allow good visualization of the fetal bones.

Although computed tomography is best avoided in pregnancy because it exposes the fetus to ionizing radiation (albeit at small doses), MRI is regarded as safe. This latter technology relies on the interaction between an applied magnetic field and the inherent nuclear magnetism of atomic nuclei within the patient’s tissues to generate a high-resolution anatomic image. Because MRI is particularly good at visualizing soft tissue rather than bony structures, it is uniquely suited to the evaluation of fetal intracranial defects and the soft tissues of the maternal pelvis (see Fig. 6.8). Although fetal motion artifact has previously been a major limitation in the use of MRI, new ultrafast technology allows for rapid image acquisition and has largely overcome this problem.

Fetal Echocardiography

Cardiac anomalies are the most common major congenital defects encountered in the antepartum period. A four-chamber ultrasonographic view of the heart during the fetal anatomic survey at 18 to 20 weeks’ gestation detects only 30% of congenital cardiac anomalies, although the detection rate can be increased to 60% to 70% if the outflow tracts are adequately visualized. Owing to the number of congenital cardiac anomalies that would be missed, however, fetal echocardiography should be performed by a skilled and experienced sonologist at 20 to 22 weeks’ gestation in all pregnancies at high risk for a fetal cardiac abnormality. Indications for fetal echocardiography include: (1) pregnancies complicated by pregestational diabetes mellitus, (2) a personal or family history of congenital cardiac disease (regardless of the nature of the lesion or whether it has been repaired), (3) maternal exposure to certain drugs (e.g., lithium, paroxetine), and (4) conception by in vitro fertilization (but not if the pregnancy was conceived through the use of clomiphene citrate or ovarian stimulation/intrauterine insemination alone).

Fetal Cells or DNA in the Maternal Circulation

To minimize the risks associated with invasive prenatal diagnosis (amniocentesis and CVS), improved noninvasive tests are being developed for fetal aneuploidy genetic testing. Fetal DNA, which has a short half-life (precluding contamination from a prior pregnancy) and accounts for 3% to 10% of all cell-free DNA in maternal serum (up to 20% if preclampsia or after major fetal-maternal hemorrhage), can be identified by high-throughput sequencing. Available for use as early as 10 weeks’ gestation, different molecular methods for analyzing the cell-free DNA offer similar detection rates of up to 99% when a result is obtained and a low false-positive rate of 0.5% in women at high risk for Down syndrome. The positive predictive value of cell-free DNA screening is 93% for Down syndrome, 64% for trisomy 18, 44% for trisomy 13, and 39% for sex chromosome aneuploidy. The positive predictive value is lower in low-risk women because of the lower prevalence of aneuploidy compared with women at high risk. Disadvantages of cell-free DNA screening include a high false-positive rate in women at low risk for Down syndrome, and the potential for false-negative results; as a consequence, this technology should not be used as a diagnostic test. Screening results for aneuploidy are reported as positive or negative by the performing laboratory, and the numerical risk for aneuploidy should be provided. Women with positive results should be offered further counseling and
cell-free DNA screening or diagnostic testing by chorionic villus sampling or amniocentesis.\textsuperscript{105}

An alternative approach under investigation for definitive genetic testing is the isolation of trophoblast cells from the cervicovaginal discharge of women in early pregnancy.\textsuperscript{165,166} These cells have been isolated from cervical canal lavage at 7 to 10 weeks’ gestation\textsuperscript{165} or with the use of a brush-type collection device at 5 to 12 weeks (the “genetic Pap smear”).\textsuperscript{166} Trophoblastic cells are found in 86% (195/227) of collected samples, and identified by immunocytochemistry with trophoblast-specific antibodies; the genetic analysis of these cells agree with those from placental tissue karyotyping via CVS in 95% (186/195) of cases.\textsuperscript{166}

Refinement in these methods may allow for a simple, reliable, and noninvasive genetic test for fetal aneuploidy in an early, singleton pregnancy with no risk to the mother or fetus.

**SPECIAL CIRCUMSTANCES REQUIRING ADDITIONAL FETAL SURVEILLANCE**

Under certain circumstances, additional antenatal fetal surveillance may be required (see Box 6.2). If appropriate, early consultation with a specialist (e.g., a maternal-fetal medicine specialist, medical geneticist, pediatric surgeon, pediatric urologist, pediatric cardiologist, or infectious disease specialist) and delivery at a tertiary care center should be considered.

**Abnormal Serum Analyte and Nuchal Translucency Screening with Normal Fetal Karyotype**

Pregnancies with abnormal serum analyte screening in the first or second trimester are at increased risk for adverse outcomes, including preterm birth, preeclampsia, and stillbirth, even if the karyotype is normal (see Tables 6.8 and 6.9).\textsuperscript{167–169} Such pregnancies therefore require more intensive fetal monitoring (Table 6.11), including serial growth evaluation and NST. Fetuses with a nuchal translucency measurement of 3.0 mm or more in the first trimester have a higher risk for congenital heart defects and other chest abnormalities, even with a negative aneuploidy screening test result and normal fetal chromosomes.\textsuperscript{170,171} Women with such pregnancies should be offered a fetal echocardiogram at 20 to 22 weeks’ gestation in addition to a routine targeted fetal anatomic survey at 18 to 20 weeks.

<table>
<thead>
<tr>
<th><strong>TABLE 6.11</strong></th>
<th>Special Circumstances Requiring Additional Fetal Surveillance during Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-Related Condition</td>
<td>Additional Testing Recommended</td>
</tr>
<tr>
<td><strong>Maternal Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Growth scans q3-4 wk</td>
</tr>
<tr>
<td>Weekly NST ± AFV</td>
<td>32 weeks</td>
</tr>
<tr>
<td>Diabetes mellitus:</td>
<td></td>
</tr>
<tr>
<td>Pregestational diabetes</td>
<td>Growth scans q3-4 wk</td>
</tr>
<tr>
<td>Weekly NST ± AFV</td>
<td>32 weeks</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Growth scans q3-4 wk</td>
</tr>
<tr>
<td>Weekly NST ± AFV</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Maternal obesity (body mass index &gt; 30 kg/m(^2))</td>
<td>Weekly NST ± AFV</td>
</tr>
<tr>
<td>Advanced maternal age</td>
<td>Weekly NST ± AFV</td>
</tr>
<tr>
<td>Abnormal serum analyte screening result (MS-AFP &gt; 2.0 MoM; pregnancy-associated placental protein-A [PAPP-A] &lt; 0.4 MoM) with normal fetal karyotype</td>
<td>Growth scans q3-4 wk</td>
</tr>
<tr>
<td>Weekly NST ± AFV</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Prior unexplained preterm birth &lt; 35 weeks</td>
<td>Weekly to biweekly cervical length measurements ± Weekly to biweekly fFN</td>
</tr>
<tr>
<td>24 weeks to 32-34 weeks</td>
<td></td>
</tr>
<tr>
<td>Prior cervical cone biopsy</td>
<td>Weekly to biweekly cervical length measurements ± Weekly to biweekly fFN</td>
</tr>
<tr>
<td>24 weeks to 32-34 weeks</td>
<td></td>
</tr>
<tr>
<td>Postterm pregnancy</td>
<td>Twice-weekly NST and AFV</td>
</tr>
<tr>
<td>Isoimmunization</td>
<td>Weekly middle cerebral artery Doppler velocimetry</td>
</tr>
<tr>
<td><strong>Uteroplacental Conditions</strong></td>
<td>Growth scans q3-4 wk</td>
</tr>
<tr>
<td>Chronic abruption</td>
<td>Weekly NST ± AFV</td>
</tr>
<tr>
<td>Uterus didelphys</td>
<td>Weekly to biweekly cervical length measurements</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td>Daily NST</td>
</tr>
<tr>
<td>Growth scans q3-4 wk</td>
<td>From diagnosis</td>
</tr>
<tr>
<td>Weekly AFV</td>
<td>From diagnosis</td>
</tr>
</tbody>
</table>
TABLE 6.11  Special Circumstances Requiring Additional Fetal Surveillance
during Pregnancy—cont’d

<table>
<thead>
<tr>
<th>Pregnancy-Related Condition</th>
<th>Additional Testing Recommended</th>
<th>Gestational Age at Which Testing Should Be Started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained oligohydramnios</td>
<td>Growth scans q3-4 wk</td>
<td>From diagnosis</td>
</tr>
<tr>
<td></td>
<td>Weekly AFV</td>
<td>From diagnosis</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>32 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly UA Doppler velocimetry</td>
<td>From diagnosis</td>
</tr>
<tr>
<td>Fetal Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin pregnancy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichorionic, diamniotic twin pregnancy</td>
<td>Biweekly AFV</td>
<td>18–20 weeks</td>
</tr>
<tr>
<td></td>
<td>Growth scans q3-4 wk</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>28–32 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly to biweekly cervical length measurements</td>
<td>16–18 weeks to 30–32 weeks</td>
</tr>
<tr>
<td></td>
<td>± Weekly to biweekly fFN</td>
<td>22–24 weeks to 30–32 weeks</td>
</tr>
<tr>
<td>Monochorionic, diamniotic twin pregnancy</td>
<td>Weekly AFV</td>
<td>16–18 weeks</td>
</tr>
<tr>
<td></td>
<td>Growth scans q3-4 wk</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>28–32 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly to biweekly cervical length measurements</td>
<td>16–18 weeks to 30–32 weeks</td>
</tr>
<tr>
<td></td>
<td>± Weekly to biweekly fFN</td>
<td>22–24 weeks to 30–32 weeks</td>
</tr>
<tr>
<td>Monochorionic, monoamniotic twin pregnancy</td>
<td>Weekly AFV</td>
<td>16–18 weeks</td>
</tr>
<tr>
<td></td>
<td>Growth scans q3-4 wk</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly to biweekly cervical length measurements</td>
<td>16–18 weeks to 30–32 weeks</td>
</tr>
<tr>
<td></td>
<td>± Weekly to biweekly fFN</td>
<td>22–24 weeks to 30–32 weeks</td>
</tr>
<tr>
<td></td>
<td>± Continuous fetal heart rate monitoring</td>
<td>24–26 weeks to delivery</td>
</tr>
<tr>
<td>Twin pregnancy complicated by demise of one twin</td>
<td>Weekly NST with AFV</td>
<td>From diagnosis</td>
</tr>
<tr>
<td>Higher-order multiple pregnancy (≥ triplets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Growth scans q3-4 wk</td>
<td>From diagnosis</td>
</tr>
<tr>
<td></td>
<td>Weekly AFV</td>
<td>16–18 weeks</td>
</tr>
<tr>
<td></td>
<td>Growth scans q3-4 wk</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>28–32 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly to biweekly cervical length measurements</td>
<td>16–18 weeks to 30–32 weeks</td>
</tr>
<tr>
<td></td>
<td>± Weekly to biweekly fFN</td>
<td>22–24 weeks to 30–32 weeks</td>
</tr>
<tr>
<td>Fetal growth restriction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10th percentile</td>
<td>Growth scans q3-4 wk</td>
<td>From diagnosis</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>From diagnosis</td>
</tr>
<tr>
<td>&lt; 5th percentile</td>
<td>Growth scans q3-4 wk</td>
<td>From diagnosis</td>
</tr>
<tr>
<td></td>
<td>Weekly to twice-weekly NST with AFV</td>
<td>From diagnosis</td>
</tr>
<tr>
<td>Major fetal structural anomaly</td>
<td>Growth scans q3-4 wk</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly NST with AFV</td>
<td>32 weeks</td>
</tr>
<tr>
<td></td>
<td>Weekly UA Doppler velocimetry</td>
<td>32 weeks</td>
</tr>
</tbody>
</table>

AFV, Amniotic fluid volume; biweekly, every 2 weeks; fFN, fetal fibronectin; MoM, multiple of median; MS-AFP, maternal serum level of alpha-fetoprotein; NST, nonstress test; UA, umbilical artery.

Hydrops Fetalis

*Hydrops fetalis* (”edema of the fetus”) is a rare pathologic condition that complicates approximately 0.05% of all pregnancies. It is an ultrasonographic diagnosis requiring the presence of an abnormal accumulation of fluid in more than one fetal extravascular compartment, including ascites, pericardial effusion, pleural effusion, subcutaneous edema, and/or placental edema. Polyhydramnios is seen in 50% to 75% of cases. Although classically seen in fetuses with severe anemia resulting from Rh isoimmunization, the introduction of Rh(D) immune globulin has led to a substantial decrease in the incidence of immune hydrops. Indeed, 90% of hydrops fetalis cases are a result of nonimmune causes, such as maternal infection (e.g., with parvovirus B19, cytomegalovirus, syphilis), massive fetal-maternal hemorrhage, and fetal abnormalities (e.g., congenital cardiac defects, fetal thalassemia, twin-to-twin transfusion syndrome). Although the overall perinatal mortality rate in the setting of hydrops fetalis exceeds 50%, the prognosis depends on the underlying cause, severity, and gestational age.

Immune hydrops occurs when fetal erythrocytes express a protein that is not present on maternal erythrocytes. The maternal immune system can become sensitized and produce antibodies against these “foreign” proteins. These immunoglobulin (Ig) G antibodies can cross the placenta and destroy
fetal erythrocytes, leading to fetal anemia and high-output cardiac failure. Immune hydrods is typically associated with a fetal hematocrit less than 15% (normal fetal hematocrit is 50%). The most antigenic protein on the surface of fetal erythrocytes is the D antigen of the Rhesus protein complex, also known as Rh(D). Other antigens that can cause severe immune hydrods are Kell (“Kell kills”), Rh(E), Rh(c), and Duffy (“Duffy dies”). Antigens causing less severe hydrods are ABO, Rh(e), Rh(C), Ce, k, and s. Lewis a and b (Le^a, Le^b) incompatibility can cause mild anemia but not hydrods, because this condition primarily results in production of IgM antibodies, which do not cross the placenta (“Lewis lives”). For identification of women at risk for isoimmunization, every pregnant woman should undergo blood type and antibody screening at the first prenatal visit and again in the third trimester.

Sixty percent of cases of immune hydrods result from ABO incompatibility; however, only Rh(D) isoimmunization can be prevented. The Rh(D) antigen is expressed only on primate erythrocytes and becomes evident by 38 days of intrauterine life. A mutation in the Rh(D) gene on chromosome 1 results in lack of expression of Rh(D) antigen on circulating erythrocytes (Rh[D] negative). This mutation arose in the Basque region of Spain, and the difference in prevalence of Rh(D)-negative individuals between the races likely reflects the amount of Spanish blood in their ancestry: Caucasian, 15%; African-American, 8%; African, 4%; Native American, 1%; and Asian, less than 1%.172 If the fetus of an Rh(D)-negative woman is Rh(D) negative, Rh(D) sensitization will not occur. However, 60% of Rh(D)-negative women have Rh(D)-positive fetuses, and exposure of these women to as little as 0.25 mL of Rh(D)-positive blood may induce an antibody response. Because the initial immune response is production of IgM, the index pregnancy is rarely affected. However, immunization in subsequent pregnancies triggers an IgG response that crosses the placenta and causes hemolysis. Risk factors for Rh(D) sensitization include a mismatched blood transfusion (95% sensitization rate), ectopic pregnancy (<1%), abortion (3% to 6%), amniocentesis (1% to 3%), and pregnancy itself. Indeed, the sensitization rate is 16% to 18% after a normal pregnancy without Rh(D) immune globulin administration, 1.3% with Rh(D) immune globulin at delivery only, and 0.13% with anti-Rh(D) immune globulin at 28 weeks and again after delivery.172,173 The risk for isoimmunization depends on the volume of fetal-maternal hemorrhage (Table 6.12). Passive immunization with Rh(D) immune globulin can destroy fetal erythrocytes before they evoke a maternal immune response, thereby preventing sensitization. Therefore, Rh(D) immune globulin should be given within 72 hours of potential exposure; 300 µg given intramuscularly is adequate for exposure to as much as 30 mL of fetal whole blood or 15 mL of fetal red blood cells.

Once isoimmunization has occurred, passive immunoglobulin is not useful. Such pregnancies should be observed closely for evidence of fetal compromise. Fetal hemolysis results in release of bile pigment into the amniotic fluid, which can be quantified as a change in optical density measured at a wavelength 450 nm. Traditionally, the extent of hemolysis had been measured with serial amniocenteses, with amniotic fluid optical density plotted against gestational age; increased density (upper 80% of zone 2 of zone 3 of the Liley curve) is associated with a poor prognosis,174,175 and prompt intervention is indicated. Measurements of peak systolic velocity in the fetal MCA by means of noninvasive Doppler velocimetry have now emerged as the best tool to accurately identify fetuses with severe anemia requiring urgent intervention, regardless of the cause of the anemia.94,176,177 The sensitivity of an elevated MCA peak systolic velocity (i.e., >1.5 MoM for a given gestational age) for predicting moderate to severe anemia approaches 100%.94 Depending on gestational age, these interventions may include immediate delivery or intrauterine blood transfusion.

### Postterm Pregnancy

Postterm pregnancy is defined as any pregnancy that continues to or beyond 42 weeks (294 days) from the first day of the last normal menstrual period or 14 days beyond the best obstetric estimate of the EDD, while a late-term pregnancy is defined as one between 41 0/7 weeks and 41 6/7 weeks of gestation.177 The prevalence of postterm pregnancy depends on the patient population (e.g., percentage of primigravidas, incidence of pregnancy complications, frequency of spontaneous preterm births) and the local practice patterns (e.g., use of ultrasonographic assessment of gestational age, cesarean delivery rates, use of labor induction); the incidence of postterm pregnancy in the United States has steadily decreased over time to 0.35% in 2016.178 Compared with delivery at 40 weeks, postterm pregnancies pose significant risks to both the mother (including higher risk for cesarean delivery, severe perineal injury, and postpartum hemorrhage) and the fetus (including stillbirth, fetal macrosomia, birth injury, and meconium aspiration syndrome).183 A Cochrane review of 22 randomized control trials involving 9383 women determined that induction of labor at term is associated with a decreased risk for perinatal death, cesarean delivery, and meconium aspiration syndrome.183 For this reason, induction of labor after 42 0/7 weeks and by 42 6/7 weeks' gestation

<table>
<thead>
<tr>
<th>Transfusion Volume</th>
<th>Incidence at Delivery (%)</th>
<th>Risk for Isoimmunization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmeasurable</td>
<td>50</td>
<td>Minimal</td>
</tr>
<tr>
<td>&lt; 0.1 mL</td>
<td>45–50</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 5.0 mL</td>
<td>1</td>
<td>20–40</td>
</tr>
<tr>
<td>&gt; 30 mL</td>
<td>0.25</td>
<td>60–80</td>
</tr>
</tbody>
</table>

*Without Rh(D) immune globulin.

is recommended, while induction of labor between 41 0/7 weeks and 42 0/7 weeks’ gestation can be considered.184

Postterm pregnancy is an indication for antenatal fetal surveillance,185 although the efficacy of this approach has not been validated by prospective randomized trials.185 Options for evaluating fetal well-being include NST with or without amniotic fluid volume assessment, BPP, CST, and a combination of these modalities. There is no consensus as to which of these modalities is preferred, and no single method has been shown to be superior.185 The ACOG has recommended that antepartum fetal surveillance be initiated by 42 weeks’ gestation at the latest, without making a specific recommendation about the type of test or frequency.185 Many investigators would advise twice-weekly testing with some evaluation of amniotic fluid volume at least weekly. Doppler ultrasonography has no benefit in monitoring the postterm fetus and is not recommended for this indication.86,87 Although the data are inconsistent, there is a suggestion that antenatal testing at 40 to 42 weeks’ gestation may be associated with improvements in perinatal outcome. In one retrospective study, women with routine antenatal testing beginning at 41 weeks’ gestation had lower rates of cesarean delivery for nonreassuring fetal test results than women in whom testing was started at 42 weeks (2.3% versus 5.6%, respectively; P < .01).184 In addition, the group with delayed antenatal testing experienced three stillbirths and seven other neonatal major morbidity events, compared with none in the group who had antenatal testing from 41 weeks (P < .05).184

In the postterm period, evidence of fetal compromise (nonreassuring fetal test results) or oligohydramnios (e.g., low amniotic fluid volume) should prompt delivery.185 Oligohydramnios, defined as amniotic fluid index of 5 cm or less or a single deepest pocket of 2 cm or less, has been associated with an increased risk for fetal demise and is an indication for delivery at or beyond 41 0/7 weeks’ gestation. Recent studies concluded that use of a deepest vertical pocket of 2 cm or less to diagnose oligohydramnios, rather than an amniotic fluid index of 5 cm or less, was associated with a reduction of unnecessary interventions without an increase in adverse perinatal outcomes.186,187 Oligohydramnios may result from uteroplacental insufficiency or increased renal artery resistance and may predispose to umbilical cord compression, thus leading to intermittent fetal hypoxemia, meconium passage, and meconium aspiration. Adverse pregnancy outcomes (nonreassuring FHR tracing, low Apgar score, and neonatal intensive care unit admission) are more common when oligohydramnios is present. Frequent screening of postterm patients for oligohydramnios is important, because amniotic fluid can become dramatically reduced within 24 to 48 hours.188

Intrauterine Fetal Demise

Intrauterine fetal demise (IUFD), also known as stillbirth, is defined in the United States as demise of the fetus after 20 weeks’ gestation and before delivery.189 The stillbirth rate in the United States was 5.96 per 1000 live births in 2013, with approximately half occurring before 28 weeks.186 However, it remains a vastly underappreciated clinical problem, with antepartum stillbirths accounting for more perinatal deaths than either complications of prematurity or sudden infant death syndrome.190 Risk factors for stillbirth include extremes of maternal age, chromosomal disorders, congenital malformations, antenatal infection, multiple pregnancy, prior unexplained IUFD, postterm pregnancy, fetal macrosomia, male fetus, umbilical cord and placental abnormalities, and underlying maternal medical conditions (e.g., chronic hypertension, preeclampsia, congenital heart disease, diabetes mellitus, autoimmune disorders, inherited or acquired thrombophilia).189,191,192

Although older studies observed that approximately 50% of cases of IUFD were unexplained, an aggressive approach may identify the cause in up to 80% to 90% of cases (Table 6.13).192–195 Pathologic examination of the fetus and the placenta/fetal membranes is the single most useful means of identifying a cause for the IUFD.192–195 Early detection and appropriate management of underlying maternal disorders (e.g., diabetes, preeclampsia) may also reduce the risk. Genetic testing should be considered for determining the cause of stillbirth. Compared with karyotype testing, microarray analysis is more likely to yield a result because it does not require dividing cells to detect genomic abnormalities.196 Some 6% to 10% of stillborn fetuses have an abnormal karyotype.195 On occasion, amniocentesis may be recommended to salvage viable amniocytes for cytogentic analysis before delivery. Fetal-maternal hemorrhage occurs in all pregnancies but is usually minimal (< 0.1 mL total volume); in rare instances, a significant hemorrhage may occur, leading to fetal demise. The Kleihauer-Betke (acid elution) test allows an estimate of the volume of fetal blood in the maternal circulation, and a maternal blood sample should be drawn within 6 to 8 hours of the purported bleeding episode because of rapid clearance of fetal cells from the maternal circulation.197 Intra-amniotic infection resulting in fetal death is usually evident on clinical

<table>
<thead>
<tr>
<th>TABLE 6.13 Causes of Intrauterine Demise</th>
<th>Causes of Intrauterine Demise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal causes</td>
<td>Underlying medical conditions (diabetes mellitus, thyroid disease, antiphospholipid antibody syndrome)</td>
</tr>
<tr>
<td></td>
<td>Preeclampsia</td>
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<tr>
<td></td>
<td>Isoimmunization</td>
</tr>
<tr>
<td></td>
<td>Illicit drug use (cocaine)</td>
</tr>
<tr>
<td></td>
<td>Antepartum drug/toxin exposure</td>
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<tr>
<td></td>
<td>Placental abruption</td>
</tr>
<tr>
<td></td>
<td>Placenta previa</td>
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<tr>
<td></td>
<td>Vasa previa</td>
</tr>
<tr>
<td></td>
<td>Fetomaternal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Cord accident</td>
</tr>
<tr>
<td>Uteroplacental causes</td>
<td>Fetal chromosomal/genetic anomalies</td>
</tr>
<tr>
<td></td>
<td>Fetal structural abnormalities</td>
</tr>
<tr>
<td></td>
<td>Intra-amniotic infection</td>
</tr>
<tr>
<td></td>
<td>Complications of multiple pregnancies (including twin-to-twin transfusion syndrome)</td>
</tr>
</tbody>
</table>
examination. Placental membrane culture and autopsy examination of the fetus, placenta/fetal membranes, and umbilical cord may be useful. Fetal radiography or MRI may sometimes be valuable if autopsy is declined.198,199

The inability to identify fetal heart activity or the absence of uterine growth may suggest the diagnosis. Ultrasonography is the “gold standard” for confirming IUFD by documenting the absence of fetal cardiac activity. Other ultrasonographic findings in late pregnancy include Spalding’s sign (overlapping of the cranial sutures), scalp edema, and soft tissue maceration, although these usually take a few days to develop. Every effort should be made to avoid cesarean delivery in the setting of IUFD. Thus, in the absence of a contraindication, expectant management is often recommended. Latency (the period from fetal demise to delivery) varies according to the underlying cause and gestational age. In general, the earlier the gestational age, the longer the latency period. Overall, more than 90% of women go into spontaneous labor within 2 weeks of fetal death. However, many women find the prospect of carrying a dead fetus distressing and want the pregnancy terminated as soon as possible. Management options include surgical dilation and evacuation or induction of labor with prostaglandins or oxytocin has been shown to be safe in the setting of an IUFD. Therefore, delivery should be effected within this period. Induction of labor with prostaglandins or oxytocin has been shown to be safe in the setting of an IUFD.

The death of one fetus in a twin gestation poses a particular challenge, and the risks are related to the type of placentation. In monochorionic twin gestations, the death of one twin puts the surviving co-twin at significant risk for major morbidity, including IUFD, neurologic injury, multiorgan system failure, thromboembolic events, placental abruption, and preterm birth.202–204 The prognosis for the surviving twin depends on the cause of death, gestational age, chorionicity, and the time between death of the first twin and delivery of the second. However, there is some level of shared circulation in almost all monochorionic twin pregnancies, and death of one fetus in this setting raises the risk for death of its co-twin owing to profound hypotension and/or purported transfer of thromboplastic proteins from the dead fetus to the live fetus.205 If it survives, the co-twin has a 20% risk for development of permanent neurologic injury (multicystic encephalomalacia), which may not be prevented by immediate delivery.206,207 Dichorionic twin pregnancies do not share a circulation, and death of one twin may have little impact on the surviving twin. The dead twin may be resorbed completely or may become compressed and incorporated into the membranes (fetus papryraceus). Disseminated intravascular coagulation in the surviving fetus and/or mother is rare.208

Regardless of type of placentation, management of the surviving twin should include regular fetal surveillance (kick counts, NST, BPP), and consideration of delivery in the setting of nonreassuring fetal test results or at a favorable gestational age.

**FETAL THERAPY**

Continued assessment of the fetus throughout pregnancy is critical to optimizing pregnancy outcomes. In most cases, evidence of fetal compromise prompts delivery. However, in certain situations, treatment may be available to improve or even correct the underlying problem in utero. These interventions can be noninvasive (e.g., administration of digoxin to the mother to treat a fetal supraventricular tachycardia) or invasive (e.g., placement of a vesicoamniotic shunt) and are summarized in Tables 6.14 and 6.15, respectively.209–244 Some

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**TABLE 6.14** Noninvasive Treatment Options to Improve Perinatal Outcome

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Treatment</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imminent risk for preterm birth &lt; 34 weeks</td>
<td>Antenatal corticosteroids</td>
<td>Effective in decreasing respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis209</td>
</tr>
<tr>
<td>Pregestational diabetes mellitus</td>
<td>Strict glycemic control</td>
<td>Effective in decreasing rate of stillbirths and birth defects210</td>
</tr>
<tr>
<td>Phenylketonuria (autosomal recessive disorder caused by phenylalanine hydroxylase deficiency)</td>
<td>Dietary manipulation (low-phenylalanine diet)</td>
<td>Effective in decreasing birth defects and brain damage in affected fetuses211</td>
</tr>
<tr>
<td>Alloimmune thrombocytopenia</td>
<td>Maternal intravenous immunoglobulin ± corticosteroids</td>
<td>Data conflicting on effect of intravenous immunoglobulin on fetal platelets; steroids probably of no benefit212,213</td>
</tr>
<tr>
<td>Fetal thyrotoxicosis</td>
<td>Maternal propylthiouracil</td>
<td>Effective in decreasing fetal growth restriction and subsequent neurodevelopmental defects214,215</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia (usually caused by 21-hydroxylase deficiency)</td>
<td>Maternal dexamethasone</td>
<td>Effective in preventing virilization of female fetus if given before 8 to 9 weeks’ gestation216</td>
</tr>
<tr>
<td>Fetal supraventricular tachycardia (SVT)</td>
<td>Maternal digoxin</td>
<td>Data conflicting on effect of digoxin to correct fetal SVT</td>
</tr>
</tbody>
</table>
TABLE 6.15 Invasive Treatment Options to Improve Perinatal Outcome

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Treatment</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe fetal anemia with or without hydrops fetalis</td>
<td>Intrauterine transfusion</td>
<td>Effective217,218</td>
</tr>
<tr>
<td>Fetal supraventricular tachycardia</td>
<td>Digoxin given directly to fetus by intramuscular injection</td>
<td>Effective</td>
</tr>
<tr>
<td>Severe obstructive uropathy</td>
<td>Vesicoamniotic shunting</td>
<td>Effective in preventing renal injury and improving survival219</td>
</tr>
<tr>
<td>Isolated fluid collection in the fetus (severe ascites, hydrothorax)</td>
<td>Fetoamniotic shunting</td>
<td>Effective220</td>
</tr>
<tr>
<td>Severe valvular stenosis</td>
<td>Fetal surgery (in utero valvuloplasty)</td>
<td>Investigational221</td>
</tr>
<tr>
<td>Fetal lung masses (congenital cystic adenomatous malformation, pulmonary sequestration)</td>
<td>Fetal surgery (in utero resection of lesion)</td>
<td>Investigational222,223</td>
</tr>
<tr>
<td>Congenital hydrocephalus</td>
<td>Fetal surgery (in utero shunting)</td>
<td>Investigational224</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>Fetal surgery (in utero repair; tracheal occlusion)</td>
<td>Investigational225,226</td>
</tr>
<tr>
<td>Fetal neural tube defect</td>
<td>Multifetal pregnancy reduction</td>
<td>Investigational227-229</td>
</tr>
<tr>
<td>Higher-order multiple pregnancy (≥ triplets)</td>
<td>Serial amnioreduction versus septostomy versus fetal surgery (endoscopic laser ablation, cord ligation)</td>
<td>Effective in improving perinatal outcomes with reduction to twins230-233</td>
</tr>
<tr>
<td>TTTS</td>
<td>Laser ablation appears to give the best chance of intact survival in severe TTTS234-239</td>
<td>Investigational240-242</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td>Serial amniinfusion versus fetal surgery (laser coagulation, intra-amniotic amniopatch)</td>
<td>Case reports of success243,244</td>
</tr>
<tr>
<td>EXIT</td>
<td>To facilitate oxygenation at delivery before ligation of the umbilical cord when the infant’s airway is obstructed; may facilitate transition to ECMO in infants with severe pulmonary or cardiac malformations</td>
<td></td>
</tr>
</tbody>
</table>

ECMO, extracorporeal membrane oxygenation; EXIT, ex utero intrapartum therapy; TTTS, twin-to-twin syndrome.

of these interventions have been subjected to rigorous clinical trials and have been shown to be effective, whereas others remain investigational. The intervention that has perhaps had the greatest effect on perinatal outcome is antenatal maternal administration of corticosteroids.

Antenatal Corticosteroids

Respiratory distress syndrome (RDS) refers to respiratory compromise presenting at or shortly after delivery as a result of a deficiency of pulmonary surfactant, an endogenous detergent that serves to decrease the surface tension within alveoli, thereby preventing alveolar collapse. Overall, neonatal RDS affects approximately 1% of live births, but not all infants are at equal risk. The pulmonary system is among the last of the fetal organ systems to become functionally mature. Thus, RDS is primarily, although not exclusively, a disease of preterm infants, with the incidence and severity highly dependent on gestational age. For example, RDS affects more than 80% of infants younger than 28 weeks’ gestation and 10% to 15% of all infants weighing less than 2500 g.245,246 RDS remains a major cause of perinatal morbidity and mortality in extremely preterm infants. In addition to gestational age, a number of other factors influence the risk for RDS in a given fetus. For reasons that are not clear, African-American ethnicity, female gender, preeclampsia, and intrauterine exposure to cigarette smoke are protective against the development of RDS.

In 1972, Liggins and Howie247 demonstrated that the administration of a single course of two antenatal doses of a corticosteroid (betamethasone) reduced the incidence of RDS by 50%. A meta-analysis of 12 randomized controlled trials with more than 3000 participants concluded that antenatal administration of corticosteroids to women in preterm labor reduced the incidence of neonatal RDS by 40% to 60% and resulted in an improvement in overall survival.209 In one study, a single course of antenatal corticosteroids resulted in a threefold rise in the chance of unaffected survival in neonates with a birth weight less than 1500 g.248 Certain steroids cross the placenta and induce cellular differentiation at the expense of growth. Type II pneumocytes in the lungs differentiate and begin making pulmonary surfactant, which accounts for the decrease in risk for RDS, and endothelial cells lining the vasculature undergo cellular maturation and stabilization, which explains the concomitant drop in incidence of bleeding into the brain (intraventricular hemorrhage) or gastrointestinal tract (necrotizing enterocolitis).249 Prednisone does not cross the placenta and therefore does not have a similar protective effect.

The National Institutes of Health and the ACOG have recommended that a single course of antenatal corticosteroids,
defined as either betamethasone (12 mg intramuscularly q24h × two doses) or dexamethasone (6 mg intramuscularly q12h × four doses), be given after 23 to 34 weeks’ gestation to any pregnant women in whom delivery before 34 weeks’ gestation is threatening. More recently, the ACOG has recommended a course of corticosteroids for women with a singleton pregnancy in whom delivery is threatening between 34 0/7 weeks and 36 6/7 weeks’ gestation, in the absence of chorioamnionitis and who have not received a previous course of antenatal corticosteroids. Although the maximum benefit of antenatal corticosteroids is achieved 24 to 48 hours after the first injection, as little as 4 hours of treatment exerts some protective effect. This protective effect lasts for 7 days, after which further benefit is unclear. Multiple (three or more) courses of antenatal corticosteroids have been associated with fetal growth restriction, smaller head circumference, and (in animals) abnormal myelination of the optic nerves; consequently, multiple courses are not routinely recommended. A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks’ gestation and at risk for preterm delivery within the next 7 days, at least 7 days after the prior dose.

Fetal Surgery

Fetal surgery has been proposed in selected cases to prevent progressive organ damage or to restore normal anatomy and fetal development (see Chapter 7). The ideal case for fetal surgery consists of a singleton pregnancy before fetal viability (i.e., before 23 to 24 weeks’ gestation) in which the fetus has a normal karyotype and an isolated malformation that, if untreated, will result in fetal or neonatal demise. A detailed understanding of the natural history of the malformation is essential when one is considering whether to recommend surgery. Fetal surgery should not be attempted if the natural history of the disorder is unknown or if the chances of survival without in utero treatment are greater than or equal to the risks associated with the procedure. The only two randomized controlled trials published to date in fetal surgery—one on tracheal occlusion for the management of congenital diaphragmatic hernia and the other on prenatal versus postnatal repair of myelomeningocele—found little significant benefit to in utero surgery. Moreover, although pediatric benefit with open maternal-fetal surgery for myelomeningocele repair has been observed, there are significant maternal risks, including the need for cesarean delivery with all future pregnancies (similar to that for women with a history of a classical cesarean delivery). Repair of lesions that are not believed to be life threatening (e.g., cleft lip and palate) should be deferred until after delivery to minimize risks to the mother.

Before in utero surgery can be recommended, a thorough evaluation must be performed to (1) precisely characterize the defect, (2) exclude associated malformations, (3) perform a fetal karyotype analysis, and (4) eliminate the possibility that the condition can be treated using less aggressive technologies. Detailed counseling about the risks and benefits of the proposed procedure is required, and written informed consent is mandatory. Such a discussion must include a detailed review of the risks to both the fetus and the mother, including preterm PROM (28% to 100%), preterm labor and delivery (> 50%), maternal pulmonary edema (20% to 30%), placental abruption (5% to 10%), chorioamnionitis and sepsis (< 5%), and maternal death (rare). Specific examples of fetal surgical procedures are summarized in Table 6.15.
# REFERENCES


The ability to treat underlying fetal conditions with medical procedures or surgery is a relatively recent development. Fetal therapy originated in 1963 with Sir William Liley’s successful intraperitoneal blood transfusion to a fetus with erythroblastosis fetalis.1 In 1981, following sheep and primate studies, the first successful human fetal surgery, a vesicostomy, was performed in a fetus with bilateral hydronephrosis secondary to a lower urinary tract obstruction.2

Advances in prenatal diagnosis, imaging, and surgical equipment have all contributed to the development of fetal surgery. Some fetal abnormalities are amenable to intrauterine fetal surgery, but the majority of anatomic malformations diagnosed in utero remain unsuitable for fetal intervention. Prenatal diagnosis of serious malformations (e.g., those that are uncorrectable and incompatible with normal postnatal life) allows the choice of pregnancy termination. Most correctable malformations are best managed after delivery, with antepartum recognition allowing time for the coordination of appropriate prenatal and postnatal care. Some defects, especially those that cause airway obstruction or irreversible end-organ damage, are suitable for intrapartum intervention. This allows the benefit of intervention while the uteroplacental unit remains functional and often eliminates any urgency that would be associated with undertaking the procedure in the postnatal period.

Guidelines for performing fetal surgery (Box 7.1) were originally developed more than 35 years ago but remain relevant today with only minimal modifications.3,4 All fetal interventions should undergo multidisciplinary deliberation and planning. Potential maternal risks should be discussed as part of the consent process and a detailed maternal preoperative evaluation completed to ensure minimal risk to the mother. Guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) recommend that fetal treatment centers include a multidisciplinary comprehensive consent and counseling process, oversight of fetal research, and participation in a data-sharing fetal intervention network.5

Fetal surgical interventions can be broadly categorized into three kinds of procedures, namely, minimally invasive procedures, open surgical procedures, and intrapartum procedures. A summary of fetal conditions, therapy, and intervention is detailed in Table 7.1.

**Minimally invasive procedures** involve either fetoscopic or image-guided percutaneous procedures, typically performed near mid-gestation. They entail a lower risk for preterm labor and delivery than open procedures because they do not require a hysterotomy, yet the risk for preterm premature rupture of membranes (PROM) remains.6

**Open surgical procedures** involve both a maternal laparotomy and hysterotomy with use of pharmacologic agents to maintain uterine relaxation. These procedures are typically performed near mid-gestation and entail greater maternal and fetal risks compared with the minimally invasive procedures.
techniques, including a significant risk for preterm PROM, preterm labor and delivery, uterine dehiscence, oligohydramnios, hemorrhage, pulmonary edema, and fetal mortality. In addition, after an open surgical procedure, a cesarean delivery is required for the pregnancy and all future deliveries owing to the location of the hysterotomy and the associated risks for uterine dehiscence or rupture.7,8

The third kind of procedure involves a modification of cesarean delivery to allow intrapartum fetal therapy while the fetus remains supported by placental gas exchange. These delivery techniques are termed ex utero intrapartum therapy (EXIT) procedures.9 EXIT procedures are most often employed in order for gas exchange to continue across the placenta (placental bypass) while (1) securing the airway by endotracheal intubation, bronchoscopy, or tracheostomy in fetuses with congenital airway obstruction or neck mass or (2) performing invasive fetal procedures required before delivery. The EXIT procedure enables the prevention of asphyxia in neonates in whom securing an airway after birth can be problematic. The procedure can also be used as a bridge to extracorporeal membrane oxygenation (ECMO) for a fetus with cardiopulmonary disease at risk for postnatal cardiac failure or failure of adequate pulmonary gas exchange.10,11

### Guidelines for Performing Fetal Procedures

1. Accurate diagnosis and staging is possible.
2. Other anomalies that would contraindicate fetal intervention are excluded.
3. Progression, severity, and prognosis of the condition are understood.
4. No effective postnatal therapy is currently available, and if not treated before birth, the anomaly would result in fetal death, irreversible organ damage, or other severe postnatal morbidity.
5. Intrauterine surgery has been proven feasible in animal models, with demonstrated reversal of the deleterious effects of the condition.
6. The maternal risk is acceptably low.
7. Interventions are performed in specialized multidisciplinary fetal treatment centers within strict protocols and approval of the local ethics committee, with informed consent obtained from the mother or parents.
8. There is access to high-level specialized medical care, including bioethical and psychosocial care and counseling.


### TABLE 7.1 Fetal Conditions and Interventions

<table>
<thead>
<tr>
<th>Fetal Condition</th>
<th>Therapy Rationale</th>
<th>Type</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal anemia or thrombocytopenia</td>
<td>Prevention of heart failure and fetal hydrops</td>
<td>Fetal image guided</td>
<td>Intrauterine transfusion</td>
</tr>
<tr>
<td>Aortic stenosis, intact atrial septum, or pulmonary atresia</td>
<td>Prevention of fetal hydrops, myocardial dysfunction, and hypoplastic left (and right) heart</td>
<td>Fetal image guided</td>
<td>Percutaneous fetal valvuloplasty or septoplasty</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>Bladder decompression with reduction in renal dysfunction, pulmonary hypoplasia, oligohydramnios, and limb malformation</td>
<td>Fetal image guided or fetoscopy</td>
<td>Percutaneous vesicoamniotic shunting or fetoscopic laser ablation of urethral valves</td>
</tr>
<tr>
<td>Twin reversed arterial perfusion sequence</td>
<td>Prevention of high-output cardiac failure in the normal twin by stopping flow to the acardiac twin</td>
<td>Fetal image guided or fetoscopy</td>
<td>Umbilical radiofrequency ablation or fetoscopic cord coagulation</td>
</tr>
<tr>
<td>Twin-to-twin transfusion syndrome</td>
<td>Reduction of twin-to-twin blood flow and prevention of cardiac failure</td>
<td>Fetoscopy</td>
<td>Fetoscopic laser photoocoagulation of placental vessels and/or amnioreduction</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>Prevention of pulmonary hypoplasia</td>
<td>Fetoscopy</td>
<td>Fetoscopic tracheal occlusion</td>
</tr>
<tr>
<td>Myelomeningocele</td>
<td>Reduction in hydrocephalus and hindbrain herniation with improved neurologic function</td>
<td>Open</td>
<td>Closure of fetal defect in utero</td>
</tr>
<tr>
<td>Sacrococcygeal teratoma</td>
<td>Prevention of high-output cardiac failure, hydrops, and polyhydramnios</td>
<td>Fetal image guided or open</td>
<td>Ablation of tumor vasculature or open fetal tumor debulking</td>
</tr>
<tr>
<td>Congenital cystic adenomatoid malformation</td>
<td>Reversal of pulmonary hypoplasia and cardiac failure</td>
<td>Fetal image guided or open</td>
<td>Thoracoamniotic shunting or open fetal lobectomy</td>
</tr>
<tr>
<td>Fetal airway compression</td>
<td>Secured airway and/or circulatory support to prevent respiratory compromise at birth</td>
<td>Open intrapartum</td>
<td>Ex utero intrapartum therapy that allows stabilization while on uteroplacental circulation</td>
</tr>
</tbody>
</table>

**INDICATIONS AND RATIONALE FOR FETAL SURGERY**

**Fetal Anemia and Intrauterine Transfusion**

The rate of fetal anemia secondary to rhesus D (RhD) sensitization has decreased to 1 in 1000 pregnancies following the use of RhD immunoglobulin prophylaxis. Fetal anemia can occur secondary to other red cell antigens, viral infections, homozygous thalassemia, maternal-fetal hemorrhage, and placental chorioangiomas. Serial Doppler studies of the middle cerebral artery (MCA) peak velocity are used to diagnose fetal anemia. A sample of fetal umbilical cord blood just before starting the intrauterine transfusion (IUT) is the most accurate test for fetal anemia. Before 18 weeks’ gestation, intraperitoneal transfusion may be chosen for treatment of fetal anemia given that accessing the umbilical vein may not be possible. In this procedure, donor red blood cells are injected into the fetal peritoneal cavity and transported through the lymphatic system to the fetal circulation. With early diagnosis of severe cases, combining these two procedures with immunoglobulin therapy may provide added benefit.

IUTs are frequently performed using a 20- or 22-gauge needle with local anesthesia at the needle insertion site. The needle is inserted percutaneously through the maternal abdomen and uterus under ultrasonographic guidance to access the umbilical vein (Fig. 7.1). The cord is often accessed near its placental insertion for stability, but a loop of umbilical cord or an intrahepatic portion of the cord can also be used. The volume of O-negative, cytomegalovirus (CMV)-negative, irradiated, leukocyte-depleted, packed red blood cells is determined based on the estimated fetal weight, gestational age, autologous hemoglobin, and hemoglobin of the sampled fetal blood. Following an IUT, the fetal hemoglobin levels slowly decrease, and multiple IUTs are often required at 1- to 3-week intervals. Although the umbilical cord does not have pain receptors, if the needle is advanced into the fetus for intrahepatic vascular access, a fetal stress response will occur; fentanyl or another opioid should be administered to blunt this response. An intramuscular paralytic agent can be administered to the fetus to decrease the chance of fetal movement dislodging the transfusion needle or sheering the cord vasculature. Providers should be prepared for a possible emergent cesarean delivery at any point during the IUT if the fetus is of viable age. Rates of fetal demise following IUT range from 1% to 5%. Increased risk for fetal demise is associated with fetal hydrops, early gestational age, not using fetal paralysis, operator inexperience, and severity of fetal anemia. Other complications include transient fetal bradycardia (8%), emergent cesarean delivery (2%), intrauterine infection (0.3%), and rupture of membranes (0.1%).

**Obstructive Uropathy**

Lower urinary tract obstruction (LUTO) occurs in approximately 1 in 5000 live births. Congenital bilateral hydronephrosis results from fetal urethral obstruction at the bladder outlet, most commonly by either posterior urethral valves (typically male fetuses) or urethral atresia. Other causes of fetal obstructive uropathy include obstruction at the ureteropelvic or vesicoureteric junction and a number of complex disorders in females (e.g., cloacal plate anomalies). These uropathies are typically evaluated by ultrasonography, which is often performed to investigate oligohydramnios from diminished fetal urine output. Magnetic resonance imaging (MRI) can also be used, but there is no evidence that it is superior. LUTO may lead to progressive renal dysplasia and dysfunction, bladder distention, and oligohydramnios, and ultimately result in devastating developmental consequences, such as limb and facial deformities, pulmonary hypoplasia, and even neonatal death (Fig. 7.2). A disease severity classification system for LUTO based primarily on amniotic fluid index, renal imaging, and urinary biochemistries has recently been proposed. Although postnatal correction relieves the obstruction, 25% to 30% of survivors develop end-stage kidney disease requiring dialysis by 5 years of age. Early intrauterine intervention with placement of a vesicoamniotic shunt (VAS) allows drainage of urine from the fetal bladder into the amniotic cavity, thereby decompressing the urinary tract. In animal models, intrauterine relief of obstructive uropathy improves dysplastic renal histology, restores normal...
Current evidence supports the use of fetal intervention for LUTO in selected fetuses in an effort to restore amniotic fluid volume, prevent pulmonary hypoplasia, and decrease perinatal mortality. However, the effects on long-term renal function, bladder function, and other morbidities remain unclear.

**Congenital Diaphragmatic Hernia**

Approximately 1 in 2500 live-born infants has a congenital diaphragmatic hernia (CDH). Without fetal intervention, this anomaly causes significant morbidity and mortality from pulmonary hypoplasia and insufficiency. Survival rates have improved to greater than 70% over the past 25 years and are closely associated with the degree of pulmonary hypertension and respiratory insufficiency.\(^{28,29}\) Significant mortality occurs despite optimal postnatal surgical management at tertiary care medical centers (i.e., procedures involving removal of the herniated viscera from the chest, administration of surfactant, ventilation techniques that minimize lung trauma, use of ECMO, and closure of the diaphragm). Intrauterine correction of CDH has the potential to prevent pulmonary hypoplasia and allow the fetal lung to develop before delivery.\(^{30}\)

Fetal lamb models of CDH demonstrated that parenchymal hypoplasia and associated pulmonary vascular changes could be reversed by correction *in utero*.\(^{30}\) Primary open repairs of human CDH *in utero* have been undertaken only for fetuses with severe disease, with limited success but many lessons learned, including the development of minimally invasive approaches.\(^{31}\)

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associated with CDH. It is a less extensive, palliative fetal surgical procedure that enhances lung growth to improve postnatal survival, with postponement of the definitive repair until after birth.\(^3\) Once the trachea is occluded, fetal pulmonary fluid slowly accumulates and expands the lung, pushing the viscera out of the thorax. A small detachable balloon for endoluminal tracheal occlusion is placed in the trachea via percutaneous endoscopic endotracheal intubation and is either left in place until delivery or deflated earlier (Fig. 7.3).\(^3\)\(^5\)\(^6\)

A prospective randomized trial (1999–2001) evaluated fetal tracheal occlusion for intrauterine treatment of severe CDH.\(^3\)\(^7\) Inclusion criteria included (1) a gestational age of 22 to 28 weeks, (2) left-sided herniation of the liver into the hemithorax, and (3) a low lung-to-head ratio (LHR) (i.e., \(< 1.4\)). The LHR is a ratio of the contralateral lung cross-sectional area compared with head circumference and is correlated with the severity of pulmonary hypoplasia and survival for a given gestational age.\(^3\)\(^8\) The trial was closed early \((n = 11)\). Fetal tracheal occlusion resulted in no improvement in survival compared with the control group \((77\% \text{ versus } 73\%)\) and no reduction in morbidity at 90 days. The rates of preterm PROM and preterm delivery were higher in the fetal intervention group.\(^3\)\(^7\) However, the survival rate was unexpectedly high in the control group. It is speculated that the LHR criterion of less than 1.4 was not sufficiently restrictive and allowed inclusion of fetuses in the study that were likely to survive with standard postnatal tertiary medical care. Table 7.2 notes improved survival for left-sided CDH fetuses treated in utero with an LHR \(< 1.0\) compared with standard postnatal care.

Use of fetal endoscopic tracheal occlusion (FETO) began to focus on more severe cases of CDH with a high risk for death.\(^3\)\(^7\) FETO intervention criteria for fetuses at high risk included both an LHR less than 1.0 and liver herniation into the hemithorax.\(^4\) Owing to concern for tracheal damage by very early tracheal balloon placement,\(^4\) the tracheal balloon is placed between 26 and 28 weeks’ gestation and removed before birth by a second fetoscopic procedure near 34 weeks’ gestation (if the fetus is still in utero).\(^4\)\(^2\) This second procedure is performed to minimize the risk for preterm labor, avoid the need for the EXIT procedure (discussed later in the chapter), and possibly improve lung growth and minimize the reduction of type II alveolar cells associated with prolonged tracheal occlusion. Recently, a single institution, prospective observational cohort study compared treatment of left-sided severe CHD (LHR \(< 1.0\) and liver herniation) with FETO to historic controls.\(^4\)\(^3\) The FETO group had mean balloon placement and removal at 28 and 34 weeks’ gestation, respectively. The FETO group had increased 2-year survival (67\% versus 11\%) and reduced need for ECMO. A recent meta-analysis examined five trials published between 2004 and 2012 that compared FETO to contemporary controls.\(^4\)\(^4\) All studies included isolated severe CDH with an LHR \(\leq 1.0\) and liver herniation into the thorax. Survival outcome was improved with FETO (odds ratio 13). In all these studies, it is possible that the comparative results may represent selection bias or improvements in technique and clinical care over time. Although promising, there is currently inadequate evidence to recommend intrauterine fetal intervention to treat CDH as a routine clinical practice.\(^4\)\(^2\)

In 2009, a randomized Tracheal Occlusion to Accelerate Lung growth trial (TOTAL) was started.\(^4\)\(^5\) It compares postnatal CDH management to both late (30 to 32 weeks’ gestation) FETO intervention for moderate lung hypoplasia

### Table 7.2 Postnatal Survival in Fetuses With Left-Sided Congenital Diaphragmatic Hernia and Intrathoracic Liver Herniation Based on Fetal Lung-to-Head Ratio

<table>
<thead>
<tr>
<th>LHR (mm)(^a)</th>
<th>POSTNATAL MANAGEMENT</th>
<th>FETOSONIC TRACHEAL OCCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Fetuses</td>
<td>Survival Number (%)</td>
<td>Number of Fetuses</td>
</tr>
<tr>
<td>0.4–0.5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>19</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>1.0–1.1</td>
<td>23</td>
<td>14 (60.8)</td>
</tr>
<tr>
<td>1.2–1.3</td>
<td>19</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>1.4–1.5</td>
<td>11</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>(\geq 1.6)</td>
<td>6</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>43 (50)</td>
</tr>
</tbody>
</table>

LHR, Lung-to-head ratio.

\(^a\)LHR measurements in the table were obtained at 23 to 29 weeks’ gestation.

and also earlier FETO intervention (27 to 30 weeks’ gestation) for severe lung hypoplasia. In both arms of the TOTAL trial, the balloon is removed in the 34th week of gestation. In addition, it is now appreciated that LHR depends on gestational age and that a ratio of observed to expected LHR is a better expression of CDH severity and likelihood of survival.\(^\text{37,38}\) This ratio is used as part of the ongoing TOTAL trial. Results of this trial will help determine if FETO should be offered and whether there is an optimal gestational age to intervene.

**Congenital Pulmonary Airway Malformation**

Congenital pulmonary airway malformations (CPAMs) are pulmonary tumors with cystic and solid components usually isolated to a single lung. These malformations were previously described as congenital cystic adenomatoid malformations (CCAMs). The incidence is approximately 1 in 25,000 pregnancies. A second-trimester ultrasonogram is reliable and accurate in detecting pulmonary lesions, with MRI and color Doppler ultrasonography facilitating differentiation between CPAM, bronchopulmonary sequestration, bronchogenic cysts, neurogenic cysts, and CDH.\(^\text{39}\) The classification scheme for CPAM proposed by Stocker includes five subtypes, based on cyst size, characteristics of the epithelial lining, cyst wall thickness, and the presence of mucous cells, cartilage, and skeletal muscle.\(^\text{50}\) Lesions are assessed by ultrasonography and can be divided by the presence of cysts either larger (macrocystic) or smaller (microcystic) than 5 mm in diameter.\(^\text{40}\) Lesions can regress, resulting in minimal associated morbidity, or progressively enlarge, often resulting in fetal hydrops (fetal heart failure). The size and growth of the lesions, rather than their specific type, are the primary determinate of overall prognosis. Small lesions detected in utero or in the neonate are treated after birth by surgical excision of the affected pulmonary lobe. Large lesions can cause mediastinal shift, hydrops, polyhydramnios, and pulmonary hypoplasia and can interfere with fetal or neonatal survival. Fetuses with untreated lesions associated with hydrops have a survival rate of less than 5%.\(^\text{51}\) In a retrospective single-institution review of 71 cases, the initial antenatal ultrasonographic ratio of CPAM volume-to-fetal head circumference (congenital pulmonary airway malformation volume ratio [CVR]) was evaluated for hydrops formation and postnatal outcomes.\(^\text{52}\) Fetuses with a CVR less than 0.56 were noted to have no adverse postnatal outcomes, whereas a CVR greater than 0.56 had a positive predictive value for adverse postnatal outcomes of 33%. In addition, a CVR greater than 1.6 was associated with a greater risk for hydrops, and a CVR less than or equal to 1.6 with absence of a dominant cyst was associated with a < 3% risk for hydrops.\(^\text{53}\)

Depending on size, location, and other characteristics, CPAMs can be managed with either fetal intervention or postnatal resection. Macrocystic lesions can be decompressed in utero by thoracocentesis or placement of shunt catheters between the cystic area and the amniotic cavity, resulting in sustained decompression and resolution of hydrops.\(^\text{54}\) These in utero procedures are followed by postnatal surgery. However, not all lesions can be decompressed successfully with a shunt because the cysts are not always contiguous (i.e., in communication with each other) and can refill rapidly. In addition, thoracoamniotic shunts have associated risks, including malfunction, displacement, fetal hemorrhage, preterm PROM, preterm labor, and chorioamnionitis.\(^\text{55}\) In a series of 68 fetuses with macrocystic CPAMs treated with thoracoamniotic shunts, the overall survival rate was 68% in hydropic and 88% in nonhydropic fetuses.\(^\text{56}\) CPAMs inappropriate for drainage can be resected with open fetal surgery. Intrauterine pulmonary lobectomy for lesions associated with fetal hydrops has resulted in a 30-day postnatal survival rate of 50%, with tumor resection allowing for compensatory lung growth and resolution of hydrops.\(^\text{57}\) Additional, less common options include resection while on placental circulation (EXIT procedure) or on postnatal ECMO, radiofrequency or laser ablation, and percutaneous ultrasound-guided sclerotherapy.\(^\text{58}\) Maternal administration of betamethasone has been noted to improve fetal hydrops and overall outcome in selected fetuses with CPAM.\(^\text{59-60}\) Thoracoamniotic shunts have also been successfully placed to decompress massive congenital pleural effusions caused by fetal chylothorax that otherwise would result in hydrops fetalis, pulmonary compression, and fetal or neonatal death.\(^\text{61}\)

**Sacrococcygeal Teratoma**

With a prevalence of approximately 1 in 20,000 to 40,000, sacrococcygeal teratoma (SCT) is associated with perinatal demise in 25% to 37% of cases.\(^\text{62}\) Management of these tumors requires serial ultrasonographic assessments, as some undergo rapid, substantial growth (i.e., 1000 cubic centimeters),\(^\text{63}\) function as large arteriovenous fistulas, and result in high-output cardiac failure, hydrops fetalis, and placentomegaly. SCTs are staged using the Altman criteria,\(^\text{64,65}\) which focuses on their location. Stage I tumors are based entirely outside the pelvis and are suitable for intervention; by contrast, Stage IV tumors are completely within the pelvis and not amenable to fetal resection. Tumor size is estimated based on a tumor volume-to-fetal weight ratio, with large SCTs considered > 0.12 cm\(^3\)/g;\(^\text{66}\) rapid growth (>150 cm\(^3\)/week) is associated with adverse outcomes, including tumor rupture and hemorrhage, as well as intrapartum dystocia.\(^\text{64,67}\) Fetuses with lesions diagnosed before 30 weeks’ gestation have a poor prognosis (< 7% survival) but may benefit from in utero intervention.\(^\text{64}\) Current surgical techniques do not allow complete resection of lesions that deeply invade the pelvis; however, in utero radiofrequency ablation, embolization, and thermocoagulation of the tumor or feeding vessels can reduce the tumor burden and resolve hydrops. Large multicenter studies are needed to determine which therapies deliver the most definitive, optimal benefits (Fig. 7.4A).\(^\text{64,68}\) During open fetal tumor resection (Fig. 7.4B), catheterization of a fetal limb or umbilical cord vein may be needed to allow for blood or fluid administration.

Some SCT cases are accompanied by “maternal mirror” or Ballantyne syndrome, a hyperdynamic state (i.e., hypertension, peripheral and pulmonary edema) in which the maternal physiology mimics the abnormal circulatory physiology
of the hydropic fetus. This syndrome is associated with a substantial increase in fetal mortality and maternal morbidity and requires aggressive management similar to that used for preeclampsia with severe features, a disease from which it must be distinguished. Platelet count, aspartate aminotransferase, alanine aminotransferase, and haptoglobin are typically unaffected in maternal mirror syndrome and may serve as diagnostic clues. Unfortunately, maternal mirror syndrome does not resolve quickly, even with rapid correction of the fetal pathophysiology, and severe life-threatening maternal complications including pulmonary edema occur in about 20% of cases.

Myelomeningocele

Although not lethal, a myelomeningocele (MMC) is the most common form of spina bifida and characterized by a protrusion of the meninges and spinal cord through a congenital defect in the vertebrae and overlying muscles and skin (Fig. 7.5A). MMC has an incidence of about 1 in 3000 live births and can result in lifelong morbidity and disability, including paraplegia, bowel and bladder incontinence, hydrocephalus, Arnold-Chiari II malformation, and impaired cognition. Neonates with MMC have become less common owing to maternal folate supplementation and detection by ultrasonography and alpha-fetoprotein screening of maternal blood, which has allowed for earlier consideration of pregnancy termination.

The specific cause of MMC remains unknown but includes a variety of genetic factors, maternal nutrition factors, maternal co-morbidities, and environmental factors. Animal models demonstrated improved neonatal neurologic function with fetal closure of the defect in utero. These outcomes support a “two-hit” disease model in which the pathology is produced by both failure of the fetal neural tube to form, combined with prolonged exposure to the uterine amniotic fluid.

The 5-year mortality rate of MMC is approximately 8% for live births; if it is not corrected in utero, surgical closure must be performed within a few days after birth. With postnatal
MMC repair, ventriculoperitoneal shunting is required in nearly all neonates with thoracic level lesions, approximately 85% of lumbar level lesions, and approximately 70% of sacral lesions.\textsuperscript{72} Despite successful shunting, permanent deficits such as central hypoventilation, vocal cord dysfunction, and oromotor and swallowing dysfunction can still occur from the associated Arnold-Chiari malformation. In addition, lifelong complications also include fecal and urinary incontinence, orthopedic abnormalities, neurocognitive abnormalities, and lower-extremity paralysis. Cognitive and motor deficits are directly related to spinal lesion level; higher-level defects are associated with more severe brain dysmorphology.\textsuperscript{72}

The purpose of in utero surgery for MMC is to improve function later in life. Primarily performed through an open fetal surgical technique, in utero MMC repair involves removing the cystic membrane covering the deficit and separating the meninges from the fetal skin and soft tissues (see Fig. 7.5B). The fetal dura is then closed over the neural placode, followed by closure of the paraspinous myofascial flaps and, finally, the mobilized skin. If the defect is too large for primary closure, an acellular human dermis graft is used.

A randomized, prospective, multicenter clinical trial completed between 2003 and 2010 examined the risks and benefits of open fetal surgery versus standard postnatal surgery for MMC repair in 183 patients.\textsuperscript{76} In utero repair reduced the need for ventriculoperitoneal shunt placement (40% versus 82%, \(P < .001\)) and improved motor function at 30 months of age, as assessed by ability to walk without orthotic devices (42% versus 21%, \(P = .01\)). However, in utero repair also increased the risk for chorionic membrane separation, oligohydramnios, preterm birth, and a partial or complete uterine dehiscence (Table 7.3).\textsuperscript{8,76} Two perinatal deaths occurred in each group; expected future data from the trial will assess long-term outcomes from both interventions.

Although the vast majority of in utero MMC repairs use an open technique, a few centers have employed a minimally invasive endoscopic repair approach that includes intrathecocerebrospinal fluid and carbon dioxide insufflation of the amniotic cavity for improved fetal visualization and manipulation.\textsuperscript{77} A biocompatible patch or primary closure is used to cover the neural defect following release of the placode, and then the fetal skin layer is closed. A 2012 study of 19 patients undergoing endoscopic intrauterine MMC repair observed high maternal and fetal complication rates;\textsuperscript{78} three procedures were aborted because of severe hemorrhage, and in an additional three cases, the fetus died intraoperatively. A 2016 phase I trial of endoscopic fetal repair in 10 MMC patients resulted in 2 of the 10 procedures aborted because of loss of uterine access, 1 fetal and 1 neonatal demise, and PROM in 100% of the cases.\textsuperscript{79} Six of the seven neonates who had successful in utero MMC repairs had reversal of hindbrain herniation (although three required shunting), and a functional motor level that was the same or better than the anatomic level of the defect.

Although endoscopic MMC repairs have comparable shunt rates to open MMC repairs and can diminish uterine thinning or dehiscence,\textsuperscript{74} they have been associated with longer operative times, increased membrane complications, earlier gestational age at time of birth, more persistent CSF leakage, and increased perinatal demise.\textsuperscript{71,78-80} Although promising, further optimization of the endoscopic approach will be needed before widespread clinical use.\textsuperscript{71,74} Additional minimally invasive fetal treatment techniques being examined include the use of tissue engineering methods and the infusion of stem cells.\textsuperscript{73}

**Twin-to-Twin Transfusion Syndrome**

An abnormal connection of chorionic blood vessels in the placenta between two monochorionic twins can result in twin-to-twin transfusion syndrome (TTTS). One-third of twin pregnancies are monozygotic, and 75% of monozygotic twins are monochorionic diamniotic (MCDA). TTTS typically complicates about 10% of these MCDA pregnancies, or about 1 per 5000 births in general.\textsuperscript{81} Twin screening for TTTS starts at the end of the first trimester, with recognition typically occurring between 15 and 26 weeks’ gestation.\textsuperscript{82} Inter-twin transfusion is common between monochorionic twins and is usually balanced by the presence of arterioarterial (AA) and venovenous (VV) connections; the presence of AA connections is associated with a ninfold reduction in TTTS.\textsuperscript{83} By contrast, unidirectional and imbalanced blood flow

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**Figure 7.5** Myelomeningocele (MMC). (A) Spine with myelomeningocele. (B) Myelomeningocele repair during open in utero fetal surgery. Note the cystic membrane covering the deficit has been incised and meninges are visible inside the cystic cavity. The absorbable copolymer staples used during creation of the hysterotomy are visible along the uterine edges. (A) Modified from Kerr LM, Huether SE. Alterations of neurologic function in children. In McCance KL, Huether SE, Brashers VL, Rote NS, eds. Pathophysiology: The Biologic Basis for Disease in Adults and Children, 7th ed. St. Louis, MO: Elsevier; 2014:660–688. B courtesy of author Mark Rollins during his affiliation with the UCSF Fetal Treatment Center.)
TABLE 7.3 Maternal and Fetal or Neonatal Complications for MOMS Trial Patients*

<table>
<thead>
<tr>
<th>Maternal Outcomes</th>
<th>Prenatal (n = 78)</th>
<th>Postnatal (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamniotic membrane separation</td>
<td>20 (26%)</td>
<td>0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5 (6%)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>16 (21%)</td>
<td>3 (4%)</td>
<td>.001</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>5 (6%)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Spontaneous rupture of membranes</td>
<td>36 (46%)</td>
<td>6 (8%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Spontaneous labor</td>
<td>30 (38%)</td>
<td>11 (14%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Blood transfusion at delivery</td>
<td>7 (9%)</td>
<td>1 (1%)</td>
<td>.03</td>
</tr>
<tr>
<td>Hysterotomy site thin, or partial or complete dehiscence noted at delivery</td>
<td>27 (36%)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal Outcomes</th>
<th>Prenatal (n = 78)</th>
<th>Postnatal (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal bradycardia during repair</td>
<td>8 (10%)</td>
<td>0</td>
<td>.003</td>
</tr>
<tr>
<td>Mean gestational age at birth (weeks)</td>
<td>34.1 ± 3.1</td>
<td>37.3 ± 1.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mean birth weight (g)</td>
<td>2383 ± 688</td>
<td>3039 ± 469</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>16 (21%)</td>
<td>5 (6%)</td>
<td>.008</td>
</tr>
</tbody>
</table>

*The table lists maternal and fetal/neonatal complications that were significantly different (P < .05) between the prenatal and postnatal repair groups in the Management of Myelomeningocele Study (MOMS). Other outcomes were evaluated, but only those that were different between the two groups are included. Data for each group are shown as both an absolute number and as a percentage.


Through arteriovenous (AV) chorial vessels results in TTTS. In normal fetoplacental vasculature, the umbilical artery branches at the placenta surface, traverses, and then descends into the tissue, where it further branches into capillary divisions for gas and nutrient exchange. The arterial system is “paired” with venous vasculature, which returns blood to the umbilical cord. In TTTS, the umbilical artery similarly descends into the placenta and cotyledon, but rather than connecting with a paired vein from the same twin, it connects with a vein that transports blood to the other twin.82,84 The pathophysiology of TTTS is complex, dynamic, and related to various hemodynamic, humoral, biochemical, and functional changes in the two fetuses.

The twin serving as the recipient demonstrates polycythemia, polyuria, polyhydramnios, and hypertrophic cardiomyopathy; this twin is at risk for hydrops fetalis and fetal death. The twin serving as the donor is typically hypovolemic, growth restricted, and pressure against the endometrium in an oligohydramnionic sac (hence the designation “stuck” or “pump” twin) and often has a velamentous cord insertion. This twin is at risk for neonatal renal failure, tubular dysgenesis and dysfunction, and high cardiac output hydrops fetalis.

The diagnosis of TTTS requires two criteria: (1) the presence of an MCDA pregnancy; (2a) the presence of oligohydramnios, defined as a maximal vertical pocket (MVP) of < 2 cm in one amniotic sac, and (2b) the presence of polyhydramnios, defined as MVP of > 8 cm in the other amniotic sac.81 The most commonly used staging system describing the severity of TTTS was published by Quintero and is displayed in Table 7.4. Serial fetal echocardiographic assessments, using a myocardial performance index, can assess and monitor the severity of TTTS in the recipient twin.85 Although the donor twin typically has normal cardiac function, the recipient twin can develop ventricular hypertrophy, atrioventricular valve regurgitation, ventricular diastolic and systolic dysfunction, and right ventricular outflow tract obstruction.

Fetuses with TTTS are at risk for neurologic injury with white matter lesions and long-term disability, preterm PROM, and preterm delivery. If TTTS remains at Stage I or resolves, the overall survival rate is about 85%81; however, if TTTS progresses, the overall mortality rate of one or both fetuses can increase to more than 80% if untreated.86

A variety of therapeutic management techniques have been developed to treat TTTS: (1) serial amnioreduction, which can control polyhydramnios, thereby reducing the risk for preterm labor, reducing hydrostatic pressure in the amniotic cavity, and potentially improving placental blood flow; (2) ultrasound-guided needle septostomy, which can equalize amniotic pressures between the amniotic sacs; (3) selective feticide, which can improve the survival of the other fetus; and (4) selective fetoscopic laser photocoagulation (SFLP) of the vascular anastomoses between the twins.

In a retrospective review of 223 twin sets with TTTS, amnioreduction resulted in an overall birth survival rate of 78%, with 65% of recipient twins and 55% of donor twins alive at 1 month of age.87 In a prospective randomized trial comparing serial amnioreduction to septostomy, there was no difference in the rate of survival between the two techniques85; consequently, septostomy is rarely used because it offers no survival benefit, and the creation of a single amniotic sac can increase the risk for umbilical cord entanglement. Selective fetoside of one twin is reserved for the most severe cases of TTTS and uses techniques described in the section on twin reversed arterial perfusion sequence later in the chapter.
The laser used for SFLP is typically inserted through a fetoscope to allow visualization of the vascular anastomoses to be ablated. The fetoscope enters the maternal abdomen and uterus through a 3-mm percutaneously inserted cannula that allows passage into the recipient twin’s amniotic sac (Fig. 7.6). Maternal anesthesia is commonly managed with either neuraxial blockade or local anesthetic infiltration from skin to myometrium. The fetoscope placement is guided by ultrasonography and ideally positioned at 90 degrees to the placental vascular surface. The location of the abnormal vascular connections (vascular equator) is determined by tracing vessels visualized by the fetoscope from each fetus and determining their connections and cessations. In addition, Doppler ultrasonographic imaging can be used to determine the magnitude and direction of vessel blood flow. A vessel traveling from one fetus, inserting into a cotyledon, and then exiting and traveling to the cord root of the other fetus is considered nonfunctional, pathologic, and a target for photocoagulation.89 Arteries always travel over veins, allowing the two vessels to be distinguished. Nonselective laser ablations of vessels were initially performed, until lower fetal survival rates were demonstrated when compared with selective techniques. After completion of the SFLP, amniotic fluid may be removed to reduce the degree of polyhydramnios and decrease the risk for preterm labor.

A 2004 randomized multicenter trial demonstrated the benefits of SFLP compared with amnioreduction for treatment of severe TTTS diagnosed between 15 and 26 weeks’ gestation.90 Rates of at least one twin survival were significantly higher in the laser treatment group at both 28 days (76% versus 56%, \( P < .01 \)) and 6 months of life (76% versus 51%, \( P < .01 \)). In addition, neurologic outcomes were better in the SFLP group. A systematic review and meta-analysis of 34 studies examining TTTS treated with laser therapy published between 1995 and 2014 noted that treatment of TTTS with laser ablation resulted in improved survival rates over

![Fig. 7.6 In utero fetoscopic laser ablation for twin-to-twin transfusion syndrome. Under ultrasound guidance, a fetoscope is inserted percutaneously into the recipient twin’s amniotic sac. Using both ultrasonographic guidance and fetoscopic visualization, intertwin vessels are identified and ablated with the laser. (From Graves CE, Harrison MR, Padilla BE. Minimally invasive fetal surgery. Clin Perinatol. 2017;44:729–751.)](image-url)
time; the most recent studies (2011 to 2014) demonstrate a 62% mean survival rate for both twins and an 88% survival rate for at least one twin. A variation of the SFLP technique requires laser ablation of abnormal vasculature in a specific sequence. First, ablation occurs at the donor-to-recipient AV anastomoses, then at the recipient-to-donor AV anastomoses, then at the AA superficial anastomoses, and finally at the VV superficial anastomoses. The order of the procedure is designed to reduce the chance of hemodynamic compromise and hypotension during the procedure in the donor twin. Although associated with longer operative times, the use of the sequential technique has been associated with improved dual neonatal survival and decreased fetal demise in cohort studies.

In an effort to reduce both recurrent TTTS and the twin anemia-polyglobulinaemia sequence that can subsequently develop, the Solomon technique photoagulates a line across the surface of the placenta at the vascular equator following SFLP. A randomized controlled trial of the Solomon technique, compared with SFLP, noted a significant decrease in both of these adverse outcomes; however, no difference in long-term (2-year) survival without neurodevelopmental impairment was observed. Major neurologic abnormalities in long-term survivors of TTTS following SFLP range from 5% to 18%.

The most common complications of SFLP are preterm PROM with subsequent preterm labor and delivery, and intrauterine infection. Other possible complications include placement of the trocar through the placenta, hemorrhage, and possible membrane perforation resulting in limb entrapment and ischemia. Overall, trial results and meta-analyses provide evidence that SFLP results in superior outcomes compared with amnioreduction for the treatment of TTTS, but further research is needed to optimize the timing and technical aspects of the various interventions.

**Twin Reversed Arterial Perfusion Sequence**

In monozygotic twins, one twin can perfuse the other by retrograde blood flow though AA anastomoses. Twin reversed arterial perfusion (TRAP) sequence affects 1% of monozygotic twins, 1 in 35,000 pregnancies, and 1 in 30 triplet pregnancies. Inadequate perfusion of the recipient twin via retrograde blood flow through AA anastomoses results in the development of a lethal set of abnormalities that include acardia and acephalus. The normal (“pump”) twin perfuses both itself and the nonviable twin and is at risk for high-output congestive heart failure, polyhydramnios, and preterm birth. If untreated, TRAP sequence is associated with a 55% risk for intrauterine death of the pump twin. Diagnosis is confirmed with ultrasonographic demonstration of reverse flow to the acardiac twin via the umbilical artery. Cardiovascular failure in the pump twin is the indication for intervention, and early diagnosis is beneficial for optimal treatment. The mortality risk of the pump twin is related to the high-output cardiac failure, preterm delivery, and the size ratio of the acardiac twin to the pump twin.

The goal of therapy is to interrupt the vascular communication between the two twins. In contrast to the treatment of TTTS, treatment of TRAP sequence results in the death of the anomalous nonviable fetus. Ultrasound-guided bipolar or radiofrequency coagulation of the umbilical cord and/or placental vascular anastomoses is the most viable therapeutic option. Alternative therapies include use of endoscopic laser coagulation, sectio parva (selective cesarean delivery of one of multiple fetuses), percutaneous thrombosis of the acardiac twin’s umbilical cord with coils or other thrombogenic material, and alcohol-impregnated suture cord ligation. Although these procedures are typically done after 16 weeks’ gestation, earlier intervention may be beneficial, as approximately 30% of pump twins suffer demise before intervention. A recent meta-analysis and review of the literature noted the survival rate of the pump twin was about 80% for most techniques, except when performed by ligation of the cord, the placement of cord coils, or the injection of intrafetal alcohol. A significant inverse association between gestational ages at treatment and at birth has been observed; when an intervention was performed at 13 or 27 weeks’ gestation, the mean gestation at birth was 38 and 34 weeks, respectively.

TRAP intervention procedures are typically performed with either infiltration of local anesthesia at the ablation device insertion site or the administration of neuraxial anesthesia. The procedures are guided by ultrasonography, and absence of flow to the nonviable acardiac twin is confirmed with Doppler imaging at the end of the procedure and again 12 to 24 hours later. The most common complication is preterm PROM. Additional research is needed to determine optimal timing and method of intervention.

**Congenital Heart Defects**

Congenital heart abnormalities are the leading cause of mortality from birth defects and occur in approximately 1% of live births. Fetal valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome is the most common, minimally invasive intervention performed for a congenital heart defect. The procedure uses an angioplasty balloon placed over a percutaneously inserted guide wire, with technical success as high as 77%. The valvuloplasty allows improved left ventricular function, augmented aortic and mitral valvular growth, and progression to live birth in 90% of cases. Although 40% to 50% of successful fetal valvuloplasty cases enable biventricular circulation present at birth, approximately 40% of cases result in aortic regurgitation and minimal left ventricular growth.

Additional closed fetal cardiac interventions include: (1) septoplasty for hypoplastic left heart syndrome with an intact or highly restrictive atrial septum; (2) pulmonary valvuloplasty for evolving hypoplastic right heart syndrome with pulmonary atresia or stenosis without a ventricular septal defect; and (3) fetal pericardiocentesis to treat aneurysms or congenital cardiac tumors.

Open fetal cardiac surgery for severe hypoplastic left heart syndrome has also been described using maternal-placental support. Fetal intrapericardial teratomas have been successfully resected with in utero open fetal surgery or while on placental support during an EXIT procedure. Correction of
Anesthesia for Fetal Surgery and Other Intrauterine Procedures

Because of the absorption of significant amounts of crystalloid during uterine irrigation. Moreover, although fetal surgical procedures do not affect future fertility, open procedures involve a hysterotomy through the upper uterine segment and a requirement for cesarean delivery in subsequent pregnancies. The fetal risks of intrauterine surgery remain relatively high and include central nervous system injuries, membrane separation, PROM, placental abruption, preterm labor and delivery, blood loss, chorioamnionitis, postoperative amniotic fluid leaks with oligohydramnios, and fetal demise. Preterm delivery accounts for significant morbidity and mortality. Chorioamniotic membrane separation can cause amniotic bands, umbilical cord strangulation, and fetal demise. Improved techniques for sealing the membranes are being devised, including different surgical patching techniques, sealants, and intra- or extra-amniotic platelet or cryoprecipitate injections.

ANESTHETIC MANAGEMENT

Fundamental considerations for the anesthetic management of fetal surgery are similar to those for nonobstetric surgery during pregnancy (see Chapter 17). Maternal safety is paramount. Anesthesiologists should participate in preoperative maternal assessment and exclude women when their perioperative risk is not acceptably low given the potential fetal benefit. To ensure both maternal and fetal safety, the anesthesiologist must understand the physiologic impact of pregnancy on anesthetic management (see Chapter 2) and serve as an active member of the multidisciplinary team. Imaging studies should be reviewed for placental location, anatomic information about the congenital lesion, and estimated fetal weight.

Surgical Benefits and Risks

The primary goal of intrauterine fetal surgery is to improve neonatal outcomes compared with interventions performed after a preterm or term delivery. The intrauterine environment supports rapid wound healing (i.e., without scarring before mid-gestation), provides adequate nutritional and respiratory needs, and limits robust immune responses to interventions (through a minimally developed fetal immune surveillance system). However, continued refinement of surgical and anesthetic techniques, with appropriate attention to reducing maternal and fetal risks, and conducting appropriate clinical trials for each intervention, must occur before fetal surgery can be performed more routinely for specific congenital anomalies.

Serious maternal morbidity from intrauterine fetal surgery is relatively uncommon, but maternal welfare must always be emphasized; for example, pulmonary edema may occur because of the absorption of significant amounts of crystalloid during uterine irrigation. Moreover, although fetal surgical procedures do not affect future fertility, open procedures involve a hysterotomy through the upper uterine segment and a requirement for cesarean delivery in subsequent pregnancies. The fetal risks of intrauterine surgery remain relatively high and include central nervous system injuries, membrane separation, PROM, placental abruption, preterm labor and delivery, blood loss, chorioamnionitis, postoperative amniotic fluid leaks with oligohydramnios, and fetal demise. Preterm delivery accounts for significant morbidity and mortality. Chorioamniotic membrane separation can cause amniotic bands, umbilical cord strangulation, and fetal demise. Improved techniques for sealing the membranes are being devised, including different surgical patching techniques, sealants, and intra- or extra-amniotic platelet or cryoprecipitate injections.

Percutaneous fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome. The needle is inserted percutaneously through the maternal abdomen and uterus, and enters the apex of the fetal heart in alignment with the left ventricular outflow tract. A guide wire and a coronary dilation balloon catheter are advanced through the aortic valve, which is then dilated. (From Van Mieghem T, Baud D, Devlieger R, et al. Minimally invasive fetal therapy. Best Pract Res Clin Obstet Gynaecol. 2012;26:711–725.)

Fig. 7.7 Percutaneous fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome. The needle is inserted percutaneously through the maternal abdomen and uterus, and enters the apex of the fetal heart in alignment with the left ventricular outflow tract. A guide wire and a coronary dilation balloon catheter are advanced through the aortic valve, which is then dilated. (From Van Mieghem T, Baud D, Devlieger R, et al. Minimally invasive fetal therapy. Best Pract Res Clin Obstet Gynaecol. 2012;26:711–725.)
Unlike other surgical procedures performed during pregnancy in which the fetus is an innocent bystander (e.g., maternal appendectomy), fetal surgery involves two surgical patients. This requires the anesthesiologist to balance the anesthetic needs of both patients, as well as control uterine tone throughout the perioperative period. Complete uterine relaxation is necessary during open fetal surgical procedures.

Maternal analgesia and anesthesia can be provided by local infiltration, intravenous sedation, neuraxial anesthesia, general anesthesia, or a combination of these techniques, depending on the procedure, location of the placenta, and maternal co-morbidities. Fetal analgesia and anesthesia can be achieved via placental transfer of anesthetic agents given to the mother, via direct fetal intravenous (peripheral fetal vein or umbilical vein) or intramuscular administration of agents, or by a combination of these methods. An appropriate method of fetal monitoring and the potential requirement for fetal intravenous access and volume resuscitation during open surgical cases should be determined preoperatively. The operative team should be prepared for emergency situations such as maternal hemorrhage, need for intrauterine fetal resuscitation (e.g., fetal epinephrine administration), and/or delivery and resuscitation of the viable neonate.

**Anesthesia for Minimally Invasive and Percutaneous Procedures**

Local anesthetic infiltration of the maternal abdominal wall is sufficient to reduce maternal discomfort for many percutaneous procedures (e.g., amniocentesis, cordocentesis, intravascular blood transfusion, needle aspiration of cysts, shunt placement into the fetal bladder or thorax, SFLP for TTTS). Supplemental maternal analgesia and anxiolysis can be achieved by maternal administration of an opioid, a benzodiazepine, and/or a low-dose propofol infusion, and may reduce fetal mobility via placental transfer of drug. However, neuraxial anesthesia is often used to minimize maternal movement, enable positioning, and provide sensory coverage for multiple percutaneous instrumentation sites or a mini-laparotomy. General anesthesia is rarely necessary for minimally invasive procedures unless the placental location, fetal position, and/or the potential need for uterine exteriorization (e.g., certain MMC repair approaches) are valid concerns.

Fetal movement may be hazardous for the fetus in cases of intravascular transfusion, cord blood sampling, or thoracic shunt placement, because displacement of the needle or catheter may lead to trauma, bleeding, or compromise of the umbilical circulation. Placental transfer of maternally administered opioids and benzodiazepines can reduce, but not necessarily eliminate, fetal movement. A randomized controlled trial of the use of a maternal remifentanil infusion (0.1 µg/kg/min) demonstrated improved fetal immobility and operating conditions during fetoscopic surgery, when compared with maternal administration of diazepam.110 Fetal immobility can be safely achieved with direct fetal intramuscular or umbilical venous administration of rocuronium (2.5 mg/kg IM, 1 mg/kg IV) or vecuronium (0.2 mg/kg IM, 0.1 mg/kg IV) using ultrasonographic guidance. The onset of fetal paralysis occurs in 2 to 5 minutes, with an approximate duration of 1 to 2 hours.111 For procedures that can cause noxious stimulation to the fetus, such as shunt catheter placement or cardiac septal defect closure, an opioid (e.g., fentanyl 10 to 20 µg/kg) can be administered to the fetus intramuscularly or intravenously.17

When general anesthesia is employed, placental transfer of a volatile halogenated agent is usually sufficient to immobilize and anesthetize the fetus; however, a muscle relaxant is frequently administered directly to the fetus if fetal immobility is critical to the procedure.

The surgical team should be prepared to immediately administer appropriate fetal weight-based intramuscular doses of atropine (20 µg/kg) and epinephrine (10 µg/kg), and perform an emergent cesarean delivery if the gestational age is compatible with extraterine viability. The anesthesiologist should be prepared to provide maternal general anesthesia if required.

Tocolysis typically is unnecessary after cordocentesis or intrauterine transfusion. For more invasive percutaneous procedures (e.g., shunt catheter placement, fetoscopic techniques), some fetal surgery groups administer prophylactic perioperative tocolytic agents such as indomethacin or nifedipine to the mother.112

**Anesthesia for Open Fetal Surgery**

When corrective fetal surgery or an intrauterine procedure requires surgical access through a hysterotomy, general anesthesia is typically administered. Unique considerations for open fetal procedures include the need for profound uterine relaxation, intraoperative fetal monitoring, fetal anesthesia or analgesia, and postoperative maternal analgesia and uterine tocolysis (Box 7.2). In addition, significant maternal and fetal blood loss may occur, and the anesthesiologist must be prepared to provide maternal and fetal resuscitation. A high concentration of a volatile halogenated agent is typically administered to provide both maternal and fetal anesthesia as well as uterine relaxation. Adequate uterine relaxation may require greater than twice the minimum alveolar concentration (MAC) of a volatile halogenated agent. Some centers use supplemental intravenous anesthesia (SIVA) or other agents (e.g., nitroglycerin) to augment the uterine relaxation provided by a reduced concentration of the halogenated agent.112

Preoperatively, the mother receives agents for aspiration prophylaxis and uterine tocolysis (e.g., rectal/oral indomethacin), and a high lumbar epidural catheter is placed for postoperative analgesia. The patient is placed in the supine position with left uterine displacement. A final assessment of the fetus is performed, and the availability of all appropriate personnel, equipment, resuscitation medications, and blood products is confirmed before induction. Medications to provide fetal analgesia (e.g., fentanyl 10 to 20 µg/kg), immobility (e.g., vecuronium 0.2 mg/kg), and resuscitation (e.g., atropine 20 µg/kg, epinephrine 10 µg/kg) are prepared in sterile, labeled syringes; each syringe should contain a single weight-based unit dose. Cross-matched blood should be available for maternal transfusion. In addition, O-negative, cytomegalovirus (CMV)-negative, irradiated, leukocyte-depleted,
**BOX 7.2** Perioperative Considerations for Open Fetal Surgery

### Preoperative Considerations
- Complete maternal history and physical examination
- Fetal workup to exclude other anomalies and imaging studies to determine fetal lesion, placental location, and estimated fetal weight
- Maternal counseling by multidisciplinary team and preoperative team meeting
- Emergent delivery plan determined if needed based on gestational age
- High lumbar epidural catheter placed and tested
- Prophylactic premedications for aspiration and tocolysis
- Blood products available for potential maternal and fetal transfusion
- Sequential compression devices on lower extremities for thrombosis prophylaxis
- Fetal resuscitation drugs and fluid transferred steriley to scrub nurse in unit doses

### Induction and Intraoperative Considerations
- Left uterine displacement and standard monitors
- Fetal assessment before induction
- Preoxygenation for 3 minutes before induction
- Rapid sequence induction and intubation
- Maintain maternal FIO2 > 50% and end-tidal CO2 28 to 32 mm Hg
- Forced air warmer to maintain maternal normothermia
- Ultrasonography to determine fetal and placental positioning
- Urinary catheter placed; additional large-bore IV access placed; possible arterial line
- Prophylactic antibiotics administered
- Blood pressure maintained (± 10% baseline with intravenous phenylephrine, ephedrine, and/or glycopyrrolate)

### Early Postoperative Considerations
- Complete a postoperative debrief
- Administer maternal anesthetic and opioids as needed
- Monitor uterine activity and fetal heart rate
- Administer maternal anesthetic and opioids as needed
- Ongoing periodic fetal evaluation

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**CO2**: Carbon dioxide; **CMV**: cytomegalovirus; **FIO2**: fraction of inspired oxygen; **IM**: intramuscular; **IV**: intravenous; **MAC**: minimum alveolar concentration; **SIVA**: supplemental intravenous anesthesia.

maternally cross-matched blood should be available for fetal transfusion.

After administration of 100% oxygen and denitrogenation of the lungs, a rapid-sequence induction of general anesthesia with cricoid pressure and endotracheal intubation is performed. Fetal heart rate (FHR), umbilical cord blood flow, and fetal cardiac function are often monitored with ultrasonography during induction. End-tidal carbon dioxide concentration should be maintained at 28 to 32 mm Hg, which is normocarbic for pregnancy. Initially, anesthesia is maintained with approximately 1 MAC of a volatile halogenated agent or intravenous anesthetic agents while further preparations for surgery are undertaken, including (1) obtaining additional maternal vascular access, (2) prophylactic antibiotic administration, (3) urinary bladder catheterization, and (4) ultrasonographic assessment of fetal presentation and placental location. For open procedures with a high risk for significant fetal blood loss (e.g., resection of a fetal mass), a fetal intravenous catheter should be placed after hysterotomy to provide access for blood and fluid transfusions. An arterial catheter should be placed for maternal blood pressure monitoring if uterine tocolysis with a nitroglycerin infusion is planned or if maternal hemodynamic instability occurs. Total intraoperative maternal intravenous fluids are restricted (less than 2 L) to reduce the risk for postoperative pulmonary edema. Some fetal surgery centers administer colloid as a portion of the fluids to better maintain maternal blood pressure and/or choose to limit fluids even further (less than 500 mL). No clinical trials have proven a benefit of further fluid restriction in this setting.

A final discussion (surgical time-out) should occur before skin incision. Mean maternal arterial blood pressure is typically maintained within 10% of baseline values and greater than 65 mm Hg. A phenylephrine infusion provides titratable blood pressure control with minimal changes in the fetal acid-base status. Bolus doses of ephedrine and/or glycopyrrolate also can be administered to maintain maternal heart rate near baseline and improve cardiac output. Maternal administration of a nondepolarizing muscle relaxant is usually not required owing to the profound depth of anesthesia provided by the volatile agent, but may be used to improve operative conditions. The intrauterine
location and position of the fetus is confirmed with ultrasonography just before hysterotomy to optimize the incision location.

Before hysterotomy, it is desirable to achieve an increased end-tidal concentration (2 to 3 MAC) of the volatile halogenated agent to provide both fetal anesthesia and uterine relaxation. The uterus is assessed both visually and by palpation for contractions or increased tone. Further tocolysis can be achieved with intravenous nitroglycerin as an infusion or in bolus doses (100 µg). Because the use of high levels of volatile anesthetic is associated with fetal cardiac dysfunction and abnormal umbilical artery blood flow, a combination of volatile anesthetic (1 to 1.5 MAC) and intravenous propofol and remifentanil infusions (SIVA technique) is used at some institutions. For circumstances in which volatile halogenated agents or general anesthesia must be avoided (e.g., family history of malignant hyperthermia), a neuraxial anesthetic can be administered and combined with an intravenous anesthetic to provide both fetal anesthesia and uterine relaxation. The uterus is assessed both visually and by palpation for contractions or increased tone. Further tocolysis can be achieved with intravenous nitroglycerin as an infusion or in bolus doses (100 µg). This technique does not have any clear advantage for fetal outcome and may be associated with more morbidity, as nitroglycerin administration during open fetal surgery has been associated with maternal pulmonary edema.

Fetal well-being is periodically assessed with ultrasonography to monitor FHR, umbilical artery blood flow, and cardiac contractility. In certain open cases, a sterile pulse oximetry probe may be attached to a fetal digit or limb. An opioid and a muscle relaxant are administered to the fetus intramuscularly, either before or after uterine incision with ultrasonographic guidance or direct vision, respectively. Some anesthesiologists also administer intramuscular fetal atropine at this time in an effort to prevent opioid-induced fetal bradycardia. Further studies are needed to determine the optimal anesthetic technique for ensuring maternal and fetal cardiovascular stability, optimal uteroplacental perfusion, and adequate fetal anesthesia to cause immobility and blockade of the fetal stress response.

A small uterine incision is created remote from the location of the placenta. A stapling device with absorbable synthetic copolymer (Lactomer) staples is used to extend the incision, seal the membranes to the endometrium, and prevent excessive bleeding. During surgery, the exposed fetus and uterus are bathed with warmed fluids. The intracranial pressure is closely monitored to prevent fetal circulatory compromise associated with hypothermia.

At the conclusion of the fetal procedure, when uterine closure is initiated, a loading dose of maternal magnesium sulfate is administered (4 to 6 g intravenously over 20 minutes), followed by an intravenous infusion of 1 to 2 g per hour. As magnesium potentiates neuromuscular relaxation, close monitoring of twitch recovery is needed if a nondepolarizing muscle relaxant was administered. The volatile halogenated agent can be significantly decreased or discontinued after the magnesium sulfate bolus has been administered. The epidural analgesia can be initiated, and maternal analgesia is maintained with additional opioid and intravenous anesthetics as appropriate.

Postoperative concerns include maternal and fetal pain, preterm PROM, preterm labor, infection, and a variety of potential fetal complications, including heart failure, intracranial hemorrhage, constriction of the ductus arteriosus from indomethacin, and demise. Maternal analgesia can be maintained with an epidural infusion of a dilute solution of local anesthetic and opioid for several days. Effective analgesia may help prevent postoperative preterm labor. Intravenous opioids can also be used to provide postoperative maternal analgesia; however, decreased FHR variability may occur.

Postoperative preterm labor is the “Achilles heel” of fetal surgery. Tocolysis is typically provided by an infusion of magnesium sulfate for at least 24 hours, although supplemental agents may include indomethacin, nifedipine, or terbutaline. Magnesium most likely competes with calcium at voltage-operated calcium channels, indomethacin blocks the synthesis of prostaglandins, and beta-adrenergic agonists activate adenylate cyclase in the uterine muscle, thereby reducing intracellular calcium levels. Not infrequently, two tocolytic agents are required to create uterine quiescence. Uterine activity and FHR are monitored closely during the first 2 to 3 postoperative days. The fetus is evaluated postoperatively by ultrasonography, and if indomethacin is used, periodic fetal echocardiography is performed to determine if premature closure of the ductus arteriosus has occurred.

Patients recovering from open fetal surgery should remain near the fetal treatment center after hospital discharge. These patients are at high risk for preterm PROM, preterm labor, infection, and uterine rupture. Unless preterm labor occurs, cesarean delivery is typically planned at 37 weeks’ gestation.

Anesthesia for the Ex Utero Intrapartum Treatment Procedure

Initially described as a method to remove the iatrogenic airway obstruction created for intrauterine treatment of CDH, the EXIT procedure has evolved into a technique useful for a number of fetal disorders that compress the airway and/or render neonatal tracheal intubation difficult or impossible. It is also useful when resuscitation and surgical intervention are required immediately before birth, while the fetus is still supported by the placental circulation. Cases appropriate for an EXIT procedure include cervical masses, severe craniofacial anomalies, lung masses, mediastinal masses, severe congenital cardiac lesions, and CDH with anticipated respiratory compromise. The use of an EXIT procedure may also assist the transition to ECMO for pulmonary insufficiency or the stabilization of conjoined twins before separation. Similar to open fetal surgery procedures, sustained uterine relaxation and delay of placental separation are necessary for a successful EXIT procedure.

Anesthesia for EXIT procedures is most commonly performed with the use of general anesthesia, with many considerations similar to those detailed earlier for open fetal surgery. Preparation for fetal monitoring, airway management, fetal/neonatal resuscitation, and postdelivery care should be completed before entering the operating room.
Fetal heart ultrasonography, a sterile pulse oximeter probe, and an end-tidal carbon dioxide indicator or gas analyzer are frequently used for fetal monitoring during the procedure. Unit doses of atropine (20 µg/kg) and ephedrine (10 µg/kg), as well as supplemental fetal anesthetic agents (for subsequent fetal intramuscular injection) are prepared and transferred in a sterile manner to the scrub nurse (see later discussion). A sterile ventilation bag with an air/oxygen source and manometer is available for the fetus, along with multiple endotracheal tube sizes and devices for fetal tracheal intubation, including a rigid and flexible bronchoscope. Catheters for intravenous access as well as crystalloid and blood (O-negative, CMV-negative, leukocyte-depleted, irradiated, maternally cross-matched) should be available for fetal volume resuscitation if needed.

A maternal epidural catheter may be placed preoperatively for postoperative analgesia. Maternal anesthetic considerations should include large-bore intravenous access, availability of uterotonic agents and cross-matched blood, and the ability to quickly obtain invasive maternal monitoring if needed. Techniques of induction and tracheal intubation do not differ from those typically used for cesarean delivery. Although techniques for maintenance of anesthesia vary between medical centers, administration of 2 to 3 MAC of a volatile halogenated agent is often needed to achieve and maintain adequate uterine relaxation. Occasionally, nitroglycerin administered as a bolus dose (50 to 100 µg) or as an infusion may also be required to maintain appropriate uterine relaxation. Fetal anesthesia from the halogenated agent transferred across the placenta is typically supplemented by direct fetal intramuscular administration of an opioid (e.g., fentanyl 5 to 15 µg/kg or morphine 0.1 mg/kg) and a paralytic agent (e.g., rocuronium 1 to 3 mg/kg). Some practitioners also administer intramuscular atropine (20 µg/kg) to prevent fetal bradycardia. Intramuscular agents can be administered to the fetus either before uterine incision with ultrasonographic guidance or after uterine incision under direct visualization. Significant variability in serum fentanyl concentrations has been documented in umbilical cord blood during EXIT procedures, and similar variability may exist with muscle relaxants and other agents.

Following exposure of the uterus, the placental location and edges are determined by intraoperative ultrasonography. Similar to open fetal procedures, the uterine incision is extended with a stapling device to minimize blood loss. The fetal head and shoulders are delivered in preparation for tracheal intubation. In an effort to maintain fetoplacental circulation, warmed fluids are continuously irrigated into the uterine cavity, and care is taken to avoid manipulation of the umbilical cord. The warmed irrigant maintains fetal eutermia and helps prevent decreased uterine volume, placental separation, and spasm of the cord vessels. The fetus is initially monitored with (1) a pulse oximeter probe placed on the fetal hand, (2) periodic cardiac ultrasonography, and (3) direct visualization. For more extensive procedures, such as fetal thoracotomy, or when there is fetal bradycardia suggestive of umbilical cord compression, the fetus can be delivered from the uterus and placed on the maternal chest and abdomen to facilitate the procedure.

The duration of the fetal procedure can range from a few minutes (e.g., bronchoscopic or intubation) to several hours (e.g., neck or thoracic mass resection, tracheostomy, or central intravascular cannulation). Although the majority of procedures require less than 1 hour, the anesthetic technique is capable of providing maternal, fetal, and uteroplacental stability over several hours. Once surgery is completed and the trachea secured, surfactant is administered if indicated. Fetal oxyhemoglobin saturation is typically 40% to 70% at this time, but increases significantly to above 90% with ventilation of the fetal lungs.

Upon umbilical cord clamping, the maternal anesthetic technique is altered by reducing or eliminating the volatile anesthetic agent to help achieve uterine tone and diminish the risk for postpartum hemorrhage. Typically, a combination of an opioid, propofol, and nitrous oxide are used to maintain anesthesia. Oxytocin is administered, as well as other uterotonic agents if needed to achieve uterine tone. Finally, epidural analgesia is initiated.

If general anesthesia with a halogenated agent is contraindicated (e.g., history of malignant hyperthermia) an alternative technique for EXIT procedures involves the use of neuraxial anesthesia combined with intravenous infusions of propofol, remifentanil, and nitroglycerin to maintain uterine relaxation. Large doses of intravenous nitroglycerin are often required to achieve adequate uterine relaxation; if significant doses are to be used for a prolonged period, an arterial catheter is recommended and the patient should be observed for evidence of pulmonary edema. Fetal analgesia and immobility can be achieved with fetal administration of intramuscular drugs (see earlier discussion). Maternally administered intravenous remifentanil undergoes significant transfer across the placenta and may serve as an adjuvant for fetal analgesia and immobility.

**Fetal Response to Surgical Stimulation**

The subjective phenomenon of pain has not been, and perhaps cannot be, assessed adequately in human fetuses. Pain is a multidimensional, subjective, psychological construct that can exist in the absence of physical stimuli (e.g., phantom limb pain), and it includes emotional and affective components that require higher-level cortical processing. As such, although pain is commonly associated with noxious physical stimuli, it is more than nociception or a simple reflex activity associated with a withdrawal response. Attempts have been made to correlate pain with surgical stress; however, the physiologic responses are not equivalent. The stress response is mediated primarily in the spinal cord, brainstem, and/or basal ganglia, without involvement of the cortex.

In studies of intrauterine blood transfusion in the human fetus, surgical needling of the intrahepatic vein (in contrast to the insensate umbilical cord) is associated with evidence of a stress response, including increases in plasma beta-endorphin and cortisol concentrations and decreases...
in the middle cerebral artery pulsatility index (determined by Doppler imaging).128 These responses can be blunted by the fetal administration of fentanyl 10 µg/kg.129 Human fetuses elaborate pituitary-adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli as early as 16 to 18 weeks' gestation.129,130 Immature skin nociceptors likely begin to emerge at 10 weeks' gestation and are present by 17 weeks' gestation.131 In internal organs, nociceptors develop slightly later. Peripheral nerve fibers that control movement grow into the spinal cord at about 8 weeks' gestation. When these fibers connect with nociceptors is unknown, but one human study suggests that nociceptive nerve fibers do not enter the spinal cord before about 19 weeks' gestation.132 The cerebral cortex develops after the fetal spinal cord and brainstem. Thalamocortical connections to the somatosensory cortex are significantly developed at 24 to 30 weeks' gestation.

The developing cerebral cortex consists of transient fetal zones where neuronal proliferation, cell migration, apoptosis, axonal outgrowth, and synaptogenesis occur according to a highly specific timetable. Originating as a smooth layer without sulci and gyri, the cerebral cortex, like the thalamus, has no internal cellular organization. The cortical subplate is a temporary structure that serves as a waiting and organizing zone for various afferents destined for the cortex. It develops at about 13 weeks' gestation and recedes after 32 to 34 weeks' gestation.

Studies of fetal electroencephalograms (EEGs) at 24 weeks' gestation demonstrate electrical activity only 2% of the time, predominantly in 20-second bursts, with periods of inactivity lasting up to 8 minutes. At 30 weeks' gestation, EEGs begin showing patterns of wakefulness and sleep, but these are not concordant with fetal behavior. By 34 weeks' gestation, electrical activity is present 80% of the time, with more distinct wakefulness and sleep cycles similar to adult patterns.133

Two studies using near-infrared spectroscopy in preterm infants demonstrated differences in cerebral oxygenation over the somatosensory cortex with noxious and non-noxious stimulation.134,135 This appears to indicate that noxious information is at least transmitted to the infant cortex by 25 weeks' gestation. These responses can be blunted by fetal anesthesia, especially after 24 to 26 weeks' gestation. Noxious stimulation is clear evidence that the fetal nervous system is reactive.137 Administration of fetal anesthesia has been the standard practice worldwide since the inception of fetal surgery more than 35 years ago.138

Effects of Anesthesia on the Fetus

With maternal administration of general anesthesia, volatile agents readily cross the placenta to the fetus. The fetal level of halogenated anesthetic agent depends on both the inspired maternal concentration as well as the duration of administration. Based on data from cesarean delivery, after 10 minutes of general anesthesia, fetal levels of both isoflurane and halothane reach approximately 70% of maternal levels.139 Of interest, studies in sheep models have shown a lower fetal-to-maternal ratio of volatile agents at 10 minutes, demonstrating that the fetal concentrations remain lower than maternal concentrations for significant periods of time (Fig. 7.8). Significant levels of maternal inhaled anesthetics (2 to 3 MAC) can affect fetal cardiac function and blood flow. A retrospective analysis of cardiac imaging from both open fetal cases and EXIT procedures noted severe left ventricular systolic dysfunction in the fetus with use of high concentrations of desflurane.116 Echocardiographic findings from 100 open fetal MMC cases under desflurane anesthesia noted intraoperative ventricular dysfunction in 60% of cases, tricuspid regurgitation in 35%, and mitral valve regurgitation in 19%, with serious cardiovascular events in 7% of cases.140 In another review of open fetal surgery for MMC repair utilizing a volatile anesthetic agent (2 to 3 MAC), 34 of 37 fetuses developed intraoperative umbilical artery flow abnormalities.117 Brief fetal exposure to deep maternal inhalation stimulation could have both short- and long-term adverse effects on the developing central nervous system.
anesthesia (2 to 3 MAC) does not appear to result in significant fetal hypoxia, hypercarbia, or acidosis even after exposures of 2 hours if maternal arterial pressure is maintained. However, others have seen acidosis after 45 minutes of fetal exposure to anesthesia.

Another concern is that anesthetic agents may result in neuronal apoptosis in the developing fetal brain (see Chapter 10). Initial evidence was found in 2003, when an anesthetic consisting of midazolam, nitrous oxide, and isoflurane was shown to alter neurons in the developing brain of 7-day-old rats and to cause long-term impairment of brain function. Evidence for neuronal apoptosis in the developing brain after exposure to a wide range of anesthetic agents, such as halogenated agents, propofol, and benzodiazepines, has since been demonstrated in a variety of animal studies. It is not currently known if anesthetic agents similarly affect human fetuses or neonates. Nonetheless, in December 2016, the U.S. Food and Drug Administration (FDA) issued a communication warning that “repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women currently known if anesthetic agents similarly affect human fetuses or neonates. Nonetheless, in December 2016, the U.S. Food and Drug Administration (FDA) issued a communication warning that “repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.” Currently no specific anesthetic agent (e.g., volatile agents, propofol, ketamine, benzodiazepines) is known to be safer than another. There does not appear to be any association between the use of general anesthesia for emergent cesarean delivery and future learning disability. The long-term neurocognitive effect of anesthetic exposure and surgical stimuli on fetuses during fetal surgery remains an area for future research.

Fetal Monitoring

Maternal and fetal anesthesia, uterine incision, fetal manipulation, and surgical stress may adversely affect uteroplacental and fetoplacental circulation by several mechanisms. Maternal hypotension, increased uterine activity, and maternal hyperventilation and hypocarbia impair uteroplacental and/or umbilical blood flow. Fetal manipulation may affect fetal cardiac output, regional distribution of cardiac output, and umbilical blood flow. Direct compression of the umbilical cord, inferior vena cava, and mediastinum also adversely affect fetal circulation. Current methods of intraoperative fetal monitoring include FHR monitoring, pulse oximetry, ultrasonography (including echocardiography and Doppler assessment of umbilical cord blood flow), and blood gas and acid-base analysis.

Plethysmography combined with pulse oximetry is very useful, particularly for the EXIT procedure. It remains unclear whether pulse oximetry or FHR monitoring is a more sensitive method of detecting changes in umbilical cord flow. Bradycardia has been found to be a late sign of fetal compromise in fetal lambs subjected to umbilical cord compression. However, bradycardia can also precede oxyhemoglobin desaturation during human fetal surgery.

Ultrasonography is a crucial intraoperative fetal monitoring device. The FHR can be determined with visualization of the heart or with Doppler assessment of umbilical cord blood flow. Both absent and reversed umbilical artery diastolic flow are associated with increased perinatal morbidity and mortality in obstetric patients, but the implications during fetal surgery remain unclear. Fetal cardiac contractility and volume also can be assessed qualitatively by echocardiography. Unfortunately, the sterile transducer often cannot be positioned continuously because its location interferes with surgery. When prolonged fetal bradycardia, oxyhemoglobin desaturation, and/or significant changes in fetal cardiac function and umbilical artery blood flow are noted, maneuvers should be done to improve uterine perfusion and relieve umbilical cord compression. These maneuvers can include improving maternal blood pressure, cardiac output, and oxygenation through administration of vasoactive agents, fluids, and supplemental oxygen, as well as maximizing uterine relaxation. In severe cases requiring administration of fetal resuscitation drugs and fluids, ex utero fetal resuscitation including advanced cardiac life support (ACLS) may be necessary.

THE FUTURE OF FETAL THERAPY

Successful diagnosis and management of complex congenital anomalies and other fetal conditions amenable to prenatal intervention rely on well-organized, multidisciplinary, professional, and comprehensive fetal treatment programs to innovate new techniques, challenge dogma, and ensure ongoing success. More collaborative clinical investigation among international research centers will drive improvement, variety, and availability of fetal interventions, assist in the miniaturization of invasive techniques, and decrease maternal and fetal risk.

Although the rationale for prenatal fetal therapy seems straightforward, many issues remain problematic. Questions remain regarding the manner in which fetal development is modulated by intraterine intervention. Other questions revolve around maternal and fetal rights, safety, efficacy, long-term outcomes, cost-effectiveness, and societal resource allocation. Societal expectations and the availability of therapy must be balanced against the budgetary constraints in contemporary health care. In addition, there is concern about the sensitivity, specificity, and appropriate use of diagnostic testing. Fetal therapy raises complex social, ethical, and legal issues that go beyond those customary for therapeutic interventions. The ethical framework for the transition from innovation to clinical trials to offering fetal surgery as a standard of care must be managed thoughtfully and responsibly. A bioethics committee with representatives from both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists has provided recommendations for medical institutions offering fetal surgery.

Fetal therapy must be evaluated carefully in properly conducted trials and undertaken only with great caution and informed maternal consent. Publication in scientific journals and open communication with colleagues nationally and internationally facilitates the moral obligation of researchers to report all results to allow peers review of the merits and liabilities of fetal surgery. The principal concept...
of *primum non nocere* argues that it is unethical to undertake human trials until a procedure is appropriately tested in animals. Training programs are necessary to safely expand access and services from academic fetal centers to smaller facilities. Fetuses that may benefit from invasive surgery typically require (1) provision of analgesia for the fetus, (2) more intensive intraoperative fetal monitoring, and (3) intraoperative uterine relaxation.

- Randomized controlled trials have demonstrated improved outcomes with use of fetoscopic laser ablation to treat twin-to-twin transfusion syndrome and intrauterine open fetal repair to treat myelomeningocele.
- Preterm premature rupture of membranes and preterm labor after surgery are significant barriers to optimal outcomes with fetal surgery.
- There are many medical, social, ethical, and legal considerations regarding the efficacy and safety of intrauterine fetal surgery. Careful evaluation of fetal benefits and maternal risks is fundamental to the decision as to when and whether fetal intervention is appropriate.

### KEY POINTS

- Most fetal malformations diagnosed in utero are not suitable for antenatal intervention. Fetal surgery is a reasonable option for anomalies that cause harm to the fetus before adequate development necessary for extraterine survival (particularly lung maturity).
- Maternal safety is a primary consideration and must be weighed against potential long-term benefit to the fetus and neonate.
- Local or neuraxial anesthesia is normally suitable for percutaneous or minimally invasive procedures. Open intrauterine procedures typically require administration of general anesthesia.
- Anesthetic considerations for intrauterine fetal surgery are similar to those for nonobstetric surgery in pregnant women. However, in addition to maintaining adequate maternal anesthesia and uteroplacental blood flow, fetal oxygenation procedure change morbidity outcomes for high-risk congenital diaphragmatic hernia survivors? *J Pediatr Surg.* 2017;52:22–25.

### REFERENCES


Accurate fetal assessment in labor remains challenging despite the application of new technologies. An elevated cesarean delivery rate and persistent cases of fetal/neonatal neurologic injury indicate the need to further optimize fetal/neonatal outcomes while minimizing unnecessary maternal interventions.

**FETAL RISK DURING LABOR**

The fetus is at risk during labor and delivery. Worldwide, intrapartum stillbirths account for almost 1.3 million perinatal deaths per year, with a range of 10% to 50% of all stillbirths in developed and developing countries, respectively. Obstetric care can influence the intrapartum stillbirth rate. With each percentage increase in cesarean delivery rate up to 15%, intrapartum stillbirth rates decrease by 1.61/1000. Experimental models support the hypothesis that intrapartum events can have long-term neurologic sequelae for the offspring. Fetal monkeys subjected to hypoxia in utero suffer neurologic injuries similar to those seen in children who presumably suffered asphyxia in utero. Work with rodent, rabbit, piglet, and sheep models have shown similar patterns of damage.

Some fetuses appear to be at greater risk for adverse intrapartum events than others. Older studies report that high-risk mothers constitute 20% of the pregnant population, but their offspring represent 50% of the cases of perinatal morbidity and mortality. Various methods for identification of high-risk pregnancies have been published. High-risk pregnancies include, but are not limited to, women with (1) medical complications (e.g., hypertension, preeclampsia, diabetes, autoimmune disease, hemoglobinopathy); (2) fetal complications (e.g., fetal growth restriction, nonlethal anomalies, preterm delivery, multiple gestation, post-datism, hydrops); and (3) intrapartum complications (e.g., abnormal vaginal bleeding, maternal fever, meconium-stained amniotic fluid, oxytocin augmentation of labor). Owing to inadequate sensitivity, poor positive predictive values, and the inability to modify risk factor–related outcomes, high-risk scoring systems have not been proven to improve pregnancy outcomes. In one study, more than half of infants with asphyxia had no clinical risk factors. However, scoring systems may be useful in the management of low-risk parturients who do not warrant continuous monitoring during labor. One European strategy for identifying high-risk parturients integrates the analysis of the fetal heart rate (FHR) tracing at the time of admission; if the FHR tracing is abnormal, patients receive intensive monitoring. A meta-analysis of this approach failed to demonstrate outcome improvement, but did increase cesarean delivery rates. The magnitude of risk for intrapartum fetal neurologic injury is a matter of some dispute. In 2014, the American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy concluded that 70% of these types of fetal neurologic injuries result from events that occur before the onset of labor. Examples of antepartum events that may cause fetal neurologic injury include congenital anomalies, chemical exposure, infection, and fetal thrombosis/coagulopathy. Only 4% of cases of neonatal encephalopathy result solely from intrapartum hypoxia, an incidence of approximately 1.5/1000. The Task Force criteria are consistent with clinical findings in a case series of neurologically impaired infants with intrapartum compromise. An additional case series of sentinel events (i.e., uterine rupture,
cord prolapse, placental abruption, amniotic fluid embolus) during labor described a high rate of hypoxic-ischemic encephalopathy in surviving infants. Although a low percentage of neonatal encephalopathy is caused by intrapartum hypoxia, approximately 25% of fetuses may have antepartum and intrapartum risk factors for neurologic injury. Box 8.1 lists findings that suggest an acute intrapartum hypoxic-ischemic event contributed to neonatal encephalopathy.

The ability of obstetricians to recognize and treat pregnancies at risk for hypoxia during labor is an evolving science. With the current understanding of pathophysiology and the contemporary technology used clinically, the extent to which obstetricians can prevent intrapartum injury remains unclear. Obstetricians need clear pathophysiology-based definitions of intrapartum injury. Improved monitoring technologies and standardized interpretation will enhance ascertainment of the fetus at risk. Research may result in the development of new strategies and interventions that can specifically identify and correct reversible pathophysiology.

Efforts to understand placental physiology and pathophysiology are central to efforts to support the health of the pregnant woman and her fetus, both antepartum and intrapartum. The fetus depends on the placenta for the diffusion of nutrients and for respiratory gas exchange. Many factors affect placental transfer, including concentration gradients, villus surface area, placental permeability, and placental metabolism (see Chapter 4). Maternal hypertensive disease, congenital anomalies, and intrauterine infection are examples of conditions that may impair placental transfer.

One of the most important determinants of placental function is uterine blood flow. A uterine contraction results in a transient decrease in uteroplacental blood flow. A placenta with borderline function before labor may be unable to adequately maintain gas exchange to prevent fetal asphyxia during labor. The healthy fetus may compensate for the effects of hypoxia during labor. The compensatory response includes (1) decreased oxygen consumption, (2) vasoconstriction of nonessential vascular beds, and (3) redistribution of blood flow to the vital organs (e.g., brain, heart, adrenal glands, placenta). Humoral responses (e.g., release of epinephrine from the adrenal medulla, release of vasopressin and endogenous opioids) may enhance fetal cardiac function during hypoxia. Prolonged or severe hypoxia overwhels these compensatory mechanisms, resulting in fetal injury or death.

### INTRAPARTUM FETAL ASSESSMENT

#### Electronic Fetal Heart Rate Monitoring

There is need for a sensitive yet specific method for determination of fetal health during labor and delivery. Most contemporary methods include assessment of the FHR. The FHR can be monitored intermittently with a simple DeLee or Pinard stethoscope. Alternatively, either Doppler ultrasonography or a fetal electrocardiography (ECG) electrode can be used to monitor the FHR intermittently or continuously.

Experimental models have provided insight into the regulation of the FHR. Both neuronal and humoral factors affect the intrinsic FHR. Parasympathetic outflow by means of the vagus nerve decreases the FHR, whereas sympathetic activity increases FHR and cardiac output. Baroreceptors respond to increased blood pressure, and chemoreceptors respond to decreased PaO₂ and increased PacO₂ to modulate the FHR through the autonomic nervous system. Cerebral cortical activity and hypothalamic activity affect the FHR through their effects on integrative centers in the medulla oblongata (Fig. 8.1). Both animal studies and clinical observations have helped establish a correlation between FHR and perinatal outcome.

An electronic monitor simultaneously records the FHR and uterine contractions. Use of an electronic monitor allows determination of the baseline rate and patterns of the FHR and their relationship to uterine contractions. External or internal techniques can assess the FHR and uterine contractions (Fig. 8.2). Doppler ultrasonography detects the changes in ventricular wall motion and blood flow in major vessels

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**BOX 8.1 Neonatal Encephalopathy and Association with Peripartum Intrapartum Events**

**Definition of Neonatal Encephalopathy**

Syndrome of disturbed neurologic function in the earliest days of life in an infant born at ≥35 weeks’ gestation

Neonatal signs consistent with an acute peripartum or intrapartum event:

1. Apgar scores less than 5 at 5 minutes and 10 minutes of life
2. Evidence of metabolic acidosis in umbilical cord arterial blood obtained at delivery (i.e., pH < 7.00, base deficit > 12 mmol/L)
3. Neuroimaging evidence of acute brain injury seen on brain magnetic resonance imaging or magnetic resonance spectroscopy consistent with hypoxia-ischemia
4. Presence of multisystem organ failure consistent with hypoxic-ischemic encephalopathy

Type and timing of contributing factors that are consistent with an acute peripartum or intrapartum event:

1. Sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery (i.e., uterine rupture, abruption, amniotic fluid embolus)
2. Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event
3. Type and timing of brain injury pattern based on imaging studies consistent with an etiology of an acute peripartum or intrapartum event
4. No evidence of other proximal or distal factors that could be contributing events

Developmental outcome is spastic quadriplegia or dyskinetic cerebral palsy.

The following features of the FHR pattern can be assessed: (1) baseline measurements, (2) variability (the extent to which the rate changes both instantaneously and over longer periods), (3) accelerations, and (4) decelerations and their association with uterine contractions.

**Baseline Fetal Heart Rate**

A normal baseline FHR is defined as 110 to 160 beats per minute (bpm) and is determined by assessing the mean heart rate over a 10-minute period rounded to increments of 5 bpm. In general, term fetuses have a lower baseline FHR than preterm fetuses because of greater parasympathetic nervous system activity. Laboratory studies suggest that bradycardia (caused by increased vagal activity) is the initial fetal response to acute hypoxemia. After prolonged hypoxemia, the fetus may experience tachycardia as a result of catecholamine secretion and sympathetic nervous system activity. Changes in baseline FHR may also be caused by fetal anatomic or functional heart pathology, maternal fever and/or intrauterine infection, or maternally administered medications, such as beta-adrenergic receptor agonists (e.g., terbutaline) or the anticholinergic agent atropine.

**Fetal Heart Rate Variability**

Fetal heart rate variability is the fluctuation in the FHR of two cycles or greater per minute (bpm) and is determined by assessing the mean heart rate over a 10-minute period rounded to increments of 5 bpm. In general, term fetuses have a lower baseline FHR than preterm fetuses because of greater parasympathetic nervous system activity. Laboratory studies suggest that bradycardia (caused by increased vagal activity) is the initial fetal response to acute hypoxemia. After prolonged hypoxemia, the fetus may experience tachycardia as a result of catecholamine secretion and sympathetic nervous system activity. Changes in baseline FHR may also be caused by fetal anatomic or functional heart pathology, maternal fever and/or intrauterine infection, or maternally administered medications, such as beta-adrenergic receptor agonists (e.g., terbutaline) or the anticholinergic agent atropine.

**Fig. 8.1 Regulation of fetal heart rate.** (Drawing by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
animal models, perfusion of the CNS with calcium results in depolarization of electroencephalographic (EEG) activity, which abolishes FHR variability. Clinically, the presence of normal FHR variability predicts early neonatal health, as defined by an Apgar score of greater than 7 at 5 minutes.39 In a case series of monitored fetal deaths, no fetus had normal variability immediately before demise.31 However, in a cohort of 500 deliveries, presence or absence of variability was not associated with neonatal acidosis.40 The differential diagnosis of decreased variability includes fetal hypoxia, fetal sleep state, fetal neurologic abnormality, and decreased CNS activity that results from exposure to drugs such as opioids.

Accelerations
Accelerations are abrupt changes in the FHR from baseline. Beyond 32 weeks' gestation, an acceleration is defined by a peak of at least 15 bpm above baseline and lasting at least 15 seconds. (Before 32 weeks' gestation, a peak of 10 bpm above the baseline, lasting at least 10 seconds, is required.)32,35 While...
Fig. 8.3 (A) Normal intrapartum fetal heart rate (FHR) tracing. The infant had Apgar scores of 8 and 8 at 1 and 5 minutes, respectively. (B) Absence of variability in a FHR tracing. Placental abruption was noted at cesarean delivery. The infant had an umbilical arterial blood pH of 6.75 and Apgar scores of 1 and 4, respectively. (C) Early FHR decelerations. After a normal spontaneous vaginal delivery, the infant had Apgar scores of 8 and 8, respectively. (D) Late FHR decelerations. The amniotic fluid surrounding this fetus was meconium-stained. Despite the late FHR decelerations, the variability remained acceptable. The infant was delivered by cesarean delivery and had an umbilical venous blood pH of 7.30. Apgar scores were 9 and 9, respectively.

Continued
Variable decelerations vary in depth, shape, and duration. They often are abrupt in onset and offset. Variable decelerations result from baroreceptor- or chemoreceptor-mediated vagal activity or possible transient hypoxemia. Experimental models and clinical studies suggest that umbilical cord occlusion, either partial or complete, results in variable decelerations. During the second stage of labor, variable decelerations may result from compression of the fetal head. In this situation, dural stimulation leads to increased vagal discharge. The healthy fetus can typically tolerate mild to moderate variable decelerations (not below 80 bpm) without decompensation. With prolonged, severe variable decelerations (less than 60 bpm) or persistent fetal bradycardia, it is difficult for the fetus to maintain cardiac output and umbilical blood flow.

Some practitioners additionally characterize decelerations as “atypical” when they demonstrate “shoulders,” “overshoot,” “biphasic” or “W pattern,” “slow return,” or absent variability at the nadir. The 2008 National Institute for Child and Human Development (NICHD) Consensus guidelines do not categorize atypical decelerations separately from other decelerations. There is controversy whether these atypical patterns indicate additional hazard for the fetus.

Sinusoidal and saltatory patterns are two unusual FHR tracing results that may indicate fetal compromise. The sinusoidal FHR pattern is a regular, smooth, wavelike pattern that may signal fetal anemia. Occasionally, maternal administration of an opioid can lead to a sinusoidal FHR pattern. The saltatory pattern consists of excessive swings in variability (more than 25 bpm) and may signal the occurrence of acute fetal hypoxia; there is a weak association between this pattern and low Apgar scores.

Limitations of Electronic Fetal Heart Rate Monitoring

Despite laboratory and early clinical data suggesting that FHR monitoring accurately reflects fetal health, controversy exists.
Regarding the ability of this assessment tool to improve fetal and neonatal outcomes, FHR monitoring was first introduced some 40 years ago and now is utilized in over 85% of monitored deliveries. Retrospective reports of continuous FHR monitoring associate its use with a lower incidence of intrauterine fetal demise, neonatal seizures, and neonatal death. By contrast, the only consistent finding from multiple case-control studies and more than a dozen prospective, randomized trials of electronic FHR monitoring (with control arms that employed intermittent FHR auscultation) is an increased rate of operative delivery. Meta-analyses of these trials and a large U.S. birth cohort found a decreased incidence of 1-minute Apgar scores less than 4 and a decreased incidence of neonatal seizures with the use of continuous FHR monitoring.

It remains unclear why prospective studies have not confirmed greater benefit of the use of continuous electronic FHR monitoring during labor; the intensity of intrapartum assessment and care may be partially responsible. In prospective trials, women were randomly assigned to receive intermittent FHR auscultation and were monitored by dedicated nursing staff who provided intensive intrapartum care. By contrast, the historical cohort studies compared patients who received continuous electronic FHR monitoring and intensive intrapartum care with patients who had intermittent FHR auscultation with non-intensive nursing care. There are no published studies that have randomly assigned a group of patients to receive no FHR monitoring; however, the continuous high rate of intrapartum stillbirth in unmonitored births in the developing world suggests that FHR assessment may be beneficial.

Consistent with the results of the prospective trials, the ACOG endorses the use of either intermittent auscultation or continuous electronic FHR monitoring during labor. In high-risk patients, ACOG guidelines recommend that the obstetrician or nurse review the electronic FHR tracing every 15 minutes during the first stage of labor and every 5 minutes during the second stage. For low-risk patients, the intervals may be lengthened to 30 minutes for the first stage and 15 minutes for the second stage. The optimal interval for intermittent FHR monitoring has not been studied, but the intervals of 15 to 30 minutes in the active phase and every 5 minutes in the second stage have some indirect support. Adherence to these standards for intermittent auscultation may be difficult to achieve in the clinical setting; in one study, only 3% of parturients met this standard. A Cochrane review compared use of handheld Doppler/intermittent cardiotocography to use of Pinard (non-electronic device) and demonstrated no improvement in neonatal outcome but an increase in operative delivery.

Several hypotheses to account for the apparent failure of intrapartum FHR monitoring to reduce the incidence of cerebral palsy have been proposed, and include the following:

- A larger proportion of very-low-birth-weight (VLBW) infants survive and thus contribute to the number with cerebral palsy;
- Infection is associated with abnormal FHR patterns and the subsequent development of cerebral palsy, and it is unclear if early intervention offers any benefit in such cases;
- The amount of asphyxia required to cause permanent neurologic damage approximates the amount that causes fetal death, leaving a narrow window for intervention. The number of patients in whom cerebral palsy develops from intrapartum asphyxia is probably quite small.
- Limitations of FHR monitoring include a poor positive predictive value in distinguishing between abnormal FHR tracings and abnormal outcomes. Because of this imprecision, the ACOG recommended that abnormal FHR tracings be described with the term nonreassuring fetal status rather than fetal distress or birth asphyxia. In one population-based case-control study of children with cerebral palsy, FHR tracings were retrospectively reviewed. While a markedly higher incidence of abnormal FHR tracings were found in children with cerebral palsy than in controls, there was a 99.8% false-positive rate of abnormal tracings. Later case-control studies have yielded similar results.

While poor specificity of EFM is a documented concern, inadequate sensitivity is also an issue. A 2017 report noted that 20% of fetuses born with acidaemia do not have an abnormal FHR tracing even with expert retrospective evaluation.

Further limitations of continuous FHR monitoring include: (1) poor intra-observer and inter-observer agreement despite the use of trained observers, especially when FHR patterns are observed; (2) the required continual presence of a nurse or physician to assess the FHR tracing; (3) the inconvenience to the patient (e.g., confinement to bed and the application of monitor belts or a scalp electrode); and (4) the need to maintain the FHR tracings as legal documents.

Despite little evidence for its efficacy, Parer and King suggested that obstetricians continue to rely on electronic FHR monitoring for the following three reasons: (1) professional obstetric organizations (e.g., the ACOG) advise some form of monitoring during labor, (2) electronic FHR monitoring is logistically easier and less expensive than one-on-one nursing care during labor, and (3) individual (often anecdotal) experiences cause “many obstetricians [to] believe that in their own hands FHR monitoring is … efficacious.”
In 2008 the National Institute of Child Health and Human Development (NICHD) sponsored a workshop that resulted in the publication of updated definitions, interpretation, and research guidelines for intrapartum electronic FHR monitoring. The published report proposed a three-tier system for the categorization of FHR patterns. The ACOG has described this system in a 2009 Practice Bulletin with suggested options for management.

- **Category I (normal):** Strongly predictive of normal fetal acid-base status at the time of observation.
- **Category II (indeterminate):** Not predictive of abnormal fetal acid-base status, but without adequate evidence to classify as normal or abnormal.
- **Category III (abnormal):** Predictive of abnormal fetal acid-base status at the time of observation and thus requiring prompt evaluation (Box 8.2).

### BOX 8.2 Three-Tiered Fetal Heart Rate Interpretation System

**Category I Tracings Include All of the Following:**
- Baseline rate: 110–160 beats per minute (bpm)
- Baseline FHR variability: moderate
- Accelerations: present or absent
- Late or variable decelerations: absent
- Early decelerations: present or absent

**Category II Tracings Include:**
- All tracings not categorized as Category I or Category III
- Baseline FHR
  - Bradycardia not accompanied by absent baseline variability
  - Tachycardia
- Baseline FHR variability
  - Minimal baseline variability
  - Absent baseline variability not accompanied by recurrent decelerations
  - Marked baseline variability
- Accelerations
- Absence of induced accelerations after fetal stimulation
- Periodic or episodic decelerations
- Recurrent variable decelerations accompanied by minimal or moderate variability
- Prolonged deceleration ≥ 2 minutes but < 10 minutes
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics such as slow return to baseline, overshoots, or shoulders

**Category III Tracings Include Either:**
- Absent baseline FHR variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

In a large population review, 78% of tracings were Category I, 22% of tracings were Category II, and Category III was present 0.004% of the time. Whereas only 0.2% of Category I tracings had low Apgar scores and NICU admissions, this increased to 0.7% with Category II tracings, suggesting a greater association with increased short-term morbidity.

An overriding concern with the three-tier system is the number and heterogeneity of patients with Category II tracings. A five-tier system has been proposed to offer better sensitivity than the three-tier system; however, the ability of both classification systems to predict fetal acidemia appears equivalent.

### Methods for Improving the Efficacy of Electronic Fetal Heart Rate Monitoring

Several technologies have been employed to enhance the value of electronic FHR monitoring. To facilitate continual FHR assessment, many labor and delivery units transmit the tracings from the bedside to the nurses’ station. Presumably, this practice facilitates a more rapid response to worrisome FHR tracings.

Computerized analysis may assist in the interpretation of FHR tracings. While commercially available programs with sound or light alerts have been developed, are consistent with expert analysis, and demonstrate accuracy in identifying fetal acidemia, randomized controlled trials have not shown improvement over visual interpretation of tracings.

Continuous FHR monitoring requires the patient to wear FHR and uterine contraction monitoring devices and to remain within several feet of the monitor. An alternative is the use of telemetry, which transmits the FHR from the patient to the monitor and consequently allows ambulation. The low-risk patient who wishes to ambulate probably does not require continuous electronic FHR monitoring.

Electronic archiving allows for the electronic storage and retrieval of FHR tracings and eliminates the need for long-term storage of the paper record. The FHR tracing is a medico-legal document, and if it is lost, the plaintiff’s lawyer may allege that the tracing was discarded intentionally because it was detrimental to the defendant.

### Supplemental Methods of Fetal Assessment

A normal electronic FHR monitor tracing is more than 99% accurate in predicting a 5-minute Apgar score higher than 7. Unfortunately, an abnormal FHR tracing has a false-positive rate of more than 99%. Adding other fetal assessment tools may help identify the compromised fetus with greater specificity and allow appropriate intervention.

An older method used to confirm or exclude the presence of fetal acidosis when FHR monitoring suggests the presence of fetal compromise is the fetal scalp blood pH determination. Suggested indications include the presence of decreased or absent FHR variability or persistent late or variable FHR decelerations. The obstetrician inserts an endoscope into the vagina, makes a small laceration in the fetal scalp (or buttock), and uses a capillary tube to collect a sample of fetal capillary blood (Fig. 8.4). Data suggesting a lack of benefit of fetal
blood sampling beyond FHR interpretation, the technical challenges of obtaining a sample, and the requirement for having readily available instrumentation to conduct the test, have led most U.S. centers to abandon this technique. An alternative method, which remains in use in Europe, analyzes the fetal blood sample for the presence of lactate. Sampling of lactate requires a smaller amount of blood and is therefore more frequently successful. While some data suggest fetal blood sampling may decrease operative deliveries, there is no evidence to suggest improvement in fetal outcomes.

An alternative to fetal scalp blood sampling is fetal scalp stimulation (although fetal scalp blood sampling is a form of fetal scalp stimulation). The fetal scalp can be digitally stimulated during vaginal examination or squeezed with an Allis clamp. The heart rate of a healthy, nonacidotic fetus accelerates in response to scalp stimulation; FHR acceleration is associated with a fetal pH of at least 7.19. Vibroacoustic stimulation is another method for assessing a worrisome FHR tracing. Advocates of this technique contend that application of an artificial larynx to the maternal abdomen results in FHR acceleration in a healthy fetus and improves the specificity of FHR monitoring. Used primarily in antepartum testing situations, there is less evidence for intrapartum use. A meta-analysis of intrapartum stimulation tests (i.e., fetal scalp blood pH determination, Allis clamp scalp stimulation, vibroacoustic stimulation, and digital fetal scalp stimulation) found the tests to be equivalent at predicting fetal acidemia, with digital fetal scalp stimulation having the greatest ease of use.

The intrapartum use of umbilical artery velocimetry has been applied as an adjunct to FHR monitoring, but has demonstrated poor correlation with fetal outcomes. However, middle cerebral artery (MCA) Doppler evaluation, alone or in conjunction with umbilical artery Doppler evaluation, has been suggested to have a good negative predictive value as a screening test for at-risk fetuses.

Just as the antenatal use of the biophysical profile (BPP) decreases the false-positive rate of a positive nonstress test before labor, the BPP has been proposed as a potential tool to assist with intrapartum management. The presence of meconium-stained amniotic fluid has long been associated with an increased risk for infant depression at birth. Moderate to thick meconium is associated with lower Apgar scores, lower umbilical arterial blood pH, an increased incidence of neonatal seizures, and higher rates of cesarean delivery and admission to an intensive care nursery. Although approximately 4% to 22% of all deliveries are complicated by meconium-stained amniotic fluid, few of these infants experience neonatal depression. The odds ratio for complications increases with meconium, but the majority of infants with neonatal complications have clear fluid. Meconium-stained fluid has a poor positive predictive value and poor sensitivity in predicting adverse neonatal outcomes.

The physiology associated with the passage of meconium is incompletely understood. Ultrasonographic imaging suggests that the fetus regularly passes rectal contents into the amniotic fluid throughout gestation. However, meconium-stained amniotic fluid is more common in pregnancies complicated by postdatism or fetal growth restriction. Putative triggers for the passage of meconium include umbilical cord compression and hypoxia. The presence of meconium combined with an abnormal FHR tracing or another risk factor (e.g., fetal growth restriction, postdatism) appears to be associated with an increased likelihood of neonatal depression.

Among the newborns with meconium-stained amniotic fluid, approximately 3% to 12% develop significant neonatal respiratory compromise termed meconium aspiration syndrome. Antenatal risk factors for this syndrome include moderate or thick meconium (suggesting recent passage and lower amniotic fluid volume) and abnormal FHR tracings. The lung injury likely originates from intrapartum fetal hypoxia. Oropharyngeal suctioning at delivery has not proved beneficial; randomized controlled trials have suggested that vigorous neonates do not need aggressive airway cleansing with endotracheal intubation (see Chapter 9). Aggressive management of postdate pregnancies has led to a decreased incidence of meconium-stained amniotic fluid over the past decade.

Additional Technologies for Fetal Assessment

Because FHR monitoring provides only an indirect measure of fetal oxygenation and acid-base status, alternative technologies such as ST waveform analysis of fetal electrocardiography (ECG) have been proposed to enhance assessment of fetal oxygenation. Animal and human studies indicate that fetal hypoxia induces changes in the ECG morphology of the ST segment and T wave collected by a fetal spiral electrode. In early European trials, a device utilizing computerized analysis of ST waveform collected from the fetal electrocardiographic tracing (STAN S31, Neovahta Medical, Motald, Sweden)
showed promise in reducing the risk for neonatal hypoxic encephalopathy.\textsuperscript{13,14} A 2015 randomized controlled trial of more than 11,000 parturients in the United States did not demonstrate an improvement in neonatal outcomes or a decrease in cesarean delivery rates with use of STAN S31 versus conventional monitoring.\textsuperscript{15} A meta-analysis of studies showed a decrease in the use of fetal scalp sampling and fewer operative vaginal births with use of STAN S31 but likewise no improvement in neonatal outcomes or cesarean delivery rates.\textsuperscript{16} Explanations of outcome differences with STAN in American and European trials include use of three-tier (American) versus four-tier (European) classification systems for FHR tracings. Also, the American trial encouraged intervention based on clinical suspicion without an abnormal ST signal.\textsuperscript{16,17} Need for electrode placement, early application of the STAN monitor before suspected fetal compromise, and unclear benefit of the technique have led to limited use in the United States.

**Reflectance pulse oximetry** was adapted for assessment of fetal oxygenation. The United States Food and Drug Administration (FDA) approved the Nellcor N-400 fetal pulse oximeter (Nellcor Puritan Bennett, Pleasanton, CA) for use in the setting of a term, singleton fetus at more than 36 weeks’ gestation with a vertex presentation and a nonreassuring FHR pattern after rupture of membranes.\textsuperscript{18,19} The most commonly used probes are held in place against the fetal head or cheek with pressure from the cervix. A reliable pulse oximetry signal can be obtained in 60% to 70% of cases. Fetal pulse oximetry used in conjunction with FHR monitoring appeared to reduce the rate of cesarean delivery for a nonreassuring FHR tracing; however, this reduction was offset by an increased rate of cesarean delivery for dystocia.\textsuperscript{20–22} A meta-analysis of four randomized trials of fetal pulse oximetry showed similar results.\textsuperscript{23} The absence of an effect on the overall cesarean delivery rate prompted the ACOG to withhold an endorsement of fetal pulse oximetry.\textsuperscript{19}

**Research Technologies for Fetal Assessment**

Transcutaneous \( \text{PO}_2 \), \( \text{PCO}_2 \), and \( \text{pH} \) monitors have been developed to provide a more direct fetal assessment.\textsuperscript{15,16,104–106} These monitors, however, are limited by technical difficulties in application of the probe(s), drift of baseline measurements, artifactual measurements, and difficulty in establishing diagnostic criteria for intervention. None of these monitors are in routine clinical use for fetal assessment in labor.

**Proton magnetic resonance spectroscopy** (\( ^1 \text{H MRS} \)) can obtain metabolic information from the brains of humans and animals, and early investigations have suggested an ability to assess fetal brain oxygenation.\textsuperscript{107–109} \( ^1 \text{H MRS} \) has proved useful in the evaluation of hypoxic-ischemic encephalopathy and metabolic disorders in pediatric patients. Although these measurements can be correlated with the level of tissue oxygenation, the clinical utility of this technique as a means of fetal assessment remains unclear.\textsuperscript{109}

Near-infrared spectroscopy (NIRS) has the potential to measure fetal tissue oxygenation directly.\textsuperscript{110} Transabdominal NIRS has been used in research settings to assess placental oxygenation.\textsuperscript{111} NIRS can detect changes in the ratio of reduced to oxygenated cytochrome-\( c \) oxidase in the brain and in the ratio of oxygenated to deoxygenated hemoglobin in the blood perfusing the brain. This technique can also measure the total amount of hemoglobin in the tissue, which provides an estimate of tissue blood perfusion.\textsuperscript{111} Current NIRS technology is limited by a frequent inability to obtain interpretable measurements (approximately 20% of the time) and the need to correlate the measurements with long-term neurodevelopmental outcomes. Therefore, NIRS remains a research rather than a clinical tool at this time.\textsuperscript{111}

**INTRAPARTUM FETAL THERAPY**

The ACOG has suggested that intrapartum management be based on the three-tier evaluation framework.\textsuperscript{22} A Category I tracing requires only periodic re-evaluation. Category III tracings should prompt preparation for delivery if improvement of the FHR tracing is not accomplished in a timely manner. Currently, Category II tracings should be evaluated as suggested earlier by assessment of the presence of moderate variability and spontaneous or provoked accelerations, which suggest a nonacidotic fetus.\textsuperscript{22}

The identification of potential intrapartum fetal compromise with a Category II tracing should prompt a careful assessment of maternal, placental, and fetal factors. Clinical history, physical findings, laboratory findings, and fetal monitoring (e.g., FHR, ultrasonography) should be used in an attempt to identify the etiology.\textsuperscript{113,114}

Correctable maternal factors that may contribute to fetal compromise include pathologic states that result in hypoxemia or decreased oxygen delivery to the placenta. Respiratory failure caused by long-standing diseases (e.g., asthma) can be determined from the history and physical findings, whereas additional laboratory measurements may be necessary to diagnose pneumonia or pulmonary edema as an underlying cause. Decreased oxygen delivery to the placenta may result from acute (e.g., sepsis, hypotension) or chronic conditions. Decreased uteroplacental perfusion can result from reduced maternal cardiac output (e.g., cardiovascular disease) or chronic vascular disease (e.g., chronic hypertension, diabetes). Dehydration from prolonged labor is a more subtle cause of diminished uteroplacental perfusion.

Attention to the etiology of fetal hypoxemia and institution of appropriate treatments may mitigate fetal compromise. Administration of supplemental oxygen may enhance fetal oxygenation, even in the previously normoxemic mother; however, whether maternal oxygen therapy improves fetal outcome remains unclear.\textsuperscript{115,116}

Uterine hypertonus or frequent uterine contractions (tachysystole), which may result in decreased uteroplacental perfusion, are known risks of oxytocin or prostaglandin compounds used for the induction of labor. Uterine contractions constrict the uterine spiral arteries, decreasing oxygen delivery to the placenta. A rare cause of fetal compromise is uterine rupture, which may result from uterine hyperstimulation,
TABLE 8.1 Various Intrauterine Resuscitative Measures for Category II or Category III Tracings or Both

<table>
<thead>
<tr>
<th>Goal</th>
<th>Associated Fetal Heart Rate Abnormality*</th>
<th>Potential Intervention(s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote fetal oxygenation and improve uteroplacental blood flow</td>
<td>Recurrent late decelerations</td>
<td>Initiate lateral positioning (either left or right)</td>
</tr>
<tr>
<td></td>
<td>Prolonged decelerations or bradycardia</td>
<td>Administer maternal oxygen</td>
</tr>
<tr>
<td></td>
<td>Minimal or absent fetal heart rate variability</td>
<td>Administer intravenous fluid bolus</td>
</tr>
<tr>
<td>Reduce uterine activity</td>
<td>Tachysystole with Category II or III tracing</td>
<td>Reduce uterine contraction frequency</td>
</tr>
<tr>
<td>Alleviate umbilical cord compression</td>
<td>Recurrent variable decelerations</td>
<td>Discontinue oxytocin or cervical ripening agents</td>
</tr>
<tr>
<td></td>
<td>Prolonged decelerations or bradycardia</td>
<td>Administer tocolytic medication (e.g., terbutaline)</td>
</tr>
</tbody>
</table>

*Evaluation for the underlying suspected cause(s) is also an important step in management of abnormal FHR tracings.
†Depending on the suspected underlying cause(s) of FHR abnormality, combining multiple interventions simultaneously may be appropriate and potentially more effective than doing individually or serially (Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. Obstet Gynecol. 2005;105:1362–1368).


particularly in the setting of a uterine scar. Placental abruption, which may result in a partial or complete cessation of oxygen transfer to the fetus, can be associated with chronic or acute diseases. Long-standing vascular diseases, produced by chronic hypertension or smoking, and acute factors such as cocaine abuse and abdominal trauma, can precipitate a placental abruption.

The treatment of uteroplacental causes of fetal compromise includes correction of uterine hypertonus or tachysystole by cessation of oxytocin infusion (Table 8.1). Oxytocin has a plasma half-life of 1 to 6 minutes, and consequently, it may take several minutes for the hypertonus to be relieved. Alternatively, a tocolytic agent (e.g., terbutaline, nitroglycerin, magnesium sulfate) may be administered. Normal maternal circulation should be maintained by avoiding aortocaval compression with position change, expanding intravascular volume, and giving a vasopressor (e.g., phenylephrine, ephedrine) if indicated.

Fetal factors may contribute to fetal hypoxemia and acidosis. Umbilical cord prolapse through the cervix causes cord compression and often results in sudden fetal bradycardia. In the vast majority of circumstances, treatment of a prolapsed cord consists of manual elevation of the fetal head until emergency cesarean delivery can be accomplished. Only rarely should the umbilical cord be returned into the uterus and expectant care be attempted. Reports from the developing world indicate that, in some cases, expeditious vaginal delivery may produce acceptable neonatal outcome. Alternative methods to decompress a prolapsed umbilical cord include the use of the Trendelenburg position or an infusion of 500 to 700 mL of 0.9% saline into the maternal bladder until delivery can be expedited.

Umbilical cord prolapse is not the only cause of umbilical cord compression. Much more commonly, such compression occurs within the uterus and manifests as variable FHR decelerations or bradycardia. Oligohydramnios is a risk factor for this type of cord compression, and a change in maternal position or the use of saline amnioinfusion may be therapeutic. Amnioinfusion presumably restores the natural cushion of amniotic fluid, and studies suggest that it reduces the frequency of severe variable decelerations and the incidence of cesarean delivery, and increases the umbilical cord blood pH in women with preterm premature rupture of membranes (PROM), oligohydramnios, or variable decelerations during labor. A 2012 Cochrane systematic review concluded that there was no advantage between prophylactic intrapartum amnioinfusion in patients with oligohydramnios and therapeutic amnioinfusion in patients with both oligohydramnios and FHR abnormalities.

Initial studies suggested that in patients with thick, meconium-stained amniotic fluid, amnioinfusion might decrease the incidence of meconium aspiration syndrome and fetal acidosis. A meta-analysis of studies, however, suggests no benefit of amnioinfusion in the setting of meconium unless decelerations resulting from oligohydramnios are present. Saline amnioinfusion requires a dilated cervix, ruptured membranes, and the placement of an intrauterine catheter. Equipment that allows simultaneous saline amnioinfusion and measurement of intrauterine pressure is preferred. Either normal saline or lactated Ringer’s solution may be infused as a bolus or as a continuous infusion. The ideal rate of infusion has not been determined, but a commonly used regimen consists of a bolus of as much as 800 mL (infused at a rate of 10
to 15 mL/min), followed by either a continuous infusion at a rate of 3 mL/min or repeated boluses of 250 mL, as needed.\textsuperscript{128} The necessity of either an infusion pump or a fluid warmer has not been demonstrated.\textsuperscript{128} Alleviation of abnormal FHR patterns generally requires 20 to 30 minutes.\textsuperscript{128} Although most studies suggest that amnioinfusion is safe for the mother and fetus, some complications have been reported. Overdistention of the uterus, a higher rate of maternal infection, and maternal respiratory distress, including cases of fetal amniotic fluid embolism, have occurred.\textsuperscript{129,130} A causal relationship between amniotic fluid embolism and amnioinfusion has yet to be determined. Overdistention of the uterus may be controlled with proper documentation if amnioinfusion by gravity instead of an infusion pump, and the use of ultrasonography to evaluate the fluid volume.\textsuperscript{124}

Maternal fever may increase fetal oxygen consumption. Obstetricians should treat maternal fever with acetaminophen, a cooling blanket, and antibiotics as indicated to maintain maternal and fetal euthermia. Hyperglycemia also increases fetal oxygen consumption, so administration of a large bolus of a glucose-containing solution is contraindicated.

Fetal cardiac failure results in inadequate umbilical blood flow and fetal hypoxemia and acidosis. Fetal anemia caused by maternal isoinmunization, fetal hemoglobinopathy, or fetal hemorrhage results in diminished fetal oxygen-carrying capacity. There are few options for the treatment of fetal cardiac failure or anemia during labor.

Standardization of FHR tracing interpretation and staged levels of intervention based on likely etiology of the FHR abnormalities will assist in guiding obstetric management. If intrapartum assessment suggests the presence of fetal compromise and fetal therapy is unsuccessful, the obstetrician should affect an expeditious, atraumatic delivery.

### KEY POINTS

- A normal FHR tracing accurately predicts fetal well-being. An abnormal tracing is not specific in the prediction of fetal compromise. Exceptions include the fetus with prolonged bradycardia or the fetus with late FHR decelerations and absence of variability; both suggest a high likelihood of fetal hypoxia/acidemia.
- Large, prospective, randomized studies have not confirmed that continuous electronic FHR monitoring confers substantial clinical benefit over intermittent FHR auscultation as performed by dedicated labor nurses.
- The specificity of FHR monitoring may be improved by the use of fetal scalp stimulation and fetal vibroacoustic stimulation.
- Neither fetal pulse oximetry nor fetal ST segment analysis reduce the rate of cesarean delivery.
- When a Category II FHR tracing occurs, fetal resuscitation in utero may be attempted with interventions that include maternal position change, treatment of uterine tachysystole, intravenous fluid bolus, administration of supplemental oxygen, and/or saline amnioinfusion.

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Neonatal Assessment and Resuscitation

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The transition from intrauterine to extrauterine life represents the most important adjustment that a neonate will make. This transition occurs uneventfully after most deliveries and is dependent on the anatomic and physiologic condition of the infant, the ease or difficulty of the delivery, and the extrauterine environmental conditions. When the transition is unsuccessful, prompt assessment and supportive care must be initiated immediately.

At least one person skilled in neonatal resuscitation should be present at every delivery. The resuscitation team may include personnel from the pediatric, anesthesiology, obstetric, respiratory therapy, and nursing services. The composition of the team varies among institutions, but there should be some form of 24-hour coverage in all hospitals that provide labor and delivery services. A multidisciplinary team should participate in the process of ensuring that appropriate personnel and equipment are available for neonatal resuscitation.

All personnel working in the delivery area should receive basic training in neonatal resuscitation to ensure prompt initiation of care before the arrival of the designated resuscitation team. The 2015 American Heart Association (AHA) Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care led to the publication of updated guidelines for neonatal resuscitation. Changes in these guidelines reflected a review of scientific evidence by members of the American Academy of Pediatrics (AAP), the AHA, and the International Liaison Committee on Resuscitation. These guidelines have been incorporated into the Neonatal Resuscitation Program (NRP), which is the standardized training and certification program administered by the AAP. The NRP, which was originally sponsored by the AAP and the AHA in 1987, is designed to be appropriate for all personnel who attend deliveries. To ensure the implementation of current guidelines for neonatal resuscitation, the AAP recommends that at least one NRP-certified practitioner attend every delivery.

Both the American Society of Anesthesiologists (ASA) and the American College of Obstetricians and Gynecologists (ACOG) have published specific goals and guidelines for neonatal resuscitation (Box 9.1). The ASA has emphasized that a single anesthesiologist should not be expected to assume responsibility for the concurrent care of both the mother and her child. Rather, a second anesthesia provider or a qualified individual from another service should assume responsibility for the care of the neonate, except in an unforeseen emergency.

Although the anesthesia provider is not usually the primary provider of neonatal resuscitation, he or she may be asked to provide assistance in cases of difficult airway management or when the neonatal resuscitation team has not yet arrived. The anesthesia provider should be prepared to provide assistance, provided that doing so does not compromise the care of the mother. Written hospital policies should identify the personnel responsible for neonatal resuscitation, and obstetric anesthesia providers should also maintain a high level of skill in neonatal resuscitation.

**TRANSITION FROM INTRAUTERINE TO EXTRAUTERINE LIFE**

**Circulation**

At birth, the circulatory system changes from a fetal circulation pattern (which is in parallel), through a transitional
circulation, to an adult circulation pattern (which is in series) (Fig. 9.1). In the fetus, blood from the placenta travels through the umbilical vein and the ductus venosus to the inferior vena cava and the right side of the heart. The anatomic orientation of the inferior vena caval–right atrial junction favors the shunting (i.e., streaming) of this well-oxygenated blood through the foramen ovale to the left side of the heart. The blood is then pumped through the ascending aorta, where branches that perfuse the upper part of the body (e.g., heart, brain) exit proximal to the entrance of the ductus arteriosus. Desaturated blood returns to the heart from the upper part of the body via the superior vena cava. The anatomic orientation of the superior vena caval–right atrial junction favors the streaming of blood into the right ventricle. Because fetal pulmonary vascular resistance is higher than systemic vascular resistance (SVR), approximately 90% of the right ventricular output passes through the ductus arteriosus and enters the aorta distal to the branches of the ascending aorta and aortic arch; therefore, blood that is less well-oxygenated perfuses the lower body, which has a lower oxygen consumption than the heart and brain. Deoxygenated blood from the fetus returns to the placental circulation via the umbilical arteries.

At the time of birth and during the subsequent period of circulatory transition, the amount of blood that shunts through the foramen ovale and ductus arteriosus diminishes,

**BOX 9.1 Optimal Goals for Anesthesia Care in Obstetrics: Neonatal Resuscitation**

Personnel other than the surgical team should be immediately available to assume responsibility for resuscitation of the depressed neonate. The surgeon and anesthesiologist are responsible for the mother and may not be able to leave her to care for the neonate, even when a neuraxial anesthetic is functioning adequately. Individuals qualified to perform neonatal resuscitation should demonstrate:

- Proficiency in rapid and accurate evaluation of the neonate’s condition, including Apgar scoring
- Knowledge of the pathogenesis of a depressed neonate (acidosis, drugs, hypovolemia, trauma, anomalies, and infection) as well as specific indications for resuscitation
- Proficiency in neonatal airway management, laryngoscopy, endotracheal intubation, airway suctioning, artificial ventilation, cardiac massage, and maintenance of thermal stability

In larger maternity units and those functioning as high-risk centers, 24-hour in-house anesthesia, obstetric, and neonatal specialists are usually necessary.

Modified from a joint statement from the American College of Obstetricians and Gynecologists and the American Society of Anesthesiologists. Optimal goals for anesthesia care in obstetrics. Approved by the American Society of Anesthesiologists in October 2008. (See Appendix C for full document.)

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**Fig. 9.1** Modification of blood flow patterns from the fetal (left), via the transitional (center), to the neonatal (right) circulation. In the fetal circulation, oxygenated blood (white) from the placenta travels through the umbilical vein (1) into the ductus venosus and the inferior vena cava (2). The majority of oxygenated blood passes through the patent foramen ovale (PFO) from the right atrium to the left atrium (3) and ventricle (4), and distributes this blood to the brain (5). The deoxygenated blood (blue) from the brain and upper extremities enters the superior vena cava, mixing with a small portion of the oxygenated blood in the right atrium, before entering the right ventricle (RV, 7). The mostly deoxygenated blood is transported into the pulmonary artery, where the majority is diverted through the patent ductus arteriosus (PDA, 8) into the descending aorta (9), thereby bypassing the lungs. Some blood enters the lower body (10), but the majority returns to the placenta via the umbilical arteries (11). A small amount of blood from the pulmonary artery enters the lungs (12). During the transitional circulation, which occurs over a few days, the PFO closes, diverting blood from the right atrium to the right ventricle. Closure of the PDA diverts deoxygenated blood through the pulmonary arteries to the lungs. The neonatal circulation separates the oxygenated and deoxygenated blood flow pathways. (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
and flow becomes bidirectional. Clamping the umbilical cord (or exposing the umbilical cord to room air) results in increased SVR. Concurrently, expansion of the lungs and increased alveolar oxygen tension and pH result in decreased pulmonary vascular resistance and greater flow of pulmonary artery blood through the lungs. Increased pulmonary artery blood flow results in improved oxygenation and higher left atrial pressure; the latter leads to a diminished shunt across the foramen ovale. Increased P_{2}O_2 and SVR and decreased pulmonary vascular resistance result in a constriction of the ductus arteriosus. Together, these changes in vascular resistance result in functional closure of the foramen ovale and the ductus arteriosus. This process does not occur instantaneously, and arterial oxygen saturation (Sao_2) remains higher in the right upper extremity (which is preductal) than in the left upper extremity and the lower extremities until blood flow through the ductus arteriosus is minimal. Differences in Sao_2 are usually minimal by 10 minutes and absent by 24 hours after birth. Provided there is no interference with the normal drop in pulmonary vascular resistance, both the foramen ovale and the ductus arteriosus close functionally as the infant transitions to an adult circulation.

**Persistent pulmonary hypertension of the newborn** (previously referred to as persistent fetal circulation) can occur when the pulmonary vascular resistance remains elevated at the time of birth. Factors that may contribute to this problem include hypoxia, acidosis, hypovolemia, and hypothermia. Maternal use of nonsteroidal anti-inflammatory drugs may also cause premature constriction of the ductus arteriosus in the fetus and thus predispose to persistent pulmonary hypertension of the newborn.

**Respiration**

Fetal breathing movements have been observed *in utero* as early as 11 weeks’ gestation. These movements increase with advancing gestational age but undergo a marked reduction within days of the onset of labor. They are stimulated by hypercapnia and maternal smoking, and are inhibited by hypoxia and central nervous system (CNS) depressants (e.g., barbiturates). Under normal conditions, this fetal breathing activity results only in the movement of pulmonary dead space.

The fetal lung contains a liquid composed of an ultrafiltrate of plasma, which is secreted by the lungs *in utero*. The volume of this lung liquid is approximately 30 mL/kg. Partial reabsorption of this liquid occurs during labor and delivery, and approximately two-thirds is expelled from the lungs of the term neonate by the time of delivery. Preterm infants and infants requiring cesarean delivery without labor may have a greater amount of residual lung liquid after delivery owing to a reduced catecholamine surge at delivery that promotes sodium channel transport; this residual lung liquid leads to difficulty in the initiation and maintenance of normal breathing patterns, and is the presumed cause of **transient tachypnea of the newborn (TTN)**.

The first breath occurs approximately 9 seconds after delivery. Air enters the lungs as soon as the intrathoracic pressure begins to decrease. This air movement during the first breath is important, because it establishes the neonate’s functional residual capacity (Fig. 9.2).

Lung inflation is a major physiologic stimulus for the release of lung surfactant into the alveoli. Surfactant, which is necessary for normal breathing, is present within the alveolar lining cells by 20 weeks’ gestation and within the lumen of the airways by 28 to 32 weeks’ gestation. However, significant amounts of surfactant do not appear in terminal airways until 34 to 38 weeks’ gestation unless its production has been stimulated by chronic stress or maternal corticosteroid administration. Stress during labor and delivery can lead to the passage of meconium into the amniotic fluid and gasping efforts by the fetus, which may result in the aspiration of amniotic fluid into the lungs.

**Catecholamines**

Transition to extrauterine life is associated with a catecholamine surge, which may be necessary for the process to be successful. In chronically catheterized sheep, catecholamine levels begin to rise a few hours before delivery and may be higher at the time of delivery than at any other time during life. Catecholamines have an important role in the following areas: (1) the production and release of surfactant, (2) the transition to active sodium transport for absorption of lung fluid, (3) the mediation of preferential blood flow to vital organs during the period of stress that occurs during every delivery, and (4) thermoregulation of the neonate.

**Thermal Regulation**

Thermal stress challenges the neonate in the extrauterine environment. Neonates raise their metabolic rate and release norepinephrine in response to cold; this response facilitates the oxidation of brown fat, which contains numerous mitochondria. The oxidation results in nonshivering thermogenesis, the major mechanism for neonatal heat regulation.
This process may lead to significant oxygen consumption, especially if the neonate has not been dried and placed in an appropriate thermoneutral environment, for example with a radiant warmer. Thermal stress is an even greater problem in infants with low fat stores, such as preterm infants or infants who are small for gestational age. An alternative method to eliminate heat loss from evaporation is to provide an occlusive wrap rather than drying the infant. For infants born at less than 28 weeks’ gestation, the use of polyethylene wraps or bags is recommended to minimize heat loss. The maintenance of a neutral thermal environment (i.e., 34°C to 35°C) is recommended. However, in the neonate with a perinatal brain injury, mild hypothermia therapy through selective head or whole-body cooling is initiated in the first 6 hours of life and may be neuroprotective in the setting of hypoxia-ischemia. Hyperthermia may worsen neurologic outcomes and should be avoided. Hypothermia therapy, via selective head cooling or whole-body hypothermia, is continued for 72 hours after initiation. Consequently, if an infant is delivered at a center where hypothermia therapy is unavailable, passive cooling can be initiated by turning the radiant warmer off while awaiting infant transfer.

Administration of epidural analgesia during labor is associated with an increase in maternal and fetal temperature, which might result in an increase in the frequency of neonatal sepsis evaluations. However, a number of variables (e.g., preeclampsia/hypertension, gestational age, birth weight, meconium aspiration, respiratory distress at birth, hypothermia at birth, and group B beta-hemolytic streptococcal colonization of the maternal birth canal) have been observed to be strong predictors of the performance of neonatal sepsis evaluations, whereas maternal fever and epidural analgesia have not. Confounding variables may influence the findings of these types of association studies; patients who choose either to receive or not receive epidural analgesia may be inherently different. The incidence of actual neonatal sepsis is not different in term infants whose mothers either did or did not receive epidural analgesia.

In infants not requiring immediate resuscitation, providing skin-to-skin contact with the mother can allow for appropriate thermal regulation, enhance breast-feeding, and reduce maternal stress. This practice must be associated with close monitoring to prevent the infant from slipping off the mother, and to detect sudden unexpected postnatal collapse (SUPC). Although rare, SUPC can be a fatal event in an otherwise healthy appearing infant, and requires adequate personnel to provide observation, monitoring, and treatment.

**ANTENATAL ASSESSMENT**

Approximately 10% of neonates require some level of resuscitation. The need for resuscitation can be predicted before labor and delivery with approximately 80% accuracy on the basis of a number of antepartum factors (Box 9.2).

**Preterm delivery** increases the likelihood that the neonate will require resuscitation. When a mother is admitted with either preterm labor or premature rupture of membranes, plans should be made for neonatal care in the event of delivery. The antenatal assessment of gestational age is based on the presumed date of the last menstrual period, the fundal height, and ultrasonographic measurements of the fetus. Unfortunately, it may be difficult to assess gestational age accurately, because menstrual dates may be

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**BOX 9.2 Risk Factors Suggesting a Greater Need for Neonatal Resuscitation**

**Antepartum Risk Factors**
- Maternal diabetes
- Hypertensive disorder of pregnancy
- Chronic hypertension
- Fetal anemia or isoimmunization
- Previous stillbirth or neonatal death
- Bleeding in second or third trimester
- Maternal infection
- Maternal cardiac, pulmonary, renal, thyroid, or neurologic disease
- Polyhydramnios
- Oligohydramnios
- Premature rupture of membranes
- Fetal hydrops
- Postterm gestation
- Multiple gestation
- Discrepancy between fetal size and dates (i.e., last menstrual period)
- Drug therapy (e.g., lithium carbonate, magnesium, adrenergic-blocking drugs)
- Maternal substance abuse
- Fetal malformation
- Diminished fetal activity
- No prenatal care
- Maternal age > 35 years

**Intrapartum Risk Factors**
- Emergency cesarean delivery
- Forceps or vacuum-assisted delivery
- Breech or other abnormal presentation
- Preterm labor
- Precipitous labor
- Chorioamnionitis
- Prolonged rupture of membranes (> 18 hours before delivery)
- Prolonged labor (> 24 hours)
- Macrosomia
- Category II or III fetal heart rate patterns
- Use of general anesthesia
- Uterine tachysystole with fetal heart rate changes
- Maternal administration of opioids within 4 hours of delivery
- Meconium-stained amniotic fluid
- Prolapsed umbilical cord
- Placental abruption
- Placenta previa
- Significant intrapartum bleeding

Unknown or incorrect, the fundal height may be affected by abnormalities of fetal growth or amniotic fluid volume, and ultrasonographic assessment of fetal age is less precise after mid-pregnancy. The assessment of gestational age is most accurate in patients who receive prenatal care in early pregnancy and enables the health care team to plan for the neonatal needs and to appropriately counsel the parents regarding neonatal morbidity and mortality. These plans and expectations must be formulated with caution and flexibility, because the antenatal assessment may not accurately predict neonatal size, maturity, and/or condition at delivery.

A variety of intrauterine insults can impair the fetal transition to extraterine life. For example, neonatal depression at birth can result from acute or chronic uteroplacental insufficiency or acute umbilical cord compression. Chronic uteroplacental insufficiency, regardless of its etiology, may result in fetal growth restriction. Fetal hemorrhage, viral or bacterial infection, meconium aspiration, and exposure to opioids or other CNS depressants also can result in neonatal depression. Although randomized trials have not confirmed that fetal heart rate (FHR) monitoring improves neonatal outcome, a nonassuring FHR tracing is considered a predictor of the need for neonatal resuscitation.

Studies have evaluated the use of fetal pulse oximetry for the evaluation of fetal well-being during labor. This technique involves the transcutaneous insertion of a flexible fetal oxygen sensor until it rests against the fetal cheek. A randomized trial found that use of fetal pulse oximetry in conjunction with FHR monitoring led to a reduction in the number of cesarean deliveries performed for a nonassuring FHR tracing. However, this decrease was offset by an increased number of cesarean deliveries performed for dystocia, raising the concern that the presence of the probe might predispose to dystocia. As a consequence, the American College of Obstetricians and Gynecologists (ACOG) has recommended further study before fetal pulse oximetry is used routinely in clinical practice. A meta-analysis of five trials concluded that there was some benefit to fetal pulse oximetry in the presence of a nonassuring FHR tracing, but the use of fetal pulse oximetry did not lead to an overall reduction in the cesarean delivery rate.

Infants with congenital anomalies (e.g., tracheoesophageal fistula, diaphragmatic hernia, CNS and cardiac malformations) may need resuscitation and cardiorespiratory support. Improved ultrasonography allows for the antenatal diagnosis of many congenital anomalies and other fetal abnormalities (e.g., nonimmune hydrops). Obstetricians should communicate knowledge or suspicions regarding these entities to those who will provide care for the neonate in the delivery room to allow the resuscitation team to make specific resuscitation plans.

In the past, infants born by either elective or emergency cesarean delivery were considered more likely to require resuscitation than infants delivered vaginally. Evidence suggests that repeat cesarean deliveries and those performed for dystocia—in patients without FHR abnormalities—result in the delivery of infants at low risk for neonatal resuscitation, especially when the cesarean deliveries are performed with neuraxial anesthesia. Of interest, infants born by elective repeat cesarean delivery are at higher risk for subsequent respiratory problems (e.g., TTN) than infants born vaginally. In addition, infants born by cesarean delivery after a failed trial of labor are at a higher risk for neonatal sepsis than similar infants born vaginally. Emergency cesarean delivery is considered a risk factor for the need for neonatal resuscitation.

**NEONATAL ASSESSMENT**

### Apgar Score

Resuscitative efforts typically precede the performance of a thorough physical examination of the neonate. Because NRP instructions require simultaneous assessment and treatment, it is important that the neonatal assessment be both simple and sensitive. In 1953, Virginia Apgar, an anesthesiologist, described a simple method for neonatal assessment that could be performed while care is being delivered. She suggested that this standardized and relatively objective scoring system would differentiate between infants who require resuscitation and those who need only routine care.

The Apgar score is based on five parameters that are assessed at 1 and 5 minutes after birth. Further scoring at 5- or 10-minute intervals may be done if initial scores are low. The parameters are: heart rate, respiratory effort, muscle tone, reflex irritability, and color. A score of 0, 1, or 2 is assigned for each of these five entities (Table 9.1). A total score of 8 to 10 is normal, a score of 4 to 7 indicates moderate impairment, and

<table>
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<tr>
<th>TABLE 9.1 Apgar Scoring System</th>
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<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>Heart rate (bpm)</td>
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<tr>
<td>Respiratory effort</td>
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<tr>
<td>Muscle tone</td>
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<tr>
<td>Reflex irritability (nasal catheter, oropharyngeal suctioning)</td>
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a score of 0 to 3 signals the need for immediate resuscitation. Dr. Apgar emphasized that this system does not replace a complete physical examination and serial observations of the neonate for several hours after birth.

The Apgar score is widely used to assess neonates, although its value has been questioned. The scoring system may help predict mortality and neurologic morbidity in populations of infants, but Dr. Apgar cautioned against the use of the Apgar score to make these predictions in an individual infant. She noted that the risk for neonatal mortality was inversely proportional to the 1-minute score. In addition, the one-minute Apgar score was a better predictor of mortality within the first 2 days of life than within 2 to 28 days of life.

Several studies have challenged the notion that a low Apgar score signals perinatal asphyxia. In a prospective study of 1210 deliveries, Sykes et al. noted a poor correlation between the Apgar score and the umbilical cord blood pH. Other studies, including those of low-birth-weight infants, have found that a low Apgar score is a poor predictor of neonatal acidosis, although a high score is reasonably specific for excluding the presence of severe acidosis. By contrast, the fetal biophysical profile has a good correlation with the acid-base status of the fetus and the neonate (see Chapter 6). The biophysical profile includes performance of a nonstress test and ultrasonographic assessment of fetal tone, fetal movement, fetal breathing movements, and amniotic fluid volume.

Additional studies have suggested that Apgar scores are poor predictors of long-term neurologic impairment. The Apgar score is more likely to predict a poor neurologic outcome when the score remains 3 or less at 10, 15, and 20 minutes. However, when a child has cerebral palsy, low Apgar scores alone are not adequate evidence that perinatal hypoxia was responsible for the neurologic injury.

The ACOG Task Force on Neonatal Encephalopathy and Cerebral Palsy published criteria for defining an intrapartum event sufficient to cause cerebral palsy. An Apgar score of 0 to 3 beyond 5 minutes of age is not included in the list of “essential criteria”; rather, it is one of five criteria that “collectively suggest an intrapartum timing (within close proximity to labor and delivery….) but are nonspecific to asphyxial insults.

In summary, the usefulness of the Apgar score is still being debated more than 50 years after its inception. The Apgar scoring system is used throughout the world, but its limitations must be kept in mind. Low Apgar scores alone do not provide sufficient evidence of perinatal asphyxia; rather, Apgar scores can be low for a variety of reasons. Preterm delivery, congenital anomalies, neuromuscular diseases, antenatal drug exposure, manipulation at delivery, and subjectivity and error may influence the Apgar score.

Umbilical Cord Blood Gas and pH Analysis

Umbilical cord blood gas and pH measurements reflect the fetal condition immediately before delivery and can be obtained routinely after delivery or measured only in cases of neonatal depression. These measurements may be a more objective indication of a neonate’s condition than the Apgar score. However, there is a delay between obtaining the samples and completing the analysis; during this interval, decisions must be made on the basis of clinical assessment. The ACOG has recommended that cord blood gas measurements be obtained in circumstances of cesarean delivery for fetal compromise, low 5-minute Apgar score, severe growth restriction, abnormal FHR tracing, maternal thyroid disease, intrapartum fever, and/or multiple gestation.

The fetus produces carbonic acid (from oxidative metabolism) and lactic and beta-hydroxybutyric acids (primarily from anaerobic metabolism). Carbonic acid, which is often called respiratory acid, is cleared rapidly by the placenta as carbon dioxide when placental blood flow is normal. However, metabolic clearance of lactic and beta-hydroxybutyric acids requires hours; thus, these acids are called metabolic or fixed acids. In the fetus, metabolic acidemia is more ominous than respiratory acidemia because the former reflects a significant amount of anaerobic metabolism.

The measured components of umbilical cord blood gas analysis are pH, PCO₂, PO₂, and bicarbonate (HCO₃⁻). HCO₃⁻ is a major buffer in fetal blood. The measure of change in the buffering capacity of umbilical cord blood is reflected in the delta base, which is also known as the base excess or deficit; this value can be calculated from the pH, PCO₂, and HCO₃⁻. Ideally, blood samples from both the umbilical artery and vein are collected. Umbilical artery blood gas measurements represent the fetal condition, whereas umbilical vein measurements reflect the maternal condition and uteroplacental gas exchange. Unfortunately, it may be difficult to obtain blood from the umbilical artery, especially when it is small, as it is in very low-birth-weight (VLBW) infants. Caution should be used in the interpretation of an isolated umbilical venous blood pH measurement, which can be normal despite the presence of arterial acidemia.

Proper blood sampling and handling are necessary. The measurements should be accurate, provided that (1) the umbilical cord is double-clamped immediately after delivery; (2) the samples are drawn, within 15 minutes of delivery, into a syringe containing the proper amount of heparin; and (3) the samples are analyzed within 30 to 60 minutes. The Po₂ measurement is more accurate if residual air bubbles are removed from the syringe.

Historically, a normal umbilical cord blood pH measurement was believed to be 7.2 or higher. However, investigators have challenged the validity of this number, given the lack of distinction between umbilical arterial and venous blood despite clear differences in their normal measurements. One study noted that the median umbilical arterial blood pH in vigorous infants (those with 5-minute Apgar scores of 7 or higher) was 7.26, with a measurement of 7.10 representing the 2.5th percentile. Published studies suggest that the lower limit of normal umbilical arterial blood pH measurements may range from 7.02 to 7.18 (Table 9.2). A number of factors may also influence the umbilical arterial blood pH measurement. A fetus subjected to the stress of labor has lower pH than one born by cesarean delivery without labor. Offspring of nulliparous women tend to have
a lower pH than offspring of parous women, a difference that is likely related to a difference in the duration of labor.81

Some studies have suggested that preterm infants have a higher incidence of acidemia; however, later studies have observed that term and preterm infants have similar umbilical cord blood gas and pH measurements.72,73,81 Preterm infants often have low Apgar scores despite the presence of normal umbilical cord blood gas and pH measurements; therefore, the assessment of umbilical cord blood may be especially helpful in the evaluation of preterm neonates.

Physicians should use strict definitions when interpreting umbilical cord blood gas and pH measurements. Terms such as birth asphyxia should be avoided in most cases.35 Acidemia refers to an increase in the hydrogen ion concentration in the blood. Acidosis occurs when there is an increased hydrogen ion concentration in tissue. Asphyxia is a clinical situation that involves hypoxia (i.e., a decreased level of oxygen in tissue), damaging acidemia, and metabolic acidosis.

When acidemia is present, the type—respiratory, metabolic, or mixed—must be identified (Table 9.3). Metabolic acidemia is more likely to be associated with acidosis than respiratory acidemia and is clinically more significant. Similarly, mixed acidemia with a high Pco₂, an extremely low HCO₃⁻, and a high base deficit is more ominous than a mixed acidemia with a high Pco₂ but only a slightly reduced HCO₃⁻ and a low base deficit. Mixed or metabolic acidemia (but not respiratory acidemia) is associated with an increased incidence of neonatal complications and death.81 In their study of 3506 term neonates, Goldaber et al.82 noted that an umbilical arterial blood pH measurement less than 7.00 was associated with a significantly higher incidence of neonatal death. All neonatal seizures in their study occurred in infants with an umbilical arterial blood pH less than 7.05. By contrast, a short-term outcome study failed to show a good correlation between arterial blood pH and the subsequent health of an infant.49 In the previously discussed large study reported by Casey et al.,39 umbilical arterial blood pH of 7.0 or less was a poorer predictor of the relative risk for neonatal death during the first 28 days of life than a 5-minute Apgar score of 3 or less. However, 6264 infants were excluded from their study because umbilical

### Table 9.2  Studies Reporting Umbilical Cord Arterial Blood Gas Measurements

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Bicarbonate (mmol/L)</th>
<th>Base Deficit (mmol/L)</th>
<th>PO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huisjes and Arnouldse (1979)</td>
<td>852</td>
<td>7.20</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sykes et al. (1982)</td>
<td>899</td>
<td>7.20</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eskes et al. (1983)</td>
<td>4667</td>
<td>7.23</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeomans et al. (1986)</td>
<td>146</td>
<td>7.28</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1988)</td>
<td>1694</td>
<td>7.26</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruth and Raivio (1988)</td>
<td>106</td>
<td>7.29</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorp et al. (1989)</td>
<td>1694</td>
<td>7.24</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramin et al. (1989)</td>
<td>1292</td>
<td>7.28</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riley and Johnson (1993)</td>
<td>3522</td>
<td>7.27</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagel et al. (1995)</td>
<td>1614</td>
<td>7.21</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Table 9.3  Criteria Used to Define Types of Acidemia in Neonates with an Umbilical Arterial pH Measurement Less Than 7.20

<table>
<thead>
<tr>
<th>Classification</th>
<th>Pco₂ (mm Hg)</th>
<th>HCO₃⁻ (mmol/L)</th>
<th>Base Deficit (mmol/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>High (&gt; 65)</td>
<td>Normal (≥ 22)</td>
<td>Normal (−6.4 ± 1.9)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Normal (&lt; 65)</td>
<td>Low (≤ 17)</td>
<td>High (−15.9 ± 2.8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>High (≥ 65)</td>
<td>Low (≤ 17)</td>
<td>High (−9.6 ± 2.5)</td>
</tr>
</tbody>
</table>

*Mean ± SD given in parentheses.

arterial blood pH measurements could not be obtained, and these infants had a higher incidence of neonatal death than those for whom blood gas measurements were available (4.5 per 1000 versus 1.2 per 1000, respectively). In a separate review of 51,519 term deliveries, Yeh et al. found an increased risk for adverse outcomes in infants with a pH less than 7.10, with the lowest risk in infants with a pH between 7.26 and 7.30; however, 75% of infants with neurologic morbidity had a normal pH. Thus, it is important to remember that neonates may suffer multiorgan system damage, including neurologic injury, even in the absence of low pH and Apgar scores.

According to the ACOG Task Force, an umbilical arterial blood pH less than 7.0 and a base deficit greater than or equal to 12 mmol/L at delivery are considered one part of the definition of an acute intrapartum hypoxic event sufficient to cause cerebral palsy. The base deficit and bicarbonate (the metabolic component) values are the most significant factors associated with morbidity in neonates with an umbilical arterial blood pH less than 7.0. Ten percent of infants with an umbilical arterial base deficit of 12 to 16 mmol/L have moderate to severe complications, which increases to 40% when the deficit is greater than 16 mmol/L. Abnormal FHR patterns and umbilical cord blood gas measurements are not consistently correlated with poor neonatal outcomes. In a longitudinal study that evaluated outcomes at 6.5 years of age, Hafstrom et al. found that infants with an umbilical arterial blood pH less than 7.05 but a normal examination at birth had outcomes that did not differ from those for matched infants with a normal umbilical arterial blood pH.

As Virginia Apgar emphasized in 1962, the most important components of neonatal assessment are a careful physical examination and continued observation for several hours. Additional information can be gained from the antenatal history, Apgar scores, and umbilical cord blood gas and pH measurements, provided that clinicians are aware of the proper methods of interpretation as well as the limitations of these methods of assessment.

Respiration and Circulation
There are some similarities between the initial assessment of the neonate and the initial assessment of an adult who requires resuscitation. In both situations, the physician should give immediate attention to the ABCs of resuscitation (i.e., airway, breathing, circulation).

The normal neonatal respiratory rate is between 30 and 60 breaths per minute. Breathing should begin by 30 seconds and be regular by 90 seconds of age. Failure of the neonate to breathe by 90 seconds of age represents either primary or secondary apnea. During primary apnea, but not secondary apnea, tactile stimulation can initiate breathing efforts. In addition, although heart rate may be low with both periods of apnea, a reduction in blood pressure occurs only during secondary apnea. Therefore, during evaluation of the apneic neonate, aggressive resuscitation must be initiated promptly if tactile stimulation does not result in the initiation of spontaneous breathing.

Assessment of the adequacy of respiratory function requires comprehensive observation for signs of neonatal respiratory distress. These signs include cyanosis, grunting, flaring of the nares, retracting chest motions, and unequal breath sounds. The adequacy of respiratory function can also be assessed by the estimation of Sao₂. Pulse oximetry provides accurate estimates of Sao₂ during periods of stability but may overestimate values during rapid desaturation. In addition, the Sao₂ (Spo₂) measurements may fluctuate in the delivery room as a result of the ongoing transition from the fetal to the neonatal circulation, and it may take more than 10 minutes to achieve a preductal Sao₂ greater than 95% in a healthy term infant. Overall, the newer-generation pulse oximeters reliably provide continuous noninvasive Sao₂ measurements and are useful for neonatal monitoring.

When cyanosis persists beyond 5 to 10 minutes, or supplemental oxygen is needed, the pulse oximeter sensor should be applied to the neonate’s right upper extremity, which receives preductal flow (see earlier discussion); because CNS blood flow is also preductal, right upper extremity Sao₂ measurements provide a more accurate assessment of CNS oxygenation. Sensor placement can be difficult on skin that is wet and covered with vernix caseosa; therefore, it may be easier to place the sensor over the right radial artery, especially in preterm infants.

Neonatal arterial blood sampling is technically difficult and thus rarely obtained in the delivery room. Cannulation of the umbilical artery is useful in infants who will require frequent blood sampling. This procedure often requires the use of microinstruments (especially in preterm and VLBW infants) and the ability to monitor the infant when obscured from view by surgical drapes; therefore, this procedure is usually performed in the neonatal intensive care unit (NICU).

The normal newborn heart rate may be greater than 160 beats per minute (bpm) in the very early preterm neonate, but it should be within the range of 120 to 160 bpm by 28 weeks’ gestational age. Clinical determination of the heart rate can be done by lightly grasping the base of the umbilical cord to feel the arterial pulsations or by listening to the apical heartbeat. These methods have been found to be less reliable than an ECG. Additionally, several studies have found the ECG to be more accurate than pulse oximetry.

Measurement of arterial blood pressure is not a priority during the initial assessment and resuscitation of the neonate. However, observation for signs of abnormal circulatory function is considered essential. These signs include cyanosis, pallor, mottled coloring, prolonged capillary refill time, and weakness or absence of pulses in the extremities. One of the causes of abnormal circulatory function is hypovolemia, which should be anticipated in cases of bleeding from the umbilical cord or the fetal side of the placenta or whenever a neonate does not respond appropriately to resuscitation. The hypovolemic neonate may exhibit not only signs of abnormal circulatory function but also tachycardia and tachypnea (neonatal hypovolemia usually does not accompany placental abruption, which may cause maternal bleeding or other conditions associated with fetal asphyxia).
Neurologic Status

The initial neonatal neurologic assessment requires only simple observation. The neonate should demonstrate evidence of vigorous activity, including crying and active flexion of the extremities. Signs of possible neurologic abnormalities include apnea, seizures, hypotonia, and unresponsiveness. Neonates should be assessed for physical signs of hypoxic-ischemic encephalopathy (Table 9.4). The stages of hypoxic-ischemic encephalopathy are associated with different outcomes: stage I, good; stage II, moderate; and stage III, poor.95 Although detailed neurologic assessment is performed after the neonate is transferred to the NICU, assessment of tone, baseline heart rate, respirations, and reflex activity is part of both the Apgar scoring system and the assessment for hypoxic-ischemic encephalopathy and is made initially in the delivery room.

Gestational Age

When assessing a very small neonate whose gestational age appears to be lower than that of viability, the evaluator must consider whether it is appropriate to initiate and maintain resuscitation efforts. The neonatal gestational age is often assessed with the use of the scoring systems described initially by Dubowitz et al.96 and subsequently modified by Ballard et al., using physical and neurologic criteria.

The Ballard score is most accurate when used to estimate gestational age at 30 to 42 hours, rather than during the first several minutes after birth, and is less accurate in very small preterm infants.98,99

Another commonly used criterion for the estimation of gestational age is birth weight. Normal values for birth weight are published and readily available.100 Although birth weight may help physicians estimate the gestational age of an otherwise healthy preterm infant, physicians cannot rely on birth weight to provide an accurate estimate of gestational age in an infant who suffered from fetal growth restriction or who is large for gestational age.

Because of the potential for inaccurate gestational age estimation in the delivery room, it is best not to use scoring systems to guide decisions regarding the initiation or continuation of neonatal resuscitation immediately after delivery. In most circumstances, the neonate’s response to resuscitative efforts is the best indicator as to whether further intervention is warranted.

### NEONATAL RESUSCITATION

The equipment and medications needed for neonatal resuscitation are listed in Box 9.3. Equipment, supplies, and medications should be checked regularly to ensure that all components are available and functional.

Although previously published guidelines recommended suctioning of the mouth and nose after delivery of the head, current guidelines do not recommend routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born with either clear or meconium-stained amniotic fluid to avoid inducing bradycardia.2,101

Timing of cord clamping may vary by the gestational age and vigor of the infant. Current evidence supports a delay in cord clamping for 1 minute after the delivery of term and preterm infants not requiring resuscitation.2 In preterm infants, delayed cord clamping is associated with improved blood pressure and a lower incidence of intraventricular hemorrhage102; no alterations in Apgar scores or need for delivery room resuscitation have been observed with this practice.103 In nonvigorous infants, the benefits of delayed cord clamping may be outweighed by the need to promptly initiate resuscitation.

After delivery is complete, the neonate is transferred to the resuscitation area. The availability of sterile blankets allows the individual performing the delivery to remain sterile while transferring the infant; this issue is especially important during cesarean deliveries. The timing of delivery should be noted, assessment and appropriate resuscitative measures should be continued, and Apgar scores should be assigned at the appropriate intervals (Fig. 9.3).

Maintaining normal temperature during stabilization for non-asphyxiated infants is essential. The physician or nurse should place the infant beneath an overhead radiant warmer and promptly dry the skin of infants delivered at greater than 28 weeks’ gestation. The infant who is delivered preterm at less than 28 weeks’ gestation should be placed in a polyethylene bag or wrapping to prevent heat loss.25,26 Additional methods to prevent hypothermia include increasing the room temperature and using a thermal mattress. Hypothermia can result in increased oxygen consumption and metabolic acidosis104 and leads to a significantly higher mortality rate among preterm infants.105

Selective cerebral hypothermia106 or whole-body hypothermia17,28 may protect against brain injury in the asphyxiated

### TABLE 9.4 Stages of Neonatal Hypoxic-Ischemic Encephalopathy

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable</td>
<td>Lethargic/obtunded</td>
<td>Coma</td>
</tr>
<tr>
<td>Normal respirations</td>
<td>Depressed respirations</td>
<td>Apnea</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>Hypotonic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Increased reflexes</td>
<td>Decreased reflexes</td>
<td>Absence of reflexes</td>
</tr>
<tr>
<td>No seizures</td>
<td>Occasional seizures</td>
<td>Status epilepticus or nearly isoelectric electroencephalogram</td>
</tr>
<tr>
<td>Good outcome</td>
<td>Moderate outcome</td>
<td>Poor outcome</td>
</tr>
</tbody>
</table>

Modified from Eicher DJ, Wagner CL. Update on neonatal resuscitation. JSC Med Assoc. 2002;98:114–120.
### BOX 9.3 Equipment and Drugs Needed for Neonatal Resuscitation

<table>
<thead>
<tr>
<th>Suction Equipment</th>
<th>Bag-and-Mask Equipment</th>
<th>Intubation Equipment</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bulb syringe</td>
<td>• Neonatal resuscitation bag with a pressure-release valve or pressure manometer and valve to deliver positive end-expiratory pressure (the bag must be capable of delivering 90% to 100% oxygen) or a pressure limiting T-piece resuscitator</td>
<td>• Laryngoscope with straight blades: No. 0 (preterm) and No. 1 (term)</td>
<td>• Epinephrine 1:10,000 (0.1 mg/mL), 3- or 10-mL ampules</td>
</tr>
<tr>
<td>• Mechanical suction and tubing</td>
<td>• Face masks, term and preterm newborn sizes (masks with cushioned rim preferred)</td>
<td>• Extra bulbs and batteries for laryngoscope</td>
<td>• Isotonic crystalloid (normal saline or lactated Ringer’s solution) for volume expansion, 100 or 250 mL</td>
</tr>
<tr>
<td>• Suction catheters: 5F or 6F, 8F, and 10F or 12F</td>
<td>• Air source with tubing</td>
<td>• Tracheal tubes: 2.5, 3.0, 3.5, and 4.0 mm ID</td>
<td>• Sodium bicarbonate 4.2% (5 mEq/10 mL), 10-mL ampules</td>
</tr>
<tr>
<td>• 8F feeding tube and 20 mL syringe</td>
<td>• Oxygen with flowmeter (flow rate up to 10 L/min) and tubing (including portable oxygen cylinders)</td>
<td>• Stylet (optional)</td>
<td>• Normal saline, 30 mL</td>
</tr>
<tr>
<td>• Meconium aspiration device</td>
<td>• Blender to mix air and oxygen to adjust oxygen delivery</td>
<td>• Tape or securing device for tracheal tube</td>
<td>• Dextrose 10%, 30 mL</td>
</tr>
</tbody>
</table>

**ID, internal diameter.**


Infant. The use of intentional hypothermia therapy requires an NICU with defined protocols and multidisciplinary support. When assessing an infant for hypothermia therapy, the radiant warmer can be turned off to allow passive cooling. With further assessment, if the criteria for hypothermia therapy are not met, the infant can be warmed slowly. Hyperthermia should be avoided in all infants.2

The neonate should be positioned in a way that allows the airway to remain open, with the head in the “sniffing” position (the neck flexed on the chest and the head extended on the neck, thereby aligning the oropharynx, pharynx, and hypopharynx). Suctioning of the mouth and nose with a bulb syringe may be necessary if secretions accumulate.

The neonate with a normal respiratory pattern, heart rate, and color requires no further intervention. Often the neonate has a normal respiratory pattern and heart rate but may not be pink. Acrocyanosis often persists for several minutes after delivery and does not require intervention. However, an evaluation for choanal atresia can be performed at this time with the gentle insertion of a small suction catheter through each nostril into the nasopharynx. Vigorous nasal suctioning should be avoided because it can cause trauma to the nasal mucosa and result in progressive edema and airway obstruction. The neonate is an obligate nasal breather; thus, choanal atresia is a potentially lethal anomaly that requires immediate attention. If this anomaly is present (as evidenced by failure of nasal passage of the catheter), the neonate should have an oral airway or endotracheal tube inserted and an evaluation performed for repair of the obstruction. The classic clinical presentation for choanal atresia is an infant with cyanosis and respiratory distress at rest who becomes pink when crying.

Tactile stimulation should be used if the neonate does not breathe immediately; this consists of gently rubbing the back and flicking the soles of the feet. Tactile stimulation does not trigger respiratory efforts during secondary apnea in the neonate. Therefore, if the neonate does not begin to breathe spontaneously after tactile stimulation, the evaluator should begin positive-pressure mask ventilation. If the neonate has an abnormally slow heart rate (i.e., less than 100 bpm), positive-pressure ventilation should be performed until the heart rate rises to the normal range. Overzealous tactile stimulation (e.g., slapping the back) is not useful; it
**Neonatal Resuscitation Algorithm—2015 Update**

1. **Antenatal counseling**
   - Team briefing and equipment check

2. **Birth**
   - Term gestation? Yes or No
     - Yes: Infant stays with mother for routine care: warm and maintain normal temperature, position airway, clear secretions if needed, dry.
     - Ongoing evaluation

3. **Warm and maintain normal temperature, position airway, clear secretions if needed, dry.**

4. **Apnea or gasping? HR below 100/min?**
   - Yes: PPV, SpO2 monitor, Consider ECG monitor
   - No: Labored breathing or persistent cyanosis?

5. **Position and clear airway SpO2 monitor**
   - Supplementary O2 as needed
   - Consider CPAP

6. **Postresuscitation care**
   - Team debriefing

7. **Targeted Preductal SpO2**
   - After Birth
   - 1 min: 60%-65%
   - 2 min: 65%-70%
   - 3 min: 70%-75%
   - 4 min: 75%-80%
   - 5 min: 80%-85%
   - 10 min: 85%-95%

**Fig. 9.3** Algorithm for resuscitation of the newly born infant. HR, heart rate; PPV, positive-pressure ventilation; SpO2, oxygen saturation. (From Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S543–S560 with permission from the American Heart Association.)
provides no advantage over the more moderate methods and can cause traumatic injury. Infants with labored breathing or persistent cyanosis may benefit from continuous positive airway pressure.

High concentrations of oxygen (as opposed to ambient air) can raise production of oxygen free radicals, which have been linked to hypoxia-reoxygenation injury. Additionally, an association between neonatal oxygen supplementation and childhood cancer has been noted with supplemental oxygen exposure for 3 minutes or longer. In two studies, term or near-term infants were randomly assigned to receive neonatal resuscitation with either room air or 100% oxygen; no major outcome differences were observed. Subsequently a pooled meta-analysis of five trials, consisting of 1032 term or near-term infants, showed a significantly lower mortality rate with no evidence of harm when resuscitation was performed initially with room air rather than 100% oxygen. The current guidelines for neonatal resuscitation for term infants recommend the use of room air for assisted ventilation. A meta-analysis detected no significant differences in neuro-developmental outcomes at 12 to 24 months of age between infants resuscitated with either room air or 100% oxygen, with a recent publication showing more adverse outcomes using 100% oxygen.

For preterm infants, several randomized trials have compared high oxygen (65% or greater) and low oxygen (21% to 30%) concentration with no benefit in survival or outcomes such as intraventricular hemorrhage or bronchopulmonary dysplasia with infants generally requiring 30% oxygen when stabilized. As a result, the current guidelines recommend resuscitation with 21% to 30% oxygen with titration as needed. SaO2 measurements of 85% to 92% are thought to be adequate and appropriate for neonates of less than 35 weeks’ gestation.

Positive-pressure ventilation must be performed correctly to ensure that it is effective and does not cause barotrauma. A ventilation bag with a volume of 250 to 500 mL may be used. The circuit must contain a safety pop-off pressure valve (e.g., at 35 cm H2O), a visible pressure gauge, or both. An oxygen flow rate of 5 to 10 L/min is adequate. Alternatively, a T-piece, which is a valved mechanical device, may be used; it allows more consistent delivery of target inflation pressures and long inspiratory times. The mask must be of appropriate size and shape to ensure a good seal around the nose and mouth. A variety of masks should be available to accommodate infants of all sizes and gestational ages. For the infant with excessive occipital scalp edema (e.g., caput succedaneum), placing a small roll under the shoulders to alleviate hyperflexion of the neck may be helpful.

During the first assisted breath, positive pressure at 30 cm H2O in term infants should be maintained for 4 to 5 seconds at the end of inspiration to overcome the surface tension of the lungs and open the alveoli. The neonatal response to a large, rapid inflation of the lungs is a sharp inspiration of its own (Head’s paradoxical reflex). Subsequent breaths should be delivered at a rate of 40 to 60 breaths per minute, with intermittent inspiratory pauses to prevent the development of atelectasis. The maximum pressure generated should range between 20 and 30 cm H2O, with an inspiration-to-expiration ratio of approximately 1:1. In preterm infants, whose lungs may be more easily injured, initial inflation pressures of 20 to 25 cm H2O may be adequate. If mask ventilation is needed for longer than 2 to 3 minutes, the stomach should be emptied with an orogastric catheter. Distention of the stomach with air can compromise respiratory function in the neonate. This maneuver should be performed with care, because pharyngeal stimulation can result in bradycardia and apnea.

The adequacy of respiratory resuscitation can be monitored from observation of its effect on heart rate; an increase in heart rate is the first consistently reliable sign of effective oxygenation. By contrast, changes in color occur slowly, are difficult to assess, and are a relatively poor index of successful resuscitation.

When the neonate’s heart rate is higher than 100 bpm, positive-pressure ventilation can be stopped, and the infant can be reevaluated for spontaneous respiratory effort. If the neonate does not begin to breathe and if an opioid effect is the suspected etiology, administration of naloxone is not recommended. Naloxone can worsen the neurologic damage caused by asphyxia and can precipitate acute neonatal opioid withdrawal, including seizure activity in cases of maternal opioid abuse. Assisted ventilation should be continued until resolution of the opioid effect rather than attempting to reverse it with naloxone.

If positive-pressure mask ventilation does not improve oxygenation (as reflected by an increase in heart rate), prompt tracheal intubation is indicated. Tracheal intubation must be performed gently to avoid damage to the delicate neonatal neck and airway. The size of the neonate’s head is large relative to that of its body; therefore, the neonate is in the optimal position when it lies supine. In most cases, it is not necessary to elevate or hyperextend the neonate’s head during laryngoscopy. The neonatal larynx is more anterior than that of the adult, and visualization often is easier when cricoid pressure is applied. The practitioner should hold the laryngoscope and apply cricoid pressure with the same hand. The thumb and first two fingers hold the base of the laryngoscope, the third finger rests on the mandible, and the fourth finger applies cricoid pressure. This technique promotes gentleness during airway manipulation. The distance from the gums to the larynx often is surprisingly short. A common mistake is to advance the laryngoscope blade too deeply—past the larynx and into the esophagus. When this error occurs, the larynx falls into view if the laryngoscope blade is withdrawn slowly.

The diameter of the endotracheal tube should be large enough to allow adequate ventilation and insertion of a suction catheter (if needed) but small enough to avoid causing trauma and subsequent subglottic stenosis. The ratio of internal diameter to gestational age should be less than 0.1 (e.g., 3.0 mm tube/35 weeks’ gestation = 0.09). After tracheal intubation, positive-pressure ventilation should be resumed by means of an appropriate circuit, as described earlier for mask ventilation. Assessment of proper
tube placement is accomplished by listening for breath sounds in both axillae. Exhaled CO₂ detection is the recommended method for confirming placement of the tube in the trachea.\(^2,126\) False-negative results can occur in situations in which the infant is correctly intubated, with the tube in the trachea, but pulmonary blood flow is poor or absent. This may lead to unnecessary extubation in critically ill infants. As noted previously, the \(\text{FiO}_2\) should be reduced as soon as possible, especially in the preterm neonate. The use of a pulse oximeter and an oxygen blender allows more targeted delivery of supplemental oxygen to the preterm infant immediately after birth. If the neonate is to remain intubated, a chest radiograph should be obtained to confirm the exact position of the endotracheal tube. The skill and experience required for correct tracheal intubation and effective bag-and-mask ventilation may be lacking in providers who are inexperienced with neonatal resuscitation; as a consequence, the laryngeal mask airway (LMA) has been evaluated as a potential alternative airway device for neonatal resuscitation.\(^{129-131}\) The LMA is blindly inserted into the pharynx, and a cuff is inflated to provide a low-pressure seal around the larynx. When evaluated in term infants requiring resuscitation at delivery, use of the LMA was found to be highly successful and without complications.\(^{129,130}\) The current neonatal resuscitation guidelines state that the LMA is an acceptable alternative means of establishing an airway in infants born at 34 weeks’ gestation and greater and weighing more than 2000 g; it can be used by appropriately trained providers when bag-and-mask ventilation is ineffective or attempts at tracheal intubation have been unsuccessful.\(^2\)

One cause of unequal breath sounds and eventual circulatory collapse is a tension pneumothorax. Some physicians have recommended that providers of neonatal resuscitation be skilled in needle aspiration of a tension pneumothorax.\(^1\) This maneuver is accomplished by placement of a 22- or 25-gauge needle in the second intercostal space in the midclavicular line (on the side where no breath or heart sounds are heard). Air will rush out of the needle hub, thereby reducing the tension pneumothorax.

In the vast majority of resuscitations, the neonate responds to ventilatory support. Chest compressions are needed in only 0.03% of deliveries.\(^{132}\) Chest compressions are indicated when the heart rate is less than 60 bpm despite adequate ventilation with supplemental oxygen for 30 seconds.\(^{133}\)

The preferred method for providing chest compressions is with the thumbs of both hands and the hands encircling the chest.\(^{2,134-136}\) Pressure is applied over the sternum just below an imaginary line drawn between the nipples; pressure applied over the lower part of the sternum or xiphoid can injure the abdomen. The sternum should be compressed to approximately one-third the anteroposterior dimension of the chest, and the compression depth must be adequate to produce a palpable pulse.\(^{2,134-136}\) The compression time should be slightly shorter than the release time, particularly to improve blood flow in the very young infant.\(^{137}\) Ventilation is compromised if the chest is compressed simultaneously with the administration of positive-pressure ventilation. The recommended ratio of compressions to breaths is 3:1.\(^{138,139}\) This pattern is given at a rate of 120 events per minute, with 90 chest compressions and 30 breaths administered each minute. Respirations, heart rate, and color should be rechecked every 30 seconds. Compressions should be resumed until the heart rate is 60 bpm or higher. Positive-pressure ventilation with supplemental oxygen titrated to \(\text{SaO}_2\) should be continued until the heart rate is higher than 100 bpm.

Medications are rarely required during neonatal resuscitation because most neonates who require resuscitative measures respond well to satisfactory oxygenation and ventilation alone.\(^{140}\) However, a variety of pharmacologic agents should be available in the delivery room (see Box 9.3). **Epinephrine** (0.01 to 0.03 mg/kg or 0.1 to 0.3 mL/kg of a 1:10,000 solution) should be administered if the heart rate remains lower than 60 bpm after 30 seconds of adequate ventilation and chest compressions. Intravenous administration is the preferred route (via an umbilical venous line). While intravenous access is being established, intratracheal administration through an endotracheal tube may be considered; however, a larger dose of epinephrine (0.05 to 0.1 mg/kg) may be required. Administration of epinephrine is especially important if the heart rate is zero, and may require repeated dosing to be effective.\(^{141}\) Epinephrine raises the heart rate (the major determinant of neonatal cardiac output) and restores coronary and cerebral blood flow.\(^{142}\)

**Sodium bicarbonate** is not recommended during resuscitation. Because of its high osmolarity, this agent can cause hepatic injury at any gestational age and cerebral hemorrhage in the preterm infant.\(^{143,144}\) It may also compromise myocardial and cerebral function.\(^{145,146}\) It should be given only during prolonged resuscitation and when adequate ventilation and circulation have been established. Arterial blood gas measurements and serum chemistry determinations should guide the use of sodium bicarbonate, which generally occurs after stabilization.

**Atropine** is not recommended for use during neonatal resuscitation. Epinephrine is considered the drug of choice for the treatment of bradycardia.

**Calcium** administration is not recommended for neonatal resuscitation, unless it is given specifically to reverse the effect of magnesium (which may have crossed the placenta from the mother to the fetus). Evidence suggests that calcium administration causes cerebral calcification and decreases survival in stressed neonates.\(^{147}\)

**Volume expanders** must be given strictly according to recommended dosage. A continuous infusion is dangerous in the neonate, because it can easily result in the administration of an excessive fluid volume. Fluid overload can cause hepatic capsular rupture, brain swelling in the asphyxiated infant, or intracranial hemorrhage in the preterm infant. Fluids and medications can be administered either intravenously (most commonly through the umbilical vein) or, if necessary, intravasally.

The cannulation of the umbilical vein involves insertion of a soft catheter into the cut end of the vein (Fig. 9.4). The catheter is advanced until blood return is noted, but no more than
Intraosseous access is accomplished by insertion of a 20-gauge needle into the proximal tibia approximately 1 cm below the tibial tuberosity. This technique may be easier to perform for practitioners who have little experience with intravenous or umbilical neonatal catheterization. Absorption from the neonatal bone marrow into the general circulation occurs almost immediately. This rapid absorption results from the preponderance of red bone marrow over yellow bone marrow; yellow bone marrow is less vascular and is the dominant form of marrow after 5 years of age. Complications related to this technique are rare and include tibial fracture (which occurs more often in older children) and osteomyelitis. The risk for infection is proportional to the duration of intraosseous infusion; therefore, the needle should be removed after 1 to 2 hours and, if necessary, a more conventional route of access should be established. Current guidelines state that intraosseous access should be used for medication administration or volume expansion when venous access is difficult to achieve.

Volume expanders should be considered when the infant demonstrates signs of shock, such as pale skin, poor perfusion, and weak pulse, or has not shown adequate response to other resuscitative measures. Normal saline and lactated Ringer’s solution are the preferred volume expanders, given initially at 10 mL/kg over 5 to 10 minutes, with doses repeated as necessary after reassessment for ongoing hypovolemia. Intravascular volume should be assessed through evaluation of heart rate, capillary refill time, and color. If heavy blood loss is suspected, O-negative packed red blood cells may be used according to the same dosage regimen. Red blood cells replete the oxygen-carrying capacity as well as the intravascular volume. O-negative blood should be available at all times for emergency use during neonatal resuscitation. Placental blood has been used for neonatal volume expansion but this practice is discouraged in most institutions because of the risks for infection or transfusion of clotted blood. Albumin administration is not recommended, because it carries a risk for infectious disease and has been associated with higher mortality.

**SPECIAL RESUSCITATION CIRCUMSTANCES**

**Meconium-Stained Amniotic Fluid**

Meconium is present in the intestinal tract of the fetus after approximately 31 weeks’ gestation. Meconium-stained amniotic fluid is present in 10% to 15% of all pregnancies; the incidence is higher in postterm pregnancies. Intrapartum passage of meconium may be associated with fetal stress and hypoxia.

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate whose airway was exposed to meconium and whose chest radiograph exhibits characteristic findings, including pulmonary consolidation and atelectasis. Treatment of MAS often involves the use of positive-pressure ventilation and is associated with a 5% to 20% incidence of pneumothorax from pulmonary air leaks, and can be associated with persistent pulmonary hypertension of the newborn. Historically, the death rate from MAS was as high as 6 per 10,000 live infants. The use of ECMO and inhaled nitric oxide for the treatment of pulmonary hypertension associated with MAS has been shown to reduce mortality rates.

In an attempt to reduce inhalation of meconium from the pharynx and thus prevent or reduce the severity of MAS, the practice of suctioning the mouth and pharynx after delivery of the head, and subsequent intubation to remove meconium from the trachea, was common practice. However, studies have documented that airway suctioning at birth does not prevent MAS and its associated mortality; these studies indicated that MAS was primarily a result of intrauterine events such as asphyxia or sepsis. Hypoxia induces...
pathologic changes in the pulmonary vasculature, which results in pulmonary hypertension and respiratory distress after birth. The pulmonary damage is independent of meconium aspiration; therefore, it is not prevented by the suctioning of meconium. A prospective study designed to assess the efficacy of routine tracheal suctioning of meconium to prevent MAS indicated little or no benefit to this practice. 170

Amnioinfusion—the instillation of saline into the amniotic cavity—has been used successfully for reduction of cord compression in the presence of oligohydramnios during labor. It has also been proposed as a potential treatment to reduce the incidence of MAS in infants born to women with thick meconium staining of the amniotic fluid. Potential benefits include (1) the reduction of cord compression, thus alleviating fetal compromise and acidemia that contribute to MAS; and (2) the dilution or washing out of the meconium in the amniotic fluid. A large multicenter randomized trial found no difference in rates of MAS or other neonatal disorders with the use of amnioinfusion. 171,172 Thus, the routine practice of amnioinfusion for meconium-stained fluid alone is not recommended. 173

Current guidelines do not recommend routine intrapartum oropharyngeal and nasopharyngeal suctioning before delivery of the infant’s head; 1,174 given that a large multicenter randomized trial showed no benefit to this practice in term-gestation infants. 175 After stabilization of the infant, meconium may be gently cleared from the mouth and nose by means of a bulb syringe or a large suction catheter (e.g., 12F to 14F).

Preterm Infant

The preterm neonate, especially the VLBW infant, is at higher risk for problems with multiple organ systems simply because of immaturity. During resuscitation, the physician should give special attention to the effect of prematurity on the lungs and the brain. Before the addition of surfactant and high-frequency ventilation to the therapeutic armamentarium of the neonatologist, neonatal respiratory distress syndrome caused by surfactant deficiency was the overwhelming obstacle to the attempted salvage of the very preterm infant.

Between 1970 and 2005, the proportion of infants weighing less than 1500 g at delivery rose from 1.17% to 1.5%; the proportion has stabilized at 1.45%. 176 The survival rate of these 500- to 1500-g infants has increased to approximately 85%. 177 Of these, 5% to 10% have what is characterized as cerebral palsy, and 25% to 50% exhibit behavioral and cognitive deficits that lead to important school problems after birth. The overall burden of disability has sharply increased in recent years owing to the proportion of very preterm infants who are surviving. 179 Periventricular leukomalacia, which is the classic neuropathology associated with hypoxic-ischemic cerebral white matter injury in the preterm infant, commonly accompanies IVH. 180

The fragility of the immature subependymal germinal matrix predisposes the preterm infant to the development of IVH. The hemorrhage originates from the endothelial cell–lined vessels that course through the germinal matrix in free communication with the venous circulation (i.e., the capillary-venule junction). The hemorrhage can expand into the adjacent lateral ventricle. The mechanism of damage to these endothelial cells and to the integrity of these capillaries has been investigated in animal models 181,182 and in human neonates by means of Doppler velocimetry. 182 The pathogenesis of IVH is multifactorial; different combinations of factors are relevant in different patients. 183,184 The three major categories in the pathogenesis of IVH are intravascular, vascular, and extravascular. Intravascular factors include fluctuating cerebral blood flow (CBF), which can result from respiratory disturbances in the ventilated preterm infant with neonatal respiratory distress syndrome; 182,185 increases in CBF; 181,186 increases in cerebral venous pressure; 187 decreases in CBF followed by reperfusion; and platelet and coagulation disturbances. 188 Vascular factors include the tenuousness of the capillary integrity of the germinal matrix and the vulnerability of the matrix capillaries to hypoxic-ischemic injury. 189 Extravascular factors include deficient vascular support, excessive fibrinolytic activity, and a possible postnatal decrease in extravascular tissue pressure. 188

Of special interest in the discussion of antepartum and intrapartum care and neonatal resuscitation are the possible interventions that may prevent or lessen the severity of IVH. The best way to prevent germinal matrix IVH is to prevent preterm birth. Infection and inflammation are the most commonly identified causes of preterm birth at the lowest relevant gestational age. 190 Antenatal treatment of infections has not been proven to prevent preterm labor or premature rupture of membranes; however, prevention of infection, if possible, may be an important way to reduce the risk for IVH. Another intervention that lowers the incidence of IVH is the transportation of the preterm mother while the fetus is still in utero to a center that specializes in the care of high-risk neonates. 1

Various antenatal pharmacologic interventions have been evaluated for the prevention of IVH. Clinical trials of antenatal maternal administration of phenobarbital 192,193 and vitamin K 194,195 have yielded conflicting results, and their routine use is not currently recommended. 54

Corticosteroids are currently the most beneficial antenatal pharmacologic intervention for the prevention of IVH. This effect was first noticed when obstetricians began giving betamethasone and dexamethasone to pregnant women to help accelerate fetal lung maturity. The mechanism behind this
protection is thought to be improved neonatal cardiovascular stability, which results in less hypotension and less need for blood pressure treatment in these infants. Antenatal betamethasone administration leads to lower placental vascular resistance and higher placental blood flow. This improvement in placental blood flow may decrease impairment of the preterm infant's cerebral autoregulation. In addition, corticosteroids may stimulate the maturation of the germinal matrix. Recommendations regarding timing of steroid administration have been published by the ACOG, which recommends corticosteroid administration for pregnant women between 24 0/7 weeks and 33 6/7 weeks' gestation who are at risk to deliver, while corticosteroid administration can be considered for at-risk pregnancies as early as 23 0/7 weeks' gestation. A repeat course can be considered when there is risk for delivery within 7 days and the woman is less than 34 0/7 weeks' gestation and the previous course of corticosteroids occurred more than 14 days previously (see Chapter 33).

Multiple studies have demonstrated a lower incidence of cerebral palsy in infants of mothers given magnesium sulfate for the treatment of preeclampsia or for tocolysis. Subsequent studies have observed a similar benefit when magnesium has been given specifically for fetal neuroprotection. An ACOG committee opinion recommends the administration of magnesium sulfate to mothers in preterm labor. Maternal magnesium sulfate was administered for neuroprotection in anticipation of the treatment of preeclampsia or for tocolysis. Other congenital anomalies that cause upper airway obstruction include (1) micrognathia, as in Pierre Robin sequence; (2) macroglossia, as in Beckwith-Wiedemann syndrome or glycogen storage disease type II; (3) laryngeal webs; (4) laryngeal atresia; (5) stenosis or paralysis at the level of the vocal cords; (6) subglottic stenosis; (7) subglottic webs; (8) tracheal agenesis; and (9) tracheal rings. Obstruction can also occur as a result of tumors such as subglottic hemangiomas. The presence of a cleft palate may lead to difficulty with manual ventilation. In an infant with micrognathia or macroglossia, airway patency may be maintained if the neonate is kept in the prone position, which reduces posterior movement of the tongue into the pharynx. If macroglossia is extreme, use of an oral airway or a small nasogastric or orogastric suction catheter may be necessary to prevent complete obstruction of the pharynx by the tongue.

When respiratory distress and difficulty with bag-and-mask ventilation are encountered, laryngoscopy should be performed. The cause of the obstruction may be evident if it is supraglottic in location. Some supraglottic entities (e.g., laryngeal webs) may be treated successfully by passing an endotracheal tube through the obstruction and into the trachea. Subglottic lesions may require tracheostomy. The help of an otolaryngologist may be invaluable during resuscitation of a neonate with congenital airway obstruction. If there is antepartum evidence of such a condition (e.g., laryngeal stenosis), it is best to have an otolaryngologist present at the time of delivery. If obstruction is discovered after delivery, the resuscitator should not hesitate to call for surgical assistance.

Fetal neck masses such as cervical teratoma and lymphangioma can lead to extrinsic airway compression. The resulting distortion of the airway can result in airway obstruction, and it may be difficult—if not impossible—to secure an airway in a timely fashion at delivery. These masses often are diagnosed before delivery because of the associated occurrence of polyhydramnios resulting from esophageal compression. In these rare cases, a multidisciplinary team should be assembled
before delivery to assist in securing the airway. Liechty et al. described a way of providing the time necessary to secure an airway, known as the ex utero intrapartum treatment (EXIT) procedure (see Chapter 7). An EXIT procedure delivers the fetal head and shoulders, but keeps the lower torso and umbilical cord intact within the uterus, thereby maintaining placental perfusion and oxygenation. The fetus can be given additional agents intramuscularly (e.g., fentanyl, muscle relaxant, and atropine) to provide fetal analgesia and to prevent movement and breathing. The FHR and SaO2 are monitored continuously via a pulse oximeter probe attached to the fetal hand. The pediatric surgeon can then perform direct laryngoscopy, rigid bronchoscopy, or tracheostomy if necessary. After establishment of the airway, the delivery of the infant is completed.

The EXIT procedure has been considered an option for fetuses with a number of congenital anomalies. A common indication for the EXIT procedure is an intrinsic airway obstruction. Intrinsic airway obstruction of the larynx or upper trachea (e.g., laryngeal web, subglottic cyst, tracheal atresia) can lead to retention of bronchial secretions and subsequent pulmonary distention; this constellation of findings is often classified as congenital high airway obstruction syndrome (CHAOS). Use of the EXIT procedure resulted in the first long-term survival of a child with this syndrome.

Indications for EXIT procedures continue to evolve and now include conditions such as severe congenital heart disease, in which the need for emergency ECMO at birth is anticipated. The EXIT procedure allows for the placement of arterial and venous canulas before umbilical cord clamping, thereby avoiding an unstable period between the termination of placental perfusion and the institution of ECMO. Other possible indications for the EXIT procedure include the resection of congenital cystic adenomatoid malformations and as a first step in separation procedures for conjoined twins with cardiovascular involvement.

Anesthetic considerations for the mother during an EXIT procedure include those relevant to general anesthesia for the mother undergoing cesarean delivery or other surgical procedures during pregnancy (see Chapters 7, 17, and 26). Anesthetic technique is dependent upon several variables including but not limited to the anticipated surgical approach, maternal medical history, and patient preference. Anesthetic management of EXIT procedures focuses on achieving maximal uterine muscle relaxation and maintaining uteroplacental perfusion and maternal hemodynamics while minimizing fetal cardiac dysfunction.

Uterine relaxation is often achieved through the use of volatile anesthetics, as well as adjuvant medications including nitroglycerin, beta-adrenergic receptor agonists, and magnesium sulfate. Several volatile halogenated agents have been used for the EXIT procedure, including isoflurane, desflurane, and sevoflurane. To achieve maximal uterine muscle relaxation, high doses of a volatile agent can be required (up to 2 to 3 minimum alveolar concentration [MAC]). Prolonged neonatal exposure to volatile agents at the time of cesarean delivery can be associated with decreased 1-minute Apgar scores secondary to respiratory depression and hypotonia. In addition, fetal exposure to high-dose volatile anesthetic agents has been associated with fetal hypoxia and acidosis as well as fetal cardiac dysfunction, including ventricular dysfunction and bradycardia. For this reason, combination techniques that lower volatile agent requirements are often employed to optimize relaxation while balancing fetal risk. In 2010, Boat et al. retrospectively examined the records of 39 patients undergoing EXIT procedures with high-dose desflurane (2 to 3 MAC) or supplemental intravenous anesthesia (SIVA) with propofol, remifentanil, and desflurane (1 to 1.5 MAC). The SIVA group achieved adequate uterine relaxation at lower MAC of desflurane (1 to 1.5 MAC) and had a lower incidence of fetal left ventricular dysfunction when compared with the high-dose volatile agent group.

In addition to volatile anesthetic agents, intravenous agents including nitroglycerin, magnesium sulfate, and beta-adrenergic receptor agonists have been utilized to optimize uterine relaxation. Nitroglycerin is most commonly the adjuvant of choice as it allows for quick titration and is rapidly metabolized to allow for quick return of uterine tone after delivery of the neonate. Careful titration is essential to avoid maternal hypotension and possible decreases in uteroplacental perfusion. Magnesium sulfate and beta-adrenergic receptor agonists are much less frequently utilized during EXIT procedures because of their prolonged effects on uterine tone and increased fetal side-effect profile. Neonates exposed to magnesium sulfate can present with hypotonia and lethargy upon delivery, while those exposed to beta-adrenergic receptor agonists can present with fetal tachycardia and metabolic derangements.

Maintenance of uterine muscle relaxation is often complicated by vasodilation, which can lead to maternal hypotension, decreased uteroplacental blood flow, and decreased fetal cardiac output. To maintain mean arterial pressure and ensure adequate uteroplacental perfusion, vasopressor administration is often required. Ephedrine and phenylephrine are the two most commonly used vasopressor agents in obstetric and fetal surgery. While both agents are considered safe for the mother and fetus, some studies suggest that phenylephrine results in higher umbilical artery blood pH and base excess than ephedrine. However, human studies have shown no difference in Apgar scores or umbilical blood flow when the two drugs were compared.

Intraoperative monitoring including continuous fetal pulse oximetry and heart rate monitoring is critical throughout the EXIT procedure. Decreased baroreceptor activity and vasoconstrictive responses to hypovolemia make the fetus particularly susceptible to heat and evaporative fluid losses, as well as hypovolemia and hypoperfusion during exposure on the surgical field. Effort should be made to maintain fetal temperature during the course of the procedure, including higher operating room temperatures and limiting exposure of fetal parts, not critical to the procedure, to the outside environment. Fetal blood should be immediately available at the time of the procedure and fetal hemoglobin and blood gases measured as indicated.
Esophageal atresia and tracheoesophageal fistula occur in 1 of 3000 births.\(^2^{22}\) There are many variations of these anomalies, the most common being esophageal atresia with a distal tracheoesophageal fistula (80% to 90% of cases). Neonates with a tracheoesophageal fistula are at increased risk for the pulmonary aspiration of gastric contents through the fistula into the lung. When the presence of a tracheoesophageal fistula is not known antepartum, it should be suspected if bubbling secretions are observed during spontaneous or bag-and-mask ventilation. Once a tracheoesophageal fistula is suspected, bag-and-mask ventilation should be discontinued, because its use may contribute to overdistention of the gastrointestinal tract with air, possibly leading to difficulty in ventilation from impingement of the enlarged stomach on the diaphragm. A suction catheter should be placed in the esophageal pouch to facilitate the removal of oral secretions. If mechanical ventilation is necessary, an endotracheal tube should be inserted with the tip distal to the entrance of the fistula. This positioning can be accomplished by performing an intentional right mainstem bronchial intubation followed by slowly withdrawing the tube until breath sounds are auscultated on the left; a lack of breath sounds over the stomach should then be confirmed. Percutaneous gastrostomy placement may be necessary during resuscitation to facilitate decompression of the gastrointestinal tract.

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 3000 births.\(^2^{23}\) The mortality rate from CDH is 30% to 60%. In 80% to 90% of cases, the CDH occurs on the left side and is the result of herniation of the gut through the posterolateral defect of Bochdalek. During formation of the lung, herniation of the gut into the thoracic cavity results in hypoplasia of the lung tissue and pulmonary vasculature. This hypoplasia may be unilateral, but often it is bilateral because of the shift in mediastinal structures to the other side. CDH should be suspected when a neonate has respiratory difficulty and a scaphoid abdomen; this abnormal abdominal shape results from the presence of abdominal contents in the thorax.

During resuscitation of the neonate with CDH, bag-and-mask ventilation is contraindicated because it allows further distention of the gut, which would further impinge on the lung. Tracheal intubation is recommended, followed by the placement of a nasogastric or orogastric tube to ensure decompression of the gastrointestinal tract. Ventilation should consist of low-positive-pressure breaths to decrease the risk for causing a pneumothorax on the side contralateral to the CDH. If a pneumothorax does occur, it must be evacuated promptly. In the neonate, evacuation is accomplished initially by placement of a 22-gauge needle into the second intercostal space in the midclavicular line and aspiration of air with an attached stopcock and syringe. Severe pulmonary hypertension often accompanies CDH. Maintenance of euthermia, normoxia, and adequate systemic blood pressure promotes pulmonary artery blood flow.

Whenever congenital anomalies of the respiratory tract are noted, the presence of other anomalies should be suspected. It is important to evaluate the neonate promptly for cardiac malformations, especially if appropriate resuscitative efforts are not successful. Echocardiography is used to evaluate cardiac structures and function.

### Ethical Considerations

The current neonatal resuscitation guidelines address the ethical considerations of non-initiation or discontinuation of resuscitation in the delivery room.\(^7\) Extremes of prematurity (< 23 weeks’ confirmed gestation) and severe congenital anomalies (e.g., anencephaly, confirmed trisomy 13 or 18) are examples of circumstances when non-initiation of resuscitation is considered appropriate. Because intrapartum confirmation of pertinent information may not be possible, it is recognized that initiation of resuscitation may occur and that its discontinuation may then be appropriate after further information has been obtained and discussion with family has occurred. In some cases, a trial of therapy may be appropriate, which does not always mandate continued support. In situations or conditions in which there is a high rate of survival and acceptable morbidity (i.e., ≥ 25 weeks’ gestation and most congenital malformations), resuscitation is generally indicated. For those situations with a poor prognosis, including unlikely survival and potentially high morbidity (i.e., 23 to 25 weeks’ gestation), the parents’ desires as to initiation of resuscitation should be supported (Table 9.5).\(^2^{24,225}\)

<table>
<thead>
<tr>
<th>Conditions with high survival, acceptable risk for morbidity</th>
<th>≥ 25 weeks’ gestational age</th>
<th>Parental desires about initiating/continuing resuscitation should be supported</th>
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</thead>
<tbody>
<tr>
<td>Conditions with poor prognosis, high risk for morbidity</td>
<td>23 to 25 weeks’ gestational age</td>
<td>Resuscitation not indicated</td>
</tr>
<tr>
<td>Conditions with almost certain death or unacceptably high morbidity</td>
<td>&lt; 23 weeks’ gestational age, Birth weight &lt; 400 g, Anencephaly, Chromosomal abnormalities incompatible with life (e.g., trisomy 13)</td>
<td>Resuscitation nearly always indicated</td>
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Discontinuation of resuscitation of an infant with cardio-pulmonary arrest may be appropriate if spontaneous circulation has not occurred in 15 minutes. After 10 minutes of asystole, survival itself and survival without severe disabilities are very unlikely.224,226–230

### NEUROBEHAVIORAL TESTING

It is difficult to detect subtle neurobehavioral differences among neonates during the assignment of Apgar scores or the performance of the initial neurologic examination; therefore, investigators have developed and studied methods of documenting neonatal neurobehavioral status (Table 9.6). In the past, the neonate was considered incapable of exhibiting higher cortical function. However, investigators have noted that the term neonate is able to sense and respond to a variety of stimuli in a well-organized fashion.231–233

In 1973, Brazelton234 described the Neonatal Behavioral Assessment Scale (NBAS) with the following four variables as key determinants of neonatal neurobehavior: (1) various prenatal influences (e.g., infection); (2) the maturity of the infant, especially its CNS; (3) the effects of analgesics and anesthetics administered to the mother before and during delivery; and (4) the effects of difficulties encountered during delivery (e.g., trauma). The NBAS was developed as a tool to detect neurobehavioral abnormalities that resulted from any of these four variables.

This scale consists of 47 individual tests with 27 evaluating behavior and 20 evaluating elicited or provoked responses. The 47 tests can be completed in approximately 45 minutes. The NBAS evaluates the ability of the neonate to perform complex motor behaviors, to alter the state of arousal, and to suppress meaningless stimuli. The goal is to provide an extensive evaluation of neonatal cortical function and to detect subtle differences among groups of infants. Habituation (i.e., the ability to suppress the response to meaningless, repetitive stimuli) is considered an excellent indicator of normal early cortical function.231

In 1974, Scanlon235 described the Early Neonatal Behavioral Scale (ENNS), which consisted of tests that were easy to perform and score quantitatively during the neonatal period. The ENNS was developed primarily for the evaluation of the effects of maternal medications (e.g., analgesic and anesthetic agents) on neonatal neurobehavior. The ENNS consists of (1) 15 observations of muscle tone and power, reflexes (e.g., rooting, sucking, Moro), and response to stimuli (e.g., light, sound, pinprick); (2) 11 observations of the infant’s state of wakefulness; (3) an assessment of the ability of the neonate to habituate to repetitive stimuli; and (4) an overall general assessment of neurobehavioral status. This test can be performed in 6 to 10 minutes.

In 1982, Amiel-Tison et al.236 described the Neurologic and Adaptive Capacity Score (NACS) to differentiate neonatal depression secondary to maternally administered drugs from depression caused by asphyxia, birth trauma, or neurologic disease. Whereas the ENNS concentrates on the infant’s habituation ability, the NACS emphasizes motor tone as a key indicator of drug-induced abnormal neurobehavior. The basis for this emphasis on neonatal motor tone is explained as follows: unilateral or upper body hypotonus may occur as a result of either birth trauma or anoxia, but global motor depression is more likely a result of anesthetic- or analgesic-induced depression. A total of 20 criteria are tested in the areas of adaptive capacity, passive tone (e.g., scarf sign), active tone (e.g., assessment of the flexor and extensor muscles of the neck), primary reflexes (e.g., Moro), and alertness. The total possible score is 40, and a score of 35 to 40 is considered normal. The NACS can be performed in 3 to 4 minutes.

Amiel-Tison et al.236 examined interobserver reliability and assessed the correlation of results between the NACS and ENNS. The interobserver reliability was 93% for the NACS and 88% for the ENNS. Approximately 92% of infants with high scores on the ENNS scored equally well on the NACS. However, the reliability of the NACS has been questioned.237,238 Halpern et al.239 examined 200 healthy term infants with the NACS and found poor interobserver reliability. In contrast, in 2002 Amiel-Tison240 reported her later experience with the NACS and documented good interobserver reliability.

Anesthesiologists have used neurobehavioral testing to document the effects of analgesic and anesthetic agents and techniques on neonatal neurobehavior (see Table 9.6); the AAP241 and the U.S. Food and Drug Administration (FDA)242,243 have recommended that these investigations be performed. A number of studies have demonstrated transient, serum concentration–dependent depression of neonatal neurobehavior with the maternal administration of systemic agents (e.g., meperidine, diazepam).244–246 However, in a NBAS examination that controlled for patient and labor

<table>
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<tr>
<th><strong>TABLE 9.6 Neurobehavioral Tests for Neonates</strong></th>
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<tr>
<td><strong>Neurobehavioral Test</strong></td>
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<tr>
<td>Brazelton (NBAS)</td>
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<tr>
<td>Scanlon (ENNS)</td>
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<tr>
<td>Amiel-Tison (NACS)</td>
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[224,226–230] [231–233] [234] [235] [236] [237,238] [239] [240] [241,242,243] [244–246]
and delivery characteristics, only decreased habituation was observed in neonates born to mothers who had received intravenous meperidine. Similarly, maternal administration of intravenous fentanyl appears to minimally affect neonatal NACS examinations.

As is the case with many studies of systemic agents, studies of epidural anesthesia are often confounded by variables that are difficult to control, such as different patient populations, varied durations of labor, and multiple drug administrations. Scanlon et al. introduced the ENNS in a study of the effect of maternal epidural anesthesia on neonatal neurobehavior. The researchers concluded that epidural anesthesia was associated with lower ENNS scores because of decreased muscle strength and tone. In this study, all patients who had received epidural anesthesia were considered part of one group, although nine patients had received lidocaine and 19 received epidural anesthesia were considered part of one group, although nine patients had received lidocaine and 19 had received mepivacaine. Further investigation showed that epidural lidocaine, even when administered in larger doses for cesarean delivery, does not affect ENNS scores. The difference in ENNS scores between the epidural and non-epidural groups noted in the earlier study was most likely related to the use of mepivacaine rather than lidocaine. As was observed with lidocaine, epidurally administered bupivacaine, 2-chloroprocaine, and etidocaine—when given for cesarean delivery—do not affect ENNS scores. Kuhnert et al. assessed NBAS scores in a group of infants exposed to either epidural lidocaine or 2-chloroprocaine. Although the investigators observed subtle changes in neurobehavior in the group of infants whose mothers had received lidocaine, they concluded that other variables (e.g., mode of delivery) are more likely to affect performance on neurobehavioral testing.

Sepkoski et al. compared NBAS scores between two groups of vaginally delivered infants. In one group, the mothers had received epidural bupivacaine, and in the other group, the mothers had received no anesthesia or analgesia. The infants in the epidural group showed less alertness, less orientation ability, and less motor function maturity than the infants in the control group. However, variables such as duration of labor, incidence of oxytocin administration, and incidence of instrumental delivery were not similar in the two groups. Earlier, Abboud et al. performed ENNS examinations on vaginally delivered infants whose mothers had received epidural bupivacaine. In this study, epidural administration of bupivacaine did not affect the ENNS scores. The maternal doses of epidural bupivacaine and the maternal venous and umbilical cord blood bupivacaine concentrations were similar to those noted by Sepkoski et al. Abboud et al. also noted normal ENNS scores for infants whose mothers had received epidural lidocaine or 2-chloroprocaine.

Critics of the ENNS and NACS claim that the evaluations are unable to demonstrate subtle differences in neurobehavior that would be detected by the more comprehensive NBAS. However, although some differences have been observed in NBAS performance among groups of infants exposed or not exposed to local anesthetics, confounding variables have prevented clear conclusions as to cause and effect.

Hodgkinson et al. observed that the subarachnoid administration of tetracaine for cesarean delivery did not adversely affect ENNS performance. Other studies have indicated that NACS performance is not significantly affected by the maternal epidural administration of opioids or epinephrine (in combination with a local anesthetic).

The effects of general anesthetic agents on neonatal neurobehavior have been evaluated by the ENNS and NACS. In a prospective, randomized study, Abboud et al. assessed NACS performance at 15 minutes, 2 hours, and 24 hours of age in infants whose mothers received general, epidural, or spinal anesthesia for cesarean delivery. Women who underwent general anesthesia received thiopental 4 mg/kg followed by enflurane 0.5% with nitrous oxide 50% in oxygen. Although the NACS was lower at both 15 minutes and 2 hours of age in the infants in the general anesthesia group than in the infants in the neuraxial anesthesia groups, no difference in NACS results was noted at 24 hours of age.

Hodgkinson et al. used the ENNS to evaluate outcomes among three groups of infants, all of whom were delivered by elective cesarean delivery. One group of women received general anesthesia with thiopental 4 mg/kg followed by 50% nitrous oxide. A second group received general anesthesia with ketamine 1 mg/kg followed by 50% nitrous oxide. A third group received spinal anesthesia with tetracaine 6 to 8 mg. The ENNS evaluations were conducted at 4 to 8 hours of age and again at 24 hours. During the 4- to 8-hour examination, infants in the spinal anesthesia group scored significantly higher on multiple components of the ENNS than did infants in either of the general anesthesia groups. At 24 hours, infants in the spinal anesthesia group scored significantly higher than those in the thiopental group in alertness, total decrement score, and overall assessment. Similarly, infants in the spinal anesthesia group scored higher than those in the ketamine group in alertness and overall assessment. No significant differences existed between the scores of the thiopental group infants and the ketamine group infants. Palahniuk et al. observed similar results in a study that compared groups of infants whose mothers received either epidural anesthesia or general anesthesia for elective cesarean delivery. Infants whose mothers had received thiopental and nitrous oxide scored significantly lower in the alertness component of the ENNS than infants whose mothers had received epidural lidocaine with epinephrine.

Stefani et al. observed that subanesthetic maternal doses of enfurane or nitrous oxide did not affect neonatal neurobehavior (as assessed by ENNS and NACS) at 15 minutes, 2 hours, and 24 hours of age. Abboud et al. obtained similar results from NACS examinations of infants whose mothers had received subanesthetic doses of isoﬂurane.

The long-term effects of perinatal exposure to either general or neuraxial anesthesia at the time of cesarean delivery compared with vaginal delivery appear limited. In a population-based birth cohort, Sprung et al. found that children exposed to either general or regional anesthesia during cesarean delivery were not more likely to develop learning disabilities than children who were delivered by elective cesarean delivery.
vaginally. Some controversy does exist, however, regarding the issue of repeated or lengthy use of general anesthesia, specifically in the third trimester of pregnancy. In 2017 the FDA issued a drug safety communication warning about the use of general anesthetics and sedation drugs in pregnant women and young children. The statement reported that:

“Published studies in pregnant animals and young animals have shown the use of general anesthetic and sedation drugs for more than 3 hours caused widespread loss of nerve cells in the brain. Studies in young animals suggest these changes result in long-term effects on the animals’ behavior or learning. Studies have also been conducted in children, some of which support findings from previous animal studies, particularly after repeated or prolonged exposure to these drugs early in life. All the studies in children had limitations, and it is unclear whether any negative effects seen in children’s learning or behavior were due to the drugs or to other factors, such as the underlying medical condition that led to the need for the surgery or procedure.”

This statement focused on repeated or prolonged exposure, defined as greater than 3 hours, and was based primarily on animal studies with limited human data. Further research is needed to determine the true extent of neurologic impact in these cases. It is important to remember that the risks and benefits of exposure must be weighed with the indications for exposure. The ACOG, ASA, and FDA all agree that “anesthesia and sedation drugs are necessary for infants, children, and pregnant women who require surgery or other painful and stressful procedures, especially when they face life-threatening conditions requiring surgery that should not be delayed.” Patients should be appropriately counseled regarding the concerns or potential risk associated with prolonged exposure to anesthesia and sedative drugs, and decisions should be balanced with the benefits of such exposure.

In summary, subtle changes in neonatal neurobehavior may result from factors such as antepartum maternal drug exposure. Parent-infant bonding and the ability of the infant to breast-feed may be adversely affected by these neurobehavioral changes. These transient effects may seem trivial to some observers but important to others. With regard to the long-term neurologic outcome of individual infants, performance during neurobehavioral assessment may aid the observer in the formulation of a prognosis. However, as demonstrated with Apgar scores, the prognostic value of an isolated test score is likely to be lower than the prognostic value of multiple factors considered together during the overall assessment of an individual infant.

### Key Points

- The anesthesia provider attending the mother should not be responsible for resuscitation of the neonate. However, all anesthesia providers should be prepared to provide assistance during neonatal resuscitation when it is needed.
- Adverse conditions at birth (e.g., hypoxia, acidosis, profound hypovolemia, hypothermia) may impair the transition from intrauterine to extrauterine life. Impaired transition may manifest as persistent pulmonary hypertension of the newborn.
- The Apgar scoring system gives the practitioner a standard guide for assessing the need for neonatal resuscitation.
- No single factor should be considered prognostic of poor neurologic outcome. A combination of factors, including severe metabolic acidemia and Apgar scores of 3 or less beyond 5 minutes, are included among the criteria that suggest the occurrence of intrapartum hypoxia of sufficient severity to cause long-term neurologic impairment. However, not all infants who fulfill these criteria suffer permanent neurologic injury.
- Severe mixed or metabolic acidemia—but not respiratory acidemia alone—is associated with a higher incidence of neonatal complications and death.
- During evaluation of the apneic neonate, assisted ventilation should be initiated promptly if tactile stimulation does not result in the initiation of spontaneous breathing.
- Air rather than 100% oxygen should be used for initial neonatal resuscitation in term infants, and 21% to 30% oxygen should be administered in preterm infants. If necessary, the administration and titration of supplemental oxygen should be guided by pulse oximetry.
- ECG monitoring of the heart rate rather than clinical assessment of the heart rate provides a more accurate evaluation of response to resuscitation.
- Meconium-exposed neonates no longer require nasopharyngeal and oropharyngeal suctioning before delivery of the thorax or endotracheal tube suctioning after delivery. Meconium-stained fluid may represent evidence of fetal compromise; thus, the infant may be more likely to require neonatal resuscitation.
- In most circumstances, decisions about the initiation or continuation of resuscitation in the delivery room should be based on the neonate’s response to resuscitative efforts rather than an estimation of gestational age. Parental desires should be considered when the prognosis for infant survival is poor.
REFERENCES


Fetal and Neonatal Assessment and Therapy


The detection and diagnosis of fetal and neonatal brain injury have been advanced by improvements in functional imaging and the identification of potential biochemical markers. Evidence indicates that inflammatory mediators play an important role in the pathophysiology of fetal brain injury. Maternal administration of magnesium sulfate before anticipated early preterm birth reduces the risk for cerebral palsy in surviving infants. Induced hypothermia is beneficial for the treatment of neonatal hypoxic-ischemic encephalopathy. Of specific concern to anesthesia providers are rodent and nonhuman primate data that suggest that fetal exposure to anesthetic agents may have harmful effects on neurogenesis and synapse formation in the developing brain. Overall, however, little progress has been made in reducing the incidence of neonatal brain injury and cerebral palsy.

FETAL BRAIN DEVELOPMENT

Generation of the various cell types that populate the developing brain, and the subsequent layering and organization, is a precisely regulated process encoded by genetic programs and modified by epigenetic influences. Contrary to previous dogma, it is now well established that the brain continuously evolves during ontogeny and that these processes are susceptible to subtle changes in the internal and external milieu. Although such neurodevelopmental processes occur throughout the human lifespan, the process is most robust and dynamic during the perinatal period. Much of our understanding of the processes that drive fetal brain development comes from studies in rodents and nonhuman primates. With recent advances in neuroimaging, it is now possible to study brain anatomy and assess neurobehavioral changes in the human fetus.

When pathways leading to orderly brain development are deconstructed, three major events appear critical to the establishment of functional synapses. Neuronal proliferation, migration, and cellular differentiation occur in a preordained fashion to establish early neural circuitry. These processes often overlap and occur at different rates in different brain regions. Neurogenesis, a term that encompasses both neuronal proliferation and subsequent survival, begins with neural stem/progenitor cells in neurogenic niches such as the subventricular zone and the subgranular zone of the dentate gyrus. These neural progenitor cells undergo mitosis to generate immature neurons that migrate in a radial fashion and laminate the cortex in an “inside-out” fashion. Interneurons, which compose 10% to 15% of the total neuronal cells in the brain, originate from the ganglionic eminences in the developing brain. These newly generated interneurons, which play an indispensable role in circuit inhibition, migrate in a tangential manner to populate distinct brain areas. Both forms of migration are guided by cell-intrinsic mechanisms and by structural scaffolds and humoral mediators such as gamma-aminobutyric acid (GABA) and glutamate.
In humans, neurogenesis starts and peaks at 5 and 25 weeks’ gestation, respectively, while neuronal migration is completed between 30 and 36 weeks’ gestation. Between 20 and 40 weeks’ gestation, these processes are followed by the generation of an array of supporting glial cells, such as astrocytes and oligodendrocytes. Concurrently, synapse formation begins as early as the 10th week of gestation and continues to increase gradually at a rate of approximately 4% per week until the end of the second trimester. After this phase, a robust and exponential increase in synapse formation (almost 40,000 synapses/min) occurs between 28 weeks’ and term gestation. These processes, in conjunction with the onset of myelination, result in a fivefold increase in brain volume and the appearance of morphologic features of the mature brain such as sulci and gyri. By 24 weeks’ gestation, the fetus has all the neural machinery necessary to perceive pain. Many clinicians recommend that appropriate measures should be taken to provide fetal analgesia during fetal surgical procedures from this point onward.

Although the ontogeny of neurotransmitter systems is less well studied, a wealth of animal and human data indicates that these systems appear very early in life, before the phase of active synaptogenesis. The presence of these neuromodulatory substances before synapse formation lends credence to the view that they serve a trophic role during early brain development, a role that is distinct from their predominant role of facilitating synaptic neurotransmission in the mature brain. Among these neurotransmitters, GABA remains the most widely studied. Although GABA has an inhibitory action in the mature brain, GABA serves an excitatory role during fetal brain development. The major mechanism for this role reversal is the differential expression of chloride ion transporters NKCC1 and KCC2; these transporters increase the intracellular concentration of chloride in developing neurons. On stimulation of GABA receptors that are expressed in neural progenitor cells and immature neurons, chloride ions are actively extruded, causing membrane depolarization rather than the hyperpolarization seen in mature neurons. This depolarizing effect of GABA decreases DNA synthesis and inhibits proliferation of neural progenitor cells, causes concentration- and time-dependent effects on neuronal migration, and plays a major role in activity-dependent synapse formation.

The N-methyl-D-aspartate (NMDA)-subtype glutamate receptors originate later than the GABA receptors and remain functionally silent because of magnesium ion–induced channel blockade; thus, they play a limited role during early brain development. Dopaminergic, cholinergic, and serotonergic systems develop concomitantly and appear fully functional by the second trimester. Pharmacologic interventions (e.g., ethanol, antiepileptic drugs) that act directly or indirectly on these powerful neuromodulator systems induce long-lasting impairment of fetal brain development, mainly owing to impaired neurogenesis and/or altered neuronal

![Fig. 10.1 Gamma-aminobutyric acid (GABA) role in regulating embryonic cortical development. During corticogenesis, interneurons migrating in the subventricular zone (SVZ) can release GABA and activate GABAergic receptors on the radial glia, depolarizing these progenitors and decreasing their proliferation. Radial glia generate immature pyramidal neurons through asymmetric division, and the migration of these immature neurons along the radial fibers is decreased by GABA signaling. As young neurons assume their position in the cortex and begin to mature, GABA-mediated depolarization by the interneurons is required for the development of dendritic arbors and excitatory synaptic inputs from other pyramidal neurons. MZ, marginal zone; VZ, ventricular zone; SVZ, subventricular zone; CP, cortical plate. (From Wang DD, Kriegstein AR. Defining the role of GABA in cortical development. J Physiol. 2009;587:1873–1879.)](image-url)
migration. Alteration of this excitation-inhibition balance is purported to be responsible for an array of childhood neuromotoral disorders.

Experimental studies reveal that the fetal blood-brain barrier is morphologically well developed and functionally competent at term. Convincing evidence confirms that the endothelial tight junctions of the blood-brain barrier are effective in the term fetus as in the adult, although the exact time that blood-brain barrier competency is established in the human fetus is unknown. In rodents, data suggest that the fetal blood-brain barrier is established between embryonic days 11 and 17 (term gestation is 22 days), a time period that corresponds to approximately the late second and early third trimesters in humans.

## Cerebral Palsy

### History, Definitions, and Significance

In 1861, John Little, an orthopedic surgeon, first described cerebral palsy in a report to the Obstetrical Society of London. Described as a neonatal neurologic disorder associated with difficult labor or birth trauma, the disorder was known as Little’s disease until William Osler coined the term cerebral palsy in 1888. A precise definition and classification of cerebral palsy has proved elusive. In the foreword to the “Report on the Definition and Classification of Cerebral Palsy,” published in 2007 in Developmental Medicine and Child Neurology, Peter Baxter wrote, “This [supplement] illustrates the difficulties inherent in trying to agree what we mean by the terms we use and that a classification that suits one purpose, such as a diagnostic approach, may not always be ideal for others, such as therapy issues. Defining and classifying cerebral palsy is far from easy. We do need a consensus that can be used in all aspects of day-to-day care and for future research on cerebral palsy.”

Today, cerebral palsy is defined as a nonprogressive disorder of the central nervous system (CNS) present since birth that includes some impairment of motor function or posture. Intellectual disability (formerly known as mental retardation) may be present but is not an essential diagnostic criterion. Various forms of cerebral palsy exist, with differences in pathology, pathophysiology, and potential relationships with intrapartum events. The literature on cerebral palsy is difficult to review and understand. Data from individual studies are difficult to compare because of variations in the duration of follow-up, birth weight classifications, inclusion criteria for congenital abnormalities, and exclusion criteria for various causes of death. Terms such as hypoxic-ischemic encephalopathy of the newborn, newborn asphyxia, birth asphyxia, and asphyxia neonatorum are difficult to distinguish. Some authorities, including the American College of Obstetricians and Gynecologists (ACOG), have argued that the term birth asphyxia should be abandoned.

Intrapartum events continue to receive the blame for some cases of cerebral palsy. It is a widely believed theory that an intrapartum reduction in fetal oxygen delivery may cause cerebral palsy, and early reports in primates demonstrated that perinatal asphyxia could cause brain injury. Continuous electronic fetal heart rate (FHR) monitoring, which has largely replaced intermittent FHR auscultation during labor, is believed to prompt the delivery of at-risk fetuses and thus reduce asphyxial events. However, despite a higher incidence of cesarean delivery, no reduction in the incidence of cerebral palsy has been observed since the widespread implementation of continuous electronic FHR monitoring during labor. Further, among patients with new-onset late FHR decelerations, an estimated 99% of tracings would be false positive “if used as an indicator for subsequent development of cerebral palsy.”

Large randomized trials have not demonstrated better fetal and neonatal outcomes with continuous electronic FHR monitoring than with intermittent FHR auscultation. In an editorial citing observations made by Schifrin and Dame, Friedman opined, “The absence of either suggestive or overtly ominous fetal heart rate patterns is reliably reassuring.” Unfortunately, there is little objective evidence that reassuring FHR tracings exclude the subsequent occurrence of cerebral palsy. In a 1993 review of published FHR monitoring studies, Rosen and Dickinson could not identify FHR patterns that were consistently associated with neurologic injuries. These investigators concluded, “We do not advocate the abandonment of the use of electronic fetal monitoring, but we do believe that it is yet to be proved to be of value in predicting or preventing neurologic morbidity.” A more focused application of FHR monitoring may ultimately be found useful. For example, fetal inflammatory changes, which can be associated with neurologic injury, may be associated with characteristic FHR findings.

More recently, research has focused on whether expert, algorithm-assisted FHR interpretation has the potential to improve standard clinical care by leading to earlier recognition of nonreassuring FHR tracings. Although use of the algorithm identified more infants with acidemia (base deficit > 12 mM/L) than standard monitoring (46% versus 30%), less than 50% of the acidemic infants were identified. Thus, the current application of electronic FHR monitoring provides incomplete data that should be evaluated in the clinical context in which it is used.

Despite significant limitations in the use of intrapartum electronic FHR monitoring, there is no doubt that it will continue to be used for the foreseeable future. In a review of medicolegal issues in FHR monitoring, Schifrin and Cohen noted that despite its limitations, “Monitoring deserves credit for reducing intrapartum death, one of the original rationales for its development.”

A 2008 workshop (sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the ACOG, and the Society for Maternal-Fetal Medicine [SMFM]) updated the definitions of various types of FHR tracings to simplify interpretation for providers. As a result, a three-category system was developed. Category I FHR tracings provide reassuring evidence of fetal well-being and strongly predict normal fetal acid-base status at the time of observation. Category III tracings are the most ominous;
these tracings predict abnormal fetal acid-base status at the
time of observation and require prompt evaluation. Most
FHR tracings are category II (indeterminate). Category II
tracings are not predictive of abnormal fetal acid-base status,
but they do not provide sufficient evidence to be classified as
either normal or abnormal; these tracings require continued
surveillance and reevaluation (see Chapter 8).

Intrapartum events are responsible for some cases of
cerebral palsy39; however, these cases are few. After exclusion
of infants with significant congenital anomalies, intrapartum
events—including asphyxial insults—likely account for only
5% to 8% of all cases of cerebral palsy at all gestational
ages.40,41 In 1999, the International Task Force on Cerebral
Palsy published a consensus statement summarizing criteria
that are necessary and suggestive of an intrapartum etiology
for neurologic abnormalities (Box 10.1).42 In 2010, a proposed
evidence-based neonatal workup to confirm or refute allega-
tions of intrapartum asphyxia was published.43

Epidemiology and Etiology
The causes of cerebral palsy are not known, but the varying
forms suggest a multifactorial etiology. The Collaborative
Perinatal Project still represents one of the largest studies
of the antecedent factors associated with cerebral palsy.44

The investigators in this study evaluated the outcomes of
54,000 pregnancies among patients who delivered at 12
university hospitals between 1959 and 1966. They evaluated
more than 400 variables in a univariate analysis,45 which
identified potential risk factors that were then subjected to
a more rigorous multivariate analysis.45 Maternal age, parity,
socioeconomic status, smoking history, maternal diabetes,
duration of labor, or use of anesthesia was not associated
with cerebral palsy in the univariate analysis. The factors
most strongly associated with cerebral palsy in the multi-
variate analysis were (1) maternal mental retardation, (2)
birth weight ≤ 2000 g, and (3) fetal malformations. Other
factors associated with cerebral palsy included (1) breech
presentation (but not vaginal breech delivery), (2) severe
proteinuria (> 5 g/24 h) during the second half of pregnancy,
(3) third-trimester bleeding, and (4) gestational age ≤ 32
weeks. There was a slight association between cerebral palsy
and fetal bradycardia, chorioamnionitis, and low placental
weight. However, only 37% of the cases of cerebral palsy
occurred in patients with one or more of these identified
risk factors.

Rosen and Dickinson46 reviewed studies from Europe,
Australia, and the United States that were published between
1985 and 1990 and included data from 1959 to 1982. The
incidence of cerebral palsy ranged from 1.8 to 4.9 (composite
rate of 2.7) cases per 1000 live births. The incidence of certain
conditions in infants with cerebral palsy was as follows: birth
weight < 2500 g, 26%; diplegia, 34%; hemiplegia, 30%; quad-
riplegia, 20%; and extrapyramidal forms, 16%.

Two more recent studies from Australia reexamined the
risk factors for cerebral palsy. A large epidemiologic study
from 1998 noted an incidence of neonatal encephalopathy
of 3.8 per 1000 term births.47 The investigators identified
preconception and antepartum factors that were associated
with neonatal encephalopathy (Box 10.2). In the second study
from 2011, the greatest risks for cerebral palsy included (1)
preterm birth, (2) fetal growth restriction, (3) perinatal infec-
tion, and (4) multiple gestation.48 Upper respiratory tract and
gastrointestinal infections during pregnancy and instrumen-
tal (forceps or vacuum) vaginal delivery were not associated
with cerebral palsy.49 Evidence suggests that intrapartum
factors alone are associated with neonatal encephalopathy in
< 5% of cases.47,49 These data, along with the recognition that
most patients with identified risk factors do not have children
with cerebral palsy, have led the majority of investigators to
agree that most cases of cerebral palsy cannot be predicted
and that the identification of pregnancy-related conditions
contributes minimally to the identification of patients at risk
for having a child with cerebral palsy.

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**BOX 10.1** Criteria to Define an Acute Intrapartum Hypoxic Event as Sufficient to Cause Cerebral Palsy

<table>
<thead>
<tr>
<th>Essential Criteria (All Four Must Be Met)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH &lt; 7 and base deficit ≥ 12 mmol/L)4</td>
</tr>
<tr>
<td>2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks’ gestation</td>
</tr>
<tr>
<td>3. Cerebral palsy of the spastic quadriplegic or dyskinetic type6</td>
</tr>
<tr>
<td>4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, and genetic disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria That Collectively Suggest an Intrapartum Event—within Close Proximity to Labor and Delivery (e.g., 0 to 48 hours)—but Are Nonspecific to Asphyxial Insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A sentinel (signal) hypoxic event occurring immediately before or during labor</td>
</tr>
<tr>
<td>2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal</td>
</tr>
<tr>
<td>3. Apgar scores of 0 to 3 beyond 5 minutes</td>
</tr>
<tr>
<td>4. Onset of multisystem involvement within 72 hours of birth</td>
</tr>
<tr>
<td>5. Early imaging study showing evidence of acute nonfocal cerebral abnormality</td>
</tr>
</tbody>
</table>

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*Buffer base is defined as the amount of buffer in blood available to combine with nonvolatile acids. A buffer base of 34 mmol/L is equivalent to a whole blood base deficit of 12 mmol/L.

*Spastic quadriplegia and, less commonly, dyskinetic cerebral palsy are the only types of cerebral palsy associated with acute hypoxic intrapartum events. Spastic quadriplegia is not specific to intrapartum hypoxia. Hemiparetic cerebral palsy, hemiplegic cerebral palsy, spastic diplegia, and ataxia are unlikely to result from acute intrapartum hypoxia.

In 2000, the ACOG and the American Academy of Pediatrics (AAP) convened the Neonatal Encephalopathy and Cerebral Palsy Task Force. The resulting landmark report, which was released in 2003, was reviewed and endorsed by many groups. The Task Force extended the earlier international consensus statement regarding the requirements for establishing a causal relationship between intrapartum events and cerebral palsy (see Box 10.1). The consensus statement led to several medicolegal conclusions:

1. The only types of cerebral palsy associated with intrapartum hypoxia are spastic quadriplegia and, less commonly, dyskinesia.
2. Intellectual disability, learning disorders, and epilepsy should not be ascribed to birth asphyxia unless accompanied by spastic quadriplegia.
3. No statements about severity should be made before an affected child is 3 to 4 years of age, because mild cases may improve and dyskinesia may not be evident until then.
4. Intrapartum hypoxia sufficient to cause cerebral palsy is always accompanied by neonatal encephalopathy and seizures.

Phelan et al. subsequently confirmed that fetuses that experienced a sudden and sustained deterioration of the FHR, and that subsequently were found to have cerebral palsy, demonstrated characteristics consistent with the ACOG/AAP Task Force criteria for intrapartum asphyxial injury.

**Peripartum Asphyxia and Cerebral Palsy**

Asphyxia may be defined as insufficient exchange of respiratory gases. Although accurate, this definition does not include an index of severity or have any predictive value. Unfortunately, most studies have not used a uniform definition of birth asphyxia.

In 1953, Dr. Virginia Apgar, an anesthesiologist, introduced her scoring system to identify newborn infants in need of resuscitation and to assess the adequacy of subsequent resuscitation efforts. Although the Apgar score has also been used to identify infants at risk for cerebral palsy, only a weak association has been found. In the Collaborative Perinatal Project, only 1.7% of children with a 1-minute Apgar score ≤ 3 developed cerebral palsy. Among infants who weighed more than 2500 g at delivery, the incidence of cerebral palsy was 4.7% if the 5-minute Apgar score was 0 to 3 and 0.2% if the 5-minute Apgar score was at least 7. Among infants who weighed < 2500 g with the same 5-minute Apgar scores, the incidence of cerebral palsy was 6.7% and 0.8%, respectively. Among all infants, a higher incidence of cerebral palsy was observed if the Apgar score remained ≤ 3 for longer than 5 minutes. The incidence of early neonatal death increased among those infants with prolonged neonatal depression.

Most infants who subsequently manifest evidence of cerebral palsy have a normal 5-minute Apgar score. In the Collaborative Perinatal Project, only 15% of the infants in whom cerebral palsy later developed had a 5-minute Apgar score ≤ 3. It should also be noted that preterm delivery is independently associated with a low Apgar score.

Although most cases of cerebral palsy are not attributed to intrapartum insults, intrapartum asphyxia does occur and can have serious consequences. However, the degree of asphyxia necessary to produce irreversible CNS injury is unclear. In some cases, an intrapartum insult that might have otherwise been innocuous might be superimposed on subclinical chronic fetal compromise and result in permanent injury.

Umbilical cord blood gas measurements are often used to diagnose suspected asphyxia. However, the definition of normal umbilical cord blood gas and pH measurements remains unclear. In one study of 15,073 vigorous neonates (arbitrarily defined as having a 5-minute Apgar score of ≥ 7) conducted between 1977 and 1993, the median umbilical arterial blood gas measurements (with the 2.5th percentile in parentheses) were as follows: pH 7.26 (7.10), Po2 17 (6) mm Hg, PacO2 52 (74) mm Hg, and base excess −4 (−11) mmol/L. Only small differences in median pH and other measurements were present when infants were grouped according to gestational age. These data suggest that umbilical arterial blood pH in vigorous neonates can be as low as 7.10, and base excess may be as low as −11 mmol/L.

Although intrapartum events are most likely associated with a minority of cerebral palsy cases, clinical studies have attempted to define the associated extent and duration of perinatal asphyxia. Fee et al. defined asphyxia as an umbilical arterial blood pH of < 7.05 with a base deficit > 10 mmol/L; they concluded that this threshold was a poor predictor of adverse neurologic outcomes. Goodwin et al. defined asphyxia as an umbilical arterial blood pH < 7.00; with the use of this definition, hypoxic-ischemic encephalopathy and abnormal neurologic outcome were associated with acidemia. Goldaber et al. also observed greater neonatal morbidity.
and mortality among term infants (birth weight > 2500 g) with an umbilical arterial blood pH < 7.00.

Low et al. also studied complications of intrapartum asphyxia in term and preterm infants. They developed a complication score that expressed the magnitude of neonatal complications. Among term infants, the frequency and severity of newborn complications increased with the severity and duration of metabolic acidosis at birth. Importantly, respiratory acidosis at birth did not predict complications in newborns. Similar results were noted for preterm infants delivered between 32 and 36 weeks’ gestation. In contrast, in infants delivered before 32 weeks’ gestation, complications were similar in the control and asphyxia (defined as umbilical arterial blood buffer base < 30 mmol/L) groups. When this scoring system was used in term infants, the threshold for moderate or severe newborn complications was an umbilical arterial blood base deficit of 12 mmol/L.

Relatively few studies have followed neurodevelopmental examinations for a sufficient duration to make meaningful conclusions about peripartum predictors of neurologic injury. Nagel et al. performed such examinations in 30 children in whom umbilical arterial blood pH was < 7.00 at delivery, 28 of whom survived the neonatal period. Evaluation at 1 to 3 years of age detected three children who had experienced an episode of hypertonstia. Most of the children exhibited no major problems, with only one child displaying mild motor developmental delay. Another study examined neonatal complications (neonatal death, grade 3 or 4 intraventricular hemorrhage, gastrointestinal dysfunction, and neonatal seizures) in 35 newborns with an umbilical arterial blood pH < 7.00 at delivery, three of whom died during the neonatal period. An umbilical arterial blood base deficit ≥ 16 mmol/L and a 5-minute Apgar score < 7 had a sensitivity and specificity for predicting adverse neonatal outcomes of 79% and 81%, respectively.

Because metabolic acidosis may be a predictor of complications in newborns, the severity of intrapartum acidosis could be an important variable. Gull et al. studied a small cohort of 27 patients with terminal bradycardia who were delivered vaginally. Not surprisingly, the umbilical arterial blood base deficit was greater in infants with end-stage bradycardia than in controls. The loss of short-term FHR variability for more than 4 minutes during terminal bradycardia correlated with the development of metabolic acidosis.

The relationship between umbilical arterial blood base excess values and the timing of hypoxic injury has been estimated in human and animal studies. In a 2010 systematic review and meta-analysis, an umbilical cord arterial blood pH < 7.00 was significantly associated with important, biologically plausible, adverse neonatal outcomes (i.e., neonatal mortality, hypoxic ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy). Unfortunately, this relationship does not consider the role of previous or repetitive hypoxic episodes before the episode in question and therefore cannot accurately pinpoint the time of injury. Fortunately, the human fetus is quite robust, and episodes of intrauterine asphyxia usually yield a normal neonate. Blumenthal concluded that there is a fine threshold between normality and death from asphyxia.

The increased presence of nucleated red blood cells in the umbilical circulation at delivery has been proposed as a marker of the occurrence and timing of intrapartum asphyxia. However, data from these investigations demonstrated considerable variability and were influenced by birth weight and gestational age. In 2014, the ACOG concluded that biomarkers predictive of long-term outcome after a hypoxic insult have not been identified, and that it is likely that a battery of such markers, in conjunction with clinical and imaging findings, rather than a single biomarker, would better predict outcome.

**Chorioamnionitis, Fever, and Cerebral Palsy**

An association between cerebral palsy and chorioamnionitis has been demonstrated in preterm and term infants. Intra-amniotic infection and inflammation show direct evidence of causality between the intrapartum process and white matter injury. An elevated maternal temperature is one sign of chorioamnionitis, but alone it is insufficient for the diagnosis. Other signs include, but are not limited to, maternal and fetal tachycardia, foul-smelling amniotic fluid, uterine tenderness, and maternal leukocytosis. The diagnosis remains unproven until confirmed by placental culture or histologic examination.

The mechanism by which chorioamnionitis is associated with cerebral palsy is unclear; however, inflammatory cytokines may play a role (see later discussion). A landmark meta-analysis published in 2000 reported that both clinical and histologic chorioamnionitis were strongly associated with an increased risk for cerebral palsy and periventricular leukomalacia in both preterm and term infants. In a 2010 meta-analysis, both histologic (pooled odds ratio [OR], 1.83; 95% confidence interval [CI], 1.17 to 2.89) and clinical chorioamnionitis (OR, 2.42; 95% CI, 1.52 to 3.89) were again found to be significantly associated with cerebral palsy.

Several studies have demonstrated a tendency for maternal temperature to rise after administration of epidural analgesia during labor (see Chapter 23). The mechanism of epidural analgesia-associated maternal pyrexia remains unclear but appears to be inflammatory in nature. Epidural analgesia has been blamed for the common obstetric practice of antibiotic administration to mothers with fever but no other evidence of chorioamnionitis. This practice may lead to unnecessary neonatal sepsis evaluations and antibiotic exposure. Rather than treat all women with pyrexia for presumed chorioamnionitis, Mayer et al. correctly noted that physicians should make an effort to differentiate true chorioamnionitis from incidental maternal fever. These investigators found that additional signs of chorioamnionitis were present in all cases in which the diagnosis was later confirmed by culture or pathologic examination. Neuraxial anesthesia is not a risk factor for cerebral palsy.
PATHOPHYSIOLOGY OF FETAL ASPHYXIA

Intrauterine Hypoxemia and the Fetal Brain

The fetus is exclusively dependent on the placenta for oxygen and nutrients; thus, acute and chronic conditions that affect the placenta or the umbilical cord can deprive the fetus of one or more of these vital resources. Recent evidence from experimental animal models and humans suggests that both hypoxemic and inflammatory pathways interact and augment fetal brain damage.

The spectrum of neurologic injury in neonates depends on the duration and gestational age at hypoxemic-ischemic insult. Acute hypoxemia during the early- to mid-gestational period in sheep affects the predominant neurodevelopmental events such as neurogenesis and neuronal migration. Such hypoxemia causes the death of cerebellar Purkinje cells and hippocampal pyramidal neurons, and impaired neuronal migration. In contrast, acute hypoxemia in late gestation appears to spare the hippocampus and cerebellum but causes neuronal death in the cerebral cortex and striatum. Furthermore, acute perinatal anoxia causes long-term changes in dendritic arborization and synaptic connectivity.

Experimental models of chronic hypoxemia, based on restriction of placental mass or blood flow, demonstrate an array of completely different effects on the fetal brain. Chronic placental insufficiency relatively spares the fetal brain compared with other organ systems, although it results in reduced fetal brain weight. Overall, neurons appear to survive chronic and mild hypoxemia; even minor behavioral changes appear to resolve fully by adulthood in animal models. It is not known whether these effects are mediated by hypoxemia per se, or by other accompanying conditions such as chronic reduction of fetal nutrient supply or altered maternal-fetal endocrine status.

Dysregulation of neuronal calcium transport appears to be the initial pathway by which cerebral hypoxemia causes perinatal neuronal injury. Hypoxia-induced changes in the NMDA receptor increase cellular permeability to calcium; such increases in intracellular calcium trigger a variety of downstream effects, ultimately resulting in generation of free radicals, peroxidation of lipid membranes, and nuclear fragmentation. It has long been recognized that developing oligodendroglia are highly vulnerable to excitotoxic injury in preterm infants. Altered maturation or premature oligodendrocyte death can occur in areas of severe hypoxia-ischemia as a result of upregulation of inflammatory cytokines by activated microglia, elevated glutamate levels, or depleted levels of the antioxidant glutathione. It is highly likely that a combination of these mechanisms, modified by the nature and duration of insults and gestational age, determines the ultimate neurobehavioral phenotype.

Maternal Inflammation and Fetal Brain Injury

Although the development of the fetal brain is encoded by genetic programming, such programs remain highly susceptible to environmentally induced epigenetic modifications and appear closely intertwined with maternal immune and endocrine systems. Recent experimental and epidemiologic studies reveal that maternal infection and inflammation early in pregnancy can cause an array of neurodevelopmental abnormalities in offspring such as schizophrenia and autism. Among maternal infections, chorioamnionitis is the best characterized and thoroughly investigated model of perinatal neuroinflammation. Human registry studies have confirmed an association between histological chorioamnionitis and cerebral palsy. Although the exact contribution of maternal inflammation to perinatal brain injury is obscured because of the association of chorioamnionitis with preterm delivery and hypoxic-ischemic encephalopathy, inflammatory experimental models have revealed much information on cytokine induction, their transport across the placenta and amniotic fluid, and subsequent activation of the fetal immune system.

The exact mechanism by which maternal inflammation triggers a fetal immune response is likely multifactorial (Fig. 10.2). Despite the presence of circulating immune cells as early as 7 weeks’ gestation in humans, antigen presentation is suboptimal because of reduced expression of the major histocompatibility complex class II on antigen-presenting cells. Furthermore, the T-cells are relatively immature. Therefore, maternal derived humoral mediators seem credible candidates to initiate and perpetuate an inflammatory cascade across the placenta. This idea has gained traction with the identification of maternal interleukin-6 (IL-6) in the fetal circulation as early as the second trimester, suggesting the possibility of transplacental transfer of proinflammatory cytokines. Proinflammatory mediators such as IL-6 cause significant impairment of placental blood flow and fetal hypoxemia in animal models, dysregulate the barrier function of both the placenta and the immature fetal blood-brain barrier, trigger production of acute-phase proteins from the fetal liver, promote T-cell entry into the immature brain parenchyma, and disrupt the orderly patterning of the fetal cerebral cortex. The role of inflammatory mediators in this phenomenon is reinforced by the direct correlation that exists between plasma levels of IL-6 and the severity of functional deficits in offspring. In addition to IL-6, cytokines such as IL-1β, IL-7, and IL-13 are upregulated in the fetal brain after a prenatal immune insult, a phenomenon that suggests collective activation of the innate fetal immune response.

Both microglia (the major resident macrophages in the developing brain) and the complement system have been implicated as amplifiers of this immune response. During normal fetal development, microglia invade and colonize the fetal brain during the first and second trimesters and are readily activated by proinflammatory mediators such as IL-1β. Activated microglial cells either cause a direct cytotoxic effect on oligodendrocytes and impair myelination or produce long-lasting alterations in neuronal-glial crosstalk, resulting in impaired synaptic function and subsequent neurodevelopmental disorders.

At the cellular level, numerous mechanisms are involved in propagating the prenatal immune response. Intrauterine
much closer to maturity than the human brain. In this regard, rat pup and human brains are more similar to each other because they both undergo significant extrauterine development (Fig. 10.3). Nonetheless, the importance of this distinction has been challenged. Previously, investigators relied mainly on morphologic milestones (e.g., the brain growth spurt) to compare species at different stages of development. A computerized method attempted to more accurately compare observations among 10 species (including humans) by evaluating the mathematical relationships of more than 100 developmental events and factors (e.g., evolutionary, genetic, neurochemical, neuroanatomic). Although all events have not been catalogued for any one species, the iterative process allows information to be added to improve the theoretic model and is freely available online.

One advantage of the chronically instrumented fetal lamb is that it is similar in size to the human fetus, thus facilitating

Collectively, robust experimental evidence suggests that prenatal inflammation alters fetal brain development at the molecular, cellular, and circuit levels. These findings are reinforced by epidemiologic studies that show a strong correlation between maternal infection/inflammation and neurodevelopmental disorders such as schizophrenia and autism.

Animal Models of Fetal Asphyxia

Much of our knowledge of the fetal response to insufficient exchange of respiratory gases has been gained using animal models. However, the limitations of these models must be acknowledged. Raju reviewed the various animal models of fetal brain injury. At birth, sheep and guinea pig brains are much closer to maturity than the human brain. In this regard, rat pup and human brains are more similar to each other because they both undergo significant extrauterine development (Fig. 10.3). Nonetheless, the importance of this distinction has been challenged. Previously, investigators relied mainly on morphologic milestones (e.g., the brain growth spurt) to compare species at different stages of development. A computerized method attempted to more accurately compare observations among 10 species (including humans) by evaluating the mathematical relationships of more than 100 developmental events and factors (e.g., evolutionary, genetic, neurochemical, neuroanatomic).

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One advantage of the chronically instrumented fetal lamb is that it is similar in size to the human fetus, thus facilitating

"Translating Time across Developing Mammalian Brains: http://www.translatingtime.net/"
the placement of electrodes and vascular catheters in both the fetus and the mother. Investigators may obtain measurements while the mother (and fetus) remains anesthetized or from awake animals that have recovered from surgery. Studies of animals with continuous instrumentation allow the assessment of fetal breathing movements, gross body movements, brain electrical activity (electroencephalogram), and blood gas and pH measurements. Blood concentrations of glucose, lactate, and various hormones can also be determined. Microdialysis techniques have been used to evaluate neurotransmitter release within the fetal brain in vivo in acute, exteriorized, and chronic preparations. Other studies have measured fetal cerebral blood flow in vivo during episodes of hypoxemia and during maternal infusion of ethanol. Together, these studies have enhanced the understanding of the fetal brain response to pathophysiologic insults in utero. Ultimately, these insights may lead to improved diagnoses, treatment, and prevention of fetal brain injury.

Studies have used a variety of methods to produce fetal hypoxemia and acidemia in fetal lambs. Each method attempts to mimic one or more clinically relevant situation(s), including (1) decreased concentration of maternal inspired oxygen for several hours or days; (2) decreased uterine blood flow, which may be accomplished by placement of an adjustable clamp on the common iliac artery; (3) decreased umbilical blood flow, either by total obstruction or by means of a slow, progressive obstruction; (4) selective uteroplacental embolization; (5) maternal hemorrhage; and (6) a combination of two insults, such as hypoxemia plus hypotension.

Care must be exercised in the application of knowledge gained from hypoxia-ischemia studies conducted on non-fetal models (e.g., rat pups) to the problem of insufficient intrauterine gas exchange. The fetus and the fetal brain exist in a relatively hypoxemic environment. Despite preferential streaming of the most highly oxygenated blood to the brain and heart, the average Po2 measured in the carotid artery of fetal lambs at term is approximately 22 mm Hg. Further, unlike adult conditions in which global anoxia (i.e., cardiac arrest) or focal ischemia (i.e., stroke) is the clinical correlate, fetal asphyxia typically involves diminution, but not absence, of delivery of oxygen, with variable degrees of respiratory or metabolic acidosis. A complete loss of cerebral blood flow rarely occurs, except as a terminal event. Of course, prolonged hypoxemia and decreased oxygen delivery can lead to acidemia and myocardial failure, followed by ischemia and rapid fetal demise. Fetal hypoxemia may result from the compromise of any or all of the steps involved in maternal-fetal oxygen transport (Box 10.3). The impact of repeated hypoxic-ischemic insults should not be underestimated, and numerous clinical scenarios can be envisioned whereby this might occur (e.g., repetitive umbilical cord occlusion, chronic abruption). Moreover, brief insults that may be harmless could cause damage if repeated, as has been demonstrated in adult rats and in fetal lambs.

The neuropathology of intrauterine asphyxia depends, to some extent, on gestational age. In fetal lambs exposed to sustained hypoxemia with developing acidemia, immature fetuses demonstrated a predominantly periventricular
injury, whereas mature fetuses had a primarily cortical injury, although there was some overlap (Fig. 10.4).

This finding is consistent with injury patterns in humans. It is not surprising that the biophysical and biochemical responses to hypoxemia vary between preterm and term fetuses. Matsuda et al. observed that the development of metabolic acidemia, reduced fetal breathing and body movements, and an altered sleep state were much less pronounced in mid-gestational fetal lambs subjected to hypoxemia than in fetal lambs at term.

Neuropathology of Fetal Asphyxia

The mechanism and timing of an asphyxial insult can affect the resulting fetal or neonatal pathology. Acute, complete asphyxia must be distinguished from incomplete, brief, or intermittent asphyxia or chronic hypoxemia. Complete asphyxia may occur in the setting of a total placental abruption or umbilical cord occlusion (as may occur with a uterine rupture or umbilical cord prolapse), which if unrecognized and not treated rapidly leads to fetal demise. Incomplete asphyxia may occur in any setting in which oxygen delivery to the fetus is inadequate to meet all of its needs (e.g., brief and/or repeated episodes of partial umbilical cord occlusion, placental embolization, or incomplete placental abruption). This latter category of asphyxia presumably contributes to the largest proportion of cases of cerebral palsy attributed to antepartum events. In these cases, the insult is not severe enough to lead to immediate fetal death but can profoundly affect fetal brain growth and development. Ongoing studies are attempting to determine whether there is a period in utero when the fetus is especially vulnerable to neurologic injury.

Using a primate model to perform seminal research on perinatal brain injury, Myers identified two patterns of injury based on whether the fetus suffered complete or partial asphyxia. True complete asphyxia was demonstrated in fetal monkeys at term subjected to varying durations (0 to 25 minutes) of complete asphyxia. In studies of fetal monkeys subjected to partial asphyxia, some animals demonstrated cortical necrosis, subcortical white matter damage, and basal ganglia damage. Although these two studies form the core of our knowledge of perinatal brain injury in primates, there were relatively few animals in each experimental group, and considerable variation in response occurred. Some animals suffered no injury, whereas others could not be resuscitated. Volpe emphasized that the variation in neuropathology

![Fig. 10.4 Composite diagram showing distribution of hypoxic injury in mid-gestational (top) and near-term (bottom) fetal lambs at 3 days after 8 hours of arterial hypoxemia. Hypoxemia was produced by placing the pregnant ewe in a chamber with reduced ambient oxygen. Each shading pattern represents an individual animal. The severity of injury is not indicated in this diagram. (From Penning DH, Grafe MR, Hammond R, et al. Neuropathology of the near-term and midgestation ovine fetal brain after sustained in utero hypoxemia. Am J Obstet Gynecol. 1994;170:1425–1432.)](image-url)
after intrauterine asphyxia depends on the fetal gestational age and proposed a framework for these variations. The principal sites of injury in preterm fetuses are the white matter (especially periventricular white matter) and the basal ganglia, whereas older fetuses demonstrate injury primarily in the gray matter of the cortex and cerebellum.

**Cerebral white matter injury** is a term that encompasses the full spectrum of periventricular leukomalacia. **Diffuse noncystic white matter injury** is currently the predominant form of brain injury in children born prematurely. The incidence of **cystic necrotic white matter injury** has declined markedly in the past several decades. The primary reason for white matter injury in preterm infants is the vulnerability of premyelinating oligodendrocytes to hypoxia-ischemia and inflammation. Preterm infants have impaired cerebral blood flow autoregulation, particularly in vascular end zones and border zones. Premyelinating oligodendrocytes are more susceptible to oxidative stress than mature cells because they lack antioxidant enzymes.

Approximately one-third of preterm infants born between 24 and 32 weeks’ gestation have evidence of diffuse white matter injury on magnetic resonance imaging (MRI). These lesions cause disrupted white matter maturation and associated long-term neurodevelopmental consequences as these children grow.

**Fetal Adaptive Responses**

The fetus takes advantage of several adaptive responses for survival and growth in the relatively hypoxic intrauterine environment; these adaptive changes to intrauterine hypoxemia vary between immature and mature fetuses. Fetal responses to asphyxia may be categorized as an alteration of fetal metabolism or maximization of fetal oxygen transport (Box 10.4). Richardson defined the oxygen margin of safety as the extent to which fractional oxygen extraction can increase and fetal arterial Po2 can decrease before tissue oxygen supplies are inadequate. Regardless of the etiology of decreased oxygen delivery to the fetus, fetal oxygen consumption is maintained by increasing oxygen extraction until oxygen delivery is approximately 50% of normal. Lower levels of tissue oxygen tension result in progressive metabolic acidemia and a terminal decrease in oxygen consumption.
FETAL AND NEONATAL ASSESSMENT

Fetal Neurobehavioral Assessment

With recent advances in the understanding of prenatal brain development and imaging technology, there is considerable interest in monitoring and codifying fetal neurologic development and behavior to predict postnatal neurodevelopment. The driving principle is that fetal behavioral patterns reflect complex interactions between the maternal environment and primitive neuronal network generators in the developing brain. There is an overwhelming convergence of opinion that most neurodevelopmental disorders have an intrauterine origin and that there is extensive neurobehavioral continuity from the fetal to the neonatal period.

Although the assessment of high-risk pregnancies has included an analysis of certain aspects of fetal behavior, until recently there have been no unified scales for assessment of fetal neurobehavior. Current fetal neurobehavioral scales assess a variety of behaviors that can be categorized into the four main domains described by DiPietro: (1) heart rate, (2) motor activity, (3) existing behavioral state, and (4) responsiveness to external stimuli. The Fetal Neurobehavioral Coding System (FENS) incorporates most elements of fetal behavior and is a direct extension of the NICU Network Neurobehavioral Scale (NNNS) used for neonatal assessment. Using ultrasonography, FENS analysis can identify specific behaviors in fetuses with growth restriction; compared with normally developing fetuses, fetuses with growth restriction demonstrate a delayed appearance of behavioral states, longer behavioral state transitions, and disorganized behavioral patterns. These tests have been validated in other paradigms, including pregnancies that were complicated by maternal diabetes, substance abuse, and cigarette smoking.

A recently developed, more comprehensive scale is the Kurjak Antenatal Neurodevelopmental Test (KANET), which includes an assessment of eight fetal parameters related to fetal behavior, general movements, and other physical signs (e.g., head circumference, presence or absence of overlapping cranial sutures, finger movements). However, these fetal assessment studies are time-consuming and require specific training to codify behaviors. In addition, because the brain structures driving such behaviors have not been clearly identified, it is difficult to understand the significance of differences in behavior, if any.

Fetal Neuroimaging Assessment

In vivo MRI provides details of the architecture of the developing brain beginning in the 18th gestational week and can quantify brain growth and structural abnormalities. The use of more sophisticated techniques such as MR tractography and functional fetal MRI is likely to enhance our understanding of normal brain development and thus facilitate identification of abnormal development. Until controlled trials demonstrate adequate sensitivity, specificity, and positive predictive power for these tests, their clinical potential is limited. These potential advantages will need to be balanced against the potential detrimental effects of ultrasonography and MRI on fetal neuronal development and migration.

Neonatal Radiologic Diagnosis of Cerebral Injury

MRI is a useful tool in the diagnosis of neonatal brain injury. MRI can assist in the diagnosis of hypoxic-ischemic encephalopathy in newborn infants, provide three-dimensional evaluations to determine the volume of gray matter and the extent of white matter myelination (thus providing valuable insights into normal and abnormal brain development), and estimate the timing of the brain injury in patients with cerebral palsy. New imaging techniques, such as diffusion tensor imaging and magnetic resonance spectroscopy, may offer advantages over conventional MRI when performed early (i.e., hours) after a hypoxic-ischemic insult. Diffusion tensor imaging detects the microscopic movement of water particles in brain tissue. Magnetic resonance spectroscopy analyzes the signal of protons attached to molecules such as glutamate, glutamine, and lactate, among others. These methods detect acute chemical changes in brain tissue and may accurately predict motor outcome in preterm infants. Injury patterns detected with these methods are present for several days and resolve over the next week, at which point the chronic injury becomes visible with conventional MRI. Identification of injuries shortly after birth with these newer techniques can support the hypothesis that an injury occurred within days of delivery. Thus, magnetic resonance spectroscopy and diffusion tensor imaging are powerful new tools for timing the occurrence and understanding the pathophysiology of perinatal brain injury. Cerebral ultrasonography remains a useful technique in the early neurologic neonatal assessment, especially for the critically ill infant who might not be a candidate for transfer to an MRI facility.

ANESTHESIA AND BRAIN INJURY

Anesthetic agents have profound effects on brain metabolism and synaptic transmission. These effects may be direct or indirect and protective or harmful.

Labor Analgesia and the Fetal Brain

Labor analgesia usually entails administration of lower concentrations of analgesic/anesthetic agents for a longer duration than occurs during administration of anesthesia for surgical procedures. Despite widespread use of analgesic and sedative drugs during labor, little attention has been paid to the neurodevelopmental consequences of antepartum and intrapartum fetal exposure to these drugs. Because neurodevelopmental events at term are quite different from those that occur during the second trimester, there is a need to design experimental studies to investigate the effects of analgesic techniques and drugs administered during the third trimester of pregnancy.

Opioids

Among systemic opioids used for labor analgesia, meperidine remains the most widely studied. Although it is well...
recognized that opioids cross the placenta and enter the fetal circulation,\textsuperscript{152} the long-term effects of peripartum opioid exposure on the infant’s neurodevelopmental trajectory are unclear. Only a few preclinical studies have addressed this question.\textsuperscript{153,154} Endogenous opioid systems are active in the fetal brain, and the presence of their cognate receptors at critical sites during this period suggests that these systems are intricately linked to early neurodevelopment.\textsuperscript{155–158} Preclinical evidence suggests that opioid mechanisms play an important role in both early and adult neurogenesis by modulating neuronal progenitor proliferation and differentiation.\textsuperscript{159,160} Of concern, fetal rat exposure to morphine during the entire second trimester alters offspring hippocampal development.\textsuperscript{161} However, animal studies of opioid abuse in pregnancy should not be extrapolated to peripartum opioid use in humans because of differences in the gestational age and differences in drug dose and duration of administration. Only focused studies will reveal the true consequences of intravenous opioid administration for labor analgesia at term gestation.

**Neuraxial Techniques**

Studies of neuraxial analgesia in labor usually focus on analgesic quality and obstetric and short-term neonatal outcomes. To date, no randomized trials have evaluated the long-term effects of neuraxial analgesia on brain development in offspring. Epidurally administered local anesthetics cross the placenta and enter the fetal circulation. Golub\textsuperscript{162} randomized nonlaboring pregnant rhesus monkeys at term to receive epidural bupivacaine (total dose of 1.2 mg/kg) or saline. No differences in specific cognitive deficits were identified between groups; however, exposed offspring demonstrated a prolonged increase in motor disturbance behaviors at 10 to 12 months of age, suggesting that perinatal interventions can alter postnatal behavioral ontogeny. In the only human evidence to date, investigators examined the association between the use of neuraxial labor analgesia and the incidence of childhood learning disabilities in a population-based birth cohort of children from Olmsted County, Minnesota.\textsuperscript{163} The incidence of childhood learning disabilities was not associated with the use of neuraxial labor analgesia (adjusted hazard ratio, 1.05).

**Inhalational Agents**

The use of inhalational anesthetic agents during labor and delivery became popular after the successful use of chloroform by John Snow during Queen Victoria’s delivery of Prince Leopold in 1853. Other inhalational agents were subsequently introduced, including nitrous oxide, trichloroethylene, cyclopropane, and methoxyflurane. Although the use of halogenated agents has been supplanted by widespread adoption of neuraxial techniques for labor analgesia, nitrous oxide is still widely used. Typically, it is administered as 50% nitrous oxide in oxygen using a blender device (e.g., Nitronox in the United States) or premixed in a single cylinder (e.g., Entonox in the United Kingdom) (see Chapter 22). Scientific studies of the fetal and neonatal effects of inhalational analgesics are generally of limited quality.\textsuperscript{164} Available evidence suggests that inhalational anesthetic agents, including nitrous oxide, have minimal or no effect on Apgar and neurobehavioral adaptation scores immediately after delivery.\textsuperscript{165,166} However, none of these studies has evaluated long-term neurodevelopmental outcomes. This knowledge gap is critical, because robust evidence suggests that early-life neural reprogramming, following pharmacologic and inflammatory insults, affects behavioral development later in life. Of concern is compelling animal evidence that anesthetic agents, when administered during a critical period of brain development, cause widespread neurodegeneration with subsequent learning, memory, and behavioral problems (see later discussion). Nitrous oxide, in particular, is now known to be a potent developmental neurotoxin in animal models, yet its effects (if any) on human neurodevelopment are unclear. Thus, although the pattern of nitrous oxide administration during labor is unlike its administration for surgical anesthesia, the administration of nitrous oxide for labor analgesia merits closer scientific scrutiny.\textsuperscript{167}

**Maternal Anesthesia and the Fetal Brain**

Despite the widespread use of neuraxial techniques in obstetric anesthesia, many pregnant women continue to require general anesthesia for either pregnancy-related or nonobstetric surgical procedures. The commonly used anesthetic agents freely cross the placenta and reach the fetal brain, causing fetal sleep or sedation. Obstetric anesthesia research has focused primarily on the teratogenic effects of anesthetic agents administered during the first trimester (see Chapter 17) and the effects of anesthetic agents on neonatal behavior when administered during cesarean delivery. Historically, the second trimester has been assumed to be a safe period for surgery and anesthesia, primarily because of a lack of targeted studies. However, during the past decade, extensive animal research has shown that anesthetic agents, when administered during the phase of synaptogenesis, can induce a profound neurodegenerative response in the developing brain and cause functional impairment in offspring.\textsuperscript{168,169} Human epidemiologic studies appear to support an association between early childhood exposure to anesthetic agents and subsequent functional impairment. However, it is unclear whether these adverse outcomes result from the underlying disease, surgery, or anesthesia, or a combination of these factors.\textsuperscript{170–175} Because human synaptogenesis appears to begin during the third trimester, there is serious concern that intrauterine fetal exposure to these anesthetic agents may result in similar functional impairment. Because there is no precise way to monitor human fetal brain development \textit{in utero}, the potential long-term effects of maternal anesthesia on the fetal brain must be investigated in animal models. However, given the considerable differences in neural maturation among species (Fig. 10.5; see also Fig. 10.3), and the duration of anesthesia exposure in relation to the lifespan of the organism, these results should be interpreted with caution.\textsuperscript{174,175}
The exact mechanisms by which anesthetic agents impair early brain development are still under active investigation. Anesthetic agent interactions with GABA and the NMDA-subtype of glutamate receptors decrease activity-dependent synapse formation and cause apoptotic neurodegeneration in multiple areas of the developing brain. These histopathologic changes have been well investigated, especially in the hippocampal formation, which is an area that is crucial for memory. Early exposure to anesthetic agents affects long-term potentiation in the hippocampus and affects spatial working memory in animal models. These changes do not appear to be caused by direct cytotoxicity but rather by a combination of effects on both neuronal and non-neuronal cells in the developing brain (Box 10.5).

Of specific concern are the effects of anesthetic agents on neurogenesis and synapse formation in the fetal brain. Human neural ontogeny suggests that the second trimester is a period of active fetal brain development, with neuroblast proliferation peaking between the 5th and 25th postmenstrual weeks. Because GABA and glutamate play a crucial role in these processes, there is concern that prolonged and non-physiologic modulation of the fetal GABA and glutamatergic systems, as might occur during second-trimester maternal anesthesia, might affect neurogenesis, neuronal migration, and/or synapse formation.

In one of the first animal studies to simulate a clinically relevant scenario, a single exposure to 1.4% isoflurane (1 MAC [minimum anesthetic concentration]) for 4 hours during the second trimester caused long-lasting impairment of spatial working memory in rodent offspring. Although the exact mechanisms behind these behavioral disturbances are unclear, other studies suggest that mid-gestational exposure to isoflurane upregulates the proapoptotic protein caspase-12, decreases overall synapse numbers in the fetal hippocampus, and downregulates the plasticity-associated protein GAP-43. Similar results have been reported in pregnant guinea pigs and macaques, suggesting that the fetal brain remains highly susceptible to maternal mid-trimester anesthesia. Furthermore, isoflurane suppresses neurogenesis in rodents both in vitro and in vivo, causing a depletion of the neural stem cell pool. At least in vitro, this
phenomenon appears to be dose dependent. At the present time, the impact of reduced neurogenesis on behavioral deficits and the effect of anesthetic agents on neuronal migration remain unknown.

When these studies are extended to the third trimester, the results are mixed. In one rodent study, maternal administration of 1.3% isoflurane for 6 hours during the third trimester had no effect on offspring neurodevelopment. However, these investigators performed another dose-response study in term rodents and found that maternal administration of 3% isoflurane, but not 1.3% isoflurane, for 1 hour caused fetal brain hippocampal neurodegeneration. No neurodegenerative changes were observed after third-trimester exposure in guinea pigs. Thus, in rodent models it appears that the fetal brain is less vulnerable to the adverse effects of anesthetic agents during the third trimester. This phenomenon could be caused by the stage of neurodevelopment, or more likely, by an increase in the levels of neuroprotective hormones such as estrogen, progesterone, neurosteroids, and oxytocin during the third trimester. Elegant work from nonhuman primate models, however, shows that even a 5-hour exposure to either isoflurane (1% to 1.5%) or ketamine and propofol during the late second and early third trimester can cause a 2.5- to 5-fold increase in neuronal apoptosis in the fetal brain.

Experiments evaluating the neurodevelopmental effects after shorter-duration anesthesia exposure are currently lacking. This is a critical knowledge gap because most surgical procedures requiring anesthesia in pregnant women are relatively short. The relative safety of short exposures is supported by a population-based birth cohort study (in Olmsted County, Minnesota) that sought to determine the incidence of learning disabilities in children after maternal administration of general or neuraxial anesthesia during cesarean or vaginal delivery. Children exposed to general anesthesia during cesarean delivery were not more likely to develop learning disabilities compared with those born vaginally with no exposure to general anesthesia. Although the study was retrospective and used data from 1976 to 1982, it is reassuring that even the children whose mothers required emergency general anesthesia (presumably secondary to fetal compromise) did not have a higher incidence of learning disability.

Newer studies have explored the association between general anesthesia during the third trimester and autism spectrum disorders in offspring; the results are inconclusive. Using a propensity score-matched technique to adjust for underlying risk factors in a population-based data set derived from national registries in Taiwan, Chien et al. reported that general anesthesia during cesarean delivery was associated with a 52% higher risk for developing autism than vaginal delivery. By contrast, a population-based sibling cohort study from Puerto Rico found no evidence for an association, although in this study, both exposures during pregnancy and the first 2 years of life were included. Further epidemiologic work is required to ascertain the effects of maternal anesthesia during nonobstetric surgery in the second trimester.

The wealth of anesthetic neurotoxicity studies prompted the U.S. Food and Drug Administration (FDA) to issue an updated Drug Safety Communication in late 2016, warning that repeated or lengthy use of general anesthetic or sedative drugs during the third trimester of pregnancy or the first 3 years of life may have consequences for early brain development. However, the results of recent prospective clinical trials suggest that short-duration exposure to anesthesia in children younger than three 3 years of age does not have a detrimental effect on cognitive development. To date, no prospective study has addressed the effects of fetal anesthesia exposure during the third trimester on fetal/neonatal brain development.

**Fetal Neuroprotection**

Throughout gestation, the fetus remains concealed, protected, and nourished by a combination of maternal anatomic and physiologic factors. For example, the amniotic fluid cushions the fetus against trauma, and the placenta serves as a conduit to ensure a continuous supply of maternal nutrients to the developing fetus. Despite these built-in protective mechanisms, the fetus remains vulnerable to maternal insults such as infection and fever, drugs, and acute changes in placental physiology. Among all organ systems, the developing central nervous system appears to be most susceptible to such insults. Understanding the developmental aspects of neuroprotective mechanisms will therefore enable generation of targeted neuroprotective therapies.

**Role of the Placenta**

One of the fundamental neuroprotective mechanisms is the barrier function of the placenta. The placenta serves as a conduit for chemical communication between the mother and the developing fetus; endocrine signals, growth factors, and cytokines freely traverse the placenta, which dynamically adapts to chronic changes in the maternal-fetal environment to preserve fetal growth and viability. However, this function also allows transplacental transfer of an array of pharmacologically active molecules either by passive diffusion or active transport. By virtue of its enzymatic machinery, the placenta is capable of detoxification of some of these potentially harmful chemicals, making it the first line of defense against potentially harmful environmental agents.

Substances cross the placenta and enter the fetal circulation by several mechanisms, including passive and facilitated diffusion, active transport, and endocytosis (see Chapter 4). Molecules in the syncytiotrophoblast play important roles in active transport of molecules across the placenta, including phospho-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The activity of these transporters varies with gestational age and certain pathophysiologic conditions (e.g., preeclampsia, intrauterine infection) and is influenced by the steroid hormones of pregnancy. Thus, it is possible that placental permeability to certain drugs depends on a complex interplay of several factors. In addition to this barrier function, the human placenta secretes estrogen and progesterone in very high concentrations; these hormones, and others, eventually enter the fetal circulation, where they serve as substrates for de novo neurosteroid synthesis in the
fetal brain. In particular, allopregnanolone has been shown to exert neuroprotective effects in the fetal brain (see later discussion).

**Humoral Mechanisms**

Published studies have extensively investigated the intricate and symbiotic relationship between the fetus and maternal hormones throughout pregnancy. Much of our understanding comes from elaborate murine and primate research models in which changes in maternal levels of hormones closely parallel changes in the fetal plasma and/or brain. Throughout pregnancy, there is a gradual rise in the levels of many maternal hormones such as progesterone, estradiol, and oxytocin. At term or during labor, the levels of these hormones are 40- to 100-fold higher than in the nonpregnant state.

Many of these hormones freely cross the placenta and are transported to the fetal brain, where they profoundly influence neurodevelopment. For example, estradiol and progesterone influence neural stem cell proliferation, modulate apoptosis and synaptogenesis in a region-specific manner, alter subcellular signaling mechanisms, and promote dendritic growth and spinogenesis through specific receptor mechanisms. Estradiol, in particular, prevents cell death in both neuronal and non-neuronal cell lines.

Maternal plasma oxytocin levels gradually increase during pregnancy and reach a peak during the second stage of labor. Oxytocin is of particular importance because it has significant effects on GABAergic signaling in fetal neurons. In a series of elegant experiments, investigators showed that oxytocin transiently switched the action of GABA on immature rodent fetal neurons from depolarizing to hyperpolarizing at term gestation. This finding raises the possibility that oxytocin protects the fetal brain during the stressful process of labor and delivery.

**NEUROPROTECTIVE THERAPIES**

**Magnesium Sulfate and Cerebral Palsy**

Until recently there was considerable controversy regarding the role of magnesium sulfate in preventing or possibly exacerbating fetal brain injury. Some controversy remains, but the publication of several large randomized studies of the effect of antenatal maternal magnesium sulfate administration on offspring outcome has dramatically altered practice guidelines and clinical practice. Although none of these studies demonstrated significant improvement in the primary outcome, all showed reduced cognitive morbidity, and none showed any increase in pediatric morbidity or mortality associated with magnesium sulfate use for neuroprotection.

In a placebo-controlled trial of women who were thought likely to deliver within 24 hours and before 30 weeks’ gestation in New Zealand and Australia, Crowther et al. reported a lower incidence of substantial gross motor dysfunction (3.4% vs. 6.6%; relative risk [RR], 0.51; 95% CI, 0.29 to 0.91) and combined death or substantial gross motor dysfunction (17% versus 22.7%; RR, 0.75; 95% CI, 0.59 to 0.96) in children whose mothers were randomized to receive antenatal magnesium sulfate treatment. In another large trial from France, which included women in preterm labor before 33 weeks’ gestation, a significant reduction in death and/or gross motor dysfunction was again identified in the children whose mothers received magnesium sulfate (25.6% versus 30.8%; OR, 0.62; 95% CI, 0.41 to 0.99). A reduction in death and/or motor or cognitive dysfunction (34.9% versus 40.5%; OR, 0.68; 95% CI, 0.47 to 0.99) was observed in the magnesium-exposed offspring at 2 years of age. Finally, a randomized, controlled multicenter trial in the United States found that fetal exposure to magnesium sulfate within 24 hours of preterm delivery (between 24 and 32 completed weeks’ gestational age) did not reduce the combined risk for moderate or severe cerebral palsy or death. However, fetal exposure to magnesium sulfate reduced the risk for moderate or severe cerebral palsy among survivors (1.9% versus 3.5%; RR, 0.55; 95% CI, 0.32 to 0.95) and was associated with a decreased overall rate of cerebral palsy (4.2% versus 7.3%; P = .004).

Although the results are optimistic, it is difficult to compare these trials owing to differences in inclusion criteria, study interventions/dosages, and outcomes. Nonetheless, after the publications of these trials, it has been concluded from meta-analyses that fetal exposure to magnesium sulfate may reduce the risk for cerebral palsy without increasing the risk for neonatal death.

In 2010, the ACOG and the SMFM released a joint committee opinion that supported antenatal maternal magnesium sulfate administration for fetal neuroprotection, stating that the available evidence suggests that magnesium sulfate administered before anticipated early preterm birth reduces the risk for cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring. The ACOG and the SMFM have concluded that it is reasonable to use a protocol based on one of the large randomized trials; magnesium sulfate should be offered to women at high risk for anticipated preterm delivery (< 28 to 32 weeks’ gestational age) within 24 hours. A loading dose of magnesium sulfate 4 to 6 g should be administered, followed by a maintenance infusion of 1 to 2 g/h for 12 to 24 hours, at which point the risk for impending preterm delivery should be reassessed. If there is no longer a concern for impending delivery, the magnesium sulfate should be discontinued and restarted with active labor or when delivery is again thought to be imminent.

**Hypothermia**

Some investigators have described improved outcomes after the use of hypothermia in neonates at risk for hypoxic-ischemic encephalopathy. One group of investigators has described an experimental model of severe intrauterine hypoxia in preterm fetal sheep, in which asphyxia was produced by 25 minutes of complete umbilical cord occlusion. Cerebral hypothermia (fetal extradural temperature reduced
from 39° to 29° C) decreased the loss of striatal neurons and oligodendroglia. This finding was associated with improved basal ganglia function after ischemia.

These and other experimental results prompted a randomized clinical trial of whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. Eligible neonates were older than 36 weeks’ gestational age, had moderate or severe encephalopathy, and were admitted to the neonatal intensive care unit within 6 hours of birth. Body temperature was lowered to 33.5° C for 72 hours in neonates randomized to hypothermia treatment. Death or moderate to severe disability at 18 to 22 months of age occurred in 44% of 102 infants in the hypothermia group, compared with 62% of 106 infants in the control group (risk ratio, 0.72; 95% CI, 0.54 to 0.95; \( P = .01 \)). Although encouraging, these results are at odds with those from another large multicenter randomized trial. In an editorial attempting to reconcile these opposing results, several possible explanations were suggested. Importantly, in the study that demonstrated no benefit, cooling began later and more time was required to achieve complete cooling, because head (not total body) cooling was employed. Moreover, the study that showed no benefit with hypothermia may have included infants who were so severely affected that no therapy would have been beneficial. This possibility highlights the importance of patient selection in these clinical trials.

In 2012, the whole-body hypothermia investigators published the results of follow-up evaluations of the original study subjects at 6 to 7 years of age. There was no difference in the combined primary outcome of death or an IQ score less than 70 (47% versus 62%, \( P = .06 \)) between the hypothermia group and the control group. The hypothermia group had a lower incidence of death or severe disability (41% versus 60%, \( P = .03 \)), but there was no difference in moderate or severe disability (35% versus 38%, \( P = .87 \)). Attention-executive dysfunction occurred in 4% of the hypothermia group versus 13% of the usual care group (\( P = .19 \)), and visuospatial dysfunction occurred in 4% of the hypothermia group versus 3% of the usual care group (\( P = .80 \)). Thus, although there was no significant difference in the primary outcome, whole-body hypothermia decreased the incidence of death and did not increase the rate of a low IQ score or severe disability among survivors.

A 2013 meta-analysis of 11 randomized controlled trials of hypothermia therapy, which included 1505 term and late preterm infants, concluded that the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. The authors advised that hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic-ischemic encephalopathy if identified before 6 hours of age. Further trials are necessary to identify appropriate cooling techniques and to refine patient selection.

**Experimental Neuroprotection**

Perlman reviewed various strategies for treating hypoxic-ischemic neonatal injuries, including administration of inflammatory mediator modulators, excitatory amino acid receptor agonists and antagonists, free radical scavengers, and platelet-activating factor antagonists. These emerging therapeutic strategies stem from basic neuroscience research on brain development and the pathophysiology of ischemic injury.

The role of white matter in the attenuation of hypoxic-ischemic brain damage (e.g., through uptake of excitatory amino acids or sequestration of potassium and hydrogen ions) is underappreciated, and drugs that inhibit the release of excitatory amino acids or antagonize their receptors may be of benefit. Multiple strategies may be necessary to inhibit the deleterious pathways initiated by brain ischemia and hypoxia. A “brain cocktail,” consisting of free radical scavengers, modifiers of nitric oxide activity, metabolic inhibitors, calcium and iron chelators, and drugs that affect the excitatory amino acid systems, may someday be administered to fetuses and neonates at risk for brain injury. Additional compounds that may inhibit CNS necrosis or apoptosis, either in utero or in the neonatal period, include agents that interrupt the inflammatory cascade, progesterone, and other steroids.

Among the pharmacologic candidates for neuroprotection, erythropoietin (EPO) appears promising; EPO is known to have wide-ranging actions, including antiapoptotic, antioxidant, and anti-inflammatory effects. Indirectly, EPO may support angiogenesis and neovascularization. In the first human clinical study, EPO administration in full-term neonates was associated with an almost 50% reduction in death and disability at 18 months when the hypoxic-ischemic injury was moderate but not severe. A 2017 systematic review summarized nine studies in which EPO was administered to neonates born at 35 weeks’ gestation or greater with perinatal asphyxia. In six trials, EPO was administered alone, and in three trials it was administered with therapeutic hypothermia. The authors concluded that long-term neurodevelopmental outcomes are improved after EPO administration, and that the drug appears safe, without adverse effects. However, the sample sizes were small in the included trials, and other study limitations precluded definitive conclusions. Several large trials are ongoing.

Another agent with potential for fetal neuroprotection is melatonin, a highly effective antioxidant with reliable transplacental transfer and a wide therapeutic index. Administration of melatonin to fetal sheep compromised by experimental umbilical cord occlusion prevents oxidative stress, reduces lipid peroxidation, modulates microglial activation, and decreases the extent of brain damage. The translational potential of other agents such as N-acetylcysteine (NAC), allopurinol, neurosteroids such as allopregnanolone, anesthetic agents such as xenon, and creatine appears limited.

The ability to accurately predict which fetuses are at risk for neurologic injury, and when, is currently rudimentary. The most vulnerable periods of fetal development are still unknown, and large studies are required to validate the use of noninvasive (e.g., advanced neuroimaging) fetal surveillance.
techniques. Additional work has focused on identifying biomarkers of neurologic injury that could predict risk for cerebral palsy, thus identifying infants who would benefit from postdelivery interventions. The ability to identify these "at-risk" infants in utero or immediately after delivery is a necessary step in designing effective therapeutic regimens that interfere minimally with the normal trophic activities of the developing brain.

**KEY POINTS**

- Cerebral palsy is a nonprogressive disorder of the central nervous system that is present (but rarely obvious) at birth and involves some impairment of motor function or posture. Intellectual disability may or may not be present.
- The term birth asphyxia should be used sparingly, if at all, in medical records. More descriptive terms that describe the neonate's tone, color, respiratory effort, and metabolic status should be used when possible.
- The incidence of cerebral palsy is approximately 2 per 1000 live births and has not decreased despite the widespread use of intrapartum fetal heart rate monitoring and a higher cesarean delivery rate.
- The Apgar score is a poor predictor of cerebral palsy.
- Spastic quadriplegia and, less commonly, dyskinesia are the only types of cerebral palsy associated with acute intrapartum hypoxic events.
- Intrapartum hypoxia sufficient to cause cerebral palsy is always accompanied by neonatal encephalopathy and seizures.
- Fetal compensatory responses to hypoxemia in utero include (1) a redistribution of fetal cardiac output, with increased blood flow to the brain, myocardium, and adrenal glands; (2) decreased fetal energy consumption as a result of decreased fetal breathing and body movements; and (3) maintenance of essential cellular processes at the expense of fetal growth.
- Chorioamnionitis is associated with an increased risk for cerebral palsy. Epidural analgesia during labor is associated with an elevated maternal temperature (but not chorioamnionitis). Accurate diagnosis of chorioamnionitis may prevent unnecessary evaluations for sepsis in neonates of mothers with a small rise in temperature during labor.
- No published data suggest that a given anesthetic drug or technique is more likely to protect fetal neurologic function (provided that the anesthetic technique is administered according to the recommended guidelines for good anesthesia practice).

In animal models, exposure of the developing brain to anesthetic agents that interact with GABA and NMDA-type glutamate receptors induce a neurodegenerative response associated with subsequent functional impairment in adulthood. It remains to be determined whether exposure of human fetuses (via maternal anesthesia) and infants to these agents in clinically relevant doses leads to functional central nervous system impairment.

**REFERENCES**


Crowther CA, Middleton PF, Vosey M, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium


In 2000, the publication of the Institute of Medicine (IOM) report *To Err is Human: Building a Safer Health Care System* was a seminal event for the health care system in the United States. Before the publication of this report, many physicians and hospital administrators refused to acknowledge the frequent occurrence of preventable morbidity and the reality that our health care system was not adequately addressing the issue of patient safety. Subsequently, we have learned that tens of thousands of patients die each year because of medical errors. In the past 15 years, numerous changes have been advocated, including mandating minimum nurse-to-patient ratios, reducing working hours of resident physicians, use of bundles, and advancing the science of simulation training and teamwork, particularly in the medical environment.

Data from high-reliability organizations suggest that health care errors do not usually occur because of ill-trained medical personnel but rather are because of systems that trap both the patient and the health care provider. As Pratt eloquently stated, “Historically, medicine was simple, largely ineffective, and mostly safe (excluding perhaps trephination and blood-letting). Modern medicine is complex, highly effective, but dangerous.” The field of patient safety attempts to reduce that danger, which is very real in the fields of obstetrics and obstetric anesthesiology.

Unfortunately, maternal mortality in the United States has risen over the last decade despite improvements in patient safety and health care. This is particularly troubling since it has occurred during a period when global death rates fell, thus making the United States an outlier for maternal mortality rates in the developed world. In a review of maternal morbidity and mortality, Kilpatrick has suggested that communication and collaboration between all stakeholders involved in perinatal health are necessary to reverse this trend.

In this chapter, methods of improved teamwork communication and collaboration, as well as issues related to medical errors, are reviewed, and solutions to enhance maternal safety are highlighted. Although anesthesia is now an exceedingly rare cause of maternal death, the anesthesiologist on the labor and delivery suite plays a key role in safety. Several modalities that can be used by labor and delivery unit personnel to reduce both the incidence and sequelae of preventable errors are highlighted.

**PATIENT SAFETY AND MEDICAL ERRORS**

Traditional assessments of medical error often blamed individuals and failed to address the broader systems issues that allowed the error to occur. Newer approaches are based on an understanding that humans will make errors and, therefore, encourage creation of robust systems to prevent these errors from occurring or to minimize their impact on patients if they occur. This paradigm change has borrowed heavily from other high-risk arenas, such as the aviation and nuclear industries.

**The Swiss Cheese Model**

Patients are typically not injured by a single event resulting from a single act of a careless individual. More often an underlying systems problem made the error possible, and numerous individual actions “fall through the cracks” of a system that does not catch them, resulting in error and harm. James Reason described the “Swiss cheese” model of error
(Fig. 11.1), in which he explained how numerous contributing factors are responsible for the ultimate harm.\(^{11}\) Reason developed this model to illustrate how analyses of major accidents and catastrophic systems failures tend to reveal multiple, smaller failures that led up to the actual adverse event. In the model, each slice of cheese represents a safety barrier or precaution relevant to a particular hazard. For example, if the hazard were wrong-site surgery, slices of the cheese might include processes for identifying the right or left side on radiology tests, a protocol for signing the correct site when the surgeon and patient first meet, and a second protocol for reviewing the medical record and checking the previously marked site in the operating room. Each barrier has “holes”; hence, the term Swiss cheese. For some serious events (e.g., operating on the wrong person) the holes will rarely align; however, even rare cases of harm are unacceptable. Reason’s model highlights the need to think of safety as a system—a set of organizational and cultural layers that influence and shape one another. Reason has eloquently summarized the process, stating “rather than being the main instigators of an accident, operators tend to be the inheritors of system defects created by poor design, incorrect installation, faulty maintenance, and bad management decisions. Their part is usually that of adding the final garnish to a lethal brew whose ingredients have already been long in the cooking.”\(^{12}\)

Fig. 11.2 illustrates the use of the Swiss cheese model to evaluate a real near-miss case involving the misidentification of an obstetric patient who nearly underwent the wrong procedure (an unwanted tubal ligation). It describes how the combination of numerous system errors came very close to allowing the wrong procedure to be performed. The events unfolded as follows:

1. A nulliparous woman in active labor at term arrived on the labor and delivery unit in severe pain. She spoke a foreign language and was poorly understood by the labor and delivery staff. No translator was called because her husband was helping with the translation.

2. Because the patient was in such severe pain, she rushed to answer all the questions and answered several incorrectly. As per hospital policy (due to HIPAA [Health Insurance Portability and Accountability Act of 1996] regulations), the husband was asked to leave the room while the history was being taken and was therefore not present to assist in the translation.

3. There was another patient on the labor and delivery unit with the same last name and a similar sounding first name. The hospital protocol for this occurrence was not followed. Patient initials, not last names, were listed on the labor and delivery “board,” so that other staff were unaware of the identical patient names.

4. The patient developed a nonreassuring fetal heart rate (FHR) tracing and was scheduled for urgent cesarean delivery. The obstetric resident physician informed the anesthesiologist of this decision and, mistaking the two patients with identical names, booked the case for a cesarean delivery plus bilateral tubal ligation. Unlike the other patient with the same name, the patient going to the operating room did not want or expect a tubal ligation.

5. The case was delayed because of a shift change, and the obstetricians urged the nurses to hurry. This caused friction between the nurses and obstetricians, and they did not work as a team. There was no “huddle,” and communication between labor and delivery staff and operating room staff was suboptimal.

6. The patient arrived in the operating room and was very anxious and crying. The anesthesiologist administered fentanyl 50 µg to calm the patient, and she became very sedated.

7. A “time-out” was performed, but it was not taken seriously. The patient was asleep and did not participate. The attending obstetrician was not present. Conversations continued during the time-out.

8. Following the flawed time-out, it was agreed that this patient was to undergo a primary cesarean delivery and tubal ligation. Her husband was not present during the time-out but was brought to the room immediately after this activity. The surgical procedure began.

9. The attending obstetrician arrived after the start of the procedure and questioned the planned tubal ligation. Her husband was not present during the time-out, but he knew about the second patient but because he was informed that this patient was nulliparous. Immediate investigation revealed that the patient was not supposed to receive a tubal ligation. A major error was narrowly averted.

As in many such situations, a conglomeration of many missteps resulted in the potential for patient harm.

**Medical Errors**

Today there is widespread interest in changing the health care culture to build safer systems, including ensuring the appropriate physical work environment, developing redundancies in safety procedures and use of safety bundles,\(^4\) allowing health care workers to report their mistakes (including near misses) without fear of punishment, and providing mechanisms to learn from the experiences. None of these steps will achieve the ultimate goal of complete patient safety without the support of physicians as well as hospital administrators and other key stakeholders. In addition, although vital to improving the current condition, these steps do not obviate
the need for well-trained and well-rested physicians and nurses. The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Patient Safety in Obstetrics and Gynecology highlights the following seven objectives for patient safety:
1. Develop a commitment to encourage a culture of patient safety.
2. Implement recommended safe medication practices.
3. Reduce the likelihood of surgical errors.
4. Improve communication with health care providers.
5. Improve communication with patients.
6. Establish a partnership with patients to improve safety.
7. Make safety a priority in every aspect of practice.

In a different committee opinion, the ACOG also states that there is increasing awareness within the patient safety movement that fatigue and even partial sleep deprivation impairs performance. These goals and opinions relate to the anesthesia provider as well. Although the Accreditation Council on Graduate Medical Education (ACGME) has enacted restrictions on resident physician work hours to prevent sleep deprivation, there are no such limits on attending physician work hours. Rothschild et al. found that the risk for surgical complications was increased if attending physicians had slept less than 6 hours the night before the procedure.

Medical error has been defined as a “failure of a planned action to be completed as intended, or the use of a wrong plan to achieve an aim.” Communication problems are consistently identified as a leading cause of medical errors in obstetrics, and perceptions are often misaligned. The Joint Commission has found that although the majority of these events have multiple root causes, lack of effective communication along with leadership and human factors are often the primary causes of sentinel events. Several of the 2017
Joint Commission National Patient Safety Goals relate to error reduction on the labor and delivery unit (Box 11.1). Departments of anesthesiology and obstetrics and gynecology should regularly review the national patient safety goals established by the Joint Commission. Hospitals are regularly surveyed to verify their compliance with these goals.

Although those working in health care have made great efforts to reduce preventable patient harm, the progress has not been as dramatic as necessary. Leape and Berwick, two “fathers” of the field of patient safety, suggested that the lack of progress following the release of the initial IOM report is a result of the “culture of medicine.” They, and others, believe that this culture is deeply rooted, both by custom and training, in autonomous individual performance. A recently published systematic review found evidence that interventions to improve teamwork, communication, and safety culture demonstrated improvements in patient outcomes. It is probable that systematic and appropriate use of medical simulation for improved training, along with other important changes to our systems, will facilitate the necessary cultural changes and lead to improved patient safety. Labor and delivery units are no different than other medical care environments, and most still have many opportunities to change culture and practice to optimize patient safety. Nabhan and Ahmed-Tawfik have suggested that the concept of patient safety in obstetrics is “not as strong as desirable for the provision of reliable health care.” In some units, a punitive culture still exists and results in suppression of error reporting, lack of proper communication, and failure of appropriate feedback. Obviously, this culture needs to change before we can significantly improve patient safety. Kacmar has opined that achieving the ideal of a culture of safety for all obstetric units requires multidisciplinary collaboration, frequent reassessment for areas of improvement, and a culture of openness to change when improvement opportunities arise.

Pronovost and Freischlag eloquently described the operating room environment when they stated that “operating rooms are among the most complex political, social, and cultural structures that exist, full of ritual, drama, hierarchy, and too often conflict.” These authors concluded that poor teamwork contributes prominently to most adverse events, including those in the operating room.

**TEAMS AND TEAMWORK**

Health care is a team activity; it can even be considered and evaluated as a team sport. Teams take care of patients in general and especially on the labor and delivery suite. Furthermore, health care teams operate in an environment characterized by acute stress, heavy workload, and high stakes for decision and action errors. Individuals have limited capabilities; when their limitations are combined with organizational and environmental complexity, human error is virtually inevitable. The labor and delivery unit is a dynamic and complex care setting. In fact, the labor and delivery unit requires intense, error-free vigilance with effective communication and teamwork among various clinical disciplines who, although working together, have probably never trained together. This group includes obstetricians, midwives, nurses, anesthesiologists and nurse anesthetists, and pediatricians. The addition of trainees at all levels and in all disciplines enhances the potential for communication error. Siassakos et al. suggested that one of the most important components of effective training in obstetrics includes multiprofessional training and integration of teamwork training with clinical teaching. Multidisciplinary safety rounds enhance situational awareness among team members and encourage contingency plans for emergency management. Chau and colleagues at the Brigham and Women’s Hospital recently reported that providers on labor and delivery suites perceived that structured interprofessional rounds are effective in promoting teamwork.

A team consists of two or more individuals who have specific roles, perform independent tasks, are adaptable, and share common goals. Salas et al. defined teamwork as a complex yet elegant phenomenon. It can be defined as a “set of interrelated behaviors, actions, cognitions, and attitudes that facilitate the required task work that must be completed.” Lack of teamwork has been identified as a leading cause of adverse events in medicine. Team behavior and coordination, particularly communication or team information sharing, are critical for optimizing team performance. Baker et al. stated that to work together effectively, team members must possess specific knowledge, skills, and attitudes (KSAs), including skill
TABLE 11.1 Characteristics of Effective Teams

<table>
<thead>
<tr>
<th>Knowledge/Skills/Attitudes</th>
<th>Characteristics of the Team</th>
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<tbody>
<tr>
<td><strong>Leadership</strong></td>
<td>Roles are clear but not overly rigid. Team members believe leaders care about them.</td>
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<tr>
<td><strong>Backup behavior</strong></td>
<td>Members compensate for each other. Members provide feedback to each other.</td>
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<tr>
<td><strong>Mutual performance monitoring</strong></td>
<td>Members understand each other’s roles.</td>
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<tr>
<td><strong>Communication adaptability</strong></td>
<td>Members communicate often and anticipate each other.</td>
</tr>
<tr>
<td><strong>Mutual trust</strong></td>
<td>Members trust each other’s intentions.</td>
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in monitoring each other’s performance, knowledge of their own and their teammates’ task responsibilities, and a positive disposition toward working in a team. These authors have described characteristics of effective teams, which include team leadership, mutual performance monitoring, backup behavior, adaptability, shared mental models, communication, team/collective orientation, and mutual trust. Moreover, effective team performance in complex environments requires that team members hold a shared understanding of the task, their equipment, and their teammates (Table 11.1).

Teamwork is essential for safe patient care on the labor and delivery suite. The Joint Commission has recommended a risk-reduction strategy for decreasing perinatal death or injury. This strategy includes the implementation of team training and mock emergency drills for shoulder dystocia, emergency cesarean delivery, and maternal hemorrhage.

Team training promotes the acquisition of adaptive behaviors, shared cognitions, and relevant attitudes. It is an instructional strategy that ideally combines practice-based delivery methods with realistic events, guided by medical teamwork competencies (i.e., behaviors, cognitions, and/or attitudes). Murray and Enarson stated that “when a crisis complicates patient care, teamwork among health care professionals is frequently strained, resulting in more frequent as well as more serious failures in managing critical events.” This scenario occurs all too often on the labor and delivery unit. In a recent systematic review of communication in the operating room, Weldon et al. reported that communication was shown to affect operating room practices in all the reviewed studies and that anesthesiologists obtained low scores on communication.

After many years of uncertainty, there is now encouraging evidence that team training may improve safety of clinical outcomes. The obstetric literature has particularly highlighted successes related to major obstetric hemorrhage. Neily et al. reported that surgical mortality decreased by 18% at 74 United States Veterans Health Administration hospitals that implemented a team training program, compared with a 7% mortality reduction in 34 control hospitals that did not implement such a program. Nielsen et al. reported that team training effectively reduced the decision-to-delivery time for emergency cesarean delivery. Similarly, after mandatory interdisciplinary team training for all labor and delivery staff in a unit in the United Kingdom, the median decision-to-delivery interval for a prolapsed umbilical cord decreased from 25 to 14.5 minutes. Other reports have demonstrated similar findings on team training and shortening of the decision-to-delivery interval.

After initiation of team training in a community hospital, Shea-Lewis reported a reduction in the adverse outcome index from 7% to 4%. A recent meta-analysis by Hughes et al. further demonstrated that medical team training can reduce errors by 15% to 18% and save lives. Team training works, and now we have compelling data that it improves clinical outcomes.

**Team Leadership**

There is a clear difference between the leadership of individuals and team leadership. One who is leading independent individuals will diagnose a problem, generate possible solutions, and implement the most appropriate solution. In contrast, team leadership does not involve handing down solutions to team members but rather consists of defining team goals, setting expectations, coordinating activities, organizing team resources, and guiding the team toward its goals.

Team leaders can improve team performance in many ways (e.g., by promoting coordination and cooperation). These individuals not only must be technically competent but also must be competent in leadership skills. Anesthesia providers and other physicians do not routinely train to be competent team leaders. Many of the tasks necessary can and must be learned during team training. Simulation may play a key role in this education. Team leadership training has been developed to successfully train specific team leader behaviors, and the implementation of these programs has been shown to improve team performance.

**High-Reliability Organizations and Teams**

Despite the inevitability of human error, some organizations that operate in complex environments are able to maintain an exceptionally safe workplace. These organizations, including the aviation and nuclear power industries, have been termed high-reliability organizations (HROs). These organizations can also be hospitals and other health care organizations. HROs have been defined as institutions where individuals,
working together in high-acuity situations facing great potential for error and disastrous consequences, consistently deliver care with positive results and minimal errors. Teams that exhibit behaviors that facilitate the characteristics and values held by the HRO may be defined as high-reliability teams (HRTs). It has recently been argued that zero patient harm is a fundamental imperative that can be promoted by high-reliability science. Wilson et al. defined five guidelines for HRTs. These teams must do the following:

1. Use closed-loop communication and other forms of information exchange to promote shared situational awareness regarding factors internal and external to the team.
2. Develop shared mental models that allow team members to monitor other members’ performance and offer backup assistance when needed.
3. Demonstrate a collective organization that allows members to be assertive, to take advantage of functional expertise, and to seek and value input from other team members.
4. Seek to recognize complexities of their task environment and accordingly develop plans that are adequate and promote flexibility.
5. Use semistructured feedback mechanisms such as team self-correction to manage, and quickly learn from, errors.

Hunt et al. defined characteristics associated with high-performing teams, including situational awareness, leadership, followership, closed-loop communication, critical language, standardized practice, assertive communication, adaptive behaviors, and workload management. Salas et al. described an adaptive team performance framework that illustrates the relationship between variables, emergent states, and the multiple phases of the team adaptation cycle (Fig. 11.3).

Cultural factors may play a large role in team performance. According to Salas et al., these factors include attitudes (especially as they relate to previous experiences with teams) and motivation. Although it has been suggested that an individual team member’s personality may be counterbalanced by others, Janis suggested that openness and conscientiousness are essential for individuals to succeed in command positions.

Thomas et al. conducted a qualitative assessment of teamwork and suggested that factors that influence the ability to work together could be divided into three categories: provider characteristics (personal attributes, reputation, expertise), workplace factors (staffing, work organization, work environment), and group influences (communication, relationships, and teamwork). These categories can be addressed, at least in part, by working together in teams in a simulated environment and evaluating teamwork and human performance. Lyndon suggested that the application of human performance-based theory has demonstrated that “communication patterns, team function, workload, and coping mechanisms affect both individual and group ability to identify evolving problems and make appropriate management decisions in complex decision-making situations.”

**Team Training**

Patient safety is “predicated on trust, open communication, and effective interdisciplinary teamwork.” It is often the interactions among health care workers that determine whether a specific plan of care is effective or ineffective. However, in the current environment medical students, residents, attending physicians, nursing students, nurses, and midwives rarely learn or train to work as teams. It has recently been suggested that interprofessional education is a vital part of medical education, and students should not be permitted to exempt themselves from it.

The Liaison Committee on Medical Education (LCME), which is jointly composed of members of the American Medical Association and the Association of American

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remind us not only of the need for appropriate training as hypoventilation following general anesthesia. These reports two were related to neuraxial block and two were caused by venous sinus thrombosis) illustrate the need for multidisciplinary care of postneuraxial blockade complications.

Medical Colleges, has affirmed the importance of teaching communications skills and teamwork. For example, LCME standard ED19 states that “there must be specific instruction in communication skills as they relate to professional responsibilities, including communication with patients, families, colleagues, and other health professionals.” Teamwork needs to be not only taught but also monitored. Box 11.2 summarizes best practices in team performance measurement for simulation-based training.

<table>
<thead>
<tr>
<th>BOX 11.2 Summary of Best Practices in Team Performance Measurement</th>
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<tbody>
<tr>
<td>• Ground measures in theory:</td>
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<tr>
<td>• Use theory to determine what variables to measure.</td>
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<tr>
<td>• Capture aspects of Input → Process → Output models of team performance.</td>
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<tr>
<td>• Design measures to meet specific learning outcomes.</td>
</tr>
<tr>
<td>• Clearly articulate the purpose of measurement.</td>
</tr>
<tr>
<td>• Design the measurement system to capture information necessary for making decisions about the learning outcomes.</td>
</tr>
<tr>
<td>• Capture competencies.</td>
</tr>
<tr>
<td>• Measure multiple levels of performance.</td>
</tr>
<tr>
<td>• Link measures to scenario events.</td>
</tr>
<tr>
<td>• Focus on observable behaviors.</td>
</tr>
<tr>
<td>• Incorporate multiple measures from different sources.</td>
</tr>
<tr>
<td>• Capture performance processes in addition to outcomes:</td>
</tr>
<tr>
<td>• Obtain information not only about the end result but also about how the team reached that performance outcome.</td>
</tr>
<tr>
<td>• Train observers, and structure observation protocols.</td>
</tr>
<tr>
<td>• Facilitate posttraining debriefing and training remediation.</td>
</tr>
</tbody>
</table>


Medical and nursing education has relied on the treatment of real patients in actual clinical settings. That is now rapidly changing with simulation-based education, which is a means for health care practitioners to learn and practice teamwork principles such as crisis resource management. Many educators now believe that the current availability of medical simulations and the knowledge gained from the science of team training may improve practitioner competency as well as patient outcomes. Obstetricians have identified the importance of preparing for clinical emergencies and have reiterated that conducting emergency drills may reduce or prevent the severity of medical emergencies. In addition, simulation may affect patient safety because it offers opportunities to discover latent conditions and performance gaps that could adversely affect patient care. Simulation may also be useful in identifying and correcting specific institutional barriers, such as delays in transport to the operating room and initiation of emergency cesarean delivery. During *in situ* simulations of obstetric emergencies, Riley et al. identified 965 breaches of defensive barriers (system elements that serve to prevent system errors from causing injury), of which 47.8% were classified as latent conditions (existing conditions that may interact with ongoing activities to precipitate error). The authors suggested that simulation helps providers recognize and remedy both active failures and latent conditions before they combine to cause bad outcomes.

It has been suggested that drills are important on the labor and delivery unit personnel. As previously noted, communication problems are consistently identified as a leading cause of medical error, and these problems can be addressed during team training. The MBRRACE-UK report, a surveillance of maternal deaths in the United Kingdom from 2012 to 2014, reviewed lessons learned to inform maternity care from Confidential Enquiries into Maternal Deaths and Morbidity 2009 to 2014. The report emphasized that “the best multidisciplinary care occurs when different specialists consult together on the same day in the same room and talk with each other and the woman together.” The MBRRACE report evaluated 321 maternal deaths that occurred between 2009 and 2012 and found that there were relatively few deaths related directly to anesthesia, but that the role of the anesthesiologist is now shifted to indirect causes; the anesthesiologist is now a key member of the team. The term “anesthetic deaths” was replaced by “lessons for anesthesia.” Of the deaths mentioned, two were related to neuraxial block and two were caused by hypoventilation following general anesthesia. These reports remind us not only of the need for appropriate training as well as supervision of trainees but also of the need to use simulation-based training for learning and practicing both crisis management and important techniques and procedures that are not frequently encountered in clinical practice. Emergency administration of general anesthesia for the parturient is such an event. In addition, the two cases of death related to neuraxial blockade (subdural hematoma and cerebral venous sinus thrombosis) illustrate the need for multidisciplinary care of postneuraxial blockade complications.

**Simulation-Based Training in Obstetrics**

Traditional medical and nursing education has relied on the treatment of real patients in actual clinical settings. That is now rapidly changing with simulation-based education, which is a means for health care practitioners to learn and practice teamwork principles such as crisis resource management. Many educators now believe that the current availability of medical simulations and the knowledge gained from the science of team training may improve practitioner competency as well as patient outcomes. Obstetricians have identified the importance of preparing for clinical emergencies and have reiterated that conducting emergency drills may reduce or prevent the severity of medical emergencies. In addition, simulation may affect patient safety because it offers opportunities to discover latent conditions and performance gaps that could adversely affect patient care. Simulation may also be useful in identifying and correcting specific institutional barriers, such as delays in transport to the operating room and initiation of emergency cesarean delivery. During simulations of obstetric emergencies, Riley et al. identified 965 breaches of defensive barriers (system elements that serve to prevent system errors from causing injury), of which 47.8% were classified as latent conditions (existing conditions that may interact with ongoing activities to precipitate error). The authors suggested that simulation helps providers recognize and remedy both active failures and latent conditions before they combine to cause bad outcomes.

It has been suggested that drills are important on the labor and delivery unit, especially as related to inefficient verbal communication during obstetric emergencies. Sorensen stated that “mock emergency training is an opportunity for staff to learn to identify risk factors and prepare for interventions in the event of an obstetric emergency.” Gardner and Raemer suggested that simulation is a practical and safe approach to the acquisition and maintenance of task-oriented and behavioral skills across the spectrum of medical specialties. In the realm of obstetric anesthesia practice, investigators have demonstrated that simulation may be a useful tool for assessment of performance in a simulated emergency situation (e.g., failed intubation in an obstetric patient) when combined with practice and formal teaching.

Training in perinatal emergencies with high-fidelity simulation improved the speed with which anesthesia providers responded to these emergencies and improved the quality of their care. Lipman et al. demonstrated, in a dramatic fashion, the use of simulation-based assessment to evaluate optimal performance of cardiopulmonary resuscitation during simulated maternal cardiac arrest. The authors
observed numerous deficiencies in the performance of key advanced cardiac life support (ACLS) tasks that are critical to resuscitation of a pregnant woman. These tasks included the ability to correctly deliver chest compressions (56% correct), ensure left uterine displacement (44% correct), switch chest compressors every 2 minutes (33% correct), and perform appropriate defibrillation (6% correct). Box 11.3 outlines the advantages of simulation for research, training, and performance assessment.

When an adverse perinatal outcome associated with an error occurs, it is likely that more than one individual will be involved and blamed. Similarly, when an unexpected injury occurs to a mother or infant, several providers are typically involved, and often there is a problem with the “system” that allowed the error to occur. Obstetricians, anesthesia providers, pediatricians, labor nurses, midwives, and operating room staff all work together as part of this system. Therefore, optimal simulation exercises involve all these key players and evaluate not only their behaviors and communication skills but also problems within the system in which they work. Simulation of reality-based scenarios in the labor and delivery unit or operating room allows anesthesia providers, obstetricians, midwives, nurses, and pediatricians to practice their roles and communication skills. Hunt et al. suggested that medical teams require practiced interaction and communication to be effective and efficient.

Simulation of perinatal events range from high-fidelity human simulators (typically located off-site) to low-technology simulations and drills that can be performed on the labor and delivery unit. Simulated scenarios (guided by desired learning outcomes) can be designed to train nurses, obstetric and anesthesia resident physicians, and midwives individually or as teams. However, simulation should not be reserved for individuals in training; attending physicians may also benefit from participation. Simulated events commonly include maternal hemorrhage (antepartum as well as postpartum), failed intubation, failed neuraxial blockade, seizures, cardiac arrest, anaphylaxis, umbilical cord prolapse, and shoulder dystocia. Thompson et al. reported that drills to practice management of eclampsia were successful in the identification of deficiencies in team preparation. They concluded the following:

Repetition of drills in our unit has improved the care of simulated patients with eclampsia. In subsequent drills patient management has followed evidence-based practice, with an enhanced level of efficiency. Staff are summoned faster, the resuscitation process is better organized, and drugs are prepared and administered more quickly. Similarly, Crofts and colleagues reported significant improvement in participants’ knowledge after multidisciplinary obstetric training.

Maslovitz et al. used simulation to identify five recurrent obstetric management mistakes:

1. Delay in transporting a bleeding patient to the operating room
2. Unfamiliarity with prostaglandin administration to treat uterine atony
3. Poor cardiopulmonary resuscitation techniques
4. Inadequate documentation of shoulder dystocia (important for the legal defense of these cases)
5. Delayed administration of blood products to reverse disseminated intravascular coagulation

The drills advocated for use by labor and delivery staff at the University of Miami Miller School of Medicine/Jackson Memorial Hospital Center for Patient Safety are outlined in Box 11.4.

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**BOX 11.3 Advantages of Simulation for Research, Training, and Performance Assessment**

- There is no risk to patients.
- Many scenarios can be presented, including uncommon but critical situations in which a rapid response is needed.
- Participants can see the results of their decisions and actions; errors can be allowed to occur and reach their conclusion (in real life, a more capable clinician would be obligated to intervene).
- Identical scenarios can be presented to different clinicians or teams.
- The underlying causes of the situation are known.
- With mannequin-based simulators, clinicians can use actual medical equipment, exposing limitations in the human-machine interface.
- With full re-creations of actual clinical environments, complete interpersonal interactions with other clinical staff can be explored, and teamwork, leadership, and communication training can be provided.
- Intensive and intrusive recording of the simulation session is feasible, including audiotaping, videotaping, and even physiologic monitoring of participants. There are no issues of patient confidentiality; the recordings can be preserved for research, performance assessment, or accreditation.


**BOX 11.4 Drills Advocated for Use by Labor and Delivery Staff Undergoing Team Training**

- Profound fetal bradycardia
- Magnesium sulfate overdose
- Shoulder dystocia
- Maternal hemorrhage
- Failed tracheal intubation
- Anaphylaxis
- Amniotic fluid embolism
- Eclampsia/HELLP syndrome

HELLP, hemolysis, elevated liver enzymes, low platelet count. *Used at the University of Miami Miller School of Medicine/Jackson Memorial Hospital Center for Patient Safety.*
Simulation-based training must be implemented appropriately if it is to be effective. Salas et al.\(^6\) suggested the following guidelines for appropriate implementation:
1. Understand the training needs and requirements.
2. Embed instructional features (e.g., performance measurement and feedback) within the simulation.
3. Craft the scenarios based on expected/desired learning outcomes.
4. Create opportunities for assessing and diagnosing individual and/or team performance within the simulation.
6. Focus on cognitive/psychological simulation fidelity.
7. Form a mutual partnership between subject matter experts and learning experts.
8. Ensure the effectiveness of the training program.

Simulation exercises may also affect outcome by teaching improved communication to individuals and teams during transfer of patients’ care from one set of caregivers to another (i.e., so-called handovers or handoffs). A survey from the United Kingdom found that handovers were rarely documented in writing and that 4% of units reported critical incidents after inadequate handovers in the preceding 12-month period.\(^25\) This interesting study describes the use of the SBAR technique (situation-background-assessment-recommendation) and the potential to practice signoffs and handovers during practice drills. Although this study is approximately 10 years old, there are few data to suggest that much has changed in the past decade as relates to handoffs.

**Team Training in Obstetrics**

As noted, teamwork is critical for the delivery of quality health care, especially in complex environments such as the labor and delivery unit. Awad et al.\(^3\) reported that medical team training improved communication in the operating room as assessed by team members using a validated scoring system. Why initiate team training on the obstetric service? McQuaid-Hanson and Pian-Smith reported that effective communication is key for coordinated delivery of care and for “fostering a culture of community and safety in the workplace.”\(^77\) An Australian study evaluating the impact of introducing practical obstetric multiprofessional training (PROMPT) into maternity units found that there were significant improvements to 1-minute Apgar scores, cord lactate levels, and average baby’s length of stay after the training.\(^78\) The following case report by Sachs\(^79\) illustrates the need for teamwork:

*A healthy 38-year-old woman needed emergency cesarean delivery after a failed instrumental delivery. At surgery, the uterus was found to be ruptured and the infant was stillborn. After unsuccessful attempts to repair the uterus, the patient underwent a cesarean hysterectomy and required massive transfusion and a 3-week hospital stay.*

Was anyone at fault? According to the root cause analysis, lack of teamwork on many levels played a significant role in this patient’s hospital course. In particular, Sachs\(^79\) reported that communication was poor and there was a lack of mutual performance cross-monitoring, inadequate conflict resolution, suboptimal situational awareness, and work overload.

**Crew Resource Management**

Team drills have been successfully used in many areas of medicine, including anesthesia, intensive care, and emergency medicine, often using lessons learned from crew resource management (CRM) training. They are now becoming more popular on labor and delivery units and have been advocated by the ACOG.\(^61\)

The human error aspects of many air crashes are thought to include failure of communication, decision making, and leadership.\(^80\) In the airline industry, CRM began as a program to train pilots to reduce error by making better use of human resources in the cockpit.\(^81\) CRM training has led to safety and performance improvements beyond those produced by improvements in equipment and technology.\(^6,86\) Airlines use many tools to reduce human error; CRM training is just one. Other tools include use of checklists, standardized maintenance, ability to report errors without disciplinary repercussions, and simulator training. Not all of these, however, are easily adaptable to medicine. That said, Helmreich\(^82\) identified several lessons learned from CRM that can be applied to the practice of medicine. He believes that errors in competence require technical training and that errors in decisions or communication require team training. Furthermore, Helmreich\(^82\) suggested that adaptation of CRM to health care similarly requires the development of nonpunitive methods to collect information on errors so that this information can be used to evaluate team performance. It has been suggested that elements of CRM that are useful in medical settings include briefings, conflict resolution procedures, and performance reviews. There is evidence that operator attitudes about teamwork, hierarchy, errors, and stress affect performance among aviators working together in teams.\(^83\) Evidence also suggests that these attitudes are relevant in the health care environment.\(^84\)

Salas et al.\(^85\) suggested that CRM training will not be effective or achieve its desired outcomes in health care without the following 12 prerequisites:
1. The physicians must be “on board.”
2. The concept of teamwork becomes part of the “DNA” of the health care professional.
3. CRM is supplemented by other teamwork-focused training strategies.
4. The design, development, and delivery of CRM are scientifically rooted.
5. CRM training is designed systematically.
6. CRM is part of a learning organization’s strategy to promote patient safety and quality care.
7. Teamwork is rewarded and reinforced by the health care provider.
8. CRM training is evaluated at multiple levels for specific outcomes.
9. CRM is supported by simulation or practice-based approaches.
10. The health care provider is “ready” to receive training.
11. The patient is part of the team.
12. The team training is recurrent.

Some health care providers will benefit more than others from CRM training and learning. For example, Alder et al. noted that physicians with poorer performance at the beginning of CRM training showed greater improvements after training.86

A discussion of optimal communication on the labor and delivery unit must also address improved communication between the anesthesia provider and patient. A recent article87 co-written by a patient who had a traumatic experience resulting from a failed neuraxial block for cesarean delivery should be required reading for all anesthesia providers. A follow up editorial by Cyna and Simmons88 suggests that the patient’s story of her harrowing experience “represents one of the most important publications in an anesthesia journal in recent years.” The patient’s painfully described perspective reaffirms the importance of listening to our patients.

**Disruptive Behavior**

Whereas miscommunication is common on the labor and delivery unit, some events are not caused by difficulties with communication but rather result from disruptive behavior by a team member. It is estimated that 3% to 5% of physicians exhibit disruptive behavior.89 The labor and delivery suite and obstetric operating room are complex and rapidly evolving environments where stress and anxiety abound. Studies have reported that as many as four “tense” communications occur between team members during each operating room procedure, with some of them evolving into outright conflict.90 Disruptive and intimidating behavior is not only seen in the “main operating room”; it occurs frequently on labor and delivery units and is observed in personnel of diverse disciplines, including obstetricians, anesthesia providers, family practitioners, pediatricians, nurses, midwives, and administrators. In one survey, disruptive behavior was reported on more than 60% of labor and delivery units from personnel who responded to a questionnaire.91

Disruptive behavior includes angry outbursts, rudeness or verbal attacks, physical threats, intimidation, noncompliance with policies, and sexual harassment. Disruptive behavior contributes to the nursing shortage, near misses, and adverse occurrences. This behavior does not always involve physicians. Termed horizontal hostility, it occurs among nurses as well, and includes rudeness, verbal abuse, humiliating statements, unjustly critical statements, withholding information, and gossip.92 Disruptive behavior is not always effectively managed by the organization91 and should be considered when using simulation to improve team behaviors.

**Options for Simulator Training in Obstetrics**

Both high-technology and low-technology approaches to simulation have been used for training labor and delivery staff. Simulation centers often use high-fidelity simulation with interactive computerized mannequins in a realistic working environment (e.g., labor room or operating room) that includes a full complement of working equipment and staff.93 The mannequin is quite realistic; it has a pulse, heart and breath sounds, ventilatory movements, and electrocardiographic and pulse oximetry tracings. All vital signs can be adjusted via computer control, as can the ability to intubate or ventilate.93

Not all simulation exercises and drills for obstetrics need to be performed in high-fidelity simulators. Pratt and colleagues94 maintained that classroom training is a better option, particularly given the high cost95 and resources necessary for high-fidelity simulation. The inability to arrange for staff of several disciplines to be absent from the labor and delivery unit simultaneously often precludes the use of high-technology simulation and may make on-site exercises more practical.

On the other hand, Gaba96 countered that high-fidelity simulation need not be cost-prohibitive and that it provides the required “real-life” experience necessary for training in the management of complex real-life scenarios. Morgan et al.97 reported an obstetric simulation model that included the participation of real surgeons (rather than actors playing the role of surgeons). This was the first published report of high-fidelity simulation of obstetric team performance with anesthesia providers, nurses, and obstetricians involved in the hands-on management of obstetric crises. To assess the success of simulation-based training, outcomes must be measured. Onwochei et al.98 reported that the most reliable tools to assess team effectiveness in obstetric emergencies were the clinical teamwork scale, the global assessment of team performance, and the global rating scale of performance. As highlighted by Vasco Ramirez in his review of the future training of anesthesiologists in obstetric care,99 we will need to move to a competency-based curriculum in which high-fidelity simulation should be considered in the acute care setting for the training of nontechnical skills such as teamwork.

Several options are available for teaching teamwork and crisis intervention in obstetrics. Multidisciplinary Obstetric Simulated Emergency Scenarios (MOSES) was developed by the St. Bartholomew Hospital Group in the United Kingdom100 and involves participation of obstetricians, anesthesia providers, and midwives in team training using a high-fidelity simulator. MedTeams was developed by the U.S. Armed Forces and Dynamics Research Corporation. Originally employed in emergency departments,101,102 it has now been used for labor and delivery teams.103 The course consists of “train the trainer” sessions that focus on seven dimensions that are essential to teamwork. Behaviorally anchored rating scales (BARS) are used to assess various key behaviors. A recent paper by Weller et al.103 described the implementation of their multidisciplinary operating room simulation (MORSim), which was shown to have lasting effects consistent with more effective teamwork and communication. Other evidence-based programs have emerged. TeamSTEPPS was developed by the U.S. Department of Defense and Agency for Healthcare Research and Quality (AHRQ) as a team training and implementation toolkit.104 The program is adaptable, medically relevant, and based on findings from the science of team performance, and it is applicable to training on labor and delivery units.
An adapted TeamSTEPPS for obstetrics has been evaluated and was shown to be partially effective. Participants perceived the training as useful, and results of behavioral observation suggested that decision accuracy significantly improved.\textsuperscript{105}

What is the evidence that team training and simulation reduce errors and improve outcomes? Morey et al.\textsuperscript{80} reported that the MedTeams program reduced errors in the emergency department, and they observed a statistically significant improvement in team behaviors. The clinical error rate in providers who received MedTeams training decreased from 31\% to 4\%. Grunebaum et al.\textsuperscript{106} implemented team training as well as other comprehensive patient safety changes to their obstetric practice and found that their interventions resulted in decreased compensation payments and sentinel events. Clark et al.\textsuperscript{107} described implementation of a comprehensive redesign of patient safety processes that was associated with improved patient outcomes and a decline in litigation rates. They stressed that “every member of the obstetric team should be not only empowered but also required to intervene and halt any process that is deemed to be dangerous.” This behavior can be achieved as part of a team training program. Phipps et al.\textsuperscript{108} evaluated the implementation of a labor and delivery unit team training program that included CRM augmented with high-fidelity medical simulation at Women and Infants Hospital of Rhode Island. They demonstrated a correlation of clinically and statistically significant reductions in the obstetric adverse outcomes index (AOI) following implementation of their program.

Accumulating evidence suggests that medical simulation and team training, while not always perfect, improve teamwork and communication and allow recognition of potential areas of weakness in obstetric care. We, as well as others,\textsuperscript{33, 47, 109} believe that these are viable strategies to mitigate medical errors. We also agree with Pearlman et al.,\textsuperscript{110} who eloquently stated that “we have the moral imperative as a specialty to fully engage in the identification of our own best practices, to advance safety research in obstetrics and gynecology, and to implement broadly those practices which are best.”

In addition to better communication, team training, and simulation-based education, several other changes to our cultures and systems need to occur to significantly improve patient safety on the labor and delivery unit. These changes include the following:

- Learning from our mistakes
- Changing the culture on the labor and delivery floor to one of a “just culture”\textsuperscript{111}
- Having buy-in and support from hospital leadership to implement the necessary changes
- Improving the care of the high-risk parturient so that care is coordinated and every member of the team is more prepared and working as a team member\textsuperscript{112}
- Improving and automating the collection of quality metrics, collecting appropriate data on outcomes, and sharing the data with practitioners on a regular basis\textsuperscript{113}
- Developing and implementing systems to reduce drug administration errors\textsuperscript{114, 115}
- Tearing down the silos so that we learn from each other’s mistakes and improvement processes, whether from department to department, hospital to hospital, or country to country\textsuperscript{115}

The challenge for the next decade will be to implement these changes and test their effectiveness in improving patient safety.

## KEY POINTS

- Medical errors harm tens of thousands of patients each year.
- To err is human; therefore, systems should be developed to prevent or “catch” errors before the patient is harmed.
- Poor communication among health care workers is the primary cause of sentinel events.
- Teamwork is essential to safe care of the pregnant patient, and team training may improve patient safety.
- Medical team training works; it saves lives.
- Simulation-based training is an educational tool that improves communication and may improve responses to obstetric emergencies.
- Adaptation of some elements of aviation crew resource management training may improve team performance in health care.
- Disruptive behavior interferes with safe patient care and is observed in physicians as well as other members of the health care team.

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Spinal, Epidural, and Caudal Anesthesia: Anatomy, Physiology, and Technique

Naveen Nathan, MD, Cynthia A. Wong, MD

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Teaching Neuraxial Anesthesia Procedures, 265

The art and science of neuraxial anesthesia requires a thorough appreciation of neuroanatomy and the physiologic effects imposed by medications commonly administered via the spinal and/or epidural route. Successful administration and management of neuraxial anesthesia requires well-developed technical skills moderated by sound clinical judgment. The focus of this chapter is to characterize the anatomic and technical considerations for neuraxial anesthesia. The reader is referred to Chapter 23 for a corresponding discussion of the physiologic and untoward effects of neuraxial analgesia in laboring women and to Chapter 26 for a discussion of neuraxial anesthesia for cesarean delivery.

ANATOMY

Neuraxial Anatomy

The Spinal Cord, Spinal Canal, and Meninges

The cephalad aspect of the spinal cord is continuous with the brainstem through the foramen magnum. The spinal cord terminates as the conus medullaris, most often at the level of the lower border of the first lumbar vertebral body. The conus medullaris is attached to the coccyx by means of a neural-fibrous band called the filum terminale, which is surrounded by the nerves of the lower lumbar and sacral roots, known as the cauda equina. Within the bony vertebral column are three membranes: the pia mater, the arachnoid mater, and the dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord. The arachnoid mater is a delicate, nonvascular membrane closely adherent to the third and outermost layer, the dura. The subarachnoid space, located between the pia mater and arachnoid mater, contains (1) cerebrospinal fluid (CSF); (2) spinal nerves; (3) a trabecular network between the two membranes; (4) blood vessels that supply the spinal cord; and (5) lateral extensions of the pia mater—the dentate ligaments. The dura mater is a membrane, composed of collagen, that encapsulates the spinal cord, the deeper meningeal layers, and the subarachnoid space. This layer forms a connective tissue sheath along the...
The epidural space is located external to the sac of the dura mater and contains loose connective tissue, adipose tissue, lymphatics, spinal nerve roots, and the internal vertebral venous plexus (Batson’s plexus) (Fig. 12.2). This space is bound by the posterior longitudinal ligament anteriorly, the ligamentum flavum and the periosteum of the lamina posteriorly, the pedicles of the vertebrae, and the intervertebral foramina with their contents laterally. The subarachnoid space continues to the second sacral vertebral level.

The Epidural Space

The spinal cord usually ends at the lower border of the first lumbar vertebral body. The subarachnoid space continues to the second sacral vertebral level.

vertical axis of the central nervous system (CNS) that is contiguous with connective tissue covering the lateral extension of spinal nerve roots as they exit the intervertebral foramina. The interface between the dural and arachnoid layers has been described as a potential space capable of expansion subsequent to mechanical trauma. Unintentional injection of local anesthetic into this subdural space may explain some cases of failed spinal anesthesia. It may also explain the rare, slow-to-develop cases of high spinal anesthesia after the unintentional subdural injection of larger volumes of local anesthetic intended for epidural administration. Although the spinal cord ends at the level of the bodies of L1 and L2 in most people, the subarachnoid space and cauda equina continue to the S2 level (Fig. 12.1).

The Vertebral Column and Ligaments

The ligamentum flavum lies posterior to the epidural space (Fig. 12.3). The lamina, the spinous processes of the vertebral...
distance from the skin to the epidural space was 5.4 cm (1.1). The distance was greater among black parturients and white parturients than among Asian parturients at any given body mass index (Table 12.1).

**TABLE 12.1 Estimated Distance From the Skin to the Epidural Space**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>White (n = 708)</th>
<th>Asian/British Asian (n = 24)</th>
<th>Black/British Black (n = 127)</th>
<th>Chinese (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>4.7</td>
<td>4.5</td>
<td>5.0</td>
<td>4.4</td>
</tr>
<tr>
<td>25</td>
<td>5.3</td>
<td>5.1</td>
<td>5.7</td>
<td>4.7</td>
</tr>
<tr>
<td>30</td>
<td>6.0</td>
<td>6.2</td>
<td>6.5</td>
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<td>35</td>
<td>6.6</td>
<td>6.8</td>
<td>7.2</td>
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</tr>
<tr>
<td>40</td>
<td>7.2</td>
<td>8.0</td>
<td>7.2</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Estimated distance from skin to lumbar epidural space after adjusting for body mass index (BMI) and race.


bodies, and the interspinous ligaments lie posterior to the ligamentum flavum. Posterior to these structures are the supraspinous ligament (which extends from the external occipital protuberance to the coccyx), subcutaneous tissue, and skin. Historically, some have described the ligamentum flavum as a single ligament. In actuality, however, it is composed of two curvilinear ligaments that join in the middle and form an acute angle with a ventral opening. Much like the epidural space, the ligamentum flavum is not uniform from skull to sacrum; indeed, it is not uniform even within a single intervertebral space. The thickness of the ligamentum flavum varies with vertebral level, body mass index, race, and age, as does the distance between the skin and epidural space. In a mixed-race adult population, the mean (SD) distance from the skin to the epidural space was 5.4 cm (1.1). The distance was greater among black parturients and white parturients than among Asian parturients at any given body mass index (Table 12.1).

**Anatomic Changes of Pregnancy**

The normal anatomic changes of pregnancy affect neuraxial anesthesia techniques. Uterine enlargement and vena caval compression result in engorgement of the epidural veins. Unintentional intravascular epidural catheter cannulation and injection of local anesthetic are more common in pregnant patients than in nonpregnant patients. In addition, the vertebral foraminal veins, which are contiguous with the epidural veins, are enlarged and obstruct one of the pathways for
anesthetic egress from the epidural space during administration of epidural anesthesia. The enlarged epidural veins also may displace CSF from the thoracolumbar region of the subarachnoid space, as does the greater intra-abdominal pressure of pregnancy; this displacement partly explains the lowered dose requirement for spinal anesthesia in pregnant women. Subarachnoid dose requirements are also affected by the lower specific gravity of CSF in pregnant patients than in nonpregnant patients.

The hormonal changes of pregnancy affect the perivertebral ligamentous structures, including the ligamentum flavum. The ligamentum flavum may feel less dense and “softer” in pregnant women than in nonpregnant patients; thus, sensing the passage of the epidural needle through the ligamentum flavum may be more difficult. It may also be more difficult for a pregnant woman to achieve flexion of the lumbar spine. Progressive accentuation of lumbar lordosis alters the relationship of surface anatomy to the vertebral column. At least three changes may occur. First, a pregnant woman’s pelvis rotates on the long axis of the spinal column; thus, the line joining the iliac crests (Tuffier’s line) assumes a more cephalad relationship to the vertebral column (e.g., this imaginary line might cross the vertebral column at the L3 to L4 interspace rather than the L4 to L5 interspace). Second, there is less space between adjacent lumbar spinous processes during pregnancy. It may be more difficult to use the midline approach to identify the epidural or subarachnoid space in pregnant women. (Thus the often-heard comment, “She has a narrow interspace.”) Third, magnetic resonance imaging has shown that the apex of the lumbar lordosis is shifted caudad during pregnancy, and the typical thoracic kyphosis in women is reduced during pregnancy. These changes may influence the spread of subarachnoid anesthetic solutions in supine patients, leading to a higher sensory level in the pregnant patient (Fig. 12.4). Finally, labor pain makes it more difficult for some women to assume and maintain an ideal position while the anesthesia provider performs neuraxial anesthesia.

**PHYSIOLOGY**

**Obstetric Pain Pathways**

Pain during the first stage of labor results primarily from changes in the lower uterine segment and cervix. Pain is transmitted by visceral afferent nerve fibers that accompany the sympathetic nerves and enter the spinal cord at the T10 to L1 segments. During the late first stage and second stage of labor, pain results from distention of the pelvic floor, vagina, and perineum. Pelvic pain is transmitted by somatic nerve fibers, which enter the spinal cord at the S2 to S4 segments (Fig. 12.5).

During cesarean delivery, additional nociceptive pathways are involved in the transmission of pain, and a T6 to T4 sensory level of anesthesia is required to provide adequate anesthesia, depending on the modality used to test the sensory level (i.e., touch, pinprick, or temperature). Most cesarean deliveries are performed with a horizontal (e.g., Pfannenstiel) skin incision, which involves the infraumbilical T11 to T12 dermatomes. During surgery, stretching of the skin may involve dermatomes two to four levels higher. Intraperitoneal manipulation and dissection involve poorly localized visceral

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**Fig. 12.4** The curvature of the spinal column in the nonpregnant (top) and pregnant patient (bottom). The apex of the lumbar lordosis (blue circle) moves caudad in pregnancy. Additionally, the thoracic kyphosis is reduced and shifts cephalad. (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

**Fig. 12.5** Pain pathways during labor and delivery. The afferent pain pathways from the cervix and uterus involve nerves that accompany sympathetic fibers and enter the neuraxis at T10 to L1. The pain pathways for the pelvic floor and perineum include the pudendal nerve fibers, which enter the neuraxis at S2 to S4.
pain pathways. Visceral pain may be transmitted by pathways as high as the celiac plexus. Additional somatic pain impulses may occur because of diaphragmatic stimulation because the intercostal nerves innervate a portion of the peripheral diaphragm.

**Physiology of Neural Blockade**

Hormonal changes, anatomic changes, and decreases in CSF specific gravity likely are responsible for the lower local anesthetic dose requirements for spinal anesthesia in pregnant women. Local anesthetics produce conduction blockade primarily by blocking sodium channels in nerve membranes, thereby preventing the propagation of neural impulses. Differential blockade is manifested as differences in the extent of cephalad blockade of temperature discrimination and vasomotor tone, sensory loss to pinprick, sensory loss to touch, and motor function. Temperature discrimination and vasomotor tone are blocked to the greatest extent (i.e., most cephalad level) and motor function to the least extent. During spinal anesthesia, local anesthetics act directly on neural tissue in the subarachnoid space. Regression of anesthesia can be explained by the vascular uptake of local anesthetic from the subarachnoid space and spinal cord. Epidural anesthesia has a much smaller zone of differential motor–sensory–sympathetic blockade; this difference suggests that the mechanism of epidural anesthesia must involve more than simple diffusion across the dura. Nerve fiber size (i.e., smaller fibers are blocked more readily than larger fibers), myelination, and the length of nerve fiber exposed to local anesthetic are determinants of susceptibility to local anesthetic blockade and affect the extent of the differential zone of motor and sensory blockade. With spinal anesthesia, the local anesthetic concentration required to block sufficient sodium channels to affect motor, sensory, and sympathetic function is less than that needed for the better-protected nerves found in the epidural space; thus, a wider band of differential blockade occurs during spinal anesthesia than during epidural anesthesia.

The understanding of the mechanisms of spinal and epidural anesthesia likely remains oversimplified. Nonetheless, it seems clear that spinal anesthesia results primarily from the effects of local anesthetic on the spinal cord, whereas epidural anesthesia results from the effects of local anesthetic on nerve tissue within both the epidural and subarachnoid spaces.

**TECHNIQUE**

**Preprocedural Considerations**

**Monitoring**

The American Society of Anesthesiologists (ASA) has published guidelines for administration of neuraxial anesthesia in obstetric patients (see Appendix A). Among other things, these recommendations address (1) the required presence of qualified anesthesia and obstetric care providers; (2) immediate availability of resuscitation medication and equipment (Box 12.1); (3) mandatory preprocedural intravenous access; and (4) employment and documentation of maternal vital signs and fetal heart rate (FHR) monitoring.

During the initiation of neuraxial analgesia for labor, all patients are monitored with an automatic blood pressure cuff and a pulse oximeter to facilitate continuous assessment of the maternal heart rate and oxygenation. Maternal blood pressure is measured every 1 to 2 minutes after the administration of the test and therapeutic doses of local anesthetic for approximately 15 to 20 minutes, or until the mother is hemodynamically stable. Subsequently (during maintenance of neuraxial analgesia), maternal blood pressure is measured every 15 to 30 minutes or more frequently if hypotension ensues. Continuous pulse oximetry during maintenance analgesia is used in selected patients (e.g., patients with obstructive sleep apnea or cardiovascular disease). Rarely, invasive hemodynamic monitoring is necessary. The sensory level of analgesia and the intensity of motor block are assessed after the administration of the test and therapeutic doses of local anesthetic and at regular intervals thereafter.

The ASA Task Force on Obstetric Anesthesia has made the following recommendation regarding FHR monitoring during performance of neuraxial anesthesia procedures:

*Fetal heart rate patterns should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor. Continuous electronic recording of the fetal heart rate patterns may not be necessary in every clinical setting and may not be possible during placement of a neuraxial catheter.*

The anesthesia provider cannot predict when hypotension will occur during the administration of neuraxial anesthesia. In addition, there is concern that intrathecal administration
of an opioid is associated with a higher incidence of nonreassuring FHR patterns than other neuraxial techniques (see Chapter 23). Thus, we believe that continuous electronic FHR monitoring should be performed both during (if possible) and after the administration of neuraxial analgesia in all laboring women. In some cases, the mother’s position or maternal obesity precludes the use of an external Doppler device to monitor the FHR. In such cases (especially when there is concern regarding fetal well-being), it is helpful for the obstetric provider to place a fetal scalp electrode to monitor the FHR.

**Informed Consent, Patient-Procedure Verification, and Partner’s Presence**

Before initiation of neuraxial anesthesia, a preprocedural verification process (i.e., “time-out”) is performed in compliance with national patient safety recommendations. The participation of the patient, the anesthesia care provider, and the obstetric provider to place a fetal scalp electrode to monitor the FHR.

Contraindications to needle or catheter placement include patient refusal or inability to cooperate, ongoing bleeding, hypoxemia when placed in the lateral decubitus position, infection at the site of intended intervention or untreated systemic blood-borne illness, and increased intracranial pressure predisposing to cerebral herniation. Contraindications to injecting local anesthetics via the epidural or spinal route include severe hypovolemia and allergy to local anesthetics. It is axiomatic that patient refusal represents an absolute contraindication to an elective procedure. A thorough preoperative assessment of current fetal well-being, maternal volume status, intrapartum systemic opioid use, antibiotic administration for ongoing chorioamnionitis or other infectious process, and a brief reiteration of known maternal disease states, including allergies, will readily identify most of the major concerns that would render neuraxial anesthesia potentially hazardous. The anesthesia provider should weigh the risks and benefits of neuraxial anesthesia for each patient.

Informed consent should include a frank discussion about anesthetic procedures and risks (see Chapter 32). Surveys of postpartum women have demonstrated that most parturients want to know the possible complications of epidural analgesia, even those that are rare. It is best to relay this information before the onset of labor (e.g., during antenatal classes), or early in the intrapartum period, although doing so is not always feasible. Some anesthesia providers fear that distressed, desperate, or sedated parturients may not understand the discussion of anesthetic procedures. A 2017 survey study of 206 postpartum women found no difference in recall of risks (discussed early after admission for labor) between women with and without pain at the time of the consent discussion. The preanesthetic evaluation allows the physician to communicate a sense of concern and to demonstrate a commitment to the patient’s care. Most laboring women understand the need for informed consent, and they appreciate the opportunity to participate in decisions about their care. Adequacy of consent can be demonstrated not only by documentation of information provided to the patient but also by the lack of patient objection to a procedure and the cooperation provided by the patient during the procedure.

Management of the pregnant patient occurs in a unique clinical care environment in which the presence of the patient’s spouse or family members must be addressed. Most often, the dictates of local institutions will establish whether a partner’s presence during neuraxial labor analgesia is acceptable. Intuition may suggest that a partner who remains present during the conduct of neuraxial analgesia may help alleviate the patient’s ongoing anxiety regarding the procedure. Conversely, the partner may be so apprehensive or disruptive that the partner’s presence becomes counterproductive to the care of the patient. Orbach-Zinger et al. randomized 84 nulliparous women to either presence or absence of their partner during labor epidural catheter placement. Interestingly, patient and partner anxiety, as measured by a validated anxiety questionnaire, were less when partners were absent during the procedure.

**Patient Positioning**

Pregnant women have an exaggerated lumbar lordosis, and it is more difficult for them to flex the lumbar spine. However, most pregnant women are young, and youth usually allows sufficient flexibility to facilitate the insertion of a needle into the epidural or subarachnoid space. Whether the block is initiated in the lateral or sitting position is a matter of provider and patient preference. Notable advantages of the lateral position include (1) orthostatic hypotension is less likely and (2) the position often facilitates continuous FHR monitoring during placement of the epidural catheter. Vincent and Chestnut performed a study in which they observed that neither the sitting nor the lateral position was consistently superior with regard to patient comfort. The sitting position is likely associated with a higher incidence of orthostatic hypotension and syncope. However, the sitting position is preferred—and may be required—in obese parturients, in whom identification of the midline is usually significantly easier in the sitting position. Further, morbidly obese women may experience hypoxemia when placed in the lateral decubitus position.

One study demonstrated a greater reduction in maternal cardiac output with maximal lumbar flexion in the lateral decubitus position than in the sitting position during identification of the epidural space in laboring women. The researchers speculated that maximal lumbar flexion in the lateral decubitus position results in concealed aortocaval compression. They recommended that “the tight fetal curl position be avoided,” especially when the patient assumes the lateral decubitus position.

Aortocaval compression must be avoided to the extent possible (see Chapter 2). If maternal hydration is inadequate and if aortocaval compression is not avoided, the onset of
anesthesia-induced sympathetic blockade may result in decreased venous return, cardiac output, and uteroplacental perfusion.

Maternal position during placement of the epidural catheter does not seem to affect the incidence of unintentional dural puncture. However, adoption of the lateral recumbent head-down position for epidural catheter placement may reduce the incidence of unintentional epidural venous puncture.24

When spinal or epidural anesthesia is performed with the patient in a lateral position, the patient’s back should lie at, and parallel to, the edge of the bed, for at least two reasons. First, the edge is the firmest section of the mattress. If the patient lies away from the edge of the bed, the patient’s weight will depress the mattress, and the anesthesia provider must work in a “downhill” direction. Second, this position allows anesthesia providers to keep their elbows flexed, facilitating control of fine hand and wrist muscle movements. The plane of the entire back should be perpendicular to the mattress. When asked to flex the lower back, patients typically roll the top shoulder forward, an action that rotates the spine (which is undesirable) but does not flex the lower back.

Similarly, patients positioned sitting should have their feet supported by a stool with the backs of their knees against the edge of the bed, a maneuver that helps position the patient’s back closer to the anesthesia provider. The shoulders should be relaxed symmetrically over the hips and buttocks. Beds in obstetric units often break at the foot, and the split in the mattress encourages the patient’s seat to slope downhill if she is straddling the mattress split; this position will cause spine rotation and may make the procedure more difficult.

When spinal anesthesia is performed, the patient’s posture relative to the baricity of the anesthetic solution should be considered, because it influences the extent and latency of blockade, and the incidence of hypotension. The incidence, timing, and extent of hypotension in the period immediately after initiation of the block depend on the type of block (e.g., spinal, epidural, or combined spinal-epidural [CSE]), drug characteristics (e.g., baricity, concentration, dose), patient position during the procedure, and patient position in the period following the procedure. For example, when spinal anesthesia is initiated with a hyperbaric solution for instrumental vaginal delivery, it often makes sense for the patient to be sitting to ensure the rapid onset of sacral anesthesia. Conversely, spinal anesthesia for cervical cerclage can be initiated with the patient in the steep lateral Trendelenburg position with a hypobaric anesthetic solution.

Posture has less influence on the spread of epidural anesthesia.25–27 During epidural anesthesia, a unilateral block more likely results from the malposition of the catheter (or perhaps an anatomic barrier within the epidural space) than from patient position, particularly after a bolus injection. Norris and Dewan25 observed that gravity did not augment the spread of anesthesia in patients receiving epidural anesthesia for cesarean delivery, and they concluded that posture does not need to be manipulated to ensure adequate bilateral epidural anesthesia. In at least two studies, it was noted that the use of the sitting position is not necessary for the development of good sacral anesthesia when large volumes of epidural local anesthetic are given for cesarean delivery.25,27 However, Reid and Thorburn26 observed that use of the sitting position appeared to delay the spread of anesthesia to the midthoracic dermatomes. In comparison with the bolus administration of epidural local anesthetic, the extent of blockade may be more gravity dependent when the anesthetic is administered as a continuous infusion over a prolonged period.

Some anesthesiologists contend that maternal position after epidural catheter placement affects the efficacy of epidural analgesia, although this is a matter of some dispute. Beilin et al.28 observed that the placement of the laboring woman in the supine position with a 30-degree leftward tilt was associated with better epidural analgesia than maintenance of the left lateral decubitus position. In contrast, Preston et al.29 observed no difference in analgesia and a significantly higher incidence of fetal bradycardia with the supine wedged position than with the full lateral position.

Caudal anesthesia is used infrequently in modern obstetric anesthesia practice. However, there remain some circumstances in which a caudal technique is useful and/or advantageous. It is a good choice for the second stage of labor in selected patients in whom the lumbar epidural approach is hazardous or contraindicated (e.g., fusion or instrumentation of the lumbar spine). In most cases, caudal anesthesia can be successfully performed with the patient in a lateral decubitus position.

Aseptic Technique

In the past decade, there has been growing appreciation for the importance of sterile technique and the gravity of infectious complications related to neuraxial anesthesia.30–33 The incidence of epidural abscess and spinal meningitis is generally so low that many of the available recommendations are based on evidence from other domains of infection control (e.g., surgical wound site and central venous catheter-related infection).34–36 Nonetheless, death and devastating neurologic compromise resulting from neuraxial infection can occur.

Infection of the epidural space tends to result in the formation of an abscess, most commonly formed by *Staphylococcus aureus* found in the epidermis of either the patient or the anesthesia provider. In contrast, meningitis associated with neuraxial procedures is most commonly caused by *Streptococcus viridans*. Viridans species of streptococcus may reside in the oronasopharyngeal tract of providers or patients or in the patient’s vagina. Potential routes of infection include the (1) epidural catheter track, (2) bloodstream, (3) equipment, and (4) injectate contamination. A more in-depth discussion of neuraxial infection is found in Chapter 31.

Guidelines describing aseptic technique for regional and neuraxial anesthetic procedures have been published by professional anesthesiology organizations and the U.S. Centers for Disease Control and Prevention (CDC).34,35,37 The following recommendations deserve emphasis:

1. Given that the oropharyngeal and skin flora of the anesthesia provider are implicated in many cases of neuraxial
infection, the provider should don a surgical face mask and hat before initiation of spinal/epidural anesthesia. Microbial sampling in laminar-flow operating theaters has shown a 22-fold increase in bacterial counts when a face mask and hat are not worn.28

2. Washing hands with an alcohol-based antiseptic solution is recommended because this has been shown to be superior to antimicrobial soap. Jewelry (e.g., rings, watches) should be removed before and sterile gloves worn after hand cleansing.

3. The patient’s skin should be decontaminated, preferably with a chlorhexidine-in-alcohol solution.36 Evidence suggests that chlorhexidine has superior bacteriocidal and bacteriostatic efficacy compared with povidone-iodine.39 If chlorhexidine is not available, then povidone-iodine with alcohol, rather than povidone-iodine alone, is preferred.39 Of importance, the anesthesia provider is encouraged to exercise patience in allowing the antiseptic to dry, because a major mechanism of antisepsis is the desiccating action of alcohol.

**Equipment and Placement of Needle/Catheter**

**Spinal Anesthesia**

The first equipment decision involves determining whether to perform a single-shot or continuous technique. Traditionally, a large-bore epidural needle and catheter are used for continuous spinal anesthesia, because the U.S. Food and Drug Administration rescinded approval for the use of small-bore microcatheters in 1992. Therefore, the risk for post–dural puncture headache is significant. Continuous spinal analgesia or anesthesia using an “epidural” catheter sited in the subarachnoid space is useful after unintentional dural puncture with an epidural needle. In the morbidly obese patient, it may be easier to manipulate and advance a rigid epidural needle than a more flexible spinal needle; thus, the technique is useful for establishing continuous analgesia or anesthesia in this patient population, particularly when the need for anesthesia is urgent. A 23-gauge, FDA-approved, spinal catheter is now available in the United States. The catheter is inserted using a “catheter-over-needle” technique. Initial observational study found that this catheter may have clinical utility; however, further study is required to characterize ease of use and complications. Several commercial spinal catheters are available in Europe, but at the current time, a single-shot technique is preferred for spinal anesthesia for most obstetric patients.

The primary equipment choice for spinal anesthesia concerns the type and size of the spinal needle. Cutting-bevel needles (e.g., Quincke) are rarely used in contemporary obstetric anesthesia practice because of the unacceptably high incidence of post–dural puncture headache associated with their use. Instead, noncutting (“pencil-point”) needles (e.g., Whitacre, Sprotte, Gertie Marx) are used almost exclusively (Fig. 12.6). Pencil-point needles cause more trauma to the dura than occurs with cutting-bevel needles. This likely results in a more intense inflammatory response. Presumably, the inflammation results in more rapid closure of the dural defect.41

![Fig. 12.6 Spinal needle assortment often used in parturients. The Sprotte and Whitacre needles have cone-shaped bevels, whereas the Quincke and Atraucan needles have a cutting bevel. (Other sizes are available in some of these needle designs.)](image)

Needle size must also be determined. Larger needles offer a greater fidelity of tactile feedback as the anesthesia provider traverses tissue planes of variable impedance when performing spinal anesthesia. Furthermore, larger needles are more likely to withstand the high resistance encountered when contacting bone without bending or shearing. In general, the “ease-of-use” advantages associated with larger needles must be balanced against a lower incidence of post–dural puncture headache with smaller needles. Most anesthesia providers use 25- or 27-gauge noncutting needles for routine spinal anesthesia in obstetric patients. However, anesthesia providers should make individual decisions based on their own skills, the practice setting, and the patient. The urgency of the procedure may also influence the choice of needle size. For example, a 27-gauge needle might be chosen for spinal anesthesia for an elective procedure, and a larger (e.g., 22-gauge) needle might be chosen when the subarachnoid space must be entered quickly because of severe fetal compromise.

With a small-gauge needle (i.e., 24-gauge or smaller), use of an introducer needle is preferable. The introducer needle engages the interspinous ligament and more accurately guides the trajectory of the smaller spinal needle than is possible with use of a small-gauge spinal needle alone. The introducer needle also aids with skin puncture; it is often difficult to puncture the skin with noncutting needles.

Either the midline or the paramedian approach can be used to enter the subarachnoid space. The midline approach requires the patient to reduce her lumbar lordosis to allow access to the subarachnoid space between adjacent spinous processes (usually L3 to L4, sometimes L4 to L5 or L2 to L3). The interspinous space may be identified with one (usually the thumb or index finger) or two fingers (usually the index and middle fingers) of the anesthesia provider’s nondominant hand. The single finger “slides” along the skin in the midline from cephalad to caudad until it “settles” into an interspinous space. The two fingers identify the interspinous space by palpating the caudad border of the more cephalad spine. The
through the needle. If neither occurs, the needle and introducer are withdrawn and the process is repeated.

Although with time and practice the tactile feedback produced by advancing a needle through tissues of variable resistance will become utterly familiar to the anesthesia provider, the novice may be unsure of the anatomic position of the needle tip, especially if unexpected resistance (i.e., contact with bone) or an unexpected and premature “pop sensation” is encountered during needle advancement. A stepwise problem-solving approach is reasonable. First, the anesthesia provider should reconfirm that (1) the patient has normal anatomy (i.e., not scoliotic); (2) she is acceptably positioned without rotation of the spine (often recognized by asymmetric shoulder position); and (3) the chosen point of needle insertion is the true midline plane. If these assertions are true, and the needle tip encounters bone, it is highly likely that the osseous structure is either the inferior or superior spinous process. One of two maneuvers may overcome this barrier. After slight withdrawal of the needle, simple angulation in a cephalad or caudad direction may redirect the needle trajectory sufficiently to achieve access to the central neuraxial canal. One must appreciate the “toughness” of the interspinous ligament. Even a 17-gauge epidural needle can be bent if the angle is changed without some prior retraction of the needle. Furthermore, if a spinal needle/introducer complex is used, care must be exercised that angulation of the spinal needle does not occur without first withdrawing it into the lumen of the introducer. Thereafter, the entire spinal needle/introducer complex is angulated before the spinal needle is re-advanced. Angulation of the spinal needle without first withdrawing it into the introducer creates a fulcrum at the junction of the introducer tip where the spinal needle emerges and can potentially damage or even shear the delicate spinal needle (Fig. 12.8).

Alternatively, the needle may be withdrawn fully into subcutaneous tissue and either raised or lowered (cephalad or caudad) while still maintaining an angulation that is parallel to the original trajectory. Which approach is more effective may depend on the reason for the initial bone contact. If the patient has very narrow interspaces, then careful raising or lowering of the needle while maintaining a trajectory parallel to the floor may be appropriate. However, if the patient is overly flexed forward, it is possible that her lumbar spinous processes are projecting in a slightly upward angulation (relative to the perpendicular transverse plane). This may require that the needle be re-angled accordingly. If bone is still encountered despite all these considerations, it is likely that the needle tip is in fact not in the midline plane and is contacting the vertebral lamina. This may occur if the initial skin puncture is not in the midline, the needle tip deviates from the midline as it is advanced, or the patient’s spine is rotated (either from poor positioning or scoliosis). Clues that the needle tip is not midline include (1) the patient complaining of lateralizing pain, (2) lack of CSF flow despite appropriate needle depth, and (3) the perception of “soft” or “mushy” tissue (paraspinous tissue) during needle advancement rather than the more “rigid” ligamentous tissue, or even a false “pop” as the needle tip exits the interspinous ligament laterally into

Fig. 12.7 The midline approach for spinal needle insertion requires accurate identification of a lumbar interspinous space. The palpating fingers identify the midline by rolling in a medial-to-lateral direction (Fig. 12.7).

Next, the anesthesia provider injects local anesthetic intradermally and subcutaneously. The introducer needle is inserted into the substance of the interspinous ligament. It is helpful if the introducer needle is embedded in the interspinous ligament; therefore, obese patients may require a longer introducer needle. The introducer needle should lie in the sagittal midline plane. It is then grasped and steadied with the fingers of the nondominant hand while the dominant hand holds the spinal needle like a dart. The fifth finger may be used as a tripod against the patient’s back to prevent patient movement from causing unintentional needle insertion to a level deeper than intended, and to “brake” the needle. As the needle passes through the ligamentum flavum and the dura, characteristic changes in resistance are noted. A “pop” is often perceived as the needle tip traverses the ligamentum flavum. A subsequent and more pronounced pop is perceived as the needle tip exits the dura-arachnoid. The stylet is removed, and CSF should appear in the needle hub. If CSF does not appear, the stylet is replaced, and the needle is advanced a few millimeters and again checked for CSF flow. This process continues until either bone is encountered or CSF returns
paraspinous tissue. Much like the progressive modifications described earlier for correct alignment in the superoinferior plane, so too can these approaches be employed for redirecting in the lateral plane (Fig. 12.9). The novice is advised to make systematic changes in a stepwise fashion, rather than indiscriminately changing needle direction without first considering the anatomic problem.

Once CSF is freely dripping from the needle hub, the dorsum of the provider’s nondominant hand steadies the spinal needle against the patient’s back while the syringe with local anesthetic is attached to the needle. After aspirating to ensure the free flow of CSF, the anesthesia provider injects the local anesthetic at a rate of approximately 0.2 mL per second. After completion of the injection, some anesthesia providers again aspirate approximately 0.2 mL of CSF and reinject it into the subarachnoid space. This last step reconfirms the needle location and clears the needle of the remaining local anesthetic. The patient is then repositioned as appropriate.

For most patients, the midline approach is faster and less painful than the paramedian approach. The midline approach is also easier to teach than the paramedian approach, because it requires mental projection of the anatomy in only two planes, whereas the paramedian approach requires appreciation of a third plane and estimation of the depth of the subarachnoid space from the skin (Fig. 12.10).

Nevertheless, the paramedian approach is a useful technique that allows for the successful identification of the subarachnoid or epidural space in difficult cases. The paramedian approach does not require that the patient fully reduce her lumbar lordosis. This approach exploits the larger target that is available when the needle is inserted slightly off the midline.

A common error that is made with the paramedian approach is the insertion of the needle too far off the midline; the vertebral lamina then becomes a barrier to needle insertion. With the paramedian approach, the palpating fingers should again identify the caudal edge of the more cephalad spinous process. A skin wheal is raised 1 cm lateral and 1 cm caudad to this point; a longer needle is then used to infiltrate the deeper tissues in a cephalomedial plane. This step contrasts to the midline approach, in which the local anesthetic is not injected beyond the subcutaneous tissue. The spinal introducer is then inserted 10 to 15 degrees off the sagittal plane in a cephalomedial direction, and the spinal needle is advanced through the introducer needle toward the subarachnoid space. Another common error is to use an excessive cephalad angle with initial needle insertion. When the needle is inserted correctly and contacts bone, it is redirected slightly cephalad. If bone is again encountered, but at a deeper level, the slight stepwise increase in cephalad angulation is continued, and the needle is “walked” up and off the lamina. As with the midline approach, the characteristic feel of the ligamentum flavum and dura can be appreciated. The aim of the paramedian approach is to puncture the dura in the midline, even though the needle is inserted off the midline. Use of the paramedian approach requires insertion of a greater length of needle. Once CSF is obtained, the block is performed as it is with the midline approach.

During the performance of any nerve block technique, needle advancement should stop if the patient complains of pain. If pain is the result of inadequate soft tissue anesthesia, additional local anesthetic should be injected. Pain or paresthesias may also result from needle contact with central nerves or the spinal cord. Patient perception of paresthesias during the initiation of spinal anesthesia may indicate that the needle tip is in the subarachnoid space. The anesthesia provider should remove the stylet and check for CSF. If the paresthesia has resolved, the local anesthetic may be injected. If the paresthesia persists, however, the needle should be withdrawn and repositioned. In any case, the anesthesia provider should never inject the local anesthetic if the patient is complaining of paresthesias or lancinating pain, either of which may signal injection into a nerve or the spinal cord.
Fig. 12.9 Troubleshooting contact with bony structures during needle placement. The gray needle represents the initial needle trajectory; the blue needle represents the adjusted needle trajectory. (A) Assuming correct midline needle placement, the needle can be retracted slightly and angulated to overcome a spinous process. (B) Alternatively, the needle may be “lifted” after slight retraction while keeping the original trajectory constant. (C) Assuming the needle is deviating from the midline plane and contacting lamina, an action similar to that in A may be executed. (D) Alternatively, a stepwise lateral shift similar in concept to that shown in B may correctly achieve midline alignment. (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

Fig. 12.10 Vertebral anatomy of midline and paramedian approaches for spinal and epidural anesthesia. The midline approach requires anatomic projection in only two planes: sagittal and horizontal. The paramedian approach also requires consideration of the oblique plane. However, the paramedian approach requires less patient cooperation in reducing lumbar lordosis to allow for successful needle insertion. The paramedian needle insertion site is made 1 cm lateral and 1 cm caudad to the caudad edge of the more cephalad spinous process. The paramedian needle is inserted 10 to 15 degrees off the sagittal plane (inset).
However, the confidence intervals of the relative risks were wide, and the authors concluded that the evidence was of low quality. In a retrospective, single-institution study of loss of resistance to air versus saline by Segal and Arendt, no significant differences in block success were found in 929 patients. The authors intentionally chose a retrospective approach to the question; they stated that because “it is impossible to mask the anesthesiologist to the medium used for loss-of-resistance, [they] hypothesized that randomized controlled trials might overestimate the difference between air and saline by forcing the operator to use a less-preferred technique in half of the subjects.” Thus, we recommend that anesthesia providers use the technique with which they are most comfortable. We use saline with a small bubble of air.

Regardless of the technique used, success depends on correct placement of the needle tip. The needle should be advanced sufficiently into the interspinous ligament before the syringe is attached or before the hanging drop of solution is placed into the needle hub. This approach has at least three advantages. First, it encourages the anesthesia provider to use proprioception while directing and advancing the needle. Second, it shortens the time required for successful identification of the epidural space. Third, it lowers the likelihood of a false-positive loss of resistance. Undoubtedly, this false-positive identification of the epidural space is responsible for

**Epidural Anesthesia**

Special equipment for epidural analgesia or anesthesia includes an epidural needle, an epidural catheter (for a continuous technique), and a loss-of-resistance syringe (for the loss-of-resistance technique to identify the epidural space). Single-shot epidural anesthesia is rarely used in obstetric practice, because the major advantage of epidural over spinal anesthesia is the ability to provide continuous anesthesia or analgesia without puncturing the dura with a large needle. An epidural needle with a lateral opening (e.g., Hustead, Tuohy) is most commonly used because it allows a catheter to be threaded through its orifice (Fig. 12.11).

Two methods are used to identify the epidural space during needle advancement: (1) hanging drop method and (2) loss-of-resistance method. Most anesthesia providers use the loss-of-resistance method (Fig. 12.12).

The traditional loss-of-resistance syringe is a finely ground glass syringe with a Luer-lock connector. Plastic syringes are also available, and the choice is generally a matter of the anesthesia provider’s preference. The syringe is filled with 2 to 4 mL of saline, air, or saline with a small (0.25 to 0.5 mL) air bubble. There is some controversy regarding the use of air versus saline for detecting the point of loss of resistance. Saline causes some syringe plungers to stick and may be confused with CSF during initiation of CSE anesthesia. Conversely, injection of air into the epidural space may contribute to patchy anesthesia, and unintentional pneumocephalus may increase the risk for headache.

Results of investigations comparing air to saline for loss of resistance are conflicting. A 2014 meta-analysis that included 852 patients (most were obstetric patients) found no differences in inability to locate the epidural space, unintentional intravascular or intrathecal catheter placement, block failure, unblocked segments, or pain between the two mediums.45

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**Fig. 12.11** Epidural needles often used in parturients. Each needle is shown in an open-bevel view and an oblique orientation. The 18-gauge Hustead and 17-gauge Tuohy needles have lateral-facing openings, which direct epidural catheters to enter the epidural space more easily than if a single-shot Crawford needle design is used. (Other sizes and needle designs are available for obstetric epidural anesthesia.)

**Fig. 12.12** Loss-of-resistance technique for identifying the epidural space. The needle is first inserted into the interspinous ligament or ligamentum flavum, and a syringe containing an air bubble in saline is attached to the hub. After compression of the air bubble by pressure on the syringe-plunger, the needle is carefully advanced until a loss of resistance to syringe-plunger pressure is noted as the needle enters the epidural space.
many cases of unsuccessful epidural anesthesia; it is even possible to insert a catheter between the interspinous ligament and the ligamentum flavum.

During advancement of the needle-syringe assembly, the needle should be moved toward the epidural space by the provider’s nondominant hand while the thumb of the dominant hand applies constant pressure on the syringe plunger, thereby compressing the small air bubble. Alternatively, the intermittent, oscillating technique is employed when using the loss-of-resistance to air technique. When the needle enters the epidural space, the pressure applied to the syringe plunger causes the saline solution or air to flow easily into the epidural space (see Fig. 12.12).

In most obstetric cases, the anesthesia provider inserts a catheter and uses an intermittent bolus or continuous infusion technique to maintain analgesia. Most practitioners insert the catheter before injecting local anesthetic to allow for the slow, incremental injection of local anesthetic/opioid solution and the more controlled development of epidural anesthesia. If the principal reason for using an epidural technique is the provision of continuous analgesia, it seems most practical to insert the catheter before injecting the therapeutic dose of local anesthetic so that correct catheter placement can be verified promptly.

Several types of single-use, disposable epidural catheters are available.\textsuperscript{47} Catheters are made from plastic materials and differ as to the degree of “stiffness.” Wire-embedded catheters are more flexible and are associated with a lower incidence of paresthesias and intravascular placement during catheter insertion.\textsuperscript{24,48,49} The single-orifice catheter has one opening at its tip, whereas the multi-orifice catheter has a closed “bullet” tip with three lateral orifices between 0.5 and 1.8 cm from the tip (Fig. 12.13).

The proposed advantage of single-orifice, open-end catheters is that the injection of drugs is restricted to a single anatomic site. In theory, this arrangement should facilitate the detection of intravenous or subarachnoid placement of the catheter. Likewise, a theoretical disadvantage of multi-orifice, closed-end catheters is that local anesthetic may be injected into more than one anatomic site (e.g., both the epidural and subarachnoid spaces). A catheter initially placed in the epidural space can migrate into a vein or the subdural or subarachnoid space. Fortunately, this does not seem to be a common clinical problem. Regardless of the choice of catheter, aspiration should be performed before each dose of local anesthetic is injected.

An advantage of the multi-orifice catheter over the single-orifice catheter is the consistent ability to aspirate fluid (either blood or CSF) when the catheter is in a vessel or the subarachnoid space.\textsuperscript{50} Early studies suggested that multi-orifice catheters may lead to more even distribution of local anesthetic and a lower incidence of “patchy” or unilateral anesthesia when the anesthetic is injected as a bolus.\textsuperscript{51} However, during an infusion into the epidural space, the solution exits...
only the most proximal hole, and multi-orifice catheters thus behave like single-orifice catheters. A randomized trial comparing single- and multi-orifice wire-reinforced catheters found no differences in block success or complications.

If the catheter is placed before the test and therapeutic doses of local anesthetic, it may be helpful to inject 5 to 10 mL of saline before threading the catheter, because this may reduce the incidence of epidural vein cannulation, particularly when using stiffer epidural catheters. Rolbin et al. noted that there was no advantage to the injection of 3 mL of fluid into the epidural space before insertion of the epidural catheter.

Six to eight centimeters of catheter are threaded into the epidural space before the epidural needle is removed. The catheter may then be pulled back until it is at the desired distance at the skin. Occasionally, the anesthesia provider will have difficulty advancing the catheter past the tip of the epidural needle. This difficulty may indicate that the epidural needle tip is not in the epidural space. However, if the provider is convinced that the needle is correctly placed, several maneuvers may facilitate catheter advancement. Often, having the patient take a deep breath allows catheter advancement. Saline may be injected through the epidural needle if this has not been done. Although some providers rotate the epidural needle in an attempt to successfully advance the catheter, we do not recommend this maneuver, because it may increase the risk for dural puncture. Instead, the epidural needle should be withdrawn 0.5 to 1 cm and again advanced into the epidural space.

Many techniques are available for securing the epidural catheter at the skin entry site. A transparent, sterile adhesive dressing applied over the catheter after application of skin adhesive generally works well, and the periphery of the dressing can be reinforced with tape. The position of the epidural catheter may change significantly with patient movement from the sitting-flexed to the sitting-upright or lateral decubitus position. D’Angelo et al. found that the risk for catheter dislodgement was higher when catheters were inserted 2 cm into the epidural space, but the risk for unilateral blockade was greater when catheters were inserted 6 to 8 cm. Therefore, if the catheter is to be used for a short period (e.g., during cesarean delivery), it should be left 2 to 4 cm into the epidural space. In contrast, if the catheter will be used for many hours (e.g., during labor), it should be left 4 to 6 cm into the space. To minimize catheter movement at the skin, the patient should be positioned sitting upright or in the lateral position before the catheter is secured, especially if the patient is obese.

The potential for the contamination of local anesthetic solutions has prompted the use of micropore filters during the administration of continuous epidural analgesia for labor. There is no evidence that filters decrease the rate of infection or of injection of undesirable foreign substances. Additionally, filters may reduce the reliability of aspiration and absorb local anesthetic solution, unless they are primed. We believe that micropore filters have little use in clinical obstetric anesthesia practice.

**Box 12.2 Advantages of Combined Spinal-Epidural Anesthetic Technique**

**Compared With Epidural Anesthesia**

- Lower maternal, fetal, and neonatal plasma concentrations of anesthetic agents
- More rapid onset of analgesia and anesthesia
- Denser sensory blockade
- Complete early labor analgesia with opioid alone (no local anesthetic necessary)
- Lower failure rate

**Compared With Spinal Anesthesia**

- Technically easier in obese individuals: The epidural needle acts as an introducer for the spinal needle (it is easier to advance a rigid epidural needle)
- Ability to titrate anesthetic dose: Start with low subarachnoid dose, and titrate to effect using epidural injection
- Results in less hypotension
- Ability to extend the extent of neuroblockade: Spinal anesthesia for forceps delivery may be extended to epidural anesthesia for cesarean delivery after failed forceps delivery
- Continuous technique: ability to extend duration of anesthesia

**Combined Spinal-Epidural Anesthesia**

CSE anesthesia combines the advantages and mitigates the disadvantages of single-shot spinal anesthesia and continuous epidural anesthesia (Box 12.2). Anesthesia is initiated with a subarachnoid injection of opioid and local anesthetic and maintained via an epidural catheter. It is useful for both cesarean delivery anesthesia and labor analgesia. For cesarean delivery, the injection of the smaller dose of local anesthetic required for spinal (compared with epidural) anesthesia is inherently safer with regard to the possibility of unintentional intravascular injection. Additionally, the anesthesia provider can inject a local anesthetic dose that is lower than the ED95 (effective dose in 95% of cases) without fear of inadequate anesthesia. These lower doses result in less maternal hypotension. If surgical anesthesia is inadequate, the block can be “rescued” with epidural administration of local anesthetic. For example, a randomized trial comparing 7, 8, and 9 mg of intrathecal bupivacaine administered as part of a CSE technique for cesarean delivery produced equivalent latencies to T4 sensory block with lower rates of maternal hypotension in the lowest-dose group. The shorter duration of action seen in the low-dose (7 mg) group was easily addressed through the administration of local anesthetic via the indwelling epidural catheter. Compared with conventional epidural anesthesia for cesarean delivery, CSE anesthesia is associated with a more rapid onset of surgical anesthesia, less intraoperative pain and discomfort (because of a more dense block), better muscle relaxation, and less shivering and vomiting.

The CSE technique is associated with a faster onset of labor analgesia, achieved with the subarachnoid injection of an opioid alone or an opioid combined with a small dose of local anesthetic. Studies differ as to whether CSE analgesia
is associated with greater maternal satisfaction and fewer requests for supplemental analgesia. Goodman et al.\textsuperscript{64} randomized 100 parous women in early labor to receive either CSE or conventional epidural analgesia. There were no differences in requests for supplemental analgesia, although pain scores were lower in the CSE group within the first 30 minutes. A single-institution randomized trial in 800 women found better first-stage analgesia and fewer requirements for treatment of breakthrough pain in women randomized to receive CSE compared with epidural analgesia.\textsuperscript{65} A 2012 systematic review comparing CSE and epidural labor analgesia concluded that onset was faster with the CSE technique, but that there was no evidence for differences in maternal satisfaction, mode of delivery, ability to ambulate, or incidence of hypotension between the two techniques.\textsuperscript{66} Several studies have found a lower incidence of failed epidural analgesia after the initiation of analgesia with a CSE technique.\textsuperscript{67–69} Presumably, verification of the correct placement of the spinal needle by visualization of CSF increases the likelihood that the tip of the epidural needle is correctly placed in the epidural space.

A purported disadvantage of the CSE technique is that correct placement of the epidural catheter in the epidural space cannot be verified until spinal analgesia or anesthesia wanes. Therefore, it has been suggested that if a functioning epidural catheter is important to the safe care of the mother and fetus (e.g., in the setting of a suspected difficult airway or non reassuring fetal status), an epidural rather than CSE technique is indicated. However, in a retrospective study that included 2395 neuraxial labor analgesia procedures, the CSE technique did not result in delayed recognition of epidural catheter failure, and the overall catheter failure rate was lower when the catheter was cited as part of CSE analgesia.\textsuperscript{69} Therefore, fear of unrecognized catheter malposition should not be a consideration when choosing a neuraxial technique.

There are several techniques for initiation of CSE anesthesia/analgesia.\textsuperscript{70} The most popular is the needle-through-needle technique, in which the epidural needle is sited in the epidural space and serves as an introducer for the spinal needle. The spinal needle passes through the epidural needle to puncture the dura. After injection of the subarachnoid dose, the spinal needle is removed, and the epidural catheter is threaded through the epidural needle. An alternative technique uses two skin punctures and two different interspaces: the spinal needle and epidural needle and catheter are introduced sequentially in two different interspaces.

The needle-through-needle technique requires a long spinal needle. Typically, a small (25- or 27-gauge) noncutting needle is used to minimize the risk for post–dural puncture headache. The tip of the spinal needle must protrude 12 to 17 mm beyond the tip of the epidural needle when the two needles are fully engaged (Fig. 12.14). Failure to puncture the dura and visualize CSF occurred in 25% of patients when the spinal needle protruded 9 mm, compared with no patients when the needle protruded 17 mm.\textsuperscript{71} A 127-mm spinal needle is commonly used with a standard 9-cm epidural needle. However, because of differences in hub configurations among needles, the two hubs may not “mesh,” and spinal needle protrusion may vary with specific needle combinations. Alternatively, manufacturers sell CSE needle “kits,” in which the spinal needle is designed for a specific epidural needle. An additional small syringe (1 to 3 mL) is required for the spinal dose.

CSE anesthesia is initiated much like epidural anesthesia. The epidural needle is sited in the epidural space (Fig. 12.15). Before inserting the epidural catheter, the spinal needle is introduced through the epidural needle with the anesthesia provider’s dominant hand, while the nondominant hand is anchored against the patient’s back to serve as a brake for further advancement of the spinal needle. The provider usually perceives the tip of the spinal needle passing the tip of the epidural needle as a slight increase in resistance. Spinal needle advancement should stop immediately after the anesthesia provider perceives the dural puncture “pop.” Dural puncture is verified by visualization of CSF after removal of the spinal needle stylet. The provider’s nondominant hand is anchored on the patient’s back, and the spinal and epidural needle hubs are grasped together between the thumb and index finger of this hand. The dominant hand attaches the spinal syringe. If aspiration of CSF is attempted, care must be taken not to dislodge the spinal needle. After injection of the spinal dose and removal of the spinal syringe and needle as a unit, the epidural catheter is threaded in the usual fashion.
Dural-Puncture Epidural Anesthesia

Dural puncture epidural (DPE) analgesia is another neuraxial technique that aims to exploit the advantages of CSE anesthesia while minimizing its shortcomings. It is procedurally identical to CSE anesthesia except for the omission of drug injection into the subarachnoid space. Presumably, excluding direct subarachnoid administration of opioid and local anesthetic at the time of dural puncture avoids the precipitous development of adverse effects such as hypotension and fetal bradycardia. However, the presence of the dural puncture allows for augmented transdural migration of epidurally injected drugs into the subarachnoid space. Hypothetically, this facilitates more reliable block of sacral dermatomes, which may be inadequately anesthetized with conventional
epidural anesthesia. The subarachnoid translocation of drugs may also act to compensate for an epidural catheter that would otherwise provide asymmetric block, leading to breakthrough pain and the requirement for manual top-up bolus injections of local anesthetic.

Results of two early trials comparing traditional epidural to DPE analgesia were inconsistent. Thomas et al., using a 27-gauge spinal needle, found no differences in analgesia outcomes, including catheter manipulation and replacement rate, inadequate analgesia, unilateral block, sacral sparing, and the incidence of breakthrough pain. In contrast, Cappeello et al., using a 25-gauge spinal needle, found improved sacral analgesia, lower pain scores at 20 minutes, and a lower incidence of unilateral block in women randomized to receive DPE compared with epidural analgesia. A third trial compared epidural, CSE, and DPE analgesia. Onset of analgesia (the primary outcome) was faster in the CSE group than in the epidural and DPE groups, but there was no difference between the epidural and DPE techniques. Compared with the traditional epidural technique, women randomized to receive DPE analgesia had a greater incidence of bilateral sacral block at 10 minutes and a lower incidence of asymmetric block at 30 minutes. Compared with CSE analgesia, women in the DPE group had a lower incidence of pruritus and hypotension. The combined incidence of uterine tachysystole and hypertonus was greater in the CSE compared with the epidural and DPE groups. Finally, a fourth trial comparing epidural to DPE analgesia found no difference in adequate analgesia at 10 minutes (defined by a visual analog scale score less than 10 mm), but those in the DPE group had a shorter time to adequate analgesia (median time 8 minutes versus 10 minutes). There were no differences in complication rates, including maternal hypotension, nausea, and pruritus. Further investigations will likely define the role of the DPE technique in the routine management of labor pain.

**Caudal Anesthesia**

Equipment for caudal anesthesia is similar to that used for lumbar epidural techniques, except that a needle with a lateral-faced opening is not needed. A blunt-tipped needle is satisfactory even when a catheter is used, because the angle of needle insertion allows insertion of the catheter. Successful administration of caudal anesthesia requires the accurate identification of the sacral hiatus. The sacrococcygeal ligament (an extension of the ligamentum flavum) overlies the sacral hiatus between the sacral cornua. Identification of the posterior superior iliac spines facilitates the identification of the sacral cornua; the location of the sacral hiatus is approximated by using the line between them as one side of an equilateral triangle (Fig. 12.17). Alternatively, ultrasonography can assist in the identification of the sacral hiatus. Once the sacral hiatus is identified, the palpating fingers are placed on the cornua, the skin is anesthetized, and the caudal needle is inserted with the hub at an angle approximately 45 degrees from the skin. A decrease in resistance is noted when the needle enters the caudal canal. The needle is advanced until it contacts bone (the dorsal aspect of the ventral plate of the sacrum). Next, the needle is withdrawn slightly and redirected so that the angle of insertion relative to the skin surface is decreased. In pregnant women, the final angle is approximately 15 degrees from a plane parallel to the sacrum.

Accurate placement of the caudal needle is verified primarily from the “feel” of the needle passing through the sacrococcygeal ligament. An additional maneuver may help providers with less experience to verify correct needle placement: Once the needle is believed to be within the caudal canal, 5 mL of saline is rapidly injected through the needle while the anesthesia provider’s other hand is placed over the dorsum of the sacrum. If the needle is placed correctly, no mass or pressure wave is detected over the midline of the sacrum. Conversely, if the needle is malpositioned (often posterior to the caudal canal), a fluid mass or pressure wave is felt by the palpating hand.

The needle should be advanced only 1 to 2 cm into the caudal canal. Dural puncture or unintentional intravascular cannulation is more likely to occur with deeper insertion. A test dose similar to that used during administration of lumbar epidural anesthesia should be administered.

**Ultrasonographic Guidance**

The past two decades have witnessed an enormous increase in the use of ultrasound-guided regional anesthesia. Unlike the use of ultrasonography for vascular access and peripheral nerve block techniques, ultrasonography for neuraxial techniques is not used in real time. Most often, ultrasonography is a preprocedural tool used to aid the operator in the assessment of

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**Fig. 12.16 Reasons for failure of the combined spinal-epidural technique. (A) The spinal needle tents the dura but does not puncture it. (B) The spinal needle does not reach the dura. (C) The spinal needle passes to the side of the dural sac. (Redrawn with permission from Riley ET, Hamilton CL, Ratner EF, Cohen SE. A comparison of the 24-gauge Sprotte and Gertie Marx spinal needles for combined spinal-epidural analgesia during labor. Anesthesiology. 2002;97:574.)**
fellows. Following training, low-risk women with easily palpable spinous processes requesting neuraxial labor analgesia were randomized to the use of preprocedural ultrasonography versus a traditional landmark technique; the trainee used the allocated technique to perform the procedure. There were no differences in epidural procedure time and number of attempted interspaces and needle passes between the two techniques. Total procedure time was longer in the ultrasonography group. An explanation for these findings is that expert ultrasonography skills are necessary to realize the advantages of the technique as an adjunct to neuraxial procedures. Another explanation is that ultrasonography offers no advantages in low-risk patients. Indeed, in a randomized controlled trial of CSE procedures for cesarean delivery performed by a single experienced anesthesiologist and ultrasonographer in women with palpable spinous processes, there were no differences in the first needle-pass success rate, number of needle passes, or patient satisfaction when women were randomized to an ultrasound-guided technique versus a traditional technique. Thus, at the present time, an experienced anesthesiologist managing an uncomplicated pregnant patient is unlikely to benefit from the use of preprocedural ultrasonographic imaging.

needle insertion site, needle angle, and estimated depth of the epidural space. A 2016 meta-analysis of randomized controlled trials and cohort studies comparing the traditional landmark technique to preprocedural ultrasonography as an adjunct to neuraxial procedures concluded that use of ultrasonography (1) results in more accurate identification of a given lumbar interspace, (2) allows accurate prediction of the depth of needle insertion to the epidural or intrathecal space, and (3) reduces technical difficulty (fewer attempts and needle redirections necessary for a successful procedure). Evidence has not yet accumulated that preprocedural ultrasonography results in improved success of anesthesia and procedural safety (e.g., lower rate of complications such as unintentional dural puncture), although this would logically be assumed.

In the obstetric population, a host of randomized controlled trials have explored outcomes related to block placement and success comparing the traditional landmark-based technique versus the ultrasound-guided technique. In many of these studies, an experienced ultrasonographer imaged the spine and marked the midline and interspaces on the skin, and a trainee performed the actual neuraxial procedure. In contrast, Arzola et al. provided comprehensive neuraxial ultrasonography training to anesthesiology residents and
There exist, however, unique clinical circumstances in which preprocedural imaging of neuraxial anatomy may be highly beneficial. Such may be the case in patients with morbid obesity; derangements of spinal anatomy resulting from scoliosis, spinal stenosis, or a history of spinal instrumentation; and in patients in whom identification of specific vertebral levels might be warranted (e.g., known preexisting disc herniation or nerve root compression at a specific interspace). For example, Creaney et al. assessed the utility of preprocedural ultrasonography in pregnant patients with impalpable spinous processes presenting for spinal anesthesia for cesarean delivery. The mean body mass index was approximately 40 kg/m². Although there was no difference in the total procedure time between groups, women in the ultrasonography group required fewer needle passes to locate the intrathecal space.

Preprocedural ultrasonography is useful for estimating the distance from the skin to the epidural or intrathecal space. In general, although studies have shown high correlation between the ultrasonographic and actual measurement, ultrasonographic measurements underestimate the true distance from the skin to epidural space. The factors that influence the small disparity between the predicted and actual distance include (1) differences between the angulation of the imaging beam versus the angulation of the needle; (2) differences between the degree of exerted pressure and skin compression of the ultrasonographic probe versus the needle; (3) current lack of fidelity in the ability of ultrasonography to discriminate between ligamentum flavum, epidural space, and dura mater; and (4) dependency of onscreen measurement tools (e.g., digital calipers) on operator skill and consistency. In a general obstetric population, the mean difference between the needle depth and ultrasonographic depth to the epidural space was 0.01 cm (95% confidence interval, −0.67 to 0.69 cm), whereas in a second study by the same investigator group in which subjects were limited to obese parturients, the mean difference was 0.3 cm (95% confidence interval, −0.7 cm to 1.3 cm).

A low-frequency (2- to 5-Hz) curvilinear probe allows visualization of neuraxial structures beneath the skin. Low-frequency waves are preferable owing to the requisite depth of penetration. The curvilinear array allows the capture of lateral structures such as the transverse processes. The ultrasound beam can be used to identify the spinous processes if these are not palpable, the interspinous spaces, and the ligamentous structures. The ligamentum flavum–epidural space–dura mater will appear as a hyperechoic (white) complex, like bone, whereas the less dense subarachnoid space will appear hypoechoic (black).

Imaging is commonly performed in two planes, the longitudinal (sagittal) paramedian plane and the transverse plane. In the longitudinal paramedian plane, the probe is placed vertically over the sacral area, 2 to 3 cm lateral of the midline, and angled medially to focus on the neuraxial canal (Fig. 12.18). The sacrum is visualized as a hyperechoic line. As the probe is moved cephalad, a sawtooth pattern is visualized, corresponding to the laminae of the vertebrae. The gaps between the teeth of the saw are the intervertebral spaces. The ultrasonographer can mark the chosen interspace on the skin as the probe is moved cephalad. Imaging in the transverse plane is used to identify the midline and assess the distance to the epidural space. The probe is positioned horizontally at the appropriate level and moved slightly cephalad and caudal to visualize the cephalad and caudal spinous processes. The midline is marked by centering the shadow cast by the spinous processes in the middle of the ultrasonographic image. The probe is then centered in the interspinous space and manipulated to achieve a clear view of the neuraxial canal structures. The midline of the ultrasonographic probe on both the left and right is marked on the skin, and these points are joined with a horizontal line after

Fig. 12.18 Use of ultrasonography. (A) Paramedian view: A so-called sawtooth pattern may be seen as the lamina and facet joints (FJ) are captured by this view, typically achieved 1 cm lateral to the midline sagittal plane.
Fig. 12.18, cont’d (B) Paramedian view: By angulating the ultrasonographic probe, the ultrasound waves may escape through the interlaminar and transforaminal “windows” and capture the ligamentum flavum–epidural space–dura mater complex (LFED) as well as the posterior surface of the vertebral body (PVB). (C) Transverse spinous process view: A long, dark shadow is cast with little to no discernible anatomy beyond the osseous tip of the spinous process (SP). (D) Transverse interlaminar view: ultrasound waves propagate through the interspinous ligament leading to signals partially reflected by the ligamentum flavum–epidural space–dura mater complex (LFED). The rays that continue to transmit through this complex encounter the posterior wall of the vertebral body (PVB). Articular processes (AP) and transverse processes (TP) can be seen as well. Illustrations by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
removal of the probe. The intersection of this line with the midline mark is the point of needle entry. The distance from the skin to the anterior aspect of the ligamentum flavum–dura mater complex is measured on the frozen image with ultrasonographic machine calipers.

**EPIDURAL TEST DOSE**

Epidural catheter placement may be complicated by blood vessel or dural puncture with the needle or catheter. To prevent possible local anesthetic toxicity and high or total spinal anesthesia, the anesthesia provider must recognize the unintentional intravenous or subarachnoid placement of the needle or catheter. The purpose of the test dose is to allow early recognition of a malpositioned catheter. The ideal test dose must be readily available, safe, and effective. Its use should have a high sensitivity (i.e., low false-negative rate) and a high specificity (i.e., low false-positive rate). The intravascular and intrathecal test doses may be combined (a single injection to test for both intravascular and subarachnoid placement) or administered separately. A negative response to an epidural test dose does not guarantee the correct placement of the epidural catheter in the epidural space, nor does it guarantee that the catheter is not malpositioned in a blood vessel or the subarachnoid space. Rather, it decreases the likelihood that the catheter tip is in a blood vessel or the subarachnoid space.

**Intravascular Test Dose**

Intravascular placement of the epidural catheter may occur in as many as 7% to 8.5% of obstetric patients, although the rate may be lower with wire-embedded catheters. Failure to recognize intravenous placement of the epidural catheter and subsequent intravenous injection of a large dose of local anesthetic may lead to local anesthetic systemic toxicity, with CNS symptoms, seizures, cardiovascular collapse, and death.

The most common intravascular test dose contains epinephrine 15 µg. In normal volunteers, intravenous injection of epinephrine 15 µg (3 mL of a 1:200,000 solution) reliably causes tachycardia. An increase in heart rate of 20 beats per minute (bpm) within 45 seconds was 100% sensitive and specific for intravascular injection in unpremedicated patients. An increase in systolic blood pressure of between 15 and 25 mm Hg was also observed.

Some anesthesiologists have expressed concerns about the use of an epinephrine-containing test dose in laboring women. Intravenous epinephrine may cause a decline in uterine blood flow as a result of alpha-adrenergic receptor–mediated constriction of the uterine arteries (Fig. 12.19). However, this decrease in uterine blood flow is transient and comparable to the decrease that occurs during a uterine contraction. In healthy parturients, any transient effect of epinephrine on uterine blood flow likely represents a less severe insult than local anesthetic systemic toxicity. An epinephrine-containing test dose, however, may not be appropriate in parturients with severe hypertension or uteroplacental insufficiency.

Concern has been expressed that the epinephrine-containing test dose lacks specificity in laboring women. The maternal tachycardic response to intravenous injection of epinephrine cannot always be distinguished from other causes of tachycardia (e.g., pain during a uterine contraction) (Fig. 12.20). Cartwright et al. noted that 12% of laboring women had an increase in heart rate of at least 30 bpm after epidural injection of 3 mL of 0.5% bupivacaine without epinephrine. A study in laboring women compared the intravenous injection of epinephrine (10 to 15 µg) with that of saline; the sensitivity was 100%, the area under the receiver operator characteristic curve was 0.91 to 0.93, and the negative predictive value was 100%. However, the positive predictive value was 55% to 73%. The results suggested that if a positive heart rate response to an epinephrine-containing test dose occurs in 20% of patients, 5% to 9% of epidural catheters would be identified incorrectly as intravascular and removed unnecessarily.

![Fig. 12.19](image-url) The effect of intravenous epinephrine (EPI), lidocaine (LIDO), and lidocaine with epinephrine on uterine artery blood flow velocity (UBFV) in the pregnant guinea pig. The dose of lidocaine was 0.4 mg/kg. Values are presented as mean ± standard error of mean (SEM) percentage of baseline. (From Chestnut DH, Weiner CP, Martin JG, et al. Effect of intravenous epinephrine on uterine artery blood flow velocity in the pregnant guinea pig. *Anesthesiology.* 1986; 65:633–636.)
Unintentional intravenous injection. Colonna-Romano et al. administered intravenous saline, lidocaine 100 mg, or 2-chloroprocaine 100 mg to laboring women. Observers blinded to which substance was administered recorded the presence of CNS symptoms (i.e., dizziness, tinnitus, funny taste) after injection. Lidocaine 100 mg was a reliable marker of intravenous injection when the symptoms of tinnitus and funny taste were considered (sensitivity 100%; specificity 81%). 2-Chloroprocaine was less reliable (sensitivity 81% to 94%; specificity 69% to 81%). In a volunteer study, a dose of 1.5 mg/kg of 2-chloroprocaine was necessary to produce a probability of 90% that the subject would report symptoms of intravenous injection. Administration of fentanyl 100 µg has been described as a test for intravenous injection. Dizziness was the most reliable symptom of intravenous fentanyl injection, with a sensitivity of 92% and a specificity of 92%.

Some situations reduce the reliability of subjective symptoms as a signal of intravenous injection of a drug. Tests that rely on the self-reporting of subjective symptoms require clear communication with the patient and thus are less useful when the anesthesia provider and patient speak different languages. Patient exhaustion and/or prior opioid administration also may affect the reliability of the test.

Lastly, the epidural catheter design and speed of injection may affect the reliability of the epidural test dose. An epinephrine-containing test dose should be injected rapidly; otherwise rapid redistribution and metabolism of the drug decrease the actual dose administered to chronoreceptors. Multi-orifice epidural catheters have three potential sites of exit for injected fluid or air, and the orifices may lie within two different body compartments. If injected too slowly, air

![Fig. 12.20 Heart rate of a laboring patient (maternal heart rate [MHR]), fetal heart rate, and uterine contractions (UC) are shown. This tracing was obtained with the use of a fetal heart rate monitor with dual heart rate capacity. Note the variability of the MHR with uterine contractions. An intravenous injection of bupivacaine 12.5 mg and epinephrine 12.5 µg was given (arrow). Note the marked increase in MHR in response to intravenous injection of the test dose. The maternal tachycardia had a duration of approximately 40 seconds. (From Van Zundert AA, Vaes LE, De Wolf AM. ECG monitoring of mother and fetus during epidural anesthesia. Anesthesiology. 1987;66:584–585.)](image-url)
or fluid preferentially exits the proximal orifice. The rate of injection used in clinical practice typically exceeds that required to ensure that fluid will exit all three orifices. In contrast, air must be injected at a much greater rate to ensure that it exits all three orifices; this rate is not practical for clinical use. The distal orifice is both the most difficult to test and the one most likely to be positioned outside the epidural space.

### Intrathecal Test Dose

The intrathecal test dose should allow easy identification of subarachnoid (intrathecal) placement of the catheter without causing high or total spinal anesthesia and hemodynamic compromise. Bupivacaine (7.5 mg) and lidocaine (45 to 60 mg) are the local anesthetics most often used for an intrathecal test dose (see Table 12.2; Fig. 12.21).103,104

In a study of older, nonpregnant patients receiving continuous spinal anesthesia for surgery, Colonna-Romano et al.104 used plain lidocaine 45 mg plus epinephrine 15 µg and assessed patient perception of lower-extremity warmth and heaviness, sensory loss to pinprick, and ability to perform a straight-leg raise. Patients usually perceived warmth in their legs within 1 minute of the intrathecal injection; however, impaired straight-leg raise 4 minutes after an intrathecal test dose injection was the only test that had a sensitivity of 100% for intrathecal injection. The application of these data to pregnant patients is unclear.

Richardson et al.105 described the rapid onset (1 to 3 minutes) of high levels of spinal anesthesia with motor block and hypotension in five parturients who had received a test dose of plain lidocaine 45 mg plus epinephrine 15 µg. This solution is slightly hypobaric; thus, the upright posture of these parturients during the injection may have contributed to the high sensory levels of anesthesia. The anesthesia provider must recognize the possible range of responses to the dose of local anesthetic used to assess the position of an epidural catheter and should perform a careful assessment of sensory, motor, and sympathetic function 3 to 5 minutes after administration of the test dose before concluding that the

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**TABLE 12.2 Epidural Test Dose Regimens**

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<thead>
<tr>
<th>Test Dose Components</th>
<th>Positive Intravascular Test Dose</th>
<th>Positive Intrathecal Test Dose</th>
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<tr>
<td><strong>Combined Intrathecal and Intravenous Test Dose:</strong></td>
<td>Increase in heart rate of 20 bpm within 1 minute</td>
<td>Motor blockade at 3–5 minutes&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lidocaine 1.5% with epinephrine 5 µg/mL (1:200,000): 3 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine 0.25% with epinephrine 5 µg/mL (1:200,000): 3 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous Test Dose:</strong></td>
<td>Tinnitus, circumoral numbness, “dizziness”</td>
<td>Dizziness, drowsiness</td>
</tr>
<tr>
<td>Lidocaine 100 mg</td>
<td></td>
<td>Change in Doppler heart sounds over right side of heart</td>
</tr>
<tr>
<td>Bupivacaine 25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Chloroprocaine 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl 100 µg</td>
<td></td>
<td></td>
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<tr>
<td>Air 1 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intrathecal Test Dose:</strong></td>
<td></td>
<td>Motor blockade at 3–5 minutes&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lidocaine 40–60 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine 7.5 mg</td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Test doses may be less sensitive in premedicated patients, patients treated with a beta-adrenergic receptor antagonist, pregnant patients, and anesthetized patients.

<sup>b</sup>Weakness in hip flexion.

intravascular injection.\textsuperscript{50} Unintentional intravascular injection of the catheter for blood has 98% sensitivity for detection of an intravascular location.\textsuperscript{50} Unintentional intravascular injection of a small volume of solution containing a low concentration of local anesthetic is unlikely to result in serious morbidity. However, laboring women may need large doses of local anesthetic administered quickly (without incremental injection) for emergency operative delivery. The anesthesia provider must determine as soon as possible that the epidural catheter is correctly positioned within the epidural space. Even if no morbidity results, it is inconvenient for both the patient and the anesthesia provider to have to repeat the procedure and replace the catheter once the drape has been removed and the patient has been repositioned. The epinephrine-containing test dose provides an objective marker of intravascular injection.\textsuperscript{107} The application to the pregnant woman is unclear.

The epidural injection of local anesthetic-containing test dose augments epidural analgesia and should be considered in the calculation of the initial therapeutic dose of local anesthetic. Several groups of investigators demonstrated that the test dose enhanced the density of epidural blockade and adversely affected the ability to ambulate.\textsuperscript{108,109}

**Techniques to Minimize Local Anesthetic Systemic Toxicity**

No perfect test dose exists. Some anesthesia providers elect not to administer a test dose because it contributes to motor blockade.\textsuperscript{108,109} In addition, aspiration of a multi-orifice epidural catheter for blood has 98% sensitivity for detection of an intravascular location.\textsuperscript{96} Unintentional intravascular injection of a small volume of solution containing a low concentration of local anesthetic is unlikely to result in serious morbidity. However, laboring women may need large doses of local anesthetic administered quickly (without incremental injection) for emergency operative delivery. The anesthesia provider must determine as soon as possible that the epidural catheter is correctly positioned within the epidural space. Even if no morbidity results, it is inconvenient for both the patient and the anesthesia provider to have to repeat the procedure and replace the catheter once the drape has been removed and the patient has been repositioned. The epinephrine-containing test dose provides an objective marker of intravascular injection that has stood the test of time. Thus, we typically give a test dose that contains either bupivacaine 7.5 mg or lidocaine 45 to 60 mg with 15 \( \mu \)g of epinephrine. No matter whether a test dose is injected, drugs should be injected incrementally into the epidural space, because no test is 100% sensitive and catheters may migrate during use. Each incremental dose should be treated as a “test dose” (i.e., the dose should be small enough that it will not cause systemic toxicity if unintentionally injected intravascularly or total spinal anesthesia if injected intrathecally). Pregnant women are difficult to resuscitate from local anesthetic cardiovascular toxicity.\textsuperscript{95}

Steps to minimize the possibility of local anesthetic toxicity are summarized in Box 12.3. They include observation for passive return of CSF or blood (by lowering the proximal end of the epidural catheter below the insertion site), administration of the test dose between contractions, aspiration before each dose, incremental dose administration, maintaining verbal contact with the patient, and regular assessments throughout labor for an appropriate level and density of sensory and motor blockade (which indicates correct placement of the catheter in the epidural space).

**Box 12.3 Steps to Decrease Risk for Unintentional Intravenous or Subarachnoid Injection of Local Anesthetic**

- Lower the proximal end of the catheter below the site of insertion. Observe for the passive return of blood or cerebrospinal fluid.
- Aspirate before injecting each dose of local anesthetic.
- Give the test dose between uterine contractions.
- Use dilute solutions of local anesthetic during labor.
- Do not inject more than 5 mL of local anesthetic as a single bolus.
- Maintain verbal contact with the patient.
- If little or no block is produced after the injection of an appropriate dose of local anesthetic, assume that the local anesthetic was injected intravenously and remove the catheter.

**CHOICE OF DRUG\textsuperscript{a}**

The dose requirement of both epidural and spinal local anesthetics is decreased approximately 25% in pregnancy owing to anatomic and physiologic changes (see Chapter 2). These alterations begin to revert to the prepregnancy state within hours of delivery.

**Spinal Anesthesia**

Anesthesia providers may give spinal anesthesia for cerclage, nonobstetric surgery during pregnancy, instrumental vaginal delivery, cesarean delivery, removal of a retained placenta, or postpartum tubal ligation. Spinal analgesia may be used for labor analgesia. Cesarean delivery represents the most common indication for spinal anesthesia in pregnant women. Most anesthesia providers administer a hyperbaric solution of local anesthetic for spinal anesthesia in obstetric patients. Use of a hyperbaric solution as compared with a plain solution without dextrose results in a faster onset of block and a higher maximum sensory level with a shorter duration of blockade.\textsuperscript{110} The urgency and anticipated duration of surgery dictate the choice of local anesthetic agent. The most common choice in the United States is bupivacaine. Lidocaine is used less commonly. Ropivacaine, 2-chloroprocaine, and levobupivacaine may be used but are not approved for spinal administration in the United States, and levobupivacaine is not available in the United States. 2-Chloroprocaine provides a short duration of action, and lidocaine provides a short to intermediate duration of action. Bupivacaine, levobupivacaine, and ropivacaine provide intermediate to long durations of action.

Anesthesia providers often add an opioid to the local anesthetic to improve the quality of anesthesia, particularly with regard to visceral stimulation, and to provide postoperative analgesia.\textsuperscript{111} The addition of an opioid to the local anesthetic decreases the incidence of intraoperative nausea and vomiting.

\textsuperscript{a}Chapter 13 contains a detailed discussion of anesthetic agents used for neuraxial anesthetic techniques.
The short-acting, lipid-soluble opioids (i.e., fentanyl, sufentanil) contribute to intraoperative anesthesia, and morphine is often administered for postoperative analgesia. Epinephrine may be added to prolong block duration and perhaps improve block density. Adverse effects of other adjuncts (e.g., clonidine, neostigmine) have limited their wide use in obstetric anesthesia practice (see Chapters 23, 26, and 27).

**Epidural Anesthesia**

Local anesthetic agents available for epidural administration in obstetric patients include 2-chloroprocaine, lidocaine, mepivacaine, bupivacaine, and ropivacaine. Mepivacaine is used infrequently in obstetric anesthesia practice.

**Bupivacaine** remains a popular local anesthetic for analgesia during labor and vaginal delivery because of its differential sensory blockade, long duration of action, low frequency of tachyphylaxis, and low cost. Anesthesia providers infrequently administer bupivacaine for cesarean delivery because of the risk for cardiac toxicity and maternal mortality after unintentional intravascular injection of the drug.

**Ropivacaine** has gained popularity as an agent for epidural analgesia and anesthesia because it may result in less cardiac toxicity and greater differential sensory-motor blockade than bupivacaine.112

**Levobupivacaine** also has a more favorable safety profile than bupivacaine. Clinical trials have shown that ropivacaine and levobupivacaine have potency113 and analgesic qualities similar to those of bupivacaine,114,115 with the probable exception of less motor nerve block.116

Bupivacaine, ropivacaine, and levobupivacaine all have longer durations of action than lidocaine, and are preferred over shorter-acting agents when a longer duration of anesthesia or analgesia is desirable. They are more commonly used for maintenance of epidural labor analgesia, whereas the shorter-acting agents are used for epidural surgical anesthesia. Despite some variation among reports, published clinical studies suggest no more than slight differences in onset, and no differences in quality or duration of neural blockade, among the three drugs. However, bupivacaine is more cardiotoxic than the other agents in vitro and probably after unintentional intravascular administration.117 It would seem prudent to use ropivacaine or levobupivacaine rather than bupivacaine when a bolus dose of a concentrated solution is being given. When administered as a low-concentration infusion, improved safety has not been demonstrated with ropivacaine and levobupivacaine compared with bupivacaine.

The most popular choice of local anesthetic for epidural anesthesia for cesarean delivery is 2% lidocaine with epinephrine. The addition of epinephrine (5 µg/mL) causes a modest prolongation of the block. The major advantage of epinephrine is that it improves the quality of epidural lidocaine anesthesia. Lam et al.118 have shown that epidural labor analgesia can be extended to surgical anesthesia for cesarean delivery in 5.2 ± 1.5 minutes (mean ± SD) with the addition of bicarbonate and fentanyl to 2% lidocaine with epinephrine.

Many anesthesia providers reserve 2-chloroprocaine for cases in which rapid extension of epidural anesthesia for vaginal delivery or urgent cesarean delivery is necessary. The onset of surgical anesthesia was several minutes faster with 2-chloroprocaine compared with lidocaine with freshly mixed epinephrine and sodium bicarbonate in the setting of urgent cesarean delivery after epidural labor analgesia.119 Therefore, when time is of the essence, 2-chloroprocaine is the drug of choice. Typically, in an emergency, a large volume of concentrated local anesthetic solution is injected quickly. An additional advantage of 2-chloroprocaine in this situation is that it is rapidly metabolized by plasma esterases. Therefore, the unintentional intravascular injection of a large volume of 2-chloroprocaine may be less likely to have serious adverse consequences. A potential disadvantage of 2-chloroprocaine is that it may interfere with the subsequent actions of opioids and bupivacaine,120 although this possibility is controversial.122,123

As in spinal anesthesia, epidural opioids work synergistically with local anesthetics. Fentanyl 50 to 100 µg or sufentanil 5 to 10 µg is frequently added to an amide local anesthetic for both labor analgesia (allowing a lower dose of local anesthetic and less motor block) and cesarean delivery (resulting in a denser block with better blockade of visceral stimulation). Sodium bicarbonate may be added to lidocaine124 and 2-chloroprocaine125 (1 mEq/10 mL local anesthetic) to decrease latency.

**Caudal Anesthesia**

The drugs used for caudal epidural anesthesia are identical to those used for lumbar epidural block. However, a much larger volume (e.g., 25 to 35 mL) of local anesthetic solution must be administered to extend a caudal block for cesarean delivery or labor analgesia. Such large volumes entail a greater risk for local anesthetic systemic toxicity. Additionally, the caudal epidural space is highly vascular, which further predisposes to intravasation of drugs administered via this route.

**COMPLICATIONS OF NEURAXIAL TECHNIQUES**

**Unintentional Dural Puncture**

Unintentional dural puncture with an epidural needle occurs at a rate of approximately 1.5% in the obstetric population.126 Approximately 52% of women will experience a post–dural puncture headache after puncture with an epidural needle (see Chapter 30). Techniques to minimize the incidence of unintentional dural puncture include (1) identification of the ligamentum flavum during epidural needle advancement; (2) understanding the likely depth of the epidural space in an individual patient; (3) advancement of the needle between contractions, when unexpected patient movement is less likely; (4) adequate control of the needle-syringe assembly during advancement of the needle; and (5) clearing the needle of clotted blood or bone plugs. Studies are conflicting as to whether the incidence of post–dural puncture headache after unintentional dural puncture is less likely if the epidural needle bevel faced lateral rather than cephalad.127,128 An in vitro study using cadaver dura found that the fluid leakage...
rate through dural tears was not dependent on the orientation of the dura relative to the needle bevel. We prefer to insert the epidural needle with the bevel oriented in a cephalad direction so that there is no need to rotate the needle bevel within the epidural space. Cephalad bevel orientation also increases the likelihood of successful epidural anesthesia.

The anesthesia provider has two options after unintentional dural puncture: site the epidural catheter within the subarachnoid space and use a continuous spinal anesthetic technique, or site the epidural catheter in a different interspace (i.e., starting afresh). Management may depend on the clinical setting. If advancement of an epidural needle results in dural trespass and the free flow of CSF is perceived in the barrel of the epidural syringe, the anesthesia provider should halt advancement of the epidural needle and either remove the epidural needle (if the plan is to resite the epidural catheter) or replace the stylet back into the lumen of the epidural needle to prevent further egress of CSF (if the plan is to administer intrathecal medication or perform a continuous spinal technique). Reinjection of CSF contained in the syringe should not be entertained because there is a high likelihood that air will concomitantly be introduced into the subarachnoid space and cause pneumocephalus. The risks and benefits of administering an intrathecal dose of anesthetic should be considered. Although intrathecal administration of local anesthetic through the epidural needle will result in rapid analgesia for an uncomfortable patient, the rapid efflux of CSF may render the injectate ineffective. Additionally, spinal analgesia may mask paresthesias during subsequent attempts at neuraxial anesthesia. Furthermore, spinal anesthesia may cause profound hypotension. If the patient is sitting, and likely to remain so for the next few minutes, the anesthesia provider may struggle to manage two problems instead of one (i.e., a challenging neuraxial procedure and maternal hypotension). However, rapid provision of analgesia may enable the patient to better assume an optimal position without moving. One option is to administer intrathecal opioid, thus providing analgesia without the risk for hypotension.

Evidence is conflicting as to whether the insertion of an epidural catheter through the dural puncture site decreases the incidence of post–dural puncture headache. Most studies are retrospective; a prospective study in which institutions were randomized to manage unintentional dural puncture with an intrathecal catheter or siting the epidural catheter in another interspace found no difference in the rate of post–dural puncture headache or need for an epidural blood patch. Continuous spinal anesthesia is an attractive option if identification of the epidural space has been difficult or if the anticipated duration of anesthesia or analgesia is relatively short (e.g., cesarean delivery, or vaginal delivery in parous women). The major disadvantage of an intrathecal catheter is the risk that it may be mistaken for an epidural catheter. Given that the local anesthetic dose required for epidural anesthesia is many times greater than that required for spinal anesthesia, unintentional administration of an epidural dose into the subarachnoid space will lead to total spinal anesthesia. Therefore, on a busy labor and delivery unit where multiple providers are giving anesthesia care, it may be safer to use an epidural catheter rather than an intrathecal catheter in women in whom prolonged analgesia is anticipated.

Thus, the anesthesia provider may elect to initiate epidural anesthesia in another lumbar epidural interspace. However, even if the attempt results in a correctly placed catheter, the provider must be wary of an unexpectedly high level of anesthesia after the epidural administration of usual doses of local anesthetic. Leach and Smith reported a patient who had an extensive block after unintentional dural puncture and subsequent epidural injection of bupivacaine. They presented radiologic evidence of the spread of local anesthetic from the epidural space to the subarachnoid space. The extent to which a dural tear affects the movement of substances from the epidural space to the subarachnoid space depends on the size of the hole, the lipophilicity of the drug (highly lipophilic drugs cross quickly regardless of the presence of a hole, whereas water-soluble drugs cross more quickly in the presence of a hole), and whether the drug is administered into the epidural space as a bolus or an infusion. Rapid bolus administration of medications through an epidural catheter in a patient with a known dural puncture with a large-bore needle significantly increases the likelihood of high spinal anesthesia.

Unfortunately, there is no reliable method to decrease the risk for post–dural puncture headache once dural puncture occurs. Studies regarding the utility of a prophylactic epidural blood patch (injection of autologous blood before removal of the epidural catheter and before onset of a headache) for the prevention of post–dural puncture headache are conflicting, but the only randomized and blinded trial found no difference in the incidence of headache in women who received a prophylactic blood patch compared with a sham patch. Occasionally, unintentional dural puncture is not recognized until the epidural catheter is threaded and CSF spontaneously appears at the proximal end of the catheter, or the catheter aspiration or intrathecal test dose is positive. Rarely, an epidural catheter that has been correctly sited in the epidural space may migrate into the subarachnoid space. The most significant clinical threat in this scenario is the continued use of a large-volume infusion of local anesthetic drug intended for epidural administration. An unrecognized spinal catheter was the cause of 24% of high neuraxial anesthetics reported to the Serious Complication Repository Project of the Society for Obstetric Anesthesia and Perinatology. Thus, during prolonged epidural labor analgesia, the patient should be regularly monitored for evidence of high or dense neuraxial anesthesia.

Unintentional Intravascular or Subarachnoid Injection

The unintentional injection of large doses of local anesthetics into the subarachnoid space can lead to catastrophe. The rapid onset of high or total spinal anesthesia results in profound hypotension, loss of consciousness, and apnea secondary to hypoperfusion of the brain stem. Prompt treatment
necessitates assisted ventilation, volume resuscitation, and pharmacologic support of blood pressure. Administration of chronotropic agents such as epinephrine may also be necessary if blockade of cardiac sympathetic drive results in bradycardia. The patient is at high risk for awareness in this setting, and the judicious use of an amnestic agent such as midazolam should be considered once cardiorespiratory stability has been restored.

Pregnant women are at higher risk for unintentional intravenous cannulation because of the engorgement of epidural veins. Intravascular injection of a local anesthetic may initially result in altered sensorium, tinnitus, and perioral numbness. Higher blood concentrations may result in seizures, and even higher concentrations may cause dysrhythmias and cardiovascular collapse (see Chapter 13). Management of local anesthetic systemic toxicity includes prompt institution of advanced cardiac life support (ACLS), gamma-aminobutyric acid (GABA)–potentiating agents such as benzodiazepines to mitigate seizure activity, and the use of lipid emulsion to detoxify the patient. Several modifications have been made to the conventional ACLS protocol for the specific treatment of local anesthetic–induced cardiac arrest. These include (1) use of small, judicious doses of intravenous epinephrine for circulatory support (10- to 100-μg boluses in adults); (2) avoidance of vasopressin, calcium-entry blocking agents, and beta-adrenergic blocking agents; and (3) avoidance of local anesthetics for treatment of ventricular arrhythmias.

Inadequate Anesthesia

Pain during anesthesia represents a higher proportion of obstetric malpractice claims than of nonobstetric claims. During labor, inadequate epidural analgesia may result from the inadequate extent of sensory blockade, nonuniform blockade, or inadequate density of blockade. When called to evaluate breakthrough pain, the anesthesia provider should first evaluate the extent of bilateral sensory blockade in both the cephalad and caudad directions (see Chapter 23). Particularly if labor is progressing quickly, the extent of sacral blockade may not be adequate. In this case, epidural injection of a large volume of local anesthetic may improve sacral blockade. In contrast, if the extent of sensory blockade is adequate but the patient is still experiencing pain, the density of blockade may be insufficient. In this case, the provider should reestablish and maintain analgesia using a more concentrated solution of local anesthetic.

Why do some obstetric epidural anesthetics fail over time? Collier administered epidural radiocontrast dye in 25 parturients reporting unsatisfactory analgesia. The two major causes of inadequate block in this small study were transfornamental migration of the catheter tip and an obstructive barrier in the epidural space. Total block failure usually results from failure to identify the epidural space correctly or from malposition of the catheter tip outside the epidural space (e.g., in a neuroforamen). A unilateral block may occur despite the use of good technique. Unilateral blocks can often be prevented by limiting the length of catheter within the epidural space to 3 cm or less, but this may increase the risk for outward migration of the catheter over time. (Patients undergoing surgery remain still; by contrast, laboring women change position frequently.) Obese women seem to be at higher risk for outward migration of the catheter tip.

Whether catheter withdrawal in the setting of breakthrough pain is beneficial is not clear. Beilin et al. compared catheter withdrawal followed by injection of local anesthetic with injection of local anesthetic without catheter withdrawal for the treatment of breakthrough pain. The ability to rescue analgesia was not different between the groups. Gielen et al. performed a radiologic study in which they observed no consistent relationship between catheter position and the asymmetric onset of sympathetic blockade. Unilateral or patchy sensory blockade likely results from the nonuniform distribution of local anesthetic solution in the epidural space. Injection of a large volume of dilute local anesthetic solution into the epidural space usually corrects this problem, regardless of the location of the tip of the epidural catheter (provided it is actually in the epidural space). If analgesia cannot be rescued with a second injection, the catheter should be removed and replaced at another interspace.

The management of inadequate anesthesia is more problematic during cesarean delivery. Failure of spinal anesthesia may result from the maldistribution of local anesthetic within the subarachnoid space. If inadequate spinal anesthesia is noted before incision, the anesthesia provider may augment the block with additional local anesthetic by either performing a second spinal anesthetic procedure or placing an epidural catheter, or both. However, care must be taken if performing a second spinal anesthetic procedure. In the ASA Closed-Claims Project database, Drasner and Rigler identified three cases of cauda equina syndrome complicating spinal anesthesia. In two cases, “failed spinal” anesthesia had occurred, followed by a repeat injection of local anesthetic. The researchers recommended that anesthesia providers determine the presence of anesthesia in the sacral dermatomes before administering additional local anesthetic into the subarachnoid space. Additionally, they stated that if CSF was aspirated during the original procedure, it should be assumed that local anesthetic was delivered into the subarachnoid space, and the total dose of local anesthetic be limited to the maximum dose a clinician would consider reasonable to administer in a single injection. If partial blockade is present (even if it is limited to the sacral dermatomes), the second dose should be reduced accordingly. It may also be advisable to perform the second procedure at a different interspace or make other changes to the original procedure (e.g., alter the patient’s position, use a local anesthetic with different baricity, or straighten the lumbosacral curvature).

If the patient complains of pain after incision, the anesthesia provider must decide between the administration of inhalation or intravenous analgesia, and the administration of general anesthesia. Supplemental analgesia may be provided by giving 60% nitrous oxide in oxygen, small incremental boluses of ketamine (0.1 to 0.25 mg/kg), or small boluses of intravenous opioid. Supplemental infiltration of the
wound with local anesthetic is sometimes helpful, especially when spinal anesthesia regresses near the end of an unexpectedly long operation. The anesthesia provider must ensure that the patient remains sufficiently aware to protect her airway. In most cases, severe pain unrelieved by modest doses of analgesic drug requires rapid-sequence induction of general anesthesia followed by endotracheal intubation and general anesthesia.

Risk factors for failed conversion of epidural labor analgesia to epidural anesthesia for intrapartum cesarean delivery include an increasing number of clinician-administered boluses during labor (requirement for top-up doses), greater urgency of cesarean delivery, and provision of anesthesia care by a nonobstetric anesthesiologist. In some cases, inadequate epidural anesthesia results from failure to give a sufficient dose of local anesthetic or failure to wait a sufficient time after its administration. For example, after the epidural administration of 2% lidocaine with epinephrine, approximately 10 to 20 minutes must pass to achieve an adequate level of anesthesia, and additional local anesthetic may be needed to achieve an adequate density of blockade. In urgent cases or in cases with a “missed” segment, local infiltration with a local anesthetic often results in satisfactory anesthesia. Sometimes it is difficult to separate the beneficial effect of the local infiltration from the beneficial effect of waiting for the obstetrician to obtain, prepare, and inject the local anesthetic solution. Finally, the anesthesia provider should exercise caution when initiating spinal anesthesia after failure of epidural anesthesia because of a greater incidence of high spinal anesthesia in this setting. Presumably, the large volume of local anesthetic within, or near, the epidural space results in decreased lumbar CSF volume, which predisposes to high spinal anesthesia. It may be advisable to reduce the dose of intrathecal local anesthetic, particularly in the presence of partial epidural blockade.

Equipment Problems

The frequency of major equipment malfunction is very low during the administration of neuraxial anesthesia. Most anesthesia providers in the United States use disposable needles. If a needle should break, the portion of the needle that remains in the patient should be removed, because it may migrate and cause injury.

An epidural or spinal catheter may shear and break off if the catheter is withdrawn through a needle; thus an epidural or spinal catheter should never be withdrawn in this manner. Rather, if the catheter must be withdrawn, the needle and catheter should be withdrawn as a unit. It is also possible to break a catheter during attempts at removing it, although this is rare. If resistance to catheter removal is encountered, the patient should assume a position that reduces lumbar lordosis, thereby lessening the kinking of the catheter between perivertebral structures. If position change is not successful, the catheter should be taped under tension to the patient’s back and left undisturbed for several hours. The catheter usually works its way out and is then easy to remove. Once the catheter has been removed successfully, it should be examined to ensure that it has been removed completely. Complete removal of the catheter should be documented in the medical record.

Rarely, catheters do break on removal. We favor aggressive attempts to remove broken catheters located in the subarachnoid space. However, it may be unnecessary to remove broken catheters located in the epidural space; rather, in these circumstances, the patient can be informed of the complication and observed over time. The incidence of catheter migration or other delayed sequelae appears to be low. Imaging (radiography, computed tomography, magnetic resonance) may help identify the precise location of a broken catheter.

During use, an epidural catheter occasionally becomes disconnected from the catheter connector. Options include replacing the epidural catheter or reconnecting the connector to the catheter. Langevin et al. used an in vitro model to investigate whether microbial contamination precludes reconnection. They found that an area of the interior of the catheter distal to the disconnection may remain sterile for up to 8 hours if the fluid column within the catheter remains static (i.e., if “fluid does not move within the catheter when it is raised above the level of the patient”). Therefore, they concluded that it may be safe to decontaminate the exterior of the catheter, cut the catheter with a sterile instrument, and reconnect it to a new sterile connector. However, given the potential catastrophic consequences of neuraxial infection, we recommend replacing the catheter. Also, wire-embedded catheters cannot be cut.

TEACHING NEURAXIAL ANESTHESIA PROCEDURES

Teaching mastery of neuraxial anesthesia is an important skill of academic anesthesiologists. A logical approach to learning neuraxial procedures might begin with self-study aimed at mastering the spatial geometry of the central neuraxis, via written or online material, spine models, sonoanatomy, or combinations of these. This may be followed by procedural practice on a simulator, followed by procedures performed on patients with close supervision of an experienced teacher. Beyond technical skills, the safe practice of neuraxial anesthesia requires knowledge of the pharmacologic and physiologic aspects of neuraxial procedures.

The importance of applying a consistent and thoughtful methodology when teaching procedural skills cannot be understated. Unlike video laryngoscopy, which allows the observer real-time assessment of a trainee’s mechanical technique, no such analogous technology facilitates guidance during neuraxial anesthesia procedures. Spinal and epidural anesthesia remain essentially “blind” procedures. The past decade has seen the development of a number of high-fidelity simulators for teaching neuraxial techniques. Use of low-technology simulators, such as vegetables and fruits, have also been described and may be equally effective.

Offering meaningful feedback is highly conducive to shaping procedural habits. An effective debriefing session results from a systematic approach to observation and
analysis of clinical skill. One example is described by Chuan et al.\textsuperscript{163} Their comprehensive checklist identifies 25 executable actions for regional anesthetic block that are amenable to observation and assessment.

Mastery of technical skills requires practice. Kopacz et al.\textsuperscript{163} determined that a 90% success rate is not attained and maintained until first-year anesthesiology residents perform approximately 45 spinal and 60 epidural procedures.

**KEY POINTS**

- Physiologic changes of pregnancy alter neuraxial anatomy; alterations include accentuation of lumbar lordosis, a “softer” ligamentum flavum, and decreased space in the spinal canal caused by vascular engorgement of epidural veins.
- Physiologic changes of pregnancy cause a more pronounced response to neuraxial anesthesia–induced sympathetic blockade than is seen in nonpregnant patients. These include higher baseline sympathetic tone and aortocaval compression.
- Pregnant women, particularly those with neuraxial blockade, should not be cared for in the supine position but rather in lateral tilt or in the full lateral position.
- Correct patient positioning, equipment, and technique are important to the success and safety of neuraxial techniques.
- The midline approach is faster and less painful than the paramedian approach to the epidural or subarachnoid space. However, the paramedian approach may allow for the successful identification of the subarachnoid or epidural space in difficult cases.
- Use of a noncutting (“pencil-point”) needle for spinal anesthesia reduces the incidence of post–dural puncture headache.
- Combined spinal–epidural anesthesia has the advantages of both spinal anesthesia and epidural anesthesia.
- Approximately 20% to 30% less local anesthetic is required for epidural and spinal anesthesia in pregnant patients than in nonpregnant patients.
- Multiple techniques (e.g., test dose, aspiration, incremental dose injection) should be used to reduce the incidence and risk for unintentional subarachnoid or intravascular injection, because no one technique will completely exclude all cases of malpositioned needles or catheters.

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Local Anesthetics and Opioids

Brenda A. Bucklin, MD, Alan C. Santos, MD, MPH

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Local anesthetics and opioids are often used for pain relief in obstetric practice. Local anesthetics may be used for infiltration anesthesia, peripheral (pudendal) nerve block, or neuraxial block, whereas opioids are administered both systemically and neuraxially. The physiologic changes that occur during pregnancy may affect the pharmacology of both local anesthetics and opioids. In turn, these analgesic drugs may have effects on the mother and the fetus.

**LOCAL ANESTHETICS**

**Molecular Structure**

All local anesthetic molecules except cocaine contain a desaturated carbon ring (aromatic portion) and a tertiary amine connected by an alkyl chain (Fig. 13.1). The intermediate alkyl chain, by virtue of its ester or amide linkage, is the basis for the classification of local anesthetics as **amino-esters** (which are hydrolyzed by pseudocholinesterase) and **amino-amides** (which undergo hepatic microsomal metabolism) (Table 13.1). The aromatic ring of the esters, which renders the molecule lipid soluble, is a derivative of benzoic acid. The amide aromatic ring is a homologue of aniline. The tertiary-amine portion acts as a proton acceptor; thus, local anesthetics behave as weak bases. In its quaternary (i.e., “protonated”) form, the terminal amine is the water-soluble portion. The Henderson-Hasselbalch equation predicts the relative proportions of local anesthetic that exist in the ionized and un-ionized form. The higher the pKₐ (acid dissociation constant) relative to physiologic pH, the smaller the proportion of drug that exists in the un-ionized form. All clinically used amide local anesthetics (with the exception of lidocaine) exist as stereo-isomers because of an asymmetric carbon on the terminal amine.

Clinical formulations of local anesthetics are prepared as hydrochloride salts to increase their solubility in water. These formulations are usually acidic (i.e., pH of 4 to 6) to enhance formation of the water-soluble quaternary amine and to prevent oxidation of the epinephrine present in epinephrine-containing solutions.

**Chirality**

With the exception of lidocaine, amide local anesthetics are **chiral compounds** because they have a single asymmetric carbon adjacent to the amino group and thus exist in isomeric forms that are mirror images of each other. The direction in which the isomers rotate polarized light distinguishes them as either dextrorotary (d) or levorotary (l) isomers. This distinction is important, because individual isomers of the same
drug may have different biologic effects. As a rule, the levorotatory isomer of a drug has greater vasoconstrictor activity and a longer duration of action but less potential for systemic toxicity than the dextrorotary form.1

In the past, single-isomer formulations were costly to produce; and for that reason, local anesthetics used clinically (e.g., bupivacaine) have contained a racemic mixture of both the dextrorotary and levorotary forms of the drug. However, with improved techniques of selective extraction, two commercially available single-isomer formulations of local anesthetic are now available, ropivacaine and levobupivacaine. Levobupivacaine is the levorotary isomer of bupivacaine; it is currently not marketed in the United States. Ropivacaine is a homologue of mepivacaine and bupivacaine. The reduction in systemic toxicity observed with administration of the levorotary isomers may be both drug and concentration dependent. For example, one study in isolated guinea pig hearts noted that bupivacaine isomers lengthened atrioventricular conduction time more than ropivacaine isomers did. In contrast to other measured variables, “atrioventricular conduction time showed evident stereoselectivity” for bupivacaine at the lowest concentration studied (0.5 µM) but only at much higher concentrations for ropivacaine (> 30 µM).3

**Mechanism of Action**

At rest, the interior of a nerve cell is negatively charged in relation to its exterior. This resting potential of 60 to 90 mV exists because the concentration of sodium in the extracellular space greatly exceeds that in the intracellular space. The converse is true for potassium. Excitation results in the opening of membrane channels, which allows sodium ions to flow freely down their concentration gradient into the cell interior. Thus, the electrical potential within the nerve cell becomes less negative until, at the critical threshold, rapid depolarization occurs. This depolarization is needed to initiate the same sequence of events in adjacent membrane segments and for propagation of the action potential. Thereafter, sodium channels close and the membrane once again becomes impermeable to the influx of sodium. The negative resting membrane potential is reestablished as sodium is removed from the cell by active transport. At the same time, potassium passively accumulates within the resting cell.

Interference with sodium-ion conductance appears to be the mechanism by which local anesthetics reversibly inhibit the propagation of the action potential. Four major theories attempt to explain this effect. The most prominent hypothesis is that the local anesthetic interacts with receptors in the nerve cell membrane involved in sodium conductance.4 There may be more than one site at which local anesthetics bind to sodium-channel receptors (Fig. 13.2).

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**TABLE 13.1 Physicochemical Characteristics and Fetal-to-Maternal (F/M) Blood Concentration Ratios at Delivery for Commonly Used Local Anesthetic Agents**

<table>
<thead>
<tr>
<th></th>
<th>Molecular Weight (Base) (Da)</th>
<th>pKₐ</th>
<th>Lipid Solubility*</th>
<th>% Protein Bound</th>
<th>F/M Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esters:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>271</td>
<td>8.9</td>
<td>0.14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>264</td>
<td>8.6</td>
<td>4.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Amides:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>234</td>
<td>7.9</td>
<td>2.9</td>
<td>64</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>Bupivacaine (and levobupivacaine)</td>
<td>288</td>
<td>8.2</td>
<td>28</td>
<td>96</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>274</td>
<td>8.0</td>
<td>3</td>
<td>90–95</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*N-heptane/pH = 7.4 buffer.

CHAPTER 13 Local Anesthetics and Opioids

The Meyer-Overton theory offers a second explanation; it suggests that the lipid-soluble portion of the local anesthetic molecule expands the cell membrane, thus interfering with rapid sodium conductance. A third possibility is that local anesthetics may alter the membrane surface charge, a change that would inhibit propagation of the action potential. Fourth, local anesthetics may displace calcium from sites that control sodium conductance.

Both the un-ionized and ionized forms of a local anesthetic are involved in pharmacologic activity. The un-ionized base, which is lipid soluble, diffuses through the cell membrane, whereas the charged form is active in blocking the sodium channel.

**Pharmacodynamics**

Pregnant women typically require smaller doses of local anesthetic compared with nonpregnant women for neuraxial blockade. This effect may be evident as early as the second trimester and has been attributed to enhanced spread of local anesthetic caused by epidural venous engorgement. However, mechanical effects alone do not account for the observation that the spread of spinal and epidural analgesia in early pregnancy is similar to that in pregnant women at term. In fact, pregnancy may also enhance neuronal sensitivity to local anesthetics. For example, pregnancy increases median nerve susceptibility to lidocaine. In vitro studies demonstrated that the onset of neural blockade was faster, and lower concentrations of bupivacaine were required to block vagal fibers, in pregnant than in nonpregnant rabbits.

Hormonal and biochemical changes may be responsible for the greater susceptibility to neural blockade during pregnancy. It has been speculated that the hormonal effects may be caused by progesterone or a metabolite since an enhanced effect of bupivacaine in isolated vagus fibers from nonpregnant, ovariectomized rabbits only occurred after long-term (4 days) but not short-term exposure to progesterone. A higher pH and lower bicarbonate and total carbon dioxide content have been demonstrated in cerebrospinal fluid (CSF) from women undergoing cesarean delivery than from age-matched nonpregnant controls; this may increase the proportion of local anesthetic that exists as the base form and facilitates diffusion of the drug across nerve membranes.

**Pharmacokinetics**

Pregnancy is associated with progressive physiologic adaptations that may influence drug disposition (see Chapter 2). However, it is difficult to predict with certainty the effects of pregnancy on the pharmacokinetics of an individual drug.

**2-Chloroprocaine**

2-Chloroprocaine is hydrolyzed rapidly by plasma pseudocholinesterase to chloroaminobenzoic acid and H₂O. Although pregnancy is associated with a 30% to 40% decrease in pseudocholinesterase activity, the half-life of 2-chloroprocaine in maternal plasma is 11 to 21 seconds. After epidural injection, the half-life of 2-chloroprocaine in the mother ranges from 1.5 to 6.4 minutes. The longer half-life after epidural administration results from continued absorption of the drug from the injection site. Administration of 2-chloroprocaine to patients with low pseudocholinesterase activity may result in prolonged local anesthetic effect and a greater potential for systemic toxicity.

**Lidocaine**

The volume of the central compartment and the volume of distribution of lidocaine are greater in pregnant than in nonpregnant ewes. Bloedow et al. observed that the total
body clearance of lidocaine was similar in the two groups of animals but the elimination half-life of lidocaine, which depends on the balance between volume of distribution and clearance, was longer in pregnant ewes. In contrast, Santos et al. concluded that the elimination half-life of lidocaine was similar in the two groups of sheep because the total body clearance of the drug was greater in pregnant than in non-pregnant animals. This discrepancy could result from differences in the complexity of the surgical preparation and the allowed recovery period. In pregnant women, the elimination half-life of lidocaine after epidural injection is approximately 114 minutes.

Lidocaine is metabolized into two active compounds, monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Monoethylglycinexylidide can be detected in maternal plasma within 10 to 20 minutes after neuraxial injection of lidocaine, whereas glycinexylidide can be detected within 1 hour of epidural injection but rarely after subarachnoid injection. Urinary excretion of unchanged lidocaine is negligible in sheep (i.e., < 2% of the administered dose) and is not affected by pregnancy.

The physiologic changes that occur during pregnancy are progressive. However, little information is available about the pharmacokinetics of local anesthetics before term. In one study, total clearance of lidocaine was similar at 119 and 138 days’ gestation in gravid ewes (term is 148 days).

Lidocaine is predominantly bound to alpha 1-acid glycoprotein (AAG) in plasma. Pregnancy leads to a decreased concentration of AAG; thus, the free plasma fraction of lidocaine is lower in pregnant than in non-pregnant sheep is not affected by pregnancy. Pregnancy may affect metabolism of bupivacaine. For example, pregnant women have higher serum PPX concentrations, but the unconjugated 4-hydroxy metabolite is not produced in significant amounts. The reason for this finding is unclear but may be related to effects of hormonal changes on hepatic enzyme systems. Both progesterone and estradiol are competitive inhibitors of microsomal oxidases, whereas reductive enzymes are induced by progesterone.

Bupivacaine is bound extensively to AAG and albumin. This protein binding is reduced during late pregnancy in humans.

Like bupivacaine, ropivacaine is metabolized by hepatic microsomal cytochrome P450. The major metabolite is PPX, and minor metabolites are 3′- and 4′-hydroxy-ropivacaine.

Ropivacaine is highly bound (approximately 92%) to plasma proteins but less so than bupivacaine (96%). Indeed, at plasma concentrations occurring during epidural anesthesia for cesarean delivery, the free fraction of ropivacaine is almost twice that of bupivacaine. In pregnant women undergoing epidural analgesia, the free fraction of ropivacaine decreases as the concentration of AAG increases, up to the point at which the receptors are saturated. However, there is little correlation between the free fraction and umbilical cord blood levels of ropivacaine at delivery.

Effect of Histamine (H2)-Receptor Antagonists
Histamine (H2)-receptor antagonists are administered to increase gastric pH and reduce the risk for aspiration pneumonia. Drug disposition may be affected by binding to hepatic cytochrome
P450, reducing hepatic blood flow and renal clearance, especially with cimetidine. However, short-term administration of H2-receptor antagonists does not alter the pharmacokinetics of amide local anesthetics in pregnant women.\textsuperscript{34,35}

**Effects of Preeclampsia**

Pathophysiologic changes associated with preeclampsia (e.g., reduced hepatic blood flow, abnormal liver function, decreased intravascular volume) may also affect maternal blood concentrations of local anesthetics (see Chapter 35). For example, Ramanathan et al.\textsuperscript{36} found that total body clearance of lidocaine after epidural injection was significantly lower in preeclamptic than in normotensive women; however, the elimination half-life of lidocaine was similar in the two groups. Nonetheless, decreased clearance may result in greater drug accumulation with repeated injections of lidocaine in women with preeclampsia. In contrast, long-acting amides have a relatively low hepatic extraction, and changes in liver blood flow with preeclampsia may have less effect on the metabolic clearance.

**Effect of Gestational Diabetes Mellitus**

Gestational diabetes mellitus may have profound transient effects on the microcirculation. The placental transfer of lidocaine was unchanged for women at term with diabetes who received epidural lidocaine 200 mg, but the transfer of its metabolite, MEGX, was increased.\textsuperscript{37} A weakness of the methodology was that umbilical artery/vein ratios were used to estimate placental transfer (see later in the chapter).

**Effect of Diurnal Variation**

Pain may exhibit temporal variation in intensity because of diurnal neuroendocrine or external factors. In one study, the duration of action of epidural bupivacaine was approximately 25% longer when it was administered between 7:00 AM and 7:00 PM than between 7:00 PM and 7:00 AM.\textsuperscript{38} In contrast, another study found no diurnal variation with intrathecal bupivacaine administered for labor analgesia.\textsuperscript{39} The authors of this study suggested the diurnal variation may also be explained by external influences such as shift changes for nurses and anesthesiologists.\textsuperscript{39}

**Effect of Injectate Temperature**

Latency of local anesthetic affect may be affected by temperature. For instance, onset of labor analgesia is faster when a solution of epidural bupivacaine 0.125% with fentanyl 2 µg/mL is injected at 37°C compared with 20°C.\textsuperscript{40}

**Toxicity**

Systemic absorption or intravascular injection of a local anesthetic may result in local anesthetic systemic toxicity (LAST). Toxicity most often involves the central nervous system (CNS), but cardiovascular toxicity also may occur. Less common are tissue toxicity and hypersensitivity reactions.

**Central Nervous System Toxicity**

The severity of CNS effects is proportional to the blood concentration of local anesthetic. This relationship is well described for lidocaine (Fig. 13.3). Initially, the patient may complain of numbness of the tongue, tinnitus, or lightheadedness. At high plasma concentrations, convulsions occur because of a selective blockade of central inhibitory neurons that leads to increased CNS excitation.\textsuperscript{41} At still higher concentrations, generalized CNS depression or coma may result from reversible blockade of both inhibitory and excitatory neuronal pathways. Finally, depression of the brainstem and cardiorespiratory centers may occur.

The relative toxicity of a local anesthetic correlates with its potency. For lidocaine, etidocaine, and bupivacaine, the ratio of the mean cumulative doses that cause convulsions in dogs and human volunteers is approximately 4:2:1, which is similar to their relative anesthetic potencies.\textsuperscript{42} Local anesthetics may be ranked in order of decreasing CNS toxicity as follows: bupivacaine, ropivacaine, levobupivacaine, lidocaine, and 2-chloroprocaine.\textsuperscript{43} Tetracaine, etidocaine, and mepivacaine are used rarely in obstetric anesthesia practice.

Other factors (e.g., the speed of injection) may affect CNS toxicity. In humans, the mean dose of etidocaine that elicited signs of CNS toxicity was lower during a 20-mg/min infusion than during a 10-mg/min infusion.\textsuperscript{44} Metabolic factors may also affect the seizure threshold. For example, in cats, an increase in PaCO\textsubscript{2} or a decrease in pH results in a reduction in the seizure-dose threshold for local anesthetics. Respiratory acidosis may result in delivery of more drug to the brain; alternatively, respiratory acidosis may result in “ion trapping” of the local anesthetic and/or an increase in the unbound fraction of drug available for pharmacologic effect.\textsuperscript{45,46}

![Fig. 13.3](image-url) Signs and symptoms of systemic toxicity with increasing lidocaine concentrations. CVS, cardiovascular system. (Modified from Carpenter RL, Mackey DC. Local anesthetics. In Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia. Philadelphia, PA: Lippincott; 1992:527.)
**Cardiovascular Toxicity**

The cardiovascular system is typically much more resistant than the CNS to the toxic effects of local anesthetics. Severe, direct cardiovascular depression is rare, especially in association with the use of lidocaine. Prompt administration of oxygen and, if necessary, initiation of ventilatory and circulatory support usually prevent cardiac arrest after unintentional intravenous injection of lidocaine. Progressive depression of myocardial function and profound vasodilation occur only at extremely high plasma concentrations. In contrast, the more potent amide local anesthetics (i.e., bupivacaine) have a more narrow margin of safety, expressed as the ratio between the dose (or plasma concentration) required to produce cardiovascular collapse and the dose (or plasma concentration) required to produce convulsions. A partial explanation is the fact that supraconvulsant doses of bupivacaine (but not of lidocaine) precipitate lethal ventricular arrhythmias. These arrhythmias may be caused by exaggerated electrophysiologic effects (e.g., depression of ventricular conduction) out of proportion to bupivacaine's anesthetic potency.

Two theories have been proposed to explain why malignant ventricular arrhythmias occur with bupivacaine but not with lidocaine. Both bupivacaine and lidocaine rapidly block cardiac sodium channels during systole, but bupivacaine dissociates from these channels during diastole at a much slower rate than lidocaine. Thus, at physiologic heart rates, the diastolic period is of sufficient duration for lidocaine to dissociate from sodium channels, whereas a bupivacaine block becomes intensified. This difference makes bupivacaine much more potent than lidocaine in depressing conduction and inducing reentrant-type ventricular arrhythmias. Alternatively, other investigators have suggested that high concentrations of local anesthetic in the brainstem may lead to systemic hypotension, bradycardia, and ventricular arrhythmias. These effects occur more commonly with bupivacaine because of its high lipid solubility, which facilitates transfer across the blood-brain barrier. An echocardiographic study in anesthetized dogs suggested that bolus injection of bupivacaine results in systolic dysfunction, especially involving the right ventricle, which precedes the occurrence of arrhythmias.

**Metoclopramide** is used in obstetric anesthesia as an antiemetic and to enhance gastric emptying. In rat myocytes, metoclopramide inhibits cardiac sodium channels similar to local anesthetics. The potential interaction with bupivacaine is unknown and requires further study.

**Systemic Toxicity of Ropivacaine and Levobupivacaine**

*In vitro*, ropivacaine is intermediate between bupivacaine and lidocaine in its depressant effect on cardiac excitation and conduction as well as in its potential to induce reentrant-type ventricular arrhythmias. In dogs, the margin of safety between convulsive or lethal doses and plasma concentrations of drug is greater for ropivacaine than for bupivacaine but less than that for lidocaine. The arrhythmogenicity of ropivacaine in pigs also is intermediate between that of lidocaine and bupivacaine. In sheep, the ratio of fatal doses of bupivacaine, ropivacaine, and lidocaine is 1:2:9. Ropivacaine was found to cause fewer CNS symptoms and was 25% less toxic than bupivacaine (as defined by the doses and plasma concentrations that were tolerated) when administered to healthy male volunteers.

However, studies comparing the systemic toxicity of ropivacaine and bupivacaine have used equal doses of each, and, therefore, cannot resolve the controversy as to whether ropivacaine truly is less cardiotoxic or merely less potent than bupivacaine. This issue would be of concern only if larger doses of ropivacaine than bupivacaine were required to produce comparable regional blocks. Indeed, several studies in laboring women suggest that ropivacaine is 25% to 40% less potent than bupivacaine. Thus, the need for a larger dose of ropivacaine may negate the expected benefits of its wider margin of safety. Results from one laboratory study showed that ropivacaine produces less cardiotoxicity than bupivacaine, even when given at equipotent doses.

Long-acting amide local anesthetics—even the newer drugs—are very potent and may cause cardiac arrest with a misplaced injection or relative overdose. Indeed, several cardiac arrests have been reported with the use of ropivacaine, including one in a woman undergoing a cesarean delivery with epidural anesthesia. In contrast to bupivacaine, resuscitation from a cardiac arrest induced by ropivacaine may be successful more often than not.

Evidence suggests that levobupivacaine, which is not available for use in the United States, causes fewer arrhythmias than the racemic drug. Levobupivacaine caused less inhibition of inactivated sodium channels than either the dextrorotary or racemic drug. In comparison with dextrorotary and racemic bupivacaine, levobupivacaine resulted in less QRS widening and a lower frequency of malignant ventricular arrhythmias in isolated, perfused rabbit hearts. Similarly, levobupivacaine produced less second-degree heart block and atioventricular conduction delay than the other two forms of the drug in isolated perfused guinea pig hearts.

In laboratory animals, the systemic toxicity of levobupivacaine is intermediate between that of bupivacaine and ropivacaine. Potency ratio data for epidural bupivacaine, ropivacaine, and levobupivacaine in laboring women are inconsistent, but studies suggest that levobupivacaine is equipotent or slightly less potent than bupivacaine (see Chapter 23). Altogether, published data and clinical experience suggest that the benefit of a lower risk for systemic toxicity with levobupivacaine is not obtained at the expense of efficacy. Like ropivacaine, levobupivacaine may cause cardiac arrest but is associated with a better response to resuscitation than racemic bupivacaine.

**Effects of Pregnancy on Systemic Toxicity**

**Central nervous system toxicity.** Pregnancy-related hormones, such as estradiol and progesterone, have a neuroprotective effect in laboratory animals. However, it is unclear whether pregnancy lowers the seizure threshold for amide local anesthetic agents. In one study, seizures occurred at lower doses of bupivacaine, levobupivacaine, and ropivacaine in pregnant than in nonpregnant ewes. However, the difference was small.
(10% to 15%) and probably of negligible clinical significance. In studies in sheep and rats, pregnancy did not reduce the doses required to cause convulsions after intravenous administration of mepivacaine, bupivacaine, or lidocaine. Magnesium sulfate, which is frequently used in obstetric practice, does not affect the seizure-dose threshold of lidocaine.

**Cardiovascular toxicity.** In 1979, Albright alerted anesthesiologists to several cases of sudden and immediate cardiovascular collapse after unintentional intravascular injection of bupivacaine and etidocaine in pregnant women. Most of these cases were fatal, and subsequent controversy centered on whether resuscitation was instituted promptly and effectively or whether the cardiovascular collapse and inability to resuscitate were unique to bupivacaine. Nonetheless, the U.S. Food and Drug Administration (FDA) restricted the use of the highest concentration (0.75%) of bupivacaine in pregnant women.

Several physiologic changes that occur during pregnancy place the parturient at higher risk for refractory cardiac arrest than the nonpregnant patient. First, reduced functional residual capacity and a higher metabolic rate hasten the onset of hypoxemia during periods of hyperventilation or apnea. Second, aortocaval compression decreases the efficacy of closed-chest cardiac massage in the supine position. Third, a large bolus of drug injected into an epidural vein might reach the heart rapidly through a dilated azygous system. However, none of these factors adequately explains why cardiac arrest and difficult resuscitation are rare in parturients intoxicated with lidocaine or mepivacaine.

Results of laboratory studies of the effects of pregnancy on bupivacaine cardiotoxicity have been contradictory. Pregnancy-related hormones enhance the cardiotoxicity and arrhythmogenicity of bupivacaine in vitro. For example, the magnitude and severity of bupivacaine-induced electrophysiologic changes are greater in myocardium obtained from nonpregnant rabbits treated with progesterone or beta-estradiol than in myocardium from untreated controls. The electrophysiologic effects of lidocaine are less pronounced than those of bupivacaine, even in hormonally treated animals. Studies conducted in vivo have been less conclusive. In earlier investigations, significantly lower doses and plasma concentrations of bupivacaine, but not of mepivacaine or lidocaine, were required to produce circulatory collapse in pregnant than in nonpregnant sheep. However, a study involving a larger number of sheep and more rigorous methods (e.g., randomization, blinding) failed to confirm that pregnancy enhances the cardiotoxicity of bupivacaine.

Progesterone does not increase myocardial sensitivity to ropivacaine. Likewise, pregnancy does not enhance the systemic toxicity of ropivacaine or levobupivacaine in sheep.

Extrapolation of results of animal studies to obstetric anesthesia practice is difficult, for several reasons. First, in the aforementioned sheep studies, the drug was administered by constant-rate intravenous infusion. In contrast, in pregnant women intoxicated with bupivacaine, cardiac arrest occurred after unintended intravascular injection of a large bolus of drug. Second, a potential for bias existed in the animal studies because randomization and blinding were not used in all studies and some relied on historical controls. Third, it is unclear whether resuscitation in the reported clinical cases was accompanied by prompt and effective relief of aortocaval compression.

Nonetheless, bupivacaine remains a popular local anesthetic for obstetric anesthesia. In current practice, heightened vigilance, use of an appropriate test dose, and fractionation of the therapeutic dose have made epidural anesthesia a safe technique for use in obstetric patients (see Chapter 12). In a study of anesthesia-related maternal mortality, Hawkins et al. noted that the number of maternal deaths resulting from local anesthetic toxicity decreased after 1984, the year that the FDA withdrew approval for the epidural administration of 0.75% bupivacaine in obstetric patients. However, LAST has been recognized for decades as an important potential cause of maternal mortality. In our judgment, adherence to the aforementioned clinical precautions—rather than the proscription against the epidural administration of 0.75% bupivacaine—has been responsible for the lower number of maternal deaths caused by LAST. Anesthesia providers should be aware that intravenous injection of 0.25% and 0.5% bupivacaine can also cause LAST.

The availability of single levorotatory isomers of a local anesthetic may be advantageous because these drugs have a greater margin of safety than bupivacaine, with similar blocking properties, although at a higher cost. From the standpoint of systemic toxicity, the use of these isomers may be more beneficial in parturients undergoing cesarean delivery, who require higher doses than administered for analgesia during labor. Nonetheless, a greater margin of safety with these new drugs should not be a substitute for proper technique.

**Treatment of Systemic Toxicity**

Meticulous attention to good technique and adherence to guidelines for maximum recommended dose are mandatory. (The use of a test dose to identify misplaced injections is discussed in Chapter 12.) Incremental injection of the therapeutic dose, careful observation of the patient, and monitoring of vital signs usually provide early warning of an impending reaction. In mild cases, discontinuation of the administration of drug, administration of supplemental oxygen, and maintenance of normal ventilation often limit the severity of the reaction. In 2018, the American Society of Regional Anesthesia and Pain Medicine (ASRA) updated their checklist for managing LAST (Box 13.1). In patients who show signs of CNS excitation, a small dose of an intravenous sedative-hypnotic drug with strong anticonvulsant properties such as a benzodiazepine (diazepam up to 5 mg or midazolam 1 to 2 mg) may prevent progression to convulsions. Prophylactic administration of a benzodiazepine or dexmedetomidine to laboratory animals reduced the incidence of both convulsions and possibly mortality after intoxication with amide local anesthetics. Propofol should be avoided in patients with cardiovascular instability because of its cardiovascular depressant properties.
If convulsions should occur, oxygenation and ventilation must be maintained to prevent hypoxemia, hypercarbia, and acidosis. Patency of the airway must be maintained. It may be necessary to suction the airway first in some patients. Management should consist of administration of 100% oxygen and tracheal intubation, if required. Convulsions may be terminated quickly with a small dose of an anticonvulsant; a benzodiazepine is preferred. Large doses of propofol should be avoided in the setting of hemodynamic instability. Maternal circulation should be supported by maintenance of left uterine displacement and administration of a vasopressor as needed. Because a high plasma concentration of local anesthetic may cause myocardial depression and vasodilatation, a mixed alpha- and beta-adrenergic agonist (e.g., ephedrine or even epinephrine) may be preferable to a pure alpha-adrenergic agonist. Vasopressin, calcium entry-blocking agents, beta-adrenergic blocking agents, and local anesthetics should be avoided. Fortunately, convulsions induced by local anesthetics, with the exception of the long-acting amide local anesthetics, are usually self-limited because of rapid redistribution of the drug.

Persistent hypotension and bradycardia may require administration of epinephrine. However, individual epinephrine doses should not exceed 1 µg/kg. Although the mainstay of treatment, epinephrine itself may cause ventricular tachyarrhythmias and binds the very same cardiac sodium channels that bupivacaine binds, in theory, potentially worsening cardiac toxicity. Bupivacaine-induced ventricular arrhythmias should not be treated with lidocaine, because local anesthetic toxicity is additive.

Cardiac arrest should be treated according to the American Heart Association’s Advanced Cardiac Life Support (ACLS) guidelines, modified for pregnancy (see Chapter 54). The uterus should be displaced leftward, generally best achieved with manual displacement, to prevent or relieve aortocaval compression, which renders cardiac massage ineffective. Prompt cesarean delivery of the infant may be necessary to relieve aortocaval compression (venous return) and restore maternal circulation. Prolonged resuscitation may be needed until myocardial washout of bupivacaine has occurred.

Lipid emulsion therapy has been incorporated into guidelines for the treatment of LAST and should be readily available. The mechanism of lipid emulsion therapy includes a direct scavenging effect that removes the local anesthetic from tissue and a direct cardiac effect that serves to improve cardiac output once the drug is removed from cardiac tissue; the mechanisms of these effects are incompletely understood. Lipid emulsion is now an accepted therapy, and the updated 2018 American Society of Regional Anesthesia and Pain Medicine (ASRA) checklist for the treatment of LAST states that lipid emulsion therapy should be considered at the first sign of a serious LAST event (see Box 13.1). Propofol should not be used to treat LAST; its lipid content is inadequate, and the cardio depressant effects of the drug are detrimental during resuscitation from LAST. In a suspected case of bupivacaine intoxication in a parturient, manifested by facial and limb twitching and unconsciousness, prophylactic administration of 100 mL of lipid emulsion prevented progression to full cardiovascular collapse. A protocol for treatment of LAST in pregnancy, including the administration of lipid emulsion, is presented in Box 13.1.

After maternal recovery, fetal condition should be assessed promptly. In theory, a delay in delivery may allow back-diffusion of local anesthetic from the fetus to the mother, which may be of benefit to the neonate by decreasing neonatal plasma bupivacaine levels. Laboratory studies have demonstrated this phenomenon after the administration of bupivacaine but not lidocaine.

**Tissue Toxicity**

Neurologic complications of neuraxial anesthesia are rare and result mostly from direct neural trauma, infection, injection of toxic doses of local anesthetic, or the injection of the wrong drug.

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**BOX 13.1 Management of Local Anesthetic Systemic Toxicity**

- Stop injecting local anesthetic.
- Call for help.
- Position patient with left uterine displacement.
- Prepare for emergency delivery. Consider delivery of the infant if the mother is not resuscitated within several minutes, because this may facilitate successful resuscitation of the mother.
- Consider 20% intravenous lipid emulsion administration at the first sign of LAST.
  - Bolus dose: 1.5 mL/kg over 2–3 min (approximately 100 mL)
  - Infusion: 200–250 mL over 15–20 min
  - Repeat bolus dose once or twice for persistent cardiovascular collapse.
  - Recommended maximum dose: 12 mL/kg
- Administer 100% oxygen to maintain maternal oxygenation.
- Use positive-pressure ventilation if necessary. Tracheal intubation will facilitate support of ventilation and help protect the airway, but do not delay administration of oxygen to intubate the trachea.
- Control seizure (benzodiazepine preferred, avoid high doses of propofol in hemodynamically unstable patients). Be aware that hypoxemia and acidosis develop rapidly during a seizure.
- Alert the nearest facility capable of cardiopulmonary bypass.
- Monitor maternal vital signs and fetal heart rate.
- Support maternal blood pressure with fluids and vasopressors.
- Initiate advanced cardiac life support if necessary, including modifications for pregnancy (see Chapter 54).
- Avoid vasopressin, calcium entry–blocking agents, beta-adrenergic receptor antagonists, and local anesthetics.
- Reduce individual epinephrine doses to less than 1 µg/kg.

Several cases of prolonged or permanent sensory and motor deficits after subarachnoid injection of a large dose of 2-chloroprocaine intended for epidural block have been described. Studies comparing the neurotoxicity of 2-chloroprocaine with that of other local anesthetics have yielded conflicting results, most likely related to the use of different methodologies and different species. It has been suggested that neurotoxicity was caused by sodium metabisulfite, an antioxidant present in the commercial formulation used in the reported cases and a low pH (2.7 to 4.0) of the formulation. In CSF rendered more acidic by 2-chloroprocaine, metabisulfite generates sulfur dioxide, which is lipid soluble and can diffuse into the nerve cells. Intracellular hydration of sulfur dioxide generates sulfurous acid, which may cause profound intracellular acidosis and irreversible damage. In contrast, others have suggested that 2-chloroprocaine itself, and not metabisulfite, was the cause of neurologic deficits.

Subsequently, the manufacturer released another preparation of 2-chloroprocaine, which was free of bisulfite but contained ethylenediaminetetraacetic acid (EDTA). This was followed by several reports of severe, incapacitating paralumbar pain and spasm associated with epidural injection of large volumes of drug, likely resulting from chelation of calcium by disodium EDTA and tetany of the affected muscles caused by local hypocalcemia. The current preparation of 2-chloroprocaine that is marketed for epidural administration does not contain EDTA or other preservatives. It is packaged in colored vials to reduce the oxidation.

Lidocaine has been used for spinal anesthesia for more than 50 years, in thousands upon thousands of patients, with apparent safety. However, cauda equina syndrome, sacral nerve root deficits, or transient neurologic toxicity can occur after subarachnoid injection of lidocaine. Neurotoxicity of local anesthetics is concentration dependent and is not unique to lidocaine. Some investigators have speculated that slow injection of local anesthetic through a spinal microcatheter results in maldistribution and pooling of high concentrations of hyperbaric lidocaine in the cauda equina area, resulting in increased risk for neurotoxicity and cauda equina syndrome.

Milder manifestations of neurotoxicity also may occur. As early as 1954, mild, transient neurologic symptoms were reported after spinal anesthesia with lidocaine. Transient neurologic symptoms (TNS) (dysesthesia or low back pain radiating to the buttocks, thighs, and calves) have been observed in surgical patients even after conventional (i.e., single-shot) spinal anesthesia with hyperbaric 5% lidocaine (see Chapter 31). In response to concerns that intrathecal injection of hyperbaric 5% lidocaine might be associated with TNS, in 1994 the FDA Advisory Committee on Anesthetic Drugs recommended that the injected drug concentration be reduced by dilution with an equal volume of either preservative-free saline or CSF. However, Pollock et al. reported that there was no difference in the incidence of TNS when spinal lidocaine 50 mg was diluted to 2%, 1%, or 0.5% solutions before administration and that the overall incidence of TNS did not differ from that of historic controls given 5% lidocaine.

Interestingly, the exposure of frog sciatic nerve to lidocaine results in a progressive, irreversible loss of impulse activity beginning at a concentration of 1%. The investigators of this study noted that “the range of lidocaine that produces such changes in mammalian nerve awaits determination.” Meanwhile, it seems prudent to take the following precautions:
1. Dilute the commercial 5% lidocaine for intrathecal injection as recommended by the FDA.
2. Administer the lowest possible dose.
3. Avoid the use of hyperbaric lidocaine in clinical conditions (e.g., obesity) or situations (e.g., the lithotomy position) that may be associated with a higher incidence of TNS.

Generally, if pencil-point, side-hole spinal needles are used, it is recommended that the injection port should be directed cephalad. However, an epidemiologic survey did not implicate dose and needle-bevel direction as factors that affect the risk for TNS. A meta-analysis of randomized controlled trials comparing spinal lidocaine with other local anesthetics (bupivacaine, prilocaine, procaine, and mepivacaine) found that the relative risk (RR) for development of TNS was higher with lidocaine than with the other local anesthetic agents (RR, 4.35; 95% confidence interval [CI], 1.98 to 9.54). It has not been conclusively proven that TNS are manifestations of neurotoxicity.

Pregnancy may be associated with a reduced risk for TNS. Studies suggest that the incidence of TNS after spinal anesthesia with lidocaine or bupivacaine is equally low (< 3%) in women having cesarean delivery and those undergoing postpartum tubal ligation.

**Allergic Reactions**

True allergy to a local anesthetic is rare. Further, anaphylactic and anaphylactoid reactions may be the result of additives such as methylparaben and metabisulfite. Experts judged that only 15% of patients referred to an allergy clinic for suspected local anesthetic allergy actually had a clinical reaction (urticaria, bronchospasm, facial edema, and/or cardiovascular instability) consistent with a real allergic response. Adverse reactions (e.g., CNS and cardiovascular symptoms) may mimic hypersensitivity but not actually be a result of hypersensitivity. The potential range of allergic manifestations is listed in Box 13.2.

Obstetricians should refer women with alleged allergy to an anesthesiologist for appropriate evaluation well before the expected date of delivery. In many cases, a carefully obtained history excludes true hypersensitivity. If IgE-mediated hypersensitivity is suspected, patients should be referred to an allergist for further evaluation. Skin prick or intradermal testing using appropriate positive (dilated histamine) and negative (normal saline) controls is recommended. Intradermal testing is more sensitive but is associated with a false-positive rate of 8% to 15%. If the skin testing is negative, subcutaneous provocative dose testing is a useful method to confirm that the drug is safe to use clinically. Alternatively, if skin testing is positive, the testing sequence (skin testing followed by provocative subcutaneous testing) should be repeated with an alternative agent.
The subcutaneous provocative test can be performed by any physician qualified to manage hypersensitivity reactions. Appropriate emergency equipment and drugs (e.g., epinephrine, H1- and H2-receptor antagonists) should be immediately available. Establishing intravenous access before testing is prudent. The back and the ventral aspects of the forearm are the preferred sites for testing. Areas with abnormal skin coloration or dermographia should be avoided. A history of recent treatment with antihistamines, salicylates, or corticosteroids may alter the test results.109

The following protocol has been proposed by Chandler et al.110 (Table 13.2).111 After a negative needle-prick test, increasing volumes of undiluted local anesthetic (typically 1% concentration) are injected subcutaneously at 15-minute intervals. In patients with an especially strong history of a prior severe reaction, the series may be preceded by injection of diluted solutions (e.g., a 1:100 solution, followed by a 1:10 solution). A fresh syringe should be used for each subsequent injection. A negative control and a positive control injection may also be used. A local anesthetic that is not in the same class as the drug in question should be tested; if an ester is suspected as the offending agent, a local anesthetic that is not in the same class as the drug in question should be tested. If possible, the drug tested should be suitable for local infiltration and for epidural and subarachnoid block.

The test is considered positive if there is a change in the patient’s clinical status or if a skin wheal more than 10 mm in diameter, with or without a flare, arises within 10 minutes of injection and persists for at least 30 minutes.109 If provocative dose testing is completed without a reaction, the local anesthetic used and the final dose given should be recorded; the patient (and the referring physician) should be informed that her risk for an adverse reaction to subsequent administration of that drug and dose is no greater than that for the general population.110,111

**Management of an allergic reaction.** Pharmacologic therapy of a severe allergic reaction involves (1) inhibition of mediator synthesis and release, (2) reversal of the effects of these mediators on target organs, and (3) prevention of the recruitment of other inflammatory processes. In general, catecholamines, especially epinephrine, but also phosphodiesterase inhibitors, antihistamines, and corticosteroids, have been used for this purpose (Box 13.3).112 Higher doses of catecholamines may be required in a patient who has a sympathetic blockade. In addition, pregnancy itself decreases responsiveness to catecholamines.115 Once the patient is stable, a serum tryptase level should be obtained; an elevated level is suggestive of anaphylaxis.

**Effects on the Uterus and Placenta**

**Uterine Blood Flow**

The association of paracervical block with fetal bradycardia has been attributed to the high concentration of local anesthetic deposited in the vicinity of the uterine arteries (see Chapter 24). Human uterine artery segments obtained at the time of cesarean hysterectomy constrict when exposed to high concentrations of lidocaine,114 mepivacaine,114 or bupivacaine.115

These findings also have been confirmed in laboratory animals. Fishburne et al.116 observed a dose-related decrease in uterine blood flow during uterine arterial infusion of 2-chloroprocaine, lidocaine, or bupivacaine in gravid ewes. A 25% reduction in uterine blood flow occurred at the following calculated plasma concentrations of local anesthetic: bupivacaine, 7 µg/mL; 2-chloroprocaine, 11.5 µg/mL; and lidocaine, 19.5 µg/mL. However, when plasma local anesthetic concentrations mimic those that occur in ordinary clinical practice, local anesthetics have no adverse effect on uterine blood flow.117-119 For example, in pregnant ewes, uterine blood flow remained unchanged during an intravenous infusion of lidocaine or bupivacaine that resulted in plasma concentrations of 0.81 to 4.60 and 1.5 to 2.0 µg/mL, respectively.117,119 Similarly, intravenous injection of 2-chloroprocaine, 0.67 and 1.34 mg/kg, did not reduce uterine blood flow velocity in pregnant guinea pigs.118

Pregnancy itself may enhance uterine vascular reactivity to local anesthetic agents. Isolated human uterine artery segments obtained from term parturients constrict at a lower lidocaine concentration than uterine artery segments from nonpregnant patients.114,120 Uterine artery sensitivity to local

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**BOX 13.2 Non–IgE-Mediated Reactions to Local Anesthetics**

- Psychomotor responses
- Vasovagal episode
- Hyperventilation or panic attack
- Endogenous sympathetic stimulation
- Responses to procedural trauma
- Delayed hypersensitivity reaction
- Non–IgE-mediated reaction to another agent
- Epinephrine
- Metabisulfite and other additives
- IgE-mediated reaction to another agent
- Additives and preservatives
- Latex
- Antibiotic


**TABLE 13.2 A Protocol for Provocative Dose Testing With Local Anesthetics**

<table>
<thead>
<tr>
<th>Step</th>
<th>Route</th>
<th>Volume (mL)</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin prick</td>
<td>0.1</td>
<td>Undiluted</td>
</tr>
<tr>
<td>2</td>
<td>Subcutaneous</td>
<td>0.5</td>
<td>Undiluted</td>
</tr>
<tr>
<td>3</td>
<td>Subcutaneous</td>
<td>1.0</td>
<td>Undiluted</td>
</tr>
<tr>
<td>5</td>
<td>Subcutaneous</td>
<td>2.0</td>
<td>Undiluted</td>
</tr>
</tbody>
</table>

*See text for initial dilution suggestions for patients with a history of severe allergy.
BOX 13.3 Management of Anaphylaxis

Immediate Management
- If cardiac arrest, follow ACLS guidelines. 86
- Discontinue or remove all triggers (e.g., chlorhexidine, synthetic colloids, latex).
- Stop procedure; use minimal volatile anesthetic agents.
- Call for help.
- Maintain airway: FiO₂ 1.0, consider need for tracheal intubation.
- Rapid large-volume fluid administration
  - Crystalloid bolus: 2 L, repeat as needed
  - Large-bore IV access
  - Elevate legs
- IV epinephrine bolus, repeat every 1–2 min as needed
  - Mild hypotension: 5–10 µg
  - Moderate hypotension: 20 µg
  - Life-threatening hypotension: 100–200 µg
- Epinephrine infusion: 3–40 µg/min (0.05–0.5 µg/kg/min)

Refractory Management
- Consider requesting more help.
- Consider cesarean delivery if still pregnant (initiate within 4 min of cardiovascular collapse).
- Make sure triggers have been removed.
- Monitoring: consider arterial line, transthoracic or transesophageal echocardiography.
- Resistant hypotension
  - Norepinephrine infusion: 3–40 µg/min (0.05–0.5 µg/kg/min)
  - Vasopressin bolus 1–2 U, then infusion 2 U/min
  - Glucagon: 1–2 mg IV every 5 min until a response
- Resistant bronchospasm
  - Continue epinephrine infusion.
  - Salbutamol metered dose inhaler 12 puffs (1200 µg)
  - Magnesium 2 g over 20 min
- Consider volatile anesthetic agent or ketamine.
- Consider other diagnoses.

Post-Crisis Management
- Consider steroids: dexamethasone 0.1–0.4 mg/kg or hydrocortisone 2–4 mg/kg.
- Consider oral antihistamines.
- Consider canceling surgical procedure, ICU monitoring.
- Investigations: draw blood for tryptase level.
- Document in medical record, letter for patient, referral for allergy assessment

Umbilical Blood Flow
Fetal well-being also depends on the adequacy of fetal perfusion of the placenta. The regulatory mechanisms that control flow through the umbilical vessels are poorly understood. Lidocaine does not affect spiral strips obtained from human umbilical artery segments at concentrations up to 5 µg/mL, but it produces relaxation in concentrations from 30 to 900 µg/mL.125 Bupivacaine also does not constrict umbilical artery segments at clinically relevant concentrations of 0.3 and 1 µg/mL.125 At higher concentrations, the effect of bupivacaine appears to be biphasic. Constriction occurs at concentrations of 5 to 25 µg/mL, and relaxation occurs at concentrations greater than 125 µg/mL.125,126 Hypercarbia but not hypoxemia lessens the contractile response of umbilical vessels to bupivacaine in vitro.127

Decreases in umbilical blood flow of as much as 43% accompany intravenous administration of lidocaine 4 mg/kg in pregnant sheep.128 However, plasma concentrations of the drug were higher than would be expected with clinical use, and all ewes exhibited signs of CNS toxicity, which may reduce umbilical blood flow itself.

Advances in noninvasive Doppler imaging have facilitated clinical assessment of umbilical cord blood flow velocity. The ratio of the systolic (S) peak to the diastolic (D) trough of the umbilical artery waveform is used as a measure of vascular resistance. The S/D ratio in the umbilical artery decreases during normal pregnancy, and high ratios usually are associated with fetal compromise (see Chapter 6). Local anesthetics administered for epidural anesthesia do not adversely affect the umbilical artery S/D ratio.129,130 In fact, labor epidural

anesthetics increases as early as the second trimester of pregnancy and may be related to an increase in estrogen.114,116 However, these studies were performed before the recognition of the importance of intact vascular endothelium in the in vitro assessment of vascular tone.

The exact mechanism by which high concentrations of local anesthetics cause uterine artery vasoconstriction (while causing dilation in other vascular beds) is unclear. This vasoconstriction may result from modulation of calcium-channel regulation because verapamil and nifedipine ablate the response.120 Alternatively, local anesthetics may affect cyclic nucleotides and alter the ionic content and contractility of uterine vascular smooth muscle.121 Clinical experience with the use of local anesthetics supports the view that clinical concentrations of these drugs do not adversely affect the uterine vasculature (see Chapter 3).122,123

All local anesthetics can reduce uterine blood flow at plasma concentrations that greatly exceed those occurring during the routine practice of obstetric anesthesia.116 There has been an added concern that the levorotary isomers of local anesthetics, which produce vasoconstriction at clinical doses,124 may reduce uteroplacental perfusion and adversely affect fetal well-being. It is reassuring to note that ropivacaine, even at plasma concentrations that are almost two times greater than would be expected to occur during clinical use, does not reduce uterine blood flow or affect fetal heart rate (FHR), blood pressure, or acid-base measurements in pregnant sheep.117 In humans, Doppler velocimetry studies have shown that ropivacaine has little effect on the uteroplacental or fetal circulation when it is administered to provide epidural anesthesia for cesarean delivery.122 Similarly, clinically relevant plasma concentrations of levobupivacaine had no adverse effect on uterine blood flow.117

ACLS. Advanced cardiac life support; IV, intravenous.
analgesia with 1.5% lidocaine or 2% 2-chloroprocaine resulted in a decrease in the S/D ratio.\textsuperscript{129,130} This favorable change may have resulted from pain relief. Other investigators have noted no appreciable change or a slight decrease in the S/D ratio after the epidural administration of amide local anesthetics for elective cesarean delivery.\textsuperscript{122,123,131}

**Uterine Tone and Contractility**

Changes in uterine tone and contractility may affect uteroplacental perfusion. Local anesthetics exert direct effects on uterine smooth muscle. One study reported that exposure to high concentrations of local anesthetic *in vitro* led to contraction of human myometrial segments obtained at the time of cesarean delivery.\textsuperscript{132} These findings have been corroborated in laboratory animals.\textsuperscript{133} Further, Belitzky et al.\textsuperscript{134} observed that direct intramyometrial injection of 1% procaine resulted in uterine hyperstimulation and fetal compromise in pregnant women. In all of these reports, the myometrium was exposed to higher than normal concentrations of the drug. In other studies, however, intravenous infusion of lidocaine or bupivacaine that resulted in clinically relevant plasma concentrations did not affect uterine tone or uterine activity in pregnant ewes.\textsuperscript{137,139} In a study using electrohysterogram monitoring, levobupivacaine caused less uterine muscle relaxation after intramyometrial injection in rats than did bupivacaine.\textsuperscript{135}

**Drug Interactions with 2-Chloroprocaine and Lidocaine**

Epidural 2-chloroprocaine may affect the efficacy of other drugs administered in the neuraxis. Previous administration of 2-chloroprocaine (even a test dose) has been observed to reduce the quality and duration of analgesia produced by subsequent epidural injection of morphine or fentanyl.\textsuperscript{136,137} Several hypotheses have been proposed for this antagonism. The low pH of the 2-chloroprocaine solution may result in acidification of the epidural space and thus may favor formation of the poorly diffusible, charged form of the opioid. Second, it has been suggested that 2-chloroprocaine (or its metabolite, chloroaminobenzoic acid) may act as a specific \(\mu\)-opioid receptor antagonist because a \(\kappa\)-opioid receptor agonist (e.g., butorphanol) is not antagonized by 2-chloroprocaine.\textsuperscript{138} However, using an *in vitro* hippocampal slice model, Coda et al.\textsuperscript{139} concluded that 2-chloroprocaine opioid antagonism did not appear to act through a \(\mu\)-opioid receptor. Third, and most likely, a “window” may be caused by the rapid regression of 2-chloroprocaine before the onset of analgesia with epidural morphine.

2-Chloroprocaine also reduces the subsequent efficacy of bupivacaine.\textsuperscript{140} Corke et al.\textsuperscript{141} suggested that chlooraminobenzoic acid is responsible for this effect. Administration of buffered 2-chloroprocaine does not prevent the antagonism of epidural bupivacaine.\textsuperscript{142}

The use of neuraxial opioids alone or in combination with local anesthetics has become ubiquitous in obstetric anesthesia for enhancing analgesia during labor or for providing effective pain relief after cesarean delivery. Lidocaine is a frequently used drug for epidural anesthesia during cesarean delivery. In one study,\textsuperscript{143} epidural administration of 20 to 35 mL of 2% lidocaine with fentanyl 1 hour before administration of extended-release epidural morphine (EREM) increased the peak plasma concentration \(C_{\text{max}}\) of morphine compared with the peak concentration in women who received a combined spinal-epidural (CSE) technique (intrathecal bupivacaine and fentanyl) with no prior epidural medication (see Chapter 27).

**Potency of Bupivacaine, Ropivacaine, and Levobupivacaine**

The levorotary compounds ropivacaine and levobupivacaine were developed because of the concerns about the safety of high doses of bupivacaine. Many studies have addressed the question of relative potency among the three drugs. Ropivacaine is approximately 10 times less lipid soluble (\(N\)-heptane/buffer) than bupivacaine, a difference that is important for two reasons. First, ropivacaine may penetrate more slowly into the large, heavily myelinated motor neurons, resulting in less motor block than occurs with bupivacaine. Second, the issue raises questions as to whether ropivacaine is equipotent to bupivacaine. Indeed, a higher dose of ropivacaine is required to produce a sensory and motor block comparable with that produced by bupivacaine after spinal injection.\textsuperscript{143,144} Similarly, the \(EC_{50}\) (the local anesthetic concentration at which 50\% of women have pain relief, also known as the minimum local anesthetic concentration [MLAC]) of epidural ropivacaine is almost twice as great as that of epidural bupivacaine in laboring women.\textsuperscript{58} Critics of the use of \(EC_{50}\) data to compare potency argue that it provides no information on the shape and slope of the dose-effect relationship, which can vary with drug concentration, and further, that it provides no information on the effective clinical dose (ED\(_{95}\) [effective dose in 95\% of cases]).\textsuperscript{145}

Studies of the \(EC_{50}\) of epidural levobupivacaine are conflicting; one study found that levobupivacaine was essentially equipotent to bupivacaine,\textsuperscript{59} whereas others suggest that ropivacaine and levobupivacaine have similar potency.\textsuperscript{146,147} Levobupivacaine may have a greater motor-sparing effect than bupivacaine when given for the initial intrathecal injection.\textsuperscript{148}

In obstetric anesthesia practice, the clinical effects of epidural levobupivacaine and ropivacaine are indistinguishable from those of epidural bupivacaine for labor analgesia.\textsuperscript{149} The choice of bupivacaine, levobupivacaine, or ropivacaine does not affect the method of delivery or neonatal condition.\textsuperscript{149} For cesarean delivery, epidural levobupivacaine 0.5\% is virtually identical to epidural bupivacaine 0.5\%.\textsuperscript{150} The levorotary isomers (ropivacaine and levobupivacaine) may provide a greater margin of safety when large volumes of a concentrated solution of local anesthetic are required (e.g., epidural anesthesia for cesarean delivery). However, there may be little advantage to using levobupivacaine or ropivacaine when dilute solutions are used for epidural labor analgesia or when a small dose is used for spinal anesthesia.

**Placental Transfer**

Most drugs, including local anesthetics, cross the placenta. The factors that influence the placental transfer of a
Drug include (1) the physicochemical characteristics of the drug, (2) the concentration of free drug in the maternal blood, (3) the permeability of the placenta, and (4) the hemodynamic events occurring within the fetal-maternal unit (see Chapter 4).

Local anesthetics cross placental membranes by a process of simple (i.e., passive) diffusion. The rate of transfer of a particular drug is described by the Fick equation, as follows:

\[
\frac{Q}{t} = \frac{KA(C_m - C_f)}{D}
\]

where \(Q/t\) is the rate of diffusion; \(K\) is the diffusion constant for the drug; \(A\) is the surface area available for transfer; \(C_m\) is the free drug concentration in the maternal blood; \(C_f\) is the free drug concentration in the fetal blood; and \(D\) is the thickness of the trophoblastic epithelium. In general, \(K\) is affected by molecular size, lipid solubility, and degree of ionization.

**Molecular Size**

Compounds with a molecular weight of less than 500 Da cross the placenta easily, whereas drugs like digoxin, which have a molecular weight higher than 500 Da, have a slower rate of diffusion. Molecular weights of local anesthetics range from 234 to 288 Da (see Table 13.1). These small differences in molecular weight should not affect the rate of placental transfer because the diffusion constant \((K)\) is inversely proportional to the square root of the molecular weight.\(^{151}\)

**Ionization and Lipid Solubility**

Local anesthetics are weak bases; they have a relatively low degree of ionization and considerable lipid solubility at physiologic pH. The basic un-ionized local anesthetic molecule is more lipid soluble than the ionized moiety and determines placental transfer in a protein-free perfusate.\(^{152}\)

The relationship between pH and pKa may affect drug accumulation in the fetus. For the amide local anesthetics, pKa values are close enough to physiologic pH that changes in fetal pH may alter the balance between ionized and un-ionized drug. In the acidic fetus, a greater proportion of drug in the ionized form results in a larger total amount of ionized drug. In the acidotic fetus, a greater proportion of the free drug concentration in the maternal blood; of protein binding on placental transfer. Amide local anesthetics have a molecular weight higher than 500 Da, have a slower rate of diffusion. Molecular weights of local anesthetics range from 234 to 288 Da (see Table 13.1). These small differences in molecular weight should not affect the rate of placental transfer because the diffusion constant \((K)\) is inversely proportional to the square root of the molecular weight.\(^{151}\)

**Protein Binding**

Perhaps most confusing and least understood are the effects of protein binding on placental transfer. Amide local anesthetics are bound to AAG and to a lesser extent to albumin.\(^{19}\) The extent of protein binding varies among the local anesthetic agents (see Table 13.1). For a given local anesthetic, the proportion of free drug increases as blood concentration increases because of the saturation of binding sites. Binding of local anesthetics in the fetal plasma is approximately half that in the mother.\(^{88,89}\)

The fetal-to-maternal (F/M) blood concentration ratios of amide local anesthetic agents are listed in Table 13.1. The lower F/M blood concentration ratios of highly protein-bound drugs (e.g., bupivacaine) have been attributed to their more restricted placental transfer compared with less protein-bound drugs (e.g., lidocaine). Indeed, the rate of bupivacaine transfer across rabbit placenta perfused in situ is lower than that of lidocaine transfer.\(^{156,157}\) Some investigators have suggested that protein binding in the maternal plasma should not affect the diffusion of drugs across the placenta because the dissociation from plasma proteins is essentially instantaneous.\(^{151,158}\) In subsequent studies, the relatively low umbilical vein-to-maternal vein blood concentration ratio for bupivacaine has been attributed to differences in protein binding between maternal plasma and fetal plasma (Fig. 13.5).\(^{88,89,159,160}\)

Let us assume that the total concentration of lidocaine or bupivacaine in the maternal plasma is 2 mg/L. Lidocaine and bupivacaine are approximately 50% and 90% bound to maternal plasma proteins, respectively. Thus, the free concentrations of drug available for placental transfer are 1.0 and 0.2 mg/L, respectively. At equilibrium, the concentration of free drug is equal on the two sides of the placenta. In the fetus, however, lidocaine and bupivacaine are approximately 25% and 50% bound to fetal plasma proteins, respectively. Thus, the total lidocaine concentration in fetal plasma is 1.33 mg/L, resulting in an F/M ratio of 0.67; for bupivacaine, the corresponding values are 0.4 mg/L and 0.2.

In fact, accumulation of bupivacaine occurs in human fetuses whose mothers received the drug for epidural anesthesia.\(^{24}\) After delivery, measurable plasma and urine concentrations persisted for as long as 3 days.\(^{24}\) In vitro studies using a perfused human placental model have found that the placental transfer of ropivacaine is similar to that of bupivacaine.\(^{161}\) Intravenous infusion of ropivacaine or bupivacaine to pregnant sheep results in steady-state maternal plasma concentrations of 1.5 to 1.6 µg/mL and fetal concentrations of approximately 0.28 µg/mL.\(^{17}\) Tissue concentrations of ropivacaine in fetal heart, brain, liver, lung, kidneys, and adrenal glands were similar to those of bupivacaine.\(^{17}\) Datta et al.\(^{10}\) noted that the free fraction of ropivacaine at delivery was approximately twice that of bupivacaine in neonates whose mothers received the drug for epidural anesthesia during labor or cesarean delivery.
Maternal Blood Concentration of Drug

The maternal blood concentration of local anesthetic is determined by (1) the dose, (2) the site of administration, (3) metabolism and excretion, and (4) the effects of adjuvants such as epinephrine (see later discussion). For a given local anesthetic, the maternal blood concentration determines fetal drug exposure and is the only variable of the Fick equation that may be influenced by the clinician.

**Dose.** In general, higher doses result in higher maternal and fetal blood concentrations. For example, Kuhnert et al. found that doubling the mean (± SD) dose of epidural lidocaine from 300 ± 195 mg to 595 ± 127 mg almost doubled the concentration in umbilical cord blood. The elimination half-life of amide local anesthetics is relatively long; thus, repeated epidural injection or continuous infusion of the drug may lead to accumulation in the maternal plasma. This does not apply to 2-chloroprocaine, however, which is rapidly hydrolyzed by pseudocholinesterase.11

**Site of administration.** The rates of absorption and peak plasma concentrations depend on the vascularity at the site of administration. The peak plasma concentration of lidocaine is achieved within 9 to 10 minutes after paracervical block.162 In contrast, absorption from the lumbar epidural space, which is less vascular, occurs at a slower rate; the peak plasma concentration is not achieved until 25 to 40 minutes after administration.17 Injection of local anesthetic into the caudal rather than the lumbar epidural space may result in higher blood levels because of the need for a higher drug volume to provide comparable anesthesia to that provided by lumbar epidural injection.163

The transversus abdominis plane (TAP) block is sometimes used for postcesarean delivery analgesia. In a study of TAP block with bupivacaine 100 mg (50 mg on each side), plasma levels of drug reached the low toxic range in 3 of 17 parturients.164 No women exhibited signs or symptoms of LAST.164

In the past, it was thought that subarachnoid administration of a local anesthetic resulted in less systemic absorption than epidural administration. However, peak blood concentrations of lidocaine have been reported to be similar after subarachnoid and epidural administration.165 In another study, subarachnoid administration of lidocaine 75 mg for cesarean delivery resulted in low but measurable fetal plasma concentrations of the drug.16

**Placenta.** Maturation of the placenta may affect the rate of drug transfer. In pregnant mice, diazepam and its metabolites cross the placenta more rapidly in late pregnancy.166 Uptake and metabolism of drugs by the placenta would be expected to reduce transfer to the fetus. However, placental drug uptake of local anesthetics is limited, and it is unlikely that this organ metabolizes the amide local anesthetic agents.167 The same may not be true for the ester local anesthetics. For example, cocaine is biotransformed when it is incubated with human placental microsomal fraction, presumably because of cholinesterase activity within the placenta.166 Placental metabolism of para-aminobenzoic acid also has been demonstrated.169

**Teratogenicity**

The teratogenicity of local anesthetics is not an issue during parturition, but local anesthetics often are used for procedures during the first trimester of pregnancy (see Chapter 17). In vitro studies have suggested that local anesthetics may have some adverse developmental effects. Even at low concentrations, these agents have caused reversible reduction of cell division in tissue culture.176–177 However, structural anomalies...
have not been observed in intact animals.\textsuperscript{176–179} Mid-pregnancy administration of lidocaine or mepivacaine in rats has been associated with behavioral changes in the offspring.\textsuperscript{179,180}

Extrapolation of laboratory findings to humans is tenuous for several reasons. First, a drug may be teratogenic in one species but not in others. Second, a 1-hour drug exposure in a pregnant rat (with a gestation of 21 days) is excessive and not analogous to several hours of clinical anesthesia during human pregnancy. Third, the doses of local anesthetics used in animal studies greatly exceed those administered for clinical anesthesia. Indeed, a large, multicenter study demonstrated that the risk for congenital anomalies in humans was not increased by the administration of benzocaine, procaine, tetracaine, or lidocaine during early pregnancy.\textsuperscript{181} However, a twofold increase in the incidence of congenital anomalies was noted in infants whose mothers had received mepivacaine. The small number of patients who received mepivacaine in this study ($n = 82$) and the fact that no adverse effects occurred with the use of other amide agents have raised doubts about the validity of this observation.\textsuperscript{182}

**Fetal and Neonatal Effects**

**Pharmacokinetics**

Local anesthetics, once transferred across the placenta, are distributed in the fetus. Factors that influence tissue uptake of the drug include (1) fetal plasma protein binding, (2) lipid solubility, (3) the degree of ionization of the drug, and (4) hemodynamic changes that affect the distribution of fetal cardiac output. Fetal plasma protein-binding capacity of local anesthetics is approximately 50% that of maternal plasma.\textsuperscript{88,89,183} Thus, there is greater availability of free drug in the fetus than in the mother.\textsuperscript{88,89,183–185} Studies have examined the distribution of lidocaine in fetal tissues after an intravenous injection of the drug to animals.\textsuperscript{18,186} The higher concentration of lidocaine in the liver, myocardium, and brain (compared with other fetal tissues) reflects rapid distribution of the drug to highly perfused tissues. Only the liver had lidocaine concentrations that exceeded those in the mother. This finding is not surprising, given the high lipid content of the fetal liver and the fact that it receives most of the blood returning from the placenta by means of the umbilical vein.\textsuperscript{186} Fetal asphyxia results in adaptations that increase blood flow to vital organs (e.g., brain, heart, adrenal glands).\textsuperscript{187} The concentration of lidocaine in these organs is higher in asphyxiated fetuses than in healthy fetuses.\textsuperscript{155,187}

Any drug that reaches the fetus undergoes metabolism and excretion. The term newborn has the hepatic enzymes necessary to metabolize local anesthetics.\textsuperscript{16,17,188–190} Nonetheless, the elimination half-life of these drugs is longer in the neonate than in the adult.\textsuperscript{189,190} The use of mepivacaine in obstetric epidural analgesia fell into disfavor after a report indicating that the elimination half-life of the drug in the neonate was approximately 9 hours, or three times as long as the neonatal half-life for lidocaine.\textsuperscript{191} It is ironic that the neonatal elimination half-life for bupivacaine may be as long as 14 hours.\textsuperscript{192} In contrast, a study suggested that lidocaine had greater placental transfer in term pregnant women having epidural analgesia for labor than the bupivacaine enantiomers.\textsuperscript{193} The study is difficult to interpret because single time-point concentrations of drugs were compared in the maternal vein and the umbilical artery and vein; the F/M ratio may reflect the difference in plasma protein binding between the mother and the fetus and not placental drug transfer.\textsuperscript{89,90,160,161}

Morishima et al.\textsuperscript{190} compared the pharmacokinetics of lidocaine among adult ewes and fetal and neonatal lambs. The metabolic (hepatic) clearance in the lambs was similar to that in adults, but renal clearance was greater in adults. Nonetheless, the elimination half-life was prolonged in the lambs. This latter finding has been attributed to a greater volume of distribution in the neonatal lamb. Thus, at any given time, a smaller fraction of lidocaine accumulated in the body is available for clearance by hepatic metabolism. The greater renal clearance noted in neonates is a result of decreased protein binding, which increases the proportion of drug available for excretion.

The elimination half-life of local anesthetics in the fetus is similar to that in the adult because, unlike the newborn, the fetus can excrete drug across the placenta back to the mother.\textsuperscript{88,190} With bupivacaine, this transfer may occur even though the total plasma drug concentration in the mother may exceed that in the fetus.\textsuperscript{88}

**Systemic Toxicity**

In general, the neonate is more sensitive than the adult to the depressant effects of drugs. However, the seizure threshold for local anesthetics in the neonate appears to be similar to that in the adult. Morishima et al.\textsuperscript{194} compared the relative CNS toxicity and cardiovascular toxicity of lidocaine in adult ewes and fetal and neonatal lambs. Greater doses (when calculated on a milligram-per-kilogram basis) were required to elicit toxic manifestations in the fetus and neonatal lamb than in the adult. However, the plasma concentrations of the drug associated with toxic manifestations were similar in the three groups of animals. The greater dose tolerated by fetuses than by neonates and adults was attributed to placental clearance of drug back to the mother and better maintenance of blood gas tensions during convulsions. In the neonate, a large volume of distribution is most likely responsible for the high doses of local anesthetic required for fetal toxicity.

Studies of bupivacaine cardiotoxicity are inconsistent. In vitro, the sinoatrial node of neonatal guinea pigs was found to be more sensitive than that of adults to the cardio depressant effect of bupivacaine.\textsuperscript{195} In contrast, 2-day-old piglets demonstrated greater resistance than older animals to the arrhythmogenic and CNS effects of bupivacaine.\textsuperscript{196}

**Fetal Heart Rate**

Changes in FHR after administration of local anesthetics are most often related to indirect effects such as maternal hypotension and uterine tachysystole (see Chapter 23). Local anesthetics probably have little direct effect on FHR, except perhaps after paracervical block. Rather, labor itself may be the single most important factor that alters FHR patterns.\textsuperscript{197} Transient changes in FHR variability and an increase in the
incidence of periodic decelerations have been observed during neuraxial analgesia in laboring women. In contrast, in the absence of labor, FHR patterns are not affected even by the larger doses of local anesthetics required during epidural anesthesia for cesarean delivery. The FHR changes noted in laboring women were transient and did not affect the condition of the newborns. Further, Becker et al. found no significant difference in the number or type of fetal electrocardiographic ST-segment changes (ST-waveform analysis [STAN] events) in women with a high-risk singleton gestation who received epidural analgesia for labor compared with a control group of women who did not receive epidural analgesia.

Neurobehavioral Tests
Many neurobehavioral tests have been developed to detect subtle changes in organized behavior in the newborn. However, these tests are not reliable because they are subjective and lack specificity. Other perinatal factors appear to have a more important effect on neonatal test performance than the choice of local anesthetic.

Preterm Fetus and Newborn
It has become axiomatic that the preterm infant is more vulnerable than the term infant to the effects of analgesic and anesthetic drugs. Causes of enhanced drug sensitivity in the preterm newborn that have been postulated are as follows: (1) less protein is available for drug binding, (2) higher levels of bilirubin are present and may compete with the drug for protein binding, (3) greater access of the drug to the CNS occurs because of a poorly developed blood-brain barrier, (4) the preterm infant has greater total body water and less fat content, and (5) the preterm infant has a diminished ability to metabolize and excrete drugs. Unfortunately, few systematic studies have determined the maternal and fetal pharmacokinetics and pharmacodynamics of drugs throughout gestation; nevertheless, these deficiencies of the preterm infant may not be as serious as we have been led to believe. Although the plasma albumin and AAG concentrations are lower in the preterm fetus, these factors primarily affect drugs that are highly bound to these proteins. Most local anesthetics, however, exhibit only low to moderate degrees of binding in fetal plasma.

The placenta efficiently eliminates fetal bilirubin. Thus, the hyperbilirubinemia of prematurity normally occurs in the postpartum period. Bupivacaine has been implicated as a possible cause of neonatal jaundice. High affinity of the drug for fetal erythrocyte membranes may lead to a decrease in filterability and deformability, which may render red blood cells more prone to hemolysis. However, increased bilirubin production has not been demonstrated in newborns whose mothers received bupivacaine for epidural anesthesia during labor and cesarean delivery.

Greater total body water in the preterm fetus results in a larger volume of distribution for drugs. Thus, to achieve equal blood concentrations, the immature fetus must receive a greater amount of drug transplacentally than the mature fetus. The diminished ability to metabolize or excrete drugs associated with prematurity is certainly not a universal phenomenon. One study of the pharmacokinetics of lidocaine in preterm newborns noted that plasma clearance was similar to that in adults.

During anesthesia for preterm labor, concerns about drug effects on the newborn are far less important than the prevention of asphyxia and trauma to the fetus. Indeed, healthy preterm fetal lambs tolerated clinically relevant plasma concentrations of lidocaine (e.g., approximately 1.5 µg/mL) as well as mature ones. Asphyxia
Circulatory adaptations important for fetal survival during asphyxia result in increased blood flow and oxygen delivery to vital organs (e.g., heart, brain, adrenal glands). Little information exists about the effects of local anesthetics on these fetal responses. Adaptation to asphyxia was unaffected in mature fetal lambs exposed to lidocaine. In contrast, lidocaine adversely affected asphyxiated preterm fetal lambs, which experienced a further deterioration of acid-base status and a reduction in cardiac output and blood flow to the brain and heart (Fig. 13.6). Also in asphyxiated preterm fetal lambs, exposure to bupivacaine reduced blood flow to vital organs; however, FHR, blood pressure, and acid-base measurements did not change.

After performing an in vitro study using perfused human placenta, Johnson et al. suggested that bupivacaine might be preferable to lidocaine in the presence of fetal acidosis because the greater maternal protein binding of bupivacaine may limit its placental transfer. However, this methodology does not consider the potential for greater fetal tissue uptake of bupivacaine (than of lidocaine) because it is more lipid soluble and more protein bound than lidocaine.

In 1997, Santos et al. reported that the effects of bupivacaine appeared less severe than those of lidocaine in asphyxiated preterm fetal lambs. However, the lidocaine data were generated in a separate experiment reported in 1989. There are inherent limitations in a historical comparison of two studies performed 8 years apart. Further, it is unclear whether these findings are applicable to humans because both lidocaine and bupivacaine have enjoyed a long history of safe use in obstetric anesthesia practice; prospective clinical studies are required before one drug can be recommended over the other in the setting of fetal asphyxia.

OPIOIDS
Neuraxial opioid administration is unique in that it produces analgesia without loss of sensation or proprioception. Opioids are often co-administered with local anesthetic agents during intrapartum administration of neuraxial analgesia and anesthesia.

The term opioid refers to a series of compounds that are related to opium. These compounds may be classified as follows: (1) naturally occurring (e.g., morphine), (2) semi-synthetic compounds (e.g., dihydromorphone), and (3)
Three broad opioid receptor systems have been identified: µ (mu: MOR), δ (delta: DOR), and κ (kappa: KOR) receptors. Although there is a fourth receptor system, the opiate receptor–like protein (ORL1 or NOP), its role in pain modulation is not well characterized. Each opioid receptor is encoded by a different gene and mediates different physiologic effects. Although all these receptors may be involved with pain processing, the µ and κ receptors have the most important clinical pharmacologic effects.

Common pharmacologic effects (e.g., analgesia, respiratory depression) of morphine are mediated by µ-opioid receptors. Widely distributed throughout the brain and spinal cord, the µ, δ, and κ receptors are also present in a wide variety of peripheral tissues, including vascular, cardiac, airway/lung, and the gut. Opioids also act at several receptor sites with different affinities. Morphine has the greatest affinity for µ receptors and has less affinity for δ and κ receptors. However, morphine also has effects at δ and κ receptors when higher doses are administered. Responsible for analgesic, sedative, dysphoric, and diuretic effects, δ and κ receptors are located both within the CNS and peripherally. Peripheral κ agonists have been shown to modulate visceral pain, particularly in conditions that involve inflammation.

The δ receptor is responsible for mediating some of the analgesic effects of the endogenous opioids (e.g., enkephalins, prodynorphin, pro-opiomelanocortin, pro-oporphan, endomorphins) in the spinal cord. Few of the opioids have effects at the δ receptor in clinically relevant doses, but if a δ receptor agonist drug is administered in high doses (e.g., for treatment of pain in an opioid-tolerant patient), the drug may be less µ-receptor selective and produce δ-receptor effects.

Since their discovery, opioid receptors and their signaling continues to be an area of great research interest with potential development of better opioid analgesics with less risk for tolerance and addiction.

**Molecular Structure**

Naturally occurring opioids of significance can be divided into two distinct chemical classes, phenanthrenes (e.g., morphine) and benzylisoquinolines (e.g., papaverine, codeine) (Fig. 13.7). The phenanthrenes are five-ring structures, and the benzylisoquinolines are three-ring structures. The semisynthetic opioids are morphine derivatives that have undergone relatively simple modifications of the morphine molecule. However, these modifications can produce profound alterations in the pharmacologic activity of the opioid. For example, substitution of an ester for the hydroxyl group on carbon 6 of morphine results in hydromorphone (Fig. 13.8). Synthetic opioids can be classified into the following four groups: (1) morphinan derivatives (e.g., levorphanol),

---

**Fig. 13.6** Blood flow to the brain and heart in the preterm fetal lamb before and during asphyxia and during exposure to lidocaine while asphyxiated (mean ± SEM). *Significantly different from control. †Significantly different from asphyxia. (Modified from Morishima HO, Pedersen H, Santos AC, et al. Adverse effects of maternally administered lidocaine on the asphyxiated preterm fetal lamb. *Anesthesiology.* 1989;71:110–115.)
(2) diphenyl or methadone derivatives (e.g., methadone, d-propoxyphene), (3) benzomorphan derivatives (phenazocine, pentazocine), and (4) phenylpiperidines (e.g., meperidine, fentanyl, alfentanil, sufentanil, remifentanil).

Morphine is the prototypical opioid with a five-ring structure that conforms to a T shape. Three of the rings lie in one plane, and the other two rings are perpendicular to the plane (Fig. 13.9). Although the analgesic activity of the opioid depends on its stereoechemical structure, the levorotary isomer is usually the only isomer capable of producing analgesia. Morphine demonstrates several other characteristics that are common to other opioids: (1) a tertiary, positively charged basic nitrogen; (2) a quaternary carbon that is separated from the basic nitrogen by an ethane chain and attached to a phenyl group; (3) a phenolic hydroxyl group (morphine derivatives) or a ketone group (meperidine); and (4) the presence of an aromatic ring.

A phenylpiperidine structure (i.e., an aromatic ring attached to a six-member ring containing five carbons and one nitrogen) is also part of the morphine molecule and is present in some other opioids (e.g., fentanyl) (Fig. 13.10). Phenylalanine and tyrosine moieties are structural elements that are important to all opioids, including endogenous neurotransmitters and modulators.

**Mechanism of Action**

Since first described in 1979, neuraxial opioid administration has become a mainstay in obstetric anesthesia practice. Clinical and laboratory research has focused on the mechanisms of synaptic transmission as well as the study of opioids and neurotransmitters that modulate this transmission.

Pain perception involves a complex series of nociceptive transmissions that begin with stimulation of sensory nerves in the periphery, resulting in generation of action potentials within the spinal cord and synaptic transmission to other supraspinal sites. Intraspinal administration of an opioid exploits the pharmacology of pain-modulating and pain-relieving systems that exist within the spinal cord (see Fig. 20.9). In early studies, Yaksh demonstrated that morphine could produce selective suppression of nociceptive processing without affecting motor function, sympathetic tone, or proprioception when it was administered to the superficial layers of the dorsal horn of the spinal cord. However, when small amounts of opioid were administered to the cortex, the effects on nociceptive processing were negligible. Collectively, this work demonstrated that small doses of opioid can be selectively administered to a receptor site (i.e., spinal cord) and produce profound analgesia. In contrast, systemic administration of a much larger dose of opioid results in activation of multiple central and peripheral receptors to produce analgesia, but with unwanted side effects.

**TABLE 13.3 Subtypes of Opioid Receptors**

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Physiologic Response</th>
<th>Receptor Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (µ)</td>
<td>Analgesia</td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
<td>Sufentanil</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Meperidine</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased gastrointestinal transit</td>
<td></td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Analgesia</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Pentazocine</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diuresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychotomimesis</td>
<td></td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Analgesia</td>
<td>Prodynorphin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endomorphins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enkephalins</td>
</tr>
</tbody>
</table>

**Fig. 13.7** Naturally occurring opioids: phenanthrenes (e.g., morphine) and benzylisoquinolines (e.g., papaverine).

**Fig. 13.8** Semisynthetic opioids are morphine derivatives. For example, substitution of an ester for the hydroxyl group on carbon 6 of morphine results in hydromorphone.

Fig. 13.9 The T-shaped molecule of morphine.
Opioid receptors are nonuniformly distributed throughout the CNS. Although parenterally administered opioids most likely have both direct spinal and supraspinal effects, neuraxially administered opioids block the transmission of pain-related information by binding at presynaptic and postsynaptic receptor sites in the dorsal horn of the spinal cord (i.e., Rexed laminae I, II, V) (Fig. 13.11). However, the rate and extent of neuraxial analgesia depends largely on the specific drug’s physicochemical properties and ability to reach the opioid receptors in the spinal cord.

**Pharmacokinetics and Pharmacodynamics**

Many of the pharmacologic differences observed among neuraxially administered opioids depend on an opioid’s ability to reach opioid receptors. An opioid’s physicochemical properties, especially lipophilicity or hydrophilicity, largely determine the bioavailability of neuraxially administered opioids as well as the drug’s ability to produce spinally mediated analgesia.

Before G protein–receptor activation can occur, the opioid must undergo a series of complex processes. Although several mechanisms have been proposed to explain the movement of opioids from the epidural space to the spinal cord, studies demonstrate that the only relevant mechanism is diffusion through the spinal meninges. The opioid must traverse the dura and arachnoid membranes, diffuse through the CSF, and cross the pia membrane to reach the spinal cord (Fig. 13.12). Once the drug reaches the surface of the spinal cord, it must diffuse through the white matter and then the gray matter to reach the site of action, the dorsal horn. The rate and extent of opioid transfer to receptors largely depend on a drug’s physicochemical properties, particularly lipid solubility, because competing processes (e.g., uptake into the epidural fat or systemic circulation) limit the agent’s diffusion to opioid receptors. Greater lipid solubility of a drug results in more rapid onset of analgesia. For example, fentanyl is a highly lipid-soluble opioid (i.e., 600 times more lipid soluble...
Systemic side effects: 
- Pruritus 
- Nausea 
- Vomiting 
- Respiratory depression 

Fig. 13.12 Epidural opioids traverse the dura and arachnoid membranes, diffuse through cerebrospinal fluid, and cross the pia membrane before reaching the spinal cord. Several factors, including physicochemical properties (e.g., pKₐ), affect the distribution of opioids within the neuraxis. (From Ross BK, Hughes SC. Epidural and spinal narcotic analgesia. Clin Obstet Gynecol. 1987;30:552–565.)

than morphine); therefore, it has a more rapid onset of action than morphine (Table 13.4).

Latency, potency, and duration are also affected by other physicochemical properties, including molecular weight, pKₐ, and protein binding. For example, the lower the pKₐ, the greater the percentage of opioid existing in uncharged form (i.e., the anionic base) at a pH of 7.4. In the uncharged form, opioids penetrate the dura mater and dorsal horn more easily, resulting in a more rapid onset of analgesia.

The boundaries of the epidural space are the vertebral bodies, ligaments, and spinal meninges. Fat and the epidural venous plexus account for a large volume of the epidural space. The spinal meninges consist of the dura, arachnoid, and pia mater. Of these membranes, the arachnoid is the primary barrier for drug transfer from the epidural space to the spinal cord. The arachnoid mater has multiple layers of overlapping cells that represent both a hydrophilic domain (consisting of extracellular and intracellular fluid) and a hydrophobic domain (the cell membranes). For an opioid to navigate the arachnoid, it must diffuse through both domains before entering the CSF. Therefore, drugs of intermediate hydrophobicity move most readily across the arachnoid. Other physical characteristics of drugs (e.g., molecular weight) do not appear to play an important role in determining redistribution from the epidural space to the subarachnoid space.

The efficacy of a drug also depends on its physicochemical properties, particularly lipid solubility. For example, the amount of drug that is sequestered in the epidural fat is entirely dependent on the drug’s octanol-to-buffer distribution coefficient. Consequently, lipophilic drugs (e.g., fentanyl) with a high octanol-to-buffer coefficient may never reach the arachnoid membrane and may partition in epidural fat. This lack of drug transfer across the meninges results in poor CSF bioavailability. Bernards et al. used a porcine model to evaluate the movement of opioids from the epidural to the subarachnoid space. Alfentanil, fentanyl, and sufentanil were administered by bolus injection into the epidural space, and opioid concentrations were continuously sampled and measured over time in the epidural and subarachnoid spaces, and in the systemic venous and epidural plasma, using microdialysis techniques. They found a strong linear relationship between lipid solubility and mean residence time, indicating that more lipid-soluble opioids spend a longer time in the epidural space. Consequently, these drugs partition themselves into the epidural fat with ongoing slow release back into the epidural space. Because of their long residence time in the epidural space, more lipid-soluble drugs are found in lower concentrations in the CSF (i.e., decreased bioavailability to opioid receptors in the dorsal horn).

Several human studies have evaluated whether epidurally administered fentanyl produces analgesia by a selective spinal mechanism or by systemic absorption and redistribution. Results of studies of lipophilic opioids (administered by epidural infusion) have suggested that low concentrations of lipophilic opioids are subject to rapid vascular uptake from the epidural space or sequestration in epidural fat, thereby limiting access to the spinal cord. However, the results of other studies have suggested a spinal effect when lipophilic opioids are administered by epidural bolus injection or by epidural infusion of short duration. Ginosar et al. compared the analgesic effects of epidural bolus injection and epidural infusion of fentanyl in human volunteers. Study results suggested that epidural fentanyl infusion produced analgesia by uptake into the systemic circulation with redistribution to brain and

### Table 13.4 Physicochemical Properties of Opioids Used for Neuraxial Analgesia

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Lipid Solubilitya</th>
<th>pKₐ</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.70</td>
<td>7.9</td>
<td>35</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.28</td>
<td>8.1</td>
<td>19</td>
</tr>
<tr>
<td>Meperidine</td>
<td>39</td>
<td>8.5</td>
<td>70</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>280</td>
<td>7.8</td>
<td>40</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>717</td>
<td>8.4</td>
<td>84</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2842</td>
<td>8.0</td>
<td>93</td>
</tr>
</tbody>
</table>

peripheral opioid receptors. However, epidural bolus administration of fentanyl produced analgesia by selective spinal mechanisms. These results were consistent with previous reports that an epidural fentanyl bolus results in a larger amount of fentanyl in the epidural space than occurs at any time during an epidural infusion of clinically relevant doses, leading to the greater availability of drug to activate opioid receptors in the dorsal horn of the spinal cord.

Although hydrophilic drugs (e.g., morphine) are subject to less systemic and epidural fat uptake than lipophilic drugs, the transfer of the former into the CSF is an inefficient process because they have difficulty in crossing the lipid bilayer of the arachnoid. However, despite these inefficiencies, morphine content in the spinal cord is significantly greater than lipophilic drug (e.g., fentanyl) content, and morphine has much greater bioavailability in the spinal cord than do fentanyl and sufentanil. Thus, although morphine clearly produces analgesia via a spinal mechanism, the extent of spinal analgesia produced by the neuraxial administration of fentanyl and sufentanil is less clear.

After a drug reaches the subarachnoid space, either by diffusion across the meninges or by direct injection into the CSF, its effects depend on its lipid solubility. All opioids produce at least some analgesia by spinal-specific mechanisms. Movement of these drugs within the CSF depends on their physicochemical properties. Drugs can diffuse within the CSF in either a cephalad or a caudad direction. Both morphine and fentanyl have been shown to move rapidly within the CSF. Lipophilic drugs can also return to the epidural space by traversing previously mentioned structures.

Ummenhofer et al. used a porcine model to investigate intrathecal administration of opioids. These investigators found that lipophilic opioids have a very large volume of distribution compared with hydrophilic drugs; the volume of distribution of sufentanil was 40 times greater than that of morphine. This is caused by sufentanil’s extreme lipid solubility, with the drug rapidly leaving the CSF and entering the epidural fat, from where it is absorbed systemically.

The goal of neuraxial opioid administration is for the drug to penetrate the dorsal horn of the spinal cord and activate µ-opioid receptors. A drug’s ability to move from the CSF to the dorsal horn depends on its physicochemical properties. Of the clinically relevant opioids, morphine has the most favorable physicochemical properties to allow penetration of the dorsal horn of the spinal cord (i.e., gray matter). Because of its extreme lipid solubility, sufentanil redistributes itself or partitions itself on the superficial layer (i.e., white matter) of the spinal cord. Data suggest that the spinal bioavailability of the hydrophilic drugs (e.g., morphine, hydromorphone) is greater than that of hydrophobic opioids (e.g., fentanyl, sufentanil).

Morphine is a commonly used neuraxial opioid for postcesarean analgesia (Chapter 27). Limited availability of preservative-free morphine has led to investigation of hydromorphone as an alternative agent. The estimated effective intrathecal morphine : hydromorphone dose ratio is 2:1. Because morphine is more hydrophilic than hydromorphone, a shorter duration of analgesia can be expected with hydromorphone. Indeed, a retrospective study in 1020 women undergoing cesarean delivery found that both intrathecal and epidural hydromorphone had a shorter duration of action (defined as time interval from administration to first request for analgesia) than intrathecal and epidural morphine, respectively. The adverse effect profiles of the two drugs were similar.

Extended-release epidural morphine (EREM) was developed to prolong the duration of a single epidural injection of morphine or obviate the need for a continuous catheter. Multivesicular liposomal preparations gradually release morphine so that a larger epidural dose can be administered, providing analgesia for up to 48 hours (see Chapter 27). Studies that compared EREM 10 to 15 mg with conventional epidural morphine for provision of analgesia after cesarean delivery determined that EREM provided superior and prolonged analgesia without increasing the incidence of adverse effects (e.g., nausea, pruritus, sedation, respiratory depression). This morphine formulation is no longer available in the United States.

In summary, the onset and duration of analgesia as well as adverse effects produced by neuraxial opioid administration depend on the specific type of opioid receptor that is activated as well as the dose, lipid solubility, and rate of movement and clearance of the opioid in the CSF.

**Pharmacogenetics**

Pain associated with labor and delivery is influenced by a multitude of physiologic, psychosocial, and environmental factors (see Chapter 20). Among these factors, genetic variability may also contribute to patients’ sensation, experience, and perception of pain. In obstetric patients, the µ-opioid receptor gene (OPRM1) has been most widely studied, particularly polymorphism at position 118. At this position, a single nucleotide polymorphism (SNP) occurs in some individuals when guanine is substituted for adenosine. The allelic frequency of this variant is population dependent; it is more common in Asians and less frequent in whites and blacks. Although the literature on the genetic influences of pain and opioid responses is extensive, results are inconsistent.

In an early investigation of the role of the A118G variant in neuraxial opioid analgesia, Landau et al. used both up-down sequential allocation and random allocation methods to estimate the ED₅₀ of intrathecal fentanyl in nulliparous A118 homozygotes and G118 hetero/homozygotes as part of a CSE technique for labor analgesia. The ED₅₀ of intrathecal fentanyl was 1.5- to 2-fold higher in women with the wild-type allele (A118) compared with the minor allele (A118G). However, when Wong et al. evaluated the duration of intrathecal fentanyl analgesia (25 µg) in women who were classified into the same genetic groups, there were no differences between the groups in the duration of analgesia or treatment of breakthrough pain. A possible explanation was that the high dose of intrathecal fentanyl, Camorcia et al. examined the effect of the A118G variant on the ED₅₀ of epidural sufentanil in nulliparous women. Similar to the findings of Landau et al., the estimated ED₅₀ was significantly lower.
in women with the variant allele compared with women without the variant. Landau et al.243 also evaluated the possible effects of common OPRM1 and COMT (gene encoding catechol-O-methyltransferase) SNPs on the analgesic efficacy of intravenous fentanyl labor analgesia. No differences were detected. The authors concluded that the study was likely underpowered to detect a difference between groups and, if differences exist, the impact on response to opioid labor analgesia is likely to be modest.

The potential role of the A118 genetic variant in influencing opioid analgesic requirements after cesarean delivery has been investigated in several studies. Wong et al.244 in a mixed race/ethnicity population, found no difference in duration of intrathecal morphine analgesia or need for supplemental analgesia in women carrying the variant allele. In contrast, Sia et al.245 reported that Asian women with the variant allele had an increased incidence of breakthrough pain (as assessed by patient-controlled intravenous morphine requirements) after intrathecal administration of morphine compared with women without the variant allele. In a second study, the variant allele was found to independently predict increased postoperative morphine use in women undergoing cesarean delivery.245

The results of these studies are difficult to reconcile.239,246 Although genetic components may influence patients’ responses to noxious stimuli, current evidence suggests that genetic polymorphism in OPRM1 plays a minor role, if any, in opioid pain management.246,247 A meta-analysis examining the A118 genetic variant of OPRM1 failed to identify a strong association between this variant allele and the response to opioids in different clinical settings.247 Finally, other factors besides genetics may influence pain and opioid response including: (1) type of pain (visceral versus somatic), (2) type of opioid (hydrophilic versus hydrophobic), (3) route of administration, and (4) differences in metabolic pathways.

Toxicity

Any agent that is injected into the epidural or subarachnoid space should be administered with caution owing to the potential for neurotoxicity and permanent neurologic damage. Although there is concern about injecting any type of medication into the neuraxis, the epidural space is more forgiving than the subarachnoid space (see Chapter 31). In many cases, clinicians have injected medications that were not well tested in animal models. Yaksh and Collins248 have urged careful administration of neuraxial drugs, stating that “studies in animals should precede human use of spinally administered drugs.”

The most commonly administered neuraxial opioids in obstetric patients are preservative-free formulations of morphine, fentanyl, and sufentanil. Preservative-free morphine is commercially available for both epidural and intrathecal administration. In the animal model, clinically relevant doses of preservative-free intrathecal morphine (< 5 mg) were administered for 28 days via an indwelling subarachnoid catheter. Spinal cord blood flow and histopathology were unaffected.249,250 To further evaluate preservative-free morphine for potential neurotoxicity, Yaksh et al.251 studied the effects of continuous infusions of high-dose intrathecal morphine (1.5 to 12 mg/day for 28 days) in dogs. At higher doses (9 to 12 mg), the animals demonstrated allodynia soon after beginning the infusion, and at 12 mg, an inflammatory process developed and caused local tissue compression. In humans, long-term neuraxial opioid administration (up to 480 mg of epidural morphine over 124 days or 60 mg intrathecal morphine over 47 days) in patients with cancer pain resulted in no evidence of physiologic or neurologic adverse effects.252

Fentanyl is also available in a preservative-free formulation. Despite its widespread clinical use, few studies have assessed the histologic, physiologic, or clinical evidence of neurotoxicity with spinally administered fentanyl. One in vitro study evaluated the effects of fentanyl administration on nerve conduction.253 Histopathologic studies of isolated rabbit vagus nerve axons did not show localized nerve damage after nerves were bathed in an isotonic solution of fentanyl. When axons were bathed in a hypotonic solution of fentanyl, permanent conduction deficits were noted. However, in clinical practice, large doses of fentanyl would be required to create a hypotonic intrathecal environment.

Although no formal neurotoxicology studies have evaluated sufentanil administration in humans, there are no clinical reports of neurotoxicity despite its widespread use. In one study, sufentanil was administered to cats through an indwelling intrathecal catheter over 5 days.249 Sabbe et al.254 administered clinically relevant doses of intrathecal sufentanil to dogs over several weeks and reported no histopathologic changes. In a sheep model, Rawal et al.255 demonstrated dose-dependent spinal cord histopathologic changes after intrathecal administration of sufentanil (50 to 100 µg) every 6 hours for 72 hours. These doses are much larger than those used in clinical practice. It is possible that these findings reflect an artifact of experimental design (e.g., the frequent administration of a large-volume, hypotonic preparation).

Despite the paucity of data about possible neurotoxicity, both fentanyl and sufentanil are widely used in clinical practice. Although these drugs are not approved by the FDA for neuraxial use,256 there are no published reports of neurologic deficits after epidural or intrathecal administration of either agent in humans. In general, anesthesia providers should exercise extreme caution before injecting any untested agent into the spinal or epidural space, to prevent irritation or damage to neural structures.

Side Effects

Neuraxial opioid administration is associated with beneficial effects as well as potential complications and side effects. Intrathecal administration of clinically relevant doses of morphine is associated with a high incidence of side effects, including somnolence, nausea and vomiting, pruritus, urinary retention, and respiratory depression (Table 13.5). However, epidural and intrathecal injection of more lipid-soluble opioids have fewer side effects.
TABLE 13.5  Incidence of Adverse Side Effects After Intrathecal Injection of 0.5 or 1.0 mg of Morphine

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Morphine 0.5 mg (n = 12)</th>
<th>Morphine 1 mg (n = 18)</th>
<th>Overall (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>58</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>50</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>42</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>33</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>


Sensory Changes

An early study evaluating intrathecal sufentanil in laboring women reported sensory changes and hypotension, although no local anesthetics were administered.257 Other investigators have reported high cervical sensory blockade associated with mental status changes, dysphagia, dyspnea, and automatism after intrathecal sufentanil or fentanyl injection.258,259 These symptoms are likely to be related to a dose-dependent opioid effect rather than neuraxial blockade–induced sympathetic symptoms.260 Further, these changes do not predict the quality or duration of analgesia or degree of hemodynamic change.260 These sensory changes can be clinically significant, especially when they extend to the cervical dermatomes. Patients may feel that they cannot breathe or swallow, an effect that can be distressing. Fortunately, neither intrathecal sufentanil nor fentanyl affects the efferent limb of the nervous system, and motor function is not impaired. Patients should be reassured that their respiratory efforts are not impaired and that these symptoms will subside in 30 to 60 minutes. One report described the use of naloxone to treat the sensory changes associated with intrathecal sufentanil.258

Nausea and Vomiting

Nausea and vomiting are common during labor and delivery. Intrapartum nausea and vomiting can occur from a variety of causes, including pregnancy, physiology of labor itself, pain associated with labor, and parenteral administration of an opioid that may have preceded the neuraxial opioid administration. Therefore, it is difficult to determine the incidence of nausea and vomiting as direct side effects of neuraxial analgesia. Although the mechanism of neuraxial opioid–mediated nausea is unclear, there are suggestions that it may be caused by modulation of afferent input to the area postrema (i.e., the chemoreceptor trigger zone) or at the nucleus of the tractus solitarius, a key relay station in the visceral sensory network.261 Because opioid receptors and others (i.e., dopaminergic, muscarinic) are abundant in these areas, neuraxial opioids are an important cause of nausea and vomiting in the obstetric population.

In two dose-response studies in women undergoing cesarean delivery with spinal and epidural anesthesia, the incidence of neuraxial morphine–induced nausea and vomiting was not dose-related.262,263 Studies suggest that the incidence of nausea and vomiting is lower with lipophilic opioids compared with morphine. Moreover, adding lipophilic opioid to local anesthetic for neuraxial cesarean delivery anesthesia may actually prevent intraoperative nausea and vomiting because of the improved quality of analgesia. Manullang et al.264 randomized 30 healthy parturients to receive either intrathecal fentanyl or intravenous ondansetron for prevention of intraoperative nausea and vomiting during cesarean delivery performed with spinal anesthesia. The incidence of intraoperative nausea was decreased in the fentanyl group compared with the ondansetron group.

A number of prophylactic options are available for reducing the incidence of neuraxial opioid–induced nausea and vomiting (see Chapters 26 and 27). In a systematic review, the efficacy of prophylactic dexamethasone in reducing opioid-related side effects in patients receiving neuraxial morphine was examined.265 Dexamethasone reduced the incidence of postoperative nausea (relative risk [RR] 0.57, 95% confidence interval [CI], 0.45 to 0.72), vomiting (RR 0.56, 95% CI, 0.43 to 0.72), and the use of rescue antiemetic therapy (RR 0.47, 95% CI 0.36 to 0.61) compared with placebo. In a randomized, double-blind placebo-controlled study, Cardoso et al.266 evaluated 72 patients undergoing cesarean delivery with spinal anesthesia including intrathecal morphine. Pain scores and the incidence of nausea were decreased in the group receiving prophylactic dexamethasone.

George et al.267 performed a systematic review of randomized, controlled trials comparing prophylaxis or treatment of nausea and vomiting using one of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists (i.e., ondansetron, granisetron, or placebo) in women receiving spinal anesthesia with intrathecal morphine for cesarean delivery. The authors determined that 5-HT3 receptor antagonists reduced the incidence of postoperative nausea and vomiting as well as the need for postoperative rescue antiemetic therapy compared with placebo.

A meta-analysis suggested that metoclopramide administration (10 mg) before initiation of spinal anesthesia or after delivery resulted in a significant reduction in intraoperative nausea and vomiting as well as early postoperative nausea and vomiting.268 In a study comparing transdermal scopolamine 1.5 mg, intravenous ondansetron 4 mg, and placebo, scopolamine was an effective prophylactic medication against nausea in parturients who received intrathecal morphine for analgesia after cesarean delivery.269 However, the use of scopolamine may be limited by bothersome side effects, including dry mouth, drowsiness, and blurred vision.

Droperidol is effective for the treatment of nausea; however, the FDA has issued a “black box” warning against its use because of concern for QT-interval prolongation in association with droperidol administration. Acupuncture and acupuncture have been used for antiemetic prophylaxis with inconsistent results.270
Pruritus

Pruritus is the most common side effect of neuraxial opioid administration, with reports suggesting that more than 60% of parturients experience pruritus after neuraxial opioid administration.271,272 Presentation is highly variable, but the incidence is dependent upon opioid, dose, and route of administration. Pruritus is more common after intrathecal than epidural opioid administration. A systematic review concluded that pruritus was more common in women who received CSE labor analgesia compared with epidural analgesia.273 Some observers have noted segmental pruritus, especially with lipophilic opioids. For example, patients often complain of perineal and truncal pruritus after intrathecal sufentanil injection.257 The onset of pruritus occurs shortly after analgesia develops, though many patients do not complain and thus appear asymptomatic. However, when questioned, they acknowledge the symptom. The incidence and severity of pruritus is dose-dependent.274 Administration of a minimum effective dose of intrathecal lipophilic opioid in combination with local anesthetic appears to reduce the incidence and severity of pruritus.275

Although the cause of opioid-induced pruritus is unknown, it appears to be unrelated to histamine release.276 Some investigators have suggested that pruritus results from a perturbation of sensory input resulting from rostral spread of the opioid within the CSF to the trigeminal nucleus or subnucleus caudalis.277 Itch-specific neuronal pathways may interact with pain pathways so that continuing activity of the pain-processing system suppresses activity in the spinal itch-processing neurons. Consequently, if pain is inhibited, pruritus can be unmasked.

The serotoninergic system may contribute to modulation of pain by providing a balance between nociception and antinociception in the network of pain-processing neurons.277,278 The dorsal horn of the spinal cord and the spinal tract of the trigeminal nerve are abundant in 5-HT₁ receptors. Because morphine is known to activate 5-HT₁ receptors by a mechanism independent of opioid receptors,279 it is postulated that morphine may directly stimulate 5-HT₁ receptors and may cause intrathecal morphine–induced pruritus. Consequently, occupation of 5-HT₁ receptors by a 5-HT₁-receptor antagonist potentially prevents the pruritus.

Several pharmacologic treatments have been proposed to decrease the incidence of neuraxial opioid–related pruritus. A systematic review evaluated the efficacy of 5-HT₁ receptor antagonists for the prophylaxis and treatment of neuraxial opioid–induced pruritus. The investigators determined that prophylactic 5-HT₁ receptor antagonists did not alter the incidence of pruritus compared with placebo but did reduce the incidence of severe pruritus and the need for therapy.267 Additionally, 5-HT₁ receptor antagonists were efficacious for the treatment of established pruritus.

Opioid antagonists have also been used to treat opioid-induced pruritus. Naloxone (40 to 80 µg intravenously) is very effective in treating the pruritus but may reverse the analgesia as well. Administration of nalbuphine (2.5 to 5 mg intravenously280,281 or 10 mg subcutaneously280,282) may be helpful in reducing symptoms. The advantage of nalbuphine compared with naloxone is that it is less likely to reverse neuraxial opioid analgesia.261 Paech et al.283 randomized women who underwent elective cesarean delivery under spinal anesthesia with intrathecal morphine 100 µg to receive either subcutaneous methylnaltrexone bromide 12 mg (an opioid antagonist) or placebo after delivery. They did not find a difference in the overall severity of pruritus in the treatment group. Opioid antagonists have also been administered by the neuraxial route. Nalbuphine 0.2, 0.8, or 1.6 mg was co-administered with intrathecal morphine in a randomized, double-blind multicenter trial of women undergoing cesarean delivery.284 All doses of nalbuphine reduced the incidence of pruritus; however, the duration of analgesia was also reduced. Jeon et al.285 co-administered naloxone or placebo with morphine for continuous epidural postoperative analgesia in a randomized double-blind trial in women who had undergone cesarean delivery. The incidence and severity of pruritus were reduced in the group receiving epidural naloxone (82% versus 47%) without significant differences in pain scores or in the incidence of nausea, vomiting, or urinary retention between groups. The opioid antagonists have not been approved by regulatory bodies for neuraxial administration.

**Diphenhydramine** (25 mg) has also been administered to treat opioid-induced pruritus.286 Despite the probability that the pruritus is unrelated to histamine release, there may be some benefit from the modest sedation that follows diphenhydramine administration. Propofol 10 to 20 mg was effective for the treatment of pruritus in several studies in nonobstetric patients, but its efficacy was no better than placebo in an obstetric study.287 Regardless of the chosen treatment, pruritus can contribute significantly to patient dissatisfaction and should be treated promptly upon request.

**Hypotension**

Decreased blood pressure was reported in early studies that evaluated intrathecal opioid administration.257,260 Although hypotension occurs in 5% to 10% of parturients who receive intrathecal opioids,257,260 the incidence is higher when a local anesthetic or clonidine is added to the opioid. Early reports suggested that hypotension was caused by a sympathectomy, but later work suggests that hypotension results from pain relief260 and decreased maternal levels of catecholamines, especially epinephrine.288 Wang et al.289 demonstrated that intrathecal opioids block the afferent information from A-delta and C-fibers to the spinal cord but that efferent nerve impulses (e.g., sympathetic efferents) are not directly blocked.

**Respiratory Depression**

All opioids can cause respiratory depression regardless of their route of administration. The incidence of respiratory depression after neuraxial morphine is low and varies from 0% to 0.9%.286,288 When opioids are administered either epidurally or intrathecally, the following factors affect the risk for respiratory depression: (1) choice of drug and its pharmacokinetics, (2) drug dose, and (3) concomitantly administered
CNS depressants. Morphine is the prototype opioid against to which all other opioids are measured. The dose of opioid has been shown to be an important factor in the occurrence of respiratory depression. In a dose-response study, Palmer et al. concluded that there was little justification for giving more than 0.1 mg of intrathecal morphine for analgesia after cesarean delivery. Similarly, a dose-response study of epidural morphine administration after cesarean delivery determined that the quality of analgesia increases as the dose of epidural morphine increases to 3.75 mg but that increasing the dose to 5 mg does not improve analgesia.

The most important factor affecting the onset time of neuraxial opioid-induced respiratory depression is lipid solubility. Respiratory depression may occur within minutes of the administration of a lipophilic opioid (e.g., fentanyl, sufentanil) because of rapid absorption of the opioid from the CSF to lipophilic tissues. Its subsequent clearance and elimination are similar to those of the drug injected intravenously; thus the “time frame” for respiratory depression is short. In contrast, hydrophilic drugs (e.g., morphine, hydrocodone) are associated with a delayed onset of respiratory depression. This potentially serious side effect occurs because hydrophilic opioids remain in the CSF for several hours. Although this characteristic improves the bioavailability of these opioids, there is a biphasic pattern of respiratory depression with early (less than 2 h after administration) or late (6 to 12 h after administration) respiratory depression caused by rostral migration in CSF and absorption of the drug into the respiratory centers in the brainstem (Fig. 13.13).

Although most cases of respiratory depression associated with sufentanil administration occur with larger doses, respiratory depression has also been reported with as little as 10 µg of intrathecal sufentanil administered for labor analgesia. Larger doses (e.g., 15 µg) have not been found to produce better or more prolonged analgesia but do result in increased plasma opioid concentrations and a higher risk for respiratory depression. In a female volunteer study, reported that doses of intrathecal sufentanil larger than 12.5 µg did not produce a proportionate increase in intensity or duration of analgesia. Similarly, there is little benefit to increasing the dose of intrathecal fentanyl beyond 25 µg when it is used as the sole agent for labor analgesia. Higher doses (i.e., more than 10 µg of sufentanil or more than 25 µg of fentanyl) should not be used in routine clinical practice. Respiratory depression from epidural fentanyl is rare, and most studies have used up to 100 µg without evidence of respiratory depression. Doses greater than 100 µg have not been studied.

Several case reports have implicated previous parenteral administration of opioid as a contributing factor in respiratory arrest associated with intrathecal sufentanil administration in laboring women. For example, Jaffee et al. reported a case of apnea and unresponsiveness in a parturient who had received several doses of intravenous fentanyl in the 4 hours before intrathecal sufentanil administration. Although the pregnancy-induced increase in respiratory drive continues throughout labor and into the postpartum period and may provide some protection against respiratory depression, respiratory depression is the most serious side effect of neuraxial opioid administration.

Practice guidelines from the American Society of Anesthesiologists recommend that all patients who receive neuraxial opioids should be monitored for adequacy of ventilation (e.g., respiratory rate, depth of respiration), oxygenation (e.g., pulse oximetry when appropriate), and level of consciousness. In patients who receive a single neuraxial injection of a lipophilic opioid (e.g., fentanyl), monitoring should be continual for the first 20 minutes after administration, followed by monitoring at least hourly until 2 hours have passed. In patients who receive a single neuraxial injection of a hydrophilic opioid (e.g., morphine), monitoring should be performed at least hourly for the first 12 hours and then at

Fig. 13.13 Respiratory rate of an obstetric patient who received 5 mg of morphine after cesarean delivery and who experienced delayed respiratory depression. (From Leicht CH, Hughes SC, Dailey PA, et al. Epidural morphine sulfate for analgesia after cesarean section: a prospective report of 1000 patients [abstract]. Anesthesiology. 1986;65:A366.)
suggests that the rapid onset of this side effect is produced by relaxation of the detrusor muscle (Fig. 13.14), 301 which most likely results from the sacral spinal action of opioids. Urinary retention can be treated with naloxone; however, because many parturients require catheterization for other reasons, urinary retention is often treated with bladder catheterization.

Delayed Gastric Emptying

Labor may delay gastric emptying, and opioids may further exacerbate this delay (see Chapter 28). Parenterally administered opioids are known to delay gastric emptying in laboring women.302 However, clinically useful doses of epidural fentanyl have minimal effects on gastric emptying. Intrathecal administration of fentanyl produces greater delays in gastric emptying than epidural administration.303 Delays in gastric emptying may increase the risk for nausea and vomiting and also increase the risk for aspiration if general anesthesia is necessary for emergency cesarean delivery.

Recrudescence of Herpes Simplex Virus Infections

Genital herpes infection (herpes simplex virus [HSV]) is the most common type of herpes virus infection during pregnancy;304; however, oral HSV infections (common cold sore or fever blister) resulting from reactivation of latent HSV infection also occur during pregnancy. Reports have suggested a relationship between neuraxial opioid administration and reactivation of oral herpes infection. Crone et al.305 reported a 10% incidence of reactivation after cesarean delivery in patients who had received epidural morphine, compared with a 1% incidence in similar patients who did not receive

Urinary Retention

Urinary retention is a bothersome side effect of intraspinal opioid administration. The reported rates following neuraxial opioids vary widely and range from 9% to 80% depending on the procedure performed, type of local anesthetic and/or opioid administered, and definition of urinary retention.300 Urinary retention is more common with neuraxial opioid administration than with intramuscular or intravenous administration of equivalent doses. It is unrelated to systemic absorption and is dose independent. The onset of urinary retention appears to parallel the onset of analgesia. Evidence

\[ \text{Time (h)} \]

\[ \begin{array}{cccc}
\text{21 Volunteers} & \\
\text{2 Mg Ep. Morphine (n = 5)} & \\
\text{4 Mg Ep. Morphine (n = 5)} & \\
\text{10 Mg Ep. Morphine (n = 5)} & \\
\text{10 Mg I.M. Morphine (n = 3)} & \\
\text{10 Mg I.V. Morphine (n = 3)} & \\
\end{array} \]

\[ \begin{align*}
\text{Change in detrusor function (mean)} & = \frac{\text{Baseline detrusor function} - \text{Detrusor function at time t}}{\text{Baseline detrusor function}} \times 100 \\
\end{align*} \]

\[ \text{Fig. 13.14 Urodynamic effects of epidural (Ep.), intramuscular (I.M.), and intravenous (I.V.) morphine administration in male volunteers. Depression of detrusor muscle function persisted for many hours after epidural morphine administration. This did not occur with parenteral opioids and may represent a local spinal cause (i.e., opioid receptors). (From Rawal N, Molleffors K, Axelsson K, et al. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg. 1983;62:641-647.)} \]
epidural morphine. These observations have been confirmed in two prospective studies. Davies et al. reported an increased incidence of postpartum herpes infection in patients with a history of HSV-1 who had received intrathecal morphine.

The mechanism of herpes reaction is unknown. Viral reactivation is known to occur with exposure to ultraviolet light, immunosuppression, trauma, and fever. Proposed causes include (1) a skin trigger mechanism, whereby pruritus and scratching trigger reactivation; (2) an altered immunologic response; and (3) a ganglion trigger mechanism, whereby the intraspinal opioid spreads rostrally and binds to the trigeminal nerve. The ganglion trigger mechanism involves an alteration of sensory modulation that results in reactivation. We are unaware of any serious maternal or neonatal complications that have resulted from neuraxial administration of an opioid and reactivation of oral herpes infection.

**Placental Transfer and Fetal and Neonatal Effects**

Neuraxial opioid administration may have a direct effect on the infant (i.e., respiratory depression at delivery) that results from systemic absorption of the opioid followed by transplacental transfer. The fetus may also be affected indirectly by opioid-related maternal side effects (i.e., hypoxemia, respiratory depression).

**Neonatal Depression**

Systemic opioid absorption can result in neonatal respiratory depression, which is sometimes observed after systemic opioid administration during labor. Neuraxial opioid analgesia techniques may result in better Apgar scores and umbilical cord blood gas and pH measurements at delivery than systemic opioid analgesia. Despite the rapid systemic uptake of intrathecally administered opioids, the neuraxial analgesia requires the administration of smaller doses of opioid.

Several studies have evaluated neonatal outcome after continuous maternal epidural infusion of opioids and local anesthetics. Collectively, these studies have demonstrated that maternal epidural opioid administration by continuous epidural with systemic opioid analgesia. They reviewed 12 trials with a total study population of 2102 parturients. Epidural analgesia was associated with better umbilical cord blood acid-base measurements than systemic opioid analgesia, suggesting that placental perfusion and gas exchange was well preserved despite maternal sympathetic blockade and effective analgesia. Although not all of the studies used neuraxial opioid infusions, the researchers suggested that replacement of systemic opioids with modest doses of neuraxial opioids not only produces superior analgesia but also may have a favorable effect on neonatal outcome.

The effect of epidural fentanyl on breast-feeding has been investigated. Historically, most studies have been observational and poorly controlled. In a randomized controlled trial that included parous women who had previously successfully breast-fed, Beilin et al. found that women who received greater than 150 μg of epidural fentanyl during labor were less likely to be breast-feeding at 6 weeks postpartum compared with women who did not receive any fentanyl or those who received less fentanyl. In contrast, Lee et al. performed a similar study and found that increasing doses of epidural fentanyl does not affect breast-feeding at 6 weeks and 3 months postpartum. However, only 19% of women in the study received a cumulative fentanyl dose greater than 150 μg. Further study is needed to address this important concern.

**Fetal Heart Rate Abnormalities**

An association between neuraxial labor analgesia and FHR abnormalities has been observed (see Chapter 23). Several reports have described the abrupt onset of fetal bradycardia after intrathecal administration of fentanyl or sufentanil. Clarke et al. suggested that the bradycardia is an indirect effect of decreased circulating maternal epinephrine associated with the rapid onset of analgesia. Epinephrine has a tocolytic effect and causes uterine relaxation by stimulating β₂-adrenergic receptors. Consequently, reduced epinephrine levels may lead to increased uterine tone. Because uteroplacental perfusion occurs during periods of uterine diastole (i.e., uterine relaxation), uterine tachysystole may result in diminished uteroplacental perfusion and fetal hypoxia. Nor-epinephrine is known to have a uterine-stimulating effect; thus, the decrease in epinephrine concentration alongside an unchanged norepinephrine concentration may produce uterine hyperactivity and fetal compromise.

An earlier published report suggests that uterine tachysystole and fetal bradycardia may follow administration of either intrathecal opioids or epidural local anesthetics for labor analgesia. In the study, FHR abnormalities and obstetric outcome were evaluated after administration of either intrathecal sufentanil or epidural bupivacaine in a prospective blinded comparison. There were no observed differences in the incidence of FHR abnormalities (i.e., recurrent late decelerations and/or bradycardia) between groups (22% in the intrathecal sufentanil group versus 23% in the epidural bupivacaine group).

Subsequently, Van de Velde et al. investigated whether intrathecal sufentanil 7.5 μg produced more FHR abnormalities than either conventional epidural analgesia or intrathecal bupivacaine 2.5 mg combined with sufentanil 1.5 μg and epinephrine 2.5 μg. The high-dose sufentanil group had more FHR abnormalities (i.e., late decelerations, fetal bradycardia) but less hypotension than the low-dose sufentanil/bupivacaine group. The incidence of FHR abnormalities was similar in the low-dose sufentanil/bupivacaine/epinephrine and conventional epidural analgesia groups. The rates of cesarean delivery for FHR abnormalities were similar in the three groups.

To further evaluate these findings, Abrao et al., in a randomized trial, evaluated the effects of CSE versus traditional epidural analgesia on basal uterine tone and the occurrence of FHR abnormalities. Use of the CSE technique was the only
independent predictor of an increase in basal intrauterine pressure of 10 mm Hg or more (OR, 3.53; 95% CI, 1.21 to 10.36; \( P = .022 \)). The authors also demonstrated that the only predictor of FHR abnormalities was an increase in intrauterine pressure after initiation of analgesia (OR, 18.62; 95% CI, 4.46 to 77.72). A decrease in visual analog scale pain scores immediately after administration of analgesia also correlated with an increased probability of increased intrauterine pressure and FHR abnormalities. No emergency cesarean deliveries resulted from either neuraxial technique, but the authors concluded that more studies are needed to better understand the effects of the CSE technique on labor progress and fetal physiology.\(^\text{[25]}\) Of note, in a letter to the editor, Landau et al.\(^\text{[26]}\) suggested that the analgesic techniques were not equipotent. Additionally, monitoring for FHR abnormalities was only performed for 15 minutes. Given that the onset of analgesia is slower with epidural compared with CSE techniques, FHR abnormalities may occur earlier after intrathecal analgesia. Patel et al.\(^\text{[27]}\) evaluated fetal/neonatal outcome in patients who were randomized to either a CSE or an epidural technique containing both bupivacaine and fentanyl. There were no significant differences in FHR patterns, Apgar scores, or umbilical artery acid-base measurements between groups. However, there was a significant increase in the incidence of abnormal FHR patterns following administration of neuraxial analgesia in both groups. Given the inconsistencies in the data, further study is necessary to determine the mechanisms and risk factors for fetal bradycardia following the initiation of neuraxial labor analgesia.

Other mechanisms may also be relevant to explain the fetal bradycardia sometimes observed after CSE analgesia. Van de Velde et al.\(^\text{[28]}\) questioned the catecholamine imbalance theory, because intrathecal bupivacaine combined with low-dose sufentanil (1.5 \( \mu \)g) produced analgesia similar to that provided by intrathecal sufentanil (7.5 \( \mu \)g), but the incidence of fetal bradycardia was greater with sufentanil 7.5 \( \mu \)g. Russell et al.\(^\text{[29]}\) demonstrated that intravenous opioids have central effects, altering the release of oxytocin and vasopressin and inducing uterine hyperactivity. Lipid-soluble opioids undergo rapid systemic redistribution after neuraxial injection; therefore, even neuraxial opioids may have central effects.

Given the potential risk for fetal bradycardia after neuraxial analgesia in laboring women,\(^\text{[30,29]}\) the FHR should be monitored before and after the initiation of epidural and intrathecal analgesia. FHR changes are usually transient and may be managed successfully with conservative in utero fetal resuscitation measures, including the administration of a tocolytic agent for persistent uterine tachysystole.

Historically, intravenous or subcutaneous terbutaline was used to treat persistent uterine tachysystole, but nitroglycerin, also a potent tocolytic agent, may have several advantages. First, nitroglycerin has a short duration of action and labor resumes shortly after the period of tachysystole. In addition, nitroglycerin rarely produces significant hypotension, and if hypotension occurs, it is easily treated. Several studies have evaluated nitroglycerin for the treatment of uterine tachysystole. Mercier et al.\(^\text{[31]}\) described consistent success in treating FHR abnormalities resulting from uterine tachysystole after the administration of one or two doses of nitroglycerin (60 to 90 \( \mu \)g), and Bell\(^\text{[32]}\) described the successful use of sublingual nitroglycerin (400 \( \mu \)g) in the treatment of uterine tachysystole. In a randomized trial comparing intravenous terbutaline 250 \( \mu \)g to nitroglycerin 400 \( \mu \)g for the treatment of intrapartum tachysystole and non reassuring FHR tracings, acute intrauterine resuscitation success rates were similar between the two groups (72% versus 64% for terbutaline and nitroglycerin, respectively; \( P = .38 \)), but the incidence of tachysystole 10 minutes after drug administration was lower in the terbutaline group.\(^\text{[32]}\) Therefore, if there is no response within 2 to 3 minutes of nitroglycerin administration, terbutaline 0.25 mg (250 \( \mu \)g) should be administered, and preparations should be made for emergency cesarean delivery if the fetal bradycardia does not resolve.

**ADJUVANTS**

**Epinephrine**

Epinephrine is added to local anesthetic solutions to increase the duration of anesthesia, reduce peak plasma drug concentrations, improve block reliability, and intensify analgesia/anesthesia.\(^\text{[33-35]}\) Uptake of epinephrine varies with the choice and concentration of local anesthetic, concentration of epinephrine, and site of injection. The effect of epinephrine is greater when it is combined with lidocaine than when it is combined with bupivacaine.\(^\text{[151,191]}\) Even concentrations of epinephrine as low as 3.3 \( \mu \)g/mL (1:300,000) have been shown to be effective in reducing the plasma concentrations of lidocaine.\(^\text{[35]}\)

The efficacy of epinephrine depends on the specific local anesthetic as well as the site of injection. Epinephrine prolongs the duration of epidural lidocaine anesthesia by reducing uptake of local anesthetic into the systemic circulation through constriction of the epidural venous plexus and maintaining the concentration of local anesthetic at the site of injection. An epinephrine concentration of 5 \( \mu \)g/mL (1:200,000) nearly doubles the duration of epidural lidocaine anesthesia.\(^\text{[36]}\) In contrast to lidocaine, the addition of epinephrine 3.3 \( \mu \)g/mL to epidural bupivacaine 0.5% had no effect on maternal venous plasma concentrations of drug in laboring women.\(^\text{[37]}\) Similarly, Reynolds et al.\(^\text{[38]}\) observed no effect when epinephrine 5 \( \mu \)g/mL was added to bupivacaine during administration of epidural anesthesia for cesarean delivery. Although epinephrine did not prolong the epidural anesthesia produced by ropivacaine,\(^\text{[39]}\) one group reported that the addition of epinephrine to bupivacaine resulted in a 50% decrease in maternal plasma concentrations of bupivacaine after paracervical block,\(^\text{[40]}\) and Katz et al.\(^\text{[41]}\) found that epinephrine 200 \( \mu \)g added to intrathecal hyperbaric bupivacaine for cesarean delivery prolongs the time until T-10 regression by 40 minutes.

Greater reliability and intensity of the block can be observed when epinephrine is added to epidurally administered local anesthetics because of stimulation of \( \alpha_2 \)-adrenergic receptors. These presynaptic adrenergic receptors are found...
at the terminals of primary afferent neurons as well as centrally on neurons in superficial laminae of the spinal cord and in several brainstem nuclei.

In addition to the intrinsic analgesic effects of epinephrine, the inherent lipid solubility of each local anesthetic affects the degree of sensory blockade. Each local anesthetic has a lipid-to-water partition coefficient that determines the drug uptake between the aqueous and lipid phases within the spinal canal. If a local anesthetic is more lipid soluble, the advantage of adding epinephrine to the local anesthetic is less significant. For example, the lipid-to-water partition coefficient of lidocaine is 2.7. When epinephrine is added to lidocaine, there is marked improvement in the intensity of the block. However, bupivacaine, which has a lipid-to-water partition coefficient 10 times greater than that of lidocaine, is affected by epinephrine to a lesser degree. Ropivacaine has a lipid-to-water partition coefficient similar to that of lidocaine, and epinephrine will intensify a ropivacaine block similar to that of lidocaine. However, the duration of the block remains unchanged.

Despite the advantages of epinephrine, concern remains about the effects of epinephrine on uterine blood flow and the maternal cardiovascular system. In healthy fetuses, epidural administration of epinephrine does not affect umbilical cord blood flow. However, in fetuses with increased vascular resistance, epidural epinephrine administration may increase the umbilical artery S/D ratio. Studies of the effects of epinephrine on the placental transfer of local anesthetics have yielded contradictory results. In rabbits, epinephrine did not affect the F/M ratio of bupivacaine. As a result of the addition of epinephrine, the F/M ratio for bupivacaine has been found to be increased or unchanged. For lidocaine, the F/M ratio has variously been reported to be increased, decreased, or unchanged.

**Bicarbonate**

The addition of sodium bicarbonate to a local anesthetic solution increases the pH closer to the pKₐ of the local anesthetic. This change increases the proportion of drug in unionized form that is available to penetrate the nerve sheath and membrane, thereby accelerating the onset of the block and decreasing the minimum concentration required for conduction blockade. Most studies have demonstrated that the addition of sodium bicarbonate to lidocaine, bupivacaine, or 2-chloroprocaine hastens the onset of epidural blockade by as much as 10 minutes. The speed of onset of a ropivacaine block does not seem to be affected by alkalinization, but as with the other local anesthetics, evidence suggests that alkalinization intensifies epidural ropivacaine anesthesia and improves spread to sacral dermatomes. The effects of alkalinization are most pronounced in epinephrine-containing solutions, particularly commercially prepared epinephrine-containing formulations. These solutions are prepared at a lower pH, ranging from 3.2 to 4.2. Although the lower pH of these solutions stabilizes the solution and provides bacteriostasis, it increases the latency of onset.

Sodium bicarbonate 1 mEq/mL (8.4%) may be freshly added to local anesthetic solutions shortly before use (Table 13.6). Alkalinization of bupivacaine must be performed carefully because the margin between satisfactory alkalinization and complete precipitation is very narrow. All local anesthetics have a tendency to precipitate, so solutions containing bicarbonate should be inspected for precipitation before being administered.

Hypotension occurs more frequently with epidural administration of an alkalinized local anesthetic than with administration of an unbuffered solution. This likely results from an accelerated onset of sympathetic blockade. Carbonated salts of local anesthetics can also be administered for a rapid onset of epidural blockade. However, these drugs have limited availability. Like alkalinized local anesthetics, these preparations are more likely to produce hypotension.

**Clonidine**

α₂-Adrenergic agonists (e.g., clonidine) have been investigated as adjuvants to local anesthetics and opioids to improve analgesic efficacy without increasing side effects. The advantage of clonidine is its ability to provide analgesia without affecting sensation or producing motor blockade. However, epidural and intrathecal administration of α₂-adrenergic agonists are known to produce hypotension, probably by acting on α₂-adrenergic receptors on preganglionic cholinergic neurons. In addition, α₂-adrenergic agonists produce dose-dependent sedation, which results from α₂-adrenergic stimulation in the locus ceruleus.

Neuraxial clonidine exerts its effects by binding to α₂-adrenergic receptors located on primary afferent terminals of the spinal cord, substantia gelatinosa, and brainstem nuclei as well as via a cholinergic mechanism. Conduction blockade is produced by increases in potassium conductance and in acetylcholine and norepinephrine in the CSF, leading to decreased release of substance P and subsequent analgesia.

Approximately 70% of α₂-adrenergic receptors on human myometrium are α₂-α₂-adrenergic receptors, therefore, the potential effects of clonidine on labor and delivery have been evaluated. In an in vitro study, clonidine directly enhanced the frequency and amplitude of human myometrial contraction. α₂-Adrenergic receptor stimulation in the uterus could theoretically enhance uterine contractions and decrease uterine blood flow. Indeed, in animal studies, large doses of clonidine produced a decrease in FHR. This effect probably resulted from direct fetal transfer of drug and from direct and indirect effects on baroreflexes. However, this effect is unlikely to occur with clinical doses of neuraxial clonidine.

### Table 13.6 Alkalinization of Local Anesthetic Solutions

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Sodium Bicarbonate (mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>1.0</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.1</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Sodium bicarbonate 8.4% (1 mEq/mL) added to 10-mL local anesthetic solution.
Studies have evaluated neuraxial clonidine administration in humans as an analgesic adjunct for labor analgesia (see Chapter 23). When combined with local anesthetics and opioids, lower doses may be used, resulting in less hypotension and sedation. The FDA has issued a “black box” warning against the use of neuraxial clonidine in obstetric patients because of concerns about hemodynamic instability. Therefore, clonidine is rarely used for labor analgesia in North America; however, it is more widely used in some European countries. Clonidine may be particularly useful in women in whom other epidural analgesics are contraindicated or in those who have breakthrough pain with standard local anesthetic/opioid solutions despite a functioning epidural catheter. In this setting, the bolus administration of clonidine 75 µg without a local anesthetic is not usually associated with hypotension. It appears safe to add small doses of intrathecal clonidine (15 to 30 µg) to opioids or local anesthetics, but side effects must be treated promptly to avoid fetal compromise.

Epidural clonidine has been administered for analgesia after cesarean delivery (see Chapter 27). One study suggested that epidural clonidine (400 to 800 µg) provided postoperative analgesia, but a continuous infusion was required after 6 hours. Others have demonstrated that the addition of epidural clonidine (75 to 150 µg) to neuraxial morphine lengthens the duration of postoperative analgesia without increasing the incidence of side effects.

Neostigmine

Both nicotinic and muscarinic cholinergic receptors are present in the dorsal horn of the spinal cord. Acetylcholine stimulates muscarinic and possibly nicotinic receptors in the spinal cord. Neostigmine prevents breakdown of acetylcholine. Stimulation of muscarinic receptors facilitates release of gamma-aminobutyric acid (GABA) in the dorsal horn of the spinal cord, resulting in analgesia. Neostigmine appears to be more effective at alleviating somatic pain than visceral pain. Visceral afferents are located deep within the spinal cord. Because neostigmine has low lipid solubility, it has a limited ability to traverse biologic membranes. When administered without other agents, it provides minimal analgesia because it is unable to reach the visceral afferents responsible for much of labor pain.

Early studies of intrathecal neostigmine demonstrated analgesic efficacy and safety at the expense of dose-dependent nausea and vomiting that were unresponsive to standard antiemetics. However, single and intermittent-dose epidural neostigmine administration has been found to significantly reduce local anesthetic consumption without increasing the risk to the mother or fetus. A systematic review of 16 randomized controlled trials including 1183 patients evaluated the efficacy of neuraxial neostigmine administration and its effect on local anesthetic dose for cesarean delivery and labor analgesia as well as the incidence of adverse events. Although the dose of neostigmine varied across studies, a final analysis of 8 studies revealed that women randomized to receive epidural neostigmine required lower local anesthetic doses compared with women who received placebo, both for labor analgesia as well as for postcesarean analgesia. The incidence of pruritus was decreased, likely a result of decreased opioid consumption. Other findings included an increased risk for nausea in patients receiving intrathecal but not epidural neostigmine. There were no adverse effects on FHR patterns or Apgar scores, and the risk for hemodynamic instability, sedation, and dizziness were not increased.

A randomized controlled trial compared the effect of the addition of neostigmine and fentanyl to epidural bupivacaine on total hourly bupivacaine requirements when the study solutions were used for patient-controlled epidural analgesia (PCEA). Parturients were randomized to receive epidural bupivacaine 0.125% with neostigmine 2, 4, or 8 µg/mL or fentanyl 2 µg/mL. No difference in the total hourly bupivacaine consumption was identified. Although the incidence of pruritus was higher in the group receiving fentanyl, there were no differences among groups in other adverse effects (maternal heart rate and blood pressure, neonatal Apgar scores, mode of delivery, motor block, nausea, sedation).

Although not routinely used in clinical practice in the United States, collectively, studies suggest there may be a role for epidural neostigmine in laboring patients with opioid substance use disorders and patients with severe opioid-related nausea and vomiting. Neostigmine is not approved by the FDA for neuraxial use.

### Aggregate Analysis

**Key Points**

- Pregnancy enhances the effect of local anesthetic agents.
- Appropriate administration of epidural anesthesia does not adversely affect uterine tone or uterine or umbilical blood flow.
- Bupivacaine has greater cardiotoxicity than lidocaine because of its greater electrophysiologic effects, which predispose to ventricular arrhythmias.
- Single (levorotary) isomer formulations of amide local anesthetics, such as ropivacaine and levobupivacaine, have a lower potential for cardiotoxicity than racemic bupivacaine.
- Lipid emulsion therapy should be considered at the first sign of a serious local anesthetic systemic toxicity event.
- Fetal acidosis results in a greater accumulation of amide local anesthetic in the fetus.
- Local anesthetics, as used clinically, are not teratogenic.
- The elimination half-life of amide local anesthetics is longer in the newborn than in the adult because the former has a greater volume of distribution.
- The fetus and newborn seem to be no more vulnerable to the toxic effects of local anesthetics than the adult.
• Neonatal neurobehavior depends on many factors other than the choice of local anesthetic.
• Alkalization of a local anesthetic solution shortens the latency of neural blockade but increases the risk for hypotension during administration of epidural anesthesia.
• Neuraxial opioid administration produces analgesia without loss of sensation or proprioception.
• The combination of a neuraxial local anesthetic and an opioid increases block density and allows for administration of a lower total dose of local anesthetic and a lower incidence of side effects.
• Spinal bioavailability of the hydrophilic drugs (e.g., morphine, hydromorphone) is greater than that of hydrophobic (lipophilic) opioids (e.g., fentanyl, sufentanil).
• The most common side effects of neuraxial opioid administration are pruritus and nausea and vomiting. Fetal bradycardia and maternal respiratory depression are the most serious complications.

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Drug therapy during pregnancy can be complex because the physiologic changes of pregnancy may alter drug disposition and effect. Maternal medications may have direct effects on the fetus after placental transfer, or indirect effects through changes in placental and uterine function. Even after delivery, drugs may affect breast-feeding, and drug transfer to breast milk is a concern. Nevertheless, pregnant women still require medications to treat many acute and chronic conditions. Worldwide, the use of medications during pregnancy has been increasing, with pregnant women in the United States taking an average of 4.2 medications between 2006 and 2008. Recent data from the United States showed that 97.1% of women took at least one medication during pregnancy, and 30.5% were taking at least five medications. The most common medications were antiemetics, antibiotics, and analgesics. However, at least 10% were taking drugs with long-term effects on the central nervous system such as antidepressants, anticonvulsants, and antipsychotics. The challenge is to find the balance between the benefits and risks associated with therapy.

Maternal variation in drug effect is not usually difficult to manage, and a change in dosing regimen or the choice of drug may be all that is required. The greatest fear and concern is for potential fetal effects that may manifest as teratogenicity with fetal loss or congenital malformations, fetal growth restriction (also known as intrauterine growth restriction), preterm labor, and other complications of pregnancy. After delivery, immediate neonatal adaptation may be affected, and in the longer term there may be impaired neurodevelopment and behavioral problems in childhood.

The anesthesia provider should understand the implications of pregnancy on drug disposition and effect. Although not usually responsible for primary maternal drug therapy, the anesthesia provider will encounter women taking many different medications and may need to administer a variety of nonanesthetic drugs during the peripartum period, either for

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maintenance of chronic therapy or for acute indications, especially when managing critically ill patients.

In this chapter, the way maternal physiology affects pharmacology is summarized, placental transfer and maternal and fetal effects of the main classes of drugs encountered during pregnancy are addressed, and drug transfer to breast milk is reviewed, with discussion of the effects of common perioperative drugs. Specific drugs used in the management of individual obstetric conditions are discussed in other chapters.

**Changes in Drug Disposition and Effect**

**Pharmacogenetics**

Genetic differences are responsible for some of the variation in drug response among individuals. Pregnancy does not obviously modify these pharmacogenetic differences, although some obstetric conditions such as preeclampsia are related to complex genetic factors. There are, however, some examples in which underlying genetic differences do affect obstetric management.

The metabolism of codeine to morphine is greatly affected by polymorphisms of the cytochrome P450 (CYP) isoenzyme CYP2D6. It has been recognized only recently that mothers who are ultra-rapid metabolizers of codeine may produce and transfer sufficient morphine through breast milk to cause neonatal central nervous system (CNS) depression and even death. Codeine is now not recommended in women who are breast-feeding.

Two of the possible changes at the β2-adrenergic receptor are an arginine-to-glycine substitution at codon 16 (Arg-16Gly) and a glutamine-to-glutamic acid substitution at codon 27 (Gln27Glu). Women with Arg16 and/or Gln27 are less likely to have preterm delivery and more likely to have longer labor. Conflicting results are reported for vasopressor requirements in the management of hypotension during spinal anesthesia for cesarean delivery. In North American studies, Gly16 homozygotes and Gln27 homozygotes required less ephedrine, and Arg16 homozygotes required more phenylephrine. However, no differences were detected in an Asian cohort, and a Brazilian group found that Arg16 and Gln27 homozygotes required less ephedrine.

The μ-opioid receptor gene may have an adenine-to-guanine substitution at nucleotide position 118 (A118G). There have been many studies of the effects of this polymorphism on opioid dose requirements and response. Studies in laboring women showed that AA homozygous carriers had an increased intrathecal fentanyl requirement for analgesia. However, most studies of postoperative pain, including after cesarean delivery, have shown that AA polymorphism was associated with less pain. Many other genetic factors influence opioid disposition and response, and even more factors influence pain perception. A meta-analysis found that A118G polymorphism only explained 7% of the variability in opioid requirements. Currently, given the conflicting results and limited clinical effects of genetic polymorphisms, specific single nucleotide polymorphism (SNP) testing does not appear to be indicated in routine obstetric anesthesia practice.

**Pharmacokinetic Changes**

The major physiologic changes during pregnancy alter drug disposition. However, the magnitude and time course of these changes vary throughout pregnancy and among individuals. The results of many older studies are unreliable because the studies were often of low quality. Making generalizations about the effects of pregnancy on drug disposition can be difficult, and individualized dosing is important. Even though there is increased clearance of many drugs in pregnancy, the standard dosing regimens for many drugs have not been updated for pregnancy, consequently resulting in underdosing.

**Maternal Pharmacokinetics**

**Absorption and uptake.** Oral absorption and bioavailability are not usually affected by pregnancy, although nausea and vomiting may limit oral intake. Intestinal motility is decreased during pregnancy, but gastric emptying is only delayed during labor or after opioid administration. Cardiac output is increased by 30% to 50% during pregnancy, and the increased blood flow to skin and mucous membranes will enhance absorption from these sites. Reduced functional residual capacity and increased minute ventilation lead to increased pulmonary uptake of inhalational anesthetic agents.

**Distribution.** The increased cardiac output during pregnancy increases distribution of drug to all tissues. Drugs acting peripherally (e.g., neuromuscular blockers) will be delivered to their site of action more quickly. However, the onset of intravenous and inhalational anesthetics is dependent on the time course of their cerebral drug concentration. A delay in the increase in arterial and brain anesthetic concentration will result from increased peripheral perfusion. However, increased peripheral perfusion will increase the return of drug during the elimination phase. During pregnancy, total body water increases on average by 8 L, and intravascular plasma volume is increased by 40%, whereas extravascular volume increases by a variable amount, depending on weight gain and edema. Thus, hydrophilic drugs, such as neuromuscular blockers, will have a small increase in the volume of distribution. Body fat is increased on average by 4 kg, but this is unimportant given the large volume of distribution of lipophilic drugs.

Changes in protein binding are more important clinically. Plasma albumin concentration is reduced to about 70% of normal, whereas α2-acid glycoprotein concentration is largely unchanged. Protein binding of drugs may be reduced by increased concentrations of free fatty acids and other endogenous displacing substances. This leads to increased concentrations of free drug, but with chronic drug administration this is offset by increased clearance of that free drug. The total (free + bound) concentration of drug will decrease, and it may be necessary to reset the therapeutic target range lower to compensate. Thus, it is important to know whether monitored concentrations are for free or total drug. Only a few
drugs (e.g., theophylline, phenytoin) require monitoring and modification of dose because of changes in protein binding.

**Metabolism.** Most drugs are metabolized in the liver, and the rate of metabolism may depend on hepatic blood flow or intrinsic enzyme activity. Although cardiac output is increased in pregnancy, it is not clear whether blood flow to the liver is significantly increased. Most cytochrome P450 isoenzymes (CYP3A4, CYP2D6, and CYP2C9) and uridine diphosphate glucuronosyltransferase (UGT) isoenzymes (UGT1A4 and UGT2B7) have increased activity during pregnancy, which increases the metabolism of drugs such as phenytoin (CYP2C9), midazolam (CYP3A4), and morphine (UGT2B7). A few isoenzymes (CYP1A2 and CYP2C19) have decreased activity, which reduces the metabolism of drugs such as caffeine and theophylline (CYP1A2).

**Elimination.** Renal blood flow is increased by 60% to 80%, and glomerular filtration rate is increased by 50% in pregnancy; thus, the renal excretion of unchanged drugs such as cephalosporin antibiotics is increased. There is also increased activity of many transporter proteins such as renal P-glycoprotein. Increased minute ventilation enhances elimination of inhalational anesthetic agents.

The physiologic changes of pregnancy will affect individual drugs depending on their physicochemical characteristics and metabolic pathways. Bioavailability is not usually changed significantly. Changes in volume of distribution as a result of changes in protein binding may affect drugs such as phenytoin, but monitoring and modification of therapy is usually straightforward. Drugs metabolized by the liver may require increases or decreases in dose, depending on the metabolic pathway involved. Drugs excreted unchanged by the kidneys often require an increased dose.

**Placental Transfer and Metabolism**

Our understanding of placental transfer and metabolism is rapidly improving (see Chapter 4). Early research was often limited to measuring drug concentration in the umbilical vessels and maternal vein at delivery. Results were variable and difficult to interpret, especially for drugs such as anesthetic agents that are administered shortly before delivery. Umbilical blood samples are obtained at variable times after drug exposure, well before steady-state conditions are achieved. The theory of a placental barrier was proposed because maternal and fetal concentrations were often different. However, differences in concentration of binding proteins are mainly responsible for the fetal-maternal distribution of drugs at steady state. The fetal concentration of albumin is only one-third of the maternal value at term. Umbilical-to-maternal blood ratios of total drug may be misleading because it is the free drug that equilibrates across the placenta. Maternal-to-fetal ratios of drugs do not provide information on the rate of drug transfer or the amount of drug that has already been transferred to the fetus.

Drug transfer across the placenta was previously thought to occur mainly by diffusion. This would favor the movement of lipophilic drugs, and placental perfusion would be an important factor affecting transfer. Fetal pH is lower than maternal pH, so that weak bases become more ionized in the fetus, thus limiting their transfer back across the placenta. Normally, the difference in pH is only 0.1 and this “ion trapping” is irrelevant, but fetal acidosis can significantly increase the fetal concentration of drugs such as local anesthetics.

It is now known that the placenta contains many drug transporters that can modify fetal drug exposure. In the treatment of sustained fetal tachyarrhythmia, placental P-glycoprotein, an adenosine triphosphate–dependent drug efflux pump, will reduce net transfer of substrates such as digoxin and verapamil from the mother. Although placental transport of immunoglobulin makes it possible to immunize the mother to protect the newborn, this transport also raises concerns when immunoglobulin tumor necrosis factor antagonists are used to treat maternal diseases.

The placenta contains many active enzymes responsible for Phase I and Phase II biotransformation. Clearance of substrates by UGT in full-term placentas may be sufficient to contribute to overall maternal metabolism.

**Fetal and Neonatal Elimination**

The fetus and neonate metabolize drugs, but at a reduced rate compared with adults. Early animal studies showed that maternal anesthetic requirements were reduced during pregnancy. Minimum alveolar concentration (MAC) values for inhalational agents were reduced by 25% to 40% in pregnant ewes and by 16% to 19% in pregnant rats. Ethical and practical difficulties with research in pregnant women delayed confirmation of this finding in humans. Isoflurane MAC (determined using transcutaneous electrical stimulation instead of the classic skin
incision) was decreased by 28% in women undergoing termination of pregnancy at 8 to 12 weeks’ gestation. Similar reductions in MAC were found for enflurane (30%) and halothane (27%). MAC was reduced by 30% in the immediate postpartum period, with a return to nonpregnant values by 12 to 72 hours after delivery (Fig. 14.1). 

Increased progesterone is probably the cause of the reduced anesthetic requirement during pregnancy; chronic progesterone administration reduced MAC in rabbits, dogs, and sheep. Although human studies have not found a good correlation between progesterone concentration and the reduction in anesthetic requirement, a poor correlation may be expected if the effect of progesterone is not dose-dependent; it is possible that progesterone concentration only needs to exceed a low threshold to decrease anesthetic requirement. A lower concentration of sevoflurane was required to maintain anesthesia in nonpregnant women during the luteal phase of the menstrual cycle, when progesterone concentration is elevated, compared with during the follicular phase. Progesterone concentration during pregnancy is much greater than that seen during the luteal phase of the menstrual cycle. The reduced MAC during pregnancy may also be a result of the increased endogenous endorphins that mediate the increase in nociceptive threshold during pregnancy; it is well known that opioids reduce MAC.

Pregnancy also alters other measures of anesthetic effect. In early pregnancy, the isoflurane concentration required for hypnosis was reduced by 31% and the bispectral index (BIS) was decreased at isoflurane concentrations over the range 0.1% to 2.0%. During the second trimester, the sevoflurane concentration required to achieve a targeted BIS of 50 was reduced by 31%. Both in early and term pregnancy, the median concentration of nitrous oxide required for loss of consciousness (MACawake) was reduced by 25% to 27%. One study did not show any difference in electroencephalographic (EEG) measures between women having cesarean delivery or gynecologic surgery, but there were many confounding factors such as the study being conducted partly during and partly after surgery, the concurrent use of significant doses of fentanyl, large variations in EEG measures, and small sample size.

Data for intravenous anesthetic agents are more variable, partly because of methodologic challenges. It is difficult to produce a stable effect-site concentration of intravenous drugs to allow accurate measurement of drug effect. Increased cardiac output usually results in an increase in intravenous anesthetic dose requirements to produce central effects, and this change would counter any decrease in requirements with pregnancy. The bolus dose of thiopental for hypnosis (failure to open eyes to command) was 17% lower, and that for anesthesia (no purposeful movement to a transcutaneous electrical stimulus) was 18% lower in early pregnancy compared with nonpregnant women (Fig. 14.2). A similar reduction was found in the early postpartum period, less than 60 hours after delivery.

Studies using target-controlled infusions may not be reliable because the pharmacokinetic models may not be accurate in pregnancy, and they are known to predict concentrations poorly at induction of anesthesia. These methodologic problems may be the reason one study found no differences in the concentration of propofol required for loss of consciousness.
spinal anesthesia. One small study suggested that although 13% to 35% in pregnant women at term. Magnetic resonance imaging has confirmed that pregnant women have increased epidural blood volume, decreasing the capacity of the epidural space and decreasing the volume of lumbar cerebrospinal fluid. These mechanical factors would explain the increased spread of local anesthetic. However, several studies have also shown that there is increased sensitivity to local anesthetics during pregnancy. The onset of conduction block in the vagus nerve with bupivacaine was faster in pregnant versus nonpregnant rabbits. Sciatic nerve block was of longer duration and the lidocaine content in the nerves was lower at the time of return of deep pain in pregnant versus nonpregnant rats. Sensory nerve action potentials were inhibited to a greater extent during median nerve block at the wrist with lidocaine in pregnant versus nonpregnant women. The increased sensitivity may be caused by progesterone because exogenously administered progesterone increased the susceptibility of rabbit vagus nerves to bupivacaine. One study found no changes in conduction block in pregnant rats and suggested that enhanced block may be caused by pregnancy-induced changes that facilitate diffusion of local anesthetic or an interaction with endogenous analgesic systems.

### Regional Anesthesia

The spread of neuraxial block is increased in pregnant women (see Chapter 2). This has been shown as early as the first trimester for epidural anesthesia and the second trimester for spinal anesthesia. One small study suggested that although the spread of epidural block was increased, the latency and density of sensory and motor block were not. However, two more recent studies showed that the median effective dose of intrathecal bupivacaine for motor block was decreased by 13% to 35% in pregnant women at term. Magnetic resonance imaging has confirmed that pregnant women have increased epidural blood volume, decreasing the capacity of

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**Fig. 14.2** Calculated dose-response curves (log [dose] scale) for thiopental for hypnosis (A) and anesthesia (B) in pregnant and nonpregnant women. The 95% confidence intervals for the values of ED50 and ED95 are also displayed, slightly offset for clarity. Raw data are shown for pregnant women (x) and nonpregnant women (•). (Modified from Gin T, Mainland P, Chan MTV, Short TG. Decreased thiopental requirements in early pregnancy. Anesthesiology. 1997;86:73–78.)

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in early pregnancy. Another study used a slow infusion of propofol for induction of anesthesia and found that the dose and calculated effect-site concentrations at loss of consciousness were 8% lower than in nonpregnant women. The reduction in anesthetic requirement for intravenous agents appears to be less (8% to 18%) than that for inhalational agents (approximately 30%). It is not known whether this reflects real differences between the drugs or the methodologic problems just outlined.

### Analgesia

Pregnancy is associated with increases in nociceptive response thresholds that are mediated by endogenous opioid systems. The changes in threshold can be reproduced using exogenous progesterone and estrogen and appear to involve spinal cord kappa (κ) and delta (δ) opioid receptors and descending spinal α₂-noradrenergic pathways. Neurologic pain was also reduced in pregnant rats in a chronic constriction injury model. Human studies continue to produce mixed results. Heat pain threshold was increased in term pregnant women, and this persisted during the first 24 to 48 hours after delivery. However, a longitudinal study found that endogenous pain modulation evaluating both inhibitory and excitatory pain pathways did not change significantly during pregnancy. Given the many different factors that influence pain behavior, especially those unique to pregnancy and delivery, it is difficult to determine how this change in pain threshold influences perioperative analgesic requirements.

### DRUG USE DURING PREGNANCY

#### General Principles and Teratology

It would seem prudent to use only drugs considered safe in pregnancy. Unfortunately, the potential adverse effects of many drugs remain unclear. The U.S. Food and Drug Administration (FDA) approved 213 new medications between 2003 and 2012, and only 5% of them had human data in the pregnancy section of the label. Pregnant women are not usually included in early clinical trials, and because of the low incidence of some complications, the first suggestion of adverse effects may be revealed only from postmarketing surveillance and registries of complications. For long-term complications such as impaired neurodevelopment in children of mothers taking drugs acting on the central nervous system, it can be difficult to separate specific drug effects from
the influence of the underlying psychological disease and environment. There are often conflicting studies for many adverse events. This uncertainty about safety, and the difficulties in determining what public information is reliable, may convince mothers to refuse appropriate drug treatment. New improved drugs are available in many areas of therapeutics, but many prescribers prefer to use older drugs that have a longer empirical history of safety.

To avoid unnecessary exposure, nonpharmacologic techniques should be used when possible, and drugs should be used only when necessary. The risk-to-benefit ratio should justify the use of a drug given to a pregnant woman, and the minimum effective dose should be employed. Long-term effects of fetal drug exposure may not become apparent for many years. Therefore, physicians and patients should exercise caution in the use of any drug during pregnancy.

Sensitive serum pregnancy tests can diagnose pregnancy as early as 1 week after conception. Before drug therapy is started, a sensitive test should be used if there is any question about drug safety during a potential pregnancy.

Many resources on the safety of drugs in pregnancy are freely available online, in addition to the commercially available databases (Table 14.1). The FDA Office of Women’s Health has created a pregnancy registry website that lists a variety of registries that women who have used specific medications during pregnancy can consult (see Table 14.1).

Teratology is the study of abnormal development or birth defects. Teratogens are substances that act to irreversibly alter growth, structure, or function of the developing embryo. Typically, preclinical studies would identify teratogens, but drug teratogenicity unfortunately can be markedly species-specific. For example, thalidomide produces phocomelia in primates but not in rodents.

In the United States, major malformations affect 2% to 3% of neonates. A major malformation is defined as one that is incompatible with survival (e.g., anencephaly), one that requires major surgery for correction (e.g., cleft palate, congenital heart disease), or one that causes mental retardation. If all minor malformations (e.g., ear tags, extra digits) are included, the incidence of congenital anomalies may be as high as 7% to 10%. Exogenous causes of birth defects (e.g., radiation, infections, maternal metabolic disorders, drugs, environmental chemicals) account for almost 10% of all major birth defects and therefore affect only 0.2% to 0.3% of all births. Drug exposure explains only 2% to 3% of birth defects, and the majority of birth defects are of unknown etiology.

Drug teratogenicity is affected by the timing of exposure. Teratogen exposure in the first 2 weeks after conception is generally thought to be an all-or-nothing phenomenon (i.e., having either no effect or resulting in spontaneous fetal loss). Among women with a 28-day menstrual cycle, the classic period of susceptibility to teratogenic agents is during the period of organogenesis, which occurs primarily at 2.5 to 8 weeks after conception (31 to 71 days, or 4 to 10 weeks, after the first day of the last menstrual period) (Fig. 14.3). During organogenesis, each organ system has different critical periods of sensitivity, and there may be striking differences in effect. When administered between 35 and 37 days’ gestation, thalidomide produces ear malformations; when administered between 41 and 44 days’ gestation, it produces amelia or phocomelia. After this period, embryonic development is characterized primarily by increasing organ size; thus, the principal effect of exposure consists of growth restriction and/or effects on the nervous system and gonadal tissue. For example, diethylstilbestrol exposure during the second

<table>
<thead>
<tr>
<th>TABLE 14.1 Internet Resources for Additional Drug and Teratogen Information</th>
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<tbody>
<tr>
<td>American Academy of Pediatrics: The Transfer of Drugs and Other Chemicals into Human Milk</td>
</tr>
<tr>
<td>The American Botanical Council</td>
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<tr>
<td>The American College of Obstetricians and Gynecologists</td>
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<tr>
<td>Motherisk Organization of Teratology Information Specialists: Fact sheets on a variety of diseases, medications, and herbal remedies</td>
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<tr>
<td>The National Library of Medicine PubMed</td>
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<tr>
<td>The National Institutes of Health National Center for Complementary and Integrative Health</td>
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<tr>
<td>The National Institutes of Health Office of Dietary Supplements Perinatology.com: Drugs in Pregnancy and Breastfeeding</td>
</tr>
<tr>
<td>The Reproductive Toxicology Center* RxList: The Internet Drug Index</td>
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<tr>
<td>SafeFetus.com</td>
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<tr>
<td>University of Washington Clinical Teratology Web* U.S. Food and Drug Administration Office of Women’s Health</td>
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<td>Drugs and Lactation Database (LactMed)</td>
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*Databases, including Reprotox, Reprotext, Teris, and Shepard’s Catalog of Teratogenic Agents, can be purchased from these websites.
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CHAPTER 14 Pharmacology during Pregnancy and Lactation

In response to the many concerns, the FDA held a public meeting in 1997 to discuss labeling of drugs. After much consultation and discussion, the FDA produced a final guideline in 2014, the Pregnancy and Lactation Labeling Rule (PLLR), with a webpage containing explanatory and guidance documents. The PLLR was implemented on June 30, 2015, and it required drug and biologic data sheets to have increased narrative and detailed reporting of relevant risks and clinical considerations supported by data for each of three sections: pregnancy, lactation, and use of drugs by women and men with reproductive capability.

The pregnancy section is divided into four subsections:

1. **General Information:** This is a statement of background risk (without drug exposure for any complication subsequently mentioned), and contact details for any registry that is monitoring the drug.

   - **Category A:** Controlled studies have shown no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

   - **Category B:** No evidence of human fetal risk exists. Either animal reproduction studies have not demonstrated fetal risk but no controlled studies in pregnant women have been reported, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).

   - **Category C:** Risk cannot be ruled out. Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) but no controlled studies in women have been reported, or studies in women and animals are not available. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.

   - **Category D:** Positive evidence of human fetal risk exists. However, the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed for a life-threatening condition or for a serious disease for which safer drugs cannot be used or are ineffective).

   - **Category X:** Contraindicated in pregnancy. Studies in animals or human beings have demonstrated fetal abnormalities, or evidence exists of fetal risk based on human experience, or both, and the risk in pregnant women clearly outweighs any possible benefit. These drugs are contraindicated in women who are or may become pregnant.


In response to the many concerns, the FDA held a public meeting in 1997 to discuss labeling of drugs. After much consultation and discussion, the FDA produced a final guideline in 2014, the Pregnancy and Lactation Labeling Rule (PLLR), with a webpage containing explanatory and guidance documents. The PLLR was implemented on June 30, 2015, and it required drug and biologic data sheets to have increased narrative and detailed reporting of relevant risks and clinical considerations supported by data for each of three sections: pregnancy, lactation, and use of drugs by women and men with reproductive capability.

The pregnancy section is divided into four subsections:

1. **General Information:** This is a statement of background risk (without drug exposure for any complication subsequently mentioned), and contact details for any registry that is monitoring the drug.
2. **Risk Summary:** This is a narrative summary of all the fetal risks.
3. **Clinical Considerations:** This section provides a discussion about risks of not treating, dosing adjustments, adverse effects, and effects on the course of labor and the neonate. Recommendations are given on how to avoid adverse effects.
4. **Background Data:** This section provides more detail about all the research used to support the risk summary and clinical considerations.

The **lactation** section has three subsections:
1. **Risk Summary:** This reports the effect of the drug on lactation, the concentration of drug in breast milk, and the relative infant dose. The summary must include the statement that the drug is compatible with breast-feeding if that is supported by the available data.
2. **Clinical Considerations:** Recommendations are given to minimize adverse effects.
3. **Background Data:** This section provides detailed summaries of data used to support the above.

The **females and males of reproductive potential** section has three subsections that cover issues of pregnancy testing, contraception, and infertility that may be relevant to use of the drug.

Drugs approved before June 30, 2001, and over-the-counter drugs are exempted, and there is phased implementation by 2020 for more recently approved drugs. The information must be updated whenever new information is available, so the data sheets should be a reliable source of the best information available in a standardized format.

The following sections provide detail for perioperative drugs commonly used or encountered by anesthesia providers. As the FDA requires the drug data sheets to be continually updated, the reader is advised to check those for the detailed information.

**Anesthetic Drugs**

Anesthetic drugs are discussed in Chapter 17. No anesthetic drugs have been shown to be teratogenic. There is continued debate about anesthetic neurotoxicity in neonates and infants, and these issues could also be applicable to the fetus of mothers receiving anesthesia. In December 2016, the FDA issued a safety announcement that repeated or lengthy anesthetics in women during their third trimester could affect subsequent neurodevelopment in the child. However, this was updated in April 2017, to state that any planned anesthesia (and surgery) in the third trimester was usually medically necessary and that pregnant women should not delay or avoid these procedures.

**Analgesics**

There is no known teratogenic risk associated with the use of acetaminophen (paracetamol), which is the preferred mild analgesic and antipyretic agent during pregnancy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk for some birth defects. The use of NSAIDs and aspirin in the first trimester has increased risk for pregnancy loss (adjusted odds ratio [OR], 1.8 to 8.1). In the third trimester, NSAIDs and aspirin are usually avoided because of fetal risks, such as renal injury, oligohydramnios, and intrauterine constriction of the ductus arteriosus. So although chronic use of NSAIDs is common in pain and rheumatology, they are not recommended for use during pregnancy.

Opioids such as propoxyphene and codeine are not considered to have teratogenic risk, but they have well-known potential for addiction. Excessive antepartum use can also lead to neonatal opioid-withdrawal symptoms. However, recent studies have concluded that maternal opioid use was associated with an increased OR of 1.8 to 2.7 for various cardiac birth defects, spina bifida, and gastrochisis.

Tramadol has analgesic effects from weak opioid activity and inhibition of serotonin and norepinephrine uptake. Despite availability in some countries for more than 30 years, few data are available regarding potential adverse effects in pregnancy. Tramadol exposure in early pregnancy was associated with a higher number of spontaneous abortions, and it should be avoided in the first trimester. Chronic tramadol use in later pregnancy may result in neonatal withdrawal syndrome.

**Sedatives**

Some studies have suggested that first-trimester exposure to diazepam increases the risk for cleft lip with or without cleft palate, neural tube defects, intestinal atresia, and limb defects. Other reports have not suggested an increase in rate of congenital abnormalities after fetal exposure to benzodiazepines. Perinatal use of diazepam has been associated with hypotonia, hypothermia, and respiratory depression.

Overall, it appears that the teratogenic risk associated with benzodiazepines is small at most, but there may be a small risk for preterm birth and low birth weight. Benzodiazepines should only be used in the first trimester if the perceived benefit offsets the possible teratogenic risks and later neonatal effects of continued use. Short-acting agents are preferred.

**Anticonvulsants**

Anticonvulsant drugs are now prescribed for a large number of indications other than epilepsy, so that women without epilepsy taking these medications greatly outnumber women with epilepsy. Most of this increase in prescriptions has been for the newer drugs for indications such as pain and psychiatric disorders. However, most studies of adverse effects have been in women taking anticonvulsant drugs during pregnancy for epilepsy.

Valproate has the highest teratogenic risk, followed by phenytoin, phenobarbitone, and topiramate. Valproate alone or combined with other antiepileptic drugs has the highest risk for adverse neurodevelopment, and oxcarbazepine and lamotrigine were associated with increased autism.

Gabapentin and pregabalin are not prescribed for epilepsy and can often be stopped during pregnancy; the overall risk with these two drugs is low.
Epilepsy is the most common serious neurologic problem during pregnancy. It has been estimated that 3 to 5 births per thousand will be to women with epilepsy. If a patient first presents for care during pregnancy, most authorities agree that the benefits of anticonvulsant therapy during pregnancy outweigh the risks of discontinuing the drug. All anticonvulsants cross the placenta. The fetal congenital anomaly rate in pregnant women with epilepsy who ingest anticonvulsant drugs is 4% to 8%, compared with a background incidence in the general population of 2% to 3%. A twofold higher risk for minor malformations also exists in this population. Cleft lip, with or without cleft palate, and congenital heart disease are especially common. Administration of valproate or carbamazepine entails a 1% risk for neural tube defects and other malformations; thus, alphafetoprotein screening and targeted ultrasonography are appropriate for patients taking these agents. In addition, the offspring of epileptic women have a 2% to 3% incidence of epilepsy, which is five times that of the general population.

No congenital malformations appear to be unique to any one anticonvulsant. The characteristics of these syndromes are so similar that the broad term fetal anticonvulsant syndrome, consisting primarily of orofacial, cardiovascular, and digital malformations, has been applied to almost every anticonvulsant drug.

Among women taking phenytoin, there is a 2% to 5% risk for major congenital anomalies, primarily midline heart defects, orofacial clefts, and urogenital defects. Fetal hydantoin syndrome is a constellation of minor anomalies, such as craniofacial abnormalities (short nose, flat nasal bridge, wide lips, hypertelorism, ptosis, epicanthal folds, low-set ears, and low hairline) and limb anomalies (distal digital hypoplasia, absent nails, and altered palmar crease). In addition, neonatal growth and performance delays have been documented. The risk for fetal hydantoin syndrome for the child of a woman taking phenytoin is approximately 10%. Phenytoin may act as a competitive inhibitor of the placental transport of vitamin K. In addition, phenytoin may induce fetal hepatic metabolism of the coagulation factors. The resulting reduction in fetal coagulation factors is associated with a higher risk for hemorrhagic disease of the newborn. To help prevent this coagulopathy, some physicians advocate oral vitamin K supplementation (10 mg/day) for pregnant epileptic patients during the last month of pregnancy in addition to the parenteral administration of vitamin K to the neonate at birth. Several anticonvulsant medications have metabolites that typically are eliminated by the enzyme epoxide hydrolase. In one study, all women with low enzyme activity in amniocytes had affected fetuses.

Carbamazepine is commonly used in the treatment of psychomotor (temporal lobe) epilepsy and grand mal epilepsy. In one prospective study, there was an 11% incidence of craniofacial defects, a 26% incidence of fingernail hypoplasia, and a 20% incidence of developmental delay in the children of women treated with carbamazepine during pregnancy. This constellation of fetal effects, named fetal carbamazepine syndrome, closely resembles the malformations seen in cases of fetal hydantoin syndrome. Fetal exposure to carbamazepine also carries a 0.5% to 1% risk for spina bifida. Although it is generally agreed that the use of carbamazepine in pregnancy is associated with a risk for neural tube defects and other anomalies, the exact magnitude of the risk from use of carbamazepine alone is unclear.

Fetal phenobarbital syndrome is characterized by minor dysmorphic features similar to those seen with fetal hydantoin syndrome. Fetal exposure to phenobarbital has also been associated with decreased neurodevelopment in neonates and children. Maternal phenobarbital use during pregnancy can result in hemorrhagic disease of the newborn and neonatal withdrawal symptoms after delivery. The withdrawal symptoms consist mostly of irritability, begin at about 7 days of life, and usually last for 2 to 6 weeks.

Valproate is used to treat mood and psychiatric disorders, migraine, and epilepsy. Infants exposed to valproate have a 1% to 2% risk for spina bifida. Fetal valproate syndrome has been described; it is characterized by dysmorphic features, including epicanthal folds, shallow orbits, hypertelorism, low-set ears, flat nasal bridge, upturned nasal tip, microcephaly, thin vermillion borders, downturned mouth, thin overlapping fingers and toes, and hyperconvex fingernails. Jentink et al. found a markedly increased risk for spina bifida (OR, 12.7), craniosynostosis, cleft palate, atrial septal defect, and hypospadias, and they concluded that valproate monotherapy should be avoided during pregnancy. In recent years, warnings against the use of valproate have increased, and it is labeled as requiring a pregnancy prevention program, contraindicated, or even banned in some countries.

Psychotropic Drugs

Up to 10% of pregnant women are prescribed antidepressants. The tricyclic antidepressants do not appear to be associated with congenital abnormalities or neurodevelopmental problems, but the monoamine oxidase inhibitors (MAOIs) should be avoided. Selective serotonin reuptake inhibitors (SSRIs) and related serotonin norepinephrine reuptake inhibitors (SNRIs) are now the usual first-line therapy for depression (see Chapter 50). These drugs cross the placenta to varying degrees, greater for venlafaxine and citalopram and less for paroxetine and sertraline. As a class, they increase the rate of cardiac malformations and risk for perinatal complications. Fetal echocardiography should be considered in monitoring the pregnancy. There is a high (30%) rate of neonatal adaptation problems, and at least double the risk for persistent pulmonary hypertension of the newborn. There are no effects on neurodevelopmental delay or autism. The American College of Obstetricians and Gynecologists (ACOG) has recommended that use of paroxetine be avoided in pregnant women (and in women planning pregnancy), and that fetal echocardiography should be considered in women who have used it during early pregnancy.

The antipsychotic drugs are generally not associated with increased congenital malformations, with the possible exception of risperidone. There are more data for the older antipsychotic drugs such as trifluoperazine and haloperidol.
than for the newer atypical antipsychotics. There appears to be an increased risk for poor neonatal adaptation, but no effects on short-term neurodevelopment.

**Lithium** therapy is associated with a small increased risk for cardiac defects, especially **Ebstein’s anomaly**. Women should be monitored with fetal echocardiography as well as serum concentrations because pregnancy accelerates the excretion of lithium. There appear to be no effects on child neurodevelopment.

**Cardiovascular Drugs**

Antihypertensive agents such as methyldopa, labetalol, calcium entry–blocking agents, and hydralazine are safe in pregnancy. The safety of beta-adrenergic receptor antagonists (apart from labetalol) is less clear, although atenolol and metoprolol are often used during pregnancy. They are probably not associated with congenital malformations, but there are reports of preterm birth, fetal growth restriction, and poor neonatal adaptation. Spironolactone should be avoided.

The **angiotensin-converting enzyme inhibitors** (ACEIs) and **angiotensin receptor blockers** (ARBs) should be avoided during pregnancy. It is clear that second- and third-trimester use can cause fetal renal failure and oligohydramnios, which may result in fetal limb contractures, craniofacial deformities, and pulmonary hypoplasia. During the first trimester, there is some debate about congenital malformations, but given that subsequent use is not recommended, it is logical to switch drugs or not use them in the first place.

There are no reports of teratogenicity related to the use of inotropic agents such as **dopamine, dobutamine**, or **digoxin**. Physicians should monitor the maternal digoxin level to ensure a therapeutic level of drug during pregnancy.

**Amiodarone** is structurally similar to thyroxine and contains 37% iodine by weight. In a review of 64 reported pregnancies in which amiodarone was administered to the mothers, there was no clear increase in the incidence of malformations. However, 11 (17%) infants had evidence of hypothyroidism, and two (3%) neonates had goiter. The use of amiodarone in pregnancy was associated with mild abnormalities of neurodevelopment in some of the hypothyroid infants, although this was also observed in some euthyroid infants. This agent is most often used during pregnancy to treat fetal arrhythmias, and first-trimester exposure is rare.

**Respiratory Drugs**

Maternal **asthma** is relatively common in pregnancy, affecting 4% to 12% of pregnant women. It is important to maintain appropriate treatment because asthma can increase the risk for adverse fetal and maternal outcomes.

Inhaled **β₂-adrenergic receptor agonists**, **cromolyn sodium**, and **corticosteroids** have not been associated with congenital malformations. Currently, **albuterol** (salbutamol) is the preferred short-acting β₂-adrenergic receptor agonist, and **salmeterol** is the preferred long-acting β₂-adrenergic receptor agonist. **Budesonide** is the recommended inhaled corticosteroid because it has a long history of safe usage, but there is no evidence against the other options.

Severe persistent asthma may require systemic oral corticosteroid therapy, and this has been associated with low birth weight and a 3- to 5-fold increase in the relative risk for cleft lip and palate. However, other studies have found no adverse effects and, given the risks from severe asthma, oral corticosteroids should be used if required.

The 5-lipoxygenase inhibitors such as **montelukast** and **zafirlukast** are considered safe. Women using montelukast enrolled in several teratogen information services around the world showed no increased risk for birth defects in 160 live births. The leukotriene receptor antagonist **zileuton** is not recommended because of adverse effects in animals, and there are no known adverse effects in pregnancy for the monoclonal antibody **omalizumab**.

Methylxanthines such as **theophylline** and **aminophylline** have no adverse fetal effects, but the protein binding and metabolism of theophylline are both reduced during pregnancy, making it necessary to monitor drug concentrations and adjust maintenance doses.

**Anticoagulants**

Pregnancy is a hypercoagulable state because of relative increases in many coagulation factors and increased venous stasis. Pregnant women have five times the normal risk for venous thromboembolism, and thrombosis is a significant cause of maternal death.

**Heparins** are large water-soluble molecules that do not cross the placenta. **Low-molecular-weight heparin** (LMWH) is usually preferred over **unfractionated heparin** (UFH) because it is easier to administer, does not require monitoring for prophylactic dosing, and has a more predictable effect. LMWH is also less likely to cause heparin-induced thrombocytopenia and osteoporosis. Therapeutic dosing of LMWH is weight-based and can be monitored by anti-Xa levels. The shorter half-life of UFH means that anticoagulation is easier to reverse, and so UFH is often used closer to the time of delivery or in any situation in which this flexibility is useful. As pregnancy progresses, pharmacokinetic changes require doses to be increased.

**Warfarin** is a vitamin K antagonist that can cause an embryopathy, especially with first-trimester exposure. Warfarin embryopathy is characterized by nasal bone hypoplasia, depressed nasal bridge (often with a deep groove between the alae and nasal tip), and stippled epiphyses. Second- and third-trimester exposures can result in neurologic complications probably from intracranial microhemorrhages. Warfarin is thus not used in pregnancy except in patients with mechanical heart valves where warfarin therapy gives the best maternal outcomes at the expense of increased fetal loss and malformations. Lower warfarin doses (less than 5 mg/day) are sometimes used in the first trimester. The lower doses appear to have less teratogenic potential, but the risk is not eliminated.

The indirect factor Xa inhibitor **fondaparinux** (administered subcutaneously) and the direct thrombin inhibitor **argatroban** (administered intravenously) appear to be safe alternative options in patients unable to take heparin.
However the direct oral anticoagulants such as the factor Xa inhibitor rivaroxaban and the thrombin inhibitor dabigatran cross the placenta and are not recommended in pregnancy.124 Patients who become pregnant while taking these drugs are usually switched to heparin.

Low-dose aspirin and clopidogrel are safe during pregnancy.121

**Antiemetics**

Most women in early pregnancy have nausea, with or without vomiting (see Chapters 2 and 16).124 Complementary therapies such as acupressure and ginger may be effective, but more than 20% of women will still receive prescription drug therapy.125 The ACOG recommends vitamin B<sub>6</sub> (pyridoxine), with or without the antihistamine doxylamine as the initial drug of choice.126 A combination of vitamin B<sub>6</sub> with doxylamine was previously available as Bendectin, but this was withdrawn by the manufacturer in 1983 because of allegations of teratogenicity that were later found to be false. Other formulations are now available, and there is no evidence of teratogenicity with them or other antihistamines. If symptoms persist, the next suggestions are antihistamines such as diphenhydramine, dimenhydrinate, and promethazine, and dopamine antagonists such as prochlorperazine and trimethobenzamide, but they may all cause sedation. Metoclopramide is a nonsedating dopamine antagonist, but it has a “black box” warning because chronic usage has been associated with rare cases of tardive dyskinesia. There are no specific safety concerns during pregnancy. The 5-hydroxytryptamine receptor antagonists such as ondansetron are very effective antiemetics, and ondansetron is now the most popular antiemetic, being used in 22% of pregnancies in the United States in 2014 compared with just 1.8% for doxylamine/ pyridoxine.127 Initial suggestions that ondansetron was associated with septal defects and cleft palate have not been confirmed, and it is generally considered safe.127,128

Corticosteroids are now commonly used for postoperative and chemotherapy-induced nausea and vomiting, and methylprednisolone has been used for refractory nausea and vomiting during pregnancy. However, a meta-analysis concluded that the use of glucocorticoids before 10 weeks’ gestation was associated with a 3- to 5-fold increased risk for cleft lip with or without cleft palate114; thus, they should not be used during this period.

**Antihistamines**

Over 25% of breast-feeding women have taken histamine type 1 (H<sub>1</sub>)-receptor antagonists that are available as over-the-counter medications or prescribed for many indications such as nausea and vomiting, allergies, or upper respiratory tract infections. These drugs provide symptomatic therapy with no influence on the course of the disease. Topical nasal sprays result in less fetal exposure than systemic medication. They are generally considered safe,129,130 but the nonsedating antihistamines with the longest history of use such as cetirizine and loratadine are considered the first choice.131

**Antidiabetic Drugs**

Treatment of gestational diabetes mellitus with insulin, metformin, or glyburide is safe, although there is some debate over which drug should be the first-line treatment132,133 (see Chapter 43).

**Anti-Infective Drugs**

**Antibacterial and Antiparasitic Agents**

Approximately 25% of women will receive an antibiotic during pregnancy.134 Sepsis is a leading cause of maternal mortality, and treatment is essential. When administering perioperative antibiotics, anesthesia providers should be aware of the considerations regarding their use during pregnancy.135 Although penicillins and cephalosporins are considered first-line treatment because of their long safety record, therapy is ultimately guided by local microbiology policies and bacterial sensitivity. Carbapenems, monobactams, macrolides, and glycopeptides are also considered safe.

Short-term use of aminoglycosides is acceptable, but streptomycin is avoided because of the risk for congenital deafness after first-trimester exposure. Metronidazole is considered safe, but some recommend avoiding it during the first trimester. Sulphonamides and nitrofurantoin are also considered safe, but the combination of sulphamethoxazole-trimethoprim is usually avoided in the first trimester because of concerns with trimethoprim, which is a folate antagonist.134

Tetracyclines should not be administered after the fifth week of pregnancy. They bind to developing enamel and cause discoloration of the teeth. They affect deciduous teeth when administered between approximately 26 weeks’ gestation and 6 months of age in the infant, and they affect permanent teeth only if administered to children between approximately 6 months and 5 years of age. In addition, tetracyclines deposit in developing osseous sites and inhibit bone growth beginning in the second trimester.135

Fluoroquinolones should not be used in pregnancy or in children. They have a high affinity for bone tissue and cartilage and may cause arthropathies in children. However, no malformations or musculoskeletal problems were noted in 38 infants exposed during the first trimester.135

Malaria is a significant cause of maternal and fetal death. Pregnant women should avoid traveling to malaria-endemic areas, but chloroquine or mefloquine can be used for malaria chemoprophylaxis. They are not associated with an increase in spontaneous abortions or congenital malformations. Doxycycline, primaquine, and atovaquone-proguanil are not to be used in pregnancy.

**Drugs for Treatment and Prophylaxis of Viral Infections**

Treatment of herpes simplex and herpes zoster infections in the first trimester with acyclovir or valacyclovir has not been associated with an increased risk for birth defects.116 Combination antiretroviral therapy has not been associated with major infant toxicity, even when the therapy was initiated in the first trimester of pregnancy.137 The Antiretroviral
Pregnancy Registry was established in 1989 to detect any major teratogenic effect of the antiretroviral drugs. Each year it enrolls approximately 15% of all human immunodeficiency virus (HIV)-positive women who give birth to live infants in the United States plus a small number from other countries. It depends on voluntary reporting of prenatal exposure; therefore, drug-associated adverse events may not necessarily reflect true rates. Results of retrospective and clinical studies are also reviewed. Through July 2017, no apparent increase in the frequency of birth defects after first-trimester exposure to antiretroviral drugs compared with population-based comparators was reported. A modest but statistically significant elevation of defect rates with didanosine and nelfinavir was reported, the clinical relevance of which is unclear. For treatment of chronic hepatitis B, pegylated interferon has been used but is usually not recommended. Given that treatment of maternal hepatitis and HIV have been well-studied and generally safe, postexposure prophylaxis is also considered safe, although some specific drugs are avoided.

It is generally appropriate to administer vaccinations during pregnancy because the risk associated with the disease may outweigh the risk associated with the vaccine. No evidence exists of risk to the fetus from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids. However, live vaccines pose a theoretical risk to the fetus, so vaccination with live attenuated virus (e.g., varicella, measles-mumps-rubella [MMR]) or tuberculosis (e.g., bacillus Calmette Guérin [BCG]) is considered contraindicated. Influenza vaccination is recommended with the inactivated virus preparation. Prevention and treatment of influenza with either zanamivir or oseltamivir is possible during pregnancy; no adverse fetal effects have been reported.

**Caffeine**

No evidence suggests that caffeine has teratogenic effects in humans. In 2010, the ACOG published a committee opinion that was reaffirmed in 2016. They concluded that (1) daily intake of less than 200 mg of caffeine was not associated with an increased risk for miscarriage, but contradictory data did not allow for a recommendation regarding daily intake above this level; (2) moderate caffeine intake does not appear to contribute to preterm birth; and (3) the association between caffeine intake and fetal growth restriction was equivocal. A subsequent review concluded with more certainty that moderate or even high amounts of caffeine-containing foods and beverages did not increase the risk for congenital malformations, miscarriage, or fetal growth restriction.

**Cannabis**

The prevalence of marijuana use in pregnancy usually ranges from 2% to 5%, but can be as high as 28% in some groups. Although marijuana may be prescribed for medical indications, most women taking marijuana do not have these indications. There do not appear to be any effects of marijuana on congenital defects, preterm birth, or perinatal mortality. Women are advised to stop marijuana because of the adverse effects of smoking and concerns regarding impaired neurodevelopment. Smoking during pregnancy is clearly linked to multiple adverse fetal, neonatal, and childhood effects. The benefits and risks in pregnancy of nicotine replacement therapies and alternative forms of nicotine such as e-cigarettes and vaping are not known. Other drugs such as bupropion and varenicline are not associated with congenital malformations. However, both drugs have an FDA warning about the risk for maternal psychiatric symptoms and suicide.

**Specific Highly Teratogenic Drugs**

Some drugs are so highly teratogenic that two simultaneous forms of reliable contraception are recommended or required during treatment of either partner, sometimes to be continued for months or years after stopping the drug. Some examples include (1) thalidomide (and analogues), which is still used for erythema nodosum leprosum and multiple myeloma; (2) the antiviral ribavirin, which is used for hepatitis C and viral hemorrhagic fevers; (3) isotretinoin, which is used for cystic acne; and (4) acitretin, which is used for severe psoriasis. In Europe, valproate now cannot be used unless there is a pregnancy prevention program.

**DRUG USE DURING LACTATION**

With current recommendations to breast-feed exclusively for 6 months, and maintain breast-feeding for 2 years if possible, it is likely that most infants will be exposed to maternal medications through breast milk. Women on average take four medications during lactation. Nursing mothers are understandably concerned about the transfer of drugs and chemicals to breast milk. Correct advice is important to prevent them from unnecessarily stopping breast-feeding or discontinuing appropriate drug treatment. Unfortunately, only about 5% of drugs have human data on breast-feeding. It can be difficult to decide which of the many, sometimes conflicting, sources of public information to trust.

Pharmaceutical information leaflets from manufacturers often discourage the use of drugs during breast-feeding simply as a general precaution. The most comprehensive up-to-date information is found in the Drugs and Lactation Database (LactMed) of the National Library of Medicine’s Toxicology Data Network (TOXNET). The American Academy of Pediatrics (AAP) has published policy statements on the benefits of breast-feeding and the use of drugs during lactation. The Centers for Disease Control and Prevention (CDC) provides online information regarding breast-feeding and various toxins and infectious diseases.

For the future, it is expected that the revised FDA Pregnancy and Lactation Labeling Rule (PLLR) will lead to better information on drugs and breast-feeding. Human data
are used whenever possible, and animal data are purposefully omitted when human data are available. The lactation section has three parts that must be updated whenever new information is available. The risk summary outlines the drug absorption and transfer to milk, estimated infant exposure, effects on infant and possibly maternal milk production, and a risk/benefit statement including a statement that the drug is compatible with breast-feeding if human data are available to support that conclusion. The clinical considerations part gives advice on minimizing infant drug exposure and recommendations for monitoring possible drug effects. The data section gives more details about the available evidence to support the risk summary. Given the large knowledge gap, there are still many issues to resolve, such as the level of evidence required for the appropriate advice on the label, setting research priorities for the large number of older drugs still being used for which there is no information, and best research methods for human studies depending on the drug. These were discussed and summarized at a recent 2-day FDA meeting in June 2016.

Only a few types of drugs such as cytotoxic and immunosuppressive drugs (e.g., cyclophosphamide, methotrexate) and radioactive compounds are strongly contraindicated during breast-feeding. Mothers breast-feeding infants with glucose-6-phosphate-dehydrogenase (G6PD) deficiency should avoid fava beans and drugs such as sulfonamides, including the combination of sulfamethoxazole and trimethoprim, nitrofurantoin, primaquine, and phenazopyridine.

Maternal drugs may also affect lactation, and some are used therapeutically for this purpose. Drugs that increase the secretion of prolactin can stimulate milk production; these include dopamine antagonists such as phenothiazines, haloperidol, and antipsychotics such as sulpiride and risperidone. Metoclopramide and domperidone are the drugs most commonly used off-label as galactagogues even though the FDA specifically warns against domperidone because of QT interval prolongation and the risk for cardiac arrhythmias. Drugs that decrease the production of milk include sympathomimetic vasoconstrictors, anticholinergics, diuretics, high-dose estrogen, and dopamine agonists such as bromocriptine and cabergoline. Bromocriptine is no longer approved for postpartum lactation suppression because of its association with puerperal seizures, stroke, and myocardial infarction, so that cabergoline off-label is often the only choice. Women who smoke also have lower milk production.

Transfer of Drugs to Breast Milk

Mammary epithelial cells form a barrier separating plasma from milk. For the first few days postpartum, larger molecules such as maternal immunoglobulins are able to pass to colostrum. The intracellular junctions gradually close so that by 1 week postpartum, only molecules less than 200 daltons readily pass across the membrane. However, mastitis may cause membrane disruption and allow larger molecules to pass into milk.

Drug transfer to breast milk occurs mainly by passive diffusion. The rate of passive transfer into breast milk depends on the lipid solubility, molecular weight, degree of ionization, and protein binding of the drug. Nonionized molecules of small molecular weight (e.g., ethanol) are readily transferred into breast milk. The pH of milk is slightly acidic (pH approximately 7.1) but variable (pH 6.7 to 7.3), affecting the transfer of weak bases and acids with pKa near that range. Protein binding is one of the main determinants of drug transfer because human milk has a relatively low concentration of proteins (8 g/L) such as casein that do not bind drugs well. Drugs that have more than 85% maternal protein binding are often not detectable in the infant. The fat composition of breast milk shows diurnal variation, and decreases after months of breast-feeding.

There are also a few active transport systems in humans, including the sodium iodide symporter that transports iodide, and the breast cancer resistance protein that transports a variety of drugs such as acyclovir and methotrexate.

Animal studies are usually not useful indicators of human transfer because of large differences in anatomy, milk composition, and transport processes. Obtaining initial human data can be difficult. Pharmacokinetic modeling is now being used to provide preliminary predictions of milk transfer and to guide the appropriate pharmacokinetic study design in women. Simple concentration data in breast milk may be sufficient to provide reassurance for some drugs not expected to have any adverse effect on infants. Otherwise, one can attempt to quantify infant exposure.

The amount of a drug in breast milk is a variable fraction of the maternal blood concentration, which is proportional to the maternal dose. Quoted maternal milk-to-plasma ratios can vary because drug transfer is a time-dependent process. Even when calculated under steady-state conditions, there can be large individual variation. Absolute infant dose (µg/kg/day) can be calculated as the product of the average concentration in milk and the estimated daily volume of milk intake, and relative infant dose can be estimated by dividing the absolute infant dose by the maternal dose. It has been suggested that a relative infant dose less than 10% is generally safe, but this will also depend on the oral bioavailability of the drug in the infant and the relative toxicity of individual agents.

However, physicians and patients should be aware of the following disclaimers. First, in the case of toxic drugs, any exposure may be inappropriate. Second, the infant may be allergic to a drug consumed by the mother. Third, there may be unknown, long-term effects of even small doses of drugs. Fourth, individual variability in drug disposition may lead to unexpectedly high maternal blood and breast milk concentrations. Finally, infants have immature enzyme systems and metabolic pathways, and some drugs are eliminated more slowly. The benefits of breast-feeding are well known, and the risk for drug exposure must be weighed against these benefits.

Lactation is not fully established during the first several days postpartum. The neonate receives only a small volume
of colostrum, and little drug is excreted through milk at this time. Thus, only very small amounts of drugs administered after vaginal or cesarean delivery would reach the neonate, and significant effects should be unlikely. However, neonatal metabolism and elimination are also poorly developed, and several days of maternal opioid analgesia may result in neonatal accumulation and side effects.

When a mother requires a daily dose of a drug during lactation, the minimum effective dose should be used. Some mothers requiring long-term therapy would already have been taking drugs during pregnancy, and the fetus would have been exposed to concentrations much greater than those achieved in the infant through breast-feeding. Thus, if a drug has been acceptable during pregnancy, it is often reasonable to continue it during breast-feeding unless there are drug-specific factors to the contrary. For example, poor neonatal elimination of lamotrigine may eventually lead to drug accumulation in the infant and adverse effects. In general, medications should be taken after breast-feeding, and long-acting preparations should be avoided. If the infant nurses less frequently overnight, ingestion of a drug dose at night after nursing will decrease the infant’s exposure.

The following sections provide more detail for perioperative drugs commonly encountered by anesthesia providers. As the FDA is continually updating information, the reader is advised to check the information on LactMed for the latest recommendations.

### Anesthetic Drugs

There is generally no concern regarding anesthetic drugs in the breast milk of women who require an anesthetic during delivery and the immediate postpartum period, or in women with established breast-feeding well after delivery. Hospitals should have a perioperative policy that supports mothers to continue breast-feeding. The short exposure time and rapid elimination of anesthetic drugs means that mothers can often breast-feed immediately following anesthesia or procedural sedation. However, the prolonged use of postoperative analgesics will increase the infant dose, and adverse effects have been described, particularly for opioids. Analgesics will be discussed in the subsequent section.

A variety of adjunct drugs are sometimes used as part of a multimodal analgesia regimen. These include ketamine, gabapentin, pregabalin, dexametomidine, and local anesthetics administered by various routes. Postoperative infusions of ketamine are probably best avoided because limited safety data are available, and there is some concern for neurotoxicity. Gabapentin has less transfer to breast milk and is thus considered safer than pregabalin. Dexametomidine transfer is negligible, and a single dose of neuraxial clonidine is also unlikely to have any relevance to breast-feeding. Local anesthetics are large polarized molecules that do not transfer well to breast milk and are poorly absorbed orally. Other perioperative medications such as antiemetics are also considered safe, with nonsedating drugs such as 5HT3 receptor antagonists, dexamethasone, and metoclopramide preferred, although drugs such as promethazine and prochlorperazine have a long history of safe use.

### Analgesics

Acetaminophen (paracetamol) is the standard analgesic recommended for nursing mothers. The dose to the infant is less than 2% of the maternal dose and is considered safe.

NSAIDs are generally considered safe because they have low lipid solubility, high protein binding, and limited transfer to breast milk. Some NSAIDs specifically recommended as compatible with breast-feeding are ibuprofen, flurbiprofen, naproxen, and celecoxib. Ketorolac previously had a “black box” warning that it was “contraindicated in nursing mothers,” but current recommendations only say that it should be used with caution. Theoretically, NSAIDs with antiplatelet effects should be avoided by mothers who are breast-feeding neonates with platelet dysfunction, and all NSAIDs should be avoided in infants with ductal-dependent cardiac abnormalities. With aspirin, there is limited transfer of salicylic acid into breast milk because it exists mostly in the ionized form. After single oral doses, peak milk levels occur at approximately 3 hours with milk-to-plasma concentration ratios between 0.03 and 0.05. However, maternal ingestion of high doses (e.g., more than 3 g per day) may result in maternal and breast milk concentrations sufficiently high to affect platelet aggregation in the infant. Reduced neonatal clearance of salicylic acid may lead to drug accumulation and toxic effects, even when repeated exposures are small. Because of these concerns, the World Health Organization (WHO) Working Group on Human Lactation has classified salicylates as unsafe for use by nursing women. Low doses of aspirin prescribed as antiplatelet therapy may be acceptable.

It was thought previously that opioids used by nursing mothers were highly unlikely to have adverse effects on breast-fed infants. Normal maternal doses of codeine, morphine, tramadol, and meperidine (pethidine) do not have obvious adverse effects on most nursing infants. The dose detectable in breast milk is 1% to 2% of the mother’s dose and is unlikely to have significant pharmacologic activity. Neonates are particularly vulnerable because their drug metabolism and elimination are poorly developed. Neonates of mothers receiving meperidine by intravenous patient-controlled analgesia after cesarean delivery had significant neurobehavioral depression by the third day. The cumulative maternal meperidine dose at 48 hours postpartum was 14 mg/kg. No neonatal depression was seen in a morphine group in whom the cumulative maternal dose at 48 hours was 2.1 mg/kg. Both opioids and their major metabolites accumulated in colostrum. In a subsequent study, the cumulative opioid doses at 48 hours were lower (meperidine 4.7 mg/kg and morphine 0.54 mg/kg), but infants in the morphine group were still more alert and oriented. With lower maternal morphine doses, concentrations in colostrum may even be undetectable.
Recently, it has been recognized that infants of breastfeeding mothers taking codeine may have CNS depression. In 2006, the full-term 13-day-old infant of a mother taking a modest dose of codeine for episiotomy pain died of an apparent morphine overdose. It was discovered that the mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2×2 gene duplication, making her an ultrarapid metabolizer of codeine. This condition resulted in a breast milk morphine concentration of 87 ng/mL, compared with the expected typical range of 1.9 to 20.5 ng/mL. This case prompted the FDA to release a Public Health Advisory advising caution in the use of codeine-containing medications by breast-feeding women. The number of ultrarapid metabolizers is estimated to vary between 1 and 28 per 100 people. The updated warning notes that breast-feeding is not recommended when taking codeine because of the risk for serious adverse reactions. In addition, genetic variability in UGT2B7 may increase the formation of active morphine-6-glucuronide. It is estimated that 1.4% of Western European women would have both the CYP2D6 and UGT2B7 variants promoting neonatal depression.

Polymorphisms have less effect on the metabolism and analgesic effects of oxycodone, hydrocodone, and tramadol than codeine. Maternal oxycodone has been associated with neonatal depression. The FDA also gave a warning on April 20, 2017, against tramadol based on its CYP2D6 metabolism. This is controversial because tramadol continues to be used in other parts of the world where it is considered safe. Tramadol also has a nonopioid mechanism of action, and proponents of tramadol argue that banning it will force prescribers to use other opioids that have greater inherent risk.

Professional organizations differ in their recommendations for opioids, partly shaped by their normal clinical practice. Although anesthesia providers may be comfortable using tramadol, oxycodone, and hydrocodone in limited doses, the AAP recommends oral morphine and hydromorphone. Nevertheless, breast-feeding babies of all mothers receiving opioids should be observed for sedation and respiratory depression.

Sedatives
The benzodiazepines are considered safe, although long-acting drugs such as diazepam are metabolized slowly in the infant, and accumulation can lead to sedation and poor feeding. Relatively short-acting agents with inactive metabolites, such as oxazepam, lorazepam, alprazolam, or midazolam, are preferred.

Anticonvulsants
Some anticonvulsant drugs are used for many other indications apart from epilepsy, so that up to 80% of these drug prescriptions may be for patients without epilepsy. In contrast to use during pregnancy, congenital malformations are no longer a concern. Carbamazepine and valproate have low excretion into breast milk and are considered the safest choices. Studies have detected only small amounts of phenytoin, phenobarbital, and diazepam in breast milk. However, infants eliminate phenobarbital and diazepam slowly, so these agents may accumulate. Women taking a barbiturate or a benzodiazepine should observe their infants for evidence of sedation and withdrawal. There are conflicting recommendations for the newer anticonvulsants. Lamotrigine concentrations in breast-fed infants can be very high, and some recommend that the drug should be avoided. However, other authors note that the mother has usually been taking this drug throughout pregnancy already and that there is no evidence to recommend stopping the drug. It has been suggested that breast-feeding may improve the development of children exposed to anticonvulsants during pregnancy.

Cruikshank et al. measured breast milk magnesium concentrations in 10 preeclamptic women who were receiving magnesium sulfate 1 g/h intravenously for 24 hours after delivery. The mean breast milk magnesium concentration was 6.4 ± 0.4 mg/dL, compared with 4.8 ± 0.5 mg/dL in controls. Breast milk calcium concentrations were not affected by magnesium sulfate therapy.

Psychotropic Drugs
Psychotropic agents may be of concern because many of these medications have long half-lives and the effect of even small doses on the developing nervous system is not known. Nevertheless, most antidepressants have low milk-to-plasma ratios and appear to have little if any immediate effect on the infant. Benefits of treatment usually outweigh any risks.

The SSRIs are the most commonly prescribed antidepressants. Although they are found in breast milk, concentrations in infant plasma are very low and sometimes undetectable, especially with sertraline, which is often the preferred choice. The SNRIs and norepinephrine reuptake inhibitors (NRIs) have safety profiles similar to SSRIs, but fewer studies are available so they may be considered second-line. There are more data for venlafaxine, so this drug may be preferred. For the remaining antidepressants, there are concerns for neonatal seizures with bupropion, and St John’s wort is considered safe.

Data are available for only a few of the traditional antipsychotics, such as perphenazine and haloperidol, but there are no reported adverse effects on the infant. For the newer atypical antipsychotics, the most experience is with olanzapine and quetiapine, so they are considered the best choices.

Breast milk concentrations of lithium are one-third to one-half of maternal serum concentrations and infant serum concentrations during breast-feeding are much lower than fetal serum concentrations that occur when mothers take lithium during pregnancy. Neonatal clearance of lithium is reduced, and it may be useful to monitor neonatal lithium concentrations.

Cardiovascular Drugs
In general most of the first-line antihypertensive drugs are considered safe, although it would be prudent to use those
for which more safety information exists. High-dose thiazide diuretics have been used to suppress postpartum lactation, but this should not be a problem with the normal antihypertensive doses. Calcium entry–blocking agents have been well studied, especially nifedipine, which has minimal transfer to breast milk. Except for losartan, most ACEIs are usually metabolized to the active drug, which is poorly absorbed orally. Lactation data are available for several ACEIs, including captopril and enalapril, so that these are often the recommended choices. There are currently no data for ARBs, and an alternative drug may be preferred, even though ARBs are all very highly protein bound and theoretically safe. Beta-adrenergic receptor antagonists are a diverse group, and it is best to avoid those with low protein binding and thus have a relatively higher transfer to breast milk, and those that are excreted renally, which are more likely to accumulate in neonates. Both atenolol (10% protein binding and 85% renal excretion) and acebutolol have been associated with neonatal cyanosis, bradycardia, hypotension, tachypnea, and hypothermia. However, these beta-adrenergic receptor antagonists are usually better tolerated by the mother than those with poor transfer to breast milk such as propranolol. Labetalol and metoprolol are often used as they lie between these two extremes. Among second-line drugs, central alpha-adrenergic agonists can cause sedation and have mixed effects on serum prolactin, and so they are probably best avoided.

Amiodarone concentrations in the infant are unpredictable but may be sufficiently high to cause cardiac effects. Iodine released during its metabolism may cause thyroid dysfunction. Amiodarone has a very long half-life and is still excreted in breast milk weeks after stopping the drug. Maternal protein binding of digoxin limits infant drug exposure; after a maternal dose of 0.25 mg, a peak breast milk concentration of 0.6 to 1.0 ng/mL occurs and the milk-to-plasma concentration ratio at the 4-hour peak is between 0.8 and 0.9 ng/mL. In 24 hours, an infant might receive approximately 1% of the maternal digoxin dose, and no adverse effects have been reported in nursing infants of mothers taking this drug.

There are no safety data for statins, but they are not recommended during breast-feeding because of concerns that they may disrupt infant lipid metabolism.

Respiratory Drugs and Corticosteroids
Albuterol (salbutamol), terbutaline, and salmeterol inhalers are considered compatible with breast-feeding. Maximum milk concentrations of theophylline are achieved between 1 and 3 hours after an oral dose. It has been calculated that the nursing infant receives less than 1% of the maternal dose. Such exposure appears to have no adverse effects.

Inhaled and oral corticosteroids are also considered safe. Katz and Duncan obtained breast milk 2 hours after an oral dose of 10 mg of prednisone in one nursing mother. They detected breast milk concentrations of prednisone and prednisolone that would be unlikely to result in any deleterious effect on the infant. McKenzie et al. administered 5 mg of radioactive prednisolone to seven patients and found that 0.14% (a negligible quantity) of the radioactive label was secreted in the milk in the subsequent 60 hours. Thus, breast-feeding is not contraindicated in mothers taking corticosteroids. Even at a maternal dosage of 80 mg/day, the nursing infant would ingest a dose equivalent to less than 10% of its endogenous cortisol production.

Anticoagulants
Heparin is not excreted into breast milk because of its high molecular weight and charge, and LMWHs behave similarly. In addition, these drugs are not active when given orally, and so they are all considered safe during breast-feeding. Warfarin is highly (98%) protein bound and only appears in breast milk in insignificant quantities, so it is also considered safe. There are no data for the direct thrombin inhibitors, and their package inserts recommend that they should not be used during breast-feeding. On first principles, significant transfer is unlikely, although there are differences among these drugs. Dabigatran has a low molecular weight and is likely to have the greatest oral bioavailability, but this is still only about 7%. The newer direct factor Xa drugs are orally active, and they are currently not recommended for use during breast-feeding. However, data for rivaroxaban show that the infant only receives about 1% of the maternal weight-adjusted dose. Antiplatelet drugs such as clopidogrel and dipyridamole are not recommended during breast-feeding, but low-dose aspirin is considered acceptable.

Antihistamines
No harmful effects have been noted with maternal use of antihistamines. These drugs do not appear to affect the milk supply. Little antihistamine is excreted into breast milk, further confirming safety of use during lactation.

In theory, histamine type 2 (H2)-receptor antagonists might suppress gastric acidity or cause CNS stimulation in the infant, but these effects have not been confirmed in published studies. Famotidine, nizatidine, and ranitidine are less concentrated in breast milk and may be preferable to cimetidine.

Antidiabetic Drugs
Of the antidiabetic drugs, insulin is normally present in breast milk and not absorbed by the infant. Insulin-dependent mothers should continue insulin with close monitoring of glucose. Metformin is found in low doses in maternal milk, and infants are exposed to less than 0.5% of the maternal dose. Nevertheless it should be used with caution while nursing preterm infants and neonates. Second-generation sulphonylureas are falling out of favor, but there are data for glyburide and glipizide. Although glyburide was not detected in human milk, monitoring of infant blood glucose is still advised. The thiazolidinediones are greater than 99% bound to plasma proteins and so should not affect the infant, but rosiglitazone is labeled as contraindicated, leaving only pioglitazone to be used in this class. There are no data for the dipeptidyl peptidase-4 inhibitors or the glucagon-like
peptide-1 receptor agonists, but the current recommendation is to use with caution rather than avoid. Saxagliptin currently has the highest protein binding and shortest half-life, and so it is probably the best choice among the dipeptidyl peptidase-4 inhibitors. The sodium-glucose cotransporter-2 inhibitors are not currently recommended because of theoretical risk to the developing kidney, even though no data are available.

Anti-Infective Drugs

Penicillin and its derivatives are considered safe in nursing mothers. With the usual therapeutic doses of ampicillin, the milk-to-plasma concentration ratio is 0.2 or less and no adverse effects have been noted in nursing infants. Theoretically, infant diarrhea or candidiasis might occur with prolonged therapy. Cephalosporins appear in trace amounts in breast milk and are also considered safe.

Sulfonamides displace bilirubin from binding sites on albumin, so these drugs are best avoided during the first 5 days of life or in mothers of preterm infants with hyperbilirubinemia. Sulfonamides appear in breast milk in small amounts. Sulfasalazine has been associated with diarrhea and bloody diarrhea in an infant. Sulfonamides should be avoided in infants with G6PD deficiency.

Tetracyclines are normally avoided during breast-feeding because of the potential for tooth staining and delayed bone growth. The breast milk concentration of tetracycline is about one-half the maternal plasma concentration, but tetracycline has a high affinity for both calcium and protein, and the amount of free tetracycline available for systemic absorption is very small. Thus, some references consider a short course of tetracyclines to be compatible with breast-feeding. Fluoroquinolones are usually avoided in pregnancy, but there is disagreement over their safety during breast-feeding.

Use of drugs for treatment and prophylaxis of viral infections is a controversial area requiring specialist consultation, and recommendations may depend on the resources available. Infants should have been immunized against hepatitis B. Breast-feeding is usually not a contraindication to the use of the various anti–hepatitis C drugs.

Tetracyclines are normally avoided during breast-feeding, but the current recommendation is to use with caution rather than avoid. Saxagliptin currently has the highest protein binding and shortest half-life, and so it is probably the best choice among the dipeptidyl peptidase-4 inhibitors. The sodium-glucose cotransporter-2 inhibitors are not currently recommended because of theoretical risk to the developing kidney, even though no data are available.

Alcohol

About 50% of nursing mothers consume alcohol. The alcohol concentration in breast milk is similar to that in maternal blood, but it is estimated that the infant dose is only about 5% of the weight-adjusted maternal dose. Neonates take twice as long as adults to metabolize alcohol, but neither short-term behavioral changes nor long-term effects of alcoholic milk have been established. Advice on alcohol varies widely. Occasional maternal alcohol consumption within normal recommendations (approximately 10 to 20 g/day) should not affect the breast-fed infant, although some advise not breast-feeding for 2 hours after alcohol intake to be prudent.

Caffeine

Moderate maternal intake of caffeine does not adversely affect the breast-fed infant. One study noted that breast milk contains only 1% of the total maternal dose of caffeine. If a mother drinks excessive amounts of coffee, caffeine might accumulate in the infant and the infant might show signs of caffeine stimulation (e.g., irritability, poor sleeping pattern). Nursing mothers should limit their intake to a moderate level of caffeinated beverages (e.g., 2 to 3 cups per day).

Cannabis

The prevalence of marijuana use during pregnancy is 2% to 5%, but may be as high as 28% in some demographic groups. Apart from the possible effects of cannabis on the infant, an additional concern is the possible effect of the drug on the mother affecting her ability to care for the child. Women who smoke marijuana have a lower prolactin level, and tetrahydrocannabinol (THC) can alter the mother’s perception of the environment. Passive smoking is another route for drug exposure. There are regulatory and methodologic issues complicating interpretation of data on the effects of THC and non-THC cannabinoids such as cannabidiol. The percentage of THC in marijuana has also been rising steadily in recent years. THC is lipophilic and will be transferred to the breast-feeding infant who will test positive for the substance. Although oral bioavailability of THC is low, there are few data for the effects of THC on the newborn and infant. In general there have been more studies that show possible adverse effects to the infant than those that show no effect. Thus the prevailing medical opinion is that cannabis should not be used during breast-feeding. However, in mothers determined to continue cannabis, the benefits of breast-feeding may outweigh the effects of cannabinoids in breast milk.

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KEY POINTS

- Appropriate maternal treatment is essential to maintain fetal health.
- On average, women take over four drugs during pregnancy.
- Few drugs have detailed safety information for pregnancy and breast-feeding.
- The basis of safety for many drugs during pregnancy is a long history of uneventful use.
- Potential adverse fetal outcomes of the use of drugs during pregnancy include teratogenic effects, fetal loss, and fetal growth restriction. After delivery, there may be problems with neonatal adaptation and neurodevelopment.
- The U.S. Food and Drug Administration has implemented the Pregnancy and Lactation Labeling Rule.
- Physiologic changes of pregnancy can alter drug disposition and drug effect.
- Anticonvulsants and antidepressants have a high risk for adverse fetal effects.
- Acetaminophen is the safest analgesic for use during pregnancy, and NSAIDs should probably be avoided during pregnancy.
- Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should be avoided during pregnancy.
- LactMed is an up-to-date resource for safety of drugs during breast-feeding.
- Oral opioids such as codeine and tramadol are not recommended during breast-feeding.

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**In Vitro** Fertilization and Other Assisted Reproductive Technology

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**ASSISTED REPRODUCTIVE TECHNOLOGY PROCEDURES**

**Hormonal Stimulation**

Limited initially by the single preovulatory oocyte generated with each natural menstrual cycle, the introduction of follicular hormonal stimulation has significantly increased the probability of a live birth through the retrieval of *multiple* oocytes per cycle. Hormonal regimens typically initiate a cycle with a gonadotropin-releasing hormone agonist to induce pituitary and ovarian suppression, followed by follicle-stimulating hormone and human menopausal gonadotropin to stimulate the development and growth of multiple ovarian follicles. Human chorionic gonadotropin (hCG) is later added to induce maturation and demargination of the oocyte from the follicular wall before retrieval. Although the goal of these regimens is...
Oocyte retrieval is performed promptly between 34 to 36 hours after hCG administration to prevent spontaneous ovulation from occurring. With the use of a needle introduced through the vaginal fornix and affixed to a channel on the side of a transvaginal ultrasound probe, the ovary is punctured and follicular fluid is aspirated. Oocytes are identified in the aspirated fluid, immediately washed in culture media, and microscopically examined to determine their stage of meiosis. Oocytes are classified as postmature metaphase II, mature metaphase II, metaphase I, or prophase I based on their nuclear, cytoplasmic, and extracellular composition.

In vitro Fertilization

Although the term in vitro fertilization is often used synonymously with any aspect of ART, technically it applies only to the process of oocyte fertilization with spermatozoa in culture media. After a microscopic examination, oocytes are incubated for 4 to 6 hours in culture media that resembles human fallopian tube fluid and are then inseminated. The insemination process is sometimes delayed with immature oocytes.
(e.g., metaphase I) to increase the probability of normal (i.e., monospermic) fertilization.

At 16 to 20 hours after insemination, the oocytes are examined for evidence of fertilization (i.e., the presence of two pronuclei and two polar bodies in the perivitelline space) (Fig. 15.4). The advantages of IVF include the ability to document the process of fertilization and to enhance sperm motility or penetration (e.g., intracytoplasmic sperm injection). IVF followed by ET represents approximately 99% of the ART procedures used in the United States; less than 1% occur via GIFT or ZIFT procedures (see later discussions). Male factor infertility is present in approximately 35% of the couples seeking ART procedures, with intracytoplasmic sperm injection being the most frequently used therapeutic intervention.

**Embryo Transfer**

Following incubation for 3 to 5 days, embryos resulting from IVF may be transferred via a catheter into the fallopian tubes (i.e., ZIFT) or, more commonly, into the uterine cavity (IVF-ET). The advantages of transcervical ET are (1) simplicity—it does not require laparoscopy or anesthesia; (2) low cost, especially compared with laparoscopic intrafallopian transfer procedures; and (3) the ability to proceed without patent fallopian tube(s).

The primary disadvantage of transcervical ET is that the probability of successful pregnancy is slightly less than that with ZIFT. Embryos in excess of those required for transfer may be frozen in 1,2-propanediol or glycerol and stored for possible later transfer.

**Gamete Intrafallopian Transfer**

GIFT procedures consist of the transabdominal or transvaginal collection of oocytes followed by a microscopic inspection of the oocytes’ quality and maturation in a laboratory adjacent to the operating room. Mature oocytes are aspirated into a transfer catheter with washed partner or donor sperm, and the contents (gametes) are injected into the distal 3 to 6 cm of one or both fallopian tubes. The catheter is subsequently inspected microscopically to verify that oocytes have not been retained. The GIFT procedure does not involve IVF, because fertilization occurs *in vivo* in the natural milieu of the fallopian tube.

Specific advantages of the GIFT procedure include (1) the convenience of oocyte retrieval and ET occurring within a single operative event, (2) the elimination of IVF, and (3) the embryos reaching the uterine cavity at a potentially more appropriate (i.e., later) stage of development than with IVF-ET. The primary disadvantage is that fertilization cannot be documented, a critical factor when this capacity is in question (e.g., couples with male or immunologic factors). Normally, 50% to 70% of inseminated oocytes become fertilized; however, lower fertilization rates are often observed in couples with severe male factor infertility or in women with antisperm antibodies. Other limitations are the required presence of at least one patent fallopian tube and the requirement for laparoscopic surgery.

**Zygote Intrafallopian Transfer**

ZIFT (also known as pronuclear stage transfer [PROST]) consists of oocyte retrieval followed by IVF. At 16 to 20 hours after insemination, the oocytes are examined for the presence...
of two distinct pronuclei (i.e., the pronuclear stage; see Fig. 15.4), which indicates that fertilization has occurred. The patient is anesthetized for laparoscopy, and pronuclear stage embryos (usually no more than four) are transferred through a catheter into the distal portion of a fallopian tube (as described for GIFT). Advantages of ZIFT include (1) the documentation of fertilization, (2) the avoidance of laparoscopy if fertilization is not successful (approximately 13% of inseminations), (3) a shorter exposure to the laboratory environment than with IVF-ET, and (4) the potential for embryos to reach the uterine cavity at a more appropriate stage of development than with IVF-ET (i.e., approximately the fifth day after insemination). Its disadvantages and limitations include (1) the added inconvenience and cost of a two-stage procedure, (2) the requirement for laparoscopic surgery, and (3) the requirement for at least one patent fallopian tube.

**SUCCESS OF ASSISTED REPRODUCTIVE TECHNOLOGY**

The Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) collaborate with the Centers for Disease Control and Prevention (CDC) to maintain a data registry and analyze the results of all ART cycles initiated during each calendar year in the United States. Maternal age is the dominant factor in predicting successful pregnancy after an ART procedure (Fig. 15.5), affecting the ovarian response to fertility medications and rates of fertilization, implantation, miscarriage, and live birth. For example, in 2014, 37% of ART cycles in women younger than 35 years of age, compared with 1% in women older than 44 years of age, led to the delivery of one or more infants. In 2014, the average age of a woman having an ART procedure in the United States was 36 years.

Although pregnancy and delivery rates have historically been greater for tubal transfers (i.e., GIFT, ZIFT) than for transcervical uterine transfers (IVF-ET), greater parity in these rates has developed in recent years. The early postovulatory uterine environment has been postulated to be unfavorable to early embryo growth. Tubal transfer procedures allow embryos 3 to 5 days to reach the uterine cavity, when the environment for implantation may be more receptive. Lower implantation rates after transcervical ET may also be explained by (1) adverse uterine effects produced by the transfer procedure, (2) uterine contractions expelling transfer fluid and embryos, and (3) the absence of yet undiscovered tubal factors that promote early embryo growth and implantation.

**OBSTETRIC COMPLICATIONS**

ART hormonal stimulation regimens are associated with increased coagulation and decreased fibrinolysis when evaluated by individual hemostatic markers and global assessment tools (i.e., thromboelastography). These alterations are especially significant in the setting of the most common ovarian stimulation complication, a phenomenon termed *ovarian hyperstimulation syndrome* (OHSS). Mild cases of OHSS may manifest as abdominal discomfort, bilateral ovarian enlargement, and ascites, whereas severe cases may result in follicular rupture and hemorrhage, pleural effusion, hemocoagulation, oliguria, and thromboembolic events. In the presence of OHSS, the oocyte retrieval may be triggered earlier, and in severe cases, the embryo transfer may be delayed to limit exposure to exogenous and endogenous hormones. Anesthetic

![Fig. 15.5](https://via.placeholder.com/150) Percentage of transfers that resulted in live births with assisted reproductive technology (ART) cycles using fresh nondonor eggs or embryos, according to the women’s age in the years from 1995 to 2014, as reported to the Centers for Disease Control and Prevention, Division of Reproductive Health, and the Society for Assisted Reproductive Technology Registry. The first year in which data for women older than 42 years of age were subdivided into 43 to 44 years of age and older than 44 years of age was in 2007. (Data from U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Reproductive Health. 2014 Assisted Reproductive Technology (ART) Report. Atlanta, CDC/DRH, 2017.)
implications of OHSS include increased free drug concentrations (see later discussion) and greater perioperative pain from larger follicle numbers. Rarely, an emergency laparoscopy or laparotomy is required for excision of an ovarian cyst rupture or release of an ovarian pedicle torsion. Abdominal paracentesis and thoracentesis may be necessary before the induction of general anesthesia in patients with respiratory compromise caused by massive ascites or pleural effusions.

Multiple-gestation pregnancies represented 25% of the deliveries that followed ART procedures in the United States in 2014, of which 96% were twins. Although the transfer of a greater number of embryos or oocytes increases both the probability of a live birth and the likelihood of a multifetal pregnancy, maternal and perinatal morbidity and mortality for multiple versus singleton gestation pregnancies are at least doubled, but are no different than spontaneously conceived pregnancies. In an effort to reduce the incidence and sequelae of multifetal pregnancies, many ART programs and societies, and even some countries, have mandated a limit on the number of embryos or oocytes that are transferred. In the presence of triplet or higher-order gestation pregnancies, selective reductions can be performed; however, these procedures are subject to a number of medical and ethical considerations.

Ectopic pregnancies occur up to five times more frequently in ART pregnancies than with natural pregnancies (2%), primarily owing to the greater prevalence of fallopian tube disease among infertility patients. The transfer site (uterine versus fallopian tube) per se does not appear to be a predisposing factor in the development of ectopic pregnancies; however, a greater number occur after uterine transfer, because women with bilateral tubal disease are not candidates for GIFT or ZIFT procedures. In approximately 10% of ectopic pregnancy cases, the ectopic embryo develops in conjunction with an ongoing intrauterine pregnancy and requires a termination or surgical removal within the first trimester.

Preterm, low-birth-weight, and small-for-gestational-age infants are more common with ART singleton pregnancies than with natural pregnancies, although the prevalence of admission into the neonatal intensive care unit, duration of infant hospital stay after birth, and the incidence of infant death appear similar (Fig. 15.6). The difference appears to be a result of infertility per se rather than the ART procedures, because previously infertile women who conceive independent of ART also are at greater risk for preterm delivery.

![Fig. 15.6 Outcomes associated with births from assisted reproductive technology (ART) and spontaneous pregnancies in the general population. (Data from Sunderam S, Kissin DM, Crawford SB, et al. Assisted Reproductive Technology Surveillance—United States, 2014. MMWR Surveill Summ. 2017;66:1–24.)](image)

### EFFECTS OF ANESTHESIA ON REPRODUCTION

#### General Considerations

In 1987, Boyers et al. reported that oocytes recovered by laparoscopic techniques in patients who had received general anesthesia (isoflurane or enflurane with a 50% nitrous oxide–oxygen mixture) were less likely to be fertilized if the duration of the procedure was prolonged. Specifically, fertilization rates for the first- and last-recovered oocytes were 69% and 54%, respectively, when the difference in exposure time exceeded 5 minutes. The investigators advanced the following two plausible explanations for this difference: (1) the acidification of follicular fluid by intraperitoneal carbon dioxide and (2) the effects of anesthesia.

The potential association between anesthetic techniques and agents, and outcomes of ART procedures must be interpreted with caution. For example, one study concluded that oocyte cleavage rates were significantly lower with general anesthesia than with epidural anesthesia. However, a laparoscopic (instead of transvaginal) retrieval method was used in the general anesthesia group, and carbon dioxide pneumoperitoneum may significantly decrease both follicular fluid pH and oocyte fertilization rates. Another report commented on the effects of different anesthetic techniques, but failed to disclose the actual anesthetic agents that were administered.

In addition, conclusions based on animal data may not reflect the human experience owing to significant interspecies and assay method differences.

Assessment of specific anesthetic drugs must also be interpreted in context; relevant factors include (1) the method of administration, (2) dose of anesthetic agents, (3) combination with other drugs, (4) timing of administration, and (5) duration of exposure. For example, local anesthetic agents yield dissimilar pharmacokinetic profiles when administered via paracervical, epidural, and intrathecal techniques. Anesthetic agents may also affect unfertilized oocytes and fertilized embryos differently; thus, studies of anesthetic agents used for a GIFT (prefertilization) procedure should not be directly compared with studies of agents used for a ZIFT (postfertilization) procedure. Finally, significantly greater free concentrations of certain agents (e.g., bupivacaine) exist during ART stimulation because of a decrease in plasma protein binding capacity associated with hormonal manupulation. Thus, when selecting anesthetic techniques or agents for an ART procedure, the clinician should weigh their known benefits (e.g., greater hemodynamic stability, less nausea, less psychomotor impairment) and potential risks (e.g., lower delivery rates).
Local Anesthetic Agents

In animal models, the effect of local anesthetic agents on reproductive physiology appears to be related to the agent, timing, and dose of exposure. Using mouse oocytes incubated for 30 minutes in culture media with known concentrations of lidocaine, bupivacaine, or 2-chloroprocaaine, Schnell et al. demonstrated that lidocaine and 2-chloroprocaaine adversely affected both fertilization and embryo development at concentrations of 1.0 and 0.1 µg/mL, respectively (Figs. 15.7 and 15.8). In contrast, bupivacaine produced adverse effects only at the highest concentration studied (100 µg/mL). Similarly, Del Valle and Orihuela demonstrated that after 48 hours of culture, 24% of mouse embryos exposed to lidocaine 10 µg/mL, in comparison with none in the control group, showed evidence of degeneration. Finally, Ahuja observed that hamster oocytes exposed to procaine or tetracaine had impaired zona reactions, potentially allowing additional sperm to enter the oocyte and create abnormal chromosomal numbers (polyploidy).

These in vitro findings may have limited clinical relevance, however, given the lower anesthetic concentrations that are administered in clinical practice and the washing and screening procedures that oocytes undergo before fertilization and transfer. Human trial data appear to indicate minimal oocyte and embryo alterations with local anesthetic agents used during oocyte retrieval, GIFT, or ZIFT procedures. Wikland et al. reported that the incidence of oocyte fertilization and clinical pregnancy was not reduced among women who received a modified paracervical block with lidocaine for transvaginal oocyte retrieval (Fig. 15.9). Favorable pregnancy rates have also been reported after GIFT procedures performed during epidural anesthesia with lidocaine.

Opioids and Benzodiazepines

Fentanyl, alfentanil, remifentanil, and meperidine do not appear to interfere with either fertilization or preimplantation embryo development in animal and human trials. When given during oocyte retrieval, fentanyl and alfentanil
were detected in extremely low (or undetectable) follicular fluid concentrations. With alfentanil, a 10:1 ratio between serum and follicular fluid was observed 15 minutes after the initial bolus dose. Morphine appears unique in terms of adverse effects; when sea urchin eggs were incubated in morphine (equivalent to a human dose of 50 mg), more than one sperm entered approximately 30% of the oocytes.

Midazolam administered systemically in preovulatory mice did not impair fertilization or embryo development in vivo or in vitro, even when given in doses up to 500 times those used clinically. When used in small bolus or infusion doses for anxiolysis and sedation for ART in humans, midazolam has not been detected in follicular fluid and does not appear to be teratogenic.

Propofol, Thiopental, and Ketamine

Most animal and human trials suggest minimal to no detrimental effects of propofol on fertilization and early embryo development, despite accumulating in a dose- and duration-dependent manner within the follicular fluid. General anesthesia provided with propofol and a 50% oxygen-air mixture was associated with fertilization, embryo cleavage, and implantation rates similar to those produced by a paracervical block with mepivacaine. Hamster oocytes exposed to very high concentrations of propofol (20 µg/mL) demonstrated no DNA damage—even through two metaphases—when evaluated by sister chromatid exchange assays, a sensitive index of genotoxic effects. These concentrations were 40 times greater than those detected clinically in the follicular fluid of patients undergoing oocyte retrieval. The induction and maintenance of general anesthesia with propofol for GIFT procedures demonstrated negligible differences in reproductive outcomes from women receiving other forms of anesthesia. By contrast, a smaller incidence of ongoing pregnancies was observed among women given propofol–nitrous oxide anesthesia for ZIFT procedures compared with thiopental–nitrous oxide–isoflurane anesthesia. Further investigation is necessary to further elucidate the full effects of propofol on various reproductive outcomes.

Both thiopental and thiamylal (5 mg/kg) can be detected in follicular fluid as early as 11 minutes after their administration for induction of general anesthesia in patients undergoing GIFT procedures. No adverse reproductive effects have been observed with these agents, and when they were specifically compared with propofol (2.7 mg/kg) for GIFT procedures, no differences in clinical pregnancy rates were noted.

Ketamine (0.75 mg/kg), administered with midazolam (0.06 mg/kg), has been reported to be an acceptable alternative to general anesthesia with isoflurane for oocyte retrieval. No differences in reproductive outcomes were observed; however, the study was not powered to adequately assess this result.

Nitrous Oxide

Nitrous oxide reduces methionine synthetase activity, non-methylated folate derivatives, and DNA synthesis in animals and humans. Nitrous oxide also impairs the function of mitotic spindles in cell cultures. Although Warren et al. reported that two-cell mouse embryos exposed to nitrous oxide within 4 hours of the expected onset of cleavage were less likely to develop to the blastocyst stage, this difference had resolved by later stages of embryo development.

Clinical studies of anesthesia for laparoscopic ART procedures support the administration of nitrous oxide during GIFT and ZIFT procedures. In a multicenter study, Beilin et al. observed a delivery rate of 35% among women given nitrous oxide for GIFT procedures, compared with 30% among women who did not receive nitrous oxide. In women undergoing oocyte retrieval, Handa-Tsutusi and Kodaka reported lower target-controlled propofol doses with a 50% nitrous oxide–oxygen mixture than with an oxygen-air mixture. The authors reported that there were no alterations in pregnancy rates, but the study was not adequately powered to identify a difference.

Volatile Halogenated Agents

Volatile halogenated agents have been observed to depress DNA synthesis and mitosis in cell cultures. Sturrock and Nunn noted that volatile halogenated agents prevent cytoplasmic cleavage during mitosis, leading to a greater number of abnormal mitotic figures (e.g., tripolar and tetrapolar nuclear phases). Isoflurane adversely affects embryo development in vitro. Warren et al. reported that two-cell mouse embryos exposed to 3% (but not 1.5%) isoflurane for 1 hour were less likely to develop to the blastocyst stage, but only when isoflurane was given within 4 hours of the predicted onset of cleavage.

Volatile halogenated agents may also affect ART outcomes through an increase in prolactin levels. High prolactin levels have been associated with diminished oocyte development...
and uterine receptivity (see later discussion); whether volatile halogenated agents can affect mature oocytes in the process of being retrieved, however, is questionable. Critchlow et al. observed dramatic rises in plasma prolactin levels with an enflurane in nitrous oxide–oxygen technique for GIFT procedures, although these changes did not occur until 4 to 10 minutes after induction and did not affect follicular fluid prolactin levels or fertilization rates.

Volatile anesthetic agents have been compared in clinical studies. Fishel et al. reported that pregnancy rates were significantly lower among women given halothane anesthesia for ET than in a similar group of women given enflurane; of interest, the anesthesia was administered in an attempt to decrease uterine activity during ET. Similarly, Critchlow et al. reported lower pregnancy and delivery rates among women who received halothane for GIFT procedures than in women who received enflurane (Fig. 15.12). In a retrospective sequential study design, Wilhelm et al. noted lower pregnancy rates in patients undergoing oocyte retrieval with general anesthesia (isoflurane or propofol in combination with 60% nitrous oxide in oxygen) than in subsequent patients who received analgesia with a remifentanil-based technique. The investigators acknowledged that the success rates of ART programs have improved over time and that it is possible that physician-related factors may have improved the outcomes in the later sedation analgesia phase of the study.

Although these data suggest that specific volatile halogenated anesthetic agents can affect ART outcomes, the mechanisms remain incompletely evaluated. For example, compound A, the metabolic byproduct of sevoflurane, has been associated with genotoxic ovarian cell effects, although reproductive outcomes have not been assessed. As a consequence, caution is advised in the selection of newer agents, such as sevoflurane and desflurane, until further work has been done.

**Antiemetic Agents**

At least one study noted that droperidol and metoclopramide rapidly induce hyperprolactinemia with subsequent impairment of ovarian follicle maturation and corpus luteum function. Moreover, Forman et al. demonstrated that low plasma prolactin concentrations during ART procedures were associated with a higher incidence of pregnancy. In contrast, when a single dose of intravenous metoclopramide 10 mg was given the day preceding oocyte retrieval, a prolactin level increase of greater, versus less, than 200% yielded larger follicles, more mature oocytes, and improved IVF success rates. The effect of agents that do not affect prolactin levels, such as ondansetron, have not been studied.

**ANESTHETIC MANAGEMENT**

Because most patients undergoing ART procedures are young and otherwise healthy, many institutions do not require preoperative laboratory studies, electrocardiograms, or chest radiographs before the procedure. However, the use of ART procedures in patients with a growing spectrum of pathologic processes, such as morbid obesity, cancer (with oocyte retrieval performed before chemotherapy or radiation therapy), and severe cardiac, pulmonary, or renal morbidities (with oocyte retrieval performed for ET in surrogate gestational carriers), has created special concerns that should be addressed in individual patients.

All patients should follow the fasting guidelines typically used for patients undergoing ambulatory surgery. In patients with risk factors for pulmonary aspiration of gastric contents, a nonparticulate antacid should be given before the procedure. On occasion, a patient may not adhere to strict fasting
guidelines; although delay or cancellation of the procedure is an option, the decision should be made after careful analysis of the potential risks and benefits. If the window for maximal oocyte retrieval (34 to 36 hours after hCG administration) is missed, ovulation with loss of oocytes can occur, invalidating the considerable effort and expense that have been incurred to that point. Moreover, if oocyte retrieval is not performed, the patient is at increased risk for OHSS, with its potential for significant morbidity. In contrast, the risk for pulmonary aspiration of gastric contents is low, particularly when spinal anesthesia is administered (see later discussion).

As with other ambulatory surgery cases, the ideal anesthetic technique provides effective pain relief with minimal postoperative nausea, sedation, pain, and psychomotor impairment.

**Ultrasound-Guided Transvaginal Oocyte Retrieval**

Although transvaginal oocyte retrievals can be performed under paracervical, spinal, epidural, and general anesthetic techniques, conscious or deep sedation analgesia (often administered by an anesthesia provider as a component of monitored anesthesia care) is the most commonly used technique. Although usually adequate for surgical analgesia, deep sedation analgesia may need to progress to loss of consciousness (i.e., general anesthesia) to prevent patient movement at critical points in the procedure. The need for additional pain relief should be anticipated when the needle penetrates the cul-de-sac and, later, each ovary. A greater rate of hospital admission after oocyte retrieval, mostly secondary to intra-abdominal bleeding, has been reported with sedation analgesia compared with general anesthesia.

Because paracervical anesthesia incompletely blocks sensation from the vaginal and ovarian pain fibers, additional analgesia is required. Epidural and spinal techniques provide excellent anesthesia with minimal oocyte exposure to anesthetic agents. Compared with sedation using propofol and mask-assisted ventilation with nitrous oxide, epidural bupivacaine anesthesia resulted in fewer complications, especially nausea and emesis. Spinal anesthesia may be preferable to epidural anesthesia owing to the reduced anesthetic failure rate, reduced systemic and follicular concentrations of anesthetic agent, and faster recovery profile. Spinal administration of 1.5% hyperbaric lidocaine (60 mg) is associated with significantly shorter recovery times than spinal administration of 5% hyperbaric lidocaine (60 mg) in patients undergoing ART procedures. The addition of intrathecal fentanyl 10 µg to lidocaine 45 mg improves postoperative analgesia for the first 24 hours, with no increase in time to urination, ambulation, and discharge compared with intrathecal lidocaine alone. Given the frequent association of spinal lidocaine with postoperative transient neurologic symptoms (see Chapter 31), low-dose spinal bupivacaine represents a viable alternative, with recognition of the prolonged time to urination and discharge.

General anesthesia can be provided by total intravenous anesthesia (TIVA) using propofol (titrated) and an opioid (e.g., fentanyl 50 to 100 µg). Midazolam (1 to 2 mg) can be used as an optional premedication. Most patients can be managed with spontaneous ventilation. Individuals with significant risk factors for aspiration should undergo tracheal intubation with a cuffed endotracheal tube. This anesthetic technique can produce mean bispectral index scores that range from 47 to 53 and modified Ramsay sedation scores that are consistent with general anesthesia and results in greater patient satisfaction than sedation analgesia, owing to better pain relief and less awareness during the surgical procedure. Alternatively, tracheal intubation and maintenance of anesthesia with a volatile halogenated agent has been used successfully; however, greater rates of nausea and emesis and more unplanned admissions have been observed with this technique than with a propofol, alfentanil, and air-oxygen mixture.

Novel analgesic measures have been investigated during oocyte retrieval. One study evaluated electroacupuncture as an alternative to intravenous alfentanil, although both groups also received a paracervical block, and the acupuncture group experienced greater degrees of preoperative stress and longer periods of discomfort during oocyte aspiration.

**Embryo Transfer**

Described as relatively painless, transcervical ET procedures are most commonly performed without analgesia or anesthesia; however, on rare occasion, intravenous sedation analgesia or regional or general anesthesia may be requested. In contrast, transabdominal gamete or embryo transfer procedures (i.e., GIFT, ZIFT) are usually performed via laparoscopy under local, neuraxial, or general anesthesia. The anesthetic management for these procedures and the associated concerns with regard to the laparoscopic technique and the Trendelenburg position are described here. Major intraoperative complications associated with laparoscopy are rare but include gastric or intestinal perforation, hemorrhage, pneumothorax, pneumopericardium, mediastinal emphysema, gas embolism, and cardiac arrest.

**Pneumoperitoneum and the Trendelenburg Position**

Carbon dioxide is the gas most commonly used to establish pneumoperitoneum. The high blood solubility of carbon dioxide facilitates absorption from the peritoneal cavity after laparoscopic surgery and may represent a life-saving property of the gas in the rare but potentially catastrophic event of gas embolization. For example, rapid intravenous injection of 5 to 10 mL/kg of carbon dioxide produces only transient (<1 minute) hypotension in anesthetized dogs whereas intravascular administration of a similar volume of a less soluble gas (e.g., helium, oxygen, nitrogen) is usually fatal.

Signs of embolization of large quantities of carbon dioxide (or any other gas) in anesthetized patients may include hypoxia, hypotension, hypoxemia, ST-segment and T-wave changes, arrhythmias, and audible changes in heart sounds. Initial treatment of carbon dioxide embolism should include release of the pneumoperitoneum and pharmacologic support of the circulation. If initial resuscitation efforts are...
unsuccessful, aspiration of gas from the right atrium (using a multi-orifice central venous catheter) should be considered. Although the use of the left lateral recumbent position (Durant’s maneuver), with or without head-down positioning, has been suggested to facilitate removal of the postulated air lock from the right side of the heart, laboratory evidence suggests that this maneuver may have a detrimental effect on cardiac function after venous gas embolism.86

Nearly as soluble in blood as carbon dioxide, nitrous oxide is associated with less peritoneal and diaphragmatic irritation and has been suggested for the establishment of pneumoperitoneum in awake patients undergoing laparoscopy. A major disadvantage of nitrous oxide is its ability to support combustion, which could increase the possibility of an explosion if the surgeon uses electrocautery.

GIFT and ZIFT procedures are often performed with the patient in the Trendelenburg position to facilitate visualization of the fallopian tubes and other pelvic structures. Positioning strategies to prevent the patient from moving cephalad on the operating table and to prevent brachial plexus damage should be used. The adduction of the patient’s arms against her trunk has been suggested to reduce the risk for brachial plexus injury, but the efficacy of this precaution is unproven.

Both pneumoperitoneum and the Trendelenburg position produce physiologic changes. Hemodynamic effects of moderate pneumoperitoneum (< 20 mm Hg) in a patient in the Trendelenburg position include increased mean arterial and central venous pressures, increased systemic vascular resistance, and decreased stroke volume and cardiac output.88 Heart rate usually does not change, but in some patients pneumoperitoneum may elicit sinus bradycardia, heart block, or even cardiac arrest. Finally, pneumoperitoneum aggravates the respiratory effects of the Trendelenburg position (e.g., reduced chest wall compliance, increased venous admixture). Overall, most healthy patients easily tolerate the cardiovascular and pulmonary effects of intra-abdominal pressures lower than 20 mm Hg.

**Laparoscopic-Assisted Reproductive Technology**

The anesthetic plan for GIFT procedures is typically dictated by the method (i.e., transabdominal or transvaginal) of oocyte retrieval. Many ART programs harvest oocytes transabdominally during pelvic laparoscopy; the principal advantage is that the patient is positioned and anesthetized once for both the retrieval and transfer portions of the procedure. The major disadvantage of this technique is that oocytes are exposed to both carbon dioxide pneumoperitoneum and anesthetic agents. The induction of general anesthesia for GIFT procedures can be delayed until just before the skin incision in an effort to minimize unnecessary exposure to these agents. Induction is usually performed with intravenous propofol, lidocaine, fentanyl, and either succinylcholine or rocuronium. After tracheal intubation, the anesthesia provider may decompress the patient’s stomach with a suction catheter or Salem sump tube to reduce the risk for gastric perforation during instrumentation. Subsequently, a volatile halogenated agent in oxygen and air, with or without a short-acting muscle relaxant, is given to maintain anesthesia. The use of a propofol–nitrous oxide technique has been associated with less postoperative sedation, lower pain scores, and less emesis than an isoflurane–nitrous oxide technique.50

Alternatively, oocytes can be retrieved transvaginally and transferred—as oocytes or embryos—laparoscopically. This technique is most commonly used with ZIFT procedures, whereby oocyte retrieval and IVF occur on the preceding day. Advantages to the combined transvaginal/transabdominal approach include (1) the avoidance of laparoscopy in the 1% to 2% of cases in which oocyte quality or number is inadequate to justify proceeding with a tubal transfer and (2) the elimination of oocyte exposure to the carbon dioxide pneumoperitoneum. Disadvantages of this method include (1) the need to reposition the patient before laparoscopy and (2) a prolonged total operative time if performed on the same day (GIFT) or the need for a second procedure if performed on consecutive days (ZIFT).

A few patients prefer spinal or epidural anesthesia for GIFT procedures.89,90 Healthy, nonobese patients have been reported to successfully undergo laparoscopic surgery in the Trendelenburg position with high thoracic (i.e., T2 to T4) spinal or epidural anesthesia.89–92 Limiting intraperitoneal pressure to less than 10 mm Hg may facilitate the use of neuraxial anesthesia.

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**Fig. 15.13** Arterial tracings after rapid intravenous injection of 7.5 mL/kg of carbon dioxide (top) and helium (bottom). Recovery occurs within 1 minute after the carbon dioxide injection, but complete cardiovascular collapse occurs after the helium injection. (Modified from Wolf JS, Carrier S, Stoller ML. Gas embolism: helium is more lethal than carbon dioxide. J Laparoendosc Surg. 1994;4:173–177.)
for these procedures. Obese women are not ideal candidates for neuraxial anesthesia in laparoscopic surgery.

Adequate analgesia for laparoscopic ART procedures has also been reported with the use of local anesthesia supplemented with intravenous sedation analgesia.⁹³-⁹⁶ Padilla et al.⁹³ observed that the quality of intraoperative analgesia can be improved by limiting maximal intra-abdominal pressure to less than 10 mm Hg, reducing the rate of carbon dioxide insufflation to 1 L/min, and minimizing ovarian manipulation. The difficulty and discomfort frequently associated with cannulation of the fallopian tubes, however, may make local anesthesia an unsuitable choice for laparoscopic ART procedures.⁹⁴ The use of local anesthesia should not be interpreted as being devoid of risk for serious complications (e.g., bradycardia, cardiac arrest). These life-threatening complications are rare, but the management and outcome are greatly assisted by the presence of individuals skilled in airway management and cardiopulmonary resuscitation.⁹⁵

**Postoperative Management**

The incidence of anesthetic or surgical complications requiring hospital admission after ART procedures is low. Oskowitz et al.⁷² reported admission rates after oocyte retrieval and GIFT procedures of 0.16% and 0.18%, respectively. The most common indications for hospitalization were hemoperitoneum and syncope after oocyte retrieval, and nausea, vomiting, and bowel injury after laparoscopic GIFT procedures. Abdominal pain and uterine cramping occur commonly after oocyte retrieval. Incisional pain and referred shoulder pain as a result of diaphragmatic irritation can also occur after laparoscopic ART procedures. Postprocedural discomfort is related primarily to the number of follicles retrieved (rather than the hormonal alterations induced by the stimulation cycle) and can be effectively managed with the use of a heating pad and small doses of intravenous fentanyl (25 to 50 µg) or oral analgesic agents (acetaminophen 500 mg to 1 g).⁹⁸ The use of nonsteroidal anti-inflammatory drugs should be avoided because changes in the prostaglandin milieu can affect embryo implantation.⁹⁹

Nausea and emesis can also occur; however, exposure to droperidol and metoclopramide should be limited (see earlier discussion); treatment with nondopaminergic agents can be considered. Before discharge, patients should be able to drink and retain liquids, ambulate, and void. Patients undergoing anesthesia for an ART procedure should be called 24 hours after the procedure to allow assessment of recovery and potential complications.

**FUTURE CONSIDERATIONS**

The use of ART procedures has been extended to include patients within a broader range of ages and comorbidities. Check et al.¹⁰⁰ reported the successful delivery of infants through the use of donor oocytes, IVF, and ET in two postmenopausal women who were 51 years of age; women in the seventh decade have also successfully delivered infants. In addition, more programs are participating in the preservation of ovarian tissue as a means of extending reproductive capability. Future studies should assess the short- and long-term maternal and perinatal consequences of ART procedures as well as the obstetric and anesthetic implications.¹⁰¹

Technical improvements in ultrasonography as well as fiberoptic methods of oocyte retrieval and fallopian tube cannulation could potentially make laparoscopic interventions less invasive or unnecessary. For example, small-diameter laparoscopes with optical views comparable to conventional instruments have allowed “mini-laparoscopic” procedures to be performed for GIFT procedures.⁹⁶ These alterations may allow for changes in anesthetic options.

The identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success is an important process to which anesthesia providers can and should contribute.

**KEY POINTS**

- Assisted reproductive technology (ART) includes techniques that are being applied to an increasingly diverse population of patients with a wide range of comorbidities.
- ART procedures usually involve a regimen of hormonal stimulation and oocyte retrieval followed by either *in vitro* fertilization with embryo transfer (IVF-ET) or gamete intrafallopian transfer (GIFT) procedures.
- Hormonal stimulation creates a number of oocytes for retrieval. On occasion, ovarian hyperstimulation syndrome can occur, with severe cases being associated with ascites, pleural effusion, hemoconcentration, oliguria, and thromboembolic events.
- Oocyte retrieval must be performed promptly, or ovulation will reduce the number of mature oocytes available for harvesting. Embryo transfer usually occurs transcervically; however, laparoscopic techniques (zygote intrafallopian transfer [ZIFT]) can be used.
- Sedation analgesia, neuraxial anesthesia, and general anesthesia have all been used successfully to anesthetize women for ART procedures. Deep sedation may have to progress to loss of consciousness (i.e., general anesthesia) to prevent patient movement at critical times during the procedure.
- Laboratory studies have suggested that local anesthetic agents, nitrous oxide, and the volatile halogenated agents interfere with some aspects of reproductive physiology *in vitro*. However, few clinical data show that brief administration of any contemporary anesthetic agent for an ART procedure adversely affects live-birth rates.
- The identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success is an important process to which anesthesia providers can and should contribute.
REFERENCES


Obstetric disease of early pregnancy may result in significant maternal morbidity and even mortality. Safe care of patients with obstetric disease involves a thorough understanding of the physiologic changes of early pregnancy as well as the specific issues associated with each pathologic condition.

PHYSIOLOGIC CHANGES OF EARLY PREGNANCY

Respiratory System
The respiratory system undergoes profound physiologic changes during early pregnancy. Increased progesterone concentration stimulates respiratory efforts by increasing the sensitivity of the respiratory center to carbon dioxide. Minute ventilation increases by at least 15% by 12 weeks’ gestation and by 25% by 20 weeks’ gestation. This results from an increase in tidal volume (respiratory rate is unchanged) and exceeds the increase in oxygen consumption. The result is a respiratory alkalosis with maternal arterial partial pressure of carbon dioxide decreasing to 30 to 33 mm Hg (4.0 to 4.4 kPa) by 10 to 12 weeks’ gestation. Moreover, maternal arterial partial pressure of oxygen increases to 106 to 108 mm Hg (14.1 to 14.4 kPa) in the first trimester. Decreased bicarbonate concentration partially compensates for the modest respiratory alkalosis that results from the physiologic hyperventilation, leading to a maternal pH that is slightly above normal (i.e., approximately 7.44). There is little or no change in lung capacities during the first half of pregnancy. Women in early pregnancy who undergo mechanical ventilation require increased minute ventilation.

Cardiovascular System
The cardiovascular system also undergoes profound changes early in pregnancy. During the first trimester, cardiac output increases by about 15% above prepregnancy values; by the early third trimester, cardiac output is about 30% above prepregnancy values. Systemic vascular resistance decreases 30% by 8 weeks’ gestation. Maternal mean arterial pressure decreases approximately 6 mm Hg at 16 to 24 weeks’ gestation and returns to normal near term.

In a typical pregnancy, aortocaval compression could begin to occur after 18 to 20 weeks’ gestation, when the uterine fundus reaches the umbilicus and is potentially large enough to compress the aorta and vena cava when the patient is supine. Of note, the frequency of aortocaval compression in pregnant women in the supine position has recently been questioned with a magnetic resonance imaging study showing no aortocaval compression in 10 healthy full-term pregnant women in the supine position. Nonetheless, most experts agree that when the uterine size is equivalent to an 18- to
20-week gestation, the application of left uterine displacement should be performed if possible. This can be achieved by elevating the right hip approximately 15 degrees off midline with a wedge or blankets. The need for left uterine displacement may occur earlier in gestation in the presence of multiple gestation, polyhydramnios, or gestational trophoblastic disease.

Blood volume increases throughout pregnancy. The average prepregnancy blood volume of 4350 mL (76 mL/kg) increases to 4700 mL (81 mL/kg) at 12 weeks' gestation, to 5500 mL (89 mL/kg) at 20 weeks' gestation, and to approximately 6600 mL (97 mL/kg) at term. The increase in blood volume is primarily the result of greater plasma volume because red blood cell volume increases to a smaller degree (27 mL/kg). Because pregnant women have an expanded blood volume, most can typically tolerate a blood loss of 500 to 1500 mL in early pregnancy without requiring blood transfusion, if the blood loss is replaced with an adequate volume of crystalloid or colloid.

Gastrointestinal System

An increased progesterone level causes relaxation of the lower esophageal sphincter tone as early as the first trimester. Fasting gastric volume is approximately 30 mL in both nonpregnant women and women in early pregnancy. Metoclopramide 10 mg, administered intravenously 15 to 30 minutes before anesthesia, can reduce this volume by 50%. Obesity does not delay gastric emptying in nonlaboring pregnant women. In a study of 100 pregnant women undergoing general anesthesia by mask at 6 to 22 weeks' gestation, a pH electrode showed reflux of gastric contents into the esophagus in 17% of patients. Most episodes of reflux occurred in patients who experienced hiccups. Only 2% had regurgitation of gastric contents into the pharynx, and no patient demonstrated clinical evidence of pulmonary aspiration.

General anesthesia may be safely administered by means of a mask or a laryngeal mask airway (LMA) by experienced anesthesia providers in selected obstetric patients during early pregnancy. Many anesthesia providers are comfortable managing an airway without tracheal intubation until 18 to 20 weeks' gestation, when the uterus moves out of the pelvis. The latter movement leads to anatomic and intra-gastric pressure changes that predispose to gastroesophageal reflux. Some anesthesia providers prefer to intubate the trachea of pregnant women who require general anesthesia as early as 12 to 14 weeks' gestation, given that hormonal changes leading to sphincter relaxation are present early in pregnancy. Patients who receive general anesthesia during the first half of pregnancy should be intubated if they are at increased risk for gastric content aspiration (e.g., history of gastroesophageal reflux, morbid obesity, solid food ingestion within 8 hours). Pharmacologic prophylaxis (e.g., sodium citrate, a histamine-2 (H₂) receptor antagonist, and/or metoclopramide) is likely to further reduce the risk for aspiration pneumonia (see Chapter 28). Neuraxial anesthesia is associated with a lower risk for aspiration than general anesthesia.

Nervous System

During early pregnancy, the nervous system is more sensitive to general and local anesthetic agents. The minimum alveolar concentration (MAC) for volatile anesthetic agents is decreased by approximately 30%, although the underlying mechanism for this change is unclear. A study that compared patients undergoing cesarean delivery with nonpregnant patients undergoing elective gynecologic surgery found no difference between groups in electroencephalographic (EEG) measures during general anesthesia with similar end-tidal concentrations of sevoflurane. Because it is well-proven that MAC decreases in pregnancy, this study implies that MAC in pregnant women may not correlate well with depth of anesthesia. Conversely, another study found that pregnant women with elevated baseline serum progesterone concentrations had lesser sevoflurane consumption when the anesthetic was titrated to vital signs and a bispectral index (BIS) value. Further research is needed to clarify the effects of pregnancy and progesterone on MAC and depth of anesthesia as measured by BIS or EEG.

ECTOPIC PREGNANCY

Ectopic pregnancy occurs when the fertilized ovum implants outside the endometrial lining of the uterus. Death, infertility, and recurrent ectopic pregnancy are possible sequelae. The frequency of ectopic pregnancy is difficult to determine accurately but in the United States is approximately 5 to 20 per 1000 pregnancies.

Hemorrhage from ruptured ectopic pregnancy is the leading cause of pregnancy-related maternal death during the first trimester and accounted for 2.7% of all pregnancy-related maternal deaths in the United States from 2011 to 2013. More than 30% of women who have had an ectopic pregnancy subsequently suffer from infertility, and 5% to 23% have a second ectopic pregnancy.

The number of deaths from ectopic pregnancy has decreased in the United States since the 1970s. The case-fatality rate decreased from 35.5 deaths per 10,000 ectopic pregnancies in 1970 to 3.8 per 10,000 in 1989, and the ectopic pregnancy mortality ratio decreased from 1.15 deaths per 100,000 live births from 1980 to 1984 to 0.5 death per 100,000 live births from 2003 to 2007. The U.S. Centers for Disease Control and Prevention (CDC) attributes this decline to “improvements in the sensitivity, accuracy, and use of pregnancy testing, ultrasound for diagnosis, and improvements in therapeutic modalities, including laparoscopic surgery and medical management of ectopic pregnancy.”

Maternal death from ectopic pregnancy is more common in women with less access to obstetric care including teens, racial minorities, and women with poor socioeconomic status.

Factors that alter the risk for ectopic pregnancy include (1) previous ectopic pregnancy; (2) treatment for infertility (e.g., in vitro fertilization); (3) prior pelvic infection (e.g., pelvic inflammatory disease and ruptured appendix); (4) prior tubal surgery (e.g., tubal ligation or occlusion); and
Anesthesia before and during Pregnancy

may experience dizziness or syncope, may have the urge to defecate because of the effect of blood in the cul-de-sac, and may have shoulder pain from diaphragmatic irritation by intra-abdominal blood.

Physical findings include abdominal tenderness with or without rebound (80% to 95%), a uterus that is smaller than expected for dates (30%), and a tender adnexal mass (30% to 50%). A bulging cul-de-sac suggests hemoperitoneum. With significant hemorrhage, there may be signs of shock, but some patients may appear hemodynamically stable despite a hemoperitoneum volume of 1000 to 1500 mL. As with many young women, compensation for blood loss can occur with minimal symptoms initially followed by rapid decompensation.

Diagnosis

Ectopic pregnancy should be excluded in any patient who has pelvic pain and a positive pregnancy test. In a woman of reproductive age, the symptoms of ectopic pregnancy must be differentiated from (1) a threatened, inevitable, or incomplete pregnancy loss; (2) infection after attempted abortion; (3) pelvic inflammatory disease; (4) a degenerating fibroid; (5) appendicitis and other gastrointestinal diseases; (6) ovarian torsion; (7) a ruptured or bleeding ovarian cyst; (8) a trapped retroverted uterus in pregnancy; and (9) nephrolithiasis.

Clinical Presentation

The clinical presentation of the patient with an ectopic pregnancy depends on the gestational age, site of implantation, and extent of hemorrhage. Before rupture, the signs and symptoms are often subtle. Classic clinical signs of impending rupture or a ruptured tubal pregnancy include abdominal or pelvic pain (95%), delayed menses (75% to 95%), and vaginal bleeding (60% to 80%). Vaginal bleeding results from the breakdown and shedding of the decidual lining of the uterine wall, which is probably associated with decreased hormone production by the corpus luteum and inadequate human chorionic gonadotropin (hCG) production by the ectopic trophoblast. Pain often precedes vaginal bleeding. Patients with hemorrhage (with or without tubal rupture) may experience dizziness or syncope, may have the urge to defecate because of the effect of blood in the cul-de-sac, and may have shoulder pain from diaphragmatic irritation by intra-abdominal blood.

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Pregnancy of unknown location (PUL) exists when the hCG is positive and presumed due to pregnancy but the site of implantation has yet to be determined. Ultrasonography can reliably confirm the presence of an intrauterine pregnancy; however, the ectopic pregnancy itself may be difficult to visualize. Transvaginal ultrasonography is the current modality of choice. A gestational sac with a yolk sac is the earliest confirmation of an intrauterine pregnancy, while ultrasonographic visualization of an adnexal mass and free fluid with absence of an intrauterine pregnancy is specific for

ectopic pregnancy. Unfortunately, ultrasonographic visualization of an ectopic pregnancy has poor sensitivity.\textsuperscript{20}

Despite the challenges of early diagnosis of ectopic pregnancy, prompt treatment decreases morbidity and mortality. If concern exists for ectopic pregnancy with a PUL, serial hCG measurements spaced 48 hours apart can help clarify the viability of the pregnancy regardless of location. For a viable pregnancy, the increase in hCG over 48 hours should be at least 53%.\textsuperscript{21} A decrease in hCG by at least 10% suggests a nonviable pregnancy. In these scenarios, the decision to intervene or manage the nonviable pregnancy conservatively is based on the clinical situation and the woman’s preference. An abnormal rise (< 53% in 48 hours) or a plateau in the hCG value often indicates a nonviable pregnancy, but can also be seen with a vanishing twin where a viable pregnancy remains.\textsuperscript{22} Serial hCG measurements and transvaginal ultrasonography along with symptoms are considered when determining viability versus nonviability of a PUL.\textsuperscript{19}

A serum progesterone concentration greater than 25 ng/mL is usually associated with a viable pregnancy. A concentration less than or equal to 5 ng/mL usually indicates a nonviable pregnancy but cannot distinguish a spontaneous pregnancy loss from an ectopic pregnancy.\textsuperscript{23} Most ectopic pregnancies are associated with progesterone levels between 5 and 25 ng/mL, a fact that limits the usefulness of this test.

Uterine curettage can be performed when nonviability of a PUL is established. Identification of trophoblastic villi confirms loss of an intrauterine pregnancy. Absence of villi signals either a complete spontaneous pregnancy loss (confirmed by rapidly decreasing hCG concentration) or an ectopic pregnancy. Culdocentesis has been replaced in most all instances by transvaginal ultrasonography for detection of hemoperitoneum.

**Obstetric Management**

Management options for ectopic pregnancy are expectant, medical, and surgical. Management choice depends on the “activity” of the ectopic pregnancy, which is determined by symptoms and diagnostic findings.\textsuperscript{24}

**Expectant management** is preferred in “very less active” ectopic pregnancy or PUL with no symptoms, an hCG less than 1500 mIU/mL, and a plateauing trend in hCG values. Treatment with methotrexate does not improve resolution and is reserved for women in whom hCG levels fail to resolve. Very low positive hCG levels can have etiologies other than pregnancy. Very less active ectopic pregnancy may be difficult to localize surgically.

**Medical management with methotrexate** is a preferred option in “less active” ectopic pregnancy. Less active ectopic pregnancy is characterized by an hCG less than 5000 mIU/L and no fetal cardiac activity in an asymptomatic woman who is hemodynamically stable. Methotrexate, a folate antagonist, interrupts DNA synthesis and thus inhibits the growth of trophoblastic cells. It can be administered intramuscularly in one or more injections to women who screen negative for kidney, liver, and hematologic disease.

From day 4 to day 7 after methotrexate treatment, a decrease in hCG level of 15% must be present to consider the treatment successful. Otherwise, repeat methotrexate treatment or surgical intervention is required. Follow-up and close monitoring until the hCG level reaches nonpregnant values is imperative because of the risk for rupture and hemorrhage. Side effects of methotrexate can be severe and include abdominal pain, vomiting, stomatitis, severe neutropenia, and pneumonitis. Compared with surgical management, medical management of ectopic pregnancy provides no difference in overall tubal preservation, tubal patency, risk for repeat ectopic pregnancy, or success of future pregnancies.

**Surgical management** depends on the location of the pregnancy, the hemodynamic stability of the patient, the availability of equipment, and the surgeon’s expertise. Most often, laparoscopy is performed to confirm the diagnosis by locating the ectopic pregnancy and then proceeding with treatment. For tubal ectopic pregnancies, a salpingostomy, salpingotomy, or salpingectomy (usually partial) is performed by means of laparoscopy or laparotomy. To aid hemostasis during laparoscopic removal of the ectopic pregnancy, some obstetricians inject dilute vasopressin into the surface of the fallopian tube. This agent causes marked blanching of the tube and results in a relatively bloodless surgical field. If the vasopressin is mixed incorrectly or accidently injected intravenously, a marked increase in maternal blood pressure may occur.

A laparotomy is indicated if the surgeon is not trained in operative laparoscopy, laparoscopic removal is anticipated to be difficult (e.g., tube diameter greater than 6 cm or an interstitial location of the ectopic pregnancy), or there is uncontrollable bleeding. Laparotomy should be performed immediately if there is hemodynamic instability; these cases often require a partial or total salpingectomy. If a partial salpingectomy is performed, tubal repair may be performed primarily or during a second operation. Although some experts have noted that outcomes from randomized trials comparing salpingostomy and salpingectomy are lacking,\textsuperscript{25} the risk for persistent ectopic pregnancy may be higher after salpingostomy than after salpingectomy.\textsuperscript{26}

Interstitial, cervical, cesarean scar, and abdominal ectopic pregnancies as well as early placenta accreta may present significant diagnostic and therapeutic challenges, resulting in delay of diagnosis and treatment. There is potential for massive hemorrhage because of disruption of organs and adjacent tissues. The desire to preserve fertility may result in greater blood loss as tissue and organ preservation are attempted.

**Interstitial pregnancy** often goes unrecognized and may manifest as uterine wall rupture, massive hemorrhage, and shock. Conservative surgery (e.g., cornual resection) may be attempted, but hysterectomy may be required if uterine damage is severe.

**Cervical pregnancy** can result in massive hemorrhage because of the inability of the cervix to contract. In the past, most cervical pregnancies necessitated hysterectomy to control hemorrhage. More current management options that are more likely to maintain fertility include (1) methotrexate therapy; (2) local excision; (3) cerclage and tamponade; (4) ligation of the hypogastric arteries or the cervical branches of
Perfusion (which typically results in fetal growth restriction) until late gestation, it is associated with decreased placental functional products. If the extrauterine pregnancy is not identified, laparoscopy can be used to diagnose and remove gestation results in an increased risk for early uterine rupture and severe hemorrhage at delivery. Growth into the myometrium may lead to eventual rupture and bleeding in the first trimester; prompt surgical intervention is preferred over medical management in this situation.29

The incidence of early placenta accreta is also rising because of increasing cesarean delivery rates. It is defined as penetration of the placenta into the myometrium, which is discovered in the first or early second trimester. Because of similarities in pathogenesis, it is thought—although not confirmed—that early placenta accreta may develop from cesarean scar pregnancy. A review found that 15 of 47 (32%) patients with early placenta accreta had spontaneous uterine rupture, in most cases followed by bleeding and shock, which resulted in laparotomy, hysterectomy, or uterine artery embolization.30 Although the gestational age is early, it is imperative that the anesthesia team is aware of the risk for hemorrhage during surgical intervention for cesarean scar pregnancy and early placenta accreta.

Abdominal pregnancy is defined as implantation in the peritoneal cavity, not including the fallopian tubes, ovaries, or ligaments, and is associated with a high incidence of maternal morbidity and fetal demise. In a series of advanced extrauterine pregnancies, Worley et al.31 identified 10 women who presented with extrauterine pregnancies beyond 18 weeks’ gestation, of whom three met the diagnostic criteria for abdominal pregnancy. All patients had difficult surgery, nine patients required blood transfusion, and only five fetuses survived after complicated courses.

Diagnosis of abdominal pregnancy can be difficult, historically being missed in as many as one of nine cases.32 The diagnosis was missed before delivery in four of the ten cases in the series of Worley et al.31 Abdominal pain, vaginal bleeding, symptoms consistent with partial bowel obstruction, shock, or death may be the first indication of this unusual type of pregnancy. Ultrasonography is useful but may miss the diagnosis in more than 50% of cases. Magnetic resonance imaging may prove to be a more sensitive diagnostic tool.

If an extrauterine pregnancy is suspected in early gestation, laparoscopy can be used to diagnose and remove gestational products. If the extrauterine pregnancy is not identified until late gestation, it is associated with decreased placental perfusion (which typically results in fetal growth restriction) and oligohydramnios (which often results in pulmonary hypoplasia and anatomic deformities). In 1993, Stevens33 reviewed published cases of abdominal pregnancy since 1809 and found that 63% of infants survived when born after 30 weeks’ gestation.

Management of an advanced extrauterine pregnancy consists of laparotomy and delivery of the fetus. Once the fetus is delivered, management of the placenta is controversial and fraught with hazard. Removal of the placenta is associated with massive hemorrhage, prolonged and complicated surgery (e.g., bowel resection), and an increased risk for maternal mortality. A decision to leave the placenta in situ results in a higher risk for infectious morbidity as well as a potential greater need for additional surgery.34 In the series of Worley et al.,31 the placenta was left in situ in two patients, both of whom developed serious complications. The site of placental implantation and the ability to adequately ligate the blood supply often dictates the obstetrician’s decision about management of the placenta.

Heterotopic pregnancy describes the simultaneous occurrence of an ectopic and an intrauterine pregnancy. Historically, it was thought to occur in 1 in 30,000 spontaneous pregnancies.35 However, in patients utilizing assisted reproductive technologies, 0.2% to 3% of pregnancies may be heterotopic.16,36 Difficulty visualizing the entire fallopian tube on ultrasonography, combined with normal or slightly elevated hCG measurements (i.e., low serum levels from the ectopic pregnancy combined with normal levels from the intrauterine pregnancy), make the early diagnosis of heterotopic pregnancy difficult.37 This diagnosis should be suspected in cases in which clinical signs of an ectopic pregnancy and a confirmed intrauterine pregnancy coexist. In most cases, the ectopic pregnancy is removed surgically. Alternatively, transvaginal ultrasonography-guided injection of potassium chloride into the ectopic pregnancy has been performed successfully; however, as many as 55% of patients may require subsequent surgery.38 The patient often retains the normal intrauterine pregnancy to term. Patients with ectopic pregnancies who are Rh-negative should receive Rh0(D) immune globulin.19

Anesthetic Management

Patients with an unruptured tubal pregnancy usually have normal intravascular volume, minimal bleeding before and during surgery, and low anesthetic and surgical risk. Anesthetic considerations for laparoscopy or laparotomy are summarized in Box 16.1. Although most patients may prefer general anesthesia, neuraxial anesthesia with an upper sensory level to at least T4 may be an alternative in selected patients. Shoulder pain from diaphragmatic irritation may occur and can be treated with intravenous analgesics (e.g., fentanyl 1 to 2 μg/kg).

A ruptured ectopic pregnancy may be associated with significant preoperative blood loss, but estimation of the extent of this is difficult because young women may have normal blood pressure despite a markedly reduced circulating blood volume. General anesthesia, with preparation for
hemorrhage, is preferred if significant bleeding has occurred (e.g., ruptured tubal pregnancy) or is likely to occur (e.g., cervical, interstitial, cornual, cesarean scar, or abdominal ectopic pregnancy, or early placenta accreta). Intraoperative autologous blood transfusion can be used, and it may be useful especially in developing countries, where blood bank supplies are limited and women typically present late with significant hemoperitoneum and/or hypovolemic shock. The desire to preserve fertility often results in greater blood loss as tissue and organ preservation are attempted.

## EARLY PREGNANCY LOSS, ABORTION, AND INTRAUTERINE FETAL DEMISE

*Abortion* refers to a pregnancy loss or termination, either before 20 weeks’ gestation or when the fetus weighs less than 500 g. Changing terminology now refers to spontaneous, incomplete, and missed abortions as *early pregnancy loss* (EPL). The term *abortion* is now limited to medical or surgical procedures to terminate a pregnancy that may be performed electively or for medical reasons.

A total of 664,435 legal abortions were reported in the United States in 2013, a rate of 12.5 abortions per 1000 women and a ratio of 200 abortions per 1000 live births. The total number of abortions and rate of abortions (number of abortions per 1000 women) in the United States are at historic lows since surveillance began by the CDC in 1969. In 2013, 67.9% of induced abortions were performed by dilation and curettage by 13 weeks’ gestation, 22.2% by early medical abortion before 8 weeks’ gestation, and 8.6% by curettage after 13 weeks’ gestation. From 2011 to 2013 in the United States, 2.4% of maternal deaths were associated with early pregnancy loss or induced abortion. Maternal death from abortion is usually the result of sepsis, hemorrhage, or embolism. The case fatality rate from 2008 to 2014 for legal induced abortions was 0.08 per 100,000.

From a global perspective, unsafe abortion is a significant cause of maternal death. A global study of unsafe abortions estimated that 25.1 million abortions performed each year between 2010 and 2014 were unsafe, according to World Health Organization (WHO) definitions, of which 97% occurred in developing countries. A review of causes of maternal death from 2010 to 2014 by the WHO reported that 4.7% to 13.2% of maternal deaths were attributed to unsafe abortion. These unsafe abortions are performed by an untrained person or in conditions lacking minimal medical standards or both.

EPL occurs in 10% to 15% of clinically recognized pregnancies; when subclinical pregnancies are also considered, the incidence of spontaneous pregnancy loss may be as high as 60%. Although most spontaneous pregnancy losses manifest clinically at 8 to 14 weeks’ gestation, ultrasonography suggests that fetal demise usually occurs before 8 weeks’ gestation.

The etiology of EPL varies among patients. Chromosomal abnormalities are responsible for at least 50% to 80% of all spontaneous early pregnancy losses. Other causes include (1) immunologic mechanisms; (2) maternal infections; (3) endocrine abnormalities (e.g., poorly-controlled diabetes mellitus); (4) uterine anomalies; (5) debilitating maternal disease; (6) maternal clotting disorders; (7) trauma; and possibly (8) environmental exposures (e.g., irradiation, smoking, certain drugs).

Although some studies (conducted before scavenging of anesthetic gases was routine) suggested a higher incidence of EPL among women who were exposed to trace concentrations of anesthetic agents in operating rooms, reevaluation of these data demonstrated significant flaws in study design, casting doubt on the original conclusions. Later studies have

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**BOX 16.1  Suggested Anesthetic Techniques for Laparoscopy or Laparotomy for Patients with Ectopic Pregnancy**

<table>
<thead>
<tr>
<th>General Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood typing and antibody screening</td>
</tr>
<tr>
<td>Aspiration prophylaxis if patient has a full stomach</td>
</tr>
<tr>
<td>Routine noninvasive monitors</td>
</tr>
<tr>
<td>Large-bore peripheral intravenous catheter</td>
</tr>
<tr>
<td>Urinary catheter</td>
</tr>
<tr>
<td>If major bleeding has occurred or is expected to occur (e.g., ruptured tubal, interstitial, cervical, uterine scar, or abdominal ectopic pregnancy):</td>
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<tr>
<td>Two or more intravenous catheters</td>
</tr>
<tr>
<td>Typing and cross-matching of blood</td>
</tr>
<tr>
<td>Consideration of invasive hemodynamic monitoring (e.g., arterial catheter, central venous catheter)</td>
</tr>
<tr>
<td>Consideration of intraoperative cell salvage</td>
</tr>
<tr>
<td>Although general anesthesia is usually preferred, neuraxial (spinal or epidural) anesthesia may be considered for hemodynamically stable patients with a low likelihood of significant hemorrhage (i.e., unruptured tubal pregnancy):</td>
</tr>
<tr>
<td>Intravenous fluids, vasopressors, supplemental oxygen, and minimal sedation given as clinically indicated.</td>
</tr>
</tbody>
</table>

**General Anesthesia**

- Rapid-sequence induction with cricoid pressure if the patient has a full stomach
- Induction: propofol or thiopental (ketamine or etomidate should be considered if patient is hemodynamically unstable)
- Muscle relaxant
- Tracheal intubation
- Maintenance: volatile or intravenous anesthetic agents
- Placement of an oral gastric tube, performance of suctioning, and removal of the tube
- Reversal of neuromuscular blockade and extubation when the patient is awake and responds to verbal commands

**Spinal Anesthesia**

- Single injection with a small-gauge pencil-tip spinal needle: hyperbaric bupivacaine 12 mg with fentanyl 10 to 25 µg to achieve T4 sensory blockade

**Epidural Anesthesia**

- Placement of mid-lumbar epidural needle and catheter
- Lidocaine 2% with epinephrine 5 µg/mL (1:200,000), approximately 20 mL, and fentanyl 100 µg, injected incrementally, to achieve T4 sensory blockade

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**Problems of Early Pregnancy**

- Intrauterine fetal demise
- Early pregnancy loss
- Abortion
- Ectopic pregnancy
- Missed abortion
- Incomplete abortion
- Induced abortion

**Ectopic Pregnancy**

- Pregnancy occurs outside the uterus
- Common sites include fallopian tubes, ovaries, peritoneal cavity, or cervix
- Causes include fallopian tube damage, hormonal abnormalities, congenital anomalies, and prior pelvic surgery

**Ectopic Pregnancy, Risk Factors**

- Prior pelvic surgery
- Intrauterine device (IUD) use
- In vitro fertilization (IVF)
- Prior ectopic pregnancy
- Tubal surgery
- Endometriosis

**Ectopic Pregnancy, Diagnosis**

- Ultrasound
- Beta-human chorionic gonadotropin (β-hCG) levels
- Abdominal or pelvic pain
- Vaginal bleeding

**Ectopic Pregnancy, Management**

- Medical management with methotrexate
- Surgical management with laparoscopy or laparotomy

**Ectopic Pregnancy, Prevention**

- Use of intrauterine device (IUD)
- Avoidance of smoking
- Early diagnosis and treatment of infections

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**Ectopic Pregnancy, Complications**

- Hemorrhage
- Infertility
- Infection
- Sepsis

**Ectopic Pregnancy, Outcome**

- Obstetric outcome
- Fetal outcome
- Maternal outcome

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**References**

shown no increased incidence of spontaneous EPL in women working in operating rooms.48

Clinical Presentation
The clinical presentation and management of spontaneous pregnancy loss vary. A threatened early pregnancy loss is defined as uterine bleeding without cervical dilation before 20 weeks’ gestation. Bleeding may be accompanied by cramping or backache. While historically recommended, alteration in daily activities does not impact outcome. Approximately 25% of pregnancies are complicated by first-trimester bleeding; approximately one-half of affected women progress to a spontaneous pregnancy loss, with the percentage increasing to about 80% if cramping and bleeding are present.49,50

An inevitable pregnancy loss is defined as cervical dilation or rupture of membranes without expulsion of the fetus or placenta. Spontaneous expulsion of the uterine contents usually occurs, but infection or hemorrhage can be complications. A complete pregnancy loss is defined as a total, spontaneous expulsion of the fetus and placenta. Partial expulsion of the uterine contents (i.e., an incomplete pregnancy loss) is more common after 8 weeks’ gestation. Persistent bleeding and cramping after expulsion of tissue are signs of an incomplete pregnancy loss.

Fetal death may go unrecognized for several weeks in a patient with a first-trimester pregnancy loss. Symptoms may not start until the late first trimester, with diagnosis occurring at first-trimester screening ultrasonography. Ultrasound and hCG criteria for diagnosing early pregnancy loss have become more conservative based on observational data and a desire to avoid intervening in pregnancies that are viable. Follow-up ultrasonography is indicated when the ultrasound criteria are not definitive initially. Once an intrauterine site of pregnancy is confirmed by ultrasonography, hCG is no longer helpful in determining viability.

Fetal death in the second trimester or later is termed intrauterine fetal demise and is more likely to require medical intervention. Occasionally, coagulation defects such as disseminated intravascular coagulation (DIC) may complicate intrauterine fetal death with longer retention of fetal tissue and at more advanced gestational ages. The risk of DIC with first-trimester losses is minimal.

Recurrent or habitual pregnancy loss refers to the occurrence of three or more consecutive spontaneous pregnancy losses. These patients have a greater potential for a recurrent etiology of pregnancy loss, and thereby have an increased risk for future losses. With fewer or nonconsecutive pregnancy losses, the recurrence rate for pregnancy loss is the same as the general population rate.

Obstetric Management
First-trimester pregnancy losses can be managed expectantly, medically, or surgically. Clinical scenario, patient preference, availability, and cost can all impact management, but long-term outcome is similar. A woman who is asymptomatic or minimally symptomatic may utilize any management option. Active vaginal bleeding (especially if heavy) typically requires surgical intervention to prevent excessive blood loss and potential shock. Infection and medical disorders that would increase the patient’s risk for bleeding or decrease maternal tolerance of blood loss are other indications for surgical management.

Conservative management incurs the least medical intervention and cost. While most pregnancy losses occur in the early first trimester, spontaneous expulsion of tissue may not occur until the late first trimester. An 80% complete expulsion rate occurs within 8 weeks of diagnosis. Nonetheless, some women will require surgical intervention for bleeding. Early gestations have higher success with conservative management.

Medical management provides more control over timing of tissue expulsion without surgery. A vaginal dose of misoprostol is effective in initiating expulsion of a pregnancy loss, although it is an ineffective method for terminating a viable pregnancy. For incomplete pregnancy loss, a 71% expulsion rate within 3 days with a single dose can increase to 84% with a second dose if needed. Use of medical management in a woman with an incomplete pregnancy loss does not clearly improve complete expulsion rates. Medical management success is greater if the crown rump length of the fetus is 8-week size or less.

For second-trimester intrauterine fetal demise, medical management may involve high-dose intravenous oxytocin, multiple doses of misoprostol, or vaginal prostaglandin E2. About 8% of women will require surgical management for removal of residual placental tissue.

Choice of technique for surgically emptying the uterus after an incomplete or minimally symptomatic pregnancy loss primarily depends on the quantity of tissue that needs to be removed, the gestational age, and the amount of vaginal bleeding. Initial cervical dilation can be facilitated with vaginal misoprostol or intracervical laminaria if needed. A dilation and curettage (D & C) procedure refers to dilation of the cervix (if needed), followed by suction curettage with subsequent sharp curettage only if needed. When a smaller quantity of tissue requires removal, a manual vacuum aspirator may be used. Ossified fetal bones occur around 13 to 15 weeks’ gestation and often require grasping with forceps for complete removal. After 13 to 15 weeks’ gestation, a dilation and evacuation (D & E) procedure will be required; this involves greater cervical dilation followed by evacuation of the uterus with suction and the aid of surgical forceps. Oxytocin and/or an ergot alkaloid (e.g., methylergonovine) increases uterine tone and may be administered intraperatively and/or postoperatively to decrease the amount of uterine bleeding. To prevent massive maternal blood loss during a vaginal delivery, D & E is the procedure of choice for second-trimester fetal demise with placenta previa.

Obstetric Complications
Complications of D & C and D & E procedures include cervical laceration, uterine perforation, hemorrhage, retained products of conception, and infection. The risk for these complications is increased in pregnancies that have progressed
beyond the first trimester. Medical and surgical management of fetal demise in the second trimester have similar complication rates. Uterine perforation, vasovagal events, delayed hemorrhage, retained products of conception, DIC, and unrecognized ectopic pregnancy can occur. Management of uterine perforation may involve simple observation or immediate laparotomy with repair. Management depends on the suspected severity of injury to the uterus and adjacent structures.

Serious infection (e.g., septic pregnancy loss) complicates approximately 1 in 200,000 spontaneous pregnancy losses. It is more common after induced abortion, particularly illegal abortion. Septic abortion causes significant morbidity and is life-threatening. Blood cultures should be taken, and broad-spectrum intravenous antibiotics should be administered promptly. Patients with hemodynamic instability may require invasive hemodynamic monitoring to guide fluid, blood, and vasoactive drug therapy. Lower genital tract or bowel injury should be excluded, and the uterus should promptly be re-evacuated. Occasionally, hysterectomy is necessary and may be lifesaving. Rh\(_0\)(D) immune globulin should be administered to prevent Rh sensitization in Rh-negative woman who have a pregnancy loss because of a sensitization risk of 1.5% to 2% with a spontaneous loss and 4% to 5% after a D & C procedure. Rh\(_0\)(D) immune globulin should also be given to Rh-negative women with first-trimester bleeding because of the possibility of sensitization.

Women who suffer spontaneous pregnancy loss and especially recurrent losses are at increased risk for depressive disorders during the 6 months after pregnancy loss (see Chapter 50).

Anesthetic Management

Several anesthetic techniques are appropriate for D & C and D & E procedures (Box 16.2). The choice depends on several factors (e.g., whether the cervix is dilated; the gestational age and ossification of the fetus; the presence of significant blood loss, sepsis, or a full stomach; and the emotional state and preference of the patient). Dilation of the cervix is relatively painful, whereas suction and curettage are less painful. If the cervix is dilated and the products of conception can be

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**BOX 16.2 Suggested Anesthetic Techniques for Dilation and Uterine Suction Curettage (D & C) or Evacuation (D & E) for Early Pregnancy Loss or Induced Abortion**

**General Considerations**
- Blood typing and antibody screening or typing and cross-matching in patients with a large blood loss or those with advanced gestation
- Aspiration prophylaxis if patient has a full stomach
- Routine noninvasive monitors
- One peripheral intravenous catheter
- Administration of a short-acting benzodiazepine (e.g., midazolam) may be indicated for patients who prefer anxiolysis, sedation, and/or amnesia
- Monitored Anesthesia Care (natural airway) is an option for D & C procedures in healthy, stable patients who have appropriately fasted. If the cervix is closed, then a paracervical block can facilitate this anesthetic
- Neuraxial (spinal or epidural) anesthesia is an option for hemodynamically stable patients without sepsis
- General anesthesia may be most appropriate for patients with anticipated blood loss or for patients requiring a D & E procedure (e.g., gestation greater than 15 weeks with large fetal size and fetal ossification)
- Intravenous fluids, vasopressors, supplemental oxygen, and minimal sedation given as clinically indicated
- Oxytocin and/or an ergot alkaloid available
- In patients with significant blood loss: observation of the patient on the operating table for evidence of hypotension for at least 5 minutes after the legs have been lowered from the lithotomy to the supine position

**Spinal Anesthesia**
- Single injection with a small-gauge spinal needle: lidocaine 40 mg or hyperbaric bupivacaine 7.5 mg, with fentanyl 10 to 20 \(\mu\)g, to achieve sensory blockade from T10 to S4

**Epidural Anesthesia**
- Placement of mid-lumbar epidural needle and catheter
- Lidocaine 2% with epinephrine 5 \(\mu\)g/mL (12 to 15 mL) and fentanyl 100 \(\mu\)g, injected incrementally, to achieve sensory blockade from T10 to S4

**General Anesthesia**
- Rapid-sequence induction with cricoid pressure if the patient has a full stomach
- Induction: propofol or thiopental (ketamine or etomidate in cases of severe hemorrhage)
- Mask anesthesia or laryngeal mask airway during early pregnancy if stomach is empty and the patient is hemodynamically stable; otherwise tracheal intubation with a muscle relaxant
- Maintenance: volatile or intravenous anesthetic agents
- High concentration (greater than 0.5 MAC) of a volatile anesthetic agent should be avoided if there is significant bleeding or evidence of uterine atony
- Insertion and removal of an oral gastric tube (if trachea is intubated) to evacuate the stomach
- Tracheal extubation when the patient is awake and responds to verbal commands

**Monitored Anesthesia Care (Well Tolerated When the Cervix Is Dilated and Gestational Age Is First Trimester)**
- Intravenous analgesia with fentanyl or remifentanil and sedation with midazolam or propofol
- Paracervical block if needed
curettaged and suctioned, sedation with or without a paracervical block may suffice. If the cervix is not dilated, paracervical block and sedation, spinal or epidural anesthesia (with sensory blockade from T10 to S4), or general anesthesia should be used. General anesthesia may be most appropriate if the patient is emotionally upset or if the gestational age is 13 to 15 weeks or greater (which requires a greater degree of cervical dilation for a D & E procedure). Selected patients may benefit from premedication with a short-acting benzodiazepine (e.g., midazolam).

Typically, the cervix is already dilated in patients who have had significant preoperative bleeding; rarely does a patient with a closed cervix have significant bleeding. In the presence of significant bleeding, intravascular volume should be restored first. A paracervical block and sedation may then be adequate. Substantial hemorrhage represents a relative contraindication to the use of spinal or epidural anesthesia, which probably should also be avoided in patients with evidence of sepsis.

General anesthesia may be induced with propofol or thiopental, although ketamine or etomidate may be preferred in patients with significant bleeding. Large doses (1.5 to 2.0 mg/kg) of ketamine may increase uterine tone, which may be advantageous in patients who require evacuation of the uterus.

Drugs administered for general anesthesia may influence blood loss during the procedure. Volatile anesthetic agents cause dose-dependent relaxation of uterine smooth muscle and have been associated with increased uterine bleeding. In two studies that compared blood loss during general anesthesia for elective first-trimester abortion, blood loss was greater when anesthesia was maintained with isoflurane compared with propofol. However, the differences were small. Some obstetricians contend that relaxation of the uterus (caused by administration of a volatile anesthetic agent) increases the risk for uterine perforation, and they prefer that administration of a volatile anesthetic agent during a D & C or D & E procedure be avoided.

For D & E procedures, general anesthesia is commonly maintained with oxygen, a propofol infusion, and an opioid. Nitrous oxide or a low concentration (less than 0.5 MAC) of a volatile agent may be added. The volatile agent should be avoided or discontinued if there is any evidence of uterine atony. In most cases, oxytocin is administered intravenously to increase uterine tone and decrease blood loss. Although some anesthesia providers simply dilute oxytocin in a bag of crystalloid solution, many are moving to administering oxytocin via a controlled infusion pump to achieve more accurate titration. Oxytocin receptor expression increases with gestation. Therefore, uterine atony in early pregnancy may require other uterotonics that do not act on the oxytocin receptor such as misoprostol, carboprost, or methylergonovine. The D & C or D & E procedure is performed with the patient in the lithotomy position. After the procedure is completed and the patient’s legs are lowered, hypotension may develop in patients who have lost a substantial amount of blood, especially if neuraxial anesthesia has been used.

**CERVICAL INSUFFICIENCY OR INCOMPETENCE**

**Cervical insufficiency** is the inability of the cervix to hold a pregnancy in the uterus through the second trimester in the absence of labor. The definition and diagnostic criteria for cervical insufficiency have changed over time because of difficulty in separating it from other processes that lead to preterm delivery syndrome. Cervical insufficiency is a clinical diagnosis. Vaginal bleeding, rupture of membranes, and labor may result from cervical insufficiency, but to meet the diagnostic criteria these cannot be antecedent events. The etiology of cervical insufficiency remains unclear, and acquired factors such as obstetric cervical laceration, treatment of cervical intraepithelial lesions, or mechanical dilation for a gynecologic procedure may contribute to an increased risk. Congenital factors may include collagen disorders, Mullerian disorders, and biologic variation.

The U.S. *National Vital Statistics Report* for 2008 cited a rate of 3.0 cervical cerclages performed per 1000 live births, indicating a general decrease from prior rates likely as a result of more limited indications for the procedure. National statistics on cerclage incidence are no longer collected.

**Diagnosis**

Symptoms of cervical insufficiency include altered vaginal discharge, lower abdominal or back pressure or discomfort, vaginal fullness, and urinary frequency. The diagnosis is definitive if delivery occurs in the second trimester before 24 weeks’ gestation in the absence of bleeding, infection, or labor as the initial symptom. Cervical dilation or prolapse of membranes through the cervix in the absence of other findings or symptoms provides sufficient certainty of cervical insufficiency. As success of cerclage is less when the cervix is dilated or membranes are prolapsed, screening of asymptomatic women is also utilized.

**Obstetric Management**

Cervical cerclage may be placed based on prior obstetric history, current symptoms and findings, or both. For women with two or more second-trimester losses that suggest cervical insufficiency, a history-indicated cerclage may be placed at 12 to 14 weeks’ gestation. A rescue or emergency cerclage is placed in the setting of symptoms such as pelvic pressure, cramping, or altered vaginal discharge and evidence of cervical insufficiency before 25 weeks’ gestation. A dilated or short cervix found on visual or digital examination or a short cervix on transvaginal ultrasonography provide evidence of cervical insufficiency. Rescue or emergency cerclage carries greater risk for complications and a lower success rate. Some women will be found to have a short cervix during routine screening anatomy ultrasonography, while others with risk factors may have serial ultrasonographic examinations to detect development of a short cervix. With a history of prior preterm birth at less than 34 weeks’ gestation along with a short cervix noted on ultrasonography before 24 weeks’ gestation, cerclage placement is associated with improved outcome.
women, an estimated 20 cerclages are needed to prevent one perinatal death, and more than 6500 infants per year could be saved in the United States by this management. In contrast, cerclage placement appears to worsen outcome in women with a multifetal gestation regardless of cervical length.

The most common cerclage procedures are the modified Shirodkar cerclage and the McDonald cerclage, both of which are performed transvaginally. A ligature (e.g., polyester fiber [Mersilene®] tape or a large gauge nonabsorbable suture) is placed around the cervix at or near the level of the internal cervical os. In the more invasive modified Shirodkar procedure, the cervical mucosa is incised anteriorly and posteriorly with dissection of the bladder and rectum off the cervix. The ligature is placed submucosally and then tied, and the mucosal incisions are closed. The cervical mucosa is left intact with the McDonald cerclage; a purse-string ligature is placed around the cervix and then tied (Fig. 16.2). These two procedures result in comparable rates of fetal survival in patients with no history of a previous cerclage. In one study, a more favorable outcome (i.e., more advanced gestational age) was obtained when a Shirodkar cerclage was performed in patients who had a previous cerclage.

Transvaginal cerclage can be performed in most patients with an incompetent cervix. However, if no substantial cervical tissue is present (e.g., severe cervical laceration, shortening or scarring) or if two previous transvaginal cerclages have failed, a transabdominal cerclage may be performed, either before or during pregnancy. Most patients with transabdominal cerclage undergo cesarean delivery. The transabdominal cerclage can remain in situ if further pregnancies are desired, or it can be removed at the time of cesarean delivery. Although the efficacy of perioperative antibiotics and/or tocolytic drugs has not been confirmed, some obstetricians may choose to use them.

Contraindications to cerclage procedures include preterm labor, vaginal bleeding, fetal anomalies, fetal death, rupture of membranes, placental abruption, and evidence of intrauterine infection. Some obstetricians obtain specimens for culture of the amniotic fluid and/or cervix before placement of a cerclage.

The greatest risk during the performance of emergency cerclage is rupture of the membranes. Several techniques have been described to facilitate replacement of the bulging fetal membranes into the uterus. Uterine relaxation is essential, which can be facilitated by administration of a volatile anesthetic agent. Alternatively, a uterine relaxant like nitroglycerin may be administered. The steep Trendelenburg position allows for gravity assistance.

To assist in reduction of herniated membranes, some obstetricians fill the urinary bladder with sterile saline. Insertion of a 16-mm Foley catheter into the cervical canal with subsequent inflation of the balloon with 30 to 60 mL of saline has also been described. The balloon is deflated and the catheter is removed at the end of the procedure.

Cervical cerclage is associated with a 0.6% risk for perioperative complications. Immediate complications include rupture of the fetal membranes, hemorrhage, and preterm labor. Delayed complications include infection, suture displacement, cervical stenosis secondary to scarring, and cervical lacerations and uterine rupture if labor proceeds with the cerclage in place. Rarely, sepsis may result in death. Overall, patients who have had a cerclage have a higher rate of cesarean delivery. The Shirodkar procedure is associated with a rate of cesarean delivery almost double that associated with a McDonald cerclage (31% versus 17%, respectively).

Anesthetic Management

Transvaginal cervical cerclage is usually performed under spinal, epidural, or general anesthesia (Box 16.3). The degree of cervical dilation may influence the choice of anesthesia. If the cervix is not dilated, spinal, epidural, or general anesthesia may be administered. Spinal anesthesia provides a rapid,
predictable onset of sacral anesthesia, which is desirable for these procedures. Sensory blockade from sacral dermatomes to T10 is necessary, because both the cervix (L1 to T10) and vagina and perineum (S2 to S4) require anesthesia.

If the cervix is dilated—and especially if the fetal membranes are bulging—the choice of anesthesia is less straightforward. The advantages and disadvantages of each anesthetic technique must be weighed carefully. It is important to produce adequate analgesia for the mother and to prevent an increase in intra-abdominal and intrauterine pressure that may lead to further bulging and possible rupture of the fetal membranes.

General anesthesia may be preferred in the patient with a dilated cervix and bulging fetal membranes. Administration of a volatile anesthetic agent relaxes uterine smooth muscle and results in a decrease in intrauterine pressure. A decrease in intrauterine pressure facilitates replacement of the bulging membranes and placement of the cerclage. On occasion, an amniocentesis may be performed before or during a cerclage procedure in an attempt to decrease intrauterine pressure and facilitate reduction of the fetal membranes. During induction and maintenance of general anesthesia, it is important to avoid endotracheal tube–induced coughing, which might raise intrauterine pressure. In addition, vomiting significantly raises intrauterine pressure.

Administration of neuraxial anesthesia obviates the need for tracheal intubation and the possibility of coughing on the endotracheal tube. Although some physicians worry that the acute dorsiflexion needed during initiation of the neuraxial blockade may raise intrauterine pressure, many prefer the avoidance of general anesthesia during pregnancy whenever possible.

Few clinical studies have compared obstetric outcomes after administration of neuraxial anesthesia and general anesthesia for cerclage. One retrospective study observed no difference in fetal outcome after administration of either general anesthesia (375 cases) or epidural anesthesia (114 cases).69 Another study found no significant difference in plasma oxytocin levels or postoperative uterine activity between women who received either spinal or general anesthesia for a Shirodkar cerclage.70

Fetal heart rate monitoring should be considered during the procedure if the pregnancy is sufficiently advanced to allow monitoring to be performed easily. In theory, it is possible that replacement of bulging membranes and closure of the cervix may raise intrauterine pressure with a subsequent reduction in placental blood flow. In this case, it would be reasonable to give a tocolytic agent to help reduce intrauterine pressure.

The transvaginal cerclage is removed at 37 to 38 weeks’ gestation, or earlier if rupture of membranes or onset of labor occurs. Removal of a McDonald cerclage often requires no anesthesia. Anesthesia (e.g., paracervical block, spinal anesthesia, epidural anesthesia) is usually necessary for removal of a Shirodkar cerclage. If the Shirodkar cerclage is epithelialized, some obstetricians elect to leave it intact and perform an elective cesarean delivery.

Labor often begins within a few hours or days after suture removal. If an epidural catheter was placed for cerclage removal, the epidural anesthetic can be allowed to regress while the patient is observed for evidence of cervical dilation and the onset of labor. When labor begins, epidural labor analgesia can be initiated by injection of drugs through the in situ catheter.

**GESTATIONAL TROPHOBLASTIC DISEASE**

In normal pregnancy, trophoblastic tissue forms the placenta. Abnormal trophoblastic proliferation results in **gestational trophoblastic disease** (GTD). When GTD persists after the pregnancy is concluded (diagnosed by persistent elevation of...
Chapter 16
Problems of Early Pregnancy

Hydatidiform mole, invasive mole, and gestational choriocarcinoma. Complete molar pregnancies have a higher rate of associated complications and a higher rate of persistent GTD than partial molar pregnancies. Approximately 20% of patients with complete molar pregnancy have postmolar nonmetastatic GTD (70% to 90%) or malignant GTD (10% to 30%) and require chemotherapy; in contrast, less than 5% of patients with partial molar pregnancy require chemotherapy.76

GTD can also be classified according to the genetic makeup of the trophoblastic cells; further details are available elsewhere.73 Typically, the genetic makeup of trophoblastic cells in complete hydatidiform molar pregnancy is androgenic, meaning nearly all of the genome of the trophoblastic cell arises from the sperm. Diploid (46,XY) or triploid (e.g., 69,XXX) versions are possible. No fetus develops. Approximately 90% of hydatidiform moles are complete.77 Most invasive moles result from complete moles. In contrast, the genetic makeup of a partial hydatidiform molar pregnancy is diandric, meaning the chromosomes arise from both the

Categorization and Etiology

The classification and terminology applied to GTD are varied and can be confusing because GTD encompasses a heterogeneous group of diseases. Gestational trophoblastic neoplasia is a subset of GTD.

Classification of GTD continues to be in flux. Current terminology supported by the Society of Gynecologic Oncology and the American College of Obstetrics and Gynecology is listed (Box 16.4). The pathologic and clinical features of GTD are summarized in Table 16.1.75 The spectrum from the most benign to the most malignant form of GTD is as follows: (1) partial hydatidiform mole, (2) complete

<p>| TABLE 16.1 Pathologic and Clinical Features of Gestational Trophoblastic Disease |
|---------------------------------|---------------------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Gestational Trophoblastic Disease</th>
<th>Pathologic Features</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydatidiform mole, complete</td>
<td>46,XX (mainly); 46,XY</td>
<td>15%-20% trophoblastic sequelae</td>
</tr>
<tr>
<td></td>
<td>Absent fetus/embryo</td>
<td>hCG often &gt; 100,000 mIU/mL</td>
</tr>
<tr>
<td></td>
<td>Diffuse swelling of villi</td>
<td>Medical complications</td>
</tr>
<tr>
<td></td>
<td>Diffuse trophoblastic hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Hydatidiform mole, partial</td>
<td>Triplod (69,XXY; 69,XXX)</td>
<td>&lt; 5% trophoblastic sequelae</td>
</tr>
<tr>
<td></td>
<td>Abnormal fetus/embryo</td>
<td>hCG usually &lt; 100,000 mIU/mL</td>
</tr>
<tr>
<td></td>
<td>Focal swelling of villi</td>
<td>Rare medical complications</td>
</tr>
<tr>
<td></td>
<td>Focal trophoblastic hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Invasive mole</td>
<td>Myometrial invasion</td>
<td>15% metastatic, to lung/vagina</td>
</tr>
<tr>
<td></td>
<td>Swollen villi</td>
<td>Most often diagnosed clinically,</td>
</tr>
<tr>
<td></td>
<td>Hyperplastic trophoblast</td>
<td>rather than pathologically</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Abnormal trophoblastic hyperplasia and anaplasia</td>
<td>Vascular spread to distant sites: lung/brain/liver</td>
</tr>
<tr>
<td></td>
<td>Absent villi</td>
<td>Malignant disease</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage, necrosis</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Placental site trophoblastic tumor</td>
<td>Tumor cells infiltrate myometrium with vascular/lymphatic invasion</td>
<td>hCG levels less reliable indicator</td>
</tr>
<tr>
<td></td>
<td>Intermediate cells/absent villi</td>
<td>Relatively chemoresistant</td>
</tr>
<tr>
<td></td>
<td>Less hemorrhage and necrosis</td>
<td>Mainly surgical treatment</td>
</tr>
<tr>
<td></td>
<td>Tumor cells stain positive for hPL</td>
<td></td>
</tr>
</tbody>
</table>

hCG, Human chorionic gonadotropin; hPL, human placental lactogen.

egg and the sperm but is complicated by triploid conception (69,XXX or 69,XXY). Because both maternal and paternal chromosomes are present, a fetus may form with a partial mole. As a result, patients with partial mole may have a preoperative diagnosis of incomplete or missed pregnancy loss.

Specific care of GTN is beyond the scope of this chapter. Classification of GTN has been moving more toward a clinically based system that may better predict outcome and direct treatment. Gestational choriocarcinoma can occur after a molar pregnancy, a normal pregnancy, or even a pregnancy loss. In summary, GTN always involves trophoblastic cells with resultant positive hCG, often presents with bleeding sequela, and metastatic forms can appear in any organ but most frequently lung, brain, or liver.

Complete and Partial Hydatidiform Mole
The reported incidence of hydatidiform mole varies. In the United States, it is detected in 1 in 600 elective abortions and 1 in 1500 pregnancies. Rates of 1 in 400 pregnancies are reported in Korea and Indonesia and among Native Americans.\(^{71,78,79}\) Coexistence of an intact fetus with molar components is extremely rare, occurring in 1 in 22,000 to 1 in 100,000 pregnancies.\(^{78}\)

Patients may have a complete molar pregnancy diagnosed during first-trimester ultrasonography, or they may have vaginal bleeding after delayed menses, suggestive of a threatened, missed, or incomplete pregnancy loss. They may spontaneously pass hydropic vesicles. The absence of fetal cardiac activity, a uterus large for gestational age, and a marked elevation of hCG strongly suggest the diagnosis of hydatidiform mole. Diagnosis may be made after a D & C for an incomplete pregnancy loss;\(^{78}\) baseline chest radiography and quantitative hCG levels should be obtained promptly after surgery in such cases.

Molar pregnancies produce hCG in amounts proportional to the neoplastic volume. Excessive uterine size is associated with a marked elevation of serum hCG concentration (greater than 100,000 mIU/mL) secondary to a large tumor volume. Large ovarian cysts, hyperemesis gravidarum, and early onset of gestational hypertension are also strongly suggestive of GTD. Ultrasonography may show characteristic multi-echogenic regions that represent hydropic villi or hemorrhagic foci.\(^{75}\)

Persistent and Malignant Gestational Trophoblastic Disease
Persistent and malignant GTD can develop after any gestational event, including normal pregnancy, spontaneous pregnancy loss, induced abortion, ectopic pregnancy, and molar pregnancy. Diagnosis of persistent GTD is made when hCG levels plateau or rise.\(^{78,79}\)

The subtle signs and symptoms of malignant GTD after a nonmolar gestational event may delay diagnosis. A quantitative hCG measurement should be performed in any patient with continued or abnormal vaginal bleeding 6 weeks after the end of gestation. In any woman of reproductive age with metastatic disease from an unknown primary tumor, the diagnosis of gestational choriocarcinoma should be considered. Metastases of gestational choriocarcinoma can occur anywhere. The vagina, liver, lung, and brain are the most frequently involved sites, and imaging may show signs of local hemorrhage. Signs and symptoms are related to the affected site. Biopsy of metastases is rarely needed and can result in profuse bleeding. The diagnosis of metastatic GTD is suggested with a positive hCG result and no identifiable pregnancy. Details on staging and risk-factor scoring of GTD and their implications for therapy and prognosis are available elsewhere.\(^{78}\)

Medical Complications
Routine use of ultrasonography has led to earlier diagnosis of molar pregnancy, which has reduced the incidence of medical complications. However, excessive uterine size occurs in up to one-half of patients with complete molar pregnancy and is associated with a higher incidence of medical complications. Medical complications occur in about 25% of patients with uterine size of more than 14 to 16 weeks’ gestation and include ovarian theca-lutein cysts, hyperemesis gravidarum, gestational hypertension with anemia, hyperthyroidism, DIC, and sepsis (Table 16.2).

Ovarian theca-lutein cysts occur primarily in patients with an extremely high serum hCG concentration (greater than 100,000 mIU/mL).\(^{80}\) They typically regress over 2 to 3 months. Rarely, torsion, rupture, or infarction may necessitate oophorectomy. Patients with theca-lutein cysts and a uterus more than 4 weeks larger than expected (for dates) have a 50% likelihood of development of postmolar GTN.\(^{71}\)

Hyperemesis gravidarum can lead to significant electrolyte disturbances and volume depletion, all of which should be corrected before surgery.

Gestational hypertension is more likely to occur in women with molar pregnancy. Preeclampsia may be diagnosed if proteinuria accompanies hypertension. Although early presentation does not fit usual definitions (see Chapter 35), preeclampsia in the first trimester suggests the presence of GTD. Although it is thought that convulsions rarely occur in these patients,\(^{40}\) prophylactic use of magnesium sulfate

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive uterine size</td>
<td>28</td>
</tr>
<tr>
<td>Ovarian theca-lutein cysts, bilateral</td>
<td>15</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>8</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Other complications less common due to earlier diagnosis and treatment: anemia, hyperthyroidism, disseminated intravascular coagulation, and sepsis</td>
<td>Rare</td>
</tr>
</tbody>
</table>

should be considered if severe features of preeclampsia are present. Antihypertensive therapy (e.g., hydralazine, nifedipine, labetalol) should be administered to reduce blood pressure, similar to the management of preeclampsia without GTD.

**Anemia** can complicate a complete molar pregnancy. The visible vaginal bleeding may underrepresent the total amount of hemorrhage. Occult bleeding into and around the tumor results in multiple hemorrhagic foci. Because blood loss may occur gradually, the patient may have a normal intravascular volume despite the presence of severe anemia. In any patient with suspected GTD, blood typing and antibody screening should be performed preoperatively.

Although infrequent, **hyperthyroidism** may result from a marked elevation of hCG, which can have a thyrotropin-like effect. Alternatively, hyperthyroidism may result from some other thyrotropic substance produced by the neoplasm. Anesthesia or surgery can precipitate thyroid storm (i.e., sinus tachycardia, atrial fibrillation, hyperthermia, cardiovascular collapse).

Historically, **acute cardiopulmonary distress** was observed after evacuation of molar pregnancy in as many as 27% of patients. A higher risk for cardiopulmonary complications occurs in patients with a uterine size of 16 weeks or greater. Therefore, with earlier diagnosis, cardiopulmonary distress after molar evacuation is far rarer. For patients with poor prenatal care who present late in pregnancy, it is important to be prepared for such an event. Signs and symptoms include chest pain, cough, tachycardia, tachypnea, hypoxemia, diffuse rales, and chest radiographic evidence of bilateral pulmonary infiltrates. **Trophoblastic embolization** may be the etiology of cardiopulmonary distress in more than one-half of cases. Other causes include (1) high-output cardiac failure from thyrotoxicosis; (2) pulmonary congestion from severe anemia; (3) gestational hypertension or preeclampsia; (4) aspiration pneumonitis; and (5) iatrogenic fluid overload. Symptoms usually develop within 12 hours of uterine evacuation. Some patients require tracheal intubation, mechanical ventilation, and invasive hemodynamic monitoring. Symptoms usually subside within 72 hours; however, massive embolization or adult respiratory distress syndrome may result in death. If the patient survives trophoblastic embolization, malignant sequelae often develop.

**Obstetric Management**

The following preoperative tests are recommended for patients with suspected hydatidiform mole: (1) complete blood count including platelet count; (2) coagulation studies; (3) thyroid, renal, and liver function studies; (3) blood typing and antibody screening; (4) quantitative hCG level; and (5) chest radiography. Prompt molar evacuation should be instituted, because a delay in uterine evacuation may increase the risk for complications. Once the patient is stabilized, suction curettage is performed to evacuate the uterus in patients who want to preserve fertility. Hysterectomy may be performed in patients who have completed childbearing, especially if the uterus is markedly enlarged. Hysterotomy or medical induction of labor are not recommended because they are associated with increased blood loss and a higher incidence of persistent PGTD. Rh(D) immune globulin should be administered to Rh-negative patients.

After uterine evacuation, the hCG level should be measured every 1 to 2 weeks until it is undetectable in three tests in a row, and then every 2 months for an additional 6 months. Frequent pelvic examinations are performed while hCG levels remain high. Thorough evaluation of the patient with GTD includes screening for evidence of metastasis (e.g., vagina, liver, lung, brain) and other potential complications. Prevention of pregnancy is recommended for 6 months after the hCG is normalized.

Malignant GTD should be managed by an experienced team in a trophoblastic center to minimize mortality. Chemotherapy is indicated in patients with (1) histologic evidence of choriocarcinoma; (2) an increase in hCG levels of 10% or greater in three or more samples taken over at least 2 weeks; (3) a plateau of hCG levels in four or more samples taken over 3 consecutive weeks; (4) persistence of measurable hCG levels 6 months after molar evacuation; or (5) evidence of metastasis. Some patients may require additional surgery or radiation to manage lung, liver, or brain metastasis or resistant uterine disease.

**Anesthetic Management**

Preoperative assessment of the patient with a molar pregnancy consists of evaluation for specific complications of molar pregnancy, including hyperemesis gravidarum, gestational hypertension and preeclampsia, anemia, and thyrotoxicosis. The main anesthetic considerations are the potential for rapid and significant blood loss and the risk for cardiopulmonary distress with uterine evacuation. The anesthesia provider should establish adequate intravenous access, and blood products should be immediately available. Invasive arterial pressure and/or central venous pressure monitoring may be indicated in the patient with hypoxemia, severe anemia, hemorrhage, severe gestational hypertension or preeclampsia, hyperthyroidism, or a uterus of more than 16 weeks size.

Although neuraxial anesthesia has been described, general anesthesia is often preferred because of the potential for rapid, substantial blood loss and cardiopulmonary distress during evacuation of the uterus. For patients with acute hemorrhage and hypovolemia, induction with propofol may cause marked hypotension. In hyperthyroid patients, ketamine may result in marked tachycardia. Etidomidate is an excellent choice for patients with preoperative bleeding and preoperative evidence of hyperthyroidism. Anesthesia can be maintained using either an inhalational or intravenous technique, although it may be necessary to avoid volatile anesthetic agents in some patients to optimize uterine contractility, and care should be exercised with the use of a propofol infusion in hemodynamically unstable patients.

An intravenous oxytocin infusion (6 to 15 IU per hour) should begin either before or during uterine evacuation. Oxytocin helps the uterus contract, facilitating safe curettage.
and reducing blood loss. Some obstetricians have speculated that oxytocin may decrease trophoblastic embolization by constricting the uterine veins.\textsuperscript{82} Postoperatively, the patient should be monitored closely for any evidence of uterine hemorrhage or cardiopulmonary distress.

**HYPEREMESIS GRAVIDARUM**

As many as 50% to 80% of women experience nausea and vomiting during pregnancy; this is the most common indication for admission to the hospital during the first trimester of pregnancy.\textsuperscript{91} Symptoms can be worse during the morning hours, thus the term *morning sickness*, though symptoms can occur at any time of the day. Symptoms typically improve or resolve by the end of the first trimester.

On rare occasions (0.3% to 3% of pregnancies), women experience a persistent and severe form of nausea and vomiting called *hyperemesis gravidarum*.\textsuperscript{91} This is believed to be an extreme form of normal nausea and vomiting of pregnancy, although there is no single accepted definition. These women may develop dehydration, ketonuria, nutritional compromise, weight loss, electrolyte abnormalities, and/or transient hepatic and renal dysfunction. Intravenous rehydration, correction of electrolyte abnormalities, antiemetics, and, rarely, hyperalimentation are indicated. Gastroesophageal reflux disease may exacerbate vomiting especially after the first trimester.

Hyperemesis gravidarum may be associated with multiple gestation, thyropoieticosis, and/or GTD. Diagnosis is by exclusion, and if symptoms begin after 9 weeks’ gestation, many other underlying diseases should be ruled out including: gastrointestinal diseases (e.g., hepatitis, cholecystitis, pancreatitis, gastroparesis, partial bowel obstruction, appendicitis), genitourinary diseases (e.g., pyelonephritis, uremia, ovarian torsion, kidney stones), metabolic disorders (diabetic ketoacidosis, hyperthyroidism, Addison disease), neurologic disorders (pseudotumor cerebri, migraine headaches), psychiatric disorders, acute fatty liver of pregnancy, drug toxicity, and preeclampsia, among others.

Serious maternal complications may include Wernicke encephalopathy, acute tubular necrosis, esophageal rupture, and splenic avulsion.\textsuperscript{91}

**CORPUS LUTEUM CYSTS**

Symptomatic corpus luteum cysts occasionally occur during early pregnancy. Typically, they resolve over several weeks. In some cases, hemorrhage or ovarian torsion necessitates ovarian cystectomy or oophorectomy. After the cyst is removed, the fetus usually is not affected, provided that supplemental progesterone is administered until 10 to 12 weeks’ gestation.

### BOX 16.5  **Suggested Anesthetic Technique for Patients with Gestational Trophoblastic Disease**

**Preoperative Evaluation**
- Evaluation for complications of molar pregnancy
- Baseline arterial blood gas measurements

**General Anesthesia**
- Routine noninvasive monitors
- Consideration of invasive hemodynamic monitoring in patients with hypoxemia, gestational hypertension or pre-eclampsia, severe anemia, hyperthyroidism, or a uterine size greater than 16 weeks.
- Two large-gauge peripheral intravenous catheters
- Immediate availability of blood
- Induction: etomidate if evidence of hemorrhage or hemodynamically unstable
- Tracheal intubation with a muscle relaxant
- Maintenance: inhalation or intravenous technique; avoid volatile agents if optimization of uterine contractility is required, and exercise caution with the use of a propofol infusion in hemodynamically unstable patients
- Oxytocin infusion (6 to 15 IU per hour) after cervical dilation or after partial uterine evacuation

Aortocaval compression does not develop until the uterine fundus reaches the umbilicus (i.e., 18 to 20 weeks’ gestation in a normal singleton pregnancy, or earlier in conditions with an enlarged uterus). Left uterine tilt should be initiated when the potential for aortocaval compression exists.

General anesthesia may be administered by mask or laryngeal mask airway (LMA) for selected extra-abdominal procedures during the first 18 to 20 weeks of pregnancy, provided that the patient fulfills the criteria for an empty stomach and there is no difficulty with mask ventilation. Some anesthesia providers prefer to limit the use of mask anesthesia or the LMA to the first 12 to 14 weeks of pregnancy.

During pregnancy, the nervous system is more sensitive to local anesthetics and perhaps general anesthetic agents. Lower doses of these drugs should be considered, although it is important to be aware of the greater risk for intraoperative awareness during cesarean delivery.

Most ectopic pregnancies are located in one of the fallopian tubes. Ruptured tubal pregnancies, as well as interstitial, cervical, cesarean scar, and abdominal ectopic pregnancies as well as pregnancies with early placenta accreta, may result in substantial hemorrhage.

The most painful part of a dilation and uterine evacuation procedure is the dilation of the cervix. If the cervix is already dilated and the fetal size is first trimester, sedation (with or without paracervical block) often suffices. If the
cervix is closed, either a paracervical block with sedation or neuraxial or general anesthesia may be necessary. If the fetal size is advanced (greater than 13 to 15 weeks’ gestation), many anesthesia providers prefer general anesthesia because of the greater surgical stimulation and risk for bleeding complications.

- Neuraxial anesthesia is an excellent choice for prophylactic cervical cerclage. In a patient who requires emergency cervical cerclage, it is important to prevent a marked increase in intra-abdominal and intrauterine pressures, which might cause rupture of bulging fetal membranes.

- The patient with a molar pregnancy may have hyperemesis gravidarum, gestational hypertension, severe anemia, and/or hyperthyroidism. These complications are more common in patients with excessive uterine size.

- Rapid and profound blood loss is possible with uterine evacuation of a molar pregnancy, and acute cardiopulmonary distress can develop after uterine evacuation.

REFERENCES

30. Timor-Tritsch IE, Montenegro A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta
Estimates of the frequency of nonobstetric surgery performed during pregnancy range from 0.3% to 2.2%,¹² accounting for approximately 100,000 cases per year in both the United States and the European Union. Pregnancy may be unrecognized at the time of surgery. The incidence of positive pregnancy tests in women of childbearing age presenting for orthopedic and elective sterilization procedures have ranged from 0.002%³ to 2.6%.⁴ Medical history alone may not be a reliable means of excluding pregnancy in women presenting for elective surgery⁵,⁶; however, the practice of mandating pregnancy testing for every woman of childbearing age is controversial. A number of concerns have been raised; mandatory testing does not fully consider patient autonomy and likely disproportionately affects the most vulnerable patient populations, including minorities and women of lower socioeconomic status.⁷,⁸ Moreover, the medicolegal and health implications of a false-positive or false-negative pregnancy test have not been fully explored; litigation has occurred as a result of failure to follow-up on routine preoperative pregnancy tests and pregnancy loss following surgery.⁹

The American Society of Anesthesiologists (ASA) has stated: “Pregnancy testing may be offered to female patients of childbearing age and for whom the result would alter the patient’s management. Informed consent or assent of the risks, benefits, and alternatives related to preoperative pregnancy testing should be obtained.”¹⁰ In 2016, the UK National Institute for Health and Clinical Excellence (NICE) issued updated preoperative screening guidelines recommending the development of institutional protocols that include “… criteria for enquiry or consented testing, what information is provided to patients, how pregnancy status is recorded, and the procedures for management of consent and disclosure, particularly for groups who may find discussion of pregnancy a sensitive issue.”¹¹

Surgery may be necessary during any stage of pregnancy. Indications for pregnancy-related surgery include cervical incompetence, the presence of ovarian cysts, and conditions amenable to fetal surgery (see Chapter 7). Indications for nonpregnancy-related surgery include the presence of acute abdominal disease (most commonly appendicitis and cholecystitis), malignancies, and trauma. Among 5405 Swedish women who had operations during pregnancy, 42% occurred during the first trimester, 35% during the second trimester, and 23% during the third trimester.¹ Laparoscopy for gynecologic indications and appendectomy were the most common procedures during the first trimester (34%) and the remainder of pregnancy, respectively.¹

When caring for pregnant women undergoing nonobstetric surgery, anesthesia providers may need to modify standard anesthetic protocols to accommodate pregnancy-induced maternal physiologic changes and the presence of the fetus. The Global Burden of Disease Maternal Mortality Collaborators¹² and other maternal mortality databases, such as the Confidential Enquiries into Maternal and Child Health in the United Kingdom,¹³ have demonstrated that mothers may die, even in early pregnancy, of hemorrhage, hypertensive disorders, thromboembolism, and sepsis. In developed countries, many maternal deaths are considered preventable; multidisciplinary care should ideally follow protocols and guidelines developed for specific scenarios,
which can occur during or after nonobstetric surgical procedures. Two studies retrospectively analyzed data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database for pregnant women undergoing surgery. The rate of major complications (e.g., infections, reoperation, wound complications, respiratory complications, venous thromboembolism, blood transfusion, maternal death) for antenatal nonobstetric surgery was approximately 7%, which was not different from the rate in nonpregnant women.

Possible fetal risks of antenatal surgery include (1) the effects of the disease process itself, or related therapy; (2) the teratogenicity of anesthetic agents or other drugs administered during the perioperative period; (3) intraoperative perturbations of uteroplacental perfusion and/or fetal oxygenation; and (4) preterm delivery or fetal demise.

**MATERNAL PHYSIOLOGY: ANESTHETIC IMPLICATIONS**

During pregnancy, profound changes in physiology result from increased concentrations of various hormones, mechanical effects of the gravid uterus, greater metabolic demand, and the hemodynamic consequences of the low-pressure placental circulation. Hormonal changes are likely responsible for most of the changes that occur during the first trimester. Mechanical effects become apparent when the uterus emerges from the pelvis during the second half of gestation (see Chapter 2).

**Respiratory System and Acid-Base Balance Changes**

Alveolar ventilation increases by 30% or more by mid-pregnancy. This increase results in chronic respiratory alkalosis with a PaCO₂ of 28 to 32 mm Hg, a slightly alkaline pH (approximately 7.44), and decreased levels of bicarbonate and buffer base. Although oxygen consumption is increased, PaO₂ usually increases only slightly or remains within the normal range. Functional residual capacity (FRC) diminishes by approximately 20% as the uterus expands, resulting in decreased oxygen reserve and the potential for airway closure. When FRC is decreased further (e.g., from morbid obesity; perioperative intra-abdominal distention; placement of the patient in the supine, Trendelenburg, or lithotomy position; or induction of anesthesia), airway closure may be sufficient to cause hypoxemia.

Weight gain during pregnancy and capillary engorgement of the respiratory tract mucosa lead to more frequent problems with mask ventilation and tracheal intubation (see Chapter 29). Difficult airway management and failed intubation (a leading cause of anesthesia-related maternal death) is as much a risk during early pregnancy with nonobstetric surgery as it is during cesarean delivery.

In 2015, the Obstetric Anaesthetists’ Association and the Difficult Airway Society developed a difficult airway algorithm that was designed for the unique challenges of managing an obstetric patient, including considerations of the fetal status and urgency of a cesarean delivery; this algorithm is relevant to airway management for women with a viable fetus undergoing nonobstetric surgery (see Figs. 29.12, 29.13, 29.14).

Decreased FRC, increased oxygen consumption, and diminished buffering capacity result in the rapid development of hypoxemia and acidosis during periods of hyperventilation or apnea. Moreover, induction of inhalation anesthesia occurs more rapidly during pregnancy because alveolar hyperventilation and decreased FRC allow faster equilibration of inhaled agents. Combined with the reduction in the minimum alveolar concentration (MAC), subanesthetic concentrations of analgesic and anesthetic agents can induce unconsciousness quickly and unexpectedly in the pregnant woman.

**Cardiovascular System Changes**

Cardiac output increases by up to 50% during pregnancy because of increases in heart rate and stroke volume; diminished systemic and pulmonary vascular resistances occur from increased production of endothelial prostacyclin, relaxin, and nitric oxide. By 8 weeks’ gestation, 57% of the increase in cardiac output, 78% of the increase in stroke volume, and 90% of the decrease in systemic vascular resistance that are typically achieved by 24 weeks’ gestation have already occurred.

During the second half of gestation, compression of the inferior vena cava by the gravid uterus reduces venous return and cardiac output; in 10% of pregnant women, these effects can precipitate significant vasovagal symptoms and signs, which are collectively known as the “supine hypotension syndrome of pregnancy.” During mid-pregnancy, patient movement from the supine to the left lateral position reduces vena cava compression, resulting in a significant increase in left ventricular ejection fraction (8%), end-diastolic volume (25%), and stroke volume. By late pregnancy, the same patient movement results in even greater increases in these parameters; for example, cardiac output increases by up to 24%. In the supine position, pregnant women may maintain upper extremity blood pressure by compensatory vasoconstriction and tachycardia; however, these effects may be attenuated by neuraxial or general anesthesia. Moreover, uteroplacental blood flow and venous return can be compromised.

Although magnetic resonance imaging (MRI) studies of vena cava compression indicate virtually no compression with 30 degrees of left lateral tilt, most surgeries cannot be performed in this position. Therefore, after 18 to 20 weeks’ gestation, some degree of left lateral tilt should be applied, acknowledging that maternal or fetal hemodynamic instability may warrant a further increase in tilt, if necessary.

Vena cava compression can result in distention of the epidural venous plexus, which increases the likelihood of intravascular injection of local anesthetic during the administration of epidural anesthesia. The reduced capacity of the epidural space most likely contributes to the enhanced spread of epidural local anesthetic solution that is observed during pregnancy.
Changes in Blood Volume and Blood Constituents

Blood volume expansion begins as early as the first trimester and ultimately achieves a 30% to 45% increase by term gestation. The smaller increase in red blood cell than plasma volume results in dilutional anemia, allowing moderate blood loss to be well tolerated. However, when accompanied by anemia from other causes, a patient’s reserve during significant hemorrhage is decreased. The need for perioperative transfusions in pregnant women with iron-deficiency anemia is reduced by the intravenous administration of iron. Hemoglobin levels increase more rapidly (2 weeks) with intravenous compared with oral (greater than 6 weeks) iron therapy.

Pregnancy is associated with benign leukocytosis; thus the white blood cell count is an unreliable indicator of infection. In general, pregnancy induces a hypercoagulable state, with increases in fibrinogen; factors VII, VIII, X, and XII; and fibrin degradation products.

Pregnancy is associated with enhancement of platelet turnover, clotting, and fibrinolysis; although a wide variation in the platelet count has been observed, functionally some pregnant women with thrombocytopenia may still be hypercoagulable. Pregnancy represents a state of accelerated but compensated intravascular coagulation. Given the high risk and mortality associated with thromboembolism, thromboprophylaxis management should be applied to pregnant surgical patients (see later discussion).

Gastrointestinal System Changes

Incompetence of the lower esophageal sphincter and distortion of gastric and pyloric anatomy during pregnancy increase the risk for gastroesophageal reflux, despite similar gastric emptying rates in pregnant and nonpregnant patients. It is unclear at what gestational age the risk for aspiration becomes significant; gastroesophageal reflex starts early in the first trimester, and other mechanically induced factors become more relevant later in pregnancy. Investigators have studied the feasibility of assessing gastric contents using ultrasonography. Further study is warranted to determine if assessing gastric contents before the induction of anesthesia can be used to inform anesthetic management and reduce the risk for aspiration. It seems prudent to consider the pregnant patient as having a higher risk for aspiration from the beginning of the second trimester.

Altered Responses to Anesthesia

A 30% to 40% decrease in the MAC of volatile anesthetic agents has been observed in pregnancy, correlating with higher serum progesterone levels. Although thiopental requirements begin to decrease in early pregnancy, the effects of pregnancy on propofol requirements are conflicting and appear unrelated to progesterone levels. Higuchi et al. determined that the median effective dose (ED50) of propofol required to achieved loss of consciousness was unchanged in pregnancy, whereas Mongardon et al. reported that lower propofol doses were required in early pregnancy compared with the nonpregnant state. The relatively high risk for intraoperative awareness (estimated risk 1 in 670 general anesthetics) observed during cesarean delivery is attributable, in part, to the need for rapid-sequence induction of general anesthesia, omission or reduction in analgesic (opioids) and anesthetic medications, and need for urgent surgery. These circumstances are also commonly encountered during nonobstetric surgery in pregnancy.

Plasma cholinesterase levels decrease by approximately 25% from early in pregnancy until the seventh postpartum day. However, prolonged neuromuscular blockade with succinylcholine is uncommon, because the larger volume available for drug distribution offsets the impact of decreased drug hydrolysis.

The anesthesia provider should monitor all forms of neuromuscular blockade with a nerve stimulator to ensure adequate muscle relaxation as well as reversal before extubation of the trachea.

Decreased protein binding associated with lower albumin and alpha-glycoprotein concentrations during pregnancy may result in a larger fraction of unbound drug, with the potential for greater drug toxicity during pregnancy.

Pregnancy-associated changes in volume of distribution (caused by changes in body composition and/or plasma protein-binding capacity), metabolic activity, and hepatic or renal elimination (caused by changes in glomerular filtration rate and tubular transport processes) may contribute to changes in drug effects and metabolism, including a higher initial loading dose of any given medication. For example, in pregnant women, cefazolin clearance is approximately twice as high between 20 and 40 weeks’ gestation and acetaminophen (paracetamol) clearance is increased, compared with nonpregnant women.

Pregnant surgical patients may require drugs for which limited pharmacokinetic and pharmacodynamic information during pregnancy is available; judicious use of such agents is advisable. In addition to the altered response to systemic drugs, more extensive neuraxial and peripheral neural blockade may occur in pregnant than nonpregnant patients (see Chapter 12). Pregnancy may be associated with lower 48-hour postsurgical analgesic drug consumption, but this decrease has not been consistently demonstrated across studies.

FETAL CONSIDERATIONS

Risk for Teratogenicity

Although severe maternal hypoxia and hypotension pose the greatest risk to the fetus, considerable attention has focused on the role of anesthetic agents as abortifacients and teratogens. Teratogenicity has been defined as any significant postnatal change in function or form in an offspring after prenatal treatment. Concern about the potential harmful effects of anesthetic agents stems from their known effects on mammalian cells, which include reversible decreases in cell motility, prolongation of DNA synthesis, and inhibition of cell division. Despite these concerns, no data specifically link any of these cellular events with teratogenic changes. Unfortunately, prospective clinical studies of the teratogenic effects of...
anesthetic agents are impractical; such studies would require significant numbers of patients exposed to the drug being evaluated. Therefore, investigations of anesthetic agents have taken one of the following directions: (1) small animal studies of the reproductive effects of anesthetic agents, (2) epidemiologic surveys of operating room personnel routinely exposed to subanesthetic concentrations of inhalation agents, and (3) outcome studies in women who have undergone surgery while pregnant.

**Principles of Teratogenicity**

Like other toxicologic phenomena, a number of important factors influence the teratogenic potential of a substance, including species susceptibility, dose of the substance, duration and timing of exposure, and genetic predisposition (Fig. 17.1). Most teratologists accept the principle that any agent can be teratogenic when given at a specific dose and time. A teratogen may cause malformations following the single administration of a high dose, or the long-term administration of a low dose; however, this does not mean that a single, short exposure of a “normal” dose (e.g., during a typical anesthetic) would incur similar risk. In addition, a small dose of a teratogen may cause an effect in susceptible early embryos, whereas a much larger dose in the fetus may prove harmless, as was shown with thalidomide. Finally, the results of studies performed predominantly in small animals (e.g., chick embryos, mice, rats) cannot necessarily be extrapolated to other species, especially humans. Only a very small minority of drugs or agents listed in catalogs of teratogenic agents are proven teratogens in humans, although many more have teratogenic effects in animals.

Manifestations of teratogenicity include death, structural abnormality, growth restriction, and functional deficiency. Depending on when it occurs, death is referred to as abortion, fetal death, or stillbirth in humans, and as fetal resorption in animals. Structural abnormalities can lead to death if they are severe, although death may occur in the absence of congenital anomalies. Growth restriction is a manifestation of teratogenesis and may relate to multiple factors, including placental insufficiency and genetic and environmental factors. Functional deficiencies include behavioral and learning abnormalities, the study of which is called behavioral teratology. The stage of gestation at which exposure occurs determines the target organs or tissues, the types of defects, and the severity of damage. Most structural abnormalities result from exposure during the period of organogenesis, which extends from approximately day 31 to day 71 after the first day of the last menstrual period. Fig. 17.2 shows the critical stages of development and the related susceptibility of different organs to teratogens. Functional deficiencies are usually associated with exposure during late pregnancy or even after birth because the human central nervous system (CNS) continues to mature until the second year of life.

Consideration of the possible teratogenicity of anesthetic agents must be viewed against the naturally high occurrence of adverse pregnancy outcomes. Roberts and Lowe estimated that as many as 80% of human conceptions are ultimately lost; many are lost even before pregnancy is recognized. The rates of spontaneous miscarriage from 5 to 20 weeks’ gestation range from 11% to 22%. The incidence of congenital anomalies among humans is approximately 3%, most of which are unexplained, and of these, only 1% are attributable to exposure to drugs and environmental toxins (Table 17.1). There are several criteria for determining that an agent is a human teratogen, including the following: (1) proven exposure to the agent at the critical time of development; (2) consistent findings in two or more high-quality epidemiologic studies; (3) careful delineation of the clinical cases, ideally with the identification of a specific defect or syndrome; and (4) an association that “makes biological sense.” Documentation of teratogenicity in experimental animals is important but not essential. The agents or factors that are proven human teratogens do not include anesthetic agents (which are listed as “unlikely teratogens”) or any drug routinely used during the course of anesthesia (Box 17.1) (see Chapter 14).

![Fig. 17.1 Toxic manifestations with increasing dosage of a teratogen. A no-effect range of dosage occurs below the threshold, at which embryotoxic effects abruptly appear. Teratogenesis and embryolethality often have similar thresholds and may increase at roughly parallel rates as dosage increases to a point at which all conceptuses are affected. Increasing dosage causes increased embryolethality, but teratogenicity appears to decrease, because many defective embryos die before term. A further increase in dosage reaches the maternal lethal range. (Modified from Wilson JG. Environment and Birth Defects. New York: Academic Press; 1973:31.)](image-url)
Anesthesia before and during Pregnancy

Nondrug Factors Encountered in the Perioperative Period

Derangements of normal physiology. Anesthesia and surgery can cause derangements of maternal physiology that may result in hypoxia, hypercapnia, stress, and abnormailities of temperature and carbohydrate metabolism. These states can increase oxidative stress and be teratogenic themselves, or they may enhance the teratogenicity of other agents.42,43

Severe hypoglycemia and prolonged hypoxia and hypercarbia have caused congenital anomalies in laboratory animals, but there is no evidence to support teratogenicity

### Table 17.1 Etiology of Human Developmental Abnormalities

<table>
<thead>
<tr>
<th>Causes of Developmental Defects in Humans</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic transmission</td>
<td>15–20</td>
</tr>
<tr>
<td>Chromosomal abnormality</td>
<td>5</td>
</tr>
<tr>
<td>Maternal condition</td>
<td>4</td>
</tr>
<tr>
<td>Maternal infection</td>
<td>3</td>
</tr>
<tr>
<td>Maternal metabolic imbalance</td>
<td>1–2</td>
</tr>
<tr>
<td>Drugs/chemicals/radiation</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Unknown</td>
<td>65–70</td>
</tr>
</tbody>
</table>


### Box 17.1 Teratogenic Agents in Humans

**Radiation**
- Atomic weapons, radioiodine, therapeutic uses

**Infections**
- Cytomegalovirus, *Herpesvirus hominis*, parvovirus B19, rubella virus, syphilis, toxoplasmosis, Venezuelan equine encephalitis virus

**Maternal Metabolic Imbalance**
- Alcoholism, cretinism, diabetes, folic acid deficiency, hyperthermia, phenylketonuria, rheumatic disease and congenital heart block, virilizing tumors

**Drugs and Chemicals**
- Aminopterin and methylaminopterin, androgenic hormones, busulfan, captopril, chlorobiphenyls, cocaine, warfarin anticoagulants, cyclophosphamide, diethylstilbestrol, phenytoin, enalapril, etretinate, iodides (goiter), lithium, mercury (organic), methimazole (scalp defects), penicillamine, 13-cis-retinoic acid (Accutane), tetracyclines, thalidomide, trimethadione, valproic acid

after brief episodes in humans. Prolonged exposure to hyperglycemia is a known teratogen causing cardiac, CNS, and skeletal abnormalities, but any organ system can be affected.\textsuperscript{44} Anomalies are tightly linked with duration and degree of hyperglycemia, particularly in the first trimester,\textsuperscript{44} but it is unlikely that a brief period of intraoperative hyperglycemia has any teratogenic effects. Although severe hypoxemia causes structural teratogenesis in animals and humans, the chronic hypoxemia experienced by mothers at high altitudes results in the delivery of infants with lower birth weights but with no increase in the rate of congenital defects.\textsuperscript{45} Maternal stress and anxiety have been associated with poor fetal neurocognitive development (behavioral teratogenicity).\textsuperscript{46} Studies following obstetric outcomes in women in war zones demonstrate that maternal emotional trauma and posttraumatic stress disorder may affect fetal growth\textsuperscript{47} and increase the risk for miscarriage and hypertensive disorders of pregnancy,\textsuperscript{48} but these studies may be confounded by the lack of infrastructure to meet basic prenatal health care needs. Hypothermia is not teratogenic, whereas hyperthermia is teratogenic in both animals and humans.\textsuperscript{49} Congenital anomalies, especially involving the CNS, have repeatedly been associated with maternal fever during the first half of pregnancy. It must be remembered that fetal temperature is on average 0.5° C to 1° C higher than maternal temperature. Embryonic oxidative stress from reactive oxygen species has been implicated as one of the mechanisms involved in teratogenicity of many agents.\textsuperscript{43}

**Diagnostic procedures.** Ionizing radiation is a human teratogen that can result in an increased, dose-related risk for malignant disease, genetic disease, congenital anomalies, and/or fetal death.\textsuperscript{50} The effects of radiation are often classified as being deterministic or stochastic. Deterministic effects are dose related and are observed above a certain threshold dose (e.g., pregnancy loss, growth restriction, mental retardation, organ malformation). In contrast, stochastic effects are possible at any level of exposure with no minimum threshold but with the likelihood of worsening effects at higher doses. An increased risk for childhood cancer is a stochastic effect when fetuses are exposed to ionizing radiation in utero.

Radiation is expressed as grays (Gy) or milligrays (mGy) (1 Gy = 100 rad) and is evaluated as cumulative dose (i.e., background radiation and medical diagnostic radiation) throughout the entire pregnancy. No dose of radiation is considered safe, but the type and severity of effects vary with the radiation exposure to the uterus and fetus and with the gestational age of the fetus (Table 17.2). Background radiation during gestation is 1.3 to 5.8 mGy.\textsuperscript{51} There is no evidence that radiation exposure less than 50 mGy is associated with a teratogenic effect in either humans or animals.\textsuperscript{31} In contrast with the negligible risk for teratogenicity, observational studies suggest that there is a slightly higher risk for childhood cancer at radiation doses greater than or equal to 10 mGy.\textsuperscript{51} The relative risk for childhood malignancy after maternal abdominal radiation exposure has been estimated to be 2.28 (95% confidence interval, 1.31 to 3.97).\textsuperscript{52} The absorbed fetal dose for all conventional radiographic imaging inside or outside the abdomen and pelvis is negligible and is well below 50 mGy, with most falling under 5 mGy (Table 17.3). However, direct radiographic examination using computed tomography or fluoroscopy of the abdomen and pelvis may result in significant fetal radiation exposure, with doses that may approach 100 mGy.\textsuperscript{50–52} Interventional radiologic procedures (e.g., cerebral angiography, cerebral embolization, endoscopic retrograde cholangiopancreatography) are frequently complex and prolonged, particularly when surgery is not an option. These procedures, especially the abdominal interventions, expose the fetus to a significant radiation dose, sometimes greater than 50 mGy; thus, professional societies

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**TABLE 17.2 Radiation Exposure by Gestational Age and Outcomes**

<table>
<thead>
<tr>
<th>Radiation Dose (cGy)</th>
<th>Gestational Age</th>
<th>Fetal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>All stages</td>
<td>No fetal effects</td>
</tr>
<tr>
<td>10</td>
<td>&lt; 8 weeks</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>5–50</td>
<td>8–15 weeks</td>
<td>Growth restriction</td>
</tr>
<tr>
<td>5–50</td>
<td>16 weeks–birth</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>16 weeks–birth</td>
<td>Increase childhood cancer (0.3%–6%)</td>
</tr>
<tr>
<td>&gt; 25</td>
<td>&gt; 25 weeks</td>
<td>Death</td>
</tr>
</tbody>
</table>


**TABLE 17.3 Fetal Radiation Exposure for Common Diagnostic Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean Exposure (mGy)</th>
<th>Maximum Exposure (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Radiographic Examination</td>
<td>Absdomen 1.4</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Chest &lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Intravenous urogram 1.7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Lumbar spine 1.7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Pelvis 1.1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Skull &lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Thoracic spine &lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Fluoroscopic Examination</td>
<td>Barium meal (upper GI) 1.1</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>Barium enema 6.8</td>
<td>24</td>
</tr>
<tr>
<td>Computed Tomography</td>
<td>Abdomen 8.0</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Head 0.06</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Chest &lt; 0.005</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td></td>
<td>Lumbar spine 2.4</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Pelvis 25</td>
<td>79</td>
</tr>
</tbody>
</table>

GI, Gastrointestinal.
have developed guidance for the use of these technologies during pregnancy (Table 17.4).53,54

If the mother’s condition necessitates diagnostic testing and radiation exposure, and no other acceptable imaging modality is available, testing should not be withheld if the benefits to the mother (and, by extension, the fetus) are judged to outweigh the risks. Delayed diagnosis of a critical condition may result in significant harm to the maternal/fetal dyad. The consultation with the radiologist should include discussion of the optimal diagnostic modality that adheres to the ALARA principle (as low as reasonably achievable) for radiation and minimizes the absorbed dose, through abdominal shielding, scan length reduction, and milliampere modulation. The avoidance or minimization of intravenous radiopaque iodinated contrast media, which crosses the placenta and theoretically can cause neonatal hypothyroidism, should be considered as well.54

Diagnostic ultrasonography during pregnancy has long been considered devoid of embryotoxic effects. In animals, ultrasound intensities up to 20 W/cm² have been found to be safe.55,56 However, in rat models, when higher intensities (greater than 30 W/cm²) have been used, or when repeated exposure has occurred during early pregnancy, postnatal neurobehavioral effects have been described.57 Ultrasound waves produced by modern diagnostic equipment can induce significant increases in fetal temperature, especially when imaging is prolonged. Although Miller et al.58 concluded that the range of temperatures produced could be teratogenic, no biologic effects have been documented from diagnostic ultrasonographic examinations in the pregnant patient, despite widespread use over several decades. Nonetheless, it must be stressed that these epidemiologic studies were conducted in an era when ultrasound equipment was less potent and associated with lower increases in temperature. Doppler interrogation emits significantly more acoustic intensity, and subsequently more heat, than pulse-echo imaging equipment. Therefore, ultrasonographic examinations should be used judiciously, keeping the exposure time and acoustic output to the lowest level possible.

Gadolinium-based MRI contrast agents readily cross the placenta, enter the fetal circulation, and are excreted by the fetal kidneys into the amniotic fluid, where they may be swallowed by the fetus or resorbed by the mother. A large retrospective study designed to evaluate the effects of MRI exposure interrogated a Canadian universal-health care database of all births after 20 weeks’ gestation from 2003 to 2015.59 The relative risk for stillbirth was higher (1.68) among those pregnancies in which the fetus was exposed to gadolinium-MRI in the first trimester (n = 1737) compared with no MRI (n = 1,418,451); no conclusion could be made for MRI with and without gadolinium because of small sample sizes.59 The American College of Radiology and the American College of Obstetricians and Gynecologists (ACOG) recommend that intravenous gadolinium be avoided during pregnancy and used only if absolutely essential.54,60

### Systemic Agents

**Animal studies.** Early rodent studies documented teratogenicity (CNS malformations, skeletal abnormalities, and growth restriction) after exposure to a variety of opioids; however, these conclusions have been challenged because opioids given in large bolus injections can cause respiratory depression and impaired feeding, which may be teratogenic. In a rat study designed to avoid such problems, Fujinaga and Mazze61 maintained clinically relevant concentrations of morphine throughout most of pregnancy by means of continuously implanted osmotic mini-pumps. Structural anomalies were not observed at any morphine dose, although fetal growth restriction was present, and offspring mortality was increased. Using the same methodology, Fujinaga et al.62,63 found fentanyl, sufentanil, and alfentanil completely devoid of teratogenic effects. Additional mouse studies have confirmed the absence of structural teratogenicity with opioids.54

Use of tranquilizers and anxiolytics in pregnancy has been investigated less rigorously than opioids. Animal studies have demonstrated structural or behavioral teratogenesis after exposure to some of the barbiturate, phenothiazine, and tricyclic antidepressant agents.65,66 The reader is referred to standard teratology reference sources and package inserts for animal and human data related to specific drugs.59

Studies in rodents and nonhuman primates indicate that exposure of the immature brain to anesthetic agents such as propofol, thiopental, and ketamine (i.e., agents classified as N-methyl-D-aspartate [NMDA] antagonists and gamma-aminobutyric acid [GABA] agonists) are associated with brain cell apoptosis and functional learning deficits (see Chapter 10).67 In animal models, neurodegeneration increases with longer duration, greater dosage, and higher frequency of propofol exposure.68 Whether these effects occur in humans remains to be determined. These observed changes may represent indirect effects, such as hypoxia or hypoglycemia, as well as direct effects of the anesthetic agent on the developing brain.
**Human studies.** Teratogenesis has not been associated with any of the commonly used induction agents, including barbiturates, ketamine, and benzodiazepines, when administered in clinical doses during anesthesia.39

Although human data relating to long-term sedative-hypnotic therapy have raised questions about the possible teratogenicity of some agents, positive studies were retrospective and suffer from a variety of methodologic flaws. In a prospective evaluation of children with birth defects, a higher risk for cleft lip was not found when mothers ingested diazepam during the first trimester.69 Although the present consensus among teratologists is that diazepam is not a proven human teratogen,39 it is appropriate to consider the risk-to-benefit ratio before initiating long-term benzodiazepine therapy during the first trimester. No evidence suggests that a single dose of a benzodiazepine (e.g., midazolam) during the course of anesthesia is harmful to the fetus.

Obstetric complications of prenatal opioid exposure are well-documented and include preterm birth, small-for-gestational age, low birth weight (LBW), reduced head circumference, and sudden infant death (see Chapters 42 and 53).70 The evidence supporting structural teratogenicity of opioids in humans is of low quality, but in a systematic review of case-control and cohort studies, Lind et al.70 found a positive association between fetal opioid exposure and congenital anomalies (e.g., cleft lip, cleft palate, atrial septal defects, clubbed feet) in 17 of 30 studies. Neonatal opioid withdrawal syndrome,71 and impaired cognition, psychomotor skills, and behavioral development have been observed in infants and children exposed to opioids in utero.72,73 However, many studies did not correct for socioeconomic or environmental factors that might also influence neurobehavioral development.

Attempts should be made to reduce the amount of opioid medications prescribed to pregnant women while ensuring adequate pain management. Preference for analgesic techniques such as regional, peripheral nerve, and field blocks, and surgical techniques such as laparoscopy that reduce the need for postoperative opioids, should be used preferentially in pregnant women. Multimodal analgesia, including maximizing the use of nonopioid medications that are considered safe in pregnancy (e.g., acetaminophen) should be considered.

**Local Anesthetics**

No evidence supports morphologic or behavioral teratogenicity with lidocaine administration in rats,74 or with the clinical administration of local anesthetic agents, with the exception of cocaine. Maternal cocaine abuse is associated with adverse reproductive outcomes, including abnormal neonatal behavior and, in some reports, a higher incidence of congenital defects of the genitourinary, cardiac, facial, and gastrointestinal tracts.75 The greatest risk to the fetus most likely results from the high incidence of placental abruption and preterm delivery associated with maternal cocaine use (see Chapter 53).

**Muscle Relaxants**

Testing muscle relaxants for teratogenicity using standard in vitro animal study techniques is complicated by the requirement for very low drug doses or the need for mechanical ventilation (a complex undertaking in rodents). Fujianga et al.76 used a whole-embryo rat culture system to investigate the reproductive toxicity of high doses of \( \delta \)-tubocurarine, pancuronium, atracurium, and vecuronium. Although dose-dependent toxicity was manifested, these effects occurred only at concentrations 30-fold greater than those encountered in clinical practice. Given that fetal blood concentrations of muscle relaxants are only 10% to 20% of maternal concentrations, these drugs appear to have a wide margin of safety when administered to the mother during organogenesis. Many women have received muscle relaxants for several days during late gestation without adverse effect on the neonate.

**Inhalation Anesthetics**

**Animal studies.** Under certain conditions, the volatile halogenated anesthetic agents can produce teratogenic changes in chicks or small rodents. Basford and Fink77 observed skeletal abnormalities but no increase in fetal loss when rats were exposed in utero to 0.8% halothane for 12 hours on days 8 and 9 of pregnancy (i.e., the “critical period” in the 21-day rat gestation). Long-term exposure to subanesthetic concentrations of halothane caused fetal growth restriction in rats but no increase in the incidence of congenital anomalies,78 whereas isoflurane had no adverse effects.79

Significant reproductive effects have occurred with anesthetic concentrations of volatile anesthetic agents, including fetal skeletal abnormalities or death, following repeated or prolonged maternal exposure in mice.80 Teratogenicity in these studies was most likely caused by the physiologic changes (e.g., profound hypothermia, hypoventilation) associated with anesthetic rather than by the anesthetic agent itself. Moreover, some strains of mice are especially likely to demonstrate anomalies, such as a cleft palate. Mazze et al.71 exposed rats to 0.75 MAC of halothane, isoflurane, or enflurane, or 0.55 MAC of nitrous oxide, for 6 hours daily on 3 consecutive days at various stages of pregnancy. The animals remained conscious throughout the study, and normal feeding and sleep patterns were preserved. Under these conditions, no teratogenic effects were associated with any of the volatile agents. The only positive finding was a threelfold increase in the rate of fetal resorption with nitrous oxide. No evidence has suggested reproductive toxicity with either sevoflurane or desflurane in clinical concentrations.

In contrast with the volatile halogenated agents, nitrous oxide is a weak teratogen in rodents under certain conditions, even when normal homeostasis is maintained. Rats continually exposed to 50% to 70% nitrous oxide for 2 to 6 days (starting on day 8 of gestation) had an increased incidence of congenital abnormalities.81,82 To exclude the possibility that adverse effects were a consequence of the anesthetic state, Lane et al.83 exposed rats to 70% nitrous oxide or to a similar concentration of xenon (a slightly more potent anesthetic
devoid of biochemical effects) for 24 hours on day 9 of gestation; abnormalities occurred only in the nitrous oxide group. With the exception of one study in which extremely prolonged exposure to a low concentration of nitrous oxide had some minor effects, at least 50% nitrous oxide has been required to consistently produce anomalies. The threshold exposure time has not been rigorously determined, although exposure for at least 24 hours typically was necessary.

In vivo and embryo culture studies in rats have confirmed that nitrous oxide has several adverse reproductive effects, each of which results from exposure at a specific period of susceptibility. Fetal resorptions occurred after exposure on days 8 and 11 of gestation, skeletal anomalies after exposure on day 8 or 9, and visceral anomalies (including situs inversus) only when exposure occurred on day 8.

Initially, teratogenicity associated with nitrous oxide was thought to result from its oxidation of vitamin $B_{12}$, which interferes with its function as a coenzyme for methionine synthase. Transmethylation from methyl-tetrahydrofolate to homocysteine, with subsequent production of tetrahydrofolate (THF) and methionine, is catalyzed by methionine synthase (Fig. 17.3). Thus, methionine synthase inhibition could cause a decrease in THF (with a resultant decrease in DNA synthesis) and lower methionine levels (with resultant impairment of methylation reactions). Nitrous oxide rapidly inactivates methionine synthase in both animals and humans. Prolonged human exposure to nitrous oxide leads to adverse neurologic and hematologic outcomes, the latter probably resulting from diminished DNA synthesis.

Considerable evidence indicates that methionine synthase inhibition and a consequent lack of THF are not solely responsible for the teratogenic effects of nitrous oxide. Additional studies have implicated alpha$_2$-adrenergic receptor stimulation in the production of situs inversus by nitrous oxide. Postulated mechanisms by which sympathetic stimulation might have adverse reproductive effects include a decrease in uterine blood flow and overstimulation of G protein–dependent membrane signal transduction pathways. There is also evidence that nitrous oxide may cause neuronal apoptosis in rats, in part, as a result of oxidative stress.

In summary, evidence suggests that the etiology of nitrous oxide teratogenicity in rats is complex and multifactorial. Determination of the relative roles of methionine deficiency and sympathetic stimulation or other mechanisms awaits further study. Although nitrous oxide is considered a weak teratogen in rats and mice, reproductive effects occur only after prolonged exposure to high concentrations that are unlikely to be encountered in humans during clinical anesthesia. Whether nitrous oxide administration is associated with neuronal apoptosis and learning impairments in humans remains to be determined.

**Human studies**

Epidemiologic surveys dating to the early 1970s suggested that reproductive hazards (e.g., spontaneous abortion, congenital anomalies) were associated with exposure to trace anesthetic agents, principally nitrous oxide, in the operating room and during dental surgery. Critical reviews of these studies questioned their conclusions, noting that response bias, inappropriate control groups, lack of verification of medical data, and exposure to multiple environmental factors made definitive conclusions impossible. Studies in the late 1970s and 1980s have not confirmed an association between operating room work and higher reproductive risk. Pregnancy outcomes were comparable in exposed and nonexposed operating room nurses when questionnaire information was matched with objective data obtained from medical records and registries of abortions, births, and congenital anomalies. Similarly, in a 10-year prospective study of all female physicians in the United Kingdom, Spence found no differences in reproductive outcome when anesthesiologists were compared with other working female physicians. Although these studies may have missed a higher incidence of very early abortion, their data do not support a statistically demonstrable reproductive hazard resulting from operating room exposure to anesthetic agents.

The Nurse’s Health Study-II ($n = 8,461$), published in 2012, compared the risk for spontaneous abortion in nurses exposed to anesthetic gases (e.g., nitrous oxide, halothane, enflurane, and isoflurane) with those who were not exposed after correcting for age, parity, shift work, and hours worked. The odds for abortion were not different between groups. Dimich-Ward et al. studied the risk for fetal anomalies in live and stillborn births in an offspring cohort study of registered nurses ($n = 22,611$) in the British Columbia Vital Statistics Registry (1986 to 2000). In nurses exposed to the operating room environment, an increased risk for congenital anomalies was associated with exposure to halogenated gases (odds ratio [OR], 1.49) or nitrous oxide (OR, 1.42). A major limitation of these studies was the failure to correct for tobacco use or alcohol consumption; the relative risk for spontaneous abortion is increased with cigarette smoking (1.8), one or two alcoholic drinks per day (1.98), and more than three drinks per day (3.53).

Using a questionnaire-based survey of 744 pregnancies in 2028 female veterinarians, Shirangi et al. observed that the prevalence of preterm birth (before 37 weeks’ gestation) was higher in female veterinarians exposed to unscavenged anesthetic gases (7.3%) compared with the general Australian population (5.7%) during the same period. The identity of

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**Fig. 17.3** Pathway showing the inhibition of methionine synthase by nitrous oxide ($\text{N}_2\text{O}$) and its potential metabolic consequences (e.g., decreased DNA synthesis and impaired methylation reactions). THF, Tetrahydrofolate. (Courtesy of M. Fujinaga, Palo Alto, CA.)
the specific anesthetic gas used was not requested; however, halothane, nitrous oxide, enflurane, and methoxyflurane were commonly used during the study period. A hazards model predicted a 2.5-fold increase in preterm delivery risk in women exposed to unscavenged gas for one or more hours per week compared with an unexposed group. 104

It is possible that the higher waste levels of nitrous oxide encountered in dentists’ offices compared with operating rooms pose a reproductive risk. 105,106 In 1980, Cohen et al. 104 reported a doubling of the spontaneous abortion rate among exposed female chairside assistants and the wives of exposed male dentists. The incidence of birth defects among the children of exposed dental assistants was slightly higher than that for nonexposed assistants. However, the validity of this finding is doubtful; the incidence of anomalies among the offspring of nonexposed dentists was similar to that of the exposed assistants. Moreover, the expected dose-response relationship did not exist. In another study, 106 reduced fertility was reported among female dental assistants working with nitrous oxide in an unscavenged environment for more than 5 hours per week; the affected group consisted of only 19 individuals, making it difficult to draw firm conclusions from these data. Overall, the epidemiologic data do not support an increased risk for congenital anomalies with long-term occupational exposure to nitrous oxide.

Studies of operations performed during pregnancy. In 1963, Smith 107 reviewed the obstetric records of 18,493 pregnant women. Sixty-seven (0.36%) had had an operation during pregnancy; only 10 procedures occurred during the first trimester. Fetal mortality was 11.2%, with the poorest survival occurring after operations for appendiceal abscess and cervical incompetence. In 1965, Shnider and Webster 108 examined the records of 9073 obstetric patients; 147 (1.6%) of this group had had operations during pregnancy. Preterm delivery followed operation in 8.8% of patients, and the incidences of perinatal mortality and LBW were increased in patients who had surgery during pregnancy. Brodsky et al. 2 surveyed 12,929 pregnant dental assistants and wives of male dentists; those who were exposed to surgery had higher rates of spontaneous abortion than those in the control group (8% and 5.1% during the first trimester, and 6.9% and 1.4% during the second trimester, respectively). None of these three studies reported a higher incidence of congenital anomalies among infants of women who underwent surgery during pregnancy. A case-control study of infants born in Atlanta between 1968 and 1980 gathered information regarding first-trimester exposure to general anesthesia from the mothers of 694 infants with major CNS defects and 2984 control mothers. 109 A significant association was found between general anesthesia exposure and hydrocephalus in conjunction with another major defect (the strongest association was with hydrocephalus and eye defects). Limitations of this study include its retrospective nature and a lack of information about the types of surgery, the anesthetic agents used, and the presence or absence of complications. The investigators cautioned that further studies are necessary to confirm their observations. 106 Two additional studies 110,111 from the 1980s focused on the risks associated with nitrous oxide anesthesia during early pregnancy; no increase in the incidence of spontaneous abortion or congenital abnormalities was identified.

Duncan et al. 112 investigated obstetric outcomes based on anesthesia type using health insurance data from the entire Manitoba, Canada population between 1971 and 1978. They matched 2565 women who had operations during pregnancy with similar controls who did not undergo surgery. Type of anesthesia was classified as nil (18%), general (57%), spinal/nerve block (2%), or local (24%). Although the incidence of congenital anomalies was similar in the surgical and control groups, spontaneous abortion was more common among women who had general anesthesia for surgery during the first or second trimester. This was true for both gynecologic procedures (relative risk [RR], 2.00) and nongynecologic procedures (RR, 1.58). Unfortunately, no conclusions regarding the relationship between anesthetic technique and fetal loss could be drawn because most of the gynecologic and other major procedures were performed with general anesthesia. As in most studies, it is difficult to separate the effects of the anesthetic technique from those of the surgical procedure.

In the largest study to date investigating anesthesia type and pregnancy outcomes, Mazze and Källén 1 linked data from three Swedish health care registries—the Medical Birth Registry, the Registry of Congenital Malformations, and the Hospital Discharge Registry—for the years 1973 to 1981. Among the population of 720,000 pregnant women, 5405 (0.75%) had nonobstetric surgery, including 2252 who had procedures during the first trimester. (Cervical cerclage was excluded from analysis.) Of the women who had surgery, 54% received general anesthesia, which included nitrous oxide in 97% of cases. The researchers examined the following adverse outcomes: (1) congenital anomalies, (2) stillbirths, (3) neonatal death within 7 days, and (4) LBW or very-low-birth-weight (VLBW) infants. There was no difference between surgical and control patients in the incidence of stillbirth or the overall incidence of congenital anomalies (Fig. 17.4). Although the overall rate of anomalies among infants of women who had first-trimester operations was not higher, this group did have a higher-than-expected incidence of neural tube defects (6.0 observed versus 2.5 expected). 111 Five of the 6 women whose infants had these defects were among the 572 women who had surgery during gestational weeks 4 to 5, which is the period of neural tube formation; the researchers cautioned that this finding could have been a chance association. 113 However, if a true causal relationship exists between neural tube defects and anesthesia at this stage of gestation, it could represent an 8- to 9-fold increase in the risk for this anomaly (i.e., an absolute risk of almost 1%). Other positive findings were a higher incidence of LBW and VLBW infants in the surgical group, which resulted from both preterm delivery and fetal growth restriction. 1 A predictable consequence of preterm delivery was a higher number of deaths of live-born infants within the first 7 days of life. Finally, no anesthetic technique or operation was associated with a significantly higher number of adverse outcomes.
Most recently, a cohort study of 19,926 pregnant women in the Nationwide Inpatient Sample, which accounted for 20% of patients discharged from U.S. community hospitals from 2003 to 2012, sought to analyze risk factors for adverse outcomes associated with appendectomy and cholecystectomy; these surgeries are the most common emergency abdominal procedures performed during pregnancy. Among the 4.8% of women who experienced an adverse obstetric outcome, the most common were preterm delivery (35.4%), preterm labor without preterm delivery (26.4%), and miscarriage (25.7%). Preexisting obstetric risk factors were the largest contributors to adverse pregnancy outcomes, including cervical incompetence (adjusted OR, 24.29), prior preterm labor in pregnancy (adjusted OR, 18.34) and vaginitis/vulvovaginitis (adjusted OR, 5.17). Other risk factors associated with adverse obstetric outcomes included non-Caucasian ethnicity, multiple gestation, open surgical technique, and increased disease severity (e.g., peritonitis, sepsis). Specific anesthetic techniques or agents could not be determined from the database.

In summary, although nonobstetric anesthesia and surgery are associated with a higher incidence of abortion, fetal growth restriction, and perinatal mortality, these adverse outcomes can often be attributed to the procedure, the site of surgery (i.e., proximity to the uterus), and/or the underlying maternal or obstetric conditions. Evidence does not suggest that anesthesia during pregnancy results in an overall increase in congenital abnormalities, or that a relationship between type of anesthesia provided and adverse pregnancy outcomes exists.

**Behavioral Teratology**

Some teratogens produce enduring behavioral abnormalities without any observable morphologic changes. The CNS may be especially sensitive to such influences during the period of major myelination, which in humans extends from the fourth intruterine month to the second postnatal month (see Chapter 10). Several studies have shown that brief intrauterine exposure to halothane adversely affects postnatal learning behavior and causes CNS degeneration and decreased brain weight in rats. The rat fetal nervous system is most susceptible to the effects of halothane during the second trimester. Maternal administration of systemic drugs—including barbiturates, meperidine, and promethazine—has also resulted in behavioral changes in offspring whereas no effect has been noted with the administration of lidocaine.

Currently used general anesthetic agents act by one of two principal mechanisms: (1) the potentiation of GABAA receptors (benzodiazepines, volatile halogenated agents, and barbiturates) or (2) the antagonism of NMDA receptors (nitrous oxide and ketamine). Drugs that act by either of these mechanisms appear to induce widespread neuronal apoptosis in the developing rat brain and behavioral abnormalities when administered during the period of synaptogenesis (i.e., the brain growth spur period).

Jevtovic-Todorovic et al. observed that the administration of a general anesthetic “cocktail” (midazolam, isoflurane, and nitrous oxide), in doses sufficient to maintain general anesthesia for 6 hours in 7-day-old infant rats, resulted in widespread apoptotic neurodegeneration in the developing brain, deficits in hippocampal synaptic function, and persistent memory/learning impairments. They concluded that these deficits are “subtle enough to be easily overlooked” but may persist into adolescence and adulthood. Ikonomidou et al. described neurodegeneration in rat pups after exposure to NMDA receptor antagonists. These data suggest that prolonged exposure to anesthetic agents at a critical period in brain development may accelerate the normal developmental process of apoptotic neurodegeneration, potentially resulting in long-term behavioral deficits. Whether the duration or total dose of exposure, or both, contribute to the outcome is yet to be determined. In a rat model, Hayaishi et al. observed that repeated administration of ketamine over several hours, but not a single dose, resulted in apoptotic neurodegeneration.

Using validated postoperative neurodevelopmental testing in human children, the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) trial and the General Anesthesia versus Spinal Anesthesia (GAS) trial determined that a brief, single exposure to general anesthesia did not lead to poorer neurodevelopmental outcomes in children exposed to general anesthesia compared with control groups. The international, multicentered GAS trial randomized infants (younger than 60 weeks postmenstrual age, born at greater than 26 weeks’ gestation) who were undergoing inguinal herniorrhaphy to awake-regional (n = 238) or sevoflurane-based general anesthesia (n = 294). No difference was found in the secondary outcome, the composite cognitive score of the Bayley Scales of Infant and Toddler Development III, assessed at 2 years of age. The result of the primary outcome, the 5-year IQ, has not been published. The sibling-matched cohort design PANDA trial evaluated whether a single exposure to general anesthesia in healthy children younger than 3 years of age (determined retrospectively) was associated with a risk for impaired global cognitive function (IQ) or other neurocognitive functions and behaviors in children between 8 and 15 years of age (assessed prospectively). No differences were found in global cognitive function or
neurodevelopmental outcomes in 105 sibling-matched pairs. No studies have assessed neurocognitive outcomes after in utero exposure to general anesthetic agents during the critical period of synaptogenesis during human maternal nonobstetric surgery. On December 14, 2016, the U.S. Food and Drug Administration (FDA) issued a “Drug Safety Communication” warning that “…repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains.”

Because most repeated or lengthy procedures in pregnant women and in children younger than 3 years of age are urgent or necessary, and alternative anesthetic techniques are not feasible for many of these surgical procedures, the implications for anesthetic and surgical practice will primarily be to discuss the timing and the relative advantages and risks of different procedures.

Surgery may result not only in exposure to anesthetic agents, but also in derangements in maternal physiology (e.g., hypoxia, stress, hypoglycemia) that can lead to apoptosis during the critical period of neuronal development. It is also important to remember that painful stimuli per se can cause long-term behavioral changes.

Fetal Heart Rate Monitoring during Surgery

Continuous fetal heart rate (FHR) monitoring (using transabdominal Doppler ultrasonography) is feasible beginning at 18 to 20 weeks’ gestation, although technical problems may limit its use until after 22 weeks’ gestation. Transabdominal monitoring may not be possible during abdominal procedures or when the mother is very obese; the intraoperative use of transvaginal Doppler ultrasonography may be considered in selected cases.

The ACOG and ASA have jointly published guidelines for fetal monitoring during nonobstetric surgery. In the viable fetus, it is generally sufficient to ascertain the FHR by Doppler before and after the procedure. At a minimum, in patients with a viable fetus, simultaneous electronic FHR and contraction monitoring should be performed before and after the procedure to assess fetal well-being and the absence of contractions. The ACOG/ASA guidelines state that intraoperative electronic FHR monitoring “may be appropriate when all of the following apply: (1) the fetus is viable; (2) it is physically possible to perform intraoperative electronic [FHR] monitoring; (3) a health care provider with obstetric surgery privileges is available and willing to intervene during the surgical procedure for fetal indications; (4) when possible, the woman has given informed consent to emergency cesarean delivery; and (5) the nature of the planned surgery will allow the safe interruption or alteration of the procedure to provide access to perform emergency delivery.” Responses to a survey sent to members of the Association of Professors of Gynecology and Obstetrics indicated that only 43% routinely used intraoperative FHR monitoring.

FHR variability, which typically is a good indicator of fetal well-being, is present by 25 to 27 weeks’ gestation. Changes in the FHR baseline and variability caused by anesthetic agents or other drugs must be distinguished from changes that result from fetal hypoxia. Persistent severe fetal bradycardia typically indicates true fetal compromise.

Intraoperative FHR monitoring requires the presence of a provider who can interpret the FHR tracing. In addition, a multidisciplinary plan should address how to proceed in the event of persistent nonreassuring fetal status, including whether to interrupt ongoing surgery to perform an emergency cesarean delivery. Intraoperative FHR monitoring allows for the optimization of the maternal condition if the fetus shows signs of compromise (Box 17.2). For example, decreased FHR variability resulting from maternal hypoxemia resolved with improvement in maternal oxygenation (Fig. 17.5). An unexplained change in FHR mandates the evaluation of maternal position, blood pressure, oxygenation, and acid-base status, and the inspection of the surgical site to ensure that neither surgeons nor retractors are impairing uteroplacental perfusion.

Fetal Effects of Anesthesia

Maintenance of Fetal Well-Being

The most serious fetal risk associated with maternal surgery during pregnancy is that of intrauterine asphyxia. Fetal oxygenation is critically dependent on the maintenance of normal maternal arterial oxygen tension, oxygen-carrying capacity, oxygen affinity, and uteroplacental perfusion.

Maternal and fetal oxygenation. Transient mild to moderate decreases in maternal PaO₂ are well tolerated by the fetus, primarily because fetal hemoglobin has a high affinity for oxygen. Severe maternal hypoxemia results in fetal hypoxia and, if persistent, may cause fetal death. Any complication that causes profound maternal hypoxemia (e.g., difficult tracheal intubation, esophageal intubation, pulmonary aspiration, total spinal anesthesia, local anesthetic systemic toxicity) is a potential threat to the fetus.

Studies of isolated human placental vessels suggest that hypoxia may cause uteroplacental vasoconstriction, with potential impairment of fetal oxygen delivery. This fear has proved to be unfounded. Studies in pregnant women have demonstrated better fetal oxygenation with increasing maternal PaO₂; however, fetal PaO₂ never exceeds 60 mm Hg, even when...
maternal PaO₂ increases to 600 mm Hg. This physiologic limitation exists, in part, because of the low diffusion capacity of oxygen in the placenta, as well as the admixture of blood returning to the fetus from the placenta with deoxygenated blood from the fetal inferior vena cava (see Chapter 4). Thus, intraventricular retrolental fibroplasia and premature closure of the ductus arteriosus cannot result from high maternal PaO₂. McClaine et al. observed that the maternal administration of carbon dioxide to gravid ewes produced an initial—but not sustained—increase in fetal systemic oxygenation, but a sustained increase in cerebral oxygenation. The investigators hypothesized that the increase in fetal cerebral oxygenation resulted from greater cerebral perfusion, lower cerebral metabolic rate, or both. Histologic examination found no evidence of neurotoxicity.

**Maternal carbon dioxide and acid-base status.** Maternal hypercapnia can cause fetal acidosis, because fetal PaCO₂ correlates directly with maternal PaCO₂. Although mild fetal respiratory acidosis is of little consequence, severe acidosis can cause fetal myocardial depression and hypotension. Maternal hyperventilation with low maternal PaCO₂ and high pH can adversely affect fetal oxygenation by means of several mechanisms. Respiratory or metabolic alkalosis can compromise maternal-fetal oxygen transfer by causing umbilical artery constriction and by shifting the maternal oxyhemoglobin dissociation curve to the left. In addition, hyperventilation, independent of changes in PaCO₂, may reduce uterine blood flow and cause fetal acidosis. This decrease most likely is a consequence of mechanical ventilation, whereby increased intrathoracic pressure reduces venous return and cardiac output, which in turn decreases uteroplacental perfusion. Thus, hyperventilation should be avoided in the pregnant surgical patient. Rather, the Paco₂ should be kept in the normal range for pregnancy, which is lower than in the nonpregnant state.

**Uteroplacental perfusion.** Maternal hypotension from any cause can jeopardize uteroplacental perfusion and cause fetal asphyxia. The most common causes of hypotension in the pregnant patient undergoing surgery include (1) deep levels of general anesthesia, (2) sympathectomy with high sensory levels of spinal or epidural blockade, (3) aortocaval compression, (4) hemorrhage, and (5) hypovolemia. In monkeys, prolonged hypotension (i.e., systolic blood pressure less than 75 mm Hg) caused by deep halothane anesthesia resulted in fetal hypoxia, acidosis, and hypotension. After experiencing as much as 5 hours of severe partial asphyxia in utero (pH less than 7.00 for at least 1 hour), neonatal monkeys were depressed and experienced seizures. Postnatal survival was poor, and pathologic brain changes included swelling, necrosis, and hemorrhage. The clinical course and neuropathologic findings in these animals resembled those in infants known to have suffered severe intrauterine asphyxia and who died within a few days of birth.

However, good fetal and neonatal outcomes have been reported following deliberate use of moderate degrees of hypotension, usually to facilitate performance of a neurosurgical procedure in otherwise healthy women; maternal systolic blood pressures were maintained between 70 and 80 mm Hg, with transient periods as low as 50 mm Hg. These blood pressure parameters likely cannot be extrapolated to maternal conditions such as gestational hypertension, pre-eclampsia, or other conditions that predispose to uteroplacental insufficiency. In surgical circumstances necessitating maternal hypotension, the risk to the fetus must be balanced against the risk for uncontrolled maternal bleeding or stroke.

The multiple factors that influence uteroplacental blood flow are discussed in detail in Chapter 3. Of relevance to the pregnant surgical patient are drugs that cause uterine artery vasoconstriction. Preoperative anxiety and light anesthesia increase circulating catecholamines, possibly impairing uterine blood flow. Drugs that cause uterine tachysystole (e.g., ketamine in early pregnancy in doses higher than 2 mg/kg, toxic doses of local anesthetics) may increase vascular resistance of the vessels perfusing the uterus and placenta, decreasing perfusion.

Although historically ephedrine was the preferred first-line agent for the treatment of hypotension during the administration of neuraxial anesthesia in obstetric patients, evidence...
now supports the use of phenylephrine as the drug of choice for this purpose (see Chapter 26).\textsuperscript{145} Human studies in women receiving neuraxial anesthesia, including those that directly evaluate uterine vascular resistance by Doppler ultrasonography, have demonstrated no differences in uterine blood flow parameters when ephedrine or phenylephrine infusions were used to maintain baseline mean arterial pressure.\textsuperscript{147} Moreover, a meta-analysis of randomized controlled trials comparing ephedrine with phenylephrine for the treatment of hypotension during spinal anesthesia for cesarean delivery concluded the following: (1) there was no difference between phenylephrine and ephedrine for the prevention and treatment of maternal hypotension, (2) maternal bradycardia was more likely to occur with phenylephrine than with ephedrine, (3) women treated with phenylephrine had neonates with higher umbilical arterial blood pH measurements than those given ephedrine, and (4) there was no difference between the two vasopressors in the incidence of true fetal acidosis (i.e., umbilical arterial blood pH less than 7.20).\textsuperscript{148}

Ngan Kee et al.\textsuperscript{149} demonstrated that placental transfer was greater for ephedrine than phenylephrine, with less early metabolism and/or redistribution in the fetus. Fetal concentrations of lactate, glucose, and catecholamines were also higher with ephedrine than phenylephrine, thus supporting the hypothesis that the lower fetal pH observed with ephedrine is related to metabolic effects secondary to stimulation of fetal beta-adrenergic receptors. Recently, norepinephrine has been observed to successfully prevent and treat spinal anesthesia–induced maternal hypotension; further investigation of maternal and fetal effects, including comparison to other vasopressors, is necessary before widespread use can be recommended.\textsuperscript{150}

**Inhalation Agent Effects on the Fetus**

The volatile halogenated anesthetic agents transfer readily across the placenta and can affect the fetus directly (by depressing the fetal cardiovascular system or CNS) or indirectly (by causing maternal hypoxia or hypotension). Studies in gravid ewes have shown minimal fetal effects with maternal administration of moderate concentrations of volatile agents.\textsuperscript{152} During the inhalation of 1.0 and 1.5 MAC halothane or isoflurane, uterine artery vasodilation compensated for small decreases in maternal blood pressure to maintain uterine perfusion; however, the inhalation of 2.0 MAC concentrations for prolonged periods induced marked reductions in maternal blood pressure and uteroplacental blood flow, which resulted in fetal hypoxia, diminished fetal cardiac output, and fetal acidosis.\textsuperscript{152}

The effects of anesthesia on the healthy fetal lamb may be minimal, but the effects on a stressed fetal lamb remain unclear. In one study, the administration of 1% halothane to the mothers of asphyxiated fetal lambs caused severe fetal hypotension, acidosis, and decreases in cerebral blood flow and oxygen delivery.\textsuperscript{152} In other studies, acidosis that was less severe in magnitude or duration was associated with the maintenance of fetal cardiac output and a preservation of the balance between oxygen supply and demand.\textsuperscript{153–155} The protective compensatory mechanisms that exist during asphyxia may be abolished by high but not low concentrations of volatile agents.

The relevance of these data to women undergoing surgery during pregnancy is unclear. Volatile anesthetic agents are a common component of general anesthesia; the depressant effect of these agents on uterine myometrial contractility may be beneficial for prevention of preterm labor. Provided that maternal hypotension is prevented, FHR decelerations are not expected, although diminished FHR variability may occur as the fetus becomes anesthetized. If intraoperative FHR monitoring shows signs of fetal compromise, corrective maneuvers should be considered and implemented (see Box 17.2); if these maneuvers fail, conversion to intravenous anesthetic agents may improve the fetal condition.

**Systemic Agent Effects on the Fetus**

Opioids and induction agents decrease FHR variability, possibly to a greater extent than the inhalation agents.\textsuperscript{156,157} This finding most likely signals the presence of an anesthetized fetus and is not a cause for concern in the absence of maternal hypotension or other abnormalities. Fetal respiratory depression is relevant only if cesarean delivery is to be performed at the same time as the surgical procedure. Even then, high-dose opioid anesthesia need not be avoided if it is indicated for maternal reasons (e.g., anesthesia for patients with cardiac disease). The neonatologist should be informed of maternal drug administration so that preparations can be made to support neonatal respiration. Some data indicate that remifentanil may result in less neonatal depression than longer-acting opioids.\textsuperscript{158}

Maternal administration of muscle relaxants and reversal agents typically is not problematic for the fetus. The rapid intravenous injection of an anticholinesterase agent could stimulate acetylcholine release and theoretically increase uterine tone and precipitate preterm labor.\textsuperscript{159} Although this concern is unproven, slow administration of an anticholinesterase (after prior injection of an anticholinergic agent) is recommended. Atropine rapidly crosses the placenta and, when given in large doses, causes fetal tachycardia and loss of FHR variability.\textsuperscript{160} Although neither atropine nor glycopyrrolate significantly affects FHR when standard clinical doses are administered,\textsuperscript{161} glycopyrrolate is often recommended because it crosses the placenta less readily. Limited transplacental passage of neostigmine is expected, but mild fetal bradycardia was reported in one patient at 31 weeks’ gestation when neostigmine was administered with glycopyrrolate during emergence from general anesthesia.\textsuperscript{162} This problem did not occur during the administration of a second general anesthetic to the same patient 4 days later, when atropine was administered with neostigmine, presumably because atropine undergoes greater placental transfer than glycopyrrolate.

Sugammadex, an agent that rapidly reverses paralysis by forming a complex with neuromuscular blocking agents, has not been robustly investigated in pregnant women.\textsuperscript{163} However, in a case series of 8 women who underwent a cesarean delivery with general anesthesia and rocuronium for
rapid-sequence induction, the dosing and response to sugammadex were similar to those in nonpregnant patients. \(^{164}\) Consideration should be given to the known risks of anaphylaxis (0.3%), bradycardia, and cardiac arrest, \(^{166}\) as well as the potential unknown risks for mother and fetus. Because the effects of all reversal agents are unpredictable, monitoring of FHR during maternal drug administration may be prudent.

**Prevention of Preterm Labor**

Most epidemiologic studies of women who undergo nonobstetric surgery during pregnancy have reported a higher incidence of abortion and preterm delivery. \(^{120,10,165}\) Whether the surgery, manipulation of the uterus, or the underlying condition is responsible is unclear. In a study of 778 women who underwent appendectomy during pregnancy, Mazze and Källén \(^{165}\) found that 22% of women who underwent surgery between 24 and 36 weeks’ gestation delivered in the week after surgery. In the women in whom pregnancy continued beyond 1 week after surgery, there was no further increase in the rate of preterm birth. Although this study’s database was unsuitable for determining the incidence of preterm delivery in women who had surgery before 24 weeks’ gestation, a similar increase appeared likely. Second-trimester procedures and operations that do not involve uterine manipulation carry the lowest risk for preterm labor.

Although the volatile agents depress myometrial irritability and thus are theoretically advantageous for abdominal procedures, evidence does not show that any one anesthetic agent or technique positively or negatively influences the risk for preterm labor. Published evidence does not support the routine use of prophylactic tocolytic agents. \(^{166}\) Whether greater surveillance and early tocolytic therapy will reduce the risk for preterm delivery after surgery during pregnancy is not known. Monitoring for uterine contractions may be performed intraoperatively with an external tocodynamometer (if technically feasible) and for several days postoperatively, allowing tocolytic therapy to be instituted, if appropriate. Additional surveillance is necessary in patients who receive potent postoperative analgesics, who may be unaware of mild uterine contractions.

Magnesium sulfate is among the most common drugs used in pregnancy as a tocolytic, anticonvulsant, or fetal neuroprotective agent. Antenatal magnesium sulfate has been shown to reduce the incidence and severity of cerebral palsy after very preterm birth (see Chapter 10). \(^{167}\) Magnesium also has effects that are relevant to the delivery of anesthesia, including an increase in the rate of onset of neuromuscular blockade, \(^{168}\) the reestablishment of neuromuscular blockade in patients recovering from a nondepolarizing muscle relaxant, \(^{169}\) and a reduction in general anesthetic requirements. \(^{170}\)

**PRACTICAL CONSIDERATIONS**

**Timing of Surgery**

The ACOG/ASA guidelines on nonobstetric surgery during pregnancy state that elective surgery should not be performed during pregnancy and that necessary surgery should not be denied because of trimester considerations; however, if surgery should be deemed necessary, the second trimester is preferred because of its association with the lowest risk for spontaneous abortion and preterm labor. \(^{132}\) Urgent operations are often indicated for abdominal emergencies, some malignancies, and neurosurgical and cardiac conditions. The management and timing of most acute surgical procedures should mimic that for nonpregnant patients. Maternal appendicitis is associated with an increased risk for perinatal loss and preterm labor, particularly when the infection is advanced. \(^{114}\) Appendicular perforation may be more common in pregnant than nonpregnant patients because diagnostic difficulties may delay surgery. Generalized peritonitis may also be more likely because increased corticosteroid levels during pregnancy may suppress the normal inflammatory response and prevent the “walling off” of the appendix by the omentum. \(^{171}\)

In the event of a serious maternal illness necessitating emergency surgery, the remote fetal risks associated with anesthesia and surgery are of secondary importance. The primary goal is to preserve the life of the mother. Successful neonatal outcomes in complex, high-risk procedures requiring induced hypothermia, induced hypotension, and cardiopulmonary bypass have been reported. The decision to perform simultaneous cesarean delivery depends on several factors, including the gestational age, the risk to the mother of a trial of labor at a later date, and the presence of intra-abdominal sepsis. Cesarean delivery may be performed immediately before the surgical procedure to avoid fetal risks associated with special patient positioning (e.g., the sitting or prone position), prolonged anesthesia, major intraoperative blood loss, maternal hyperventilation, deliberate hypotension, or cardiopulmonary bypass.

**Emergency Abdominal Surgery**

Acute abdominal disease occurs infrequently in pregnancy; the most common causes include appendicitis (1 in 500 to 1 in 2000 pregnancies), cholecystitis (1 in 1600 to 1 in 10,000 pregnancies), and bowel obstruction (1 in 1500 to 1 in 16,000 pregnancies). \(^{172,173}\) Accurate diagnosis, especially of an acute abdominal crisis (e.g., appendicitis, cholecystitis), can be very difficult during pregnancy, and several conditions must be considered in the differential diagnosis (Box 17.3). \(^{171}\) Nausea, vomiting, constipation, and abdominal distention are common symptoms of both normal pregnancy and acute abdominal disease. Abdominal tenderness may be indistinguishable from ligamentous or uterine contraction pain. The expanding uterus makes the physical examination of the abdomen difficult. For example, the appendix rotates counterclockwise; thus, as term approaches, the tip typically lies over the right kidney. \(^{174}\) Because the white blood cell count in normal pregnancy may reach 15,000/mm\(^3\), it must be markedly elevated to be diagnostically helpful. Additional delay may result from the reluctance to perform imaging studies involving radiation or contrast medium. In 1991, Mazze and Källén \(^{165}\) reported the misdiagnosis of appendicitis during pregnancy in 36% of cases, with a lower rate (23%) during
However, using more recent data from the American College of Surgeons NSQIP from 2005 to 2009, Silvestri et al. found no difference in 30-day postoperative morbidity or mortality in 857 pregnant and 20,029 nonpregnant appendectomy cases, and 436 pregnant and 32,915 nonpregnant cholecystectomy cases. Moore et al. used 2006 to 2011 data from the NSQIP to compare 2764 (0.5%) pregnant and 516,705 (99.5%) nonpregnant women undergoing general surgery. No difference in 30-day postoperative mortality or morbidity were noted between groups, but pregnant women tended to be younger, have fewer comorbidities than the general population, and were more likely to be undergoing emergency surgery. There is likely significant overlap in the data from these NSQIP studies. Although it is reassuring that the risk to the mother is comparable to nonpregnant women undergoing similar surgical procedures, the severity of disease significantly affects fetal outcomes in pregnant women with acute abdominal disease.

**Laparoscopy**

Laparoscopy is performed during pregnancy for both diagnostic and therapeutic indications with increasing frequency. Concerns exist about the effects of laparoscopy on fetal well-being, especially the risks for (1) uterine or fetal trauma, (2) fetal acidosis from absorbed carbon dioxide, and (3) decreased maternal cardiac output and uteroplacental perfusion resulting from an iatrogenic increase in intra-abdominal pressure. In some animal studies, maternal and fetal acidosis and tachycardia have occurred during intra-abdominal insufflation, perhaps because maternal ventilation was guided by measurements of end-tidal rather than arterial carbon dioxide levels. Uteroplacental perfusion decreased by 61% in one study in which gravid ewes were subjected to a CO$_2$ pneumoperitoneum at a pressure of 20 mm Hg (although there were no adverse fetal consequences). It is unclear whether the severity of acidosis and decrement in uteroplacental perfusion are related to insufflation pressure.

Many practitioners believe, however, that the potential benefits of laparoscopic surgery compared with open abdominal surgery outweigh the risks. Potential benefits include (1) shorter hospitalization, (2) less postoperative pain, (3) decreased risk for thromboembolic and wound complications, and (4) faster return to normal activities, including earlier return of normal gastrointestinal function, less uterine irritability, and less fetal depression. In a 1994 survey of laparoendoscopic surgeons, Reedy et al. obtained data from 413 laparoscopic procedures performed during pregnancy and reviewed an additional 55 previously published cases. Among the procedures surveyed, 48% were cholecystectomies, 28% were adnexal operations, 16% were appendectomies, and 8% were diagnostic procedures. Thirty-two percent of operations were performed in the first trimester, 54% in the second, and 13% in the third. Several principally retrospective trials comparing open and laparoscopic interventions reported no maternal and fetal outcome differences.

Human clinical studies and experience suggest that the fetal effects of the CO$_2$ pneumoperitoneum and increased intra-abdominal pressure are limited. In one clinical study, there were no differences in the maternal pH, PaCO$_2$, or arterial-to-end-tidal CO$_2$ pressure gradients before, during, or after termination of the pneumoperitoneum during laparoscopy. Steinbrook and Bhavani-Shankar used thoracic electrical bioimpedance cardiography to measure changes in cardiac output in four pregnant women undergoing laparoscopic cholecystectomy. They observed hemodynamic changes similar to those that typically occur during laparoscopic surgery in nonpregnant patients (i.e., decrease in cardiac index with concurrent increases in mean arterial pressure and systemic vascular resistance).

Reported clinical experiences with laparoscopy during pregnancy generally have been favorable with the rare
occurrence of complications, such as intraoperative perforation of the uterus with the Veress needle. Nonetheless, Amos et al., in a case series, reported fetal deaths following four of seven laparoscopic procedures. Some practitioners have suggested the use of gasless laparoscopic techniques to avoid the potential fetal effects of CO₂ pneumoperitoneum.185,186

Careful selection and conduct of surgical and anesthetic techniques can assist in avoiding complications associated with laparoscopic surgery during pregnancy. The surgeon should be experienced with the technique, and the anesthesia provider must be aware of the accompanying physiologic alterations, including the cardiorespiratory implications. In 2011, the Society of American Gastrointestinal Endoscopic Surgeons published “Guidelines for Diagnosis, Treatment, and Use of Laparoscopy for Surgical Problems during Pregnancy” (Box 17.4). The guidelines emphasized that the indications for laparoscopic surgery in pregnant patients do not differ from those for nonpregnant patients and may be performed during any trimester of pregnancy.

General anesthesia has been used in most laparoscopic procedures, although the use of epidural anesthesia has also been described. Steinbrook et al. described their anesthetic technique for 10 cases of laparoscopic cholecystectomy during pregnancy. They administered general anesthesia with a rapid-sequence induction followed by tracheal intubation and positive-pressure ventilation to maintain end-tidal CO₂ between 32 and 36 mm Hg. Anesthesia was maintained with a nondepolarizing muscle relaxant, an opioid, and a volatile halogenated agent, but nitrous oxide was avoided to prevent bowel distention and to allow administration of a higher concentration of inspired oxygen. The pneumoperitoneum resulted in increased peak airway pressure (Fig. 17.6) and

**BOX 17.4 Selected Guidelines for Laparoscopic Surgery during Pregnancy**

**Diagnosis and Workup**
- Ultrasonography is safe and useful to identify etiology of abdominal pain.
- Ionizing radiation: Timely and accurate diagnosis takes precedence over risk associated with ionizing radiation. (Attempt to limit dose to 5–10 rads.)
- Computed tomography (CT): Contemporary multidetector CT protocols deliver a low radiation dose to the fetus and may be used judiciously.
- Magnetic resonance imaging without gadolinium can be performed at any stage of pregnancy.
- Nuclear medicine: Administration of radionuclides for diagnostic studies is generally safe for the mother and fetus.
- Intraoperative and endoscopic cholangiography: Exposes the mother and fetus to minimal radiation and may be used selectively during pregnancy. (Use protective shielding on the lower abdomen.)

**Surgical Techniques**
- Diagnostic laparoscopy is safe and effective when used selectively in pregnancy.
- Laparoscopic treatment of acute abdominal disease has the same indications in pregnant and nonpregnant patients.
- Laparoscopy can be safely performed during any trimester of pregnancy.
- Initial port placement can be safely performed with an open (Hasson) technique, Veress needle, or optical trocar.
- Insufflation pressure of 10–15 mm Hg can be safely used.

**Disease**
- Gallbladder disease: Laparoscopic cholecystectomy is the treatment of choice in the pregnant patient, regardless of trimester.
- Choledocholithiasis: May be managed with preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy followed by laparoscopic cholecystectomy, laparoscopic common bile duct exploration, or postoperative ERCP.
- Appendectomy: Laparoscopic appendectomy may be performed safely in pregnant patients with appendicitis.
- Solid-organ resection: Laparoscopic adrenalectomy, nephrectomy, splenectomy, and mesenteric cyst excision are safe procedures in pregnant patients.
- Cystic adnexal mass: Laparoscopy is a safe and effective treatment. Observation is acceptable for all other cystic lesions provided ultrasonography is not concerning for malignancy and tumor markers are normal. Initial observation is warranted for most cystic lesions <6 cm in size.
- Adnexal torsion: Laparoscopy is recommended for both diagnosis and treatment unless clinical severity warrants laparotomy.


![Fig. 17.6 Peak inspiratory pressure during laparoscopic cholecystectomy during pregnancy as a function of gestational age. The best-fit line by linear regression is shown (y = 12.1 + 0.5x; R² = 0.43). Peak inspiratory pressure tends to increase with advancing gestation. (Modified from Steinbrook RA, Brooks DC, Datta S. Laparoscopic cholecystectomy during pregnancy. Surg Endosc. 1996;10:511–515.)](image)
decreased total lung compliance, which were progressively greater with advancing gestation.

The Trendelenburg position exacerbates decreases in FRC and increases in hypoxemia from airway closure. Hyperventilation, which may be necessary to maintain normal maternal PaCO₂, may reduce uteroplacental perfusion and affect fetal oxygenation. Hypotension may result from pneumoperitoneum, aortocaval compression, or use of the reverse Trendelenburg position, and a vasopressor may be needed to maintain maternal blood pressure. As with open surgery, fetal well-being is best preserved by maintaining maternal oxygenation, acid-base status, and hemodynamic parameters within normal pregnancy limits. The FHR and uterine tone should be monitored before and after surgery (see earlier discussion).

Anesthetic Management

Preoperative Management

Appropriate preoperative management of the pregnant patient undergoing nonobstetric surgery includes ensuring that these surgeries will be performed at an institution where qualified, multidisciplinary personnel are readily available. Following a physical examination and informed anesthetic consent, including a discussion on the risks and benefits of maternal and fetal anesthetic exposure, premedication may be necessary to allay maternal anxiety. Pregnant women are at increased risk for acid aspiration after 18 to 20 weeks' gestation (see earlier discussion). Pharmacologic precautions against acid aspiration may include preanesthetic administration of a histamine₂-receptor antagonist, metoclopramide, and a clear nonparticulate antacid such as sodium citrate.

Choice of Anesthesia

Maternal indications and consideration of the site and nature of the surgery should guide the choice of anesthesia. No study has found an association between improved fetal outcome and any specific anesthetic technique, except for a single retrospective medical record analysis in which the use of general anesthesia was associated with a significantly lower birth weight despite similar gestational age at delivery. When possible, however, local or regional anesthesia (with the exception of paracervical block) is preferred, because it permits the administration of drugs with no laboratory or clinical evidence of teratogenesis. In addition, maternal airway and respiratory complications occur less frequently with local and regional anesthetic techniques. These techniques are suitable for cervical cerclage and urologic or extremity procedures. Most abdominal operations require general anesthesia, because the incision typically extends to the upper abdomen. This situation may create an unacceptably high risk for aspiration in a pregnant patient with an unprotected airway.

Prevention of Aortocaval Compression

Beginning at 18 to 20 weeks' gestation, the pregnant patient should be transported on her side, and the uterus should be displaced leftward when she is positioned on the operating table.

Monitoring

Maternal monitoring should include noninvasive or invasive blood pressure measurement, electrocardiography, pulse oximetry, capnography, temperature monitoring, and the use of a peripheral nerve stimulator. The FHR and uterine activity should be monitored before and after surgery. Intraoperative FHR monitoring may be considered when technically feasible, depending on the ease of monitoring, the type and site of surgery, and gestational age (see earlier discussion).

Anesthetic Technique

Most anesthesiologists agree that general anesthesia mandates tracheal intubation beginning at 18 to 20 weeks' gestation or if the stomach is full. Two recent retrospective studies (combined n = 3700) reported using supraglottic airway devices with esophageal drains in pregnant women undergoing elective cesarean delivery with no reported cases of aspiration. Women in these studies followed fasting guidelines and had normal body mass index, and the airway devices were placed using aspiration precautions (i.e., preoxygenation, administration, cricoid pressure, and rapid-sequence induction). Although these studies do not definitively demonstrate safety, these devices may be an alternative airway management technique for women for whom avoidance of tracheal intubation or neuromuscular paralysis is desirable (e.g., professional singer, patient with myotonic dystrophy). Denitrogenation (i.e., preoxygenation) should precede the induction of anesthesia. Although rapid-sequence induction with the application of cricoid pressure has been a long-standing practice for the induction of general anesthesia, some experts suggest that it is unnecessary in fasted pregnant women undergoing elective surgery and may make tracheal intubation more challenging. Drugs with a history of safe use during pregnancy include thiopental, propofol, morphine, fentanyl, succinylcholine, and the nondepolarizing muscle relaxants.

A commonly used technique employs a high concentration of oxygen, a muscle relaxant, and an opioid and a moderate concentration of a volatile halogenated agent. Scientific evidence does not support avoidance of nitrous oxide during pregnancy, particularly after the sixth week of gestation. Omission of nitrous oxide may increase fetal risk if inadequate anesthesia occurs or if a high dose of a volatile agent results in maternal hypotension. A cautious approach is to restrict nitrous oxide administration to a concentration of 50% or less and to limit its use in extremely long operations. Hyperventilation should be avoided; rather, end-tidal CO₂ should be maintained in the normal range (28 to 32 mm Hg) for pregnancy.

Rapid intravenous infusion of crystalloid or colloid fluids during the initiation of spinal or epidural anesthesia with prophylactic vasopressor administration or early treatment of hypotension is prudent. Hypotension should be treated aggressively, and practitioners should be vigilant to the signs of high neuraxial blockade and local anesthetic systemic toxicity.

Regardless of the anesthetic technique, steps to avoid hypoxemia, hypotension, acidosis, and hyperventilation are the most critical elements of anesthetic management.
Postoperative Management

The FHR and uterine activity should be monitored during recovery from anesthesia. Adequate analgesia should be ensured with systemic or neuraxial opioids, acetaminophen, or neural blockade. Nonsteroidal anti-inflammatory drugs should be avoided in pregnancy, especially in the first and third trimesters. Maternal safety organizations recommend mechanical compression devices for thromboembolism prophylaxis in all women undergoing cesarean delivery and pharmacologic prophylaxis in women with additional risk factors, including obesity, thrombophilia, prolonged immobility, and any condition that may increase a pregnant woman’s risk for venous thromboembolism.25,26 Many of the principles recommended in these guidelines should be applied to pregnant patients in the nonobstetric surgery setting.

Maternal Cardiac Arrest and Resuscitation

Although Standard Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) principles apply to these patients, the anatomic and physiologic changes of pregnancy, and the presence of a fetus, require several specific modifications to the resuscitation protocol (see Boxes 41.9 and 54.5).194 Left uterine displacement should be maintained during resuscitation, optimally performed using two hands to pull the uterus to the left (see Fig. 54.2).195 Perimortem cesarean delivery (resuscitative hysterotomy) is an essential aspect of maternal resuscitation in the second half of gestation.196 The primary purpose of the hysterotomy is to improve the chance of maternal survival, but early delivery will also improve the likelihood of fetal survival.194,196 Thus, if initial resuscitative efforts are unsuccessful, perimortem cesarean delivery should be initiated within 4 minutes of the arrest with the goal of delivering the fetus within 5 minutes.194 The neonatal resuscitation team should be part of the maternal cardiac arrest team, as the fetus will likely need immediate resuscitation upon delivery. The reversible causes of cardiac arrest during pregnancy are similar to those in nonpregnant patients; however, additional causes specific to pregnancy include amniotic fluid embolism, eclampsia, placental abruption, and hemorrhage.

KEY POINTS

- A significant number of women undergo anesthesia and surgery during pregnancy for procedures unrelated to delivery.
- Maternal risks are associated with the anatomic and physiologic changes of pregnancy (e.g., difficult intubation, aspiration) and with the underlying maternal disease.
- The diagnosis of abdominal conditions may be delayed during pregnancy, increasing the risk for maternal and fetal morbidity.
- Maternal catastrophes involving severe hypoxia, hypotension, and acidosis pose the greatest acute risk to the fetus.
- Other fetal risks associated with surgery include fetal loss, preterm labor, growth restriction, and low birth weight. Clinical studies suggest that anesthesia and surgery during pregnancy do not increase the risk for congenital anomalies.
- It is unclear whether adverse fetal outcomes result from the anesthetic, the operation, or the underlying maternal disease.
- No anesthetic agent is a proven teratogen in humans, although some anesthetic agents, specifically nitrous oxide, are teratogenic in animals under certain conditions.
- Many anesthetic agents have been used for anesthesia during pregnancy, with no demonstrable differences in maternal or fetal outcome.
- The anesthetic management of the pregnant surgical patient should focus on the avoidance of hypoxemia, hypotension, acidosis, and hyperventilation.

REFERENCES


CHAPTER 17 Nonobstetric Surgery during Pregnancy


THE PROCESS OF LABOR AND DELIVERY

Labor, which is also called parturition, is the process by which sufficiently frequent and strong uterine contractions cause thinning (i.e., effacement) and dilation of the cervix, thereby permitting passage of the fetus from the uterus through the birth canal.

Onset of Labor
Timing
Fewer than 10% of pregnancies end on the expected date of delivery (EDD), although the majority of births occur within 7 days of the EDD. In the United States, approximately 10% of births occur preterm (before 37 weeks’ gestation), and approximately 3% to 7% of pregnancies remain undelivered at 42 weeks’ gestation (14 days after the EDD, known as post-term). These rates are lower for carefully dated pregnancies.

Mechanism
The cause of the onset of labor in women—either term or preterm—remains unknown. In other mammalian species, a decrease in serum progesterone concentration in association with an increase in estrogen concentration is followed by increases in prostaglandin production, oxytocin receptors, and myometrial gap junction formation. In sheep, the fetus apparently triggers parturition through a surge in fetal cortisol production. In women, progesterone concentrations do not decline before the onset of labor, and no surge in fetal cortisol secretion occurs. The laboring human uterus does manifest increases in prostaglandin production, oxytocin receptors, and myometrial gap junction formation.1,2 As more is learned, perhaps a unifying concept of the onset of mammalian labor will emerge. Preterm and postterm deliveries both constitute important obstetric problems; and when more is understood about the mechanism of the onset of labor, new approaches to preventing the preterm and postterm onset of parturition may evolve.

Stages of Labor
By convention, labor is divided into three stages. The first stage begins with the maternal perception of regular, painful uterine contractions and ends with the complete dilation of the cervix. Complete cervical dilation is the dilatation necessary to allow movement of the fetus from the uterus into the vagina. At term gestation, 10 cm approximates complete cervical dilatation. Preterm fetuses require less than 10 cm of cervical dilatation. The second stage of labor begins with the complete dilation of the cervix and ends with the birth of the infant. The third stage begins with the birth of the infant and ends with the delivery of the placenta. The first stage of labor can be considered the cervical stage, the second stage the pelvic stage (reflecting the descent of the fetus through the pelvis), and the third stage the placental stage. Some authorities identify a fourth stage of labor, corresponding to the first postpartum hour, during which postpartum hemorrhage is most likely to occur.
Components of Labor and Delivery

When the events that occur during labor and vaginal delivery are considered, it is helpful to think about the following three components of the process: (1) the powers (uterine contractions and, in the second stage, the addition of voluntary maternal expulsive efforts); (2) the passageway (the bony pelvis and the soft tissues contained therein); and (3) the passenger (the fetus). The interaction of these three components determines the success or failure of the process.

The Powers

The uterus, which is a smooth muscle organ, contracts throughout gestation with variable frequency. The parturient verifies the onset of labor when she perceives regular, uncom-

<table>
<thead>
<tr>
<th>TABLE 18.1</th>
<th>Features Determined by Clinical Pelvimetry as Related to Pelvic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal Features</td>
<td>Gynecoid</td>
</tr>
<tr>
<td>Promontory reached (diagonal conjugate ≤ 12 cm)</td>
<td>–</td>
</tr>
<tr>
<td>Sacrum flat/forward (versus curved)</td>
<td>–</td>
</tr>
<tr>
<td>Spines prominent (found by medical student)</td>
<td>–</td>
</tr>
<tr>
<td>Sacrosciatic notch narrow (≤ 2 fingerbreadths)</td>
<td>–</td>
</tr>
<tr>
<td>Subpubic arch narrow (acute angle)</td>
<td>–</td>
</tr>
</tbody>
</table>

+, Present; −, absent; ±, variable.


force of uterine contractions to hasten descent and shorten the second stage of labor.

The Passageway

The fetus must be of such size and conformation that there is no mechanical mismatch with the bony pelvis. At times, an ovarian or uterine tumor (e.g., leiomyoma), cervical cancer, or a vaginal septum may impede passage of the fetus through the birth canal, but these situations are unusual.

Four pelvic types have been described on the basis of the shape of the pelvic inlet (the plane bounded by the upper inner pubic symphysis, the linea terminalis of the iliac bones, and the sacral promontory) (Table 18.1). The type and size of the pelvis constitute important predictors of the success of vaginal delivery.

The most common pelvic type and the one theoretically best suited for childbirth is the gynecoid pelvis. The flexed fetal head presents a circle to the bony pelvis; a pelvis with gynecoid features best accommodates this circle. The inlet is round or oval, with the transverse diameter only slightly greater than the anteroposterior diameter. The pelvic sidewalls are straight and do not converge, the ischial spines are not prominent, the sacrum is hollow, and the subpubic arch is wide. The absence of prominent ischial spines is an important feature, because the distance between them—the transverse diameter of the mid-pelvis—is the narrowest pelvic dimension. The other pelvic types are less favorable for vaginal delivery.

Radiographic pelvimetry provides much more information regarding pelvic dimensions and features than can be obtained by clinical pelvimetry alone. However, it has only a limited place in clinical management because of its poor ability to predict a successful vaginal birth. In the absence of a history of pelvic fracture or musculoskeletal disease (e.g., a dwarfing condition), there are few circumstances in which the apparent pelvic anatomy precludes a trial of labor. A pelvis with smaller-than-average dimensions may be adequate for a particular fetus if the head is well-flexed, sufficient molding (i.e., overlapping of the unfused skull bones) has occurred, and the labor is strong; thus, radiographic pelvimetry does not always predict the presence or absence of cephalopelvic disproportion. Further, some risk is associated with radiographic pelvimetry. In addition to the potential for point
mutations in the maternal oocytes and fetal germ cells, there is a small but apparently real increase in the incidence of malignancy and leukemia in children who were exposed to diagnostic radiation in utero. Some obstetricians use radiographic pelvimetry in cases of fetal breech presentation to assess whether fetal presentation, position, and lie are appropriate for vaginal delivery. The hope is to save a parturient from a long, futile labor and a hazardous delivery. Computed tomography and magnetic resonance imaging are associated with less or no ionizing radiation exposure, respectively; these methods are also more accurate than conventional radiographic pelvimetry. However, these methods also have limited ability to predict a successful vaginal delivery.

**The Passenger**

Fetal size and the relationship of the fetus to the maternal pelvis affect labor progress. The lie of the fetus (the relationship of the long axis of the fetus to the long axis of the mother) can be transverse, oblique, or longitudinal. In the first two, vaginal delivery is impossible unless the fetus is very immature.

The presentation denotes that portion of the fetus overlying the pelvic inlet. The presentation may be cephalic, breech, or shoulder. Cephalic presentations are further subdivided into vertex, brow, or face presentations, according to the degree of flexion of the neck. In more than 95% of labors at term, the presentation is cephalic and the fetal head is well flexed (i.e., vertex presentation).

The position of the fetus denotes the relationship of a specific presenting fetal bony point to the maternal pelvis. In vertex presentations, that bony point is the occiput. During vaginal examination, palpation of the sagittal suture and fontanels permits determination of the fetal position. Positions of the occiput in early labor are listed in Box 18.1. Other markers for position are the sacrum for breech presentation, the mentum for face presentation, and the acromion for shoulder presentation. (See Chapter 34 for a discussion of nonvertex presentations.)

**The Mechanism of Labor**

The mechanism of labor refers to the changes in fetal conformation and position (cardinal movements; Box 18.2) that occur during descent through the birth canal during the late first stage and the second stage of labor.

The first cardinal movement is engagement, which denotes passage of the biparietal diameter (BPD) (i.e., the widest transverse diameter of the fetal head) through the plane of the pelvic inlet. A direct clinical determination of engagement cannot be made, but obstetricians assume that engagement has occurred if the leading bony point of the fetal head is palpable at the level of the ischial spines. This is true because the distance between the leading bony point and the BPD is typically less than the distance between the ischial spines and the plane of the pelvic inlet. If the leading bony point is at the level of the spines, the vertex is said to be at zero station. If the leading bony point is 1 cm above the level of the spines, the station is designated as –1. Similarly, +1, +2, and +3 indicate that the leading bony point is 1, 2, and 3 cm below the ischial spines, respectively (Fig. 18.1). At +5 station, delivery is imminent. Station refers to palpation of the leading bony point. Often marked edema of the scalp (i.e., caput succedaneum) occurs during labor. In such cases, the bony skull may be 2 to 3 cm higher than the scalp.

**BOX 18.1 Positions of the Occiput in Early Labor, Listed in Order of Decreasing Frequency**

- Left occiput transverse (LOT)
- Right occiput transverse (ROT)
- Left occiput anterior (LOA)
- Right occiput posterior (ROP)
- Right occiput anterior (ROA)
- Left occiput posterior (LOP)
- Occiput anterior (OA)
- Occiput posterior (OP)

**BOX 18.2 The Cardinal Movements of Labor**

- Engagement
- Descent
- Flexion
- Internal rotation
- Extension
- External rotation
- Expulsion

**Fig. 18.1 Stations of the fetal head. (Redrawn from Zlatnik FJ. Normal labor and delivery and its conduct. In Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, eds. Danforth’s Obstetrics and Gynecology, 7th ed. Philadelphia, PA: JB Lippincott; 1994:116.)**
The second cardinal movement is descent, although it is artificial to separate descent from the other movements because descent occurs throughout the birth process. The third cardinal movement is flexion. A very small fetus can negotiate the average maternal pelvis without increased flexion. However, under the usual circumstances at term, the force from above and resistance from below enhance flexion of the occiput (Fig. 18.2).

The fourth cardinal movement is internal rotation. At the level of the mid-pelvis, the fetus meets the narrowest pelvic dimension, which is the transverse diameter between the ischial spines. Because the BPD of the fetal head is slightly smaller than the suboccipitobregmatic diameter, in most labors the vertex negotiates the mid-pelvis with the sagittal suture in an anteroposterior direction. If this did not occur, a larger-than-necessary diameter would be forced to pass through the narrowest portion of the pelvis. Internal rotation describes the change in the position of the vertex from occiput transverse or oblique to anteroposterior. The occiput tends to rotate to the roomiest part of the pelvis; thus, in gynecoid pelvies, the fetus is delivered in an occiput anterior position.

The next cardinal movement is extension, which occurs as the fetal head delivers (Fig. 18.3). Subsequently, the occiput rotates to the side of the back (external rotation) as the shoulders pass through the mid-pelvis in an oblique diameter.

The anterior shoulder moves under the pubic symphysis. With gentle downward traction, it passes from the birth canal, and expulsion of the remainder of the fetus occurs.

This description recounts events in the typical gynecoid pelvis. Abnormalities of the pelvis affect the mechanism of labor in specific ways. In an anthropoid pelvis, the anteroposterior diameter of the pelvic inlet exceeds the transverse diameter. Often internal rotation to the occiput posterior position rather than the occiput anterior position occurs. Because the pelvis is narrow transversely, further descent of the vertex occurs with the occiput in the posterior position. Delivery occurs with the occiput in the posterior position, or rotation to the occiput anterior position occurs just before delivery. In cases of persistent occiput posterior position, delivery occurs by flexion rather than extension of the fetal head (see Fig. 18.3).

In platypelloid pelvies, internal rotation may not take place. The widest diameter is the transverse diameter, and descent of the vertex may occur with the occiput in the transverse position; rotation to the occiput anterior position occurs only at delivery.

Clinical Course

Admission

When a patient enters the labor and delivery unit, the first question that must be asked is “why?” Did she come because of regular, painful uterine contractions; decreased fetal activity; vaginal bleeding; ruptured membranes; or some other reason? If the tentative diagnosis is labor, is she at term? The time of the onset of labor and the presumed status of the membranes should be determined. Observation of the patient’s demeanor coupled with the assessment of cervical effacement and dilation will signal whether the patient is in early or advanced labor. Examination of the cervix is deferred in patients with vaginal bleeding in the second half of pregnancy, unless placenta previa has been ruled out by ultrasonography, to avoid exacerbation of bleeding. To prevent infection, cervical examination may also be deferred in patients with premature rupture of membranes and no labor.

The obstetrician also directs attention to the second patient: the fetus. Abdominal examination or ultrasonography is used to establish presentation and an estimate of fetal size. With most obstetric services, external electronic fetal heart rate (FHR) monitoring is used on admission to assess
CHAPTER 18 Obstetric Management of Labor and Vaginal Delivery

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not, to determine the significance of the delay and what the response should be. Parity is an important determinant of labor length. (Parity refers to previous pregnancies of at least 20 weeks' gestation. A pregnant woman who is gravida 2, para 1, is pregnant for the second time, and her first pregnancy resulted in delivery after 20 weeks' gestation.)

A generation of obstetricians is indebted to Emanuel Friedman, whose landmark studies of labor provide a framework for judging labor progress. Friedman’s approach was straightforward: He graphed cervical dilation on the $y$-axis and elapsed time on the $x$-axis for thousands of labors. He considered nulliparous and parous patients separately, and he determined the statistical limits of normal. The curve of cervical dilation over time is sigmoid shaped (Fig. 18.5).

Most authorities consider Friedman’s most important contribution to be his separation of the latent phase from the active phase of the first stage of labor. Many hours of regular, painful uterine contractions may take place with little appreciable change in the cervix. During this latent (or preparatory) phase, the cervix may efface and become softer. Quite abruptly, the active (or dilation) phase begins, and regular increases in cervical dilation are expected over time. The transition from the latent to the active phase of the first stage of labor does not occur at an arbitrary cervical dilation but rather is known—in retrospect—by change in slope of the cervical dilation curve. Peisner and Rosen evaluated the progress of labor for 1060 nulliparous women and 639 parous

Subsequent Care

The maternal vital signs and FHR are recorded periodically. In some obstetric services, continuous electronic FHR monitoring is used universally; with other services, it is monitored via intermittent auscultation. In low-risk patients, recording the FHR every 30 minutes in the first part of the first stage of labor, every 15 minutes in the latter part of the first stage, and every 5 minutes in the second stage is perfectly acceptable. During early labor, the patient may ambulate or assume any position of comfort on the labor bed or in a chair. During advanced labor, many women choose to lie down. Choices concerning analgesia or anesthesia are made according to the patient’s wishes. Fig. 18.4 shows a flow sheet (partogram) that may be useful for charting the course of labor.

During labor, those providing obstetric care must focus on the following two critical questions:
1. Is the fetus tolerating labor in a satisfactory fashion, or is there evidence of fetal compromise (see Chapter 8)?
2. Is the labor progress normal?

Labor Progress: The Labor Curve

One of the central tasks of those providing intrapartum care is to determine whether labor is progressing normally and, if}

fetal condition. The baseline rate and variability and the presence or absence of accelerations and decelerations are of interest.


nulliparous and parous patients separately, and he determined the statistical limits of normal. The curve of cervical dilation over time is sigmoid shaped (Fig. 18.5).
Cervical change over at least 4 hours rather than 2 hours is a
guideline. These curves reveal that cervical dilation is par-

The Friedman curve. (From Friedman EA. Patterns of labor

women. After excluding women with protracted or arrested
labor, these researchers noted that 60% of the women had
reached the latent-active phase transition by 4 cm of cervical
dilation and 89% did so by 5 cm.

A nulliparous woman may labor for 20 hours without
achieving appreciable cervical dilation; 14 hours is the limit
of the latent phase in the parous woman. Difficulty in assign-
ing length to the latent phase lies not with its end (determined
from the change in slope of the cervical dilation curve) but
rather with its beginning. The onset of labor is self-reported
by the parturient. The uterus contracts throughout gestation,
and the level of prelabor uterine activity and its perception
are variable. Often both the patient and the physician are
uncertain as to exactly when labor started.

According to Friedman, in the active phase of the first
stage of labor, a nulliparous woman’s cervix should dilate at a
rate of at least 1.2 cm per hour, and a parous woman’s cervix
should dilate at least 1.5 cm per hour. (The slopes of the dila-
tion curves in Fig. 18.5 represent the lower limits of normal.)
If a woman’s cervix fails to dilate at the appropriate rate
during the active phase of labor, she is said to have primary
dysfunctional labor. Graphically, her cervical dilation “falls
off the curve.” If cervical dilation ceases during a 2-hour
period in the active phase of labor, secondary arrest of dila-
tion has occurred.

More recent studies have reported slower rates of cervical
dilation and engendered an ongoing transition toward the
use of the “contemporary labor curve.” These newer data
have been adopted into new labor management practice
guidelines. These curves reveal that cervical dilation is par-
cularly slow prior to 6 cm and that the deceleration phase
described by Friedman is usually absent. Therefore, 6 cm
rather than 4 cm of cervical dilation more accurately reflects
the start of the active phase in contemporary labor curves—
and should be used to define the active phase for labor man-
agement. Furthermore, in the active phase, absence of
cervical change over at least 4 hours rather than 2 hours is a

A nulliparous woman may have a slower cumulative rate of cervical dilation
overall. However, before 6 cm of dilation, the times required
to dilate 1 cm are similar between nulliparous and parous
women. While these “contemporary labor curves” have been
emphasized in new practice guidelines, it is important to note
that there is an ongoing need for prospective evaluation of
these new criteria.

Abnormalities of the latent phase and active phase differ in
associated factors, apparent causes, and significance. A pro-
longed latent phase is more likely if labor begins “before the
cervix is ready.” Just as there is a wide range of prelabor
uterine activity, so too is there a wide range of cervical soft-
ess, effacement, and dilation at the start of labor. In some
women, appreciable cervical softening, effacement, and dila-
tion take place in late pregnancy; thus, when clinical labor
begins, the cervix may already be 3 to 4 cm dilated and com-
pletely effaced. Alternatively, in other women, there is no
cervical effacement or dilation at the start of labor. Given
these differences, it is not surprising that varying amounts of
uterine contractile work are needed to cause dilation of the
cervix. The most common factor associated with a prolonged
latent phase is an “unripe” cervix at the start of labor. Some
women with a prolonged latent phase are not in true labor at
all but are in “false labor”; this diagnosis is made in retrospec-
After hours of regular, painful contractions, uterine activity
may cease without the occurrence of appreciable cervical
dilation. Several hours or days later, the patient reappears in
true labor. During the latent phase of labor, it is not known
with certainty whether a woman is in true or false labor.

TABLE 18.2 Rate of Spontaneous Cervical Dilation by Parity

<table>
<thead>
<tr>
<th>Cervical Dilation</th>
<th>Nulliparous Median Time (h) (95th Percentile)</th>
<th>Parous Median Time (h) (95th Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 to 5 cm</td>
<td>1.3 (6.4)</td>
<td>1.4 (7.1)</td>
</tr>
<tr>
<td>5 to 6 cm</td>
<td>0.8 (3.2)</td>
<td>0.8 (3.4)</td>
</tr>
<tr>
<td>6 to 7 cm</td>
<td>0.6 (2.2)</td>
<td>0.5 (1.8)</td>
</tr>
<tr>
<td>7 to 8 cm</td>
<td>0.5 (1.6)</td>
<td>0.4 (1.2)</td>
</tr>
<tr>
<td>8 to 9 cm</td>
<td>0.5 (1.4)</td>
<td>0.3 (1.0)</td>
</tr>
<tr>
<td>9 to 10 cm</td>
<td>0.5 (1.8)</td>
<td>0.3 (0.9)</td>
</tr>
<tr>
<td><strong>Second Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 cm to delivery (epidural)</td>
<td>1.1 (3.6)</td>
<td>0.4 (2.0)</td>
</tr>
<tr>
<td>10 cm to delivery (no epidural)</td>
<td>0.6 (2.8)</td>
<td>0.2 (1.3)</td>
</tr>
</tbody>
</table>

Modified from Zhang J, Landy HJ, Branch DW, et al.; for the
Consortium on Safe Labor. Contemporary patterns of spontaneous
Recent studies refute the dictum that a prolonged latent phase alone is not associated with fetal compromise or cephalopelvic disproportion. An increased risk for cesarean delivery, chorioamnionitis, endometritis, excessive blood loss, depressed Apgar scores, and need for neonatal resuscitation have all been associated with a prolonged latent phase. An ongoing increase in the use of labor induction may be a mediating factor. Primary dysfunctional labor and arrest of dilation during the active phase may also indicate cephalopelvic disproportion. Friedman's original work suggested that an arrest of dilation during the active phase was associated with the need for cesarean delivery nearly half of the time. Later studies suggest a lower percentage, but it is clear that women who experience active-phase arrest of dilation are more likely to require cesarean delivery than women with normal labor progress during the active phase. Friedman's analysis suggested that active-phase abnormalities pose a threat to the fetus, especially if they are combined with operative vaginal delivery. A later study of women who delivered in the modern era of electronic FHR monitoring and decreased frequency of mid-forceps deliveries suggested that arrest disorders by themselves do not have adverse perinatal consequences.

In summary, the contemporary view is that delays in the latent phase of the first stage of labor may be associated with fetopelvic disproportion or the need for cesarean delivery, but this requires confirmation. Delays in the active phase predict fetopelvic disproportion, although not with precision. Given current obstetric practice and fetal monitoring techniques, it is unclear whether first-stage labor abnormalities are intrinsically associated with neonatal depression at delivery.

**Amniotomy**

The intact amnion serves as the vessel that contains the amniotic fluid and helps protect the uterine contents from the microbial flora of the vagina. The amniotic fluid provides mechanical protection for the fetus and umbilical cord and allows growth and movement.

In the absence of intervention, the membranes generally rupture at the onset of labor or near full cervical dilation. If the membranes are intact, should they be artificially ruptured during the course of labor? If so, when? Because there is concern about infection once the membranes are ruptured, the performance of an amniotomy commits the mother to delivery. The traditional thought was that amniotomy should not be done early in the labor course. However, newer data suggest early amniotomy (i.e., amniotomy at cervical dilation less than 4 cm or soon after cervical ripening with Foley balloon) decreases the time to complete dilation and vaginal delivery, especially in nulliparous women, without an increase in adverse perinatal outcomes.

Advantages of amniotomy during the first stage of labor are that (1) the ruptured membranes permit the placement of a fetal electrocardiographic electrode, which can provide more consistent information than external FHR monitoring; (2) the amniotic fluid can be inspected for the presence or absence of meconium; and (3) amniotomy shortens time to delivery. Disadvantages of amniotomy during the first stage of labor are that it may result in increased scalp edema (i.e., caput succedaneum, which has no clinical significance) and that there may be a greater likelihood of variable decelerations of the FHR. If there is a nonvertex presentation or the vertex is high in the pelvis and not well applied to the cervix, amniotomy is deferred to decrease the risk for prolapse of the umbilical cord.

**Second Stage of Labor**

When the cervix has been completely retracted to form the lower uterine segment and is therefore not palpable on vaginal examination, full or complete dilation has been achieved, and the second stage of labor begins. Strong uterine contractions coupled with voluntary expulsive efforts by the parturient cause the fetal presenting part to descend through the pelvis, resulting in delivery. At complete cervical dilation, there is frequently an increase in bloody show, the parturient may vomit, and, in the absence of anesthesia, she may complain that she needs to defecate. This sensation of needing to “bear down” encourages strong Valsalva maneuvers during uterine contractions. The effect of this sensation on the efficiency of “pushing” efforts during the second stage is reflected by the suggestion that the duration of the second stage of labor varies not only according to parity but also with the presence or absence of epidural analgesia. According to current guidelines, a second stage longer than 3 hours may be considered prolonged for a nulliparous woman without epidural analgesia, but 4 hours are granted if the patient has epidural analgesia. For the parous woman, the time limits are 2 and 3 hours, respectively.

The contemporary obstetrician, although less concerned about the elapsed time during the second stage of labor than were earlier obstetricians, continues to balance the risks of prematurely performing a cesarean delivery with the risks of adverse outcomes associated with a prolonged second stage. A generation ago, the teaching was that a long second stage meant trouble. It often did, for at least two reasons. First, if cephalopelvic disproportion existed, the second stage was prolonged; this often resulted in a difficult operative vaginal delivery and serious fetal trauma. Second, umbilical cord compression may become severe with descent of the presenting part during the second stage of labor. If FHR monitoring was not performed conscientiously, considerable fetal/neonatal compromise could occur in association with delayed delivery. Umbilical cord arterial blood pH varies inversely with the length of the second stage of labor. While multiple studies have shown that a second-stage duration longer than recommended is associated with an increase in maternal obstetric trauma, postpartum hemorrhage, infection, birth depression, and admission to the neonatal intensive care unit in both nulliparous and parous women, the contemporary view is that the second stage of labor does not need to be terminated at any arbitrary time provided that progress in descent continues and the FHR pattern is reassuring. Thus, given recent guidelines, a longer second-stage duration is recommended to decrease the cesarean delivery rate.
If the parturient is allowed to choose her own position during labor and delivery, she does not need to stay in one place. Without instruction from birth attendants, the parturient frequently chooses to walk or sit in a chair during early labor. Late in the first stage, however, she often returns to the labor bed. During the second stage of labor, some women assume the squatting position, whereas others, with their legs supported by the nurse and the father of the baby, assume a semi-sitting position. The goal is to achieve a position in which the parturient’s bearing-down efforts are most effective. The patient should avoid the supine position, which results in aortocaval compression. Aortocaval compression seems to be less severe with the patient in the semi-sitting position, and it is avoided altogether with the patient in the lateral position. Indeed, it is perfectly acceptable for the patient to push and deliver while remaining in the left lateral position. A vaginal examination during a contraction may provide information as to which position is best for a particular individual.

In the past, as the fetal head distends the perineum shortly before delivery, an episiotomy was often performed. An episiotomy is an incision extending either directly posteriorly from 6 o’clock (midline) or in a 45-degree angle to either side (mediolateral). The former causes less discomfort, is more anatomic, and is easier to repair than the latter. The mediolateral episiotomy’s advantage is that extension through the anal sphincter and rectal mucosa is less likely to occur, but its major disadvantage is that it may cause more bleeding or severe postpartum pain. (If the patient has an epidural catheter, the anesthesia provider may give additional epidural local anesthetic or opioid to provide postpartum analgesia.)

The role of episiotomy in contemporary obstetrics is limited. In the past, episiotomy was advocated not only to shorten labor but also to protect the woman against the subsequent development of uterine prolapse, cystocele, and rectocele. An episiotomy hastens delivery, but only by a few minutes. Tears involving the anal sphincter (third degree) and rectal mucosa (fourth degree) are more common after midline episiotomy than if episiotomy is not performed; in the absence of an episiotomy, however, anterior periurethral lacerations are common. Although the latter rarely cause immediate problems, scientifically valid data on long-term outcome are lacking. Given the recognized association between midline episiotomies and third- and fourth-degree tears, the fact that these tears may be associated with long-term morbidity, and the failure to observe any benefits to routine episiotomy, more restrictive use of this incision is now recommended. For example, an episiotomy may be indicated in some instances of operative vaginal delivery of a large infant, with suspected fetal compromise, or to manage shoulder dystocia.

**Third Stage of Labor**

The third stage of labor begins with the delivery of the infant and ends with the delivery of the placenta. The placenta typically separates from the uterine wall within a few contractions after delivery of the infant, and expulsion follows a few minutes later. Signs of placental separation are listed in **Box 18.3**.

When the placenta has separated from the uterine wall, gentle traction on the umbilical cord, coupled with suprapubic pressure to elevate the uterus, serves to deliver the placenta and membranes. In the absence of excessive bleeding, the obstetrician waits for the signs of placental separation before attempting to deliver it. If traction is exerted on the umbilical cord before the placenta has separated, problems result. The least serious—but nonetheless embarrassing—complication involves separating the umbilical cord from the placenta. This tear in the cord leads to bleeding, which is of no concern because the blood is fetoplacental blood that would be discarded; however, the obstetrician’s reputation for gentleness suffers because the detached segment of umbilical cord is held with the placenta remaining *in situ*. A much more serious problem is uterine inversion, which can occur in a case of fundal implantation of the placenta. If the placenta has not separated and the umbilical cord does not break, excessive traction turns the uterus inside out, resulting in severe hemorrhage (see Chapter 37).

If the placenta does not separate in a timely fashion after delivery (prolonged third stage) or if significant bleeding occurs, manual removal of the placenta is indicated. Although some obstetricians advocate performing this procedure with sedation or systemic analgesia, neuraxial or general anesthesia is ideal. The obstetrician’s hand is then passed into the uterine cavity, and the edge of the placenta is identified. The hand is used as a trowel to separate the placenta from the uterine wall. If the obstetrician cannot easily develop a plane between the placenta and the uterine wall, the diagnosis of *placenta accreta* should be considered. Placenta accreta typically results in severe hemorrhage, which frequently mandates emergency hysterectomy (see Chapter 37). Classically, a duration of 30 minutes has been used to define a prolonged third stage; however, recent data suggest that increased postpartum hemorrhage may occur when the third stage of labor duration exceeds 20 minutes. However, in the absence of significant bleeding, more time may be allowed for placental separation, particularly at earlier gestational ages when it may be difficult to access the uterus.

After delivery, and either before or after the placenta has been removed, uterotonic agents are administered to reduce bleeding. **Oxytocin** is given intravenously in a dilute solution (e.g., starting at an infusion rate of 20 to 80 units/h), or 10 units are given intramuscularly. Bolus intravenous injection of oxytocin can cause hypotension and should be avoided (see Chapter 37).
If the uterus does not respond to oxytocin, other agents can be tried. Methylergonovine (Methergine, 0.2 mg every 2 to 4 hours) has long been available for intramuscular administration. It contracts vascular smooth muscle and may cause hypertension. Methylergonovine should not be given intravenously except in cases of severe, life-threatening hemorrhage. In such cases, the physician should give the drug slowly and carefully monitor the maternal blood pressure.

15-Methylprostaglandin F\textsubscript{2α} (carboprost, Hemabate) is a newer ecbolic agent. Given intramuscularly, 0.25 mg (every 15 to 90 minutes, with a maximum of 8 doses) of 15-methylprostaglandin F\textsubscript{2α} has been demonstrated to be an effective uteronic agent when other drugs have failed.\textsuperscript{7} It can also cause hypertension, but the hypertension is typically not as severe as that associated with administration of methylergonovine. More important, 15-methylprostaglandin F\textsubscript{2α} may cause bronchospasm and is relatively contraindicated in patients with asthma.

Most obstetricians in the United States do not use ecbolic agents until the placenta has been delivered, whereas European obstetricians typically administer an ecbolic agent immediately after delivery of the infant or even with delivery of the anterior shoulder. The timing probably does not matter.\textsuperscript{26} Immediately after the delivery of the placenta, if the obstetrician suspects an abnormality, the hand can be passed into the uterine cavity. Within several minutes, however, the cervix and birth canal contract. Subsequent uterine exploration typically requires the administration of anesthesia.

Fourth Stage of Labor

Many obstetricians consider the first 60 minutes after delivery of the placenta to be the fourth stage of labor. Labor is completed, but this designation emphasizes that the patient must be watched carefully for bleeding. More than 90% of cases of postpartum hemorrhage result from uterine atony. If uterine atony is not identified during the first hour after delivery, it is unlikely to occur subsequently. The patient should be evaluated frequently to be certain that excessive bleeding is not occurring and that the uterus remains contracted. Considerable blood loss can occur in the presence of “normal” vital signs; a modest increment in additional blood loss can then be followed by profound shock. Uterine relaxation and excessive bleeding after delivery are initially treated with uterine massage and further ecbolic drug administration (see Chapter 37). Management options for persistent hemorrhage include uterine tamponade, surgery, and vascular embolization.

LABOR PROGRESS: FIVE MANAGEMENT QUESTIONS

The purpose of this section is to provide a step-by-step approach to the management of the laboring woman by serially posing and answering the following five critical questions:

1. Is the patient in labor? If the answer is “Yes,” certain factors must be considered before proceeding. Is the patient at term? If she is preterm, is she a candidate for antenatal corticosteroids and tocolytic therapy? If the patient is at term, are there medical or obstetric conditions that affect management? Abnormal fetal size or presentation, twin gestation, preeclampsia, and vaginal bleeding are obstetric factors that may alter management of labor from the outset. If a singleton vertex presentation is identified in a patient without complications, the physician proceeds to the following question.

2. Is the labor progress abnormal? If progress is normal according to the labor curve, no problem exists. If progress is abnormal, the physician proceeds to the following question.

3. Is the abnormality in the active phase? An apparent prolongation of the latent phase may represent false labor. In the absence of some other indication for effecting delivery, the obstetrician should not administer oxytocin or perform amniotomy, which would involve committing the patient to labor. However, if the decision is to proceed with delivery, augmentation with oxytocin or early amniotomy can be considered to expedite entry into the active phase of labor.\textsuperscript{7} Long latent phases do increase patient anxiety and fatigue; reassurance is essential. At this point, ambulation and sedation are alternatives that may be selected on an individual basis, with input from the woman. If false labor has occurred, contractions will cease over time, or the patient will enter the active phase. Specifically, a diagnosis of failed induction in the latent phase should require at least 12 to 24 hours after rupture of membranes. If primary dysfunctional labor is the diagnosis or if a secondary arrest of dilation has occurred during the active phase (6 cm cervical dilation), the physician is faced with an abnormality that may indicate cephalopelvic disproportion, a mechanical obstruction to delivery. The next question can then be asked.

4. Is the fetus tolerating labor? Although the FHR pattern should be monitored from admission until delivery, a delay in the active phase of labor calls for a reassessment. If the FHR pattern is nonreassuring, the physician should effect delivery. If not, the next question is asked.

5. Does the pelvis appear to be adequate for the infant? An active-phase delay indicates either insufficient uterine contractile effort to dilate the cervix or a mechanical obstruction to delivery. Obviously this is a critical issue, because the therapeutic alternatives are very different. If the pelvis is clinically small and/or the fetus is large and the labor seems strong (e.g., intense uterine contractions occurring every 2 minutes), the choice is cesarean delivery. If the fetopelvic relationship is favorable for vaginal delivery and the contractions are infrequent, the choice is intravenous oxytocin, amniotomy, or both. In the vast majority of cases, however, the obstetrician is uncertain as to whether oxytocin augmentation will result in successful vaginal delivery or whether cesarean delivery will ultimately be required despite oxytocin augmentation. Given the uncertainty about whether mechanical obstruction or insufficient uterine activity is the problem, the proper choice typically is to administer oxytocin to correct the
latter, a decision that recognizes that, if the former is present, the attempt will ultimately fail. Data support longer periods of oxytocin augmentation for nonprogressive active-phase labor (at least 4 to 6 hours) provided the FHR pattern is reassuring.\textsuperscript{29}

The benefit of intravenous oxytocin administration for labor arrest during the active phase of the first stage of labor is that the majority of the time it succeeds and cesarean delivery is avoided.\textsuperscript{12} The risks associated with oxytocin stimulation are both maternal and fetal. If mechanical obstruction to delivery exists, greater uterine activity predisposes the patient to uterine rupture, which is one of the gravest obstetric complications. Multiparity and a scarred uterus are additional predisposing factors to uterine rupture. Oxytocin has an antidiuretic effect, and in the past there were reports of water intoxication with seizures and even coma and death as iatrogenic complications of its use. In these cases, oxytocin was administered over many hours (often days) in electrolyte-free solutions, with little attention paid to maternal urine output; infusion of electrolyte-containing solutions and close attention to the parturient’s fluid balance should make this a theoretical rather than a practical concern. However, \textit{uterine tachysystole with FHR decelerations} is a real concern when infusing oxytocin. The force generated during uterine contractions interrupts blood flow through the intervillus space because placental perfusion occurs during periods of uterine relaxation, and uterine contractions can be regarded as episodes of “fetal breath-holding.” If the contractions are occurring very frequently (e.g., at intervals less than 2 minutes apart, defined as uterine tachysystole), there may be insufficient time between contractions for placental gas exchange, the fetus may become hypoxic, and fetal compromise may result. Continuous observation permits a timely diagnosis of uterine tachysystole. Decreasing the infusion rate, temporarily stopping the infusion, or, rarely, giving terbutaline promptly corrects the problem.

Currently, in the United States, oxytocin for inducing or augmenting labor is given intravenously, typically by infusion pump. Continuous electronic FHR monitoring is used, and a physician or nurse constantly monitors the FHR pattern. Although the foregoing procedures are quite uniform from service to service, the selected doses of oxytocin are not.

The variability in protocols for oxytocin induction or augmentation of labor reflects confusion in the literature.\textsuperscript{30–34} The goal is to increase uterine activity efficiently to dilate the cervix without causing fetal compromise as a result of uterine tachysystole. However, the best way to do this is unclear. Recommended starting doses of oxytocin vary from 1 to 6 mU/ min, and additional drug is administered until a satisfactory labor pattern is achieved. Dosage increments typically vary from 1 to 6 mU at intervals of 15 to 40 minutes. High-dose oxytocin regimens involve the use of higher starting doses and incremental doses of 4 mU/min or greater. A systematic review of available trials suggests that the use of a higher dose regimen for labor augmentation is associated with shortened labor and a decrease in the incidence of cesarean delivery.\textsuperscript{25,36}

### The Active Management of Labor

\textbf{Dystocia,} which is also called abnormal labor progress, both directly and indirectly (through subsequent repeat cesarean deliveries) is the single most important reason for the high rate of cesarean delivery in the United States. Concern for the high cesarean delivery rate has created interest in the remarkable results achieved in the 1980s with the use of active management of labor at the National Maternity Hospital in Dublin, Ireland.\textsuperscript{30,37} Components of the active management of labor include (1) a rigorous definition of labor; (2) early amniotomy; (3) constant nursing attendance; (4) the demand for continued progress in cervical dilation (1 cm or more per hour); (5) vigorous oxytocin stimulation for lack of progress; and (6) a “guarantee” that the parturient’s stay in the labor unit will last no longer than 12 hours. In Dublin, these practices were associated with a cesarean birth rate of less than 5%; however, the rate has been higher in more recent years.

The introduction of the active management of labor in other obstetric services has been associated with lower cesarean delivery rates than those among historic controls. One randomized trial indicated that active management shortened labor, reduced the incidence of cesarean delivery for dystocia, and resulted in fewer maternal infectious complications without increasing maternal or neonatal morbidity.\textsuperscript{38} However, data from other clinical trials and a Cochrane review suggest that active labor management is associated with little or no decrease in the cesarean delivery rate.\textsuperscript{39,40} Nonetheless, in order to decrease the rate of cesarean delivery, recent efforts have been made to specifically create new guidelines for the active management of labor.\textsuperscript{9}

### SPECIAL SITUATIONS

#### Premature Rupture of Membranes

\textit{Premature rupture of the membranes} (PROM) is defined as a rupture of the fetal membranes (i.e., the chorioamnion) before the onset of labor. It may occur preterm (before 37 weeks’ gestation) or at term.

#### Preterm Premature Rupture of Membranes

The most significant complication of preterm PROM is preterm birth.\textsuperscript{41} Although the length of the \textit{latent period} (the interval between membrane rupture and the onset of labor) is inversely related to gestational age, only one in five women with preterm PROM have latent periods exceeding 1 week. Indeed, PROM is the precipitating factor in nearly one-third of preterm deliveries. Other risks for preterm PROM include chorioamnionitis and prolapse of the umbilical cord. If membrane rupture occurs during the second trimester and if the fetus experiences a long exposure to oligohydramnios, there is risk for pulmonary hypoplasia, perinatal death, neonatal sepsis, and orthopedic deformities.

Current management of preterm PROM is conservative. After the diagnosis is confirmed by inspection and nitrazine and fern testing (or rarely by ultrasound-guided instillation of dye into the amniotic fluid and observation of its passage
vaginally), electronic FHR monitoring is used to identify variable FHR decelerations that signal umbilical cord compression. The mother is also evaluated for fever and uterine tenderness, which may indicate chorioamnionitis. If these are absent, the clinician awaits the onset of labor or the subsequent development of infection. The adjunctive use of maternally administered corticosteroids to enhance fetal pulmonary maturaity and antibiotics to prevent chorioamnionitis and delay the onset of labor is indicated. Current evidence does not support the use of tocolytic therapy to prolong pregnancy. Delivery is recommended routinely at 34 weeks (a point beyond which the rate of severe neonatal morbidity and mortality is very low).  

**Term Premature Rupture of Membranes**  
Approximately 8% of term pregnancies are complicated by PROM; the natural history is summarized in Table 18.3. Although chorioamnionitis is more likely to occur preterm than at term with PROM, no clear relationship exists between the length of the latent period and chorioamnionitis in the preterm patient. By contrast, chorioamnionitis at term is more likely if the latent period exceeds 24 hours. The relationship between prolonged latency and chorioamnionitis accounts for the usual practice in the United States of oxytocin induction of labor for a woman with PROM at term if she is not already in active labor. Expectant management is only acceptable for women who decline induction with adequate counseling regarding the risks associated with prolonged rupture of membranes.

### Chorioamnionitis

If chorioamnionitis develops, the uterus must be emptied. Intrapartum antibiotic administration improves the outcome for both the mother and infant. Ampicillin and gentamicin are often chosen to combat group B streptococcus and *Escherichia coli*, which are important neonatal pathogens. Because no relationship exists between the number of hours that chorioamnionitis has been present and perinatal outcome, chorioamnionitis alone is not an indication for cesarean delivery. Antibiotics, oxytocin, and close observation of the mother and fetus are indicated.

### Induction of Labor

**Induction of labor** can be defined as a surgical or medical intervention that leads to uterine contractions that progressively dilate the cervix. Because elective and indicated inductions differ in terms of eligibility criteria and the methods used, they are considered separately.

#### Elective Induction

The rationale for elective induction of labor is convenience, both for the patient and for the physician. Because it is elective, the delivery should be easily accomplished and the risks should approach zero. Factors associated with the success of elective induction of labor include (1) a parous patient; (2) a singleton vertex presentation; (3) a certain gestation of at least 39 weeks; (4) a favorable cervix; and (5) no contraindications to labor and vaginal delivery. The Bishop score (Table 18.4) helps quantitate the favorability of the cervix; the higher the score, the shorter the labor and the less likely induction will fail. Bishop observed that a score of 9 or greater was not associated with failure. With the modified Bishop score, cervical length replaces cervical effacement. Friedman et al. determined that the Bishop score primarily predicts the latent phase of labor. This finding is not surprising, because a high Bishop score indicates that the cervix is ready to dilate with uterine contractions (i.e., the cervix will soon enter the active phase). By contrast, a low score suggests that many hours of uterine contractions may be needed to soften and efface the cervix. When the components of the Bishop score are considered separately in terms of their effects on the latent phase, dilation is most critical. Effacement (or length), station, and consistency are each half as important, and position has little effect.

With a favorable cervix, elective induction is begun by performance of an amniotomy with or without concomitant oxytocin administration, which some obstetricians reserve for the patient who is not experiencing uterine contractions 4 to 6 hours after amniotomy. Amniotomy is typically performed early in the morning and is followed by delivery in the afternoon. Elective inductions have been criticized by some

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**TABLE 18.3** Natural History of Premature Rupture of the Membranes at Term

<table>
<thead>
<tr>
<th>Element</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>10</td>
</tr>
<tr>
<td>Spontaneous labor within 24 hours</td>
<td>90</td>
</tr>
<tr>
<td>If cervix is unfavorable and no labor at 6 hours, percent laboring by 24 hours</td>
<td>60</td>
</tr>
</tbody>
</table>

**TABLE 18.4** The Bishop Cervix Score

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilation (cm)</td>
<td>0</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0–30</td>
</tr>
<tr>
<td>Latent period</td>
<td>1–2</td>
</tr>
<tr>
<td>Consistency</td>
<td>Firm</td>
</tr>
<tr>
<td>Position</td>
<td>Posterior</td>
</tr>
</tbody>
</table>

*Modified Bishop Score: Effacement is replaced by cervical length: 0 points for > 3 cm, 1 for > 2 cm, 2 for > 1 cm, 3 for > 0 cm. From Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol. 1964;24:266–268.*

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physicians because of the possibilities of induction failure and iatrogenic prematurity. However, a recent British study noted no increase in the risk for cesarean delivery or adverse perinatal outcomes in women older than 35 years of age undergoing elective induction of labor at 39 weeks’ gestation. A large multicenter randomized trial recently found that elective induction of labor in low-risk nulliparous women at 39 weeks’ gestation did not result in a greater frequency of adverse perinatal outcomes than expectant management, and it resulted in a lower frequency of cesarean delivery.

**Indicated Induction**

Indicated induction of labor is performed when delivery is indicated for maternal or fetal reasons and both the mother and fetus can tolerate labor and vaginal delivery. An indicated induction of labor often arises in the setting of a medical or obstetric complication such as diabetes mellitus, preeclampsia, fetal growth restriction (also known as intrauterine growth restriction), or the postterm pregnancy. By definition, the physician is dealing with a complicated pregnancy when performing an indicated induction of labor; therefore, close maternal and fetal monitoring is indicated. When considering the critical question whether induction should be undertaken, the obstetrician must weigh the perinatal risks of continued intrauterine versus extruterine existence and must also consider the potential adverse maternal consequences of induction, including a higher risk for infection and/or cesarean delivery.

If the Bishop score is favorable, amniotomy or oxytocin administration suffices as a means of inducing labor. Often, however, the cervix is not favorable, and induction is typically initiated with application of cervical ripening agents (prostaglandin E analogues) or use of a Foley catheter bulb to mechanically dilate the cervix. Both osmotic cervical dilators and pharmacologic techniques are effective in improving the Bishop score. Alternatively, a Foley catheter bulb may also be used for mechanical dilation. Typically these adjunctive measures are instituted the evening before the planned induction. A common pharmacologic method involves the topical application of prostaglandin E2, either in the vagina or in the cervical canal. Prostaglandin E2 has a local effect in the initiation of softening, effacement, and dilation of the cervix, and it also has an oxytocin-like effect on the myometrium. Women treated with prostaglandin E2 commonly experience contractions and labor before amniotomy or oxytocin administration. The same is true for misoprostol, a prostaglandin E1 analogue that is now widely used for cervical ripening and labor induction. Prostaglandins should not be administered to induce labor in women with a prior cesarean delivery, because their use is associated with an increased risk for uterine rupture. Overall, mechanical dilation with a Foley catheter bulb (16 to 20 French, filled 30 to 60 mL saline) or prostaglandin E analogues are considered equally efficacious methods of cervical ripening.

**Operative Vaginal Delivery**

Cesarean delivery has become a too frequent solution to labor room problems. This safe operation is certainly preferable to the continuation of labor in the setting of genuine fetal compromise or to the performance of a difficult and traumatic vaginal delivery. Unfortunately, however, more traditional obstetric interventions (e.g., labor, additional labor, operative vaginal delivery) are often bypassed in favor of cesarean delivery, perhaps more for medicolegal than for medical concerns. The appropriate use of operative vaginal delivery techniques requires an accurate assessment of the situation, technical skills, and an honest and humble physician.

**Vertex Presentation**

Carefully selected and performed forceps or vacuum-assisted delivery shortens the second stage of labor in cases of nonreassuring fetal status, maternal illness or exhaustion, and/or undue prolongation of labor with little or no progress (Box 18.4). The station of the presenting vertex is critical to the safety of the procedure for mother and infant. The current American College of Obstetricians and Gynecologists classification permits a more rational approach to operative vaginal delivery than was available previously.

For any operative vaginal delivery, adequate anesthesia is required. Outlet operative deliveries are perfectly safe for both mother and fetus. The low station effectively rules out cephalopelvic disproportion, and little traction is required. Outlet operative deliveries shorten the second stage by only a few minutes. Sustained fetal bradycardia is a common indication for outlet operative delivery. An experienced physician may safely perform low-station operative deliveries in cases of fetal compromise or maternal illness or exhaustion. The higher the head, the harder the pull. Rotations increase the likelihood of vaginal tears.

Mid-pelvic deliveries reflect a more complicated problem. If the station is overestimated, the vertex may be barely engaged. The hollow of the sacrum is incompletely filled. Midpelvic deliveries should be regarded as “trials.” The obstetrician must avoid excessive traction and must be willing to abandon the attempt in favor of cesarean delivery if vaginal delivery does not proceed easily.

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**BOX 18.4 Classification of Forceps Delivery**

<table>
<thead>
<tr>
<th>Outlet Forceps Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scalp is visible.</td>
</tr>
<tr>
<td>• Skull has reached the pelvic floor, and head is on the perineum.</td>
</tr>
<tr>
<td>• Sagittal suture is in the anteroposterior diameter or within 45 degrees (e.g., occiput anterior, left occiput anterior, right occiput posterior).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Forceps Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Station is +2 or greater.</td>
</tr>
<tr>
<td>• Hollow of the sacrum is filled.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mid-Forceps Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vertex is engaged, but the station is 0 or +1.</td>
</tr>
</tbody>
</table>
Although operative vaginal delivery was traditionally accomplished with obstetric forceps, there has been interest in the soft plastic cup vacuum extractor.\textsuperscript{66–67} Neither is uniformly better. The vacuum extractor is easier to apply, especially if the obstetrician is uncertain of the position of the occiput, and most likely it is associated with less maternal trauma. Forceps—but not the vacuum extractor—permit the correction of deflection or slight abnormalities of position that may impede progress. The vacuum extractor is more likely to slip off; whether this feature enhances safety is unknown. Neonatal results are comparable, but retinal hemorrhages, which are of unclear significance, are more likely with vacuum extraction. The obstetrician should be trained in both techniques and should individualize their use. A recent study observed that mandating resident competency in use of forceps before beginning training with vacuum extraction was associated with greater use of epidural analgesia, more forceps deliveries, fewer cases of postpartum hemorrhage, and no increase in perineal injury or neonatal morbidity.\textsuperscript{68}

Persistent occiput-posterior positions often occur in anthropoid and android pelvises. In modern obstetrics, the infants in most of these cases are delivered with the occiput posterior. Extension of the episiotomy is a common complication in this circumstance, which argues for the consideration of a mediolateral episiotomy.

Deep transverse arrests of the occiput were traditionally managed with rotation and delivery with Kielland’s forceps. Current trainees typically have little experience with this instrument, and they are more likely to select the vacuum extractor in this circumstance.

### Nonvertex Presentations

A persistent brow presentation or a transverse lie mandates cesarean delivery. Most face presentations and selected breech presentations can be safely delivered vaginally.\textsuperscript{69} However, in response to a large international multicenter trial in which planned vaginal delivery was associated with worse perinatal outcomes than planned cesarean delivery,\textsuperscript{70} the American College of Obstetricians and Gynecologists now recommends cesarean delivery for the persistent singleton breech presentation at term as the preferred mode of delivery for most physicians, particularly in light of diminishing experience in vaginal breech deliveries.\textsuperscript{71}

### Fetal Death

If fetal death has occurred, the obstetrician no longer has two patients, making maternal safety the only concern. Although placenta previa or absolute cephalopelvic disproportion may indicate cesarean delivery, the obstetrician is often more willing to choose a more complicated operative vaginal delivery than if the fetus were living.

### Shoulder Dystocia

With vertex presentations, most mechanical difficulties are resolved with delivery of the head; once the head is delivered, the remainder of the fetus follows easily. In as many as 3% of vaginal deliveries, this is not the case. After the (often large) head is delivered, it seems to be “sucked” back into the perineum (the turtle sign). With maternal pushing and gentle traction, nothing happens. In this case, the anterior shoulder is trapped above the pubic symphysis. This serious complication is called shoulder dystocia. Recognition that shoulder dystocia exists is often followed by equanimity giving way to panic. If delivery is not accomplished soon, umbilical cord compression may result in asphyxia. Excessive traction on the fetal head may result in damage to the brachial plexus (e.g., Erb palsy), which may be permanent or temporary. During the manipulations undertaken to effect delivery, a fracture of the clavicle or humerus may result.

Risk factors for shoulder dystocia are those that predict or reflect mechanical difficulty (Box 18.5).\textsuperscript{72–77} Women with diabetes mellitus are predisposed to shoulder dystocia, not only because fetal macrosomia is more common but also because the fetus of a mother with diabetes has a shoulder circumference that is disproportionately large relative to the head circumference. Desultory labor may be a harbinger of mechanical mismatch, and operative vaginal delivery can exacerbate the situation. Although risk factors are known, it is important to recognize that shoulder dystocia cannot be accurately predicted or prevented.\textsuperscript{75}

Appropriate management of shoulder dystocia begins with the recognition that there is sufficient time to deliver the infant safely. Neuraxial anesthesia is ideal but not essential. Extension of the episiotomy should be considered. The anterior shoulder is stuck behind the pubic symphysis. Although greater posterior room does not directly permit delivery, it does permit vaginal manipulations that may be necessary to effect delivery. Table 18.5 lists a personal plan of management for shoulder dystocia, but other choices are available.\textsuperscript{72,75,76} Emergency drills and simulation training may improve proficiency in the management of shoulder dystocia.

If suprapubic pressure (directed toward the floor) coupled with gentle traction on the head is not efficacious, the mother’s thighs are removed from their supports and are hyperflexed alongside her abdomen. This maneuver (i.e., the McRoberts maneuver) elevates the symphysis in a cephalad direction and often frees the impacted shoulder and allows easy delivery. If the McRoberts maneuver is not successful, recent guidelines now recommend attempts to deliver the posterior arm as the next step.\textsuperscript{75} Despite previous assumptions to the contrary, vaginal delivery of the head does not necessarily commit one
to vaginal birth of the infant. Cephalic replacement (i.e., the Zavanelli maneuver) must be kept in mind as a last resort. If all measures have failed, the “tape is rewound,” and the mechanism of labor is reversed. The position of the vertex is rotated back to the position prior to external rotation (usually occiput anterior), flexion is achieved, and the head is elevated, which may be facilitated by tocolysis (e.g., sublingual or intravenous nitroglycerin 100 µg, subcutaneous or intravenous terbutaline 0.25 mg, or general anesthesia with a volatile anesthetic agent). After the fetal head has been placed back into the vagina, prompt cesarean delivery is performed.  

### TABLE 18.5  Management of Shoulder Dystocia

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Desired Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprapubic pressure</td>
<td>Anterior shoulder dislodged from above pubic symphysis</td>
</tr>
<tr>
<td>Hyperflexion of maternal thighs alongside abdomen (McRoberts maneuver)</td>
<td>Cephalad rotation of pubic symphysis</td>
</tr>
<tr>
<td>Intravaginal pressure on posterior shoulder</td>
<td>Anteroposterior position of shoulders transformed to oblique position</td>
</tr>
<tr>
<td>Delivery of posterior arm</td>
<td>Once accomplished, added room permits delivery</td>
</tr>
<tr>
<td>Cephalic replacement (Zavanelli maneuver)</td>
<td>Cesarean delivery</td>
</tr>
</tbody>
</table>

### KEY POINTS

- The outcome of labor reflects the interaction of three components: the powers, the passageway, and the passenger.
- Assuming that the fetus is tolerating labor satisfactorily, the most important obstetric determination is whether the patient is in the latent or the active phase of the first stage of labor.
- Amniotomy shortens labor.
- Oxytocin is the most valuable obstetric drug, and judicious use of a higher dose regimen may increase vaginal birth and shorten labor.
- Expectant management is the standard choice for the very preterm patient with premature rupture of membranes; induction of labor is generally undertaken in patients exhibiting this condition at term.
- Elective induction of labor is an appropriate choice for a patient with a favorable cervix.
- The declining numbers of operative vaginal deliveries reflect medicolegal concerns rather than new scientific information.

### REFERENCES

CHAPTER 18 Obstetric Management of Labor and Vaginal Delivery


In 1916, Edward Cragin stated, “Once a cesarean, always a cesarean.” This edict has had a profound effect on obstetric practice in the United States. The cesarean delivery rate increased from 5.5% of all deliveries in 1970 to 24.7% in 1988 (Fig. 19.1). Much of the increase in the cesarean delivery rate resulted from performance of repeat cesarean deliveries. In contemporary practice, elective repeat cesarean deliveries account for one-third of all cesarean deliveries. Cesarean delivery is the most frequently performed major surgery in the United States.

For many years, most US physicians ignored Cragin’s subsequent statement, “Many exceptions occur.” In 1981, the National Institute of Child Health and Human Development Conference on Childbirth concluded that vaginal birth after cesarean (VBAC) is an appropriate option for many women. In 1991, Rosen et al. modified Cragin’s original dictum as follows: “Once a cesarean, a trial of labor should precede a second cesarean except in the most unusual circumstances.” In 1998 and again in 1994, the American College of Obstetricians and Gynecologists (ACOG) concluded:

“The concept of routine repeat cesarean birth should be replaced by a specific decision process between the patient and the physician for a subsequent mode of delivery…. In the absence of a contraindication, a woman with one previous cesarean delivery with a lower uterine segment incision should be counseled and encouraged to undergo a trial of labor in her current pregnancy.”

The VBAC rate increased from 2% in 1970 to 28% in 1995. This change in practice helped reduce the overall cesarean delivery rate from 24.7% in 1988 to 20.7% in 1996 (see Fig. 19.1). Subsequently, the safety of a trial of labor after cesarean (TOLAC) underwent further scrutiny and criticism, and the VBAC rate sharply declined. The VBAC rate in the United States dropped from 28% in 1995 to 9% in 2004. In 2009, the overall cesarean delivery rate rose to 32.9%, the highest rate ever recorded in this country. Subsequently the cesarean delivery rate declined slightly to 32.0% in 2015.

PRIMARY CESAREAN DELIVERY: CHOICE OF UTERINE INCISION

Obstetric practice in 1916 hardly resembled obstetric practice today. In 1916, only 1% to 2% of all infants were delivered by cesarean delivery. Most cesarean deliveries were performed in patients with a contracted bony pelvis, and obstetricians uniformly performed a classic uterine incision (i.e., a long...
vertical incision in the upper portion of the uterus) (Fig. 19.2). A patient with a classic uterine incision is at high risk for catastrophic uterine rupture during a subsequent pregnancy. Such uterine rupture may occur before or during labor, and it often results in maternal and perinatal morbidity or mortality.

In 1922, De Lee and Cornell advocated the performance of a vertical incision in the lower uterine segment. Unfortunately, low-vertical incisions rarely are confined to the lower uterine segment. Such incisions often extend to the body of the uterus, which does not heal as well as the lower uterine segment. Kerr later advocated the performance of a low-transverse uterine incision (see Fig. 19.2). A low-transverse uterine incision results in less blood loss and is easier to repair than a classic uterine incision. Further, a low-transverse uterine incision is more likely to heal satisfactorily and to maintain its integrity during a subsequent pregnancy. Thus, obstetricians prefer to make a low-transverse uterine incision during most cesarean deliveries.

Obstetricians reserve the low-vertical incision for patients whose lower uterine segment does not have enough width to allow safe delivery. Preterm parturients may have a narrow lower uterine segment. In these patients, delivery through a transverse uterine incision may cause an extension of the incision into the vessels of the broad ligament. For example, a patient with preterm labor at 26 weeks’ gestation may undergo cesarean delivery because of a breech presentation, and the obstetrician may perform a low-vertical incision to facilitate an atraumatic delivery of the fetal head.

Obstetricians rarely perform a classic uterine incision in modern obstetric practice. An obstetrician may perform a classic uterine incision when the need for extensive

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Fig. 19.1 Incidence of cesarean delivery in the United States.

Fig. 19.2 Uterine incisions for cesarean delivery. (A) Low-transverse incision. The bladder is retracted downward, and the incision is made in the lower uterine segment, curving gently upward. If the lower segment is poorly developed, the incision also can curve sharply upward at each end to avoid extending into the ascending branches of the uterine arteries. (B) Low-vertical incision. The incision is made vertically in the lower uterine segment after reflection of the bladder, with avoidance of extension into the bladder below. If more room is needed, the incision can be extended upward into the upper uterine segment. (C) Classic incision. The incision is entirely within the upper uterine segment and can be at the level shown or in the fundus. (D) J-shaped incision. If more room is needed when an initial transverse incision has been made, either end of the incision can be extended upward into the upper uterine segment and parallel to the ascending branch of the uterine artery. (E) T-shaped incision. More room can be obtained in a transverse incision by an upward midline extension into the upper uterine segment. (Modified from Landon MB. Cesarean delivery. In Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies. 5th ed. Philadelphia, PA: Churchill Livingstone; 2007:493.)
intrauterine manipulation of the fetus (e.g., delivery of a fetus with a transverse lie) is anticipated. Some obstetricians prefer a classic uterine incision in patients with an anterior placenta previa. In such cases, the performance of a classic incision allows the obstetrician to avoid cutting through the placenta, which might result in significant hemorrhage. The obstetrician may perform a classic uterine incision in morbidly obese women in whom it is difficult to expose the lower uterine segment, especially when the skin incision is supra-umbilical.

**MATERNAL AND NEONATAL OUTCOMES**

Multiple studies have demonstrated that TOLAC results in a successful VBAC in 60% to 80% of women in whom a low-transverse uterine incision was made for a previous cesarean delivery.\(^{10-14}\) A 2010 National Institutes of Health (NIH) consensus development panel\(^ {15}\) concluded that although the TOLAC rate has declined dramatically in recent years, the VBAC rate after TOLAC has remained constant at approximately 74%. In 2015, the Royal College of Obstetricians and Gynaecologists (RCOG)\(^ {16}\) concluded that the success rate of planned VBAC is 72% to 75%. The NIH panel\(^ {15}\) also noted that a history of vaginal delivery, either before or after a prior cesarean delivery, is consistently associated with an increased likelihood of successful VBAC.

**Maternal Outcomes**

Flamm et al.\(^ {10}\) performed a prospective multicenter study of TOLAC. Of the 7229 patients, 5022 (70%) underwent TOLAC and 2207 underwent elective repeat cesarean delivery. Some 3746 (75%) of the women who opted for TOLAC delivered vaginally. The incidence of uterine rupture was 0.8%. The incidence of postpartum transfusion, the incidence of postpartum fever, and the duration of hospitalization were significantly lower in the TOLAC group than in the elective repeat cesarean group. Likewise, in a 1991 meta-analysis of 31 studies, Rosen et al.\(^ {1}\) noted that maternal febrile morbidity was significantly lower among women who attempted VBAC than among those who underwent elective repeat cesarean delivery.

In contrast, McMahon et al.\(^ {17}\) performed a population-based longitudinal study of 6138 women in Nova Scotia who had previously undergone cesarean delivery and who delivered a single live infant between 1986 and 1992. Some 3249 women attempted VBAC, and 2889 women chose a repeat cesarean delivery. There was no difference between the two groups in the incidence of “minor complications” (e.g., puerperal fever, transfusion, wound infection). However, “major complications” (e.g., hysterectomy, uterine rupture, operative injury) were nearly twice as common among women who attempted VBAC than among women who underwent elective repeat cesarean delivery.

Landon et al.\(^ {11}\) subsequently conducted a prospective 4-year observational study of all parturients with a singleton gestation and a prior cesarean delivery at 19 academic medical centers. Among the 17,898 women who attempted VBAC, 13,139 (73.4%) delivered vaginally. Symptomatic uterine rupture occurred in 124 (0.7%) women who underwent a trial of labor. The rate of endometritis was higher in women who underwent a trial of labor than in women who had an elective repeat cesarean delivery (2.9% versus 1.8%), as was the rate of blood transfusion (1.7% versus 1.0%).\(^ {17}\)

In a 2004 systematic review of published studies of attempted VBAC, Guise et al.\(^ {18}\) observed no significant difference in the incidence of maternal death or hysterectomy between women who attempted a trial of labor and those who underwent repeat cesarean delivery. Uterine rupture was more common in the women who attempted a trial of labor, but the rates of asymptomatic uterine dehiscence did not differ.

Wen et al.\(^ {19}\) performed a retrospective cohort comparison of outcomes after TOLAC or elective repeat cesarean delivery in 308,755 Canadian women with a history of previous cesarean delivery. These investigators observed that the rates of uterine rupture (0.65%), transfusion (0.19%), and hysterectomy (0.10%) were significantly higher in the TOLAC group. However, the maternal in-hospital death rate was significantly lower in the TOLAC group (1.6 per 100,000) than in the elective cesarean delivery group (5.6 per 100,000). Similarly, Guise et al.\(^ {20}\) observed a lower maternal mortality rate in women who underwent TOLAC than in women who underwent elective repeat cesarean delivery (0.004% versus 0.013%, respectively).

Cahill et al.\(^ {21}\) performed a multicenter cohort study in which they concluded that among TOLAC candidates who had a prior vaginal delivery, those who attempted VBAC had a lower risk for overall major maternal morbidities, as well as maternal fever and transfusion, than women who chose repeat cesarean delivery. These investigators concluded that women who have had a prior vaginal delivery have “less composite maternal morbidity if they attempt VBAC compared with [those] undergoing an elective repeat cesarean delivery.” Further, they concluded that a trial of labor is “a safer overall option for women who have had a prior vaginal birth.”\(^ {21}\)

Rossi and D’Addario\(^ {12}\) performed a meta-analysis of studies published from 2000 to 2007 that compared maternal morbidity in women who underwent TOLAC versus women who underwent elective repeat cesarean delivery. Successful VBAC occurred in 17,905 (73%) of 24,349 women who underwent TOLAC. Overall maternal morbidity did not differ between women who underwent TOLAC and women who underwent elective repeat cesarean delivery. Likewise, the incidence of blood transfusion and hysterectomy did not differ between the two groups. The incidence of uterine rupture was higher in the TOLAC group (1.3% versus 0.4%). Further, maternal morbidity, uterine rupture, blood transfusion, and hysterectomy were more common in women who had a failed TOLAC.

The 2010 NIH consensus development panel\(^ {15}\) noted that the overall benefits of TOLAC “are directly related to having a [successful] VBAC as these women typically have the lowest morbidity.” Likewise, the panel noted that the harms of TOLAC “are associated with an unsuccessful trial of labor.
resulting in cesarean delivery because these deliveries have the highest morbidity. However, the panel concluded that women who undergo TOLAC, regardless of the ultimate mode of delivery, are at decreased risk for maternal mortality compared with women who undergo elective repeat cesarean delivery. The panel also cited low-grade evidence of a shorter hospitalization overall for women attempting TOLAC compared with women undergoing elective repeat cesarean delivery.

**Neonatal Outcomes**

Lydon-Rochelle et al. conducted a population-based, retrospective cohort analysis of obstetric outcomes for all 20,095 nulliparous women who gave birth to a live singleton infant by cesarean delivery in civilian hospitals in Washington between 1987 and 1996 and who subsequently delivered a second singleton child during the same period. These investigators observed that spontaneous labor was associated with a tripling of the risk for uterine rupture (i.e., a uterine rupture rate of 5.2 per 1000 women who had spontaneous onset of labor versus 1.6 per 1000 women who underwent elective repeat cesarean delivery without labor). Further, the incidence of infant death was more than 10 times higher among the 91 women who experienced uterine rupture than among the 20,004 who did not (i.e., a 5.5% incidence of infant death versus a 0.5% incidence, respectively).

In the study performed by McMahon et al., there was no difference between the two groups in perinatal mortality or morbidity. However, two perinatal deaths occurred after uterine rupture in the TOLAC group. Landon et al. observed that hypoxic-ischemic encephalopathy occurred in no infants whose mothers underwent elective repeat cesarean delivery and in 12 infants delivered at term whose mothers underwent a trial of labor ($P < .001$).

The 2010 NIH consensus development panel concluded that the perinatal mortality rate (death between 20 weeks’ gestation and 28 days of life) is increased with TOLAC when compared with elective repeat cesarean delivery (i.e., 130 deaths per 100,000 infants compared with 50 deaths per 100,000 infants, respectively). Likewise, the panel concluded that the neonatal mortality rate (death between 20 weeks’ gestation and 28 days of life) is also increased with TOLAC when compared with elective repeat cesarean delivery (110 deaths per 100,000 infants versus 50 deaths per 100,000 infants, respectively).

On the other hand, elective cesarean delivery results in some cases of iatrogenic neonatal respiratory sequelae, including respiratory distress syndrome and transient tachypnea of the newborn. Kamath et al. observed that newborns born after elective repeat cesarean delivery had significantly higher rates of respiratory morbidity and neonatal intensive care unit admission—and a longer length of hospital stay—than infants whose mothers attempted VBAC. However, the 2010 NIH consensus development panel concluded that there is insufficient evidence to determine whether substantial differences in respiratory outcomes occur in infants born via elective repeat cesarean delivery compared with infants born after TOLAC.

### ELIGIBILITY AND SELECTION CRITERIA

Most studies suggest a high likelihood of success with TOLAC, even in women in whom the indication for previous cesarean delivery was dystocia or failure to progress in labor. Rosen and Dickinson performed a meta-analysis of 29 studies of attempted VBAC. Among women whose previous cesarean deliveries were performed for dystocia or cephalopelvic disproportion, the average rate of successful VBAC was 67%. Later studies have concluded that a history of previous vaginal delivery (especially previous VBAC) is the greatest predictor for successful VBAC and is associated with a VBAC success rate of 85% to 90%.16,25

The highest risk for maternal morbidity and mortality is associated with unsuccessful TOLAC. The ACOG concluded that women with at least a 60% to 70% chance of successful VBAC have equal or less maternal morbidity when they undergo TOLAC than women who undergo elective repeat cesarean delivery. Conversely, the ACOG noted that women who have a lower than 60% probability of successful VBAC have a greater likelihood of morbidity than women who undergo elective repeat cesarean delivery. Thus, the ability to identify women with a high likelihood of successful VBAC would improve the safety of TOLAC. Investigators have developed scoring systems for predicting the success or failure of TOLAC. Grobman et al. developed a nomogram specifically for women undergoing TOLAC at term gestation with one previous low-transverse cesarean delivery, a singleton gestation, and a vertex fetal presentation. The nomogram incorporates six variables that may be ascertained at the first prenatal visit; those variables include maternal age, body mass index, ethnicity, prior vaginal delivery, prior VBAC, and a recurring indication for cesarean delivery. This model was validated in a subsequent study and a VBAC calculator is now available online.

Mardy et al. subsequently developed a prediction model for preterm women undergoing TOLAC between 26 and 36 weeks’ gestation. They identified eight predictive variables: chronic hypertension, hypertensive disease of pregnancy, diabetes (pregestational or gestational), any prior vaginal delivery, prior VBAC, dilation on admission cervical examination, a recurring indication for prior cesarean delivery, and a need for induction of labor. A preterm VBAC prediction calculator is now available online.

The ACOG concluded that “most women with one previous cesarean delivery with a low-transverse incision are candidates for and should be counseled about and offered TOLAC.” A history of dystocia, a need for induction of labor, and maternal obesity are associated with a lower likelihood of successful VBAC.

### History of More Than One Cesarean Delivery

Studies that have assessed outcomes of TOLAC in women with a history of more than one cesarean delivery have not demonstrated consistent conclusions. One large multicenter study found no increased risk for uterine rupture (0.9% versus 0.7%) in women with more than one previous cesarean delivery, when compared with women with only one previous...
cesarean delivery. A second large study observed that the risk for uterine rupture increased from 0.9% to 1.8% during TOLAC in women with two previous cesarean deliveries. Both studies observed that TOLAC was associated with some increase in maternal morbidity in women with more than one previous cesarean delivery, although the absolute magnitude of the difference in morbidity was relatively small. The ACOG concluded that it is reasonable to consider TOLAC for women with two previous low-transverse cesarean deliveries. In 2015, the RCOG stated that “women who have had two or more prior lower segment cesarean deliveries may be offered VBAC after counselling by a senior obstetrician.” Data regarding the risk for TOLAC in women with more than two previous cesarean deliveries are limited.

**Previous Low-Vertical Incision**

Some obstetricians allow a trial of labor after a previous low-vertical uterine incision, provided that there is documentation that the uterine incision was confined to the lower uterine segment. (Low-vertical uterine incisions often extend above the lower uterine segment, especially when performed in preterm patients.) Naef et al. retrospectively reviewed outcomes for 174 women who attempted VBAC after a previous low-vertical cesarean delivery; 144 (83%) women delivered vaginally. Uterine rupture occurred in 2 (1.1%) of the patients. These investigators concluded that “the likelihood of successful outcome and the incidence of complications are comparable to those of published experience with a trial of labor after a previous low-segment transverse incision.” Adair et al. made similar observations. The ACOG concluded that there is no consistent evidence of an increased risk for uterine rupture in women with a previous low-vertical uterine incision, and that obstetricians and patients may choose to undergo TOLAC in the presence of a documented prior low-vertical uterine incision.

**Twin Gestation**

Some obstetricians believe that uterine overdistention, which occurs with twin gestation, increases the risk for uterine rupture in patients with a history of previous cesarean delivery. Early reports suggested otherwise, but these studies were limited by the small number of patients. Cahill et al. performed a retrospective cohort study of 25,005 obstetric patients with at least one previous cesarean delivery, which included 535 patients with a twin pregnancy. The investigators observed that women with a twin gestation were less likely to attempt VBAC but were no more likely to have a failed VBAC or to experience major morbidity than women with a singleton gestation.

Likewise, a report from the Maternal-Fetal Medicine Unit Cesarean Registry included outcome measures for 186 women with a twin gestation who attempted VBAC. Some 120 (64.5%) women delivered vaginally. Women who attempted a trial of labor with twin gestation had no higher risk for transfusion, endometritis, intensive care unit admission, or uterine rupture than women who underwent elective repeat cesarean delivery. The investigators concluded that a trial of labor in women with a twin gestation after previous cesarean delivery does not appear to be associated with a higher risk for maternal morbidity.

Ford et al. subsequently examined outcomes for 6555 women with a twin gestation who delivered between 1993 and 2002. Among 1850 women who underwent a trial of labor, 836 (45.2%) delivered vaginally. The rate of uterine rupture was higher in the trial-of-labor group than in the elective cesarean delivery group (0.9% versus 0.1%), but the rate of wound complications was lower in the trial-of-labor group (0.6% versus 1.3%).

The ACOG concluded that “women with one previous cesarean delivery with a low-transverse uterine incision, who are otherwise appropriate candidates for twin vaginal delivery, are considered candidates for TOLAC.” In contrast, the RCOG stated that “there is uncertainty about the safety and efficacy of planned VBAC in pregnancies complicated by … twin gestation.”

**Unknown Uterine Scar**

For some patients, there is no documentation of the type of uterine incision performed during a previous cesarean delivery. Some obstetricians require documentation of the type of previous uterine incision before they allow a patient to attempt VBAC. At least two studies have concluded that a trial of labor does not significantly increase maternal or perinatal mortality in patients with an unknown uterine scar. Perhaps this conclusion is true because most patients with an unknown uterine scar had a low-transverse uterine incision at previous cesarean delivery. Ultrasonography may help the obstetrician confirm the presence of a low-transverse uterine scar in the pregnant woman with an unknown uterine scar. The ACOG concluded that “women with one previous cesarean delivery with an unknown uterine scar type may be candidates for TOLAC, unless there is a high clinical suspicion of a previous classical uterine incision such as cesarean delivery performed at an extremely preterm gestational age.”

**Suspected Macrosomia**

In 1994, the ACOG concluded that an estimated fetal weight of more than 4000 g does not contraindicate TOLAC. However, in 1999, the ACOG included suspected macrosomia on the list of TOLAC eligibility criteria that are controversial. In 2004, the ACOG noted that macrosomia is associated with a lower likelihood of successful VBAC but did not include a specific recommendation regarding TOLAC in cases of suspected macrosomia. However, the ACOG cited one report that observed that the rate of uterine rupture appeared to be higher only in women without a previous vaginal delivery. A report from the Maternal-Fetal Medicine Unit Cesarean Registry concluded that for women with a history of previous cesarean delivery for dystocia, a higher birthweight in a subsequent pregnancy (relative to the first pregnancy birth weight) diminishes the chances of successful VBAC. In 2010, the ACOG concluded that “suspected macrosomia alone should not preclude the possibility of TOLAC.”
Gestation beyond 40 Weeks

Studies have consistently demonstrated decreased rates of successful VBAC in women who undergo TOLAC after 40 weeks’ gestation. One study observed an increased incidence of uterine rupture in women undergoing TOLAC beyond 40 weeks’ gestation, but other studies (including the largest study that has assessed this risk factor) have not confirmed an increased risk for uterine rupture in these patients. The ACOG concluded that although the likelihood of successful VBAC may be diminished in more advanced gestations, a “gestational age greater than 40 weeks alone should not preclude TOLAC.”

Breech Presentation and External Cephalic Version

Breech presentation itself does not increase the risk for uterine rupture. In contemporary practice, most obstetricians do not allow a trial of labor in any patient with a breech presentation. Thus, most patients with a breech presentation undergo elective cesarean delivery, with or without a history of previous cesarean delivery. The ACOG concluded that external cephalic version is not contraindicated in women with a previous low-transverse uterine incision who are at low risk for adverse maternal and neonatal outcomes from external cephalic version and TOLAC.

Size of Hospital

Most studies of VBAC have been conducted in university or tertiary care hospitals with in-house obstetricians, anesthesia providers, and operating room staff. In 1999, the ACOG noted that “the safety of [a] trial of labor is less well documented in smaller community hospitals or facilities where resources may be more limited.” A 2007 study evaluated outcomes for women who attempted VBAC in 17 diverse hospitals, including six university hospitals, five community hospitals with an obstetrics-gynecology residency program, and six community hospitals without an obstetrics-gynecology residency program. The incidence of uterine rupture with attempted VBAC was significantly higher in community hospitals than in university hospitals (1.2% versus 0.6%, respectively). However, the rates of maternal blood transfusion and composite adverse maternal outcome were identical in community and university hospitals. The ACOG and the Society for Maternal-Fetal Medicine have recommended that attempted VBAC should occur in a level I center or higher.

Contraindications

Contraindications to planned TOLAC include:

- Previous classic or T-shaped incision or extensive transfundal uterine surgery
- Previous uterine rupture
- Medical or obstetric complication that precludes labor and vaginal delivery
- Inability to perform emergency cesarean delivery because of unavailable surgeon, anesthesia provider, or operating room staff

Social and Economic Factors

Why do most eligible patients choose to undergo elective repeat cesarean delivery? The low frequency of TOLAC has resulted, in part, from both physician and patient preference. VBAC requires more physician effort than elective repeat cesarean delivery. In some cases, physician reimbursement is greater for elective repeat cesarean delivery than for VBAC, despite the fact that VBAC requires greater physician effort.

Stafford reviewed the impact of nonclinical factors on the performance of repeat cesarean delivery in California. He observed that “proprietary hospitals, with the greatest incentive to maximize reimbursement, had the highest repeat cesarean [delivery] rates.” Nonteaching hospitals and hospitals with low-volume obstetric services had lower VBAC rates than teaching hospitals and hospitals with high-volume obstetric services. Likewise, Hueston and Rudy found that women who undergo elective repeat cesarean delivery are more likely to have private insurance than women who attempt VBAC. Stafford concluded: “Because a cesarean [delivery] is nearly twice as costly as a vaginal birth,... the higher repeat cesarean [delivery] rates associated with proprietary hospitals, non-teaching hospitals, and low-volume hospitals contribute to increased health care expenditures.”

In contrast, after assessing both the direct and indirect costs of VBAC, Clark et al. concluded that “any economic savings for the healthcare system of a policy of trial of labor are at best marginal, even in a tertiary care center with a success rate for vaginal birth after cesarean of 70%.” Further, they stated that “a policy of trial of labor does not result in any cost saving under most birthing circumstances encountered in the United States today.” The ACOG had earlier acknowledged that “the difficulty in assessing the cost-benefit of VBAC is that the costs are not all incurred by one entity.” In 2004, the ACOG made the following conclusion:

_A true analysis of the cost-effectiveness of VBAC should include hospital and physician costs, the method of reimbursement, potential professional liability expenses, and the probability that a woman will continue with childbearing after her first attempt at VBAC. Higher costs may be incurred by a hospital if a woman has a prolonged labor or has significant complications or if the newborn is admitted to a neonatal intensive care unit._

Some women reject TOLAC because they have experienced prolonged, painful labor during a previous pregnancy. They fear that they will again experience a prolonged, painful labor and ultimately need a repeat cesarean delivery. This fear is more common in women who have delivered in smaller hospitals without the availability of neuraxial analgesia during labor. Other women reject TOLAC because they prefer to schedule the date of elective repeat cesarean delivery. (A scheduled, elective cesarean delivery allows the patient to arrange for a relative or friend to provide child care.) Kirk et al. questioned 160 women regarding factors affecting their choice between VBAC and elective repeat cesarean delivery. These investigators concluded that “social exigencies
appeared to play a more important role than an assessment of the medical risks in making these decisions.” Similarly, Joseph et al. observed that fear and inconvenience are the most common deterrents to attempted VBAC. Finally, some women reject a trial of labor because of their concern about the adverse effects of labor and vaginal delivery on the maternal pelvic floor, with the risk for subsequent problems such as urinary and fecal incontinence.

Some insurance carriers previously required that eligible women with a history of previous cesarean delivery attempt VBAC in subsequent pregnancies. These carriers denied partial or full reimbursement to women who chose elective repeat cesarean delivery unless there was a medical reason to perform repeat cesarean delivery. The ACOG and others have agreed that hospitals and insurers should not mandate a trial of labor for pregnant women with a history of previous cesarean delivery. In 2004, the ACOG concluded, “After thorough counseling that weighs the individual benefits and risks of VBAC, the ultimate decision to attempt this procedure or undergo a repeat cesarean delivery should be made by the patient and her physician.”

Bernstein et al. found that TOLAC-eligible women undergoing either TOLAC or elective repeat cesarean delivery were not adequately informed about the risks and benefits of the two options, and they also found that provider preference drove the decision regarding the planned mode of delivery. Cox emphasized and discussed the importance of shared decision-making when choosing the mode of delivery after a previous cesarean. It is important to discuss with the patient her family planning goals, as the risk for a morbidly adherent placenta and major hemorrhage in subsequent pregnancies increases with each cesarean delivery (see Chapter 37). A patient who is planning to have several children should take this factor into consideration when deciding between TOLAC and repeat cesarean delivery.

Medicolegal Factors
What is the risk for uterine rupture during VBAC? A lower uterine segment scar is relatively avascular, and massive hemorrhage rarely follows separation of a lower segment scar. In contrast, rupture of a classic uterine scar may result in massive intraperitoneal bleeding. Unfortunately, there is some inconsistency and confusion in reports of the incidence of asymptomatic uterine scar dehiscence as opposed to frank uterine rupture. Uterine scar dehiscence may be defined as a uterine wall defect that does not result in fetal compromise or maternal hemorrhage and that does not require emergency cesarean delivery or postpartum laparotomy. In contrast, uterine rupture may be accompanied by extrusion of the fetus or placenta and results in fetal compromise, maternal hemorrhage, or both, sufficient to require cesarean delivery or postpartum laparotomy.

Some obstetricians have suggested that earlier studies underestimated the risks associated with TOLAC. Scott reported 12 women from Salt Lake City, Utah, who experienced clinically significant uterine rupture during TOLAC. Some of the women did not experience optimal obstetric management. For example, Scott’s series included two women whose labor occurred at home. Of interest, the number of home VBACs in the United States increased from 664 in 2003 to approximately 1000 in 2008, perhaps as a result of restricted access to TOLAC in some hospitals.

Obstetricians understandably fear that they will be found liable if an adverse event occurs during TOLAC. In one case, a jury awarded a verdict of $98.5 million because of a delayed diagnosis of uterine rupture. Phelan cited another court decision that he predicted would have a “chilling effect on the future of VBAC.” In this case, the fetal heart rate (FHR) was normal until it abruptly decreased to 80 beats per minute at a cervical dilation of 9 cm. The interval between the onset of the FHR deceleration and emergency cesarean delivery was 27 minutes. At delivery, the fetal head was found in the left adnexa. The mother required transfusion, and the child suffered from developmental delay and cerebral palsy. The court found that the defendants were negligent in their failure to deliver the infant in a timely manner and to provide adequate informed consent. The court also concluded that “the ACOG 30-minute rule represented the maximum period of elapse” and did not represent the minimum standard of care. As a result of this verdict, Phelan proposed the use of a VBAC consent form that includes the following statement: “I understand that if my uterus ruptures during my VBAC, there may not be sufficient time to operate and to prevent the death of or permanent brain injury to my baby.” Flamm responded that “widespread implementation of this or similar consent forms essentially would mean the end of VBAC.”

Greene wrote a sobering editorial on the risks associated with attempted VBAC. Observing that the study performed by Lydon-Rochelle and others was an observational study that reflected “broad experience in a wide range of clinical-practice settings,” he stated that “there is no reason to believe that improvements in clinical care can substantially reduce the risks of uterine rupture and perinatal mortality.” Greene concluded his editorial as follows:

After a thorough discussion of the risks and benefits of attempting a vaginal delivery after cesarean section, a patient might ask, “But doctor, what is the safest thing for my baby?” Given the findings of Lydon-Rochelle et al., my unequivocal answer: elective repeated cesarean section.

In an earlier editorial, Pitkin made the following statement regarding VBAC: “Many women with previous cesareans can be delivered vaginally, and thereby gain substantial advantage, but neither the decision for trial [of] labor nor management during that labor should be arrived at in a cavalier or superficial manner.”

PROFESSIONAL SOCIETY PRACTICE GUIDELINES
In 1999, the ACOG issued guidelines stating that because uterine rupture may be catastrophic, VBAC should be attempted in institutions equipped to respond to emergencies with physicians immediately available to provide emergencies
care. Likewise, the RCOG\textsuperscript{16} has stated that planned VBAC should be conducted in a facility “with resources available for immediate caesarean delivery and advanced neonatal resuscitation.” The ACOG\textsuperscript{75} defended their “immediately available” recommendation by noting that “VBAC is a completely elective procedure that allows for reasonable precautions in assuming this small but significant risk [of uterine rupture].” In contrast, other obstetric catastrophes (e.g., placental abruption, umbilical cord prolapse) cannot be predicted. The ACOG\textsuperscript{72} has also noted that “the operational definition of ‘immediately available’ personnel and facilities remains the purview of each local institution.” However, this requirement for the immediate availability of physicians and other personnel clearly represents a more stringent standard than the “readily available” requirement in other published guidelines for obstetric care.

Earlier, Zlatnik\textsuperscript{73} made the following comments regarding VBAC in a community hospital: “If a timely cesarean [delivery] cannot be performed in a community hospital, VBAC is out of the question, but the larger question is: Should obstetrics continue to be practiced there? Timely cesarean [delivery] is an essential option for all laboring women.”

In contrast, the American Academy of Family Physicians (AAFP)\textsuperscript{74} published the following recommendations:

- **Women with one previous cesarean delivery with a low transverse incision are candidates for and should be offered a trial of labor (TOL).**…Trial of labor after cesarean (TOLAC) should not be restricted only to facilities with available surgical teams present throughout labor since there is no evidence that these additional resources result in improved outcomes. At the same time, it is clinically appropriate that a management plan for uterine rupture and other potential emergencies requiring rapid cesarean section should be documented for each woman undergoing TOLAC.

The AAFP\textsuperscript{73} has argued that the ACOG guidelines suggest that “one rare obstetrical catastrophe (e.g., uterine rupture) merits a level of resource that has not been recommended for other rare obstetrical catastrophes that may actually be more common.” The AAFP has acknowledged that these other complications are “largely not predictable,” whereas a TOLAC is a “planned event that may demand a different degree of preparedness.” Nonetheless, they stated that their recommendations significantly differ from ACOG guidelines because they could find “no evidence to support a different level of care for TOLAC patients.”

In response, Dr. Gary Hanks, Chair of the ACOG Committee on Obstetric Practice, made the following statement:\textsuperscript{75}

> It’s very troubling when people who may not even be qualified to perform a cesarean section start issuing guidelines about the safety of this kind of thing…. Their argument is that the available data don’t prove it’s unsafe—they’re not arguing that it is safe….Our main concern is with having the best possible outcome for mother and baby. If women are given the true numbers about the bad outcomes that can be associated with VBAC, no woman is going to take the chance [of laboring without immediately available surgical support].

The 2010 NIH consensus development panel\textsuperscript{15} noted that approximately one-third of hospitals and one-half of obstetric physicians in the United States no longer offer TOLAC largely because of fear of liability and litigation. The panel\textsuperscript{15} expressed concern that practice guidelines have created barriers that prevent women from choosing TOLAC. The panel concluded that TOLAC remains “a reasonable option for many pregnant women with one prior low-transverse uterine incision.” The panel acknowledged that decision-making may be difficult, because the benefit of TOLAC for the woman may come at the price of increased risk for the infant. The panel stated that pregnant women should be given the opportunity to make informed decisions about the risks and benefits of TOLAC versus elective repeat cesarean delivery. The panel also urged professional societies to reassess the requirement for immediate availability of surgical and anesthesia providers.

Subsequently the ACOG\textsuperscript{14} stated that restricting access was not the intention of their “immediately available” requirement. The ACOG\textsuperscript{14} noted that “much of the data concerning the safety of TOLAC is from centers capable of performing a timely emergency cesarean delivery.” Further, they stated that “although there is reason to think that more rapid availability of cesarean delivery may provide a small incremental benefit in safety, comparative data examining in detail the effect of alternate systems and response times are not available.” A 2012 study\textsuperscript{64} evaluated neonatal outcome after 36 cases of uterine rupture that occurred among 11,195 cases of TOLAC between 2000 and 2009. None of the 17 infants who were delivered less than 18 minutes after the identification of uterine rupture had either an umbilical arterial blood pH less than 7.0 or evidence of neurologic injury. In contrast, three infants who were delivered more than 30 minutes after the diagnosis of uterine rupture had an umbilical arterial blood pH less than 6.8 and suffered neonatal neurologic injury.\textsuperscript{64}

In 2017 the ACOG\textsuperscript{14} modified their practice bulletin as follows:

> Because of the risks associated with TOLAC, and [because] uterine rupture and other complications may be unpredictable, ACOG recommends that TOLAC be attempted in facilities that can provide cesarean delivery for situations that are immediate threats to the life of the woman or fetus. When resources for immediate cesarean delivery are not available, ACOG recommends that obstetricians or other obstetric care providers and patients considering TOLAC discuss the hospital’s resources and availability of obstetric, pediatric, anesthesiology, and operating room staff…. The decision to offer and pursue TOLAC in a setting in which the option of emergency cesarean delivery is limited should be carefully considered by patients and their obstetricians or other obstetric care providers. In such situations the best alternative may be to refer patients to a facility with available resources.
Further, the ACOG\textsuperscript{14} also encouraged respect for patient autonomy, as follows:

*Respect for patient autonomy also dictates that even if a center does not offer TOLAC, such a policy cannot be used to force women to have cesarean delivery or to deny care to women in labor who decline to have a repeat cesarean delivery.*

Birnbach et al.\textsuperscript{76} reviewed the impact of anesthesia provider availability on the incidence of VBAC in the United States. They concluded that the “immediately available” requirement necessitates having an in-hospital anesthesia provider who is not performing another simultaneous anesthetic. Their economic analysis prompted a conclusion that “the minimum requirement to provide immediate anesthesia care for all deliveries would be to have all deliveries at facilities with greater than 1500 deliveries annually.”

### OBSTETRIC MANAGEMENT

#### Intravenous Access and Availability of Blood

It seems prudent to recommend the early establishment of intravenous access in women who undergo TOLAC. Resources for transfusion of blood and blood products should be readily available.

#### Fetal Heart Rate Monitoring

The RCOG\textsuperscript{16} recommends “continuous electronic [FHR] monitoring for the duration of planned VBAC.” Continuous electronic FHR monitoring represents the best means of detecting uterine rupture.\textsuperscript{77–79} Rodriguez et al.\textsuperscript{78} reviewed 76 cases of uterine rupture at their hospital. A nonreassuring FHR pattern occurred in 59 of the 76 patients and was the most reliable sign of uterine rupture.

#### Intrauterine Pressure Monitoring

The intrauterine pressure catheter provides a quantitative measurement of uterine tone both during and between contractions. In the past, some obstetricians contended that an intrauterine pressure catheter should be used in all patients who undergo TOLAC, arguing that a loss of intrauterine pressure and cessation of labor will signal the occurrence of uterine rupture. In one study,\textsuperscript{79} 39 patients had an intrauterine pressure catheter at the time of uterine rupture. None of these patients experienced an apparent decrease in resting uterine tone or cessation of labor, but 4 patients experienced an increase in baseline uterine tone. In these 4 patients, the increase in baseline uterine tone was associated with severe variable FHR decelerations that prompted immediate cesarean delivery. The authors concluded that the information obtained from the use of the intrauterine pressure catheter did not help the obstetricians make the diagnosis of uterine rupture.\textsuperscript{78}

#### Use of Prostaglandins

Lydon-Rochelle et al.\textsuperscript{72} observed a uterine rupture rate of 24.5 per 1000 women who attempted VBAC with prostaglandin-induced labor. The ACOG\textsuperscript{13} cited evidence from small studies that observed an increased risk for uterine rupture after the use of misoprostol (prostaglandin \(E_1\)) in women who attempted VBAC. The ACOG\textsuperscript{13,80} has concluded that “misoprostol should not be used for third trimester cervical ripening or labor induction in patients who have had a cesarean delivery or major uterine surgery.” The RCOG\textsuperscript{16} concluded that “induction of labor using mechanical methods (amniotomy or Foley catheter) is associated with a lower risk for scar rupture compared with induction using prostaglandins.”

### ANESTHETIC MANAGEMENT

In the past, some obstetricians contended that epidural analgesia might mask the pain of uterine scar separation or rupture and thereby delay the diagnosis of uterine scar dehiscence or rupture.\textsuperscript{83,84} In a 1991 meta-analysis, Rosen et al.\textsuperscript{3} noted that the use of oxytocin did not increase the risk for uterine scar dehiscence or rupture during VBAC. In contrast, in one large retrospective study of more than 20,000 women, uterine rupture was nearly five times more common among women undergoing induction of labor with oxytocin than in those who had an elective repeat cesarean delivery.\textsuperscript{82} Zelop et al.\textsuperscript{83} observed a higher rate of uterine rupture in women undergoing oxytocin induction of labor for attempted VBAC than in similar women attempting VBAC with spontaneous labor. Further, the rate of uterine rupture was also higher in women receiving oxytocin for augmentation of labor, but the difference was not statistically significant. The ACOG\textsuperscript{13} has concluded that “the varying outcomes of available studies and small absolute magnitude of the risk reported in those studies support that oxytocin augmentation may be used in patients undergoing TOLAC.”

First, pain, uterine tenderness, and tachycardia have low sensitivity as diagnostic symptoms and signs of lower uterine...
segment scar dehiscence or rupture. Some uterine scars separate painlessly. Obstetricians occasionally discover an asymptomatic lower uterine segment scar dehiscence at the time of elective repeat cesarean delivery. Molloy et al. reported 8 cases of uterine rupture among 1781 patients who attempted VBAC. None of these 8 patients had abdominal pain, but all had FHR abnormalities. Johnson and Oriol reviewed 14 studies of VBAC published between 1980 and 1989. Among 10,967 patients who attempted VBAC, 1623 patients received epidural analgesia. Of those who experienced uterine rupture, 5 of 14 patients (35%) with epidural analgesia experienced abdominal pain, compared with 4 of 23 patients (17%) without epidural analgesia. FHR abnormalities represented the most common sign of uterine rupture among patients who did and did not receive epidural analgesia. None of these investigators observed that epidural analgesia delayed the diagnosis of uterine rupture.

Second, pain, uterine tenderness, and tachycardia have low specificity as diagnostic symptoms and signs of lower uterine segment scar dehiscence. Case et al. reported 20 patients with a history of previous cesarean delivery in whom the indication for urgent repeat cesarean delivery was severe hypogastric pain, tenderness, or both. At surgery, they confirmed the presence of scar dehiscence in only one of the 20 patients. Eckstein et al. suggested that the unexpected development of pain during previously successful epidural analgesia might be indicative of uterine rupture. Crawford referred to this phenomenon as the “epidural sieve.” Others have described patients who received epidural analgesia and subsequently complained of pain and tenderness secondary to uterine scar rupture. I have provided epidural analgesia for several patients in whom the first suggestion of scar separation was the sudden and unexpected development of “breakthrough pain” despite the continuous epidural infusion of local anesthetic. A 2010 study found evidence of “epidural dose escalation immediately before uterine rupture in women who attempted VBAC, when compared with women who did not have uterine rupture.” The authors concluded that “clinical suspicion for uterine rupture should be high in women who require frequent epidural dosing during a VBAC trial.” Likewise, the RCOG stated that “an increasing requirement for pain relief in labour should raise awareness of the possibility of an impending uterine rupture.” Thus, epidural analgesia may improve the specificity of abdominal pain as a symptom of uterine scar separation or rupture.

Third, most cases of lower uterine segment scar dehiscence do not lead to severe hemorrhage. In one report of six cases of uterine scar dehiscence or rupture, only one patient had intrapartum vaginal bleeding. However, if significant bleeding should occur, epidural anesthesia may attenuate the maternal compensatory response to hemorrhage. Vincent et al. observed that epidural anesthesia (median sensory level of T9) significantly worsened maternal hypotension, uterine blood flow, and fetal oxygenation during untreated hemorrhage (20 mL/kg) in gravid ewes. Intravascular volume replacement promptly eliminated the differences between groups in maternal mean arterial pressure, cardiac output, and fetal PaO₂. Maternal heart rate did not change significantly during hemorrhage in the control animals. However, there was a significant drop in maternal heart rate during hemorrhage in the animals that received epidural anesthesia.

Fourth, several published series have reported the successful use of epidural analgesia in women undergoing TOLAC. There is little evidence that epidural analgesia either decreases the likelihood of vaginal delivery or adversely affects maternal or neonatal outcome in women who have uterine scar separation or rupture. Flamm et al. reported a multicenter study of 1776 patients who attempted VBAC. Approximately 134 (74%) of 181 women who received epidural analgesia delivered vaginally, compared with 1180 (74%) of 1595 women who did not receive epidural analgesia. A 2017 retrospective study from Israel reported a slightly higher rate of successful VBAC in women who received labor epidural analgesia than in women who did not (91.2% versus 88.3%), but women in the epidural group were more likely to undergo instrumental vaginal delivery (11.7% versus 2.8%). Phelan et al. reported that among patients who received both oxytocin augmentation and epidural analgesia, 69% delivered vaginally. This did not differ from the incidence of vaginal delivery among patients who received oxytocin without epidural analgesia. Other investigators have reported results of smaller studies suggesting a lower rate of successful VBAC among patients who received epidural analgesia. However, this effect was limited to patients who received oxytocin for the induction or augmentation of labor. These investigators concluded that epidural analgesia does not decrease the likelihood of successful VBAC.

Fifth, in the past some obstetricians favored the use of epidural analgesia because it facilitates postpartum uterine exploration to assess the integrity of the uterine scar. Meehan et al. earlier supported routine postpartum palpation of the uterine scar. However, Meehan et al. subsequently acknowledged that it is not necessary to repair all such defects. Many obstetricians manage asymptomatic uterine scar dehiscence with “expectant observation.” Thus, they argue that routine palpation of the uterine scar is unnecessary after successful VBAC.

Sixth, epidural analgesia provides rapid access to safe, surgical anesthesia if cesarean delivery or postpartum laparotomy should be required.

Finally, it is inhumane to deny effective analgesia to women who undergo TOLAC. Further, the ACOG has concluded that adequate pain relief may encourage more women to choose TOLAC. Thus, the availability and use of neuraxial analgesia may decrease the incidence of unnecessary repeat cesarean delivery.

The ACOG has stated that good and consistent scientific evidence supports a conclusion that epidural analgesia may be used during TOLAC. In my judgment, the availability of neuraxial analgesia is an essential component of a successful VBAC program. It seems reasonable to provide analgesia— but not total anesthesia—during labor in patients attempting VBAC.
KEY POINTS

• Cesarean delivery is the most commonly performed major operation in the United States, and previous cesarean delivery is the most common indication.
• A trial of labor is successful in 72% to 75% of women in whom a low-transverse uterine incision was made during a previous cesarean delivery.
• A previous vaginal delivery is the greatest predictor for successful vaginal birth after cesarean delivery (VBAC). A history of dystocia, the need for induction of labor, and/or maternal obesity are associated with a lower likelihood of successful VBAC.
• Hospitals and insurers should not mandate a trial of labor for pregnant women with a history of previous cesarean delivery.
• The American College of Obstetricians and Gynecologists has recommended that resources for performing emergency cesarean delivery should be immediately available in women attempting a trial of labor after previous cesarean delivery (TOLAC). Other groups have argued that this guideline is too restrictive and has created barriers that prevent women from choosing TOLAC.
• Continuous electronic fetal heart rate monitoring represents the best means of detecting uterine rupture.
• Women are more likely to undergo TOLAC if they know that they will receive effective analgesia during labor.
• Epidural analgesia does not delay the diagnosis of uterine rupture or decrease the likelihood of successful VBAC.

REFERENCES


The gate control theory of pain, described more than 50 years ago by Melzack and Wall, has revolutionized the understanding of the mechanisms responsible for pain and analgesia. Originally explained as the regulation of pain signals from the peripheral nerve to the spinal cord by the activity of other peripheral nerves, interneurons in the spinal cord, and central supraspinal centers (Fig. 20.1), the theory has been refined with the concept of a neuromatrix, a remarkably dynamic system capable of undergoing rapid change. Neural circuits and intraneural mechanisms regulate sensitivity at peripheral afferent terminals; along the conducting axons of peripheral nerves; in the spinal cord, pons, medulla, and thalamus; and at cortical sites of pain transmission and projection. For example, the peripheral application of capsaicin to the skin alters spinal gating mechanisms within 10 minutes, resulting in a light touch signal being interpreted as burning pain.

Despite extensive research (initiated by the gate control theory) into the mechanisms and treatments for chronic pain, virtually no research on the neurophysiologic basis or therapies for labor pain has been performed. This discrepancy in focus has led to vastly different approaches to the treatment of patients with chronic versus obstetric pain. A patient with chronic pain typically undergoes a sophisticated physical assessment of sensory function; is offered therapies, on the basis of the assessment, from nearly a dozen different classes of analgesics; and can benefit from the enormous resources expended by the pharmaceutical industry to introduce agents that act on novel receptors or enzymes. By contrast, a laboring woman receives no physical assessment of sensory function and is offered only a handful of systemic drugs that act primarily through the anatomic blockade of neural traffic.

In this chapter, this paradox in the approach to labor pain is examined and the basis for current therapy (anatomy), the basis for future therapy (neurophysiology), and the effects of labor pain on the mother and the infant are reviewed.

**MEASUREMENT AND SEVERITY OF LABOR PAIN**

The recognition and acceptance of chronic pain, which frequently lacks an obvious outward cause, contrasts to the recurrent denial of labor pain, which is accompanied by visible tissue injury. Dick-Read suggested that labor is a natural process not considered painful by women in primitive cultures that should be handled with education and preparation rather than through pain medications. Lamaze popularized psychoprophylaxis as a method of birth preparation; this method now forms the basis for prepared childbirth training in the developed world. Although childbirth training acknowledges the existence of pain during labor, some scientific-thought leaders still consider labor pain to be minor.

The severity of labor pain has been recognized previously. Melzack, using a questionnaire developed to assess the intensity and emotional impact of pain, observed that nulliparous women with no prepared childbirth training rated...
labor pain to be as painful as a digit amputation without anesthesia (Fig. 20.2). More than 30 years before Melzack's quantification of pain, Javert and Hardy trained subjects to reproduce the intensity of labor pain with the sensation of noxious heat applied to the skin from a radiant heat source. In these experiments, several women achieved “ceiling pain”—resulting in second-degree burns to the skin—when they attempted to match the intensity of uterine contraction pain. Individual women also reported a close positive correlation between cervical dilation and pain intensity. Logistic regression analysis of the investigators' original data indicates a high likelihood of severe pain as labor progresses, with a time course closely associated with cervical dilation (Fig. 20.3).

Other investigators have noted that uterine pressure during contractions accounts for more than 90% of the variability in labor pain intensity. These observations are consistent with the conclusion that cervical distention is the primary cause of pain during the first stage of labor.

In an effort to objectively measure pain in laboring women, Charier et al. studied the physiologic fluctuations of the iris, which is dependent on the input from the sympathetic and parasympathetic systems. By measuring the variation coefficient of the pupillary diameter (VCPD) as a mathematical extraction of pupil size fluctuation in 40 laboring women, researchers were able to demonstrate a stronger correlation between pain and the fluctuations in pupil size. This method provides a non-invasive way to assess pain during labor.

Fig. 20.1 Gate control theory of pain. Activity in small-diameter afferents (S) stimulates transmission cells in the spinal cord (T), which send signals supraspinally and results in the perception of pain. Small-diameter afferents also inhibit cells in the spinal cord substantia gelatinosa (SG), the activity of which reduces excitatory input to T cells. Activity in large-diameter afferents (L) also stimulates T cells in a manner that is perceived as nonpainful and excites SG cells to “close the gate” and reduce small-diameter afferent activation of T cells. The gate mechanism is under regulation by central sites. (From Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–975.)

Fig. 20.2 A comparison of pain scores obtained through the McGill Pain Questionnaire. Scores were collected from women in labor, patients in a general hospital clinic, and patients in the emergency department after accidents involving traumatic injury. Note the modest difference in pain scores between nulliparous women with and without prepared childbirth training. PRI, Pain rating index, which represents the sum of the rank values of all the words chosen from 20 sets of pain descriptors. (Modified from Melzack R. The myth of painless childbirth [The John J. Bonica Lecture]. Pain. 1984;19:321–337.)

Fig. 20.3 Likelihood of severe pain during labor. A significant minority of women (approximately one-third) have severe pain in early labor, and the proportion of women with severe pain increases to nearly 90% later in labor, in close relationship with cervical dilation. (Data from Hardy JD, Javert CT. Studies on pain: measurements of pain intensity in childbirth. J Clin Invest. 1949;28:153–162.)
(r = .77 versus r = .42) with numerical pain scores in labor during a uterine contraction than pupillary diameter alone. However, there is considerable variability in the rated intensity of pain during labor. Nulliparous women rate labor pain as more severe than do parous women; however, the differences are small and of questionable clinical relevance. There is a correlation between the intensity of menses and labor pain, especially back discomfort, although the reason for this relationship is unknown. It is possible that the rated intensity of labor pain reflects individual differences in the perception of all types of pain. In a study of factors affecting labor pain, 10 of 97 subjects reported that they had never experienced pain before childbirth; these women reported significantly less pain during labor and delivery compared with women who had previously experienced pain. In other studies, the variability of pain after cesarean delivery could be predicted with preoperative quantitative sensory testing (such as rating the intensity of pain with a standardized noxious thermal stimulus), psychological constructs, and their combinations.

The mechanism by which people perceive different levels of pain from the same stimulus remains unclear. A study involving brain imaging and a fixed acute noxious heat stimulus showed a strong correlation between verbal pain assessment and the level of activation of various cortical brain regions, especially the contralateral somatosensory cortex and anterior cingulate cortex. The investigators also found that the degree of activation of the thalamus was essentially identical in all subjects, suggesting that differences in perceived pain resulted from modulation at suprathalamic levels rather than in the peripheral nerves or spinal cord. The situation in labor may be more complex. For example, a large genetic polymorphism regulates cytokine production and function as well as pregnancy outcome. It is possible that interindividual differences in labor pain may partially reflect genetic differences in cytokine production or response.

In evaluating and studying labor pain and its treatment, most studies have tended to assess labor pain by using a set of discrete pain scores. However, labor pain is a complex, subjective, multidimensional, and dynamically changing experience with both sensory and affective components that are influenced by many factors. As a result, there are substantial individual differences in labor pain. Therefore, better identification of the covariates that affect labor progress and its associated pain is needed. Conell-Price et al. developed and validated a dynamic model to account for labor progress in the assessment of labor pain. Subsequently, Debiec et al., at the same institution, combined a biexponential model that describes labor progress with a sigmoidal labor pain model to assess the influence of patient covariates on labor pain. Both studies used retrospective patient data to develop and test their models. In the former study, the prediction error for the pain scores was large, but the purpose of the model was to identify and remove variability associated with labor progress so that other factors (e.g., genetic polymorphisms) can be quantitatively studied. In this study, cervical dilation accounted for only 16% to 20% of the variability in reported pain. In the latter study, the covariate of ethnicity was found to have a statistically significant but clinically trivial effect on labor progress. The modeling described by these investigators provides a useful quantitative tool for future studies to identify and assess the effect—or the lack of effect—of patient and/or environmental covariates on labor progress, labor pain, and therapeutic responses. Better understanding of underlying causes of interindividual variability in labor progress, labor pain, and therapeutic responses is likely to lead to more tailored therapy.

In summary, although significant variability exists in the rated intensity of pain during labor and delivery, the majority of women experience more than minimal pain. The close correlation between cervical dilation and the rated severity of pain implies the existence of a causal relationship and increases the likelihood that a parturient will request analgesia as labor progresses.

### Personal Significance and Meaning

The International Association for the Study of Pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Recognition of an intensity-discriminatory component and an emotional-cognitive component, with powerful interactions between the two, has fostered current interventions heavily weighted toward the first component and assumes that labor pain is severe and in need of pharmacologic treatment. Largely ignored are coping strategies and the personal meaning of labor pain, which varies considerably among women. Williams and Craig suggested that the definition of pain should include the often overlooked cognitive and social elements, and Whitburn et al. suggested a further extension to etiologies that do not include tissue damage. These alterations would make the experience and study of pain more relevant to the labor experience; nociceptive pain intensity increases with cervical dilation, despite the absence of tissue damage.

Although many women rate the pain of labor and delivery as severe, the terms used to more fully describe this pain reflect an emotional meaning. In a pioneering study of the quantification of pain from experimental dilation of the cervix, Bajaj et al. compared pain descriptors in women who were in labor, had experimental cervical dilation, were undergoing spontaneous abortion, or who had dysmenorrhea (Table 20.1). Women with dysmenorrhea used words that indicate suffering, such as “punishing” and “wretched,” whereas those in labor did not. Some researchers have drawn parallels between the pain derived from mountain climbing, which is associated with a sense of euphoria, and the pain of labor. As noted by one woman, “You mature and become a stronger personality when you’ve had a baby and have gone through the pain. I think that is the purpose of it, what the meaning of life is . . . to protect our children, to be stronger.” However, other women have found no deeper meaning to the pain of labor or reasons why it should not be treated. Many conditions that involve pain (e.g., trauma, severe dental
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Local anesthetic field block experience pain from cervical distention (which mimics that of labor pain) but do not experience pain from uterine distention.\(^29\)

The uterine cervix has dual innervation; afferents innervating the endocervix and lower uterine segment have cell bodies in thoracolumbar dorsal root ganglia (DRG), whereas disease, cancer) are considered a “normal” part of human life without a spiritual meaning, thereby making labor pain unique.

In summary, there are large interindividual differences in how women experience the personal significance or meaning of labor pain. These different perceptions can lead to a long-term sense of failure and guilt when pharmacologic pain relief is accepted or emotional trauma when it is withheld. The use of educational interventions and improved management of labor expectations may improve the birth experience by creating realistic pain expectations during labor and delivery.\(^25\)

**ANATOMIC BASIS**

### First Stage of Labor

Several lines of evidence suggest that the pain experienced during the first stage of labor is transduced by afferents with peripheral terminals in the cervix and lower uterine segment rather than the uterine body, as is often depicted (Fig. 20.4). Uterine body afferents fire in response to distention, but in the absence of inflammation, uterine body distention has no or minimal effect on the behavior of laboratory animals.\(^26,27\)

These observations suggest that uterine body afferents may be an important site of chronic inflammatory disease and chronic pelvic pain but are much less relevant to acute obstetric and uterine cervical pain. In addition, afferents to the uterine body regress during normal pregnancy, whereas those to the cervix and lower uterine segment do not.\(^28\) This denervation of the myometrium may protect against preterm labor by limiting α\(_1\)-adrenergic receptor stimulation by locally released norepinephrine. Javert and Hardy\(^7\) reproduced the pain of uterine contractions in women during labor by manual distention of the cervix. Bonica and Chadwick\(^29\) later confirmed that women undergoing cesarean delivery under a local anesthetic field block experience pain from cervical distention (which mimics that of labor pain) but do not experience pain from uterine distention.\(^29\)

The uterine cervix has dual innervation; afferents innervating the endocervix and lower uterine segment have cell bodies in thoracolumbar dorsal root ganglia (DRG), whereas

### TABLE 20.1 Word Descriptors from the McGill Pain Questionnaire Used to Describe Pain from the Uterus and Cervix

<table>
<thead>
<tr>
<th>Pain Descriptors</th>
<th>Balloon Distention of the Cervix(^a)</th>
<th>Labor(^b)</th>
<th>Abortion(^c)</th>
<th>Dysmenorrhea(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Shooting, boring, sharp, hot, dull, taut</td>
<td>Throbbing, shooting, sharp, cramping, aching, taut</td>
<td>Cutting, cramping, tugging, pulling, aching</td>
<td>Pulsing, beating, shooting, prickling, boring, drilling, sharp, cutting, pinching, pressing, cramping, tugging, pulling, hot, stinging, dull, hurting, heavy, taut</td>
</tr>
<tr>
<td>Affective</td>
<td>Exhausting, tiring, frightening, grueling</td>
<td>Tiring</td>
<td>Intense</td>
<td>Tiring, sickening, punishing, wretched</td>
</tr>
<tr>
<td>Evaluative</td>
<td>Annoying</td>
<td>Drawing, squeezing</td>
<td>Numb, squeezing</td>
<td>Annoying, intense</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Tearing</td>
<td>Pulsing, beating, shooting, prickling, boring, drilling, sharp, cutting, pinching, pressing, cramping, tugging, pulling, hot, stinging, dull, hurting, heavy, taut</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


afferents innervating the vaginal surface of the cervix and upper vagina have cell bodies in sacral DRG. These two innervations result in different sensory input and referral of pain. Pelvic afferents that innervate the vaginal surface of the cervix are almost exclusively C fibers, with the majority containing the peptides substance P and calcitonin gene–related peptide (CGRP). These afferents express alpha and beta estrogen receptors and have an innervation pattern that is not affected by pregnancy. Stimulation of the vaginal surface of the cervix in rats results in antinociception, lordosis, ovulation, and a hormonal state of pseudopregnancy, all of which are related to mating behaviors in this species. In rats, these vaginal afferent terminals are activated only during delivery and not during labor, which suggests that they are not relevant to the pain of the first stage of labor. By contrast, dilation of the endocervix in rats results in the activation of afferents entering the lower thoracic spinal cord and nociception rather than antinociception. These afferents, which are mostly or exclusively C fibers, are activated during the first stage of labor, suggesting that they are relevant to pain during this period.

More than 80 years ago, experiments in dogs allowed Cleland to identify T11 to T12 as the segmental level of entry into the spinal cord of afferents that transmit the pain of the first stage of labor. Because dysmenorrhea could be treated through the destruction of the superior or inferior hypogastric plexus, Cleland reasoned that the sensory afferents and sympathetic efferents were likely intermingled; he subsequently demonstrated that the bilateral blockade of the lumbar paravertebral sympathetic chain could produce analgesia during the first stage of labor. First-stage labor pain is transmitted by afferents that have cell bodies in T10 to L1 DRG and pass through the paracervical region, the hypogastric nerve and plexus, and the lumbar sympathetic chain.

Classical teaching states that pain-transmitting C and A-delta nerve fibers enter the spinal cord through the dorsal roots and terminate in a dense network of synapses in the ipsilateral superficial laminae (I and II) of the dorsal horn, with minimal rostrocaudal extension of fibers. Whereas this characterization is true for somatic afferents, visceral C fiber afferents enter the cord primarily—but not exclusively—through the dorsal roots and terminate in a loose network of synapses in the superficial and deep dorsal horn and the ventral horn. These afferents also cross to the contralateral dorsal horn, with extensive rostrocaudal extension of fibers. This anatomic distinction underlies the precise localization of somatic pain and the diffuse localization of visceral pain, which may cross the midline; it may also determine the potency or efficacy of drugs that must reach afferent terminals, such as intrathecal opioids.

Pain-transmitting neurons in the spinal cord dorsal horn send axons to the contralateral ventral spinothalamic tract (stimulating thalamic neurons) with further projections to the somatosensory cortex, where pain is perceived. These spinal neurons also send axons through the spinoreticular and spinomesencephalic tracts to provide signals to the areas of vigilance (locus coeruleus, reticular formation), cardiorespiratory regulation (nucleus tractus solitarius, caudal medulla), and reflex descending inhibition (periaqueductal gray, locus coeruleus and subcoeruleus, nucleus raphe magnus, rostral medial medulla, cerebellum). Thalamic activation from painful stimuli results in the activation not only of the somatosensory cortex but also areas of memory (prefrontal cortex), motor response (M1 motor cortex), and emotional response (insula cortex, anterior cingulate cortex). Supraspinal pain pathways activated by pain of the first stage of labor can be briefly described sequentially, starting with the ascending pathways projecting to the pons and medulla, thereby activating centers of cardiorespiratory control and descending pathways as well as the thalamus, which in turn sends projections to the anterior cingulate, motor, somatosensory, and limbic regions.

The anatomic basis for pain of the first stage of labor implies that amelioration of pain should occur after blockade of peripheral afferents (by paracervical, paravertebral, lumbar sympathetic, or epidural [T10 to L1 dermatome] block) or after blockade of spinal cord transmission (by intrathecal injection of local anesthetic and/or opioid) (Fig. 20.5). In addition, the widespread distribution of visceral synapses in the spinal cord implies that intrathecally administered drugs (e.g., opioids) must have physicochemical properties that facilitate deep penetration into the cord to reach the terminals responsible for pain transmission.

Second Stage of Labor
Pain during the second stage of labor is transmitted by the same afferents activated during the first stage of labor but with additional afferents that innervate the cervix (vaginal surface), vagina, and perineum. These additional afferents course through the pudendal nerve DRG at S2 to S4 and are somatic. Thus, the pain specific to the second stage of labor is precisely localized to the vagina and perineum and reflects distention, ischemia, and frank injury, either by stretching to the point of disruption or by surgical incision. Studies in nonpregnant women indicate a minor analgesic effect of mechanical self-stimulation of the vaginal surface of the cervix; this effect may result from the stimulation of C fibers, because in women with a high oral intake of capsaicin, the activity of such fibers is reduced. The relevance of this minor effect in reducing the pain of the second stage of labor is questionable and has not been examined; however, it does appear to provide evidence that noxious input during labor may activate endogenous analgesia (see later discussion).

The anatomic basis for pain of the second stage of labor implies that analgesia can be obtained through a combination of methods used to treat the pain of the first stage with a pudendal nerve block or extension of the epidural blockade from T10 to S4 (see Fig. 20.5).

**NEUROPHYSIOLOGIC BASIS**

**Peripheral Afferent Terminals**

Visceral nociceptors, such as those that transduce the pain of the first stage of labor, are activated by stretching and
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**Mechanical distortion**

1. A variety of ion channels respond to the distortion of the cell membrane, and one of them—brain sodium channel-1 (BNC-1) or acid-sensing ion channel-2 (ASIC-2)—is exclusively expressed in sensory afferents and might directly depolarize the nerve terminal by opening its channel when the membrane is distorted (Fig. 20.6).41

2. Mechanical distortion may result in the acute release of a short-acting neurotransmitter that directly but transiently stimulates ion channel receptors on nerve terminals. Although this process has not yet been examined in the uterine cervix, studies have observed that stretching the bladder urothelium releases adenosine triphosphate, which directly stimulates a type of ligand-gated ion channel—P2X3—on sensory afferents in the bladder wall.42 Because P2X3 receptors are widely expressed in C fibers,43 this mechanism might be responsible for the pain that results from the acute distention of the uterine cervix.

3. Local ischemia during contractions may result in gated or spontaneous activity of other ion channels. Some of these ion channels—the ASIC family—respond directly to the low pH that occurs during ischemia,44 whereas other classes of ion channels may be activated to open spontaneously. For example, the vanilloid receptor type 1 (VR-1) can be stimulated by capsaicin. It is likely that VR-1 receptors (which also respond to noxious heat) are expressed on visceral afferent terminals, given that the application of capsaicin or heat to the distal esophagus in humans results in pain.45 VR-1 receptor-gated ion channels are not normally open in the absence of high temperature or capsaicin-like ligands; however, in the presence of low pH, the temperature response of these receptors shifts so that their channels open at body temperature.46
Uterine cervical afferents (including the C fibers that innervate the vaginal surface of the cervix) contain substance P, CGRP, and the enzyme nitric oxide synthase.\textsuperscript{67} C fibers can be divided into two groups: (1) those that contain substance P and CGRP and respond to nerve growth factor through actions on tyrosine kinase A receptors and (2) those that contain somatostatin, instead of substance P and CGRP, and respond to glially derived growth factor through actions on a c-ret complex.\textsuperscript{46} Some overlap exists between these rough classifications, and further definition of C fiber subtypes will likely occur as more markers and neuropeptides are examined. Other compounds commonly contained in C fiber terminals include glutamate, vasoactive intestinal peptide, and neuropeptide Y. The variable role of C fiber subtypes in the transmission of pain is also unclear. Given that somatostatin typically inhibits substance P release and pain transmission,\textsuperscript{49,50} the net transmission of nociception at the spinal cord level may reflect a complex interaction between excitatory and inhibitory C fiber subtypes.

The peripheral afferent neurophysiology of pain during the first stage of labor suggests that the largely unexplored multiple ion channels that transduce the mechanical signal of cervical stretching to an electrical signal generating the perception of pain may represent important new targets for local or systemic analgesic drug delivery. In addition, the understanding of the classification, function, and relevance to pain of different C fiber subtypes remains in its infancy. Research involving endocervical C fiber subtypes may identify new targets for the treatment of labor pain.

**Role of Sensitization**

Peripheral afferent terminals, like other parts of the sensory system, can change their properties in response to various conditions. Afferent terminals can be directly stimulated by the low pH associated with inflammation (Fig. 20.7), and selective ligand-gated ion channels on these terminals can be stimulated by the release of bradykinin.\textsuperscript{51} In addition, peripheral inflammation sensitizes afferent terminals by changing their properties; this process can result, over a short time, in a change in gene expression by these nerve fibers, thereby leading to a large amplification of pain signaling.

Although peripheral inflammation is most commonly associated with the pain that results from acute postoperative and chronic arthritic conditions, it may also play an essential role in labor pain. The cervical ripening process and labor itself both result from local synthesis and release of a variety of inflammatory products. The clinical implications of these inflammatory pathways include the application of inflammatory mediators (e.g., prostaglandin E\textsubscript{2} [PGE\textsubscript{2}]) to prepare the cervix for labor induction and the administration of inflammatory mediator inhibitors (e.g., indomethacin) to stop preterm labor.

PGE\textsubscript{2} is an especially important sensitizing agent for uterine cervical afferents. In most species, the onset of labor is triggered by a sudden decrease in circulating estrogen concentration. This decrease removes a tonic block on the expression of cyclooxygenase, leading to an increase in local production of prostaglandins, especially PGE\textsubscript{2}.\textsuperscript{32} PGE\textsubscript{2} is central to a variety of processes that are activated to allow ripening and dilation of the uterine cervix. During the 24 to 72 hours preceding the onset of labor, collagen in the cervix becomes disorganized owing to the activation of prostaglandin receptors and the activity of inflammatory cytokines (mostly interleukin-1-beta [IL-1\textbeta]) and tumor necrosis factor-alpha [TNF-\alpha]) and matrix metalloproteinases (especially types 2 and 9).\textsuperscript{53,54} A series of studies in the rat paw have demonstrated that PGE\textsubscript{2} induces peripheral sensitization in a sex-independent manner by activation of protein kinase A\textsuperscript{55} and nitric oxide synthase.\textsuperscript{56}

Cytokines and growth factors are also released into the uterine cervix immediately before and during labor. The cytokine IL-1\textbeta enhances cyclooxygenase activity and substance P release in the DRG and spinal cord.\textsuperscript{57,58} TNF-\alpha increases the spontaneous activity of afferent fibers\textsuperscript{59} and enhances CGRP release and VR-1 receptor expression in DRG cells in culture.\textsuperscript{60} Nerve growth factor also induces mechanical hypersensitivity.\textsuperscript{61} These sensitizing substances (prostaglandins, cytokines, and growth factors) signal peripheral nerves in a manner that results in a host of changes in DRG cell number, peptide expression and release, receptor and ion channel expression, and biophysical properties. For example, inflammatory mediators alter the expression of sodium (Na\textsuperscript{+}) channel subtypes,\textsuperscript{62,63} thereby resulting in more rapid, repetitive firing capability and spontaneous afferent activity.\textsuperscript{55}

Estrogen receptor signaling can dramatically affect the structure of the uterine cervix and possibly modulate pain
Opioid receptors have achieved the widest attention. Although µ-opioid receptors are expressed in some afferents in the setting of inflammation, the efficacy of morphine provided by local instillation has proved disappointing, with the exception of an intra-articular injection. Similarly, µ-opioid receptor agonists produce antinociception to uterine cervical distention through actions in the central nervous system but not in the periphery.

κ-Opioid receptor agonists may effectively treat visceral pain owing to the presence of these receptors in visceral, but not somatic afferents, at least in the gastrointestinal tract. κ-Opioid receptor agonists can also produce antinociception in response to uterine cervical distention through actions in the peripheral nervous system. Pharmaceutical firms are developing drugs of this class that are restricted to the periphery, have few central side effects, and presumably express little potential for placental transfer; potentially, such agents would be useful for labor analgesia. One of these new agents has been observed to effectively treat chronic visceral pain from pancreatitis in patients receiving poor analgesia from µ-opioid receptor agonists.

Estrogen and progesterone can alter the analgesic response to opioids. In most cases involving somatic stimulation, tonic estrogen treatment reduces the efficacy of µ-opioid but not κ-opioid receptor agonists. Further, κ-opioid receptor agonists have greater analgesic efficacy in women than in men. In animals, tonic estrogen exposure reduces the inhibitory responses to uterine cervical distention by morphine but not to the κ-opioid receptor agonist U-50488. In contrast, the inhibitory action of intrathecal morphine against responses to uterine cervical distention is unaffected by tonic estrogen exposure, which is consistent with the observation that intrathecal opioids relieve the pain of the first, but not second, stage of labor.

Implications of inhibitory receptors on afferent terminals are that κ- but not µ-opioid receptor agonists may produce pain relief through their actions in the periphery. Selective, peripherally restricted drugs are under development for the systemic treatment of visceral pain. In addition, estrogen-dependent inhibition of the supraspinal (but not the spinal) analgesic action of µ-opioid receptor agonists may underlie the limited analgesic effect produced by systemic opioids, a finding that is in contrast to the efficacy of intrathecal opioids in relieving the pain of the first stage of labor.

Peripheral Nerve Axons

The current approach to labor analgesia relies primarily on an understanding of the afferent axons and their level of entry into the spinal cord and on the administration of local anesthetics to block afferent traffic conduction. Traditionally, axons have been considered conduits that allow for the propagation of action potentials by the transitory opening of sodium channels. More recent investigations have confirmed the existence of a variety of sodium channel subtypes and axons that modulate transmission through other ion channels.
Although a number of voltage-gated sodium channel subtypes exist, most studies have focused on three specific subtypes that are expressed in sensory afferents.93 Two of these, NaV1.8 and NaV1.9, are relatively resistant to blockade by tetrodotoxin (TTX-R); NaV1.9 is often referred to as "persistent," owing to its very slow inactivation kinetics.84 Inflammation and injury to nerves decrease the TTX-R current density in afferent cell bodies.85 Some investigators have suggested that NaV1.8 is selectively trafficked to the periphery after injury and inflammation85 and that a reduction of its expression reduces hypersensitivity.86 Other investigators, using sucrose gap measurements of compound action potentials, have demonstrated a shortened refractory period and a decrease in delayed depolarization after nerve injury87,88 that are consistent with the greater expression of rapidly repriming tetrodotoxin-sensitive (TTX-S) channels and the decreased expression of kinetically slow TTX-R channels. To date, these studies have focused primarily on peripheral nerve injury models of chronic pain, and neither the subtypes nor their change during the cervical inflammation of labor has been studied.

Several pharmaceutical firms have discovery programs to produce sodium channel subtype-selective blockers that could improve both the safety and efficacy of the treatment of labor pain, because such agents would not interact with sodium channels in the brain, heart, or motor nerve fibers. Some investigators have observed that injection of the antidepressant amitriptyline, an agent known to block the NaV1.8 sodium channel around the peripheral nerves provides a neural blockade twofold to fivefold longer than that provided by injection of long-acting local anesthetics.89,90

Another subject of current research is the extension of the duration of selective antinociception with no motor or sympathetic block by manipulation of the TRPV-1 receptor, which is a nonselective ligand-gated cation channel. TRPV-1 receptors are expressed in peripheral primary afferent neurons, the nociceptive C and A-delta fibers, and the dorsal root ganglia, as well as the structures involving the endogenous antinociceptive descending pathway. TRPV-1 receptors can be activated by capsaicin, heat, and endovanilloids, leading to release of substance P, which in turn excites inhibitory neurons in laminae I, III, and IV. Further, activation of the TRPV-1 receptors causes opening of the small TRPV-1 channels on the neurons and allows entry of co-administered charged molecules of certain sizes. Permanently charged local anesthetics, when applied alone, would not be able to cross the nerve membrane to exert its effect on sodium channels in small sensory neurons, but when applied in the presence of capsaicin or other TRPV-1 agonists, the permanently charged local anesthetic would become permeant to exert its local anesthetic effect. Binshtok et al.91 reported the inhibition of nociceptors by TRPV-1–mediated entry of impermeant sodium channel blockers. However, stimulation of TRPV-1 receptors, such as with capsaicin alone, will also result in the induction of receptor-mediated acute pain. Therefore, these investigators subsequently performed another study in rodents, and they observed that the co-application of lidocaine and its quaternary permanently charged derivative QX-314 produces a prolonged, predominantly charged QX-314 entry through the TRPV-1 channels without the nocifensive behavior associated with capsaicin when lidocaine is used instead to activate the TRPV-1 receptors.92 The issues of pain elicited with administration of TRPV-1 agonists such as capsaicin and, more importantly, the neurotoxicity of permanently charged Na+ channel blockers remain to be overcome and require further research. Additional investigations of the exploitation of new targets may allow provision of safer and prolonged selective antinociception. Should future research prove the absence of toxicity, it is conceivable that amitriptyline or other agents that interact with Na+ channel subtypes and/or TRPV-1 receptors could be considered for single-injection techniques to produce prolonged and selective analgesia for labor pain and postoperative pain relief.

Interactions within the large number of ion channels expressed on axons can alter neural conduction. An example is the transient refractory period caused by the membrane hyperpolarization that follows a short burst of nerve firing. This phenomenon results from activation of the Na+/K+ exchange pump and dampens high-frequency nerve activity. The Na+/K+ exchange pump activity, in turn, can be reduced by a hyperpolarization-induced current termed Ih. Drugs that block the Ih current enhance the hyperpolarization caused by the Na+/K+ exchange pump and ultimately serve to reduce nerve traffic93 and provide prolonged analgesia.94 A second example is the desensitization of VR-1 receptors present on the axons of C fibers. The perineural injection of drugs that desensitize these receptors without first stimulating them avoids the induction of receptor-mediated acute pain and instead produces very long periods of selective sensory analgesia without motor effects.95 The mechanism by which VR-1 receptor desensitization alters the transmission of action potentials is under investigation.

Implications of the neurophysiology of axonal transmission of labor pain are that sodium channel subtype–selective agents—or those that affect other ion channels expressed on axons—may provide safer and more selective tools for regional analgesic techniques.

**Spinal Cord**

When action potentials invade the central terminals of C and A-delta fiber afferents in the spinal cord, voltage-gated calcium channels open and cause intracellular calcium concentration to increase; this increase triggers a multistep process of neurotransmitter docking and fusion with the plasma membrane, which results in neurotransmitter release.96 Inhibition of these calcium channels produces analgesia. Studies in animals suggest that at least one agent that affects the calcium channels, gabapentin, produces antinociception to visceral stimulation.97 A nociceptive stimulus can result in the release of multiple excitatory neurotransmitters, including amino acids (glutamate, aspartate) and peptides (especially substance P, CGRP, and neurokinin A) that interact with specific receptors on
spinal cord neurons. Although the stimulation of neurokinin receptors is necessary for the perception of moderate to severe pain, a complex and poorly understood interplay exists among these released neurotransmitters.

Neurotransmitter release at sensory afferent terminals is controlled by presynaptic receptors that act primarily by altering the flux of intracellular calcium when an action potential arrives. Some of these neurotransmitters are excitatory; for example, the action of acetylcholine on nicotinic acetylcholine receptors amplifies further neurotransmitter release. Gamma-aminobutyric acid (GABA) is the key endogenous inhibitory neurotransmitter in the nervous system, and stimulation of GABA receptors significantly reduces the afferent terminal release of other neurotransmitters. Multiple compounds produce analgesia by enhancing the release of GABA at afferent terminals in the spinal cord. The existence of excitatory and inhibitory systems can make the response to a neurotransmitter or an exogenously-administered agent (such as a local anesthetic drug given intrathecally) difficult to predict. For example, acetylcholine can enhance or reduce the afferent terminal release of neurotransmitters by actions on nicotinic and muscarinic receptors, respectively. The net effect of acetylcholine appears to be inhibitory, which is indicated by the analgesic effect of intrathecal administration of the cholinesterase inhibitor neostigmine.

The primary mechanism of action of the neurotransmitter enkephalin, which is released by spinal cord interneurons, and of norepinephrine, which is released by axons descending from pontine centers, is the inhibition of neurotransmitter release from primary afferent terminals. These substances act on µ-opioid and α2-adrenergic receptors, respectively, and may produce some of the similar effects observed after the intrathecal administration of opioids and α2-adrenergic agonists for the treatment of labor pain.

Amino acids and peptides released from sensory afferents stimulate a heterogeneous group of spinal cord neurons, including neurons that project to supraspinal structures, interneurons that modulate transmission at the afferent terminal itself (the “gate” of the control theory), and interneurons that stimulate motor and sympathetic nervous system reflexes. Large and sustained glutamate release from an intensely noxious stimulus can activate N-methyl-D-aspartate (NMDA) receptors, resulting in sustained depolarization and enhanced excitability of projection neurons (Fig. 20.9). Although the intrathecal injection of NMDA receptor antagonists (e.g., ketamine) has been restricted because of neurotoxicity concerns, systemic infusion of magnesium sulfate has been observed to produce postoperative analgesia. Magnesium is an endogenous inhibitory modulator of NMDA receptors, and it is conceivable that magnesium sulfate administered systemically for obstetric indications may have a minor effect on labor pain.

Prolonged and intense nociceptive stimuli can produce sensitization and amplification of pain signaling at the spinal cord level like the peripheral sensitization that occurs as a result of inflammation. Some of these processes are a direct consequence of receptors (e.g., NMDA receptors) that are activated only with highly intense and prolonged stimulation or by the long-term release of neurotransmitters that simultaneously activate the glutamate and substance P receptors on the same cell. Others reflect the synthesis and release of classic “inflammatory” substances by the spinal cord glial cells in response to prolonged afferent stimulation from nitric oxide and prostaglandins, especially PGE2. Some non-opioid analgesic drugs produce analgesia by actions exclusively (e.g., acetaminophen [paracetamol]) or primarily (e.g., aspirin) in the central nervous system (especially the spinal cord).

Spinal sensitization processes represent a novel target for the treatment of labor pain. More than 80 years ago, Cleland noted the presence of hypersensitivity to light touch on the skin of dermatomes T11 and T12 in laboring women, which likely represents the enhanced sensitivity of spinal cord neurons receiving both visceral input from the cervix and skin input at those levels. When the visceral stimulation to these dermatomes was blocked by a paravertebral local anesthetic injection, Cleland observed that the hypersensitivity was ablated; this observation is consistent with the later finding that ongoing C fiber input is required for hypersensitivity to occur. Uterine cervical distention (UCD) results in a pattern of spinal cord neuronal activation similar to that witnessed during labor and delivery. In a study in rats reported by Tong et al., UCD significantly increased c-fos immunoreactivity in the spinal cord from T12 to L2, with most of the c-fos expression occurring in the deep dorsal horn and central canal regions. UCD-evoked c-fos expression was prevented by prior infiltration of lidocaine into the cervix or by intrathecal administration of ketorolac (a cyclooxygenase [COX] inhibitor) in a dose-dependent manner. Intrathecal administration of indomethacin (a nonspecific COX inhibitor) and the selective COX-2 inhibitor SC-58238 effectively ablated...
UCD-induced electromygographic activity without altering the hemodynamic response to UCD. By contrast, the selective COX-1 inhibitor SC-58360 was ineffective in ablating UCD-induced electromygographic activity, as was ketorolac, an agent with higher affinity for COX-1 than COX-2. Together, these data suggest that targeting COX-2 is necessary to treat the acute visceral pain often associated with brief infrequent contractions in late pregnancy; therefore, intrathecal ketorolac would be predicted to be ineffective. However, in the setting of sustained, frequent, and repetitive contractions for a prolonged period (as occurs during active labor), intrathecal ketorolac might be effective. The intrathecal injection of ketorolac has been introduced into experimental human trials and warrants examination as a potential modality for selective treatment of labor pain.

The neurophysiologic basis for labor pain in the spinal cord implies that purely inhibitory mechanisms (e.g., opioid and α2-adrenergic receptors) can be mimicked by the intrathecal injection of agonists to these receptors. However, the administration of other agents (e.g., acetylcholine) in this location has less predictable results. Central sensitization mechanisms in the spinal cord most certainly occur during labor, and future treatments may target these mechanisms.

**Ascending Projections**

Spinal cord neurons project to multiple brainstem sites as well as the thalamus. Forty years ago, it was noted that descending systems—activated primarily by stimulation of the nucleus raphe magnus, the periaqueductal gray, and the locus coeruleus—could reduce pain transmission as described in the gate control theory. Activation of descending pathways results in the spinal release of endogenous ligands for serotoninergic, opioid, and α2-adrenergic receptor–mediated analgesia. Spillover of neurotransmitters into the cerebrospinal fluid has been used as a measure of activation of these systems, and studies measuring these substances have shown no increase in enkephalin, but an increase in norepinephrine, in laboring women. These descending systems can be activated by psychoprophylactic methods, and agents that prolong or intensify the action of these ligands, such as enkephalinase inhibitors and blockers of monoamine reuptake, might further enhance analgesia.

Brainstem activation by the pain of labor leads to other reflexes, such as increases in sympathetic nervous system activity and respiratory drive and, with prolonged activation, stimulation of descending pathways that amplify rather than reduce pain transmission at the spinal cord. The circuitry and pharmacology of such pain-enhancing systems in the brainstem and their potential applications for treatment are under current investigation.

Our understanding of the areas of the brain activated during labor pain is limited, although studies of other types of experimental nociception in healthy volunteers indicate that visceral pain is considered more unpleasant than somatic pain; this difference reflects, in part, the greater activation of centers for negative emotions, including fear. Although distraction methods do not alter the thalamic activation from noxious stimulation, a reduction in cortical activation and the report of pain have been observed, supporting a suprathalamic mechanism of psychoprophylaxis in the reduction of pain.

The neurophysiologic basis of labor pain and ascending projections suggests the activation of multiple supraspinal sites. Some of these sites stimulate potentially detrimental cardiorespiratory reflexes. Other sites, which send descending projections that either reduce or enhance pain transmission in the spinal cord, may be targeted for the provision of analgesia. In addition, suprathalamic modulation of pain signals appears to account for the interindividual differences in pain perception and for the relative efficacy of psychoprophylaxis in reducing the intensity of reported pain.

### EFFECT ON THE MOTHER

**Obstetric Course**

Several aspects of labor pain can affect the course of labor and delivery (Fig. 20.10). Pain-induced increases in the activity of the sympathetic nervous system lead to higher plasma concentrations of catecholamines, especially epinephrine. The provision of labor analgesia reduces the plasma concentration of epinephrine and its associated beta-adrenergic tocolytic effects on the myometrium. This process may underlie the observations by some investigators who have noted, either anecdotally or under controlled conditions, a shift from dysfunctional to normal labor patterns in some women when analgesia is achieved with paravertebral or epidural blocks or with systemic meperidine (pethidine) analgesia. The abrupt reduction in plasma epinephrine concentration that follows the rapid onset of intrathecal opioid analgesia may reduce basal uterine activity and increase the intensity of pain.

![Fig. 20.10 Aspects of pain that may affect the course of labor. In addition to indirect effects (e.g., beta-adrenergic tocolysis from increased secretion of epinephrine, greater release of oxytocin via Ferguson’s reflex), depolarization of afferent terminals in the lower uterine segment and cervix can directly alter aspects of labor. Substances released by nerve terminals include those that increase local blood flow (CGRP [calcitonin gene–related peptide], sP [substance P], NO [nitric oxide], NK [neurokinin], those that stimulate immune cell function, and those that stimulate (+) or inhibit (–) myometrial smooth muscle activity, including vasoactive intestinal peptide (VIP).]
result in an acute reduction of beta-adrenergic tocolysis and a transient period of uterine hyperstimulation; in some cases, these changes may lead to transient fetal stress and fetal heart rate abnormalities. Ferguson’s reflex involves neural input from ascending spinal tracts (especially from sacral sensory input) to the midbrain, thereby leading to enhanced oxytocin release. Although spontaneous labor and delivery occur in women with spinal cord injury (which disrupts this tract), some investigators have argued that neuraxial analgesia can inhibit this reflex and prolong labor, especially the second stage. However, strong evidence for this does not exist. Some studies have noted a reduction in plasma oxytocin concentration with epidural local anesthetic or intrathecal opioid analgesia, whereas others have not noted such a reduction. Papka and Shew suggested that afferent terminals in the lower uterine segment and cervix might have an important secretory (efferent) function in the regulation of labor. Afferent terminals contain many substances that can stimulate (substance P, glutamate, vasoactive intestinal peptide) or inhibit (CGRP, nitric oxide) myometrial activity, and these substances can be released locally into the cervix and lower uterine segment when terminals are depolarized by contraction-related tissue distortion. In addition, depolarization of the afferent terminal can result in an action potential that, upon reaching a site of nerve branching, invades adjacent branches and travels distally to depolarize distant terminals of the same nerve. This axon reflex has long been recognized to occur in somatic nerves; owing to the more extensive arborizations believed to exist in visceral nerves, local stimulation should result in more widespread release of these transmitters. Therefore, it is tempting to speculate that these axon reflexes are more profoundly affected when local anesthetic is administered closer to the terminals associated with cervical dilation and labor (e.g., as occurs with paracervical and paravertebral blocks) than occurs when local anesthetic is administered farther away from the terminals (e.g., with epidural block). This speculation would imply that the net effect of afferent terminal–released substances inhibits rather than accelerates labor.

In summary, neural stimulation through pain pathways leads to the release of substances that either increase (oxytocin) or inhibit (epinephrine) uterine activity and cervical dilation. Therefore, the effect of analgesia on the course of labor can vary between and within individuals. In addition, axon reflexes can result in the release of neurotransmitters from afferents into the lower uterine segment and cervix. It is hoped that future investigation will determine whether the proximity of local anesthetic deposition affects the response of cervical dilation and labor.

Cardiac, Respiratory, and Gastrointestinal Effects

Labor exerts stresses on the cardiovascular and respiratory systems. The elevated plasma catecholamine concentrations observed during labor pain can increase maternal cardiac output and peripheral vascular resistance and decrease uteroplacental perfusion. Even transient stress is associated with dramatic increases in plasma concentration of norepinephrine and subsequent decreases in uterine blood flow (Fig. 20.11). Plasma epinephrine concentrations in women with painful labor are similar to those observed after intravenous administration of a bolus of epinephrine 15 µg, intravenous bolus injection of epinephrine 10 to 20 µg resulted in a significant (albeit transient) reduction in uterine blood flow in gravid ewes. Effective neuraxial analgesia, provided by epidural local anesthetic or intrathecal opioid administration, significantly reduces (50%) maternal catecholamine concentrations. By contrast, neonatal catecholamine concentrations do not appear to be altered by maternal neuraxial anesthetic techniques; this relative independence of neonatal catecholamine responses may be important for the neonatal adaptation to extrauterine life.

The intermittent pain of uterine contractions also stimulates the respiratory system and leads to periods of intermittent hyperventilation. In the absence of supplemental oxygen administration, compensatory periods of hyperventilation between contractions result in transient episodes of maternal, and even fetal, hypoxemia (Fig. 20.12). Treatment of labor pain with epidural analgesia minimizes the increase in net minute ventilation and the accompanying increase in oxygen consumption. In general, the cardiovascular and respiratory system changes induced by labor pain are well tolerated by healthy parturients (with normal uteroplacental perfusion) and their fetuses. Some authors have concluded...
that these changes are of no concern or relevance in uncomplicated labor. However, when maternal or fetal disease or compromise is observed, significant cardiopulmonary alterations may lead to maternal or fetal decompensation; effective analgesia may be especially important in such cases.

Labor pain, anxiety, and emotional stress increase gastric release and inhibit the segmental and suprasegmental reflexes of gastrointestinal and urinary motility. This in turn results in an increase in gastric acidity and volume and a delay in bladder emptying. These changes are further aggravated by the recumbent position, opioids, and other depressant medications (e.g., barbiturates), putting laboring parturients at risk for pulmonary aspiration of gastric contents, especially during emergency induction of general anesthesia for cesarean delivery.

In summary, pain-induced activation of the sympathetic nervous system during labor is associated with cardiovascular, respiratory, and gastrointestinal effects that may alter maternal and fetal well-being. The provision of effective neuraxial analgesia may mitigate many of these cardiopulmonary effects.

**Psychological Effects**

The meaning of labor pain is greatly influenced by psychosocial and environmental factors (as previously discussed) and varies considerably among women. Although the acceptance of labor analgesia has a minor overall effect on maternal satisfaction with the labor and delivery process, individual women can be profoundly influenced. It has been suggested that women who understand the origin of their pain and view the labor and delivery process as positive and nonthreatening may undergo pain without suffering. Billewicz-Driemel and Milne reported that a small proportion (< 5%) of women who requested and received epidural labor analgesia described a sense of deprivation from having missed the natural labor experience in its entirety; some of these women may subsequently seek psychiatric counseling.

By contrast, unrelieved severe labor pain can have psychological and physical consequences, including depression and negative thoughts about sexual relationships. In a 5-year study in Sweden, 43 women requested elective cesarean delivery owing to a fear of labor and vaginal delivery. Some countries (e.g., Brazil) have an extremely high elective cesarean delivery rate (> 80%) among upper-class women because of their concerns about reduced sexual function after vaginal delivery. Frank psychotic reactions resembling posttraumatic stress disorder can occur after childbirth, although the incidence is rare (< 1%).

Psychological effects of labor pain can occur in a small proportion of women. Psychological harm can be experienced through the provision or withholding of labor analgesia, underscoring the tremendous variability in the meaning of labor pain for different women.

**Pain after Delivery**

Many women undergo delivery without negative sequelae, but some may experience significant persistent postpartum pain and even depression. Studies of acute and chronic postpartum pain have shown a 7% incidence of perineal pain at 8 weeks after vaginal delivery, and a 43% incidence of hyperalgesia at 48 hours and a 23% incidence of residual pain at 6 months after cesarean delivery. In a multicenter, prospective, longitudinal cohort study of 1288 parturients delivering either by cesarean or vaginal delivery, Eisenach et al., using regression analyses and propensity adjustment, reported a 10.9% prevalence of severe acute pain within 36 hours postpartum, whereas the prevalence of persistent pain and depression at 8 weeks postpartum was 9.8% and 11.2%, respectively. The severity of acute postpartum pain, but not the mode of delivery, was independently related to risk for persistent pain and depression at 8 weeks postpartum, both of which also resulted in negative effects on activities of daily living and on sleep. Those women with severe acute postpartum pain had a 2.5- and 3.0-fold increased risk for persistent pain and depression, respectively, when compared with those with mild acute postpartum pain. These findings suggest these morbidities may not be related to degrees of physical tissue trauma but rather may be related to an individual’s pain response to that injury.

Although there is significant interindividual variability with regard to acute postpartum pain, the severity of acute postoperative pain in nonobstetric surgical patients has been correlated with the occurrence of chronic pain. Whether the presence and severity of labor pain or the presence and severity of acute postpartum pain after either vaginal or cesarean delivery predicts the occurrence of chronic pain is under investigation. Studies in animals suggest that acute intervention at the time of tissue injury reduces the likelihood...
of developing chronic pain. It is likely that severity of the acute pain is not just a marker of chronic pain but rather an active participatory component in the pathophysiology of transitioning from acute to chronic pain. In a prospective cohort study of 241 parturients undergoing a vaginal delivery, Ding et al. reported that the use of epidural labor analgesia was associated with a decreased risk for postpartum depression (odds ratio 0.31, 95% confidence interval 0.12 to 0.82, \( P = 0.018 \)). More careful attention to pain treatment and follow-up in days after childbirth may potentially reduce long-term morbidities and improve overall outcomes.

Reports on the incidence of chronic pain after delivery vary widely in part because of the difference in the definition and the inclusion or exclusion of types of chronic pain and not critically separating new pain after delivery from preexisting pain. Long-term follow-up of postpartum patients showed that the incidence of chronic pain (defined as new pain that began at the time of labor and delivery) at 6 months and 1 year was remarkably low at 3% and 0.1%, respectively, compared with nonobstetric surgeries with similar tissue injury. By using a sciatic nerve injury-induced neuropathic pain model in rats, it has been observed that the birthing process plus the nursing of the pups in combination, but not individually, may be protective of the development of surgical nerve injury–induced hypersensitivity to pain. This protection is likely mediated by spinal oxytocin because the protective effect is abolished by administration of spinal atosiban, an oxytocin antagonist.

The majority of pain research examines pain scores at predefined time points in the postoperative or postpartum period, but neglects the day-to-day experiences of pain recovery following surgery. Houle et al. applied growth curve modeling to patients undergoing cesarean delivery or lower limb total joint arthroplasty by evaluating daily pain scores; a Bayesian change-point model, rather than the traditional log (time) model, was observed to be a better fit to the diminution of postoperative pain scores and suggested that “meaningful subpopulations of experience may exist” wherein patients do not recover in the same manner after the same surgery.

Further research is needed to better define protective and/or predictive factors in patients who are at risk for developing severe acute and/or chronic postpartum pain. Persistent or chronic pain may be particularly difficult for postpartum patients owing to the multiple stresses (e.g., care of the neonate) and sequelae encountered. An association between pain and depression exists, and depression is the most common complication after delivery, affecting approximately 13% of postpartum women. Postpartum patients with depression are among those who frequently do not disclose depression even though they desire assistance. Immediate and effective postpartum pain management (after both vaginal and cesarean deliveries) with adequate long-term follow-up may potentially prevent long-term morbidity and improve overall outcomes. For example, one prospective study of 205 parturients evaluating risk factors for the development of persistent postcesarean pain did not find a relationship with maternal anxiety, but demonstrated an association with acute pain and postpartum depression. Further detailed research is needed to better stratify risk factors that place parturients at risk for the development of persistent pain after delivery.

**EFFECT ON THE FETUS**

Because of the absence of direct neural connections from the mother to the fetus, maternal labor pain has no direct effects on the fetus. However, maternal labor pain can affect a number of systems that determine uteroplacental perfusion, as follows: (1) uterine contraction frequency and intensity, by the effect of pain on the release of oxytocin and epinephrine; (2) uterine artery vasoconstriction, by the effect of pain on the release of norepinephrine and epinephrine; and (3) maternal oxyhemoglobin desaturation, which may result from intermittent hyperventilation followed by hypoxemia, as discussed earlier. Although these effects are well tolerated in normal circumstances and are effectively blocked by analgesia, fetal well-being may be affected in situations of limited uteroplacental reserve.

**SUMMARY**

Pain during the first stage of labor results from the stimulation of visceral afferents that innervate the lower uterine segment and cervix, intermingle with sympathetic efferents, and enter the spinal cord at the T10 to L1 segments. Pain during the second stage of labor results from the additional stimulation of somatic afferents that innervate the vagina and perineum, travel within the pudendal nerve, and enter the spinal cord at the S2 to S4 segments. These pain signals are processed in the spinal cord and are transmitted to brainstem, midbrain, and thalamic sites, the last with projections to the cortex, resulting in the sensory-emotional experience of pain. Current obstetric anesthesia practice relies nearly exclusively on the blocking of pain transmission by deposition of local anesthetic—with or without adjuncts—along the afferent nerves from sites near the peripheral afferent terminals to sites near their central terminals.

The neurophysiology of visceral pain, especially in relation to labor pain, is currently under investigation, with considerable academic and pharmaceutical targeting of (1) the normal ionic transduction mechanisms and processes of sensitization in peripheral afferent terminals, (2) the mechanisms of inhibition available in the spinal cord and brainstem, and (3) the processes by which conscious distraction methods can be amplified and can relieve pain. Labor pain is an intensely variable and personal experience, and it is essential that the anesthesia provider play a flexible role within this context.

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PART VI  Labor and Vaginal Delivery

KEY POINTS

- Labor pain exists and is severe in many women, with a close correlation between cervical dilation and pain during the first stage.
- The first stage of labor involves visceral pain from the lower uterine segment and endocervix, which results in hypersensitivity to convergent somatic dermatomes. This pain is most likely amplified over time as a result of the sensitization of peripheral and central pain-signaling pathways. The second stage of labor results in somatic pain from the vagina and perineum and is briefer than the first stage.
- Afferent terminals transduce a mechanical process into electrical signals, which are probably amplified by the release of prostaglandins, cytokines, and growth factors into the cervix as part of the normal disruption of collagen that allows the cervix to soften and dilate.
- Pain transmission in the spinal cord is not hardwired; it is remarkably and rapidly plastic, and it is altered by local neuronal activity that releases μ-opioid receptor agonists and descending pathways that release α2-adrenergic and serotoninergic receptor agonists.
- There are large individual differences in pain perception, which likely reflect differences at suprathalamic sites. The activation of suprathalamic sites is the primary mechanism of action for distraction methods of analgesia.
- Labor pain alters the obstetric course and the maternal cardiac and respiratory function in a complex manner that normally is well tolerated, can sometimes be detrimental to both mother and fetus, and is alleviated by analgesia.
- Labor pain carries meaning in distinction from most other causes of severe pain; the treatment of labor pain should be applied within this context.
- Acute postpartum pain after either vaginal or cesarean delivery deserves attention and treatment; the factors or mechanisms responsible for the development of persistent or chronic postpartum pain are under investigation.

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At their core, the experiences of labor and birthing a child are intensely personal, intimate processes for many women, regardless of culture or background. While anesthesia providers may have a particular view of what is important to a woman during childbirth, including pain management strategies, our goals should be to understand each woman’s values and beliefs and to recommend therapies when appropriate, taking into account medical and obstetric considerations as well as personal wishes. Some women seek nonpharmacologic strategies to cope with the pain in labor; these strategies may be independent of, or complementary to, some of our more “traditional” forms of labor pain relief such as neuraxial analgesia. A 2014 meta-analysis of nonpharmacologic approaches for pain management during labor compared with “usual care” found that the nonpharmacologic strategies were associated with reductions in various obstetric interventions, indicating that these therapies will remain in the lexicon of patient-centered care.¹ While some of the evidence surrounding nonpharmacologic approaches is less rigorous than evidence supporting some of our more traditional forms of pain relief, many of these approaches are rooted in pain-based theories, including (1) the gate control theory (e.g., light massage, water immersion, ambulation, birthing balls); (2) diffuse noxious inhibitory control (DNIC) [e.g., sterile water injections, acupuncture, acupressure, transcutaneous electrical nerve stimulation (TENS)]; and (3) central nervous system control (e.g., antenatal education, continuous support during labor, meditation, hypnosis, aromatherapy).¹ This chapter aims to provide obstetric anesthesia providers with a comprehensive knowledge of nonpharmacologic labor strategies and how they may contribute to coping and management of labor pain. This information provides a basis for informed discussion of pain relief options among patients, nurses, obstetricians, and anesthesia providers.

In addition to referencing their own personal beliefs, pregnant women and their support person(s) obtain information about childbirth and analgesia from many sources. The more traditional sources of information include obstetricians, childbirth preparation classes, lay periodicals, books and pamphlets, and experiences of family and friends. The Internet has become the primary source of information for many patients, and according to the Listening to Mothers III survey published in 2014, 78% of women used childbirth websites or blogs to gain access to information.² Anesthesia providers should be familiar with the information that patients in the local area are using for decision-making, because this information influences their birth experiences. Knowledge of the information and biases held by patients helps anesthesia providers in their interactions with pregnant women.

**PAIN PERCEPTION**

Anesthesia providers are indebted to John Bonica and Ronald Melzack for their studies of the pain of childbirth. Investigators have used sophisticated questionnaires³,⁴ and visual
analogue scales\textsuperscript{5} to evaluate the maternal perception of pain during parturition. Melzack et al.\textsuperscript{6,7} developed the McGill Pain Questionnaire to measure the intensity of labor pain for various conditions. They noted that labor pain is one of the most intense types of pain among those studied (see Fig. 20.2). Parous women had lower pain scores than nulliparous women, but responses varied widely (Figs. 21.1 and 21.2). Prepared childbirth training resulted in a modest decrease in the average pain score among nulliparous women, but it clearly did not eliminate pain in these women.\textsuperscript{6,7}

**CHILDBIRTH PREPARATION**

**History**

The history of modern childbirth preparation began in the first half of the 20th century; however, it is important to review earlier changes in obstetric practice to understand the perceived need for a new approach. Before the mid-19th century, childbirth occurred at home in the company of family and friends. The specialty of obstetrics developed in an effort to decrease maternal mortality. Interventions initially developed for the management of complications became accepted and practiced as routine obstetric care. Physicians first administered anesthesia for childbirth during this period (see Chapter 1). The 1848 meeting of the American Medical Association included reports of the use of ether and chloroform in approximately 2000 obstetric cases.\textsuperscript{8} The combination of morphine and scopolamine (i.e., twilight sleep) was introduced in the early 20th century. These techniques were widely used, and influential women demanded that they be made available to all parturients.\textsuperscript{9} Together, these developments moved childbirth from the home and family unit to the hospital environment.\textsuperscript{10} However, despite their desire for analgesia/anesthesia for labor and delivery, women began to resent the fact that they were not active participants in childbirth.

Beck et al.\textsuperscript{11} wrote a detailed history of childbirth preparation. Dick-Read\textsuperscript{12,13} reported the earliest method in his books, *Natural Childbirth* and *Childbirth Without Fear*. In his original publication, he asserted his belief that childbirth was not inherently painful. He opined that the pain of childbirth results from a “fear-tension-pain syndrome.” He believed—and taught—that antepartum instruction about muscle relaxation and elimination of fear would prevent labor pain. Some readers incorrectly concluded that he advocated a return to primitive obstetrics, but this was not the case. Review of his practice reveals that he used the available obstetric techniques—including analgesia, anesthesia, episiotomy, forceps, and abdominal delivery—as appropriate for the individual patient. However, he cautioned against the routine use of these procedures, and he encouraged active participation of mothers in the delivery of their infants. Unfortunately, he did not use the scientific method to validate his beliefs.

Although Dick-Read was the earliest proponent of so-called “natural” childbirth, it was Fernand Lamaze\textsuperscript{14} who introduced the Western world to psychoprophylaxis. His publications were based on techniques that he observed while traveling in Russia. Although his theories ostensibly were translations of teachings later published in the West by Velovsky et al.,\textsuperscript{15} they contained substantial differences and modifications. The “Lamaze method” became popular in the
United States after Marjorie Karmel16 wrote about her childbirth experience under the care of Dr. Lamaze. Within 1 year of the publication of her book Thank You, Dr. Lamaze: A Mother’s Experiences in Painless Childbirth, the American Society for Psychoprophylaxis in Obstetrics was born. Lamaze and Karmel published their experience at a time when organizations such as the International Childbirth Education Association and the La Leche League were formed.17 These organizations actively and aggressively encouraged a renewed emphasis on family-centered maternity care, and society was ripe for the ideas and theories promoted by these organizations. Women were ready to actively participate in childbirth and to have input in decisions about obstetric and anesthetic interventions. Childbirth preparation methods were taught and used extensively, despite a lack of scientific validation of their efficacy.

In 1975, Leboyer18 described a modification of natural childbirth in his book Birth Without Violence. He advocated childbirth in a dark, quiet room; gentle massage of the newborn without routine suctioning; and a warm bath soon after birth. He opined that these maneuvers result in a less shocking first-separation experience and a healthier, happier infancy and childhood. Although there are few controlled studies of this method, published observations do not support his claim of superiority.19,20

Physicians were the initial advocates of the various natural childbirth methods. Obstetricians had become increasingly aware that analgesic and anesthetic techniques were not harmless, and they supported the use of natural childbirth methods.11 Subsequently, natural childbirth, like the methods of obstetric analgesia introduced earlier in the century, was actively promoted by lay groups rather than physicians.21 Lay publications, national advocacy groups, and formal instruction of patients accounted for the greater interest in psychoprophylaxis and other techniques associated with natural childbirth.

## Goals and Advantages

The major goals of childbirth education that were initially promoted by Dick-Read are taught with little modification in formal childbirth preparation classes today. Most current classes credit Lamaze with the major components of childbirth preparation, even though Dick-Read was the first to promote patient education, relaxation training, breathing exercises, and paternal participation.11 Box 21.1 describes the goals of current childbirth preparation classes. In addition, some instructors and training manuals claim other benefits of childbirth preparation (Box 21.2),12,22 although a 2015 review of two methods (Bradley method and HypnoBirthing) called for more rigorous study with transparent methods rather than self-reported outcomes.24 A 2007 systematic review concluded that there is insufficient evidence to evaluate the efficacy of antenatal childbirth education on childbirth and parenting outcomes.25 Existing studies are of poor quality and dated. Despite these shortcomings, childbirth preparation classes are widely available and attended.

Socioeconomic disparities exist in childbirth education class attendance.26,27 In addition, the effect of childbirth education on attitude and childbirth experience depends in part on the social class to which the mother belongs. Most investigators have found that childbirth classes have a positive effect on the attitudes of both parents in all social classes, but this effect is more pronounced among “working class” and indigent women29; this latter finding probably reflects the greater availability and use of other educational materials by middle- and upper-class women. Childbirth classes often are the only—or at least the primary—source of information for working class and indigent women.

## Limitations

Limitations of the widespread application of psychoprophylaxis and other childbirth preparation methods remain. Proponents assume that these techniques are easily used during labor and delivery; however, Copstick et al.30 concluded that this assumption is not valid. They found that patients were able to use the coping techniques in the early first stage of labor but that the successful use of the coping skills became less and less common as labor progressed. By the onset of the second stage, less than one-third of mothers were able to use any of the breathing or postural techniques taught during their childbirth classes.30 The method of preparation influences the ability of the pregnant woman to use the breathing and relaxation techniques. Bernardini et al.31 observed that self-taught pregnant women are less likely to practice the techniques during the prenatal period or to use the techniques during labor.

Childbirth preparation classes may create false expectations. If a woman does not enjoy the “normal” delivery discussed during classes, she may experience a sense of failure or inferiority. Both Stewart41 and Guzman Sanchez et al.33 have discussed the psychological reactions of women who were unable to use psychoprophylaxis successfully during labor.

### Box 21.1 Goals of Childbirth Preparation

- Patient education about pregnancy, labor, and delivery
- Relaxation training
- Instruction in breathing techniques
- Participation of father/support person
- Early parental bonding

### Box 21.2 Purported Benefits of Childbirth Preparation

- Greater maternal control and cooperation
- Decreased maternal anxiety
- Reduced maternal pain
- Decreased maternal need for analgesia/anesthesia
- Shorter labor
- Diminished maternal morbidity
- Less fetal stress/distress
- Strengthened family relationships as a result of the shared birth experience
newer cognitive techniques (e.g., systematic desensitization, sensory transformation) may be more effective than traditional Lamaze techniques of varied breathing patterns and relaxation. Further studies may help refine childbirth preparation to maximize the positive psychophysiologic effects.

**NONPHARMACOLOGIC ANALGESIC TECHNIQUES**

Nonpharmacologic analgesic techniques range from those that require minimal specialized equipment and training and are available to all patients to those that are offered only by institutions with the necessary equipment and personnel trained in their use (Box 21.3). Many studies have assessed nonpharmacologic methods of labor analgesia; however, most published studies have not fulfilled the requirements of the scientific method.52–55 Several comprehensive reviews of alternative therapies for pain management during labor have been published,52–54 providing a foundation for discussion with patients and obstetric providers. However, clinical evidence is insufficient to form the basis for an in-depth discussion of some of the more recent therapeutic suggestions, such as music therapy, aromatherapy, and chiropractic manipulation. These analgesic techniques may provide intangible benefits that are not easily documented by a rigorous scientific study.

**Effects on Labor Pain and Use of Analgesics**

Little scientific evidence supports the efficacy of childbirth preparation in mitigating labor pain. Psychology, nursing, obstetric, anesthesia, and lay journals provide extensive discussions of childbirth preparation, but most articles describe uncontrolled clinical experiences. Outcome studies often do not include a group of women who were randomly assigned to an untreated or a placebo-control group, and statistical analysis is often incomplete. Despite these shortcomings, supporters of childbirth preparation assume that it offers benefits for mother and child. Table 21.1 summarizes a few of the studies of Lamaze and other childbirth preparation techniques and their association with labor outcomes. The findings are not consistent. Some researchers have reported a decreased use of analgesics37–39 or regional anesthesia, shorter labor,42 reduced performance of instrumental37–41 and cesarean delivery,41 and a lower incidence of nonreassuring fetal status,41 whereas others have reported no change in the use of analgesics41–45 or neuraxial analgesia,43,44 length of labor,38,39,43–46 performance of instrumental delivery43–45 and cesarean delivery,38,43–45 or incidence of nonreassuring fetal status.38,40,42,44 These diverse findings may reflect different patient populations, poor study design, or researcher bias.

To elucidate the effect of the coping techniques taught in childbirth classes, several investigators have attempted to quantify changes in pain threshold, pain perception, anxiety levels, and physiologic responses to standardized stimuli. Several studies have evaluated nonpregnant and nulliparous women in laboratory settings,47–50 and another study evaluated pregnant women in the antepartum, intrapartum, and postpartum periods.51 Conclusions varied according to the stimuli applied, the coping techniques studied, and the parameters analyzed. Together, these studies suggest that practicing these techniques facilitates their efficacy and that

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**TABLE 21.1 Effects of Childbirth Preparation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Analgesic Use</th>
<th>Neuraxial Anesthesia</th>
<th>Length of Labor</th>
<th>Cesarean Delivery Rate</th>
<th>Instrumental Delivery Rate</th>
<th>Fetal Distress</th>
<th>Oxytocin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patton et al.44</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>↑</td>
</tr>
<tr>
<td>Hetherington37</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Zax et al.39</td>
<td>↓</td>
<td>↓</td>
<td>NC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Scott and Rose38</td>
<td>↓</td>
<td>▼</td>
<td>NC</td>
<td>NC</td>
<td>▼</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hughey et al.41</td>
<td>NC</td>
<td>▼</td>
<td>NC</td>
<td>▼</td>
<td>▼</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Sturrock and Johnson45</td>
<td>NC</td>
<td>—</td>
<td>NC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Brewin and Bradley43</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Delke et al.42</td>
<td>NC</td>
<td>—</td>
<td>NC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rogers40</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NC, No change; ↑, increased; ↓, decreased; —, not studied/reported.

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**BOX 21.3 Nonpharmacologic Analgesic Techniques**

**Minimal Training/Equipment**
- Emotional support
- Touch and massage
- Therapeutic use of heat and cold
- Hydrotherapy
- Vertical position

**Specialized Training/Equipment**
- Biofeedback
- Intradermal water injection
- Transcutaneous electrical nerve stimulation
- Acupuncture
- Hypnosis

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and delivery. In addition, several women have written about their disappointment with the dogmatic approach of their childbirth instructors; these women described instructors who rigidly defined the “correct” way to have a “proper” birth experience.34,35 There is, however, some evidence that antenatal childbirth education courses may help to ease fear of childbirth.36
Continuous Labor Support

Some techniques that require minimum equipment and specialized training are taught as integral components of childbirth preparation classes. Continuous support during labor is essential to the process of a satisfying childbirth experience; typically, the parturient’s husband or friend provides this support. This support appears most helpful for the parturient who lives in a stable family unit. At least one study noted that husband participation was associated with decreased maternal anxiety and medication requirements. Studies have found that emotional support provided by unfamiliar trained individuals (e.g., doulas) also has a positive effect. Other studies have evaluated the benefits of emotional support provided by doulas or other unrelated individuals on the mode of delivery, feelings about the birth experience, use of labor analgesia, oxytocin augmentation, length of labor, perineal trauma, breast-feeding outcomes, and Apgar scores, among other outcomes. These studies all suggested that a patient’s sense of isolation adversely affects her perception of labor. Further, the companionship of another woman who is not part of the medical establishment may reduce a parturient’s anxiety more effectively than the companionship provided by her husband. In one study, women randomly assigned to receive intrapartum support from a friend or female relative (who was chosen by the parturient and trained as a doula) were more likely to have positive feelings about their delivery and had a higher rate of breast-feeding 6 to 8 weeks after delivery than women who were randomly assigned to receive usual care.46

A meta-analysis evaluated results from 26 studies that included 15,858 women who were randomly assigned to receive either continuous childbirth support or usual care (Table 21.2). The pooled data suggested that women who received one-on-one support during labor were less likely to use any type of analgesia and report negative feelings about the childbirth experience, and were more likely to have a spontaneous vaginal delivery, although evidence was generally of low quality. In addition, the mean duration of labor was slightly shorter (approximately 41 minutes) in the women who received continuous support during labor, and the likelihood of low 5-minute Apgar scores was less.

These results are fascinating and have important implications for obstetric care. The patient populations studied represent special situations, and the results may not be reproduced in all populations. For example, a large randomized, controlled trial in a North American hospital (in which intrapartum medical intervention is routine) found no differences in the rate of cesarean delivery or other labor outcomes between women randomly assigned to receive continuous labor support from a specially trained nurse and women who received usual care. In general, results from trials in North America do not appear as striking as those from Europe or Africa. The aforementioned systematic review of continuous labor support suggested that benefits were greater when the support person was present in a doula (trained labor companion) role. Further studies should compare different models of continuous childbirth support and should include longer-term outcomes, including breast-feeding and postpartum depression. Meanwhile, the preponderance of evidence suggests that all parturients should have access to emotional support, whether it is provided by the husband, a family member, a labor companion (e.g., doula), or professional hospital staff.

### Touch and Massage

Various touch and massage techniques are discussed with women and their support persons during childbirth preparation classes. These techniques include effleurage, counter-pressure to alleviate back discomfort, light stroking, and merely a reassuring pat. There has been minimal scientific study of the effects of touch and massage on labor progress and outcome; nonetheless, touch and massage provide a comfort that is appreciated by women during labor. These measures may be used by the parturient, her support person, or the professional staff members providing intrapartum care. The techniques are easily discontinued if the parturient desires. In some cases, touch and massage may reduce

### TABLE 21.2 Systematic Review: Continuous Labor Support versus Usual Care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Trials</th>
<th>Number of Subjects</th>
<th>Relative Risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of neuraxial analgesia</td>
<td>9</td>
<td>11,444</td>
<td>0.93</td>
<td>0.88 to 0.99</td>
</tr>
<tr>
<td>Use of any analgesia</td>
<td>15</td>
<td>12,433</td>
<td>0.90</td>
<td>0.84 to 0.96</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>21</td>
<td>14,369</td>
<td>1.08</td>
<td>1.04 to 1.12</td>
</tr>
<tr>
<td>Instrumental vaginal delivery</td>
<td>19</td>
<td>14,118</td>
<td>0.90</td>
<td>0.85 to 0.96</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>24</td>
<td>15,347</td>
<td>0.75</td>
<td>0.64 to 0.88</td>
</tr>
<tr>
<td>Negative feelings about childbirth experience</td>
<td>11</td>
<td>11,133</td>
<td>0.69</td>
<td>0.59 to 0.79</td>
</tr>
<tr>
<td>Labor length</td>
<td>13</td>
<td>5429</td>
<td>−0.69&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−1.04 to −0.34</td>
</tr>
<tr>
<td>Infant with a low 5-minute Apgar score</td>
<td>14</td>
<td>12,615</td>
<td>0.62</td>
<td>0.46 to 0.85</td>
</tr>
</tbody>
</table>


<sup>a</sup>For women who received continuous support.

<sup>b</sup>Weighted mean difference.
discomfort. More often, touch and massage transmit a sense of caring, which fosters a sense of security and well-being.

**Therapeutic Use of Heat and Cold**

Another simple technique for alleviating labor pain is the therapeutic use of temperature (hot or cold) applied to various regions of the body. Warm compresses may be placed on localized areas, or a warm blanket may cover the entire body. Alternatively, ice packs may be placed on the low back or perineum to decrease pain perception. The therapeutic use of heat and cold during labor has not been studied in a rigorously scientific manner.50,61 The use of superficial heat and cold for comfort is widespread (if not completely understood), and it has no discernible risk to the mother or the fetus.52 Cold and heat should not be applied to anesthetized skin.

**Aromatherapy**

Aromatherapy is the use of essential oils, which are fragrant, volatile organic compounds obtained by distillation of plant material. The oils are commonly combined with a carrier oil and massaged into the skin, inhaled, or mixed in a bath.62 Two commonly used oils are lavender and frankincense.52 Studies evaluating the use of aromatherapy during labor are lacking.62

**Hydrotherapy**

Hydrotherapy may involve a simple shower or tub bath or may include the use of a whirlpool or large tub specially equipped for pregnant women. Purported benefits of hydrotherapy include decreased anxiety and pain and greater uterine contraction efficiency.52 Results of randomized, controlled trials comparing water baths with usual care are inconsistent. For example, some studies have found no difference between groups in the use of pharmacologic analgesia,53,64 whereas others have demonstrated a lower use in the water bath group.65,66 A meta-analysis of 12 published trials involving 3243 women concluded that there was a reduction in the use of spinal/epidural/paracervical analgesia (risk ratio [RR], 0.90; 95% confidence interval [CI], 0.82 to 0.99) and duration of the first stage of labor (mean difference −32 minutes; 95% CI, −59 to −6 minutes) in women randomly assigned to water immersion compared with control subjects.67 There were no differences in the rate of operative delivery or other maternal or neonatal outcomes, including maternal and neonatal infection. In summary, bathing, showering, and other hydrotherapy maneuvers are comfort measures with little risk to the mother and the infant, provided that appropriate monitoring continues during the immersion in water that is kept at body temperature.

**Vertical Position**

Several investigators have studied the effects of various positions on pain perception and labor outcome. These positions are broadly categorized as vertical (e.g., sitting, standing, walking, squatting) or horizontal (e.g., supine, lateral). A 2013 meta-analysis of 15 studies in 2503 women found that walking and the upright position during the first stage of labor were associated with shorter labor (mean difference −1.36 hours; 95% CI, −2.22 to −0.51) as well as a lower rate of cesarean delivery and epidural analgesia.68 The authors noted study quality was variable, and there was a high degree of heterogeneity in the results; thus better quality trials are necessary to draw firm conclusions regarding the effect of position on labor outcomes.

Ambulation in the presence of neuraxial analgesia does not appear to influence the outcome of labor.66–71 In a prospective, randomized study, Bloom et al.69 noted that walking did not shorten the duration of the first stage of labor or reduce the requirement for oxytocin augmentation, the use of analgesia, or the requirement for operative delivery. They concluded that “walking neither enhanced nor impaired active labor and was not harmful to the mothers or their infants.”69 In a 2013 meta-analysis comparing outcomes in women with epidural analgesia randomized to upright and ambulant positions or recumbent positions,84 there were no differences in any maternal or neonatal outcome, including mode of delivery.

A number of studies have assessed maternal position during the second stage of labor. There is renewed interest in the squatting or modified squatting position and its greater comfort for some women during childbirth. Most authorities have noted that Western women have insufficient muscular strength and stamina to maintain an unsupported squatting position for any length of time.72–74 Squatting does not appear to alter pelvic dimensions.75 Gardosi et al.76 designed and studied a birth cushion that allows a modified, supported squat, which resulted in a higher incidence of spontaneous vaginal delivery and a lower incidence of perineal tears. Others have yet to substantiate the results of this trial.

Some studies have evaluated the use of a birth chair to facilitate delivery in the sitting position.75–77 These studies noted no difference in length of the second stage of labor, mode of delivery, occurrence of perineal trauma, or Apgar scores in parturients who used a birth chair compared with those who did not. Of concern, two studies reported greater intrapartum blood loss and a higher incidence of postpartum hemorrhage in the birth-chair group.77,78

A 2017 systematic review of studies of maternal position in the second stage of labor in women without epidural analgesia concluded that currently published trials are generally of poor quality and the results should be interpreted with caution.79 There may be a small reduction in duration of the second stage of labor and a lower rate of episiotomy and assisted deliveries, but a greater risk for postpartum hemorrhage.

A second 2017 systematic review assessed outcomes in women with epidural analgesia randomized to an upright or recumbent position for the second stage of labor.80 The authors concluded that there are insufficient data to draw conclusions regarding the effects, if any, of parturient position in the second stage of labor in women with epidural analgesia. Although the authors of both systematic reviews79,80 concluded that further study is required, many obstetricians and nurses believe that ambulation and the upright posture...
result in a shorter labor that requires less analgesia. An alternative explanation for the observation that ambulatory par- turients appear to have a less painful and shorter labor is that shorter, less painful labor is more likely to allow continued ambulation.

Other than the possibility of greater blood loss associated with the upright position during delivery, upright positions during most of labor are not associated with any harm to the mother or newborn and may aid maternal comfort. It is unclear whether birthing cushions or stools confer any benefit to the mother or the newborn.

**Biofeedback**

Biofeedback is a relaxation method that is used as an adjunct to the relaxation training taught in Lamaze classes and other childbirth education programs. Two biofeedback procedures may be applicable to the laboring woman: skin-conductance (autonomic) and electromyographic (voluntary muscle) relaxation. St James-Roberts et al. demonstrated that electromyographic but not skin-conductance biofeedback techniques could be taught effectively in Lamaze classes. They noted no difference in length of the first stage of labor, use of epidural analgesia, incidence of instrumental delivery, or Apgar scores among electromyographic, skin-conductance, epidural analgesia, incidence of instrumental delivery, or control groups. In a small study, Duchene reported reduced pain perception during labor and delivery, and a lower rate of epidural analgesia use (40% versus 70% for a control group) with electromyographic biofeedback; there was no difference between groups in Apgar scores. A 2011 systematic review assessing the effectiveness of biofeedback found that most studies had a high risk for bias, and although some studies demonstrated reduced use of analgesics with biofeedback, there was insufficient evidence to conclude that biofeedback is efficacious. Biofeedback training does not appear to confer substantial benefit beyond that of traditional relaxation training taught in childbirth education classes.

**Intradermal Water Injections**

Intradermal or intracutaneous water injections are used to treat lower back pain, which is a common complaint during labor. The afferent nerve fibers that innervate the uterus and cervix, as well as the nerve fibers that innervate the lower back, all enter the spinal cord at the T10 to L1 spinal segments; therefore, a component of the pain may be referred pain. The technique consists of injecting 0.05 to 0.1 mL of sterile water, with an insulin or tuberculin syringe, at four sites on the lower back (i.e., over each posterior superior iliac spine, and at 1 cm medial to each spine on both sides of the back, for a total of four injections). The exact locations of the injections vary, and the use of TENS at specific acupuncture points and observed a reduction in pain perception more commonly in the study group than in the control group. However, a 2011 systematic review of nine trials in more than 1000 women concluded that TENS did not reduce labor pain and did not reduce the use of additional analgesic agents. There also was no effect on the duration of labor or the incidence of instrumen
tal delivery. Patients tend to rate the device as helpful despite the fact that it does not reduce the use of additional analgesics. Advocating widespread use of TENS does not seem warranted, although it may be offered to women if they desire to use it.

**Transcutaneous Electrical Nerve Stimulation**

Transcutaneous electrical nerve stimulation (TENS) involves the transmission of low-voltage electrical current to the skin via surface electrodes. Advantages of TENS are that it is easy to use and discontinue, is noninvasive, and has no demonstrable harmful effects on the fetus. The only stated disadvantage is the occasional interference with electronic fetal heart rate monitoring. It is most widely used for childbirth in Scandinavia and the United Kingdom. Chao et al. evaluated the use of TENS at specific acupuncture points and observed a reduction in pain perception more commonly in the study group than in the control group. However, a 2011 systematic review of nine trials in more than 1000 women concluded that TENS did not reduce labor pain and did not reduce the use of additional analgesic agents. There also was no effect on the duration of labor or the incidence of instrumental delivery. Patients tend to rate the device as helpful despite the fact that it does not reduce the use of additional analgesics. Advocating widespread use of TENS does not seem warranted, although it may be offered to women if they desire to use it.

**Acupuncture/Acupressure**

Traditional Chinese medicine includes extensive use of acupuncture. Given that acupuncture can provide analgesia, there is interest in its use for intrapartum analgesia, although this is not a traditional use of the method. Early observational reports described conflicting results as to the efficacy of intrapartum acupuncture. Given the historic lack of use of acupuncture in obstetric patients, there is a lack of standardization of the acupuncture points to be stimulated.

Several randomized, controlled trials have compared “real” acupuncture to “false” or “minimal” acupuncture
using shallow insertion of needles in non-acupuncture points, whereas other investigators have used a control group that did not receive acupuncture. Four randomized trials found that pain scores were lower in women randomly assigned to receive acupuncture treatment, as was the rate of use of other modes of analgesia (e.g., epidural and systemic meperidine). These results suggest that acupuncture may hold promise for the treatment of labor pain. Hantoushzadeh et al. and Asadi et al. also observed a shorter duration of the active phase of labor. No adverse maternal or fetal effects were identified. Other randomized studies did not find reduced pain scores with acupuncture.

A randomized, controlled trial of acupressure (treatment) compared with touch (control) at the SP6 acupoint found lower pain scores and a shorter duration of labor in the acupressure group. A 2011 systematic review and meta-analysis of 13 acupuncture trials including 1986 women concluded that acupuncture may hold promise for labor analgesia; however, larger studies are required for definitive conclusions. All of the randomized, controlled acupuncture studies were performed outside the United States, in countries (primarily Scandinavian) in which the use of neuraxial labor analgesia is less widespread than in the United States. Also, the use of acupuncture requires trained personnel. (Scandinavian midwives have been trained to administer acupuncture.) For these reasons, it is unlikely that either acupuncture or acupressure will gain widespread acceptance in the United States for intrapartum analgesia.

Hypnosis

The use of hypnosis for obstetric analgesia is not new. Early proponents touted safety for the mother and the fetus, lower analgesic requirements, and shorter labor as the major advantages of intrapartum hypnosis. Whether hypnosis differs substantially from other childbirth preparation techniques is an unresolved controversy. Fee and Reilley concluded that the breathing and relaxation exercises used in childbirth preparation do not represent a hypnotic trance; support for their conclusion is provided by the successful teaching of childbirth preparation exercises to women who are not susceptible to hypnosis. However, women susceptible to hypnosis may achieve a state much like a hypnotic trance when using the same exercises.

Instruction in the techniques of self-hypnosis occurs before the onset of labor and may entail visits to the hypnotist or involvement in a childbirth education program such as HypnoBirthing. Proponents previously suggested that successful hypnosis training should begin early in the third trimester. Rock et al. found that hypnosis could be introduced to untrained, nonvolunteer patients during labor. A 2016 meta-analysis included nine randomized controlled trials of hypnosis; in eight trials the intervention was antenatal hypnosis training, and in one trial the intervention was during labor. Women in the hypnosis group were less likely to use pharmacologic analgesia (RR 0.73; 95% CI, 0.57 to 0.94), but the evidence was judged to be of very low quality. There were no differences in any other outcomes, including coping with labor and rate of spontaneous vaginal birth. The authors concluded that further high-quality, large trials are needed.

In summary, hypnosis has at least the following three limitations: (1) antepartum training sessions are required, (2) trained hypnotherapists must be available during labor, and (3) it offers no clear benefit. Therefore, hypnosis is unlikely to attain widespread use during childbirth.

**IMPLICATIONS FOR ANESTHESIA PROVIDERS**

Childbirth preparation classes and nonpharmacologic analgesic techniques are not comparable to neuraxial analgesia/anesthesia for the relief of labor pain. Thus, some might wonder whether it is important or useful for anesthesia providers to have knowledge of these techniques. If our only obligation to the obstetric patient is a technical one (i.e., to eliminate pain safely with the use of neuraxial analgesia), knowledge of these techniques is perhaps superfluous. However, the practice of obstetric anesthesia should not be limited to the performance of pain-relieving procedures; our contributions to the care of the obstetric patient and her family should extend beyond the administration of neuraxial analgesia.

Much has been written in professional and lay journals concerning the “proper” childbirth experience. Each patient’s expectations of labor influence her childbirth experience. There is a growing movement toward patient-centered maternity care, and a definite need for widespread adoption of practices that support these shifts toward inclusion of women’s values and beliefs in the birthing process. Women currently view childbirth from the perspective of educated consumers; they expect to have choices and a level of control during childbirth. We may not always be comfortable with this situation, but it is a reality for modern obstetric practice. Our challenge is to provide safe, effective analgesia in a nonthreatening, “homelike” environment. We are not solely responsible for a patient’s childbirth experience, but our interactions with the patient, her family, and her obstetrician will influence her perception of childbirth. In a 2013 qualitative study from Montreal, Canada, 17 multidisciplinary health professionals and administrators, as well as 157 women with different levels of obstetric risk, parity, and type of delivery, were interviewed regarding barriers to—and facilitators of—provision of humanized obstetric care. Major contributors to women’s satisfaction during childbirth were related to the presence of a competent provider who provided a caring and humane presence during labor and delivery, while still providing medical interventions when necessary.

Anesthesia providers must become effective educators as well as health care providers. Patients should have realistic expectations about the pain of labor and the variability of individual labor patterns. They should be encouraged to define “success” as a positive childbirth experience regardless of the mode of delivery, use of analgesia and anesthesia, or
other arbitrary definitions. An obstetrician advised prospective mothers:

*If you do end up choosing some form of pain relief during labor, do not feel inadequate if a friend had her baby without assistance. Some labors are more intense than others. Ultimately, holding your baby in your arms is more important than the method you used to bring her into the world.*

Anesthesia providers may effectively provide similar advice. Unfortunately, anesthesia providers usually have little involvement in prenatal education classes. Our active participation in childbirth education classes may help patients receive more accurate information about the risks and benefits of analgesia/analgesic techniques of epidural analgesia allow sitting with support. Even if this belief proves not to be true, many women prefer to be mobile during labor and, at a minimum, to retain the ability to walk to the bathroom. We should attempt to develop and use analgesic techniques that take advantage of these relatively simple maneuvers. For example, the use of intrathecal opioids during early labor allows for continued ambulation and the use of showers and/or tubs. Some techniques of epidural analgesia allow sitting with support. Finally, epidural analgesia/analgesia does not eliminate the beneficial effects of other comfort measures, such as massage, and continued emotional support from family and friends.

Whenever possible, anesthesia providers should provide safe anesthetic care that is compatible with reasonable patient expectations. Future studies on the efficacy of childbirth education, nonpharmacologic analgesic techniques, and neuraxial analgesic techniques should evaluate the patient's overall experience and satisfaction rather than limit assessment to the usual measures of obstetric outcome. In an editorial that accompanied a study of walking in labor,

Cefalo and Bowes commented, "In the end, the nurses, midwives, and physicians who attend a woman with compassion, understanding, and professionalism are the most important factors in the management of any labor."  

### KEY POINTS

- Childbirth preparation does not eliminate the pain of labor or substantially reduce the use of analgesia/analgesia, but it does decrease the anxiety associated with labor.
- Emotional support provided by doulas reduces the use of analgesics, the duration of labor, and the incidence of operative deliveries in selected patient populations.
- Biofeedback, transcutaneous electrical nerve stimulation, acupuncture, and hypnosis may provide mild analgesic benefits for some patients, but high-quality evidence is lacking.
- Some nonpharmacologic analgesic techniques may have benefits other than decreased pain perception. For example, some obstetricians and nurses believe that ambulation and subsequent squatting (or use of a birth cushion) shortens labor and increases the rate of spontaneous vaginal delivery. Even if this belief proves not to be true, many women prefer to be mobile during labor and, at a minimum, to retain the ability to walk to the bathroom. We should attempt to develop and use analgesic techniques that take advantage of these relatively simple maneuvers. For example, the use of intrathecal opioids during early labor allows for continued ambulation and the use of showers and/or tubs. Some techniques of epidural analgesia allow sitting with support. Finally, epidural analgesia/analgesia does not eliminate the beneficial effects of other comfort measures, such as massage, and continued emotional support from family and friends.
- Whenever possible, anesthesia providers should provide safe anesthetic care that is compatible with reasonable patient expectations. Future studies on the efficacy of childbirth education, nonpharmacologic analgesic techniques, and neuraxial analgesic techniques should evaluate the patient's overall experience and satisfaction rather than limit assessment to the usual measures of obstetric outcome. In an editorial that accompanied a study of walking in labor,

Cefalo and Bowes commented, "In the end, the nurses, midwives, and physicians who attend a woman with compassion, understanding, and professionalism are the most important factors in the management of any labor.”

### REFERENCES


Systemic Analgesia: Parenteral and Inhalational Agents

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Systemic drugs have been used to decrease the pain of childbirth since 1847, when James Young Simpson used diethyl ether to anesthetize a parturient with a deformed pelvis. Since that time, the provision of labor analgesia has advanced significantly owing to a heightened awareness of the neonatal effects of heavy sedation or general anesthesia administered during vaginal delivery and a greater desire of women to actively participate in childbirth.

Neuraxial (i.e., epidural, spinal, combined spinal-epidural [CSE]) analgesic techniques have replaced systemic drug administration as the preferred method for intrapartum analgesia in the United States and Canada (Table 22.1). By contrast, in the United Kingdom, fewer than one-third of parturients receive a neuraxial analgesic technique during labor and vaginal delivery.3 Despite the increased use of neuraxial analgesia for labor, the use of systemic analgesia remains a common practice in many institutions worldwide for several reasons. Many women labor and deliver in an environment where the provision of safe neuraxial analgesia is not available. Some parturients decline neuraxial analgesia or choose to receive systemic analgesia during early labor. Finally, some women may have a medical condition that contraindicates a neuraxial procedure (e.g., coagulopathy) or presents technical challenges (e.g., severe scoliosis, the presence of spinal hardware).

PARENTERAL OPIOID ANALGESIA

Opioids are the most widely used systemic medications for labor analgesia. These compounds are agonists at opioid receptors (Table 22.2). Their popularity lies in their low cost, ease of use, and the lack of need for specialized equipment and personnel. However, parturients commonly report dissociation from the reality of pain rather than complete analgesia. Although opioid use is associated with a high frequency of maternal side effects (e.g., nausea, vomiting, delayed gastric emptying, dysphoria, drowsiness, hypoventilation) and the potential for adverse neonatal effects, the availability of patient-controlled delivery systems has renewed interest in their administration during labor.

There is little scientific evidence to suggest that one opioid is superior to another; most often, drug selection is based on local policy or personal preference (Table 22.3). The efficacy
of systemic opioid analgesia and the incidence of side effects are largely dose-dependent rather than drug-dependent.

As a result of their high lipid solubility and low molecular weight (< 500 Da), all opioids readily cross the placenta by diffusion and are associated with the risk for neonatal respiratory depression and neurobehavioral changes. Opioids may also affect the fetus in utero. The fetus and neonate are particularly susceptible to opioid-induced side effects for several reasons. The metabolism and elimination of these drugs are prolonged compared with adults, and the blood-brain barrier is less well developed, allowing for greater central effects. Opioids may result in decreased variability of the fetal heart rate.
rate (FHR), although this change usually does not reflect a worsening of fetal oxygenation or acid-base status. The likelihood of neonatal respiratory depression depends on the dose and timing of opioid administration. Even in the absence of obvious neonatal depression at birth, there may be subtle changes in neonatal behavior for several days. In a meta-analysis, Reynolds et al. concluded that lumbar epidural analgesia was associated with improved neonatal acid-base status at delivery compared with systemic opioid analgesia using meperidine, butorphanol, or fentanyl. Similarly, in a multicenter randomized trial, Halpern et al. demonstrated an increased need for active neonatal resuscitation in a parenteral, patient-controlled analgesia (PCA) opioid group, compared with a patient-controlled epidural analgesia group using a local anesthetic combined with an opioid (52% versus 31%).

Opioids are commonly administered as intermittent boluses, but newer synthetic opioids are increasingly administered by PCA. Because the mode of delivery influences a drug's pharmacologic profile, the opioids will be discussed by route of administration.

**INTERMITTENT BOLUS PARENTERAL OPIOID ANALGESIA**

Opioids may be given intermittently by subcutaneous, intramuscular, or intravenous injection. The route and timing of administration influence maternal uptake and placental transfer to the fetus. Subcutaneous and intramuscular routes have the advantage of ease of administration but are painful. Absorption varies with the site of injection and depends on local and regional blood flow; consequently, the onset, quality, and duration of analgesia are highly variable.

Intravenous administration is generally preferred when available, as it offers several advantages. The onset of analgesia is fast, the timing and magnitude of the peak plasma concentration of drug are predictable, and titration to desired effect is possible.

**Morphine**

First isolated in 1806 and named morphium after the Greek god of dreams, morphine was introduced and soon abandoned as a labor pain medication because of neonatal depression. Its intrapartum use reappeared in the early 1900s as a component of “twilight sleep,” a combination of morphine and scopolamine; the analgesia produced would often result in maternal sedation and neonatal depression.

Morphine has a high affinity for μ-opioid receptors and is a potent long-acting analgesic. Infrequently used during labor, morphine can be given every 4 hours intravenously (0.05 to 0.1 mg/kg) or intramuscularly (0.1 to 0.2 mg/kg), with a peak effect observed in 10 and 30 min, respectively. The duration of action when given intravenously or intramuscularly is 3 to 4 h.

Morphine is principally metabolized by conjugation in the liver, with up to 70% being transformed into the largely inactive morphine-3-glucuronide. The remainder is transformed into the active metabolite morphine-6-glucuronide, an opioid agonist that is 13 times more potent than morphine and has significant analgesic properties. Both metabolites are excreted in the urine and have elimination half-lives of up to 4.5 hours in the presence of normal renal function. Morphine rapidly crosses the placenta, and a fetal-to-maternal blood concentration ratio of 0.96 is observed at 5 minutes. The elimination half-life of morphine is longer in neonates than in adults.

Maternal side effects include respiratory depression and histamine release, which may result in rash and pruritus. Like many opioids, morphine is emetogenic and is associated with sedation and dysphoria with increasing doses.

The greatest neonatal concern of morphine is that of respiratory depression, which has been attributed to an increased permeability of the neonatal brain. In a small study, Way et al. observed that intramuscular morphine given to newborns seemed to cause greater respiratory depression than an equi-dose of meperidine when response to carbon dioxide was measured.

Pregnancy alters the pharmacokinetics of morphine. Greater plasma clearance, shorter elimination half-life, and earlier peak metabolite levels occur in pregnant women than in nonpregnant women. In theory, these characteristics should reduce fetal exposure. One study observed no cases of neonatal depression after morphine administration during labor, prompting the researchers to suggest that morphine use in labor should be reevaluated. Subsequently, Olofsson et al. assessed the analgesic efficacy of intravenous morphine during labor (0.05 mg/kg every third contraction, to a maximum dose of 0.2 mg/kg) and observed clinically insignificant reductions in pain intensity. These investigators also compared intravenous morphine (up to 0.15 mg/kg) with intravenous meperidine (up to 1.5 mg/kg) and found that both groups had high pain scores despite high levels of maternal sedation.

A randomized controlled trial comparing morphine (2 mg) to intravenous acetaminophen (1000 mg) for early labor analgesia observed no differences in visual analogue scale (VAS) pain scores before and at 15 minutes and 1 hour. However, within 2 hours of administration, significantly more women receiving acetaminophen required rescue analgesia (52.9% versus 17.6%, P < .01).

**Meperidine**

In 1947, meperidine (pethidine) was the first synthetic opioid to be used for intrapartum analgesia and quickly displaced morphine as the most common opioid given for labor analgesia in the United Kingdom. An agonist that binds to both μ and κ opioid receptors, meperidine is estimated to provide 10% of the analgesic potency of morphine. The usual dose is 50 to 100 mg intramuscularly, which can be repeated every 4 hours. The onset of analgesia occurs in 10 to 15 minutes, but 45 minutes may be required to reach peak effect. The duration of action is typically 2 to 3 hours.

Meperidine is highly lipid soluble, readily crosses the placenta, and equilibrates between the maternal and fetal
compartments within 6 minutes. Meperidine is metabolized in the liver to normeperidine, a pharmacologically active metabolite that may cause prolonged neonatal side effects.\(^6\)

Maternal administration of meperidine may reduce fetal aortic blood flow, fetal muscle activity, and FHR variability.\(^13\) Sosa et al.\(^14\) demonstrated that intravenous meperidine 100 mg, given during the first stage of labor, resulted in an increased incidence of umbilical cord arterial acidemia at delivery compared with a placebo. The risk for neonatal respiratory depression is least with maternal administration of meperidine within 1 hour of delivery, and greatest when administered 3 to 5 hours before delivery.\(^13\)

Normeperidine accumulation is associated with altered neonatal behavior, manifesting as reduced duration of wakefulness, attentiveness, and breast-feeding.\(^15\) Meperidine administration is associated with lower Apgar scores and muscle tone in the neonate. Maternal side effects are of less clinical concern, although there is a high incidence of nausea, vomiting, and dysphoria.

The maternal half-life of meperidine is 2.5 to 3 hours, whereas that of normeperidine is 14 to 21 hours.\(^6\) The half-life of both compounds is increased by up to three times in the neonate as a result of reduced clearance, resulting in adverse effects up to 72 hours after delivery.\(^7\) The action of meperidine, but not normeperidine, is reversed by naloxone; consequently, antagonism with naloxone may exacerbate normeperidine-induced seizures owing to suppression of the anticonvulsant effect of meperidine.

The quality of labor analgesia produced by meperidine 50 mg is comparable to that of intravenous acetaminophen 1000 mg; a greater incidence of adverse effects has been observed (64% versus 0%).\(^16\)

The effect of meperidine on the progress of labor is unclear. Historically, meperidine has been given to decrease the length of the first stage of labor in cases of dystocia. However in 407 parturients diagnosed with dystocia, Sosa et al.\(^14\) found no differences in the duration of active labor or operative delivery rates, but significantly greater need for oxytocin augmentation (RR 2.24, 95% CI, 1.13 to 4.43), with the administration of intravenous meperidine 100 mg compared with saline-placebo.

Despite these concerns, meperidine is the most common opioid given for labor analgesia worldwide; this is most likely the result of its familiarity, ease of administration, availability, and low cost.

### Diamorphine

Diamorphine (3,6-diacetylmorphine, heroin) is a synthetic morphine derivative used for labor analgesia in 34% of obstetric units in the United Kingdom.\(^12\) Diamorphine is twice as potent as morphine. As a prodrug, diamorphine has no direct affinity for opioid receptors, but it is rapidly hydrolyzed by plasma esterases to active metabolites, which are responsible for its clinical effect.\(^8\) The metabolite 6-monooacetylmorphine is responsible for a significant proportion of analgesic activity, and it is further metabolized to morphine.\(^17\)

Although diamorphine 5 to 10 mg can be given intravenously, the same dose given intramuscularly results in approximately 90 minutes of labor analgesia. Both diamorphine and its active metabolite 6-monooacetylmorphine are more lipid soluble than morphine, resulting in a faster onset of analgesia with more euphoria but less nausea and vomiting. These pharmacokinetic properties may predispose to maternal respiratory depression. Because of rapid placential transfer, neonatal respiratory depression may also occur, although this is often associated with high doses of diamorphine.\(^18\)

Rawal et al.\(^19\) investigated the relationship between a single intramuscular dose of diamorphine 7.5 mg, the umbilical cord blood concentration of free morphine, and neonatal outcomes. A significant negative correlation between the dose-delivery interval and umbilical cord blood morphine levels was observed, with no correlation between higher free morphine concentrations and lower 1-minute Apgar scores (and the need for neonatal resuscitation). These findings suggest that infants born shortly after diamorphine administration are at greater risk for respiratory depression.

In 133 pregnant women randomized to receive intramuscular diamorphine 7.5 mg or meperidine 150 mg, Fairlie et al.\(^19\) found significantly greater reports of poor or no pain relief at 60 minutes in the group receiving meperidine, although approximately 40% of women in both groups requested a second-line analgesic agent. The incidence of maternal sedation was comparable, but the diamorphine group had less vomiting and higher neonatal Apgar scores at 1 minute.

Wee et al.\(^20\) conducted a two-center double-blinded randomized controlled trial of 484 women receiving intramuscular diamorphine 7.5 mg or intramuscular meperidine 150 mg for labor analgesia. The analgesia with diamorphine was modestly better, despite the average length of labor being 82 minutes longer (95% CI, 39 to 124). No differences in maternal sedation, nausea and vomiting, or primary neonatal outcomes were observed.

### Fentanyl

Fentanyl is a synthetic opioid that is highly lipid-soluble, protein-bound, and selective for the µ-opioid receptor, with an analgesic potency 100 times that of morphine and 800 times that of meperidine. Its rapid onset (peak effect, 2 to 4 minutes), short duration of action (30 to 60 minutes), and lack of active metabolites make it attractive for labor analgesia. Although intramuscular and intranasal routes are available, fentanyl is most commonly administered via the intravenous route and titrated to effect, often with a patient-controlled device.

Small doses of fentanyl undergo rapid redistribution, but large or repeated doses may accumulate.\(^6\) Importantly, clearance of fentanyl by elimination represents only 20% of that occurring by redistribution, resulting in a rapid increase in context-sensitive half-time with an increased duration of infusion.\(^6\) Fentanyl has a longer elimination half-life than morphine, but it is metabolized to several inactive metabolites in the liver that are excreted in the urine.
Fentanyl readily crosses the placenta as it is lipophilic; however, the average umbilical vein/maternal vein ratio remains low, most likely owing to a significant degree of maternal protein binding and drug redistribution. In a chronically instrumented sheep model, Craft et al. detected fentanyl in fetal plasma as early as 1 minute after maternal administration; however, maternal plasma levels were approximately 2.5 times greater than fetal plasma levels.

Rayburn et al. compared women receiving intravenous fentanyl (50 to 100 μg every hour at maternal request) with those who did not receive analgesia. All patients receiving fentanyl (mean 140 μg; range 50 to 600 μg) experienced brief analgesia (mean 45 minutes), sedation, and a transient reduction in FHR variability (mean 30 minutes). There were no differences between groups in neonatal Apgar scores, respiratory status, or Neurologic and Adaptive Capacity Scores (NACS). In a similar comparison of intravenous fentanyl (50 to 100 μg every hour) with an equianalgesic dose of meperidine (25 to 50 mg every 2 to 3 hours), Rayburn et al. observed less sedation, vomiting, and neonatal naloxone administration with fentanyl, but no difference in NACS. The two groups experienced similarly high pain scores, suggesting that both drugs have poor analgesic efficacy at the studied doses.

Rezk et al. randomized 80 parturients in active labor to receive intravenous fentanyl or intramuscular pethidine. A mild to moderate decrease in pain scores in both groups, but a return to baseline scores, was observed within 3 hours of fentanyl administration. Meperidine was associated with more maternal nausea and vomiting (P < .05), but less need for neonatal resuscitation and naloxone administration (P < .05).

A randomized controlled trial of 156 parturients investigated the efficacy of intranasal (i.n.) fentanyl, subcutaneous (s.c.) fentanyl, and intramuscular (i.m.) meperidine. Significant, similar reductions in pain scores were observed in all groups at 30 minutes; however, greater satisfaction (i.n. fentanyl 82.9%, s.c. fentanyl 80.6%, and i.m. meperidine 44%, P < .05) and less sedation (i.n. fentanyl 7.3%, s.c. fentanyl 2.9%, and i.m. meperidine 44%) were observed in the fentanyl groups. In a pilot study aimed at assessing the practicality and tolerability of patient-controlled analgesia with i.n. fentanyl (54 μg, lockout interval 3 min) for providing ongoing labor analgesia, most women reported satisfactory analgesia (78.2%), with a mean fentanyl dose of 734 μg over 3.5 hours, and a willingness to use it again (84.4%). However, 12.5% of neonates (n = 4) required bag-and-mask ventilation at birth.

Nalbuphine

Nalbuphine is a mixed agonist-antagonist opioid analgesic with agonist activity at κ-opioid receptors, thereby producing analgesia, and partial agonist activity at μ-opioid receptors, thus resulting in less respiratory depression. A partial agonist is a drug that has receptor affinity but produces a submaximal effect compared with a full agonist, even when given at very high doses.

Nalbuphine can be administered by intramuscular, intravenous, or subcutaneous injection, with a usual dose of 10 to 20 mg every 4 to 6 hours. The onset of analgesia occurs within 2 to 3 minutes of intravenous administration and within 15 minutes of intramuscular or subcutaneous administration. The drug is metabolized in the liver to inactive compounds that are then secreted into bile and excreted in feces.

Nalbuphine and morphine are of equal analgesic potency and result in sedation and respiratory depression at similar doses. However, because of its mixed receptor affinity, nalbuphine demonstrates a ceiling effect for respiratory depression at a dose of 0.5 mg/kg. Nalbuphine causes less nausea, vomiting, and dysphoria than morphine. Concerns that it may have an antianalgesic effect, particularly in men, led to the withdrawal of nalbuphine in the United Kingdom in 2003.

Wilson et al. performed a randomized, double-blinded comparison of intramuscular nalbuphine 20 mg and meperidine 100 mg for labor analgesia. Nalbuphine was associated with less nausea and vomiting but more maternal sedation. Analgesia was comparable between the groups. Neonatal neurobehavioral scores were lower in the nalbuphine group at 2 to 4 hours, but there was no difference between groups at 24 hours. The umbilical vein-to-maternal vein concentration ratio was higher with nalbuphine (mean ± SEM, 0.78 ± 0.03) than with meperidine (0.61 ± 0.02). A subsequent study failed to demonstrate an analgesic advantage with either drug but again reported transient neonatal neurologic depression with nalbuphine.

Amin et al. compared the neonatal outcome for women who received either nalbuphine or saline-control before elective cesarean delivery. They found lower 1-minute Apgar scores and a significantly longer time to sustained respiration in the nalbuphine group. However, 5-minute Apgar scores and umbilical cord blood gas measurements were similar between groups.

Nicolle et al. evaluated the transplacental transfer and neonatal pharmacokinetics of nalbuphine administered intramuscularly or intravenously in 28 laboring women. The investigators found a high umbilical vein-to-maternal vein concentration ratio of 0.74, which did not correlate with the administered dose. The estimated neonatal half-life was 4.1 hours, which is greater than the adult half-life and, more importantly, longer than the half-life of naloxone. There was a transient reduction in FHR variability in 54% of the fetuses, which was not associated with the plasma concentration of nalbuphine. Analgesia was rated as effective by 54% of parturients.

Giannina et al. compared the effects of intravenous nalbuphine and meperidine on intrapartum FHR tracings. Nalbuphine significantly reduced both the number of FHR accelerations and FHR variability, whereas meperidine had little effect.

A prospective pilot study of 302 nulliparous parturients (57 women who received nalbuphine, and a control group of 245 women who received neither nalbuphine nor epidural analgesia) reported a marked reduction in duration of the
active phase of the first stage of labor in the nalbuphine group (75 minutes versus 160 minutes in the control group); this effect appeared to be independent of oxytocin use. Additional investigations are needed to verify this finding.

**Butorphanol**

Butorphanol is a synthetic opioid with κ-opioid receptor agonist and µ-opioid receptor antagonist properties that resemble those of nalbuphine. It is five times more potent than morphine and 40 times more potent than meperidine. The typical dose during labor is 1 to 2 mg intravenously or intramuscularly. Butorphanol is 95% metabolized in the liver to inactive metabolites. Excretion is primarily renal. A plateau effect for analgesia and respiratory depression is noted, where butorphanol 2 mg produces respiratory depression similar to that of morphine 10 mg or meperidine 70 mg. However, butorphanol 4 mg results in less respiratory depression than morphine 20 mg or meperidine 140 mg. Higher doses do not provide any additional pain relief or respiratory depression but will increase the likelihood of other side effects.

Maduska and Hajighassemali compared intramuscular butorphanol (1 to 2 mg) with meperidine (40 to 80 mg) and found comparable labor analgesia; similar umbilical vein-to-maternal vein concentration ratios (0.84 and 0.89, respectively); and no differences in FHR tracings, Apgar scores, time to sustained respiration, or umbilical cord blood gas measurements at delivery. Conversely, in a double-blinded comparison of intravenous butorphanol (1 or 2 mg) and meperidine (40 or 80 mg) during labor, Quilligan et al. noted lower pain scores at 30 minutes and 1 hour after the administration of butorphanol. There was no significant difference in Apgar scores between the two groups of infants; however, the mean FHR was noted to be higher among those fetuses whose mothers received butorphanol.

Nelson and Eisenach investigated the possible synergistic effect of giving both intravenous butorphanol and meperidine. Women received intravenous butorphanol 1 mg, meperidine 50 mg, or butorphanol 0.5 mg with meperidine 25 mg. All three groups reported a similar reduction in pain intensity; however, only 29% of the women achieved clinically significant pain relief. There was no difference among groups in maternal side effects or neonatal Apgar scores. The investigators concluded that there was no therapeutic benefit to combining the two drugs.

Atkinson et al. performed a double-blinded trial of intravenous butorphanol (1 to 2 mg) and fentanyl (50 to 100 μg) administered hourly on maternal request. They found that butorphanol provided better analgesia initially, with fewer requests for additional drug doses or progression to epidural analgesia. There was no difference in adverse maternal or neonatal effects between the two groups.

**Meptazinol**

Meptazinol is a partial opioid agonist specific to µ-opioid receptors with a rapid onset of action (15 minutes after intramuscular administration). The intramuscular dose (50 to 100 mg) and duration of action for labor analgesia are similar to those for meperidine, with an adult half-life of 2.2 hours, and a neonatal half-life of 3.4 hours. Its partial agonist activity is thought to result in less sedation, respiratory depression, and risk for dependence compared with other opioid agonists. Meptazinol is metabolized by glucuronidation in the liver and then excreted in the urine. This process is more mature in the neonate than is the metabolic pathway of meperidine.

Theoretically, this rapid elimination should confer a lower incidence of adverse neonatal effects than occurs with meperidine. In a single-blinded study, Jackson and Robson compared the same dose (100 mg if maternal weight was ≤ 60 kg, 125 mg if 61 to 70 kg, and 150 mg if ≥ 70 kg) of intramuscular meptazinol or meperidine. Meptazinol provided significantly better analgesia than meperidine but resulted in a similar frequency of maternal side effects.

Nicholas and Robson subsequently compared intramuscular meptazinol 100 mg with meperidine 100 mg in a randomized, double-blinded trial in 358 parturients. Meptazinol provided significantly better pain relief at 45 and 60 minutes, but the two drugs provided a similar duration of analgesia, and there was no significant difference between groups in maternal side effects. Neonatal outcomes were similar between groups, except significantly more infants whose mothers had received meptazinol had an Apgar score of 8 or higher at 1 minute.

Other investigators have reported little difference in analgesic efficacy, maternal side effects, or neonatal outcomes between meptazinol and meperidine. In a study of 1100 patients, Morrison et al. found that neither drug given at equal doses (150 mg in patients weighing > 70 kg, 100 mg in those weighing ≤ 70 kg) was effective at relieving pain. Maternal drowsiness was significantly less pronounced with meptazinol, but the incidence of vomiting was higher. FHR changes and neonatal outcomes, including Apgar scores, need for resuscitation, and suckling ability, were comparable. The overall use of naloxone was similar in the two groups, but if the dose-delivery interval exceeded 180 minutes, significantly more neonates in the meperidine group required naloxone.

De Boer et al. assessed neonatal blood gas and acid–base measurements after maternal intramuscular administration of meptazinol (1.5 mg/kg) or meperidine (1.5 mg/kg) during labor. Capillary blood gas measurements at 10 minutes of life showed a significantly lower pH and a higher Paco2 in the meperidine group, although this difference resolved by 60 minutes. These findings suggest that meptazinol causes less neonatal respiratory depression.

Meptazinol may confer some benefits over meperidine in early neonatal outcome, but it is not widely used. A recent survey indicated that it is the intramuscular labor analgesic of choice in only 14% of obstetric units in the United Kingdom. The cost of meptazinol is considerably higher than that of meperidine. Meptazinol is not available in the United States.

**Pentazocine**

Pentazocine is a selective κ-opioid receptor agonist with some weak antagonist activity at µ-opioid receptors. It may be given orally or systemically by intramuscular or intravenous...
injection. The typical parenteral adult dose is 30 to 60 mg, which is equivalent to morphine 10 mg. Onset of action occurs within 2 minutes when given intravenously and within 20 minutes if given by the intramuscular route. Metabolism occurs in the liver by oxidation and glucuronidation; metabolites are then excreted in the urine.

Pentazocine causes similar respiratory depression to that seen with equipotent doses of morphine and meperidine, but it exhibits a ceiling effect with doses in excess of 60 mg. Psychomimetic effects (e.g., dysphoria, hallucinations) may complicate its use, particularly with increasing doses.

In a double-blinded study of 94 laboring women who received intramuscular administration of pentazocine (up to 60 mg) and meperidine (up to 150 mg), Mowat and Garrey observed equivalent and adequate analgesia for approximately 40% of women in each group. The incidence of sedation was comparable between groups, and fewer women in the pentazocine group complained of nausea and vomiting.

In a randomized study comparing intramuscular administration of pentazocine 30 mg with tramadol 100 mg in 100 laboring women, Kuti et al. observed greater analgesia in the pentazocine group at 1 hour, with a longer time to subsequent request for additional analgesia (181 minutes versus 113 minutes, \( P < .05 \)). The overall analgesic effect of both drugs was modest, with only 30% to 50% of women reporting satisfactory pain relief. More women in the pentazocine group were drowsy, but the result did not achieve statistical significance. There were no cases of maternal respiratory depression, and there was no difference between groups in neonatal outcomes. The investigators concluded that pentazocine provides better labor analgesia than tramadol.

**Tramadol**

Tramadol is an atypical, weak, synthetic opioid that has affinity for all opioid receptors, but particularly the \( \mu \)-opioid subtype. A racemic mixture of two enantiomers, the analgesic properties of tramadol (\( + \)) are mediated via inhibition of the central neuronal reuptake of serotonin, while tramadol (\( - \)) inhibits norepinephrine reuptake. Tramadol can be administered orally or by intramuscular or intravenous injection at a dose of 50 to 100 mg every 4 to 6 hours in adults.

The analgesic potency of tramadol is equal to that of meperidine and one-fifth to one-tenth that of morphine. In equianalgesic doses, tramadol causes less respiratory depression than morphine; at usual doses, no clinically significant respiratory depression occurs. The onset of analgesia is within 10 minutes of intramuscular administration, with an effective duration of 2 to 4 hours.

Tramadol is metabolized by demethylation and glucuronidation in the liver to several metabolites, one of which has independent analgesic activity (O-desmethyltramadol [M1]). The metabolites are almost entirely excreted in the urine. The elimination half-life is approximately 5 to 6 hours, whereas that of the active metabolite is 9 hours. Clinical experience in its use over 30 years is substantial. Since pregnant and breast-feeding women were excluded from randomized phase 1 to 3 clinical trials before marketing, research into its use in pregnancy and lactation is limited, and it is now difficult to conduct postmarketing clinical research in these populations.

Tramadol and its active metabolite M1 readily cross the placenta, and an umbilical vein-to-maternal vein ratio of 0.94 has been observed at delivery. Neonates possess complete hepatic capacity for metabolism of tramadol to its active metabolite M1. The elimination profile of M1 suggests a terminal half-life of 85 hours because of its requirement for renal elimination, which is an immature process in neonates. An observational study of women given intramuscular tramadol in doses up to 250 mg for labor analgesia resulted in normal Apgar scores and NACS, with no correlation with tramadol or M1 concentrations. However, the single neonate who required naloxone had the highest plasma concentration of tramadol.

Tramadol for maternal pain relief in labor produces limited analgesic benefit. In a comparison of intramuscular tramadol 100 mg and meperidine 100 mg for labor analgesia, Keskin et al. observed greater pain relief and a lower incidence of nausea and fatigue with meperidine. There was no significant difference between groups in neonatal outcome, but more infants in the tramadol group required supplemental oxygen for respiratory distress and hypoxemia. The investigators concluded that meperidine provided superior analgesia and was associated with a better side-effect profile.

By contrast, Viegas et al. conducted a randomized, double-blinded trial to compare intramuscular administration of tramadol 50 mg, tramadol 100 mg, and meperidine 75 mg. Tramadol 100 mg and meperidine 75 mg provided similar labor analgesia; however, a higher incidence of maternal and neonatal adverse effects was observed with meperidine.

Khooshhideh and Shahriari evaluated the intramuscular administration of tramadol 100 mg or meperidine 50 mg on labor duration and analgesic efficacy in 160 parturients. The investigators observed that tramadol was associated with a reduced duration of both the first stage (140 versus 190 minutes, \( P < .001 \)) and the second stage of labor (25 versus 33 minutes, \( P = .001 \)). There was no difference in median and maximum pain scores between groups 1 hour after drug administration; however, lower pain scores were observed during the second stage of labor in the meperidine group. Nausea, vomiting, and drowsiness occurred less frequently in the tramadol group.

Shetty et al. observed no difference with the intramuscular injection of tramadol 1 mg/kg compared with pentazocine 30 mg for labor analgesia; however, by the end of the first stage of labor, 55% and 60% of women rated their pain as severe and very severe, respectively. The mean injection to delivery interval was significantly shorter in the tramadol group compared with the pentazocine group.

**PATIENT-CONTROLLED ANALGESIA**

Patient-controlled analgesia has been used to control postoperative pain for several decades and for the provision of labor analgesia in more recent years. First described in women with...
thrombocytopenia who were unable to undergo a neuraxial analgesia procedure, its use has grown in availability and popularity. A 2007 survey demonstrated that 49% of obstetric units in the United Kingdom offered PCA for labor analgesia.49 Purported advantages of PCA include (1) superior pain relief with lower doses of drug, (2) less risk for maternal respiratory depression compared with bolus intravenous administration, (3) less placental transfer of drug, (4) less need for antiemetic agents, and (5) greater patient satisfaction.50 The smaller, more frequent dosing used with this mode of analgesia may result in a more stable plasma drug concentration and a more consistent analgesic effect compared with that of intermittent bolus administration regimens.50

PCA represents an alternative method of labor analgesia when neuraxial analgesia is not requested or is unavailable, contraindicated, or unsuccessful. The parturient can tailor the administration of analgesia according to her individual needs, and with some regimens the bolus dose can be altered to allow further titration of analgesia as labor progresses.

However, PCA for labor is not without limitations. Despite the frequency of dose administration, the coordination of peak opioid concentrations with uterine contractions can be difficult and result in suboptimal analgesia. In addition, the relatively small doses of opioid may be less effective at controlling pain as labor progresses. Finally, a number of maternal and fetal side effects have been described (see later discussion). A variety of drugs, doses, and regimens have been studied, including comparisons of PCA with and without a continuous intravenous infusion (Table 22.4).

### Meperidine
Meperidine was the first opioid to be used for PCA during labor. Isenor and Penny-MacGillivray51 compared PCA meperidine (background infusion 60 mg/h with bolus doses of 25 mg, up to a maximum dose of 200 mg) with intermittent intramuscular meperidine (50 to 100 mg every 2 hours). Women in the PCA group reported lower pain scores than women in the intramuscular group, even when adjustment was made for the increased total amount of meperidine used.51 There was no difference in maternal side effects, FHR abnormalities, or neonatal Apgar scores between groups.

When administered by PCA, meperidine appears to be less effective than shorter-acting opioids. Douma et al.52 randomized parturients in labor to receive either meperidine (49.5-mg loading dose, 5-mg bolus dose with 10-min lockout, maximum total dose 200 mg), fentanyl (50-µg loading dose, 20-µg bolus dose with 5-min lockout, maximum dose 240 µg/h), or remifentanil (40-µg loading dose, 40-µg bolus dose with 2-min lockout, maximum dose 1200 µg/h). Meperidine provided the least effective analgesia, with no change in pain scores from baseline at 2 hours after administration and the highest rate of conversion to epidural analgesia.

### Morphine and Diamorphine
Morphine and diamorphine are rarely administered by PCA for labor analgesia in parturients with a live fetus, but they are an option for women with intrauterine fetal demise.49 The accumulation of the active metabolite morphine-6-glucuronide, which is a potent respiratory depressant, is a concern in mothers with a live fetus. No studies have compared the analgesic efficacy of morphine administered by PCA versus intermittent bolus administration during labor.

In a single study of diamorphine, administered by either PCA or intermittent intramuscular bolus doses, less effective analgesia and lower satisfaction scores were observed in the PCA group.53

### Fentanyl
The pharmacokinetic profile for fentanyl (i.e., rapid onset, high potency, short duration of action, absence of active metabolites) has resulted in its selection as one of the most commonly used opioids for PCA during labor and delivery. In the United Kingdom, it is used in 26% of the units that offer PCA during labor.49

Nikkola et al.54 observed that fentanyl PCA (loading dose 50 µg, bolus 20 µg, lockout interval 5 min) provided a moderate reduction in labor pain in 50% of the parturients receiving this mode of analgesia; however, less overall pain relief was experienced when compared with a group that received epidural analgesia. The use of fentanyl was also associated with a higher incidence of maternal dizziness and sedation.

Rayburn et al.55 compared fentanyl PCA (bolus 10 µg, lockout interval 12 min) with intermittent intravenous nurse-administered boluses (50 to 100 µg every hour, on demand). The degree of analgesia, adverse maternal effects, and neonatal outcomes (e.g., Apgar scores, naloxone requirement, neurobehavioral scores) were similar between the two groups. The two groups used a similar total amount of fentanyl, had comparable umbilical serum concentrations of fentanyl, and had incomplete analgesia during late labor.

Morley-Forster and Weberpals56 observed a 44% incidence of moderate neonatal depression (1-minute Apgar score < 6) in a retrospective review of 32 neonates whose mothers had

### TABLE 22.4 Opioids Used for Intravenous Patient-Controlled Analgesia in Labor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bolus Dose</th>
<th>Lockout Interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>5–15 mg</td>
<td>10–20</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>1–3 mg</td>
<td>6–10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10–25 µg</td>
<td>5–12</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>200 µg (&lt; 200 µg/h infusion)</td>
<td>5</td>
</tr>
<tr>
<td>Remifentanil (bolus only)</td>
<td>0.2–0.8 µg/kg (low dose initially, then titrated to effect)</td>
<td>2–3</td>
</tr>
<tr>
<td>Remifentanil (background infusion with bolus dose)</td>
<td>Infusion rate: 0.025–0.1 µg/kg/min, Bolus dose: 0.25 µg/kg</td>
<td>2–3</td>
</tr>
</tbody>
</table>
received fentanyl PCA (at various initial doses, basal infusion rates, and lockout intervals) during labor. A total of 9.4% of the neonates required naloxone; the total dose of fentanyl was significantly higher in the mothers of neonates who required naloxone than in those who did not (mean ± SD, 770 ± 233 µg versus 298 ± 287 µg, respectively). By contrast, in a retrospective evaluation of fentanyl PCA (loading 50 µg, bolus 20 µg, lockout interval 5 min) compared with no analgesia during labor, Hosokawa et al.57 observed lower mean umbilical arterial blood pH measurements, but comparable Apgar scores and no requirement for naloxone or bag-and-mask ventilation in the 129 neonates whose mothers received fentanyl.

**Alfentanil**

Alfentanil is a highly selective µ-opioid receptor agonist that is administered by the intravenous route only.17 Although infrequently used during labor, it is typically administered by PCA. A fentanyl derivative, it is approximately 10 times less potent than fentanyl. It is less lipophilic and more protein bound than its parent compound, resulting in a smaller volume of distribution. Its low volume of distribution and low pKₐ result in a rapid onset (within 1 minute), a short duration of action, and rapid clearance (elimination half-life of 90 minutes). Furthermore, its context-sensitive half-time is shorter than that of fentanyl. Metabolism of alfentanil occurs by demethylation in the liver to noralfentanil, which is then conjugated and excreted in the urine. Importantly, alfentanil is a potent respirator depressant, and consequently there are concerns regarding potential adverse neonatal effects.

Morley-Forster et al.58 compared alfentanil PCA (bolus 200 µg, lockout interval 5 min, background infusion 200 µg/h) with fentanyl PCA (bolus 20 µg, lockout interval 5 min, background infusion 20 µg/h). The two drugs appeared equally effective in early labor, up to a cervical dilation of 6 cm. Subsequently, fentanyl was associated with a greater reduction in pain scores compared with alfentanil. There were no significant differences in maternal side effects or neonatal outcomes.

**Pentazocine**

The use of pentazocine is uncommon in the western world, and there has been little evaluation of its use via PCA. One study in South Africa compared pentazocine PCA with meperidine PCA and reported acceptable maternal analgesia and neonatal outcomes with both, but a higher incidence of maternal nausea and sedation with meperidine.59

**Tramadol**

Tramadol is not commonly used via PCA. Long and Yue60 compared tramadol PCA with CSE analgesia and found that both forms of pain relief resulted in a significant decrease in pain scores compared with a third group not receiving analgesia; however, the CSE technique provided the best analgesia. The tramadol group experienced a higher incidence of adverse maternal events (including one case of cardiovascular collapse) and neonatal depression.

**Nalbuphine**

Few studies have evaluated nalbuphine PCA in labor. In one study, maternal satisfaction was higher with nalbuphine PCA (bolus 1 mg, lockout interval 6 to 10 min) compared with intermittent intravenous administration (bolus 10 to 20 mg every 4 to 6 h).61 Analgesia and Apgar scores were similar between groups, and no neonates required naloxone.

Frank et al.62 concluded that nalbuphine PCA (bolus 3 mg, lockout interval 10 min) provided better analgesia in nulliparous women than meperidine PCA (bolus 15 mg, lockout interval 10 min). Maternal sedation scores were similar, and there was no difference in neonatal outcome as assessed by Apgar scores, time to sustained respiration, or neurobehavioral assessment at 6 to 10 hours after delivery.

**Remifentanil**

Remifentanil is a synthetic anilidopiperidine derivative with selective activity at the µ-opioid receptor, low lipid solubility, and a small volume of distribution (0.39 L/kg). Functional brain magnetic resonance imaging revealed an onset time of 20 to 30 seconds, peak concentration within 80 to 90 seconds at the cortical loci, and a blood-brain equilibration time of 1.2 to 1.4 minutes.63 Remifentanil undergoes rapid hydrolysis by nonspecific plasma and tissue esterases to inactive metabolites, independent of organ metabolism, resulting in a short elimination half-life of approximately 9.5 minutes. The context-sensitive half-time is 3.5 minutes, irrespective of duration of infusion. The effective analgesic half-life is 6 minutes, thus allowing effective analgesia for consecutive uterine contractions. Plasma concentrations of remifentanil in pregnant patients are approximately one-half those found in nonpregnant patients.64 This difference may be caused by the greater volume of distribution (increased blood volume and reduced protein binding), greater clearance (increased cardiac output and renal perfusion), and higher esterase activity during pregnancy.

Remifentanil is rapidly titratable, allowing for dose adjustments with labor progress or in response to side effects. Termination of a continuous remifentanil infusion results in a 50% recovery in minute ventilation within 5.4 minutes. Although remifentanil readily crosses the placenta, resulting in a fetal-to-maternal blood ratio of 0.88, the lower umbilical artery-to-vein concentration ratio of 0.29 demonstrates that the drug is extensively redistributed and/or metabolized by the fetus.64 Kan et al.64 found no adverse neonatal effects after a remifentanil infusion during cesarean delivery. The rapid onset and offset of remifentanil, with a peak effect-site concentration observed at 1 to 2 minutes, may not provide adequate or sustained analgesia for the desired or subsequent uterine contraction, respectively.

**Comparison with Other Forms of Labor Analgesia**

The efficacy of remifentanil patient-controlled intravenous analgesia (PCIA) has been compared with that of other labor analgesic agents and regimens (Table 22.5).

**Remifentanil versus Meperidine.** Thurlow et al.65 conducted a randomized unblinded study in 36 women...
comparing remifentanil PCA (bolus 20 µg, lockout interval 3 min) with intramuscular meperidine 100 mg. The remifentanil group experienced significantly lower pain scores (median maximum pain score 66.5/100 mm versus 82.5/100 mm, \( P = .009 \)) within the first 2 hours of commencing analgesia. However, parturients in the remifentanil group also used nitrous oxide analgesia (56%) and experienced more sedation and episodes of oxygen saturation less than 94%. No significant difference in Apgar scores was found.

Ng et al. conducted a randomized, double-blinded study in which 69 patients used a PCA device containing either remifentanil (PCIA group) or meperidine (meperidine group), and also received an intramuscular injection of either saline (PCIA group) or meperidine (meperidine group). The doses administered depended on patient weight; women weighing less than 60 kg or 60 kg or more were given a bolus dose of remifentanil of 25 µg or 30 µg, respectively. Similarly, the doses of meperidine were either 50 mg or 75 mg. The PCIA lockout interval was 3.75 to 4.5 minutes, and a background infusion was not used. Maternal analgesia was greater (particularly in the first 2 hours after initiation), the median time to first rescue analgesic request was longer (8.0 hours versus 4.9 hours), and maternal satisfaction scores were higher in the remifentanil PCIA group than in the meperidine group. There was no difference between groups in maternal sedation, nausea, or oxygen saturation. Neonatal outcomes were also similar.

Blair et al. observed that the use of remifentanil PCA (bolus 40 µg, lockout interval 2 min) resulted in higher maternal satisfaction scores and modest analgesic benefit compared with meperidine PCA (bolus 15 mg, lockout

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Subjects</th>
<th>Study Design</th>
<th>Groups; Drugs; Doses</th>
<th>Primary Data</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volikas et al.</td>
<td>17</td>
<td>Double-blinded, randomized</td>
<td>( n = 8 ); M PCA 10 mg b, 5 min l/o \n( n = 9 ); R PCA 0.5 µg/kg b, 2 min l/o</td>
<td>VAPS hourly \nVAPS after delivery</td>
<td>Lower mean VAPS hourly in group R ( (P = .0496) ) \nLower mean VAPS after delivery in group R ( (P = .03) )</td>
</tr>
<tr>
<td>Thurlow et al.</td>
<td>36</td>
<td>Unblinded, randomized</td>
<td>( n = 18 ); M 100 mg IM \n( n = 18 ); R PCA 20 µg b, 3 min l/o</td>
<td>VAPS at 1 h after analgesia \nMaximum VAPS at 2 h after analgesia</td>
<td>Lower VAPS in group R at 1 h ( (48 \text{ mm versus } 72 \text{ mm}; P = .0004) ) \nLower max VAPS in group R during first 2 h ( (66.5 \text{ mm versus } 82.5 \text{ mm}; P = .009) )</td>
</tr>
<tr>
<td>Blair et al.</td>
<td>39</td>
<td>Double-blinded, randomized</td>
<td>( n = 19 ); M PCA 15 mg b, 10 min l/o \n( n = 20 ); R PCA 40 µg b, 2 min l/o</td>
<td>VAPS every 30 min \nVAPS “overall” at 2 h after delivery</td>
<td>Similar VAPS in labor and overall between groups ( \text{overall pain score } 63.6 \text{ mm R versus } 68.6 \text{ mm M } (P = \text{NS}) )</td>
</tr>
<tr>
<td>Evron et al.</td>
<td>88</td>
<td>Double-blinded, randomized</td>
<td>( n = 45 ); M 75–200 mg IV \n( n = 43 ); R PCA increasing b dose in 5–µg increments, range 20–70 µg, 3 min l/o</td>
<td>VAPS at 1 hour after analgesia \nVAPS at end of first stage of labor</td>
<td>Lower VAPS in group R at 1 hour ( (35.8 \text{ mm versus } 58.8 \text{ mm}, P &lt; .001) ) \nLower VAPS at end of first stage ( (32.6 \text{ mm versus } 53.5 \text{ mm}, P &lt; .001) )</td>
</tr>
<tr>
<td>Douma et al.</td>
<td>159</td>
<td>Double-blinded, randomized</td>
<td>( n = 53 ); M PCA 49.5 mg load, 5 mg b, 10 min l/o \n( n = 52 ); R PCA 40 µg b, 40 µg b, 2 min l/o \n( n = 54 ); F PCA 50 µg load, 20 µg b, 5 min l/o</td>
<td>VAPS hourly</td>
<td>Greatest reduction in VAPS observed at 1 hour in all three groups \nLower VAPS in group R at 1 h ( (3.2 \text{ cm versus } 1.4 \text{ cm F versus } 0.8 \text{ cm M}) ) \nSimilar VAPS beyond first hour among groups \nLower mean VAPS in group R ( (P = .001) ) \nLowest VAPS in group R at 2 h after analgesia ( (44% \text{ relative reduction from baseline) } )</td>
</tr>
<tr>
<td>Ng et al.</td>
<td>68</td>
<td>Double-blinded, randomized</td>
<td>( n = 34 ); M 50 mg IM \n( n = 34 ); R PCA 25 µg b &lt; 60 kg, 30 µg b ≥ 60 kg, 3.75–4.5 min l/o</td>
<td>VAPS hourly</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Number of Subjects</td>
<td>Study Design</td>
<td>Groups; Drugs; Doses</td>
<td>Primary Data</td>
<td>Comments</td>
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<tr>
<td>Marwah et al.</td>
<td>68</td>
<td>Retrospective cohort</td>
<td>n = 47; R PCA 0.25 µg/kg b, 2 min l/o and background infusion 0.025–0.05 µg/kg/min n = 51; F PCA 20–50 µg b, 3–6 min l/o</td>
<td>Hourly verbal pain score scale 0–10</td>
<td>Mean pain score in R PCA 4.1 (baseline 7.6) Mean pain score in F PCA 4.9 (baseline 8.2)</td>
</tr>
<tr>
<td>Volmanen et al.</td>
<td>15</td>
<td>Double-blinded, randomized, crossover</td>
<td>All participants had 20 min of 50% nitrous oxide or R PCA (0.4 µg/kg b, 1 min l/o) followed by 20 min washout period (no analgesia) then 20 min of the other analgesic. n = 8; Group 1 R then nitrous oxide n = 6; Group 2 nitrous oxide then R</td>
<td>Pain intensity difference (PID = mean pain score with analgesia – mean pain score without analgesia)</td>
<td>Higher PID in group R (1.5 versus 0.5, P = .01)</td>
</tr>
<tr>
<td>Stocki et al.</td>
<td>45</td>
<td>Double-blinded, randomized</td>
<td>n = 24; R PCA 0.1–0.9 µg/kg b (0.1 µg/kg increments), 1 min l/o n = 21; Epidural 20 mL of 0.625 mg/mL levobupivacaine with 2 µg/mL fentanyl</td>
<td>Pain after each contraction (0–10)</td>
<td>Higher median pain scores in group R (7.3 versus 5.2, P = .009)</td>
</tr>
<tr>
<td>Freeman et al.</td>
<td>1414</td>
<td>Multicenter randomized controlled equivalence trial</td>
<td>n = 447; R PCA 20–40 µg b (initial 30 µg b), 3 min l/o n = 347; Epidural using various regimens: ropivacaine/sufentanil (37%), bupivacaine/sufentanil (46%), levobupivacaine/sufentanil (6%) and bupivacaine/fentanyl. No doses specified</td>
<td>Satisfaction with pain relief via a VAS 0–100 mm score reported hourly from onset of labor</td>
<td>Area under the curve for satisfaction with pain relief during labor was lower in R group</td>
</tr>
<tr>
<td>Tveit et al.</td>
<td>37</td>
<td>Unblinded, randomized</td>
<td>n = 17; R PCA 0.15–1.05 µg/kg b (0.15 µg/kg increments), 2 min l/o n = 20; Epidural ropivacaine 1 mg/mL with fentanyl 2 µg/mL. Loading dose 15 mL, then 10 mL/h infusion.</td>
<td>VAPS every 15 min</td>
<td>Similar VAPS between groups at end of first stage and during second stage Similar maximum reduction in VAPS between groups</td>
</tr>
</tbody>
</table>

b, Bolus; F, fentanyl; load, loading dose; l/o, lockout; M, meperidine; NRS, numeric rating scale; NS, nonsignificant; PCEA, patient-controlled epidural analgesia; R, remifentanil; VAPS, visual analogue pain score (0–100 mm).
interval 10 min). Douma et al.\textsuperscript{52} compared remifentanil PCIA (bolus 40 µg, lockout interval 2 min), fentanyl PCIA (bolus 20 µg, lockout interval 5 min), and meperidine PCIA (bolus 5 mg, lockout interval 10 min). The remifentanil group had the highest crossover rate to epidural analgesia. Despite similar labor analgesia in 98 women with PCIA fentanyl compared with PCIA remifentanil, Marwah et al.\textsuperscript{36} reported a greater need for neonatal resuscitation in the fentanyl group.

In a systematic review of seven randomized controlled trials (n = 349), Leong et al.\textsuperscript{29} evaluated the administration of remifentanil versus meperidine provided through a variety of drug delivery methods (e.g., PCA, continuous infusion, intramuscular) for labor analgesia. Remifentanil was noted to reduce the mean VAS pain score by 25 mm more than meperidine in the first hour. The conversion rate to epidural analgesia was less than 10% when using remifentanil. Schnabel et al.\textsuperscript{70} reported similar conclusions from a meta-analysis comparing PCIA remifentanil, PCIA meperidine, and epidural analgesia. Women who received remifentanil PCIA had lower mean pain scores after 1 hour, a lower crossover rate to epidural analgesia, and a higher satisfaction scores than women who received meperidine.

**Remifentanil versus Nitrous Oxide.** Volmanen et al.\textsuperscript{71} performed a double-blinded crossover trial comparing remifentanil (bolus 0.4 µg/kg, lockout interval 1 min) with 50% nitrous oxide during the first stage of labor. The 20 patients used both analgesics in a random order for 20 minutes, with an intervening washout period of 20 minutes. Pain relief (although modest), maternal sedation, and patient satisfaction were greater in the remifentanil group. No difference in the incidence of FHR changes was observed between the two groups.

**Remifentanil versus Epidural Analgesia.** In a randomized, double-blinded trial, Volmanen et al.\textsuperscript{72} compared remifentanil PCIA (mean effective bolus 0.5 µg/kg [range 0.3 to 0.7 µg/kg], lockout interval 1 min) with lumbar epidural analgesia (20 mL of levobupivacaine 0.0625% with fentanyl 2 µg/mL). All patients received an epidural technique and a background infusion with a titratable bolus dose. Both groups started with a remifentanil bolus dose of 0.25 µg/kg (lockout interval 2 min) and a background infusion rate of 0.025 µg/kg/min. If analgesia was inadequate, either the background infusion or bolus dose was increased in a stepwise manner to a maximum of 0.1 µg/kg/min or 1 µg/kg, respectively. The mean pain scores, satisfaction scores, and cumulative remifentanil doses were similar in the two groups; only one patient eventually requested epidural analgesia. The incidence of maternal side effects was higher in the escalating bolus dose group, including drowsiness (100% versus 30%) and frequency of oxygen saturation less than 95% (60% versus 40%). There was no difference in the incidence of adverse neonatal effects. The investigators postulated that high maternal satisfaction with remifentanil PCIA may be the result of factors other than the degree of analgesia produced.

Two meta-analyses concluded that epidural analgesia provides superior labor analgesia (mean difference in effect size 3.0 cm/10 cm [95% CI, 0.7 to 5.2] at 2 hours) and satisfaction compared with remifentanil PCIA.\textsuperscript{70,73} More recently, Stocki et al.\textsuperscript{74} conducted an unblinded controlled noninferiority study in 39 healthy women randomized to receive remifentanil PCIA (titrated from 20 to 60 µg, lockout interval 1 to 2 min), or patient-controlled epidural analgesia (PCEA) (0.1% bupivacaine with 2 µg/mL fentanyl). Analgesia with remifentanil was inferior to the epidural technique at all time points, but maternal satisfaction was similar. All apnea events occurred in the women receiving remifentanil, who also had lower mean respiratory rates and oxygen saturation.

In a multicenter randomized controlled trial, Freeman et al.\textsuperscript{75} randomized 1414 women to remifentanil PCIA or epidural analgesia. Satisfaction and analgesia were significantly higher in the women who received epidural analgesia. Remifentanil analgesia was most effective during the first few hours of use, after which pain scores returned to baseline pre-analgesia levels.\textsuperscript{70,73}

**Efficacy and Optimal Regimen**

Remifentanil can be given as a PCIA bolus, as a continuous infusion, or as a combination of the two. Although a number of studies have compared remifentanil with other opioids using fixed, non-titratable PCIA doses, Volmanen et al.\textsuperscript{76} attempted to determine the minimum effective dose of remifentanil for labor analgesia during the first stage of labor. Using an initial bolus dose of 0.2 µg/kg, and dose increases of 0.2 µg/kg (lockout interval 1 min) over a 1-hour study period, the median effective bolus dose was observed to be 0.4 µg/kg (range, 0.2 to 0.8 µg/kg). However, frequent episodes of oxygen saturation less than 94% (10 of 17 subjects), maternal sedation, and reduced FHR variability were observed.

Balki et al.\textsuperscript{77} compared the effect of a fixed remifentanil bolus dose with a titratable background infusion versus a fixed background infusion with a titratable bolus dose. Both groups started with a remifentanil bolus dose of 0.25 µg/kg (lockout interval 2 min) and a background infusion rate of 0.025 µg/kg/min. If analgesia was inadequate, either the background infusion or bolus dose was increased in a stepwise manner to a maximum of 0.1 µg/kg/min or 1 µg/kg, respectively. The mean pain scores, satisfaction scores, and cumulative remifentanil doses were similar in the two groups; only one patient eventually requested epidural analgesia. The incidence of maternal side effects was higher in the escalating bolus dose group, including drowsiness (100% versus 30%) and frequency of oxygen saturation less than 95% (60% versus 40%). There was no difference in the incidence of adverse neonatal effects. The investigators advocated the use of a titrated background infusion (range, 0.025 to 0.1 µg/kg/min) with a constant PCIA bolus dose (0.25 µg/kg, lockout interval 2 min).

D’Onofrio et al.\textsuperscript{78} conducted an observational study of 205 parturients in whom a continuous infusion of remifentanil was titrated (initial to maximum dose range; 0.025 to 0.15 µg/kg/min) with a goal of achieving pain scores less than or equal to 4 during contractions. Adequate analgesia was achieved within 30 minutes but required a median remifentanil infusion dose of 0.075 µg/kg/min. The oxygen saturation remained above 95% in all patients without supplemental oxygen, and there were no reported neonatal side effects.

Together, these studies suggest that fixed-dose remifentanil PCA protocols are less effective than titratable regimens, with the potential for low doses resulting in poor analgesia, underdosing, and maternal dissatisfaction, and high doses resulting in adverse effects such as maternal sedation, respiratory
Depression, and oxygen desaturation. Evidence is conflicting as to whether the use of a background infusion confers additional benefits, particularly given the greater risk for maternal sedation and respiratory depression.67,77

Rehberg et al.77 sought to improve labor analgesia and reduce side effects by altering the timing of the remifentanil PCA bolus. A handheld dynamometer was used to determine the peak effect of the next contraction; however, because of contraction variability, analgesia was not substantially improved. The analgesic benefit of remifentanil may be best optimized by training parturients to press the PCA button with the first perception of a contraction, given that the peak analgesic effect occurs within 1 to 3 minutes.17

Leong et al.80 devised an automated closed interactive feedback system (“step-up–step-down” regimen) with the input of continuous monitoring devices (pulse oximeter and heart rate) to modulate drug delivery and improve labor analgesia and safety. The vital sign–controlled, patient-assisted intravenous analgesia (VPIA) prototype initially administered small boluses of remifentanil, with dosing alterations based on the presence or absence of patient demands over a predefined period. In the 29 parturients who used the device, despite all using supplemental oxygen, 52% experienced oxygen desaturation less than 95% for more than 60 seconds, and 24% experienced a heart rate less than 60 beats per min (bpm) for more than 60 seconds. The median dose of remifentanil was 0.07 µg/kg/min, and the system automatically reduced dosages and temporarily halted remifentanil administration when desaturation and bradycardia thresholds were achieved. Thirty-one percent required additional analgesia including Entonox or an epidural technique.

Side Effects

Remifentanil can cause respiratory depression through reductions in the ventilatory rate and tidal volume. Although the safety profile of remifentanil PCA in labor has been specifically evaluated, the data are conflicting.78,81 Volikas et al.81 investigated the maternal and neonatal effects of remifentanil PCA (bolus dose 0.5 µg/kg, lockout interval 2 min) in 50 women. Effective analgesia was reported in 86% of study participants, and 44% experienced slight drowsiness (but were rousable to voice and maintained oxygen saturation greater than 93%). Mild itching and FHR changes occurred in the first 20 minutes of remifentanil PCA but did not require treatment. Umbilical cord blood gas measurements and neonatal Apgar scores and neurologic examinations were all within normal limits.

Even with the use of oxygen saturation and end-tidal CO2 monitoring, Stocki et al14 reported a moderate number of apneic events (respiratory arrest greater than 20 seconds), lower respiratory rates, and hypoxemic events in women receiving remifentanil PCA, compared with none in women receiving epidural analgesia. These findings suggest that the analgesia onset from a bolus dose of remifentanil may occur after the cessation of uterine contractions (which have an average duration of 60 to 70 seconds). Although Thurlow et al.85 encouraged parturients to activate a bolus dose at the very first detection of a contraction, or even between contractions, Volmanen et al82 indicated that the onset of electroencephalographic depression and subsequent onset of peak respiratory depression does not happen until approximately 2.5 minutes after bolus injection. As a consequence, the bolus administration will frequently miss the uterine contraction.

Weiniger et al.83 evaluated candidate variables (i.e., respiratory rate, end-tidal CO2, pulse oximetry, heart rate, and integrated pulmonary index) to serve as early warning apnea alerts (defined as any variable value below a prespecified threshold for 15 seconds). A total of 331 immediate early warning alerts and 62 episodes of apnea (defined as maximal CO2 less than 5 mm Hg for at least 30 consecutive seconds) occurred among 10 of 19 women (56.2%) who received remifentanil PCA. Alerts for end-tidal CO2 respiratory rate, and integrated pulmonary index detected most episodes of apnea, pulse oximetry alerts missed the majority of episodes of apnea, and all variables had a low positive predictive rate, indicating the limitations of respiratory monitors for early warning apnea surveillance in this setting.

Studies of remifentanil PCA during labor have reported a wide range in the incidence of maternal sedation, dizziness, nausea, vomiting, and pruritus.67,72,81,84 The wide incidence of nausea (0% to 60%)77,78 may reflect an opioid-induced increase in vagal activity, which can decrease mean arterial pressure and heart rate; however, this has not been reported in laboring women receiving remifentanil PCA, perhaps reflecting the doses administered and/or the high maternal sympathetic activity during labor. Pruritus occurs in approximately 16% of parturients.52 In 140 parturients randomly assigned to either remifentanil PCA or epidural analgesia, Douma et al.85 observed fever (temperature > 38° C) in 10% of remifentanil PCA patients compared with 37% in epidural analgesia patients.

Loss of heart rate variability, a potential indicator of fetal distress, and opioid-induced loss of heart rate variability may create diagnostic confusion in a labor setting.86 Comparison studies have reported a lower incidence of FHR abnormalities with remifentanil than with meperidine.67 However, similar to other opioids, available data suggest that remifentanil might induce fetal and neonatal acidosis. Marwah et al.68 observed that the need for neonatal resuscitation was higher with fentanyl compared with remifentanil (OR 4.33, 95% CI, 1.75 to 10.76).

Many studies suggest that continuous patient monitoring is required with remifentanil use during labor. Van de Velde and Carvalho67 suggested that monitoring for respiratory depression should ideally evaluate respiratory rate and sedation (one-to-one nursing or midwifery care), determine adequacy of ventilation (capnography, apnea monitors), and evaluate oxygenation (pulse oximetry). Routine use of supplemental oxygen may increase the duration of apnea and reduce the sensitivity of pulse oximetry for detecting hypoventilation. A method for assisting ventilation (e.g., self-inflating ventilating bag) should be immediately available.

A meta-analysis by Weibel et al.87 assessed the effectiveness of remifentanil PCA for labor analgesia compared with other parenteral and patient-controlled opioids, epidural analgesia,
continuous remifentanil infusion, or placebo. Remifentanil PCA was found to be likely superior to the administration of other opioids (IV/IM, PCA) but inferior to neuraxial analgesia.

To date, the studies of remifentanil administration for labor analgesia have included only healthy parturients with low-risk singleton pregnancies. In many centers, the inability to provide dedicated, one-to-one nursing care precludes the use of remifentanil PCA in laboring women. Given the significant risk for maternal sedation, respiratory depression, and oxygen desaturation with remifentanil PCA, the use of continuous pulse oximetry and continuous (or near continuous) one-to-one nursing care is critical for its safe use. An oxygen saturation less than 94% when breathing room air should prompt administration of supplemental oxygen. An anesthesia provider should be notified if excess sedation, a respiratory rate less than 8 breaths per minute, and/or oxygen saturation less than 94%, despite supplemental oxygen, occurs.84

OPIOID ANTAGONISTS

Naloxone is a pure opioid antagonist at the μ-, κ-, and δ-opioid receptors, although it has the greatest affinity for the μ-opioid receptor.6,17 It is the drug of choice to treat adverse opioid effects in both the mother and the newborn, and it may be given intravenously, subcutaneously, or intramuscularly. The onset of action after an intravenous dose (1 to 4 µg/kg) is 2 minutes, with a duration of action of 30 to 40 minutes; this duration may be less than that of the opioid whose action it antagonizes, and repeated doses or an infusion may be necessary.

The administration of naloxone during labor or before delivery may reverse the quality of analgesia and confer only a limited reduction in maternal side effects; however, some neonatal benefit may be obtained. Hodgkinson et al.89 reported significantly higher neurobehavioral scores in neonates born to mothers who had received an intrapartum combination of meperidine and naloxone compared with meperidine alone. However, this difference did not persist beyond 2 hours after birth. Clark et al.90 reported minimal differences in the neurologic and acid–base status of neonates born to mothers who had received both meperidine and naloxone compared with meperidine alone. However, this difference did not persist beyond 2 hours after birth. Clarke et al.90 reported minimal differences in the neurologic and acid–base status of neonates born to mothers who had received both meperidine and naloxone compared with meperidine alone. However, this difference did not persist beyond 2 hours after birth.

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The recommended neonatal dose of naloxone is 0.1 µg/kg (1 µg/mL solution). Administration of naloxone is not recommended during the primary steps of neonatal resuscitation; however, it may be given after positive-pressure ventilation has restored normal heart rate and oxygen saturation, if maternal opioid administration occurred during the 4 hours before delivery.92 The preferred route of naloxone administration is intravenous; intramuscular administration is acceptable, although absorption may be delayed with this route. Endotracheal administration of naloxone is not recommended. Naloxone should not be given to the neonate of a mother who is opioid-dependent or on methadone maintenance therapy; this action may result in withdrawal activity and seizures.82

OPIOID ADJUNCTS AND SEDATIVES

Historically, many drugs have been used as adjuncts to per- natal opioid analgesia. Most of them cause maternal sedation and neonatal depression and are now used infrequently, particularly because neuraxial and opioid PCA techniques achieve satisfactory analgesia more safely.

Barbiturates are sedative agents with no analgesic effect. They are lipid soluble, rapidly cross the placenta, are detectable in fetal blood, and can result in neonatal depression, especially if combined with systemic opioid administration.

Phenothiazines (e.g., chlorpromazine, promethazine, propiomazine) are dopamine antagonists that have sedative, antiemetic, and antipsychotic properties. They rapidly cross the placenta and reduce FHR variability. Neurobehavioral outcomes after the maternal administration of these agents have not been studied carefully, but there is no evidence that they cause neonatal respiratory depression. Phenothiazines (particularly chlorpromazine) may cause hypotension from alpha-adrenergic receptor blockade, and they may produce unwanted extrapyramidal movements.17 Parenterally administered promethazine (25 to 50 mg) has an onset of 15 minutes and a duration of action of up to 20 hours; it rapidly crosses the placenta, resulting in detectable fetal levels within 1 to 2 minutes of maternal intravenous administration.17 Propiomazine is a mild respiratory depressant that may further depress maternal ventilation when co-administered with opioids. It has a faster onset and shorter duration of action than promethazine.

Metoclopramide is a procainamide derivative that can increase gastric motility and reduce nausea and vomiting. As an antagonist at central dopamine receptors, it can also cause drowsiness.17 After meperidine administration for labor analgesia, Vella et al.91 found metoclopramide as effective as promethazine for reducing the incidence of nausea and vomiting. Reduced pain scores and nitrous oxide use were observed in women who received metoclopramide compared with those who received promethazine or placebo; this may reflect either an antianalgesic effect of promethazine or a possible analgesic effect of metoclopramide.

Benzodiazepines (e.g., diazepam, lorazepam, midazolam) have been used for sedation in labor but are associated with significant side effects. Diazepam rapidly crosses the placenta and accumulates in the fetus at concentrations that may
exceed maternal concentrations. The elimination half-life of the parent drug is 24 to 48 hours, but active metabolites may persist for up to 120 hours. Diazepam may cause maternal and neonatal respiratory depression, as well as neonatal hypotonicity, impaired thermoregulation, and an abnormal stress response. These effects may be dose related. Lorazepam has a half-life of 12 hours and is metabolized to an inactive glucuronide. McAuley et al. gave lorazepam 2 mg or placebo prior to the intramuscular administration of meperidine 100 mg for labor analgesia. Analgesia was better in the lorazepam group, but lorazepam administration was associated with a nonsignificant increase in neonatal respiratory depression. Neonatal neurobehavioral scores were similar in the two groups. Amnesia was common with lorazepam.

Midazolam has a rapid onset of action and an elimination half-life of 1 to 4 hours. It is metabolized in the liver to one major and several minor pharmacologically active compounds, which may persist in patients with critical illnesses accompanied by hepatic and/or renal impairment. Midazolam readily crosses the placenta and when used at high doses (e.g., induction of general anesthesia) can result in neonatal hypotonia. Midazolam causes potent anterograde amnesia at doses (1 to 2 mg/kg intravenously, 5 to 10 mg/kg intramuscularly) can be used to induce general anesthesia.

When given intravenously, ketamine has an onset within 30 seconds and a duration of action of 5 to 10 minutes; intramuscular administration has an onset of 2 to 8 minutes with a duration of 10 to 20 minutes. Ketamine is hepatocally metabolized to active metabolites, which are excreted in the urine. Ketamine’s sympathomimetic properties cause an increase in heart rate, systolic pressure, and cardiac output, which should be avoided in preeclamptic and hypertensive patients. Joselyn et al. reported acceptable labor analgesia with an intravenous infusion of ketamine (bolus 0.1 mg/kg with an infusion of 0.2 mg/kg/h, titrated to effect). The average infusion rate was 0.17 mg/kg/h, yielding an average total dose of 57 mg (range, 18 to 160 mg). No unpleasant hallucinations were experienced; however, with the initial dose, emesis and transient lightheadedness and nystagmus occurred. All neonates had a 5-minute Apgar score of 9 or 10.

Ketamine may also provide effective analgesia just before vaginal delivery in parturients without neuraxial anesthesia, or it may be used as an adjunctive agent in parturients with unsatisfactory neuraxial analgesia/anesthesia. Using incremental doses of intravenous ketamine (0.2 to 0.4 mg/kg, up to a maximum dose of 100 mg) immediately before delivery, Akamatsu et al. reported that 78 of 80 women experienced complete analgesia with no adverse maternal or neonatal effects. The occurrence of amnesia and a dreamlike state was high, but only one woman found this unpleasant.

Administration of small doses of ketamine (10- to 20-mg doses, repeated at intervals of 2 to 5 minutes, while not exceeding a total dose of 1 mg/kg during a 30-minute period) is associated with a low incidence of maternal hallucinations; however, amnesia is common. In these settings, the anesthesia provider must maintain continual verbal contact with the patient and must ensure that the patient remains sufficiently awake to maintain adequate ventilation and protect her airway.

INHALATIONAL ANALGESIA

The use of inhalational analgesia for labor varies by country. Although many of the anesthetic agents used in surgery have been administered for pain relief during childbirth, only nitrous oxide has achieved widespread clinical use.

Nitrous Oxide

Globally, nitrous oxide is the most common inhalational agent used for labor analgesia. Use of nitrous oxide during labor began in the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934. Typically it is administered as 50% nitrous oxide in oxygen using a blender device (e.g., Nitronox in the United States) or premixed in a single cylinder (e.g., Entonox in the United Kingdom); when provided alone or in combination with other forms of analgesia, the incidence of its use during labor ranges from 1% (or less) in the United States to over 50% in many parts of Europe, Scandinavia, and the United Kingdom.

A tasteless and odorless gas that is nonirritating to the airway, nitrous oxide is a weak anesthetic agent with a minimum alveolar concentration more than 100% at atmosphere. The mechanism of action of nitrous oxide is not fully understood, although it is believed to enhance the release of endogenous opioid peptides in the midbrain and modulate descending spinal pain pathways. Because of its low blood/gas solubility, nitrous oxide has a very rapid onset and offset, reaches peak brain concentrations within 60 seconds in laboring patients, and undergoes minimal metabolism. To achieve optimal analgesia from nitrous oxide, inhalation should ideally begin in anticipation of the next contraction, although this is not always predictable.

Nitrous oxide does not interfere with uterine activity, but it readily crosses the placenta, and a fetal-to-maternal concentration ratio of 0.8 occurs within 15 minutes; however, no apparent detrimental effects on FHR, Apgar scores, or umbilical cord blood gas measurements have been reported. Even when used immediately prior to delivery, there is no evidence that nitrous oxide causes neonatal respiratory depression or altered neurobehavioral scores. The neonate rapidly eliminates nitrous oxide by respiration, resulting in a half-life of less than 3 minutes.

A systematic review of 12 randomized controlled trials concluded that nitrous oxide is not a potent labor analgesic, with
less effectiveness than epidural analgesia, but confers benefit and high levels of satisfaction for some women.\textsuperscript{101} Similarly, Richardson et al.\textsuperscript{102} observed that patients who received nitrous oxide alone for labor and vaginal delivery were as likely to express satisfaction with their anesthesia care as women who received neuraxial analgesia, even though they were less likely to report excellent analgesia. Further, among all laboring women who experienced poor analgesia effectiveness, those who used nitrous oxide alone were more likely to report high satisfaction than women who received epidural analgesia alone (OR 2.5; 95% CI, 1.4 to 4.5; \( P = .002 \)). The authors concluded that analgesia quality is not the only contributor to maternal satisfaction.

Although a low incidence of serious adverse events (3 per 10,000 administrations of 50% nitrous oxide in oxygen) has been reported, suitable equipment must be available to ensure the safe administration of nitrous oxide. An apparatus that limits the concentration of nitrous oxide (e.g., a nitrous oxide/oxygen blender or a premixed 1:1 cylinder) is required and should be checked periodically for correct delivery concentrations. The constituent gases separate at approximately 7° C (19.4° F), which is not usually of practical concern.\textsuperscript{17} Inhalation should occur through a mask or mouthpiece containing a one-way demand valve, which opens only when negative inspiratory pressure is applied. This is a safety feature that limits gas delivery in a drowsy patient, and it also helps limit pollution of the environment with unscavenged gases.

Environmental pollution from unscavenged gases may be significant, and it remains unclear whether regular occupational exposure to subanesthetic concentrations of nitrous oxide results in significant health risks for health care workers. Overall, epidemiologic data do not suggest the presence of higher reproductive risks in health care workers exposed to nitrous oxide in the work environment (see Chapter 17).

Nitrous oxide has limited cardiovascular effects and little direct effect on ventilatory drive; however, it can depress ventilation through a reduction in tidal volume; partial compensation of this ventilatory effect is achieved by an increase in respiratory rate. Hyperventilation with associated hypocapnia during uterine contractions, rather than diffusion hypoxemia, may be the cause of occasional oxygen desaturation.\textsuperscript{103} It is unclear whether the incidence of intrapartum maternal hypoxemia differs among women who use nitrous oxide compared with women who receive no analgesia during labor. However, the risk for maternal hypoxemia with nitrous oxide may be more common with the concomitant administration of opioids or other sedatives; the entire obstetric care team should be aware of this possibility.

The most common maternal side effects of nitrous oxide are nausea and vomiting (occurring in up to 33% of parturients), drowsiness, dizziness, and the presence of paresthesias, which may be related to maternal hyperventilation during contractions.\textsuperscript{99} In a large systematic review of 29 studies by Likis et al.,\textsuperscript{101} nausea was reported to occur at rates up to 45% and dizziness up to 23%.

Significant adverse effects on the neonate have not been reported. Umbilical cord blood gas measurements and neonatal Apgar scores in mothers who used nitrous oxide were not different from those mothers who used other forms of labor pain relief or no analgesia.\textsuperscript{101} However, neuroapoptosis in rodents exposed to large doses of nitrous oxide (and other anesthetic agents) at specific growth time points of the developing brain indicate the need for further clinical and research studies.\textsuperscript{104}

### Volatile Halogenated Agents

All volatile halogenated agents cause dose-dependent relaxation of uterine smooth muscle. Yoo et al.\textsuperscript{105} observed that the minimum alveolar concentration (MAC) of volatile agents required to decrease the spontaneous myometrial contractility of isolated uterine muscle from pregnant women by 50% (\( \text{ED}_{50} \)) was similar for halothane, sevoflurane, and desflurane (1.72, 1.44, and 1.66 MAC, respectively). Other in vitro studies demonstrated that the \( \text{ED}_{50} \) for sevoflurane varied from 0.8 to 1.0 MAC and that the \( \text{ED}_{50} \) for desflurane varied from 0.9 to 1.4 MAC.\textsuperscript{106,107} In contrast, Yoo et al.\textsuperscript{105} observed that the \( \text{ED}_{50} \) of isoflurane was significantly higher (2.35 MAC) than that for sevoflurane, desflurane, and halothane; an additional unique feature observed with isoflurane was its ability to modulate K\textsubscript{ATP} channels.\textsuperscript{105} Whether these findings suggest that isoflurane is less likely to be associated with uterine atony in clinical practice requires further study. In general, when uterine tone is desirable (e.g., after delivery), volatile anesthetic concentrations higher than 0.5 MAC are not recommended and intravenous oxytocin should be administered concurrently.

A number of studies have examined the use of volatile agents for labor analgesia; most of these investigations used special breathing equipment and did not fully address the issue of unscavenged gases, which may limit their clinical application.

### Enflurane

Abboud et al.\textsuperscript{108} compared the analgesic effects of 0.25% to 1.25% enflurane with the administration of 30% to 60% nitrous oxide, both given in oxygen during the second stage of labor in 105 women. Satisfactory pain relief was reported in approximately 89% of women in the enflurane group and 76% of women in the nitrous oxide group; this outcome was achieved most frequently with the use of 0.5% enflurane and 40% nitrous oxide, respectively. Amnesia rates were less than 10% in both groups, and there were no differences observed in maternal blood loss, Apgar scores, or umbilical cord blood gas measurements. The mean umbilical cord concentrations of fluoride ions in the enflurane group were below that associated with nephrotoxicity. A subsequent study that compared administration of 1% enflurane in air to 50% nitrous oxide in oxygen during the first stage of labor observed lower pain scores, but higher levels of drowsiness, with enflurane.\textsuperscript{109}

### Isoflurane

McLeod et al.\textsuperscript{110} observed improved labor analgesia with the self-administration of 0.75% isoflurane in oxygen compared with Entonox. Subsequent studies observed satisfactory pain relief with minimal levels of drowsiness with various concentrations of an isoflurane-Entonox mixture. Ross et al.\textsuperscript{111} evaluated the use of a 0.25% isoflurane-Entonox mixture in 221 parturients in whom Entonox alone provided inadequate analgesia. No mother experienced significant sedation or loss of consciousness, and there was no adverse effect on Apgar
scores, neonatal respiratory status, or maternal blood loss. The requirement for neonatal resuscitation was greater in mothers who had received systemic opioids within 5 hours of birth in addition to the inhaled mixture. The same investigators verified clinically acceptable performance and safety of premixed isoflurane-Entonox cylinders.\(^\text{112}\)

**Desflurane**

Because of its low blood-gas partition coefficient, desflurane has a rapid onset and offset; however, it is also highly irritating to the airway, making it a less attractive option for inhalation analgesia. Abboud et al.\(^\text{113}\) compared inhalation of 1% to 4.5% desflurane versus 30% to 60% nitrous oxide, both in oxygen, and found similar analgesia scores and neonatal outcomes between groups. The incidence of amnesia was significantly greater with desflurane than with nitrous oxide (23% versus 0%).

**Sevoflurane**

Sevoflurane is the volatile halogenated agent most commonly used for inhalational induction of general anesthesia. It has a short onset and offset of action, but it is less irritating and has a less unpleasant odor than the other volatile agents.

Toscano et al.\(^\text{114}\) conducted a safety and feasibility pilot study of 50 parturients breathing 2% to 3% sevoflurane in an oxygen/air mixture via a compact anesthesia delivery system. They aimed for an end-tidal sevoflurane concentration of 1.2% to 1.4% (0.8 to 0.9 MAC during pregnancy) at the peak of uterine contractions. The mean (± SD) pain score was significantly lower during the times when parturients inhaled sevoflurane compared with times when they did not inhale sevoflurane (3.3 ± 1.5 versus 8.7 ± 1.0, respectively, on a scale of 0 to 10). Four women became drowsy, but there were no episodes of oxyhemoglobin desaturation or loss of consciousness, and there were no unexpected increases in blood loss. In addition, there were no reported adverse effects on FHR or neonatal Apgar scores.

In an escalating dose study, Yeo et al.\(^\text{115}\) determined that 0.8% sevoflurane was the optimal concentration for labor analgesia, beyond which an increased level of sedation with no additional analgesic benefit was observed. Ng et al.\(^\text{116}\) randomized 48 primigravida parturients to receive either 0.8% sevoflurane (via an inhaler attached to wall gas supply) or Entonox. No significant difference in median pain scores or adverse effects were observed.

Routine use of inhalational labor analgesia may be limited by the need for specialized equipment, concern for environmental pollution, and the potential for maternal amnesia and the loss of protective airway reflexes. Although sedation occurs during intermittent inhalation of volatile anesthetic agents, profound sedation to the extent that airway reflexes are jeopardized has not been reported. Further research and refinement of inhalational labor analgesia may allow the use of this technique for women in whom neuraxial anesthesia is contraindicated.

**KEY POINTS**

- Systemic analgesia is commonly used in laboring women worldwide.
- All opioid analgesic drugs rapidly cross the placenta and cause a transient reduction in fetal heart rate variability.
- Meperidine is most commonly administered as an intermittent bolus. Its active metabolite may have prolonged adverse effects on the neonate.
- There is little evidence that any individual opioid confers significant benefit over meperidine when administered as a bolus.
- Neonates whose mothers received systemic opioid analgesia are more likely to exhibit neonatal depression than those whose mothers who received no analgesia or epidural analgesia.
- Given the significant risk for maternal sedation, respiratory depression, and oxygen desaturation with remifentanil patient-controlled intravenous labor analgesia (PCIA), the use of *continuous* pulse oximetry and *continuous* (or *near continuous*) one-to-one nursing care is critical for its safe use. An oxygen saturation less than 94% when breathing room air should prompt administration of supplemental oxygen. An anesthesia provider should be notified if excessive maternal sedation, a respiratory rate less than 8 breaths per minute, and/or oxygen saturation less than 94%, despite supplemental oxygen administration, occurs.
- The optimal remifentanil PCIA regimen has not yet been determined, but titrated regimens likely confer an advantage as labor progresses. The use of a background infusion warrants extreme caution because of the significant risk for moderate to severe respiratory depression.
- Use of inhalation analgesia is less common in the United States than in other countries, but its use may increase with further study and advances in equipment and scavenging systems.
- Nitrous oxide may be used alone or with other systemic or inhaled agents. Inhalation of nitrous oxide provides variable analgesia, but high satisfaction in motivated patients. When used alone, it does not appear to be associated with adverse effects on the fetus or neonate.
- Intermittent inhalation of volatile anesthetic agents appears to provide good analgesia with few maternal or neonatal side effects, but larger studies are needed to assess the maternal and neonatal safety of these agents.

**REFERENCES**


Epidural and Spinal Analgesia: Anesthesia for Labor and Vaginal Delivery

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Epidural analgesia and spinal analgesia are the most effective methods of intrapartum pain relief in contemporary clinical practice. During the first stage of labor, pain results primarily from distention of the lower uterine segment and cervix (see Chapter 20). Painful impulses are transmitted by means of visceral afferent nerve fibers, which accompany sympathetic nerve fibers and enter the spinal cord at the 10th, 11th, and 12th thoracic and first lumbar spinal segments. As labor progresses and the fetus descends in the birth canal, distention of the vagina and perineum results in painful impulses that are transmitted via the pudendal nerve to the second, third, and fourth sacral spinal segments. Neuraxial analgesia is the only form of analgesia that provides complete analgesia for both stages of labor. During the first stage of labor, visceral pain impulses entering the spinal cord at T10 to L1 must be blocked. During the late first stage of labor and the second stage of labor, somatic impulses entering the spinal cord from S2 to S4 must also be blocked (see Chapter 20).

In a survey of 1000 consecutive women who chose a variety of analgesic techniques for labor and vaginal delivery (including nonpharmacologic methods, transcutaneous electrical nerve stimulation, intramuscular meperidine [pethidine], inhalation of nitrous oxide, epidural analgesia, and a combination of these techniques), pain relief and overall satisfaction with the birth experience were greater in patients who received epidural analgesia. Similarly, randomized studies
that pain scores are lower and patients are more satisfied with and/or inhalation analgesia (i.e., nitrous oxide) have shown that have compared epidural analgesia with systemic opioids in 2008 indicated that 61% of women who had a singleton from the U.S. Standard Certificate of Live Birth in 27 states that paternal anxiety levels were lower, and both paternal involvements in the childbirth process and paternal satisfaction were greater, in men whose partners received epidural analgesia. Specific neuraxial techniques for labor analgesia, including the neuraxial analgesia rate. Other factors include the information and advice provided to pregnant women by obstetricians, nurses, and childbirth education instructors. The personal and cultural expectations of a laboring woman, as well as obstetric complications, also affect the childbirth experience and the use of neuraxial analgesia (see Chapters 20 and 21).

Ideally, the anesthesia provider should tailor the analgesic technique to meet the individual parturient’s needs. Factors that should be considered in formulating an analgesic plan for individual parturients include the parturient’s preferences for analgesia, coexisting maternal disease, the airway examination, fetal status, spontaneous versus induced labor, stage of labor, and anticipated risk for operative delivery. The risks and benefits of the various epidural and spinal analgesic techniques should be assessed for each parturient. Good technique requires thoughtful preparation and meticulous attention to detail to ensure maternal and fetal safety.

The ideal labor analgesic technique is safe for both the mother and the infant, does not interfere with the progress of labor and delivery, and provides flexibility in response to changing conditions. In addition, the ideal technique provides consistent pain relief, has a long duration of action, minimizes undesirable side effects (e.g., motor block), and minimizes ongoing demands on the anesthesia provider’s time. No single technique or anesthetic agent is ideal for all parturients during labor. The American Society of Anesthesiologists (ASA) has published practice guidelines for obstetric anesthesia (see Appendix B), as well as guidelines for neuraxial anesthesia in obstetric patients (see Appendix A). Guidelines promulgated by professional organizations in other countries also address obstetric anesthesia care. All obstetric anesthesia providers should review their country’s respective guidelines. Specific neuraxial techniques for labor analgesia, including their advantages, disadvantages, side effects, and complications, are considered in this chapter.

**PREPARATION FOR NEURAXIAL ANALGESIA**

**Indications and Contraindications**

Epidural analgesia is indicated to treat the pain experienced by a woman in labor. In its 2017 Practice Bulletin, Obstetric Analgesia and Anesthesia, the American College of Obstetricians and Gynecologists (ACOG) reaffirmed an earlier opinion jointly published by the ASA and ACOG, which stated that “in the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor.” Furthermore, the ACOG has stated that “decisions regarding analgesia should be closely

![Fig. 23.1 Influence of epidural analgesia on maternal plasma concentrations of catecholamines during labor. *P < .05 compared with before initiation of epidural analgesia. (Modified from Shnider SM, Abboud TK, Artal R, et al. Maternal catecholamines decrease during labor after lumbar epidural anesthesia. *Am J Obstet Gynecol.* 1983;147:13–15.)

![Plasma concentration (pg/mL)](chart.png)

- **Before epidural**
  - Plasma epinephrine
  - Plasma norepinephrine
- **After epidural**
  - Plasma epinephrine
  - Plasma norepinephrine

*P < .05 compared with before initiation of epidural analgesia.*

![Chart](chart.png)
coordinated among the obstetrician-gynecologist or other obstetric care provider, the anesthesiologist, the patient, and skilled support personnel. Neuraxial analgesia is an appropriate treatment for the pain of labor, including early labor (defined as regular uterine contractions that cause progressive effacement and dilation of the uterine cervix). Randomized controlled trials and a meta-analysis have confirmed that initiation of neuraxial analgesia in early labor does not increase the risk for cesarean delivery (see later discussion).

Neuraxial analgesia may facilitate an atraumatic vaginal breech delivery, the vaginal delivery of twin infants, and vaginal delivery of a preterm infant (see Chapters 33 and 34). By providing effective pain relief, epidural analgesia facilitates blood pressure control in preeclamptic women (see Chapter 35). Epidural analgesia also blunts the hemodynamic effects of uterine contractions (e.g., sudden increase in cardiac preload) and the associated pain response (tachycardia, of uterine contractions (e.g., sudden increase in cardiac preload) and the associated pain response (tachycardia, hypertension, hyperpnea) in patients with other medical complications (e.g., mitral stenosis, spinal cord injury, intracranial neurovascular disease, asthma; see Chapters 41, 48, and 52).

Box 23.1 lists the contraindications to administration of epidural or spinal analgesia. Some anesthesiologists have suggested that systemic maternal infection, preexisting neurologic disease, or severe stenotic heart lesions are relative contraindications to neuraxial analgesia. However, most cases of systemic infection (especially if properly treated), or neurologic or cardiac disease, do not contraindicate the administration of neuraxial analgesia (see Chapters 36, 41, and 48). It is also controversial whether mild or isolated abnormalities in tests of blood coagulation preclude the use of neuraxial analgesia. The dose and timing of administration of drugs administered for thromboprophylaxis must also be considered (see Chapter 44). The anesthesia provider should consider the risks and benefits of neuraxial analgesia for each patient individually.

Thorough preparation for neuraxial labor analgesia involves several steps (Box 23.2). These include (1) a review of the parturient’s obstetric history; (2) a focused preanesthetic evaluation that includes maternal obstetric, anesthetic, and health history; and (3) a brief physical examination (i.e., vital signs, airway, heart, lungs, and back). Routine measurement of the platelet count is not necessary; however, assessment of the platelet count and other laboratory measurements may be indicated in selected patients. Similarly, routine intrapartum blood typing and screening or crossmatching is not necessary in healthy parturients, although consideration should be given to sending a blood sample to the blood bank (to facilitate the rapid availability of blood products in case of emergency need). For parturients at increased risk for hemorrhage, intrapartum typing and screening or cross-matching should be performed. Fetal well-being should be assessed by a skilled provider, and equipment (including resuscitation equipment) should be checked by the anesthesia provider (see Box 12.1). Informed consent should be obtained (see Chapters 12 and 32). Early and ongoing communication among the obstetric and anesthesia providers, nursing staff, and other members of the multidisciplinary team is encouraged.

**Types of Neuraxial Analgesia**

The technical aspects of neuraxial analgesic/anesthetic techniques are discussed in detail in Chapter 12. These techniques include continuous epidural, combined spinal-epidural, and caudal analgesia and continuous and single-shot spinal analgesia. Continuous epidural and combined spinal-epidural analgesia are the most common techniques used for neuraxial labor analgesia. There are advantages and disadvantages to each technique (Table 23.1).

**Epidural Analgesia**

Continuous lumbar epidural analgesia has been the mainstay of neuraxial labor analgesia for several decades. Placement of an epidural catheter allows analgesia to be maintained until after delivery. No dural puncture is required. The presence of

**BOX 23.2 Checklist: Preparation for Neuraxial Labor Analgesia**

1. Communicate (early) with the obstetric provider.
   - Review parturient’s obstetric history.
2. Perform focused preanesthetic evaluation.
   - Review maternal obstetric, anesthetic, and health history.
   - Perform targeted physical examination (vital signs, airway, heart, lungs, back).
3. Review relevant laboratory measurements and imaging studies.
4. Consider need for blood typing and screening or cross-matching.
5. Formulate analgesia plan.
6. Obtain informed consent.
7. Perform equipment check:
   - Check routine equipment.
   - Check emergency resuscitation equipment.
8. Obtain peripheral intravenous access.
9. Apply maternal monitors (blood pressure, heart rate, pulse oximetry).
10. Monitor fetal heart rate.
11. Perform a team time-out.

**BOX 23.1 Contraindications to Epidural and Spinal Analgesia**

- Patient refusal or inability to cooperate
- Increased intracranial pressure secondary to a mass lesion
- Skin or soft tissue infection at the site of needle placement
- Frank coagulopathy
- Recent pharmacologic anticoagulation
- Uncorrected maternal hypovolemia (e.g., hemorrhage)
- Inadequate training in or experience with the technique
- Inadequate resources (e.g., staff, equipment) for monitoring and resuscitation

*Safety depends on specific drug and timing and dose of the most recent drug administration (see Chapters 38 and 44).
a catheter and effective analgesia allow the conversion to epidural anesthesia should cesarean delivery be necessary. Injection of a local anesthetic in the lumbar epidural space allows both cephalad and caudal spread of the anesthetic solution.

Analgesia is initiated by bolus injection of drug(s) through the epidural needle, catheter, or both. Analgesia is maintained with anesthesia provider-, patient-, or infusion pump–administered intermittent bolus injections or a continuous epidural infusion, or a combination of these techniques. The catheter is removed after delivery when there is no further need for analgesia or anesthesia.

**Combined Spinal-Epidural Analgesia**

Combined spinal-epidural (CSE) analgesia has become increasingly popular in the past 20 years. Onset of complete analgesia is significantly faster than with epidural techniques (2 to 5 minutes versus 10 to 15 minutes, respectively). In a meta-analysis of the onset time of CSE compared with low-dose epidural analgesia, the mean difference in onset was −5.4 minutes (95% confidence interval [CI], −7.3 to −3.6). More women with spinal analgesia than with epidural analgesia had effective analgesia at 10 minutes (relative risk [RR], 1.9; 95% CI, 1.5 to 2.5). In particular, the onset of sacral analgesia is significantly slower after the initiation of lumbar epidural analgesia than with spinal analgesia. It may take several hours of lumbar epidural infusion, or several bolus injections of local anesthetic into the lumbar epidural space, to achieve sacral analgesia. Rapid onset of sacral analgesia is advantageous in the parturient in whom analgesia is initiated late in the first stage of labor or in a parous parturient with rapid progress of labor. Spinal analgesia requires significantly lower drug doses to attain effective analgesia than does epidural analgesia; therefore, the risk for local anesthetic systemic toxicity is decreased. In addition, there is less systemic absorption of spinal anesthetic agents into the maternal circulation, so maternal and fetal plasma drug concentrations are lower with spinal than with epidural analgesia.

**TABLE 23.1 Advantages and Disadvantages of Neuraxial Techniques in Labor**

<table>
<thead>
<tr>
<th>Neuraxial Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous epidural</td>
<td>Continuous analgesia, no dural puncture required, ability to extend analgesia to anesthesia for cesarean delivery</td>
<td>Slow onset of analgesia, larger drug doses required when compared with spinal techniques, greater risk for maternal local anesthetic systemic toxicity, greater fetal drug exposure</td>
</tr>
<tr>
<td>Combined spinal-epidural</td>
<td>Continuous analgesia, low doses of local anesthetic and opioid, rapid onset of analgesia, ability to extend analgesia to anesthesia for cesarean delivery</td>
<td>Increased incidence of pruritus, possible higher risk for fetal bradycardia</td>
</tr>
<tr>
<td>Continuous spinal</td>
<td>Continuous analgesia, low doses of local anesthetic and opioid, rapid onset of analgesia, ability to extend analgesia to anesthesia for cesarean delivery</td>
<td>Large dural puncture increases risk for post-dural puncture headache, possibility of overdose and total spinal anesthesia if the spinal catheter is mistaken for an epidural catheter</td>
</tr>
<tr>
<td>Continuous caudal</td>
<td>Continuous analgesia, avoids need to access neuraxial canal through lumbar interspace in patients with previous lumbar spine surgery</td>
<td>Requires large volumes/doses of drugs, may be technically more difficult than other neuraxial techniques, possible higher risk for infection than with other neuraxial techniques, risk for inadvertent fetal injection</td>
</tr>
<tr>
<td>Single-shot spinal</td>
<td>Technically simple, rapid onset of analgesia, immediate sacral analgesia, low drug doses</td>
<td>Limited duration of analgesia</td>
</tr>
</tbody>
</table>
subsequent cesarean delivery was more than five times higher for catheters placed as part of an epidural technique than for catheters placed as part of a CSE technique.28

Several studies have described a modification of CSE analgesia in which a dural puncture is made with a small-gauge spinal needle but no drug is injected into the subarachnoid space (dural puncture epidural analgesia).29–32 Results of studies are inconsistent, but two studies found that blockade of sacral dermatomes occurred more frequently after injection of epidural local anesthetic and opioid in parturients with a dural puncture than in those without.30,32 Presumably, enhanced sacral analgesia occurs because of increased migration of anesthetic solution across the dural puncture site.

CSE analgesia has several possible undesirable side effects. Dural puncture is required to initiate CSE analgesia, although puncture with a small-gauge pencil-point needle does not appear to increase the risk for post–dural puncture headache.24 A more serious concern, however, is that dural puncture during labor may be a risk factor for postpartum neuraxial infection, a rare but potentially life-threatening complication (see Chapter 31).

The incidence of pruritus is higher with intrathecal opioid administration than with epidural opioid administration.24 Another purported disadvantage of the CSE technique is that the correct placement of the epidural catheter in the epidural space cannot be verified until spinal analgesia or anesthesia wanes. Therefore, it has been suggested that if a functioning epidural catheter is important to the safe care of the mother and fetus (e.g., in the setting of a suspected difficult airway or nonreassuring fetal status), an epidural rather than CSE technique is indicated. However, in a retrospective study that included 2395 neuraxial labor analgesia procedures, the CSE technique did not result in delayed recognition of epidural catheter failure, and the overall catheter failure rate was lower when the catheter was sited as part of CSE analgesia.27

The most common CSE technique for labor analgesia is the needle-through-needle technique in a midlumbar interlaminar space (see Chapter 12). Analgesia is maintained via the epidural catheter, as with traditional epidural analgesia.

Continuous Spinal Analgesia

Continuous spinal analgesia is used occasionally for labor analgesia but is not practical for most parturients. Several spinal catheters are commercially available in the United States and Europe, but their use for continuous labor analgesia has not been well studied. Because the available catheters require dural puncture with a large-gauge needle, the technique may be associated with an unacceptably high incidence of post–dural puncture headache. However, continuous spinal analgesia is a management option in patients with unintentional dural puncture. Continuous spinal analgesia can readily be converted to surgical anesthesia if necessary.

Caudal Analgesia

Continuous caudal epidural analgesia is used infrequently in modern obstetric anesthesia practice. It is technically more difficult to place a caudal catheter than a lumbar epidural catheter. Large volumes of anesthetic solution are required to extend neuroblockade to the low thoracic spinal segments, resulting in higher maternal plasma concentrations of drug. There is a risk for needle/catheter misplacement and direct injection into the fetus. However, this technique is useful for parturients in whom access to the lumbar spinal canal is not possible (e.g., because of a fused lumbar spine).

Single-Shot Techniques

In general, single-shot techniques (spinal, lumbar epidural, or caudal) are not useful for most laboring women because of their limited duration of action. These techniques may be indicated for parturients who require analgesia or anesthesia shortly before anticipated vaginal delivery or in settings in which continuous neuraxial analgesia is not possible.33 Intrathecal morphine has been combined with bupivacaine and sufentanil or fentanyl in an attempt to prolong analgesia. A 2016 meta-analysis of five randomized-controlled trials comparing single-shot spinal labor analgesia (bupivacaine and sufentanil or fentanyl) with and without morphine concluded that more adequately powered trials are necessary to determine the benefits and harms of the technique.34

Informed Consent

Informed consent is an important aspect of preparation for neuraxial labor analgesia (see Chapters 12 and 32). The preanesthetic evaluation and informed consent process allow the anesthesia provider to allay the parturient’s concerns and to demonstrate a commitment to her care. Most laboring women understand the need for informed consent and appreciate the opportunity to participate in decisions about their care.

Equipment and Monitors

Resuscitation equipment, drugs, and supplies must be immediately available for the management of serious complications of neuraxial analgesia (e.g., hypotension, total spinal anesthesia, local anesthetic systemic toxicity) (see Box 12.1).35 Emergency airway equipment should be checked before the administration of neuraxial analgesia.

During the initiation of neuraxial analgesia, the parturient’s oxygen saturation is measured continuously and the blood pressure is assessed every 2 to 3 minutes for 15 to 20 minutes after the neuraxial anesthetic administration, or until the mother is hemodynamically stable (see Chapter 12). The fetal heart rate (FHR) should be monitored before and after the initiation of neuraxial analgesia; it may be difficult to monitor the FHR during the actual procedure.36 During maintenance of neuraxial analgesia, maternal blood pressure is measured every 15 to 30 minutes, or more frequently if hypotension ensues. The sensory level of analgesia and the intensity of motor block (Box 23.3) are assessed after the administration of the test and therapeutic doses of local anesthetics. Subsequently, sensory level, motor block, and pain control are assessed at regular intervals.
Before the initiation of neuraxial analgesia, ultrasonographic imaging of the back may be helpful, especially in parturients whose landmarks are difficult to palpate.

**Intravenous Hydration**

Placement of an intravenous catheter (preferably 18-gauge or larger) and correction of hypovolemia with intravenous hydration are necessary before the initiation of neuraxial analgesia to mitigate hypotension that can result from sympathetic blockade. Data from small studies are conflicting as to whether a fluid bolus administered immediately before the initiation of analgesia decreases the risk for nonreassuring FHR patterns. The ASA Task Force on Obstetric Anesthesia is silent on intravenous fluid management, although many anesthesia providers administer approximately 500 mL of lactated Ringer’s solution (without dextrose) immediately before or during the initiation of analgesia. Severe hypotension is less likely with the contemporary practice of administering a dilute solution of local anesthetic for epidural analgesia or an intrathecal opioid for spinal analgesia.

Studies of intravenous hydration and spinal anesthesia for cesarean delivery suggest that there is no advantage to administering the fluid before the initiation of anesthesia (preload) compared with administering the fluid at the time of initiation of anesthesia (co-load). Rarely, hydration should be guided by serial assessment of intravascular fluid volume (e.g., central venous pressure, thoracic echocardiography). Fluid administration should be judicious in parturients at risk for pulmonary edema (e.g., women with preeclampsia with severe features). Anesthesia and obstetric providers should avoid the bolus administration of dextrose-containing solutions in laboring women.

**Maternal Positioning**

Either the lateral decubitus or the sitting position can be used during initiation of neuraxial analgesia (see Chapter 12). Factors to consider when positioning the parturient for the procedure include patient comfort, avoidance of aortocaval compression, ability to monitor the FHR, provider comfort and experience, and optimal positioning of the spine and palpation of landmarks. Patient position relative to the baricity of the anesthetic solution should be considered during initiation of spinal analgesia/anesthesia. There is little evidence that patient position influences the extent of neuroblockade during initiation of epidural analgesia/anesthesia. After completion of the procedure, parturients should be assisted to the lateral position for the first 15 to 30 minutes after the neuraxial injection to alleviate aortocaval compression.

**BOX 23.3 Assessment of Motor Block**

- Complete: patient unable to move feet or knees
- Almost complete: patient able to move feet only
- Partial: patient just able to move knees
- None: patient capable of full flexion of knees and feet


**BOX 23.4 Suggested Procedure for Initiation of Epidural Labor Analgesia**

1. Complete preparation for neuraxial analgesia checklist (see Box 23.2).
2. Position patient with the help of an assistant (lateral decubitus or sitting).
3. Initiate maternal blood pressure and pulse oximetry monitoring and fetal heart rate monitoring.
4. Initiate an intravenous fluid bolus (500 mL of lactated Ringer’s solution).
5. Site epidural catheter in epidural space using sterile technique.
6. Administer an epidural test dose (see Table 12.2).
7. If the test dose is negative, secure epidural catheter and position patient in the lateral position.
8. Administer 5 to 15 mL of epidural local anesthetic, in 5-mL increments (usually low concentration of local anesthetic combined with a lipid-soluble opioid [see Table 23.2]).
9. Monitor maternal blood pressure every 2 to 3 minutes for 15 to 20 minutes, or until parturient is hemodynamically stable.
10. Assess pain score and extent of sensory blockade (cephalad and caudad).
11. Initiate maintenance epidural analgesia (see Table 23.5).

**INITIATION OF EPIDURAL ANALGESIA**

A procedure for initiating epidural labor analgesia is outlined in Box 23.4. Commonly, after siting the epidural catheter in the epidural space, a test dose is administered to rule out intrathecal or intravascular placement of the epidural catheter. After a negative test, epidural analgesia is established with the incremental injection of a local anesthetic, usually in combination with a lipid-soluble opioid. Maternal vital signs are monitored, and clinical analgesia is verified.

**Epidural Test Dose**

The purpose of the test dose is to help identify unintentional cannulation of a vein or the subarachnoid space. The test dose should contain a dose of local anesthetic and/or another marker sufficient to allow the recognition of intravenous or subarachnoid injection but not so large as to cause systemic toxicity or total spinal anesthesia. The most common intravascular test dose contains epinephrine (adrenaline) (see Chapter 12).

The use of the epinephrine test dose in obstetrics is not without detractors. Some anesthesia providers fear that intravenous injection of epinephrine may decrease uteroplacental perfusion and precipitate fetal compromise. However, there has been no report of adverse neonatal outcome after intravenous injection of an epinephrine-containing test dose. Another argument against routine use of a test dose is that aspiration of multi-orifice catheters is 98% sensitive in identifying their intravascular location. (The sensitivity of aspiration is significantly lower for single-orifice catheters.) The epidural test dose contributes to undesirable motor
blockade. Finally, because modern epidural labor analgesia involves the infusion of a low concentration of local anesthetic solution, unintentional intravascular or intrathecal administration is not likely to result in cardiovascular collapse or total spinal anesthesia.

Others argue that the test dose still has a role in obstetric anesthesia practice. Large volumes of a concentrated local anesthetic solution are still routinely administered for emergency cesarean delivery. Although not a safety issue, it is easier for the parturient and anesthesia provider to identify a misplaced catheter at the time of initial placement and to replace the catheter at that time rather than identify the misplaced catheter after the sterile field has been breached and the parturient repositioned.

The epinephrine test dose is less specific in laboring women because cyclic changes in maternal heart rate complicate interpretation of its effects. For this reason, if used, the test dose should be given immediately after a uterine contraction so there is less confusion as to whether tachycardia is caused by pain or intravenous epinephrine. Other methods of detecting intravascular injection are discussed in Chapter 12.

No matter whether a formal test dose is used or not, it is imperative that the anesthesia provider take the time to look for evidence of unintentional intrathecal or intravascular injection of local anesthetic. Finally, every anesthesia provider should remember that no single test dose regimen can exclude every case of unintentional intravenous or subarachnoid injection. Box 12.3 summarizes steps that may be taken to decrease the risk for unintentional intravenous or subarachnoid injection of local anesthetic.

**Choice of Drugs**

The ideal analgesic drug for labor would provide rapid onset of effective analgesia with minimal motor blockade, minimal risk for maternal toxicity, and negligible effect on uterine activity and uteroplacental perfusion. It would undergo limited transplacental transfer and thus have minimal direct effect on the fetus. Finally, this ideal agent would have a long duration of action. Although this perfect analgesic drug does not exist, the combination of a local anesthetic with an opioid allows us to approach this goal.

Traditionally, local anesthetics were administered to block both the visceral pain of labor (lower uterine segment distention and cervical dilation) and the somatic pain (descent of the fetus in the birth canal). More than 40 years ago, investigators identified dense concentrations of opioid receptors in the dorsal horn of the spinal cord. The application of small doses of an opioid to these receptor sites generates a specific and profound opioid response. The introduction of neuraxial opioids to the armamentarium of the obstetric anesthesia provider moved us closer to the prediction made by Benjamin Rush in 1805: “A medicine would be discovered which should suspend sensibility altogether and leave irritability or powers of motion unimpaired.” Intrathecal opioids effectively relieve the visceral pain of the early first stage of labor, although they must be combined with a local anesthetic to effectively relieve the somatic pain of the late first stage and the second stage of labor. The combination of a local anesthetic with a lipid-soluble opioid allows for the use of lower doses of each agent, thus minimizing undesirable side effects. For example, when used alone without an opioid, the local anesthetic dose required for effective epidural analgesia is associated with an unacceptably high incidence of motor blockade. Similarly, used alone, high doses of epidural opioid are required for satisfactory analgesia during early labor, and such doses are associated with significant systemic absorption and systemic side effects. The addition of an opioid to the local anesthetic also shortens latency, an important aspect of labor analgesia, especially with the use of long-acting (and therefore, long-latency) local anesthetics. Thus, contemporary epidural labor analgesia practice most often incorporates low doses of a long-acting local anesthetic combined with a lipid-soluble opioid.

**Local Anesthetics**

**Bupivacaine.** Traditionally, the amide local anesthetic bupivacaine has been the most commonly used agent for epidural labor analgesia. Bupivacaine is highly protein-bound, a feature that limits transplacental transfer. The umbilical vein-to-maternal vein concentration ratio is approximately 0.3. After epidural administration of bupivacaine (without opioid) during labor, the patient first perceives pain relief within 8 to 10 minutes, but approximately 20 minutes are required to achieve the peak effect. Duration of analgesia is approximately 90 minutes. Bupivacaine 6.25 to 12.5 mg (e.g., 10 to 20 mL of a 0.0625% solution, or 5 to 10 mL of a 0.125% solution) combined with fentanyl or sufentanil is adequate to initiate labor analgesia in most parturients (Table 23.2).

The potency of local anesthetics for neuraxial labor analgesia is often assessed by determining the median effective concentration of local anesthetic solution when administered as a 20-mL epidural bolus (this concentration is sometimes referred to as the minimum local anesthetic concentration [MLAC]). It is lower for women in early labor than in late labor, and it is also lower when the local anesthetic is combined with a lipid-soluble opioid.

It is important to consider both the local anesthetic dose and concentration for initiation and maintenance of epidural analgesia. Christiaens et al. randomly assigned parturients to receive epidural bupivacaine 20 mg diluted in 4 mL, 10 mL, or 20 mL (0.5%, 0.2%, and 0.1% solutions, respectively). Analgesia in the 10-mL and 20-mL groups was superior to that in the 4-mL group, and duration of analgesia was longest in the 20-mL group. Lyons et al. compared the minimum local anesthetic volume (MLAV) and minimum local anesthetic dose (MLAD) for 0.125% and 0.25% bupivacaine for epidural labor analgesia. Bupivacaine 0.125% produced analgesia equivalent to that provided by bupivacaine 0.25%, with a 50% increase in required volume and a 25% reduction in dose (Table 23.3). Stated differently, a dose-sparing effect is achieved by administering a 0.125% solution of bupivacaine rather than a 0.25% solution. Ginosar et al. randomized parturients to receive maintenance of analgesia...
higher dose than women in latent labor. Analgesia is induced in early labor. Women in active labor require a therapeutic dose. The dose of opioid should be reduced or the anesthetic-containing epidural test dose is administered before the sufentanil dose are reduced if the drugs are combined or if a local anesthetic. Together, these data suggest that epidural analgesia and safety are improved with the use of low concentration—high volume local anesthetic solutions.

**Ropivacaine.** Ropivacaine, a relatively newer amide local anesthetic, is similar to bupivacaine in structure and pharmacodynamics (see Chapter 13). It is a homologue of bupivacaine and mepivacaine, but unlike these other local anesthetics it is formulated as a single-levoisotomier rather than a racemic mixture. Studies of pregnant sheep have demonstrated that clinically relevant plasma concentrations of ropivacaine do not adversely affect uterine blood flow.

Studies *in vitro* and *in vivo* have shown that ropivacaine is less cardiodepressant and arrhythogenic than bupivacaine when doses of equal mass are compared. Ropivacaine is cleared more rapidly than bupivacaine after intravenous administration in both pregnant and nonpregnant sheep. Consequently, a larger dose of drug—but not a higher plasma concentration—is required to produce systemic toxicity. These findings suggest that ropivacaine may have a greater margin of safety than bupivacaine if unintentional intravenous injection occurs in pregnant women. However, many early investigations assumed that ropivacaine and bupivacaine are equipotent; subsequent studies have demonstrated that ropivacaine is 25% to 40% less potent than bupivacaine.

In one study that characterized the full dose-response curves, the slope of the bupivacaine and ropivacaine curves were similar, suggesting that the nature of the drug-receptor interaction is different between the two drugs. When ropivacaine concentrations are adjusted for this difference in potency, there is a less clear advantage for ropivacaine in terms of the risk for systemic toxicity. In reality, systemic toxicity is not a major concern with the contemporary administration of a dilute solution of local anesthetic for epidural labor analgesia.

Several studies that compared equal concentrations of ropivacaine and bupivacaine given by patient-controlled epidural analgesia (PCEA) have not found any significant difference in clinical efficacy between the two local anesthetics. Other studies that adjusted for the potency difference and compared equipotent concentrations (e.g., 0.0625% bupivacaine versus 0.1% ropivacaine) also found no difference in clinical efficacy. It is important to recognize that potency is anunchanging property of a drug, whereas clinical efficacy is influenced by multiple variables. For example, ropivacaine has a longer duration of analgesia than bupivacaine, which may offset its lesser potency when it is administered by continuous epidural infusion.

Early clinical studies suggested that ropivacaine is associated with less motor block than bupivacaine; avoidance of motor blockade is a desirable characteristic of neuraxial analgesia during labor. However, these studies also compared equal concentrations of ropivacaine and bupivacaine, and the observed lower degree of motor blockade may reflect the lesser potency of ropivacaine. A study of the relative motor-blocking potencies of epidural ropivacaine and bupivacaine showed that ropivacaine was less potent than bupivacaine in terms of motor blockade, a finding that corresponded to the relative analgesic potencies of the two drugs. The differences in potency of motor blockade may not be relevant.

### TABLE 23.2 Drugs Used for Initiation of Epidural and Spinal Labor Analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Epidural Analgesia</th>
<th>Spinal Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Anesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.0625%–0.125%</td>
<td>1.25–2.5 mg</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.08%–0.2%</td>
<td>2.0–3.5 mg</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.0625%–0.125%</td>
<td>2.0–3.5 mg</td>
</tr>
<tr>
<td>Lidocaine*</td>
<td>0.75%–1.0%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50–100 µg</td>
<td>15–25 µg²</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>5–10 µg</td>
<td>1.5–5 µg²</td>
</tr>
<tr>
<td>Morphinec</td>
<td>NA</td>
<td>125–250 µg²</td>
</tr>
<tr>
<td>Meperidinec</td>
<td>NA</td>
<td>10–20 mg</td>
</tr>
</tbody>
</table>

*Note: The suggested doses are based on clinical studies, potency ratios, and clinical experience. NA, not applicable.

1. The local anesthetic dose/concentration and the fentanyl or sufentanil dose are reduced if the drugs are combined or if a local anesthetic-containing epidural test dose is administered before the initial therapeutic dose. The dose of opioid should be reduced or the opioid omitted if the parturient has recently received systemic opioid analgesia.

2. Lidocaine, morphine, and meperidine are not commonly used for labor analgesia because of their short duration of action (lidocaine), long latency (morphine), and high incidence of nausea and vomiting (morphine and meperidine).

3. Opioids may be administered without local anesthetics when spinal analgesia is induced in early labor. Women in active labor require a higher dose than women in latent labor.

### TABLE 23.3 Comparison of Epidural Bupivacaine 0.125% and 0.25%: Median Effective Volume and Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bupivacaine 0.125%</th>
<th>Bupivacaine 0.25%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Effective Volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up-down analysis (mL)</td>
<td>13.6 (12.4–14.8)</td>
<td>9.2 (6.9–11.5)</td>
</tr>
<tr>
<td>Probit analysis (mL)</td>
<td>13.5 (11.4–15.9)</td>
<td>8.6 (7.2–10.3)</td>
</tr>
<tr>
<td><strong>Median Effective Dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up-down analysis (mg)</td>
<td>17.0 (15.6–18.5)</td>
<td>23.1 (17.2–28.9)</td>
</tr>
<tr>
<td>Probit analysis (mg)</td>
<td>16.8 (14.2–19.9)</td>
<td>21.5 (17.9–25.7)</td>
</tr>
</tbody>
</table>

*Median effective volume at a fixed local anesthetic concentration.

*Median effective dose at a fixed local anesthetic concentration.

*95% confidence intervals shown in parentheses, which were calculated using up-down sequential and probit analysis.

Modified from Lyons GR, Kocarev MG, Wilson RC, Columb MO. A comparison of minimum local anesthetic volumes and doses of epidural bupivacaine (0.125% w/v and 0.25% w/vl) for analgesia in labor. Anesth Analg. 2007;104:412–415.

with an epidural infusion of either bupivacaine 0.25% at 5 mL/h or bupivacaine 0.0625% at 20 mL/h (10 mg/h in both groups). The median bupivacaine dose was lower and patient satisfaction was greater with bupivacaine 0.0625% than with bupivacaine 0.25%. Together, these data suggest
with the use of low concentrations of local anesthetic. Several clinical studies and a well-conducted meta-analysis of studies that compared epidural ropivacaine and bupivacaine did not demonstrate an advantage for ropivacaine in terms of outcome of labor (see later discussion), although the incidence of motor blockade was less in the ropivacaine groups.

There is no clear evidence of greater patient safety, lower risk for instrumental vaginal delivery, or other improved outcomes when ropivacaine is used to provide epidural labor analgesia. A 2010 review concluded that there is no advantage to the routine use of ropivacaine compared with bupivacaine for labor analgesia. In contrast, ropivacaine offers greater patient safety in settings in which high concentrations and greater volumes of drugs are administered (e.g., brachial plexus block or epidural anesthesia for cesarean delivery). Like bupivacaine, ropivacaine is often combined with fentanyl or sufentanil for labor analgesia. Ropivacaine concentrations used to initiate epidural analgesia range from 0.08% to 0.2% (see Table 23.2). Higher concentrations are used if the drug is administered without an opioid.

Levobupivacaine. Levobupivacaine is the levorotary enantiomer of bupivacaine (which is a racemic mixture). It is not available in the United States. Both preclinical and clinical studies have suggested that, like ropivacaine, levobupivacaine has less potential for cardiotoxicity than bupivacaine when equal doses of the two drugs are compared. One study found that levobupivacaine was essentially equipotent to bupivacaine with a potency ratio of 0.98; however, the 95% CI was wide (0.67 to 1.41). Other studies have suggested that levobupivacaine and ropivacaine have similar potency. In an MLAC study that compared the motor blocking potency of bupivacaine and levobupivacaine, levobupivacaine was less potent than bupivacaine (potency ratio, 0.87; 95% CI, 0.77 to 0.98). Belin et al. compared epidural bupivacaine, ropivacaine, and levobupivacaine (0.0625% with fentanyl 2 µg/mL) for labor analgesia. There were no differences among groups in obstetric outcomes, although the incidence of motor blockade was lower in the ropivacaine and levobupivacaine groups. Therefore, although epidural bupivacaine is more potent than ropivacaine for both sensory and motor blockade during labor, and may be more potent than levobupivacaine, there do not appear to be any clinical advantages of one drug over the other two drugs for epidural labor analgesia.

Lidocaine. Lidocaine is an amide local anesthetic with a duration of action intermediate between those of bupivacaine and 2-chloroprocaine. During labor, the administration of a 0.75% to 1.0% solution of lidocaine typically provides satisfactory analgesia. However, lidocaine is not commonly used for initiation or maintenance of epidural labor analgesia, in part because of its shorter duration of action in comparison with bupivacaine, ropivacaine, and levobupivacaine. Lidocaine is less protein-bound than these other amide local anesthetics, and at delivery, the umbilical vein–to–maternal vein lidocaine concentration ratio is approximately twice that of bupivacaine. Early studies discouraged the epidural administration of lidocaine in pregnant women because epidural lidocaine was associated with abnormal neonatal neurobehavioral findings. Subsequently, larger, more carefully controlled studies have demonstrated that the epidural administration of lidocaine, bupivacaine, and 2-chloroprocaine have similar neonatal outcomes. Although some investigators have observed subtle differences in neurobehavior between infants exposed to lidocaine and those exposed to other local anesthetics, these differences are within the inherent variability of the examinations and are not clinically significant. Other factors (e.g., mode of delivery) appear to be much more important determinants of neonatal condition.

2-Chloroprocaine. An ester local anesthetic, 2-chloroprocaine has a rapid onset of action. Epidural administration of 10 mL of 2% 2-chloroprocaine provides effective analgesia for approximately 40 minutes. The short duration of action limits its usefulness during labor. In addition, the epidural administration of 2-chloroprocaine may adversely affect the efficacy of subsequently administered epidural bupivacaine and opioids, although it is unclear whether the mechanism is related to pharmacokinetic or pharmacodynamic properties of the drug. In obstetric practice, 2-chloroprocaine is most commonly used for extension of epidural labor analgesia for instrumental vaginal delivery (see later discussion) or emergency cesarean delivery (see Chapter 26).

Opioids

Lipid-soluble opioids: fentanyl and sufentanil. Morphine was one of the first opioids to be studied for labor analgesia. However, because of its long latency, side effects, and inconsistent analgesia, morphine has largely been replaced by the lipid-soluble opioids fentanyl and sufentanil (see Chapter 13). The lipid-soluble agents have a rapid onset of action. Permeability (of the dura-arachnoid) is not a rate-limiting factor, and increasing the concentration gradient (by administration of a larger dose) facilitates faster entry into the spinal cord. The high lipid solubility of these agents also results in a shorter duration of action and greater systemic absorption than occurs with water-soluble drugs.
Some investigators have suggested that the improved analgesia results from a supraspinal action rather than a primary spinal action. However, several studies have refuted this theory, including studies of epidural opioid administration by bolus and continuous infusion. Vella et al. observed that the initiation of epidural analgesia with 0.25% bupivacaine with epidural fentanyl 80 µg resulted in more rapid, complete, and prolonged analgesia than intravenous fentanyl 80 µg, even though plasma fentanyl concentrations were higher in the intravenous group. Similarly, D’Angelo et al. demonstrated that a continuous epidural infusion but not an intravenous infusion of fentanyl reduced epidural bupivacaine requirements in laboring women. Polley et al. determined that the MLAC of epidural bupivacaine administered as a 20-mL bolus in laboring women was reduced from 0.064% to 0.034% when epidural rather than intravenous fentanyl was co-administered with bupivacaine. Ginosar et al. determined that the MLAC of bupivacaine administered by continuous epidural infusion during labor was lower by a factor of three when it was co-administered with an epidural (rather than intravenous) fentanyl infusion. Finally, in a volunteer study, lumbar epidural administration of fentanyl resulted in tolerance to experimental pain at a lumbar but not a cranial dermatome, whereas intravenous fentanyl administration resulted in pain tolerance at both dermatomes. These studies strongly suggest that during labor, epidural fentanyl provides analgesia primarily through a spinal site of action.

Epidural fentanyl alone provides moderate analgesia in early labor, but the dose needed to provide complete analgesia is accompanied by significant side effects (e.g., pruritus, nausea, maternal sedation, perhaps neonatal depression). In addition, epidural administration of an opioid alone provides inadequate analgesia during the late first stage as well as the second stage of labor. In a study comparing sufentanil alone, sufentanil with bupivacaine, and bupivacaine alone, women randomly assigned to the sufentanil-alone (30 µg) group experienced satisfactory analgesia after the initial dose but not after subsequent doses. However, the initial dose was administered after an epidural test dose that contained lidocaine 60 mg. In clinical practice, epidural fentanyl and sufentanil are usually administered with a local anesthetic for the initiation of analgesia (at a minimum, with a local anesthetic–containing epidural test dose).

In clinical practice, either fentanyl or sufentanil is frequently combined with a low-concentration, long-acting amide local anesthetic to initiate epidural labor analgesia. Epidural opioid administration allows the anesthesia provider to use a more dilute solution of local anesthetic to provide epidural labor analgesia. Epidural fentanyl and sufentanil decrease epidural bupivacaine requirements during labor in a dose-dependent fashion (Fig. 23.2). The reduction in MLAC by the addition of fentanyl or sufentanil is observed with levobupivacaine, ropivacaine, and 2-chloroprocaine, as well as bupivacaine.

The addition of a lipid-soluble opioid to a local anesthetic for neuraxial labor analgesia decreases latency, prolongs the duration of analgesia, and improves the quality of analgesia. For example, Reynolds and O’Sullivan showed that epidural bupivacaine 10 mg combined with fentanyl 100 µg was more effective for the treatment of breakthrough pain and had a faster onset and longer duration of action than either bupivacaine 25 mg or fentanyl 100 µg administered alone. Van Steenberge et al. observed that the mean (± SD) onset of analgesia was 10.3 ± 3.8 minutes in women randomly assigned to receive bupivacaine 12.5 mg without sufentanil, whereas it was 8.7 ± 2.6 minutes in women who received bupivacaine combined with sufentanil 7.5 µg. Duration of analgesia was longer in the sufentanil group (131 minutes versus 86 minutes without sufentanil). In another study, the addition of fentanyl 100 µg to 0.125% bupivacaine prolonged the mean duration of analgesia from 55 minutes to 106 minutes.

The quality of analgesia is also better with the addition of an opioid to the local anesthetic. For example, 86% of women rated their analgesia as excellent after epidural analgesia was initiated with bupivacaine combined with sufentanil, compared with 50% of those who received bupivacaine without sufentanil. The percentage of women who experienced no or short periods of pain during the first stage of labor was 94% in women who received sufentanil and 76% in women who did not. After initiation of analgesia with 0.125% bupivacaine with epinephrine 1.25 µg/mL, 43% of women randomly assigned to receive epidural fentanyl 100 µg rated their analgesia as excellent, compared with 6% in a control group that did not receive fentanyl.

The dose-sparing effects of fentanyl and sufentanil are also evident when the drugs are combined with a low-concentration solution of bupivacaine used for the maintenance of analgesia throughout labor. For example, the total bupivacaine dose (mean ± SD) was 34 ± 17 mg in laboring women who received 0.125% bupivacaine/epinephrine 1.25 µg/mL with sufentanil, compared with 42 ± 19 mg in those who received bupivacaine/epinephrine without...
sufentanil. Similarly, in women randomly assigned to receive bupivacaine/epinephrine with or without fentanyl 100 µg, the total bupivacaine dose was 55 mg or 110 mg, respectively. Advantages of a lower total dose of local anesthetic include (1) decreased risk for local anesthetic systemic toxicity, (2) decreased risk for high or total spinal anesthesia, (3) decreased plasma concentrations of local anesthetic in the fetus and neonate, and (4) decreased intensity of motor blockade.

Several studies have directly compared the administration of epidural fentanyl or sufentanil combined with a local anesthetic for the initiation of labor analgesia. There were no differences in analgesia in women in early labor randomly assigned to receive either fentanyl 100 µg or sufentanil 20 µg immediately after a lidocaine 45-mg/epinephrine 15-µg test dose. In contrast, a second study demonstrated slightly better analgesia 20 minutes after injection of 0.125% bupivacaine (15 mg) with sufentanil 15 µg than after the same dose of bupivacaine with fentanyl 75 µg.

In the United States, fentanyl is more commonly used because historically it had a lower acquisition cost than sufentanil. Additionally, the concentration of the commercially available sufentanil preparation (50 µg/mL) may make drug errors more likely with sufentanil than with fentanyl because sufentanil doses significantly lower than 50 µg are used for initiation of epidural analgesia.

There are few rigorous dose-response studies of epidural fentanyl or sufentanil combined with bupivacaine for initiation of epidural labor analgesia. Herman et al. randomly assigned 100 laboring women with a cervical dilation of 5 cm or less to receive 0.125% bupivacaine 10 mL, combined with fentanyl 0 to 100 µg (in 25-µg increments) or sufentanil 0 to 25 µg (in 5-µg increments), injected after a negative epidural test dose (bupivacaine 7.5 mg with epinephrine 15 µg). Using a probit dose-response analysis, these researchers calculated the effective dose in 95% of subjects (ED95) to be 50 µg for fentanyl and 8 µg for sufentanil; these figures equate to a sufentanil-to-fentanyl potency ratio of 6.3:1. Capogna et al. sought to determine the median effective analgesic dose (ED50) of epidural fentanyl and sufentanil alone (no local anesthetic) for the initiation of epidural analgesia in nulliparous women with a cervical dilation between 2 and 4 cm. The ED50 of fentanyl was 124 µg (95% CI, 118 to 131), and the ED50 of sufentanil was 21 µg (95% CI, 20 to 22), with a potency ratio of 5.9:1. The potency ratio in volunteers subjected to an electrical stimulus was approximately 5:1. Taken together, these data suggest that the potency ratio of sufentanil to fentanyl administered into the epidural space is approximately 6:1.

Several studies have compared bupivacaine combined with fentanyl 50 µg and 100 µg. No differences in the onset, duration, and quality of analgesia were noted in Asian women randomly assigned to receive 0.125% bupivacaine (10 mg) combined with either 50 or 100 µg of fentanyl. In contrast, when 0.125% bupivacaine (15 mg) with epinephrine 15 µg was administered to laboring Italian women with either 50 or 100 µg of fentanyl, there was no difference in the onset or duration of analgesia, but more women in the 100-µg group had excellent analgesia.

There were no differences in latency, duration of analgesia, and quality of analgesia when analgesia was induced with 0.125% bupivacaine (12.5 mg)/epinephrine 12.5 µg and either 7.5 or 15 µg of sufentanil. Similarly, after injection of a lidocaine 60-mg/epinephrine 15-µg test dose, another study found no differences in latency and quality of analgesia among epidural sufentanil doses of 5, 10, 20, 30, 40, and 50 µg. However, the duration of analgesia was longer after the higher doses of sufentanil.

The range of fentanyl and sufentanil doses used for the initiation of epidural labor analgesia is shown in Table 23.2. Pain and analgesic requirements vary depending on several factors, including parity, stage of labor, presence of ruptured membranes, oxytocin augmentation, and whether the opioid is administered in combination with a local anesthetic. One study reported that the ED50 of epidural sufentanil was higher in women undergoing prostaglandin induction of labor than in women with spontaneous labor. Conell-Price et al. developed a model of labor pain in nulliparous women and found that the use of oxytocin was associated with 48% more pain at the start of labor. Preliminary evidence suggests that pharmacogenetics may also play a role in dose requirements. Camorcia et al. reported that nulliparous women who were heterozygous or homozygous for the single nucleotide polymorphism (SNP) A118G (substitution of guanine for adenine at position 118) of the gene encoding the µ-opioid receptor (OPRM1) had a lower ED50 for epidural sufentanil administered for labor analgesia.

Several early studies suggested that the duration of epidural and spinal analgesia may exhibit circadian rhythm (chronobiology), possibly secondary to human biologic rhythms. However, in a secondary analysis of data from a large study, Scavone et al. found no evidence of a circadian response to intrathecal fentanyl or intravenous opioid labor analgesia. In a detailed analysis of data from a study designed to test whether parturient response to intrathecal bupivacaine exhibited a circadian rhythm, Shafer et al. demonstrated that external daily rhythms, such as nursing shifts, may contribute to the appearance of biologic rhythm. Thus, whether a circadian response to neuraxial local anesthetic or opioid exists, or is clinically significant, requires further study.

Current evidence supports the administration of epidural opioid doses at the lower end of the dose range for nulliparous women, for women in early labor, or when the opioid is co-administered with a local anesthetic. Higher doses are associated with a higher incidence of maternal side effects and the potential for neonatal depression (see later discussion). The major maternal side effect of epidural fentanyl and sufentanil for labor analgesia is pruritus. Neonatal outcomes do not appear to be adversely affected by the addition of fentanyl or sufentanil to a local anesthetic for epidural analgesia (see later discussion). In fact, the combination of drugs allows lower doses of both drugs to be administered, resulting in lower concentrations of both drugs in the neonate.
Two studies found that the diluent volume (2 to 20 mL) did not affect the onset and duration of epidural labor analgesia when fentanyl was injected into the epidural space after the injection of a local anesthetic solution.\textsuperscript{120,121}

**Other opioids.** Morphine was one of the first opioids used for labor analgesia. Hughes et al.\textsuperscript{122} compared analgesia using epidural administration of morphine (2.0, 5.0, and 7.5 mg) with that using epidural bupivacaine 0.5%. Morphine was effective in 7 of 11 parturients until the end of the first stage of labor, but all parturients required bupivacaine for adequate analgesia during the second stage of labor. Subsequently, investigators combined morphine with bupivacaine and observed a longer duration of analgesia compared with that for bupivacaine alone.\textsuperscript{123} However, the inconsistent analgesia, long latency (30 to 60 minutes), and high incidence of side effects of morphine (which continued after delivery), along with the introduction of lipid-soluble opioids and epidural infusion pumps into clinical practice, have made the use of epidural morphine for labor analgesia largely obsolete.

Several studies described the use of alfentanil with bupivacaine for labor analgesia.\textsuperscript{124,125} Alfentanil has lower lipid solubility than both fentanyl and sufentanil. Only a few small studies have compared alfentanil with other opioids for labor analgesia.

Several groups of investigators have reported the use of epidural hydromorphone for labor analgesia.\textsuperscript{126–128} The lipid solubility of hydromorphone lies between those of morphine and fentanyl, but is closer to that of morphine.\textsuperscript{129} In a large prospective observational study, effective labor analgesia was obtained by initiating analgesia with 0.25% bupivacaine (20 to 25 mg) with epinephrine (40 to 50 µg), followed by hydromorphone 100 µg.\textsuperscript{126} However, Mhyre\textsuperscript{128} observed that effective labor analgesia could not be provided by 0.035% bupivacaine (7 mg) with hydromorphone 100 to 110 µg. In another trial, parturients were randomly assigned to receive either epidural hydromorphone 300 µg or saline-control immediately after the initiation of analgesia with lidocaine 45 mg, epinephrine 15 µg, and fentanyl 100 µg.\textsuperscript{127} Duration of analgesia and side effects were similar in the two groups. At the current time, further investigation is required before hydromorphone can be recommended for epidural labor analgesia.

Meperidine may be used effectively alone (without a local anesthetic), in part because it possesses local anesthetic properties.\textsuperscript{130} When given during labor, epidural meperidine 100 mg provides analgesia similar to that provided by 0.25% bupivacaine, with less motor blockade. However, this dose of epidural meperidine produces more sedation, nausea, and pruritus than epidural bupivacaine. Handley and Perkins\textsuperscript{131} observed that the addition of meperidine 25 mg to 0.125%, 0.187%, or 0.25% bupivacaine (10 mL) provided adequate analgesia for the first stage of labor. Epidural administration of meperidine effectively prevents or treats the shivering that often occurs during labor.\textsuperscript{132} Investigators from Saudi Arabia randomly allocated women to receive 0.1% bupivacaine with either meperidine 1 mg/mL or fentanyl 2 µg/mL.\textsuperscript{132} No differences were noted between groups in analgesic characteristics, except that women in the meperidine group had a higher incidence of nausea and vomiting. Currently there is no evidence that meperidine alone or in combination with bupivacaine has any advantages over a combination of a long-acting amide local anesthetic and a lipid-soluble opioid.

**Butorphanol** is a lipid-soluble opioid agonist-antagonist, with weak µ-receptor and strong κ-receptor activity. Because κ-opioid receptors appear to be involved in the modulation of visceral pain, κ-receptor agonists should be useful agents for the relief of labor pain, which has a significant visceral component (see Chapter 20).\textsuperscript{123,134,135} Somnolence is the most prominent side effect of epidural butorphanol. The addition of butorphanol 1, 2, or 3 mg to 0.25% bupivacaine (25 mg) shortened latency and prolonged the duration of analgesia in comparison with epidural bupivacaine alone in one study.\textsuperscript{134} The investigators concluded that the optimal dose of butorphanol was 2 mg. Of concern was the observation of a transient sinusoidal FHR pattern in the 3-mg group that was not unlike that seen after the intravenous administration of butorphanol.\textsuperscript{135} However, there was no difference among groups in Apgar scores, umbilical cord blood gas and pH measurements, or neurobehavioral scores. Similarly, Abboud et al.\textsuperscript{123} observed that the addition of butorphanol 1 or 2 mg to 0.25% bupivacaine resulted in better quality and longer duration of analgesia than the epidural administration of bupivacaine alone, without maternal or neonatal side effects. However, some anesthesia providers have noted that the epidural administration of butorphanol results in somnolence and occasional dysphoria, which are side effects of κ-receptor stimulation.

Diamorphine (heroin) is available for epidural analgesia in the United Kingdom. Using isobolographic analysis, McLeod et al.\textsuperscript{136} concluded that the combination of diamorphine and levobupivacaine is additive when used for first-stage labor analgesia. Several studies from the United Kingdom have reported diamorphine doses between 250 and 500 µg/h (i.e., diamorphine 25 to 50 µg/mL combined with a low concentration of bupivacaine).\textsuperscript{124,137} Whether diamorphine offers any advantages over fentanyl or sufentanil has not been studied. It is not available for clinical administration in the United States.

**Adjuvants**

Although the contemporary mainstay of epidural labor analgesia includes administration of a long-acting amide local anesthetic combined with a lipid-soluble opioid, other drugs may be added as adjuvants. Adjuvants may prolong the duration of analgesia or decrease the required anesthetic dose, thus reducing the risk for specific side effects.

**Epinephrine.** Some anesthesia providers add a low dose of epinephrine (1.25 to 5 µg/mL \{1:800,000 to 1:200,000\}) to the local anesthetic solution (Table 23.4). The addition of epinephrine shortens the latency and prolongs the duration of epidural bupivacaine analgesia.\textsuperscript{135,138} The MLAC of bupivacaine with epinephrine (66 µg) is 29% lower than that of bupivacaine without epinephrine.\textsuperscript{139} Perhaps as a result of the stimulation of alpha-adrenergic receptors in the spinal cord.
### Adjuncts to Neuraxial Labor Analgesia

<table>
<thead>
<tr>
<th>Adjunct Drug</th>
<th>Epidural Analgesia</th>
<th>Spinal Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIATION BOLUS DOSE</strong></td>
<td><strong>MAINTENANCE INFUSION DOSE</strong></td>
<td><strong>INITIATION BOLUS DOSE</strong></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>25–75 µg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25–50 µg/h&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clonidine</td>
<td>75–100 µg</td>
<td>10–30 µg/h&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>500–750 µg</td>
<td>25–75 µg/h&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Morphine</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjuvants are usually co-administered with a low-concentration local anesthetic solution (e.g., bupivacaine < 0.08%), often with a lipid-soluble opioid. There is extensive experience with epidural clonidine for labor analgesia in some European countries but less overall experience with epidural neostigmine.

<sup>b</sup>Usually administered in a 1:800,000 to 1:200,000 solution (1.25–5 µg/mL).

<sup>c</sup>Administered in a concentration of 0.75–1.5 µg/mL.

<sup>d</sup>Administered in a concentration of 4 µg/mL.

**NA**, not applicable; **NR**, not recommended.

The addition of epinephrine to the local anesthetic has a variable effect on the systemic uptake of the local anesthetic in obstetric patients. However, some studies have shown that the addition of epinephrine to bupivacaine, lidocaine, or levobupivacaine does not result in longer labor than the epidural administration of bupivacaine or lidocaine without epinephrine or levobupivacaine-sufentanil without epinephrine. Epidural administration of an epinephrine-containing local anesthetic solution does not adversely affect the magnitude and duration of analgesia.

The addition of epinephrine may improve the efficacy of epidural opioids, but the enhanced effect is insufficient to make use of epidural opioids without local anesthetic an attractive regimen for the duration of labor. Finally, the addition of a third drug to the local anesthetic/opioid solution may increase the risk for drug error and contamination. For these reasons, at our institution my colleagues and I do not routinely administer epinephrine-containing local anesthetic solutions during labor. However, other anesthesia providers have a different view, and some consider epinephrine a useful adjuvant, especially when added to a very dilute solution of local anesthetic with an opioid.

**Clonidine.** Analgesia is enhanced by the direct stimulation of alpha<sub>2</sub>-adrenergic receptors and the inhibition of neurotransmitter release in the dorsal horn of the spinal cord (see Chapter 20). Epidural administration of clonidine alone provides modest analgesia. Studies have evaluated the epidural administration of clonidine as an adjuvant to a local anesthetic alone, to local anesthetic and opioid combinations, and to fentanyl, and to neostigmine (see later discussion). In an MLAC study, clonidine 60 µg, but not 30 µg, decreased the MLAC of ropivacaine by approximately two-thirds. In another study, clonidine 75 µg and sufentanil 5 µg both reduced the MLAC of ropivacaine by about two-thirds. Unlike epinephrine, clonidine does not increase the motor blockade that results from the epidural administration of a local anesthetic, but it does potentiate both the quality and duration of analgesia. However, in a “black box” warning on the package insert, the manufacturer of Duraclon (the epidural clonidine formulation approved by the U.S. Food and Drug Administration [FDA]) recommends against its use in obstetric patients because of the risk for hypotension and bradycardia. Most studies, however, have found that the hypotension is readily amenable to treatment. An additional side effect is maternal sedation. High doses (greater than 150 µg) may be associated with FHR changes, although no adverse fetal effects have been observed with lower doses.

**Neostigmine.** Neostigmine inhibits the breakdown of acetylcholine within the spinal cord. Acetylcholine binds to muscarinic receptors, leading to a reduction in neurotransmitter release and subsequent analgesia. Roelants et al. randomly assigned parturients to receive either epidural ropivacaine (20 mg) alone or epidural neostigmine (4 µg/kg) combined with ropivacaine 10 mg, with or without sufentanil 10 µg. The magnitude and duration of analgesia in the ropivacaine/neostigmine group were similar to that of the plain ropivacaine group but less than in the ropivacaine/sufentanil group. Neostigmine is hydrophilic, and the researchers hypothesized that only a small portion of the epidural dose penetrates the spinal cord. In a subsequent study, the same researchers compared epidural sufentanil 20 µg with sufentanil 10 µg combined with neostigmine 250, 500, or 750 µg. Neostigmine 250 µg with sufentanil was ineffective, but both 500 and 750 µg of neostigmine produced effective analgesia similar in duration to that obtained with sufentanil alone.

In another study, maintenance of epidural analgesia with a solution of neostigmine 4 µg/mL combined with bupivacaine 0.125% resulted in a 19% reduction in bupivacaine...
consumption compared with administration of bupivacaine alone.164 However, maternal sedation was noted in the neostigmine group in the first 5 to 20 minutes after initiation of epidural analgesia with bupivacaine and neostigmine 60 μg. Booth et al.165 randomized laboring women to receive initiation and maintenance of epidural analgesia with 0.125% bupivacaine, combined with fentanyl 2 μg/mL or neostigmine 2, 4, or 8 μg/mL. The primary outcome, hourly bupivacaine consumption, did not differ among groups, nor did patient satisfaction. Pruritus was less common in the neostigmine groups, but other adverse effects did not differ, suggesting that there is no advantage to replacing the lipid-soluble opioid with neostigmine when combined with a local anesthetic.

Because animal studies suggest a synergistic antinociceptive effect of spinal α₂-adrenergic agonists and cholinesterase inhibitors,166 researchers have also investigated epidural neostigmine combined with clonidine.159,160,167 The combination of clonidine 75 μg with neostigmine 500 or 750 μg provided acceptable analgesia (visual analog scale pain score less than 30/100 mm in 30 minutes) in approximately 80% of parturients. Epidural neostigmine 500 μg combined with clonidine 75 μg prolonged labor analgesia initiated with spinal ropivacaine and sufentanil.160 In a follow-up study,161 the same investigators initiated analgesia with spinal ropivacaine and sufentanil and maintained analgesia with ropivacaine/sufentanil PCEA. Study subjects were randomized to receive a 10-μL epidural bolus injection of a solution containing neostigmine 500 μg combined with clonidine 75 μg or placebo saline solution 15 minutes after the intrathecal injection. Hourly ropivacaine use and the incidence of breakthrough pain were less in the group that received the epidural neostigmine/clonidine bolus. Systolic blood pressures were lower in the treatment group, but the incidence of hypotension did not differ.

Taken together, the studies have not identified any significant adverse maternal or neonatal effects; however, the number of studies is small and further study is required to determine the role of epidural neostigmine for routine labor analgesia. Neostigmine is not approved for neuraxial injection in the United States.

Summary

Epidural labor analgesia is usually initiated with the bolus injection of a local anesthetic combined with a lipid-soluble opioid. The advantages of the addition of an opioid to an epidural solution of local anesthetic include (1) lower total dose of anesthetic, (2) decreased motor blockade, (3) reduced shivering, and (4) greater patient satisfaction. Some anesthesia providers contend that local anesthetic–opioid techniques result in a lower risk for hypotension, but this belief is unproven. There are no clinically significant differences among the three commonly used, long-acting amide local anesthetics (bupivacaine, ropivacaine, levobupivacaine), or between fentanyl and sufentanil. Other adjuvants (e.g., epinephrine, clonidine, neostigmine) may prove useful in selected patients. High-volume/low-concentration local anesthetic solutions compared with low-volume/high-concentration solutions are associated with lower dose requirements and better analgesia.

INITIATION OF SPINAL ANALGESIA

Initiation of neuraxial analgesia with the intrathecal injection of an opioid, or an opioid combined with a local anesthetic, usually performed as part of a CSE technique, results in a rapid onset of analgesia with a low dose of drug(s) (see Table 23.2). The onset of effective spinal analgesia occurs faster than epidural analgesia, and more women have effective analgesia at 10 minutes.24 Intrathecal opioids can provide complete analgesia during early labor when the pain stimuli are primarily visceral. An intrathecal local anesthetic without an opioid is not commonly used for labor analgesia. Doses high enough to provide analgesia are associated with significant motor blockade, and lower doses either do not provide satisfactory analgesia or are associated with an unacceptably short duration of analgesia.168,169 A lipid-soluble opioid is combined with a local anesthetic (bupivacaine, ropivacaine, or levobupivacaine) when sacral analgesia is necessary for complete analgesia (e.g., initiation of analgesia during the active first stage or the second stage of labor). The interaction between intrathecal local anesthetics and opioids is synergistic.170 Like the combination of an epidural local anesthetic with an opioid, the combination of an intrathecal opioid with a local anesthetic results in better quality and longer duration of analgesia,171,172 as well as a lower dose requirement for both drugs, compared with either drug used alone.168,169,173

Choice of Drugs

Opioids

Fentanyl and sufentanil. The two opioids most commonly used for initiation of spinal labor analgesia are fentanyl and sufentanil. When administered alone in early labor, intrathecal fentanyl and sufentanil provide complete analgesia without a sympathectomy or motor blockade. This is a particularly useful technique for patients in whom a sudden decrease in preload (secondary to neuraxial local anesthetic–induced sympathectomy) might not be well tolerated (e.g., patient with a stenotic heart lesion).

Studies suggest that the ED₅₀ of intrathecal fentanyl varies from 5.5 to 18 μg.174–178 The wide range of published values may be explained by differences in patient population (e.g., parity), cervical dilation at initiation of analgesia, and definition of successful analgesia. Nelson et al.172 hypothesized that acute mixing of fentanyl in cerebrospinal fluid (CSF) may explain the large interindividual variability observed after the injection of intrathecal opioid. In an elegant study, the investigators determined CSF fentanyl concentration at the site of the lumbar injection 60 seconds after the fentanyl injection. CSF fentanyl concentration did not correlate with onset, sensory level, or duration of analgesia. Instead, decreased diastolic and increased systolic blood pressure correlated with duration of analgesia. The authors hypothesized that hemodynamic characteristics may influence the distribution of drug in the CSF and, hence, block characteristics.
Herman et al. 176 determined that the ED95 of intrathecal fentanyl for parturients of mixed parity in early labor (cervical dilation less than or equal to 5 cm) was 17.4 μg (95% CI, 13.8 to 27.1). The duration of analgesia is dose dependent but plateaus at 80 to 90 minutes after administration of 15 to 25 μg of fentanyl (Fig. 23.3). 174 There does not appear to be any reason to administer doses higher than 25 μg, because side effects (e.g., pruritus, respiratory depression) are also dose dependent. 176

The reported ED50 of intrathecal sufentanil varies from 1.8 to 4.1 μg,178–181 and the ED95 is 8 to 10 μg. 178,181 A comparison of the potencies of fentanyl and sufentanil using ED50 estimates from different studies is difficult because of differences in patient populations and the definition of efficacy. In a single-center study, the relative potency ratio of intrathecal sufentanil to fentanyl for labor analgesia was estimated to be 4.4:1.175 When the drugs were administered at twice the ED50 (fentanyl 36 μg, sufentanil 8 μg), the duration of sufentanil analgesia was 25 minutes longer than that of fentanyl analgesia (104 versus 79 minutes), although the incidence of side effects was not different.175

Landau et al. 182 investigated the influence of genetic variability of the μ-opioid receptor OPRM1 on the ED50 of intrathecal fentanyl for labor analgesia. Nulliparous women who were heterozygous or homozygous for A118G had a lower ED50 for intrathecal fentanyl (18 μg, 95% CI, 13 to 22) than women homozygous for the wild-type allele (A118) (27 μg, 95% CI, 23 to 31). Additionally, women in the group with the A118G allele requested analgesia at a more advanced cervical dilation. However, in two other studies assessing duration of intrathecal fentanyl labor analgesia, 183,184 there was no difference in the duration of analgesia in women with the A118G allele compared with women who were homozygous for the wild-type allele. Thus, the clinical implications of genetic polymorphisms of OPRM1 on labor analgesia remain unclear. 185

Typically, an intrathecal opioid injection for labor analgesia is administered as part of a CSE technique. Maintenance epidural analgesia is usually initiated soon after initiation of spinal analgesia. Therefore, the duration of intrathecal analgesia is relatively less important. Nelson et al. 175 concluded, and we concur, that the longer duration of sufentanil analgesia in comparison with fentanyl analgesia does not necessarily justify the former’s use. Other factors, such as cost and the greater risk for a drug dose error with sufentanil (because of its greater potency), should be considered. In some European countries sufentanil is available in a dilute concentration (5 μg/mL), possibly making it easier and safer to use.

Intrathecal fentanyl (or sufentanil) is often co-administered with an amide local anesthetic (see later discussion), most commonly bupivacaine (see Table 23.2). The addition of a local anesthetic to intrathecal fentanyl or sufentanil markedly decreases the dose of opioid necessary to produce analgesia. Wong et al. 168 randomly assigned parous women to receive intrathecal bupivacaine 2.5 mg and intrathecal sufentanil 0, 2.5, 5, 7.5, or 10 μg, followed by a standard epidural test dose. There were no differences among the sufentanil groups in quality and duration of analgesia. These results suggest that a sufentanil dose as small as 2.5 μg is effective when combined with bupivacaine 2.5 mg. In current clinical practice, it is common to combine bupivacaine 2.5 mg with sufentanil 1.5 to 2 μg.186 Stocks et al. 172 demonstrated that three different doses of intrathecal fentanyl (5, 15, and 25 μg) led to similar reductions in the ED50 of intrathecal bupivacaine, although both the duration of analgesia and the incidence of pruritus were dose dependent. As with sufentanil, the dose of intrathecal fentanyl is usually reduced when combined with bupivacaine. 169 Intrathecal fentanyl 10 to 15 μg, combined with bupivacaine 2.5 mg, provides effective analgesia for most parturients.

Other opioids. Early studies demonstrated that the intrathecal administration of 0.5 to 2 mg of morphine reliably produced analgesia during the first stage of labor, but the analgesia was less reliable during the second stage of labor and during instrumental vaginal delivery.187,188 However, intrathecal administration of these relatively large doses of morphine resulted in a high incidence of side effects, including somnolence, nausea and vomiting, pruritus, and respiratory depression. In addition, the onset of analgesia is slower with intrathecal morphine than with lipid-soluble opioids, and the long duration of action may be a disadvantage (i.e., the parturient may deliver before the regression of side effects). Abouleish 189 reported a case of life-threatening respiratory depression 1 hour after delivery and 7 hours after the administration of 1 mg of hyperbaric intrathecal morphine.

In several studies, 190–192 low-dose morphine (0.1 to 0.25 mg) was successfully combined with intrathecal bupivacaine (2 to 2.5 mg) and fentanyl (12.5 to 25 μg); the combination resulted in short latency of onset and a prolonged duration of analgesia. In contrast, a single study from Sweden 192 found no
advantage to adding morphine 0.05 or 0.1 mg to bupivacaine 1.25 mg and sufentanil 5 µg. The addition of low-dose morphine to intrathecal bupivacaine and a lipid-soluble opioid may be useful in low-resource settings in which continuous epidural infusion techniques are impractical.13 When used as part of a CSE technique, the addition of intrathecal morphine to bupivacaine and fentanyl has been shown to result in less breakthrough pain during labor190–192 as well as decreased analgesic use in the first 24 hours postpartum, compared with intrathecal bupivacaine and fentanyl without morphine.190,191 The incidence of intrapartum side effects was similar190,192; however, the morphine group had a higher incidence of postpartum nausea (17% versus 0% for no morphine).190

An alternative drug is meperidine. Meperidine is unique among the opioids in that it possesses weak local anesthetic properties,130 and it has been used in large doses (e.g., 1 mg/kg) as the sole agent to provide spinal anesthesia for surgical procedures.131 Intrathecal administration of meperidine (10 to 20 mg) results in effective labor analgesia within 2 to 12 minutes, with a duration of 1 to 3 hours. Honet et al.193 compared the efficacy of intrathecal meperidine 10 mg, fentanyl 10 µg, and sufentanil 5 µg in 65 laboring women. The three drugs were similar in onset of analgesia (less than 5 minutes) and duration of effective analgesia (80 to 100 minutes). However, the meperidine group had significantly lower pain scores after cervical dilation had progressed beyond 6 cm. As labor advances, the nature of pain becomes increasingly somatic; only meperidine also functions as a local anesthetic. This fact helps explain why meperidine provided more effective analgesia during advanced labor, including the second stage. Booth et al.194 observed that intrathecal meperidine was associated with a significantly higher incidence of nausea and vomiting than a combination of fentanyl and bupivacaine for labor analgesia. Therefore, intrathecal meperidine does not seem to offer any advantages over bupivacaine-fentanyl for routine intrathecal analgesia, although it may be useful for the rare patient with a contraindication to bupivacaine-fentanyl administration.

In the United Kingdom, some anesthesia providers have advocated the intrathecal administration of diamorphine (heroin) for labor analgesia, although it is not commonly used for this purpose. This drug is not available for clinical use in the United States. Kestin et al.197 observed that the intrathecal administration of diamorphine (0.2 to 0.5 mg) provided good to excellent analgesia in 90% of laboring women. The mean duration of analgesia was approximately 100 minutes. However, 75% of patients had pruritus, nausea, and vomiting. In contrast, Vaughan et al.198 randomly assigned parturients to receive intrathecal bupivacaine 2.5 mg with either fentanyl 25 µg or diamorphine 0.25 mg. Duration of analgesia was longer in the diamorphine group, but the incidence of side effects was low in both groups.

Local Anesthetics

In the late first stage and the second stage of labor, a local anesthetic must be added to the spinal opioid to block somatic stimuli from the vagina and perineum caused by descent of the fetus. The local anesthetic works synergistically with the opioid, so lower doses of both drugs can be used.186–170,172,199 Bupivacaine is most commonly combined with fentanyl or sufentanil. The ED₅₀ of bupivacaine was 3.3 mg when combined with sufentanil 1.5 µg186 and 1.7 mg when combined with fentanyl 15 µg.200 Intrathecal bupivacaine doses between 1.25 and 2.5 mg are commonly used (see Table 23.2). Levobupivacaine and ropivacaine are not usually used for intrathecal injection in the United States. They are less potent than bupivacaine for intrathecal labor analgesia (Fig. 23.4).186,201 Spinal lidocaine has not been studied for use in labor analgesia, but it is unlikely to have any advantages compared with other, longer-acting amide local anesthetics. Common doses of spinal local anesthetics are shown in Table 23.2.

Controversy exists as to whether the lower incidence and degree of motor blockade associated with ropivacaine and levobupivacaine202,203 are a result of their inherent difference in potency or of greater sensory-motor separation with the S(−)-enantiomer drugs.186 Camorcia et al.204 have suggested that, especially during intrathecal use, ropivacaine may be associated with less motor blockade than bupivacaine, even when equipotent doses (e.g., 3.6 mg ropivacaine and 2.4 mg bupivacaine) are administered. However, this difference, even if it exists, is unlikely to have any clinical significance during spinal labor analgesia because all local anesthetics administered for this purpose are administered in low doses that lead to minimal motor blockade.

**Baricity of the intrathecal solution.** The local anesthetic/opioid solutions commonly injected for intrathecal labor analgesia have lower specific gravity relative to that of CSF.

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![Fig. 23.4 Predicted (lines) and observed (symbols) dose-response of intrathecal bupivacaine, levobupivacaine, and ropivacaine combined with sufentanil 1.5 µg in 450 laboring women. The dose-response curves were constructed with the use of a probit regression model. The curves were compared with use of likelihood ratio tests. No difference was observed between ropivacaine and levobupivacaine. Significant differences were observed between bupivacaine and ropivacaine (P = .003) and bupivacaine and levobupivacaine (P < .001). (From Van de Velde M, Dreelinck R, Dubois J, et al. Determination of the full dose-response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. *Anesthesiology.* 2007;106:149–156.)](image-url)
and hence are hypobaric. 202 The extent of cephalad sensory blockade is higher for spinal analgesia initiated with the par- turient in the sitting position than in the lateral position.203 Adding dextrose to the solution (opioid alone or opioid with local anesthetic) to make the solution hyperbaric results in less extensive sensory blockade but also in inadequate analgesia.204–206 It is probably necessary for the opioid to penetrate the spinal cord rather than just the nerve roots; therefore, injection of a hyperbaric solution of opioid and local anesthetic below the level of the spinal cord may lead to inadequate analgesia, even though the local anesthetic provides sensory blockade to the T10 dermatome.

### Intrathecal Adjuvants

Several drugs have been investigated as adjuvants to local anesthetics, opioids, or combinations of local anesthetics and opioids for intrathecal labor analgesia (see Table 23.4). In one study, the addition of clonidine 30 µg to sufentanil (2.5 to 5 µg) prolonged the duration of analgesia from 104 to 145 minutes without motor block.207 Other investigators have had similar results when clonidine was combined with sufentanil,208 bupivacaine/ropivacaine and sufentanil,209,210 and neostigmine.211 Intrathecal clonidine alone also provides analgesia.212 A disadvantage of clonidine is the high incidence of maternal hypotension and sedation as well as FHR abnormalities. The slightly longer duration of analgesia provided by the addition of clonidine to bupivacaine and sufentanil is not an advantage when maintenance analgesia is provided by a continuous epidural infusion. Therefore, at present, intrathecal clonidine cannot be recommended for routine spinal labor analgesia, although it might be considered in parturients with contraindications to the use of other drugs.213

Adding intrathecal neostigmine to sufentanil, bupivacaine/sufentanil, or clonidine has been found to potentiate the analgesia and prolong its duration.211,214 However, intrathecal neostigmine was associated with a markedly higher incidence of severe nausea that was unresponsive to standard antiemetics.211,214 Therefore, neostigmine cannot be recommended as an adjuvant for intrathecal labor analgesia.

Analgesia is prolonged by 15 to 40 minutes when epinephrine is added to intrathecal bupivacaine-opioid.215–217 Even an epinephrine dose as low as 2.25 µg prolonged analgesia by 15 minutes.216 However, epinephrine 200 µg combined with bupivacaine 2.5 mg and sufentanil 10 µg resulted in a significant incidence of motor blockade215; epinephrine doses between 12.5 and 100 µg prolonged analgesia without any difference in the quality of analgesia.217

In summary, no adjuvant studied to date prolongs the duration of fentanyl or sufentanil/bupivacaine analgesia long enough to avoid the use of maintenance epidural analgesia for most parturients, and no adjuvant reduces or eliminates the side effects associated with the analgesic drugs used clinically. Therefore, it makes little sense to routinely add adjuvant drugs, because they are associated with higher cost, higher rate or severity of side effects, and probably an increased risk for drug error.

## MAINTENANCE OF ANALGESIA

### Epidural Analgesia

Painful labor lasts several hours in most parturients; therefore, a single intrathecal or epidural injection of local anesthetic and/or opioid typically does not provide adequate analgesia for the duration of labor. Supplemental doses are needed to maintain analgesia in most women. Neuraxial analgesia is maintained with the intermittent or continuous administration of analgesics, usually a combination of a long-acting amide local anesthetic and a lipid-soluble opioid. By far the most common technique is administration of drugs via a catheter into the epidural space. It is occasionally advantageous to administer drugs via a catheter into the subarachnoid space.

### Drugs for the Maintenance of Epidural Analgesia

In the past, epidural labor analgesia was maintained with the intermittent injection or continuous infusion of a neuraxial local anesthetic alone. Currently, most anesthesia providers maintain analgesia with a combination of a low-dose, long-acting amide local anesthetic and a lipid-soluble opioid (Table 23.5). In practice, neither lidocaine nor 2-chloroprocaine is used for maintenance of analgesia. Both have a short duration of action, and tachyphylaxis may develop more quickly with either of these local anesthetics than occurs with the longer-acting local anesthetics. Lidocaine crosses the placenta to a greater extent than bupivacaine, and there is less differentiation between the dose required for sensory and motor blockade.218 There is no evidence that any one of the three long-acting local anesthetics (bupivacaine, ropivacaine, levobupivacaine) has any advantages in terms of clinical outcomes over the other two.65,74,75 Fentanyl is more often detected in umbilical artery blood samples than sufentanil (see earlier discussion)708; however, neonatal outcomes are

### TABLE 23.5 Anesthetic Solutions for Maintenance of Epidural Analgesia: Continuous Infusion or Patient-Controlled Epidural Analgesia

<table>
<thead>
<tr>
<th>Drug □</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Anesthetics</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.05–0.125%</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.08–0.2%</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.05–0.125%</td>
</tr>
<tr>
<td>Lidocaine ‡</td>
<td>0.5%–1.0%</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.5–3 µg/mL</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.2–0.4 µg/mL</td>
</tr>
</tbody>
</table>

*Local anesthetic is most often combined with an opioid.
Continuous infusions are usually administered at a rate of 8–15 mL/h into the lumbar epidural space.
"Lidocaine is not usually used for maintenance of epidural analgesia because it crosses the placenta to a greater extent than the other amide local anesthetics and may be associated with greater tachyphylaxis."
good after maintenance of epidural analgesia with either drug.

As with the induction dose, the combination of a local anesthetic with a lipid-soluble opioid allows administration of a lower concentration and a smaller total dose of local anesthetic for maintenance of analgesia. This approach improves safety and leads to less motor blockade and greater patient satisfaction. Chestnut et al. demonstrated that maintenance of epidural analgesia by a continuous infusion of 0.0625% bupivacaine with fentanyl 2 µg/mL resulted in comparable maternal and neonatal outcomes, with a lower incidence of motor blockade, compared with maintenance of analgesia by a continuous epidural infusion of 0.125% bupivacaine alone. When administered as intermittent epidural boluses for the maintenance of analgesia, the addition of sufentanil to bupivacaine resulted in better quality analgesia and decreased motor blockade at delivery.

In contemporary clinical practice, the bupivacaine concentration of maintenance bupivacaine/opioid solutions ranges from 0.05% to 0.125%. Hess et al. retrospectively analyzed the use of three solutions at their institution: bupivacaine 0.125% and bupivacaine 0.0625%, both with fentanyl 2 µg/mL, administered at 8 to 12 mL/h, and bupivacaine 0.04% with fentanyl 1.7 µg/mL and epinephrine 1.7 µg/mL, administered at 15 mL/h. There were more interventions for breakthrough pain in the two low-concentration groups and more interventions for hypotension and motor blockade in the high-concentration group. Beilin et al. initiated analgesia with intrathecal bupivacaine/fentanyl and an epidural test dose, and then randomly assigned women to receive maintenance epidural analgesia with one of four solutions: bupivacaine 0.125%, bupivacaine 0.0625%, or bupivacaine 0.04% with epinephrine 1.7 µg/mL (all with fentanyl 2 µg/mL) or placebo (saline) at 10 mL/h. The time to request for supplemental analgesia was longest in the bupivacaine 0.125% group; however, this group also had a higher incidence of motor blockade than the other groups. Therefore, to avoid motor blockade, it would seem reasonable to use a bupivacaine concentration less than 0.125%, especially if it is administered via continuous epidural infusion (see later discussion).

The dose-response relationships for fentanyl and sufentanil combined with a local anesthetic for the maintenance of epidural analgesia have not been well studied. The concentration range of fentanyl used in clinical practice is 1.5 to 3 µg/mL, and that of sufentanil, 0.2 to 0.33 µg/mL. The optimal opioid concentration probably varies according to the local anesthetic concentration, the mode of drug delivery (i.e., bolus versus infusion), the presence of epinephrine, and the stage of labor, among other factors. Bader et al. infused epidural bupivacaine 0.125% with fentanyl 2 µg/mL at 10 mL/h for 1 to 15 hours. Maternal and neonatal fentanyl concentrations, and their ratio, remained constant over the infusion period, and no adverse maternal or neonatal outcomes were noted. Porter et al. compared neonatal outcomes in women randomly assigned to receive epidural bupivacaine with fentanyl 2.5 µg/mL or bupivacaine alone to maintain analgesia. There were no differences between groups in measures of neonatal well-being at birth or 24 hours after delivery.

Bernard et al. combined sufentanil 0.078, 0.156, 0.312, or 0.468 µg/mL with bupivacaine 0.125% and epinephrine 1.25 µg/mL. Each solution was administered as a 12-mL bolus via PCEA. Sufentanil concentrations lower than 0.156 µg/mL did not provide adequate analgesia for the second stage of labor, and higher doses were associated with an increased incidence of pruritus. Loftus et al. compared bupivacaine with sufentanil 0.25 µg/mL or fentanyl 1.5 µg/mL as a continuous epidural infusion at 10 mL/h. Neonates in the fentanyl group had slightly lower 24-hour neuroadapтив capacity scores (NACS) than those in the sufentanil group.

**Administration Techniques**

**Intermittent bolus.** Before the introduction of infusion pumps, epidural analgesia was routinely maintained by the intermittent administration of an additional therapeutic bolus dose of local anesthetic when analgesia began to wane. When the patient began to experience recurrent pain, the anesthesia provider assessed the pain relative to the stage of labor and the extent of sensory blockade and then administered another epidural bolus of local anesthetic. Analgesia was usually reestablished with the bolus injection of 8 to 12 mL of a local anesthetic/opioid solution.

The spread and quality of analgesia may change with repeated lumbar epidural injections of local anesthetic. After several injections, blockade of the sacral segments, intense motor blockade, or both may develop. The sensory level and the intensity of motor blockade should be assessed and recorded before and after each bolus injection of local anesthetic.

This intermittent bolus technique has several disadvantages, the most salient of which is that pain relief is constantly interrupted by the regression of analgesia. The patient must notify the labor nurse or midwife that she is again uncomfortable and request additional analgesia. In the United States, labor nurses are not allowed to administer additional epidural analgesic drugs; therefore, the nurse must call the anesthesia provider, resulting in unavoidable delays in administration of additional analgesic drugs and additional pain for the patient.

**Continuous infusion.** Administration of a continuous epidural infusion of a dilute solution of local anesthetic combined with an opioid for the maintenance of epidural labor analgesia overcomes the disadvantages of intermittent boluses administered by an anesthesia provider or midwife. The potential benefits of a continuous epidural infusion include the maintenance of a stable level of analgesia and a less-frequent need for bolus doses of local anesthetic, which may reduce the risk for local anesthetic systemic toxicity. An additional advantage is a decreased workload for the anesthesia provider.

Published studies have suggested that the continuous epidural infusion and intermittent bolus injection techniques have a comparable safety record. Studies comparing intermittent bolus injections with continuous infusion were
performed before the era of neuraxial opioid administration; thus, the studies used concentrations of bupivacaine (0.125% to 0.25%) higher than those typically used in contemporary practice. In theory, maintenance of a constant level of anesthesia should promote maternal hemodynamic stability and improve fetal and neonatal outcomes. Only one published study has suggested a trend toward less frequent hypotension and a lower incidence of abnormal FHR patterns during the continuous epidural infusion of bupivacaine than with intermittent bolus injections of bupivacaine; however, neonatal outcomes were similar with the two techniques.255

Randomized trials of intrapartum epidural analgesia maintained by either intermittent bolus injection or continuous infusion of bupivacaine have demonstrated that women require fewer bolus injections administered by the anesthesia provider (i.e., fewer episodes of breakthrough pain) with the continuous infusion technique.225–227 The continuous infusion technique lengthens the time between bolus injections and leads to greater patient satisfaction.227,228

Most studies suggest that the continuous epidural infusion technique leads to the administration of a larger total dose of bupivacaine,226–229 but such a dose does not seem to result in higher maternal venous or umbilical venous bupivacaine concentrations at delivery.227,229 The continuous epidural infusion of bupivacaine often achieves satisfactory perineal analgesia, obviating the need for a bolus dose of local anesthetic at delivery. Unfortunately, a prolonged epidural infusion of 0.125% bupivacaine at 10 to 14 mL/h may cause significant motor blockade.85,225,226,228,229 Titrating the dose of bupivacaine to meet the individual needs of each patient (rather than administering the same dose to all patients), as well as reducing the total mass of bupivacaine by lowering the local anesthetic concentration and adding an opioid, helps minimize motor blockade while providing effective analgesia.

Migration of the epidural catheter into the subarachnoid, subdural, or intravenous space may occur with either the intermittent bolus injection or continuous infusion technique. If the epidural catheter should migrate into a vein during the continuous epidural infusion of a dilute solution of local anesthetic, it is unlikely that the patient will have symptoms of local anesthetic toxicity; rather, the level of anesthesia will regress. For this reason, the anesthesia provider should suspect the intravenous migration of an epidural catheter when a patient unexpectedly complains of pain during maintenance of analgesia during a continuous epidural infusion.

Migration of the epidural catheter into the subdural or subarachnoid space during an infusion should result in the slow ascent of the level of anesthesia and a greater density of motor blockade. These observations apply to the epidural infusion of a 0.125% solution of bupivacaine at a modest rate (e.g., 5 to 8 mL/h). The continuous infusion of a more concentrated solution or the use of a more rapid rate of infusion most likely narrows the margin of safety.

**Patient-controlled epidural analgesia.** The method of delivering the anesthetic solution into the epidural space influences the density of neuroblockade. Given the same concentration of local anesthetic, analgesia maintained by infusion results in greater drug use, a higher degree of motor blockade,226,229 and a higher incidence of instrumental vaginal delivery than intermittent boluses.229 However, intermittent manual bolus administration by the anesthesia provider results in more breakthrough pain, less patient satisfaction, and more work for the anesthesia provider. PCEA is a method of delivering anesthetic solution to the epidural space that overcomes these disadvantages. Since its first description in 1988 by Gambling et al.,230 many studies have consistently found that the analgesia with PCEA is comparable to that with continuous infusion techniques.232,233

Van der Vuyver et al.233 reported a meta-analysis of nine randomized controlled trials (n = 640) comparing PCEA (without a background infusion) with continuous epidural infusion analgesia. There were fewer anesthetic interventions in the PCEA group, and the total bupivacaine dose was lower, as was the incidence of motor blockade (Fig. 23.5). There were no differences in pain scores, patient satisfaction, and maternal and neonatal outcomes between groups.

Data are conflicting as to whether PCEA should include a background infusion.234–240 Most studies have reported background infusions of 3 to 4 mL/h. Bupivacaine consumption is higher in PCEA with a background infusion than in a pure PCEA technique without a background infusion.231 A meta-analysis of five studies reported in the ASA Practice Guidelines for Obstetric Anesthesia16 concluded that PCEA with a background infusion provides better analgesia than pure PCEA without a background infusion. Similarly, a 2015 meta-analysis that included seven studies identified a lower requirement for physician-administered rescue bolus doses in patients who receive a background infusion.241 There is no evidence that the higher local anesthetic dose associated with a background infusion has adverse effects on obstetric outcome when low-concentration infusion solutions are used. A typical background infusion provides one-third to one-half of the total hourly dose.232 Sng et al.242 described a novel PCEA system in which they used a computer-integrated infusion pump to modify the background infusion rate based on the previous hour’s requirement for patient-administered bolus doses. Future pump technology will likely incorporate machine learning to more closely tailor the administered anesthetic dose to patient need.

A wide variety of PCEA regimens have been described (Table 23.6). The anesthesia provider can manipulate the infusion solution (local anesthetic/opioid concentration), patient-controlled bolus volume, lockout interval, background infusion rate, and maximum allowable dose per hour. Patient-controlled bolus doses from 2 to 20 mL and lockout intervals from 5 to 30 minutes have been reported238,239,243–248; most studies have evaluated patient-controlled bolus doses of 5 to 12 mL. No study has found any differences in unscheduled provider interventions when investigators manipulated the patient-controlled bolus dose and lockout interval. There are no published reports of toxicity with larger bolus volumes, although the study populations were too small to allow
greater motor blockade than use of less-concentrated solutions. Thus, as with continuous infusion epidural analgesia, administration of a dilute local anesthetic solution combined with an opioid results in less local anesthetic consumption and motor blockade without a reduction in analgesia efficacy.

In summary, solutions used for PCEA are identical to those used for continuous epidural infusion analgesia (see Table 23.5). It is suggested that larger bolus volumes be used if PCEA is administered without a background infusion. Early PCEA studies investigated higher-concentration local anesthetic solutions (i.e., 0.125% to 0.25% bupivacaine), smaller bolus volumes (less than or equal to 5 mL), and low background infusion rates (3 to 5 mL/h). Given the more recent data supporting the efficacy of epidural administration of higher volumes of more dilute solutions of local anesthetic, it appears reasonable to apply this principle to PCEA. The safety of large-volume boluses (greater than 10 mL) has not been determined.

**Fig. 23.5** Meta-analysis of patient-controlled epidural analgesia (PCEA) without background infusion compared with continuous epidural infusion for maintenance of analgesia. (A) The number of patients requiring no unscheduled interventions by the anesthesia provider was lower in the PCEA group (risk difference 27%; 95% confidence interval [CI], 18 to 36). (B) The dose of local anesthetic (mg/h) was lower in the PCEA group (weighted mean difference, –3.9 mg; 95% CI, –5.4 to –2.4). (From van der Vyver M, Halpern S, Joseph G. Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. *Br J Anaesth.* 2002;89:459–465.)

**TABLE 23.6 Examples of Patient-Controlled Epidural Analgesia (PCEA) Settings**

<table>
<thead>
<tr>
<th>PCEA Technique</th>
<th>Basal Infusion Rate (mL/h)</th>
<th>Bolus Dose (mL)</th>
<th>Lockout Interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without background infusion</td>
<td>0</td>
<td>8–12</td>
<td>10–20</td>
</tr>
<tr>
<td>With background infusion</td>
<td>4–8</td>
<td>5–8</td>
<td>10–15</td>
</tr>
</tbody>
</table>

*Anesthetic solutions are shown in Table 23.5.

determination of safety. Taken together, these studies suggest that there is no ideal bolus dose/volume or lockout interval for labor PCEA.

Various local anesthetic concentrations also have been studied. No studies have reported any differences in analgesia efficacy. Use of more-concentrated local anesthetic solutions results in higher local anesthetic consumption and greater motor blockade than use of less-concentrated solutions. Thus, as with continuous infusion epidural analgesia, administration of a dilute local anesthetic solution combined with an opioid results in less local anesthetic consumption and motor blockade without a reduction in analgesia efficacy.

In summary, solutions used for PCEA are identical to those used for continuous epidural infusion analgesia (see Table 23.5). It is suggested that larger bolus volumes be used if PCEA is administered without a background infusion. Early PCEA studies investigated higher-concentration local anesthetic solutions (i.e., 0.125% to 0.25% bupivacaine), smaller bolus volumes (less than or equal to 5 mL), and low background infusion rates (3 to 5 mL/h). Given the more recent data supporting the efficacy of epidural administration of higher volumes of more dilute solutions of local anesthetic, it appears reasonable to apply this principle to PCEA. The safety of large-volume boluses (greater than 10 mL) has not been determined.

**Programmed intermittent epidural bolus injection.** Bolus administration of a local anesthetic into the epidural space...
results in better analgesia than continuous epidural infusion. Likewise, larger volumes of a less concentrated anesthetic solution provide better analgesia than smaller volumes of a more concentrated solution. Presumably, distribution of anesthetic solution in the epidural space is better when larger volumes are administered under high injection pressure. However, both provider-administered bolus dosing and PCEA are associated with inconsistent analgesia as pain relief wanes and is then reestablished with a bolus dose. Several studies have demonstrated that programmed (automated) intermittent epidural boluses (PIEB) (5 to 10 mL every 30 to 60 minutes) administered via a programmable pump result in improved patient satisfaction, less drug use, longer duration of analgesia, and less breakthrough pain than a continuous infusion of the same mass of drug per unit of time. For example, Wong et al. randomly assigned patients to receive either a continuous epidural infusion of a dilute bupivacaine/fentanyl solution at 12 mL/h or 6 mL of the same solution as a programmed bolus every 30 minutes. Similarly, Sia et al. randomly assigned patients to receive either a continuous epidural infusion of a ropivacaine/fentanyl solution at 5 mL/h or 5 mL of the same solution delivered as a programmed bolus every hour. All patients in both studies were allowed PCEA for the treatment of breakthrough pain. The total dose of local anesthetic was smaller in the PIEB groups than in the continuous infusion groups.

Capogna et al. compared motor block and mode of delivery in women randomized to receive PIEB with levobupivacaine 0.0625% with sufentanil 0.5 μg/mL (10 mL every 60 minutes) or the same solution as a continuous infusion (10 mL/h). Women were able to treat breakthrough pain with PCEA using levobupivacaine 0.125% (5-mL bolus). The incidence of motor block was greater in the continuous infusion group. Of interest, the rate of instrumental vaginal delivery was also higher in the continuous infusion group (7% versus 20%; risk ratio, 2.9; 95% CI, 1.1 to 7.9).

In a systematic review and meta-analysis of nine studies (n = 344), George et al. concluded that the PIEB technique was associated with a small decrease in total anesthetic consumption and improved patient satisfaction. Although no difference was found in the need for anesthesia provider intervention and other outcomes, the confidence intervals were wide. The authors concluded that further study is needed to ascertain whether this technique impacts clinically significant anesthetic and obstetric outcomes. Infusion pumps with the ability to deliver this mode of analgesia are now commercially available. A schematic diagram demonstrating the use of PIEB is shown in Fig. 23.6, and examples of PIEB pump parameters are shown in Table 23.7.

**Patient Monitoring during Maintenance Epidural Analgesia**

The use of a continuous epidural infusion, PCEA, or PIEB technique does not abolish the need for frequent assessment of the patient by the anesthesia provider at regular intervals. Regular assessment may be particularly important for the PIEB technique in which unwatched bolus doses are administered independent of breakthrough pain. Indeed, a 2017 case report describes the migration of a properly-sited epidural catheter into the subarachnoid space after several hours of uneventful PIEB analgesia. The patient became acutely hypotensive with new-onset nausea and dyspnea; CSF was easily aspirated from the neuraxial catheter.

Regular assessments should involve determining the quality of analgesia and progress of labor, recording the sensory level and intensity of motor block, and reviewing maternal vital signs and FHR tracings for the previous hour. An inappropriately high level of anesthesia signals the administration of an excessive dose of local anesthetic, or subdural or subarachnoid migration of the catheter. A low level of anesthesia may signal intravenous migration of the catheter, movement of the catheter outside the epidural space, or administration of an inadequate dose of local anesthetic.

**Equipment**

Anesthesia providers should consider the safety of their equipment when choosing a maintenance technique. The use of an infusion pump identical to that used for the intravenous administration of other drugs increases the chance that a nurse or physician will inject oxytocin, magnesium sulfate, or another drug into the epidural space unintentionally. Thus, the use of an infusion pump that is used exclusively for epidural analgesia and that differs from the pumps used for intravenous drug and fluid administration is recommended. The pump should be easy to use, reliable, adjustable, and sturdy. PCEA pumps should differ from patient-controlled intravenous analgesia (PCIA) pumps. The PCEA “buttons” should be labeled with instructions that only the patient (not medical providers or family members) should push the button. If possible, pumps should be preprogrammed with maximum safe limits to prevent errors in pump programming.

The anesthesia provider should use infusion tubing (which connects the pump to the epidural catheter) that is unique for the epidural administration of drugs. Some tubing is color-coded (yellow). Use of tubing that does not have an injection side-port is recommended. The epidural catheter and tubing should be clearly labeled with the word “epidural.” Patient

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**TABLE 23.7 Examples of Programmed Intermittent Epidural Bolus (PIEB) Settings**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIEB initial bolus time</td>
<td>15–45 min</td>
</tr>
<tr>
<td>PIEB bolus volume</td>
<td>5–10 mL</td>
</tr>
<tr>
<td>PIEB bolus interval</td>
<td>30–60 min</td>
</tr>
<tr>
<td>PCEA bolus volume</td>
<td>5–10 mL</td>
</tr>
<tr>
<td>PCEA lockout interval</td>
<td>10–15 min</td>
</tr>
</tbody>
</table>

**PIEB** patient-controlled epidural analgesia.

Anesthetic solutions are shown in Table 23.5.

Interval from initial neuraxial analgesia loading dose (spinal or epidural) to first programmed bolus dose.
Chapter 23: Epidural and Spinal Analgesia: Anesthesia for Labor and Vaginal Delivery

Double-checked for content and expiration date by the anesthesia provider before analgesia is initiated.

Spinal Analgesia

Placement of a catheter in the subarachnoid space allows the anesthesia provider to administer continuous spinal analgesia by intermittent bolus injection or continuous infusion of a local anesthetic combined with an opioid. Continuous spinal analgesia is an option when unintentional dural puncture has occurred (see later discussion). The technique has also been described for use in patients in whom placement of an epidural catheter is difficult (e.g., in patients with morbid obesity or abnormal vertebral anatomy, such as kyphoscoliosis, or in patients with severe cardiac disease who require careful titration of analgesia).264

Reports of this technique usually describe the use of a standard epidural catheter placed through an 18- or 19-gauge epidural needle. Over 25 years ago, to reduce the incidence of post–dural puncture headache, very small (e.g., 28- to 32-gauge) catheters were developed for insertion through small (e.g., 22- to 26-gauge) spinal needles. Unfortunately, several cases of cauda equina syndrome (associated with

Each labor unit must have a clear policy as to who may administer and adjust epidural infusion parameters. Anesthesia personnel should be responsible for changes in the content or rate of the infusion and the volume of bolus doses or develop protocols that allow nurses to make changes within the guidelines of the protocol or by order of the anesthesia provider. In the presence of maternal distress or fetal bradycardia, the nurse or obstetrician may discontinue the epidural infusion, but the anesthesia provider should be notified immediately.

Solutions for maintenance of neuraxial analgesia, consisting of dilute local anesthetic and opioid, require careful preparation. A hospital pharmacist or compounding pharmacy should prepare the solution in a clean or sterile environment. Preservative-free drugs and saline should be used to prepare the solutions. Solution contents should always be double-checked for content and expiration date by the anesthesia provider before analgesia is initiated.

Spinal Analgesia

Placement of a catheter in the subarachnoid space allows the anesthesia provider to administer continuous spinal analgesia by intermittent bolus injection or continuous infusion of a local anesthetic combined with an opioid. Continuous spinal analgesia is an option when unintentional dural puncture has occurred (see later discussion). The technique has also been described for use in patients in whom placement of an epidural catheter is difficult (e.g., in patients with morbid obesity or abnormal vertebral anatomy, such as kyphoscoliosis, or in patients with severe cardiac disease who require careful titration of analgesia).264
the use of spinal microcatheters during surgery in nonpregnant patients) prompted the U.S. FDA to remove these microcatheters from the market in 1992.\textsuperscript{265} The etiology of these neurologic deficits is unclear. Some anesthesiologists have suggested that neurologic injury may result from the maldistribution of local anesthetic within the subarachnoid space.\textsuperscript{266} The very slow rate of injection through a caudally directed microcatheter may lead to pooling of local anesthetic solution in the terminal part of the dural sac. If the local anesthetic solution is hyperbaric, the neighboring elements of the cauda equina experience prolonged exposure to a high concentration of local anesthetic and a hyperglycemic, hyperosmotic marina (e.g., 550 to 800 mOsm/L). Permanent neural damage may occur from the combination of tissue dehydration and a toxic concentration of local anesthetic. It is unclear whether this complication is unique to the use of microcatheters.

Aikoosh et al.\textsuperscript{267} reported a randomized multicenter study comparing continuous spinal labor analgesia (via a 28-gauge catheter) with continuous epidural analgesia. The incidence of neurologic complications was not different between the two groups, and patients in the spinal group had better early analgesia, less motor blockade, and better patient satisfaction. The incidence of post–dural puncture headache also was not different between the two groups (spinal 9%, epidural 4%; \( P = .10 \)), although a type II statistical error is possible given the size of the study and the low incidence of this outcome. The spinal catheter was associated with a higher incidence of technical difficulties and catheter failures.

A 23-gauge, FDA-approved, spinal catheter is now available in the United States. The catheter is inserted using a “catheter-over-needle” technique. Initial observational study found that this catheter may have clinical utility\textsuperscript{268}; however, similar to the Aikoosh et al. study,\textsuperscript{267} the study was not large enough to assess the risk for complications. Further study is required to characterize ease of use and complications. Several commercial spinal catheters are available in Europe.

Continuous spinal analgesia can be initiated with the same drug combination and dose used to initiate CSE analgesia (see Table 23.2).\textsuperscript{264} For maintenance of analgesia, my colleagues and I administer our standard epidural solution (0.06% bupivacaine with fentanyl 2 \( \mu \text{g/mL} \)) at an initial rate of 2 mL/h. The infusion is then titrated to patient needs. We prefer to use our standard PCEA pumps for the continuous infusion, with the PCEA function disabled. This approach allows the anesthesia provider to administer a small (1 to 3 mL) bolus from the infusion bag without disconnecting the spinal catheter from the infusion tubing. Alternatively, the infusion pump can be programmed to administer 1-mL patient-controlled bolus doses. The catheter and pump should be clearly labeled so that all care providers know that the catheter is a spinal, not an epidural, catheter.

Continuous spinal analgesia with opioids has also been described for patients with obstructive cardiac lesions.\textsuperscript{269,270} If intrathecal local anesthetics are used for intrapartum analgesia, the sensory level and the intensity of motor blockade should be monitored. Moreover, the anesthesia provider must be prepared to treat hypotension and other complications associated with high spinal anesthesia.

**Ambulatory “Walking” Neuraxial Analgesia**

The term “walking” or “mobile” epidural analgesia was first coined to describe low-dose CSE opioid analgesia because motor function was maintained and the ability to walk was not impaired.\textsuperscript{271} However, the term is more accurately applied to any neuraxial analgesic technique that allows safe ambulation. Initial studies using clinical testing to assess sensory and motor impairment and dorsal column function produced conflicting results. After initiation of epidural analgesia with 15 mL of 0.1% bupivacaine/fentanyl 2 \( \mu \text{g/mL} \), Buggy et al.\textsuperscript{272} demonstrated that 66% of women had altered proprioception and 38% had impaired vibration sense. In contrast, Parry et al.\textsuperscript{273} found that dorsal column function was impaired in only 7% of laboring women who received low-dose epidural or CSE analgesia. The same group of investigators then used computerized dynamic posturography to assess balance in nonpregnant women, term pregnant women not in labor, and laboring women after initiation of CSE analgesia with bupivacaine 2.5 mg and fentanyl 5 \( \mu \text{g} \).\textsuperscript{274} Pregnancy significantly affected balance function, but initiation of CSE analgesia did not further impair function. However, further supplementation of analgesia with the epidural injection of 10 mL of 0.1% bupivacaine/fentanyl 2 \( \mu \text{g/mL} \) in a subgroup of patients resulted in impaired balance function. The investigators concluded that the results support the safety of allowing ambulation after low-dose CSE analgesia, but further studies are required to understand the relative contributions of dorsal column function, proprioception, and lower limb motor strength to overall balance and ability to ambulate.\textsuperscript{274}

Several studies have shown that an epidural test dose containing lidocaine 45 mg and epinephrine 15 \( \mu \text{g} \) adversely affects the ability to ambulate after initiation of CSE or low-dose epidural analgesia.\textsuperscript{274}

The concept of the “walking epidural” is popular in the lay press; however, many women, once comfortable, prefer to rest rather than ambulate. The ability to walk to the toilet or sit in a chair at the bedside, however, remains desirable to many laboring women.\textsuperscript{275} In a small study, the ability to walk to the toilet to void resulted in lower postvoid residual volume than voiding on a bedpan.\textsuperscript{276} Although ambulation per se has not been shown to affect the progress or outcome of labor positively or negatively, dense motor blockade may adversely affect the spontaneous vaginal delivery rate (see later discussion). Thus, the intent of the “walking epidural”—minimization of motor blockade—should be the goal of the anesthesia provider, whether or not the patient wishes to ambulate.\textsuperscript{275}

Safe ambulation during labor requires several safeguards (Box 23.5). Before ambulation, orthostatic blood pressure and heart rate should be measured and motor function and balance must be assessed. The patient should not ambulate alone.
Labor with Neuraxial Analgesia

INTERMITTENT EPIDURAL ANESTHESIA

Continuous epidural infusion of bupivacaine often results in dense anesthesia for vaginal delivery. Likewise, several lumbar epidural injections of local anesthetic (given every 60 to 90 minutes) may result in sacral analgesia. If this analgesia is not adequate for the second stage of labor, the anesthesia provider can give additional doses of local anesthetic to augment perineal analgesia.

SADDLE BLOCK

A saddle block, which provides anesthesia to the pelvic floor, vagina, and perineum, is often used during vaginal delivery. This technique involves the placement of an epidural catheter in the lumbar epidural space, usually at L2-3, and the administration of a local anesthetic solution. The advantages of this technique are that it provides a rapid onset of anesthesia and who requires perineal anesthesia. A so-called saddle block can be administered to achieve blockade of the sacral spinal segments; a small dose of a hyperbaric local anesthetic solution is adequate for this purpose. A saddle block may be advantageous in the patient with a preterm fetus or a vaginal breech presentation. In these cases, dense perineal relaxation may facilitate an atraumatic vaginal delivery.

SITTING POSITION

If the obstetrician performs an episiotomy or a forceps delivery, the sitting position helps facilitate the onset of perineal analgesia. Published studies suggest that maternal position does not consistently affect the spread of local anesthetic in the epidural space; rather, the administration of a larger volume of local anesthetic solution facilitates the onset of sacral analgesia.

Dense anesthesia is often required for delivery, especially if the obstetrician performs an episiotomy or a forceps delivery. After administration of a test dose (3 mL of the local anesthetic solution), at our institution my colleagues and I administer 5 to 10 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine. We inject this “delivery dose” when the fetal head is visible on the perineum during pushing or when the obstetrician has decided to proceed with instrumental vaginal delivery. The anesthesia provider should monitor the maternal blood pressure carefully, especially if excessive blood loss occurs in a patient with extensive anesthetic.

Occasionally, a parturient tolerates the pain of labor until late in the first stage (i.e., more than 8 cm cervical dilation) and then requests analgesia. Advanced labor does not preclude initiation of neuraxial analgesia, especially in a nulliparous woman, in whom the second stage of labor may last 2 to 3 hours. However, initiation of lumbar epidural analgesia in the late first stage of labor often results in inadequate sacral analgesia unless large volumes of a concentrated local anesthetic solution are administered. This leads to higher cephalad sensory blockade than necessary and dense motor blockade. Another option is to administer CSE analgesia. The advantages of this technique are that it provides a rapid onset of spinal analgesia with sacral coverage for advanced labor and that it includes the placement of an epidural catheter. Additional local anesthetic can be administered through the epidural catheter if the extent or duration of spinal analgesia is inadequate.

Single-shot spinal anesthesia for vaginal delivery may be indicated in a parturient who does not have epidural anesthesia and who requires perineal anesthesia. A so-called saddle block can be administered to achieve blockade of the sacral spinal segments; a small dose of a hyperbaric local anesthetic solution is adequate for this purpose. A saddle block may be advantageous in the patient with a preterm fetus or a vaginal breech presentation. In these cases, dense perineal relaxation may facilitate an atraumatic vaginal delivery. A saddle block performed with the patient in the sitting position with hyperbaric local anesthetic solution provides excellent anesthesia for an outlet/low forceps delivery. A higher level (T10) of anesthesia often is required for a mid-forceps delivery.

Clear communication between the obstetrician and anesthesia provider is essential. If the obstetrician is certain that the application of forceps (or vacuum extraction) will result

<table>
<thead>
<tr>
<th>BOX 23.5 Criteria for Ambulation during Labor with Neuraxial Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reassuring fetal status</td>
</tr>
<tr>
<td>• Engagement of fetal presenting part</td>
</tr>
<tr>
<td>• Stable orthostatic vital signs (asymptomatic and within 10% of baseline)</td>
</tr>
<tr>
<td>• Ability to perform bilateral straight-leg raises in bed against resistance</td>
</tr>
<tr>
<td>• Ability to step up on a step stool with either leg taking the first step, without assistance</td>
</tr>
<tr>
<td>• Satisfactory trial of walking accompanied by a nurse or midwife</td>
</tr>
<tr>
<td>• Patient must be accompanied by a companion at all times</td>
</tr>
<tr>
<td>• Intermittent fetal heart rate monitoring (every 15 minutes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BOX 23.6 Anesthesia for Vaginal Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar Epidural Catheter</strong></td>
</tr>
<tr>
<td>• Supplement existing analgesia with 5 to 10 mL of 1% or 2% lidocaine or with 5 to 10 mL of 2% or 3% 2-chloroprocaine.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Spinal Anesthesia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intrathecal injection of hyperbaric bupivacaine 6 to 8 mg or hyperbaric lidocaine 25 to 50 mg.</td>
</tr>
<tr>
<td>• Administer a larger dose for a “trial of forceps” in case cesarean delivery is necessary.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Combined Spinal-Epidural Anesthesia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intrathecal injection of bupivacaine 2.5 to 5 mg with fentanyl 15 to 25 µg.</td>
</tr>
<tr>
<td>• Follow with administration of additional drug(s) via epidural catheter if anesthesia is inadequate.</td>
</tr>
</tbody>
</table>

**ANALGESIA/ANESTHESIA FOR VAGINAL DELIVERY**

During the second stage of labor, pain results from distention of the pelvic floor, vagina, and perineum. Pain impulses are transmitted to the spinal cord by means of somatic nerve fibers that enter the cord at S2 to S4. These somatic nerve fibers are larger than the visceral afferent nerve fibers that transmit the pain of the first stage of labor. Blockade of these larger nerve fibers may require administration of a more concentrated solution and/or a greater volume of local anesthetic than is required during the first stage of labor; this need often creates a dilemma for the anesthesia provider. Administration of a more concentrated solution of local anesthetic results in more intense motor blockade at a time when maternal expulsive efforts are helpful.

The continuous epidural infusion of bupivacaine often leads to the gradual development of sacral analgesia. Likewise, several lumbar epidural injections of local anesthetic (given every 60 to 90 minutes) may result in sacral analgesia. If analgesia is not adequate for the second stage of labor and delivery, the anesthesia provider can give additional doses of local anesthetic to augment perineal analgesia (Box 23.6). Some anesthesia providers contend that the use of the sitting position helps facilitate the onset of perineal analgesia. Published studies suggest that maternal position does not consistently affect the spread of local anesthetic in the epidural space; rather, the administration of a larger volume of local anesthetic solution facilitates the onset of sacral analgesia. Unfortunately, the larger volume also results in a higher (i.e., more cephalad) sensory level of analgesia, so the patient should be observed for evidence of hemodynamic or respiratory compromise.

Dense anesthesia is often required for delivery, especially if the obstetrician performs an episiotomy or a forceps or vacuum-extraction delivery. After administration of a test dose (3 mL of the local anesthetic solution), at our institution my colleagues and I administer 5 to 10 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine. We inject this “delivery dose” when the fetal head is visible on the perineum during pushing or when the obstetrician has decided to proceed with instrumental vaginal delivery. The anesthesia provider should monitor the maternal blood pressure carefully, especially if excessive blood loss occurs in a patient with extensive anesthetic.

Occasionally, a parturient tolerates the pain of labor until late in the first stage (i.e., more than 8 cm cervical dilation) and then requests analgesia. Advanced labor does not preclude initiation of neuraxial analgesia, especially in a nulliparous woman, in whom the second stage of labor may last 2 to 3 hours. However, initiation of lumbar epidural analgesia in the late first stage of labor often results in inadequate sacral analgesia unless large volumes of a concentrated local anesthetic solution are administered. This leads to higher cephalad sensory blockade than necessary and dense motor blockade. Another option is to administer CSE analgesia. The advantages of this technique are that it provides a rapid onset of spinal analgesia with sacral coverage for advanced labor and that it includes the placement of an epidural catheter. Additional local anesthetic can be administered through the epidural catheter if the extent or duration of spinal analgesia is inadequate.

Single-shot spinal anesthesia for vaginal delivery may be indicated in a parturient who does not have epidural anesthesia and who requires perineal anesthesia. A so-called saddle block can be administered to achieve blockade of the sacral spinal segments; a small dose of a hyperbaric local anesthetic solution is adequate for this purpose. A saddle block may be advantageous in the patient with a preterm fetus or a vaginal breech presentation. In these cases, dense perineal relaxation may facilitate an atraumatic vaginal delivery. A saddle block performed with the patient in the sitting position with hyperbaric local anesthetic solution provides excellent anesthesia for an outlet/low forceps delivery. A higher level (T10) of anesthesia often is required for a mid-forceps delivery.

Clear communication between the obstetrician and anesthesia provider is essential. If the obstetrician is certain that the application of forceps (or vacuum extraction) will result
in a successful delivery, a saddle block will likely provide satisfactory anesthesia. However, in some cases, the obstetrician will perform a trial of forces. If the trial fails, cesarean delivery must follow. We alter our technique when giving spinal anesthesia for a trial of forces. In some cases, we give a dose of local anesthetic appropriate for cesarean delivery. Alternatively, a saddle block can be administered via the CSE technique. If spinal anesthesia is inadequate for the planned procedure, additional local anesthetic can be given through the epidural catheter.

### SIDE EFFECTS OF NEURAXIAL ANALGESIA

#### Hypotension

Neuraxial anesthesia–induced sympathetic blockade leads to peripheral vasodilation and increased venous capacitance. Hypotension that occurs after extensive neuroblockade primarily reflects decreased systemic vascular resistance.\(^{286}\) Hypotension is often defined as a 20% to 30% decrease in systolic blood pressure (compared with baseline) or a systolic blood pressure less than 100 mm Hg. Modest hypotension rarely has adverse consequences in young, nonpregnant patients. However, placental circulation has limited autoregulation; thus, maintenance of uteroplacental perfusion largely depends on maintenance of maternal blood pressure (see Chapter 3). Uncorrected hypotension results in decreased uteroplacental perfusion. If hypotension is severe and prolonged, hypoxia and acidosis will develop in the fetus. Blood pressure should be monitored frequently (every 2 to 3 minutes) after initiation of analgesia, until stable blood pressure is ascertained.

The incidence of hypotension after initiation of neuraxial analgesia during labor is approximately 14%.\(^{281}\) Kinsella and Black\(^{281}\) reported that maternal position and the position of the blood pressure cuff markedly influence the measured blood pressure. With laboring patients in the full lateral position, the mean difference in systolic blood pressure between the dependent and upper arm was 10 mm Hg; the mean difference in diastolic pressure was 14 mm Hg. Therefore, the incidence of hypotension may vary with the position of both the patient and the blood pressure cuff.

A meta-analysis of studies comparing low-dose epidural analgesia with CSE analgesia found no difference in the incidence of hypotension between the two techniques.\(^{284}\)

The prevention of hypotension includes avoidance of aortocaval compression. Preston et al.\(^{282}\) noted a higher incidence of severe FHR decelerations in women placed in the supine-lateral tilt position than in those in the full lateral position after initiation of epidural analgesia. In contrast, Beilin et al.\(^{283}\) found no difference in maternal blood pressure and FHR decelerations between the two positions.

Traditionally, intravenous “preload” (also known as “prehydration”) with 0.5 to 1.5 L of crystalloid solution was used to reduce the incidence and severity of hypotension after the initiation of neuraxial labor analgesia. However, several randomized controlled trials have shown that the incidence of hypotension after preload with 0.5 to 1.0 L of fluid is no lower than that after no preload.\(^{35,39}\) In women undergoing spinal anesthesia for cesarean delivery, there is no difference in the incidence of hypotension when crystalloid is administered as a rapid bolus before the initiation of neuroblockade (preload) compared with administration concurrently with the initiation of anesthesia (co-load).\(^{40}\) Data are inconsistent as to whether a fluid bolus decreases the risk for nonreassuring FHR changes associated with the initiation of neuraxial analgesia (see earlier discussion). Many anesthesia providers omit a fluid bolus. In our practice, my colleagues and I usually administer approximately 500 mL of intravenous crystalloid (co-load) at the time of initiation of neuraxial labor analgesia.

The hypotension associated with neuraxial analgesia is usually easily treated. Treatment includes the administration of additional intravenous crystalloid, placement of the mother in the full lateral and Trendelenburg position, and administration of an intravenous vasopressor. Traditionally, ephedrine 5 to 10 mg has been administered; however, studies in women undergoing spinal anesthesia for elective cesarean delivery have shown that phenylephrine is equally efficacious in restoring blood pressure and is associated with higher umbilical arterial blood pH measurements at birth.\(^{284}\) No differences in neonatal outcome have been noted. Because there is no evidence that the choice of vasopressor influences maternal or neonatal outcome, the use of either drug is acceptable. The FHR should be monitored continuously, and treatment should be more aggressive if nonreassuring FHR patterns are noted or if the mother is symptomatic (e.g., presence of presyncope or nausea). Ephedrine crosses the placenta and may increase both FHR and FHR variability (e.g., saltatory FHR pattern).\(^{285,286}\)

Data are conflicting as to whether there is a dose-response relationship between hypotension and intrathecal local anesthetics when these drugs are administered in low doses for labor analgesia. Palmer et al.\(^{287}\) found no difference in blood pressure in women randomly assigned to receive intrathecal fentanyl combined with either 1.25 or 2.5 mg of bupivacaine. In contrast, Lee et al.\(^{288}\) noted a greater decrease in blood pressure at 10 minutes in women who received bupivacaine 2.5 mg than in women who received 1.25 mg. Because 1.25 mg is less than the ED\(_{50}\) for bupivacaine (when combined with fentanyl),\(^{289}\) and there is no apparent advantage to combining bupivacaine 1.25 mg with fentanyl over using fentanyl alone,\(^{289}\) there is little reason to manipulate the dose of intrathecal bupivacaine with the goal of decreasing the incidence and severity of hypotension when low doses are used for labor analgesia.

#### Pruritus

Pruritus is the most common side effect of epidural or intrathecal opioid administration (see Chapter 13).\(^{290}\) Intrathecal opioid administration is associated with a higher incidence and severity of pruritus than epidural opioid administration.\(^{291}\) The incidence of pruritus after intrathecal opioid administration is close to 100% in some studies, although the need for treatment is much lower.\(^{168}\) The incidence and
severity of pruritus are dose dependent for both epidural and spinal opioid administration. The co-administration of local anesthetic decreases the incidence of pruritus, whereas the co-administration of epinephrine may worsen pruritus.

The cause of the neuraxial opioid-induced pruritus is poorly understood, but it appears to be unrelated to histamine release. The pruritus appears to be mediated through central μ-opioid receptors, given that μ-opioid receptor antagonists relieve itching. The pruritus may be caused by a perturbation of sensory input that results from rostral spread of the opioid within the CSF to the level of the trigeminal nucleus in the medullary dorsal horn. A disruption of sensory modulation is consistent with the observation that a similar pattern of pruritus is seen in medical conditions in which sensory modulation is disturbed (e.g., diabetic neuropathy, multiple sclerosis).

Few studies have addressed the treatment of established pruritus (see Chapter 27). Most studies have addressed pruritus after intrathecal morphine, not lipid-soluble opioids such as fentanyl and sufentanil. The most effective treatment is a centrally acting μ-opioid receptor agonist (e.g., naloxone or naltraxone) or a partial agonist-antagonist such as nalbuphine (Table 23.8). However, the use of these agents in a bolus or continuous infusion may reverse the analgesia. Antihistamines (e.g., diphenhydramine), low-dose propofol, 5-HT3 receptor antagonists (e.g., ondansetron), and pentazocine (a κ-opioid and partial μ-opioid receptor agonist) have been studied for the treatment of pruritus after spinal morphine, but not the lipid-soluble opioids fentanyl and sufentanil that are commonly used for neuraxial labor analgesia. Results of published studies are inconsistent.

A number of drugs have been investigated for prophylaxis against neuraxial opioid-induced pruritus, primarily coincident with neuraxial morphine administration. A 2016 meta-analysis included six randomized controlled trials of prophylactic ondansetron for prevention of intrathecal fentanyl or sufentanil-induced pruritus in both obstetric and nonobstetric patients. Ondansetron 8 mg did not decrease the incidence of pruritus, although there was a trend for decreased need for rescue treatment. However, a single trial in obstetric patients who received ondansetron 4 mg or 8 mg before intrathecal fentanyl 25 μg found no benefit compared with placebo.

We do not routinely administer prophylaxis for the pruritus associated with neuraxial administration of opioids for labor analgesia. The pruritus is typically self-limiting; the severity of pruritus usually diminishes markedly in the first hour after opioid administration, and most women do not require treatment. For moderate to severe pruritus that requires treatment, we usually administer nalbuphine 2.5 mg and repeat the dose in 10 to 15 minutes if no improvement is noted. The advantage of nalbuphine is that it is less likely to reverse the intrathecal or epidural opioid analgesia.

### Table 23.8 Treatments of Neuraxial Opioid-Induced Pruritus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Naloxone</td>
<td>40–80 μg intravenous bolus</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>2.5–5 mg intravenous bolus</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>6 mg orally</td>
</tr>
</tbody>
</table>

### Nausea and Vomiting

Nausea and vomiting occur frequently during labor. It is difficult to determine the incidence of nausea and vomiting directly related to epidural and intrathecal opioid administration. Nausea and vomiting may also be secondary to neuraxial analgesia–induced hypotension. Maternal blood pressure should be measured when the patient complains of nausea in the presence of neuroblockade. Other causes of nausea and vomiting during labor are pregnancy itself, pain, opioid-induced delay of gastric emptying (see later discussion), and systemic opioids, which are sometimes administered before intrathecal or epidural opioids. In one study, the incidences of nausea (7% versus 44%) and vomiting (2% versus 17%) were significantly lower in women randomly assigned to receive intrathecal fentanyl than in those assigned to receive systemic hydromorphone analgesia in early labor.

The etiology of neuraxial opioid–associated nausea is unclear, but it may be caused by the modulation of afferent input at the area postrema (i.e., the chemoreceptor trigger zone) or at the nucleus of the tractus solitarius, which is a key relay station in the visceral sensory network (see Chapter 13). Of interest, nausea is less common after epidural or intrathecal opioid administration during labor than after the administration of the same drugs for post–cesarean delivery analgesia. Norris et al. noted that women who received epidural or intrathecal opioid analgesia during labor had an incidence of nausea of only 1.0% or 2.4%, respectively.

Although the incidence of nausea is low, treatment should be available. No studies, however, have specifically addressed the treatment of neuraxial analgesia–associated nausea and vomiting during labor. We do not routinely administer prophylactic antiemetics before the administration of neuraxial lipid-soluble opioids for labor analgesia.

### Fever

Both observational and randomized controlled trials have consistently noted a gradual rise in core temperature over several hours in laboring women receiving epidural analgesia that was not observed in women receiving no analgesia, inhaled nitrous oxide, or parenteral opioids. The mean increase in core temperature is typically small (less than 1.0°C); however, women with epidural analgesia are more likely to have clinical fever (usually defined as core temperature greater than or equal to 38°C) than those without epidural analgesia (risk ratio, 3.34; 95% CI, 2.63 to 4.23). The incidence of clinical fever ranges from 20% to 30% in women randomized to receive epidural analgesia compared with 5% to 7% in women in the control groups.
Newer evidence suggests that the slow increase in mean temperature observed in women with epidural analgesia may be an averaging artifact. In a prospective observational study of women with epidural analgesia, Goetzl et al. observed the incidence of fever was 22.2%. The mean temperature increase over 8 hours was 0.72°C, similar to that observed in earlier studies. However, the investigators noted that temperature increased in only a subset of women; the remaining cohort had no temperature increase (Fig. 23.7). In the small subset of women who eventually developed clinical fever, core temperature began to rise within 1 hour of initiation of epidural analgesia. The researchers concluded that most women do not become febrile after epidural analgesia, and therefore it is unlikely that a perturbation in thermoregulation induced by epidural analgesia is the cause of epidural analgesia–associated fever. The mechanism of temperature elevation in some women who receive epidural labor analgesia is incompletely understood but likely reflects a noninfectious inflammatory process. Several lines of evidence support this mechanism. Risk factors for intrapartum fever are similar to factors that are associated with the request for epidural analgesia, including nulliparity, prolonged rupture of membranes, and prolonged labor. Sharma et al. randomized healthy nulliparous women requesting epidural analgesia to receive prophylactic antibiotics or placebo. Fever and placental inflammation were not reduced in women who received antibiotic prophylaxis. In an observational study in women who self-selected the type of analgesia, the histologic diagnosis of placental inflammation was more common in women with epidural analgesia. However, the incidence of maternal fever was not different between women with and without epidural analgesia in the absence of placental inflammation. Additionally, Goetzl et al. noted higher baseline maternal serum levels of interleukin-6 (IL-6), a marker of inflammation, in laboring women who eventually developed fever; final IL-6 levels were directly related to the duration of epidural analgesia. In a subsequent study, women with epidural analgesia randomized to receive maternal methylprednisolone (100 mg) had a lower rate of fever than those who received placebo, again suggesting that a noninfectious inflammatory mechanism is involved.

The technique used to initiate and maintain analgesia has not been shown to influence the risk for “epidural fever.” The incidence of fever does not differ in women who receive epidural compared with CSE analgesia, in early compared with late labor initiation of neuraxial analgesia, bupivacaine epidural analgesia with and without fentanyl, or with delayed initiation of the epidural infusion.

The significance of the temperature changes during labor is unclear. Maternal fever is associated with mode of delivery; the rate of instrumental and cesarean delivery is higher in women with intrapartum fever. Epidural analgesia during labor is associated with more neonatal sepsis evaluations but not with a higher incidence of neonatal sepsis. This link likely exists because the diagnosis of intrapartum chorioamnionitis is based on the presence of fever and usually one or two additional criteria (i.e., maternal leukocytosis, maternal tachycardia, uterine tenderness, foul-smelling amniotic fluid). Because maternal fever from any cause leads to maternal and fetal tachycardia, it may be difficult to differentiate women with actual infection (based on postpartum histologic placental examination) from women with fever associated with epidural analgesia. In the interests of maternal and fetal safety, intrapartum maternal fever typically prompts an intrapartum diagnosis of clinical chorioamnionitis. Revised 2010 guidelines from the U.S. Centers for Disease Control and Prevention stipulate that even well-appearing newborns whose mothers carry the diagnosis of suspected chorioamnionitis should undergo a limited evaluation (complete blood count [CBC] with differential cell count and blood culture) and antibiotic therapy pending the culture results.

Of greater concern is the association between maternal or neonatal fever and serious adverse outcomes (i.e., neonatal seizures and encephalopathy, development of cerebral palsy). Evidence suggests that the mechanism of neonatal brain injury is inflammatory rather than fever per se.
Whether epidural analgesia plays any role in these outcomes requires further research. However, because of the growing evidence that maternal inflammation and infection, which manifest as fever, can be detrimental to the fetal brain, anesthesia providers should not dismiss this apparent physiologic effect as a mere curiosity. When maternal fever occurs, good clinical practice dictates that efforts be made to lower maternal temperature, and identify and treat a presumed maternal infection.

**Shivering**
Several factors, including hormonal factors, likely influence thermoregulatory response during labor and delivery. Shivering is frequently observed during labor and may occur more commonly after epidural analgesia. Panzer et al. performed an observational study of shivering during labor. Before delivery, 18% of women shivered, and 15% of these episodes were associated with normothermia and vasodilation, suggesting a nonthermoregulatory cause of the shivering. After delivery, shivering was observed in 16% of women, and in 28% of them, it was nonthermoregulatory. There was no difference in the incidence of shivering between women who chose epidural (bupivacaine/fentanyl) analgesia and those who chose systemic meperidine analgesia. The addition of an opioid to the local anesthetic solution may affect the shivering response. At least one study has suggested that the epidural administration of epinephrine increases shivering; the etiology of this response is unknown.

**Urinary Retention**
Urinary retention is a troublesome side effect of neuraxial anesthesia/analgesia. The bladder and urethral sphincters receive sympathetic innervation from the low thoracic/high lumbar sympathetic fibers and parasympathetic innervation from sacral fibers. Neuraxial local anesthetics cause urinary retention through blockade of sacral nerve roots. Efferent and afferent nerve traffic via the S2, S3, and S4 nerve roots controls the detrusor muscle (responsible for urine storage and micturition) and internal and external sphincter function. Intrathecal opioids cause dose-dependent suppression of detrusor muscle contractility and decreased urge sensation via inhibition of sacral parasympathetic nervous system outflow. The onset of urinary retention appears to parallel the onset of analgesia.

It is difficult to determine the magnitude of this problem during labor, because parturients often require catheterization for other reasons. Postpartum bladder dysfunction was observed in 14% of women who had a normal spontaneous vaginal delivery and in 38% of women who underwent instrumental vaginal delivery, all without epidural analgesia.

Several observational studies suggest that there is a higher risk for intrapartum and postpartum urinary retention in women who receive epidural labor analgesia than in those who receive nonepidural or no analgesia. Similarly, a meta-analysis of three small randomized controlled trials comparing neuraxial with systemic opioid analgesia, in which urinary retention was reported as a secondary outcome, also identified this association. Whether this higher risk reflects a cause-and-effect relationship or patient selection bias is not clear. Wilson et al. found that women randomized to receive neuraxial labor analgesia with low-concentration bupivacaine with opioid more often retained the ability to void spontaneously than women who received epidural analgesia with 0.25% bupivacaine (approximately 31% versus 11%), which suggests a dose-response relationship.

Any difference in bladder function appears to be short-lived; differences between groups in one study had resolved by postpartum day 1. In two studies, patients were randomly assigned to receive epidural analgesia with or without an opioid; there was no difference between groups in the incidence of intrapartum or postpartum urinary retention.

Parturients should be regularly observed during labor for evidence of bladder distention, especially if they complain of suprapubic pain during contractions. The differential diagnosis of breakthrough pain during neuraxial labor analgesia should include bladder distention. Personal observation suggests that many women can void in the presence of low-dose neuroblockade if placed on a bedpan or escorted to the toilet, even if they do not perceive a full bladder. Inability to void and bladder distention should prompt catheterization to empty the bladder.

**Recrudescence of Herpes Simplex Virus**
The common cold sore or fever blister is a manifestation of the reactivation of latent infection. Reactivation can occur after exposure to ultraviolet light, fever, immunosuppression, or trauma. Prospective randomized studies have demonstrated a higher incidence of postpartum oral herpes simplex virus (HSV) reactivation in women randomly assigned to receive neuraxial (epidural, intrathecal) morphine than among women assigned to receive systemic morphine for post–cesarean delivery analgesia. Case reports have associated intraspinal administration of meperidine and fentanyl with the subsequent recurrence of HSV infection.

In a retrospective survey of data from the University of Washington, the seroprevalence of HSV type 1 among pregnant women in the years 2000 to 2010 was 65.5%; the seroprevalence of HSV type 2 was 16.3%. HSV-1 is typically found in the trigeminal ganglia and causes orofacial lesions, whereas HSV-2 is more commonly found in the lumbar/sacral ganglia. However, either of these viruses can infect any region of the body.

To our knowledge, postcesarean reactivation of HSV infection after neuraxial opioid administration has not resulted in clinically significant maternal or neonatal complications. In addition, we are unaware of any study that has investigated whether epidural or intrathecal opioid administration during labor increases the incidence of recurrent oral HSV infection after vaginal delivery. Therefore, we do not withhold neuraxial opioids during labor in women with a history of oral herpes.

**Delayed Gastric Emptying**
Labor may result in delayed gastric emptying, which may be exacerbated by opioid administration (see Chapter 28).
Intravenous or intramuscular opioid administration results in delayed gastric emptying in laboring women. Studies suggest that epidural fentanyl combined with bupivacaine and administered as part of a continuous epidural infusion does not result in delayed gastric emptying compared with infusion of bupivacaine alone, but, delayed gastric emptying may occur with epidural fentanyl administered as a bolus (50 to 100 µg) or with a prolonged infusion. In another study, intrathecal fentanyl 25 µg resulted in delayed gastric emptying compared with epidural fentanyl 50 µg plus bupivacaine or bupivacaine alone. Delayed gastric emptying may predispose a patient to nausea and vomiting. In addition, it may result in a greater volume of gastric contents, which—in theory—might be problematic in patients who require induction of general anesthesia for emergency cesarean delivery.

### COMPLICATIONS OF NEURAXIAL ANALGESIA

#### Inadequate Analgesia

The reported failure rate for neuraxial analgesia varies according to the definition of “failure.” In survey studies, the rate of epidural catheter replacement has ranged from 5% to 13%. Successful location of the epidural space is not always possible, and satisfactory analgesia does not always occur, even when the epidural space has been identified correctly. Factors such as patient age and weight, the specific technique, the type of epidural catheter, and the skill of the anesthesia provider are associated with the rate of failure of neuraxial analgesia. Failure to provide adequate analgesia not only results in a dissatisfying experience for the patient but also may lead to litigation. The risk for failed anesthesia and the potential need to place a second epidural catheter should be discussed with the patient during the preanesthetic evaluation, before placement of the first epidural catheter.

Pan et al. used quality assurance data to retrospectively assess the failure rate among more than 12,000 neuraxial procedures performed for labor analgesia over a 3-year period (Table 23.9). The overall failure rate of 12% included procedures that resulted in no or inadequate analgesia, unintentional dural puncture with an epidural needle or catheter, intravenous cannulation with the epidural catheter, or replacement of the catheter for any reason. The rate of failed analgesia was significantly lower after CSE than after epidural analgesia (10% versus 14%, respectively; P < .001). In a follow-up study from the same group of investigators, the rate of epidural catheter failure was 6.6% after CSE analgesia and 11.6% after epidural analgesia (P = .001). Other studies have also found a higher epidural catheter failure rate when analgesia is initiated with a traditional epidural approach compared with a CSE technique. Of note, these studies were performed in academic institutions where the neuraxial procedures were performed primarily by trainees. In a randomized trial comparing CSE to epidural analgesia in a large maternity hospital staffed by private practice anesthesiologists, the epidural catheter replacement rate was lower and there was no difference between CSE and epidural analgesia (2% and 1.2% incidence, respectively; 95% CI of difference –3.3% to 1.8%).

Typically, failed analgesia after injection of intrathecal or epidural anesthetics results in no neuroblockade, unilateral block or missed segments, or inadequate density of neuroblockade. Patient complaints of pain should prompt timely evaluation and treatment (Box 23.7). The progress of labor should be assessed, and the patient should be queried as to the nature of the pain. Typically, pain becomes more intense as labor progresses; for example, an epidural block that was

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rate According to Type of Analgesia (%)</th>
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<tbody>
<tr>
<td></td>
<td>EPIDURAL (N = 7849)</td>
</tr>
<tr>
<td>Overall Failure Rate</td>
<td>14</td>
</tr>
<tr>
<td>Initial Catheter Failure</td>
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<tr>
<td>Intraocular catheter</td>
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<tr>
<td>Recognized dural puncturea</td>
<td>1.4</td>
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<tr>
<td>Other Failure</td>
<td></td>
</tr>
<tr>
<td>No cerebrospinal fluid or spinal analgesia</td>
<td>NA</td>
</tr>
<tr>
<td>Inadequate analgesia with epidural catheter</td>
<td>8.4</td>
</tr>
<tr>
<td>Catheter replacement for inadequate analgesiae</td>
<td>7.1</td>
</tr>
<tr>
<td>Multiple replacements of epidural catheter</td>
<td>1.9</td>
</tr>
</tbody>
</table>

NA, not applicable.

aRetrospective audit of all neuraxial analgesic procedures for labor analgesia at a single teaching institution over a 3-year period. Most of the procedures were performed by residents.

bDural puncture with epidural needle or catheter.

cEpidural catheter initially functional but was replaced during the course of labor.

adequate at 4-cm cervical dilation may not be adequate at 8-cm cervical dilation. Expectations and treatment may be different for women in latent versus active or second-stage labor. The bladder should be checked and emptied if distended. The position of the epidural catheter at the skin should be assessed to exclude the possibility of catheter migration out of the epidural space. Inadequate analgesia may also result from migration of the epidural catheter into a vein or movement of the catheter outside the epidural space. Before giving a bolus dose of local anesthetic, the anesthesia provider should give a test dose to exclude intravenous migration of the catheter.

The extent of neuroblockade should be assessed with a cold or sharp stimulus that starts over the lateral thighs (the dermatomal level at which the tip of the epidural catheter is sited) and moves both cephalad and caudad on both sides. Inexperienced anesthesia providers often fail to check for the presence of sacral blockade. In the case of no sensory blockade, the epidural catheter should be replaced. If the extent of neuroblockade is inadequate (in either the cephalad or caudad direction), or if there is unilateral blockade or missed segments, the injection of a large volume (10 to 15 mL) of a dilute local anesthetic solution (e.g., 0.0625% to 0.125% bupivacaine) may result in satisfactory analgesia. An advantage of using a more dilute solution of local anesthetic is the ability to increase the administered volume to ensure adequate spread of analgesia.

Some women appear to have adequate extent of sensory blockade but still complain of pain. These women may require more dense analgesia; a larger dose of local anesthetic (10- to 15-mL bolus of 0.125% bupivacaine or a 5- to 10-mL bolus of 0.25% bupivacaine) often successfully reestablishes analgesia. Alternatively, a lipid-soluble opioid (e.g., fentanyl 50 µg) may be added to the solution. The opioid is especially helpful if the parturient is experiencing back pain because the fetus is in the occiput posterior position. Epidural clonidine (75 µg) may be used to treat breakthrough pain that occurs during/after epidural administration of the standard local anesthetic-opioid solution.

Some anesthesia providers advocate pulling the epidural catheter 1 to 2 cm out of the epidural space before administering the bolus injection. Beilin et al. investigated this practice by randomly assigning women with incomplete analgesia to one of two treatments: (1) immediate injection of 0.25% bupivacaine 5 mL or (2) withdrawal of the (multi-orifice) epidural catheter 1 cm followed by injection of the same dose of bupivacaine. There was no difference in the ability to rescue analgesia between the two treatments (74% versus 77%, respectively).

Although available data are inconsistent, it appears that maternal position has little effect on the development of an asymmetric block after a bolus dose of anesthetic solution into the epidural space. It is likely that the position of the epidural catheter in relation to other epidural space structures (e.g., connective tissue, fatty tissue, blood vessels) affects the spread and quality of analgesia to a greater extent than maternal position. Anatomic barriers (e.g., a longitudinal connective tissue band between the dura and ligamentum flavum) or placement of the catheter tip in the anterior epidural space or paravertebral space may explain some cases of single nerve root, unilateral, or asymmetric blockade. The response to the bolus dose should be assessed in a timely fashion, and the epidural catheter should be replaced (with the patient’s consent) if satisfactory analgesia is not obtained.

### Unintentional Dural Puncture

In a meta-analysis of 13 studies that involved more than 300,000 obstetric patients, Choi et al. determined that the rate of unintentional dural puncture with an epidural needle or catheter was 1.5% (95% CI, 1.5% to 1.5%) (see Chapter 30). Dural puncture may be detected at the time of insertion of the epidural needle or after placement of the catheter. If dural puncture is detected with the epidural needle, the anesthesia provider has two primary options. He or she may elect to remove the needle and place an epidural catheter at another interspace; if CSE analgesia was planned, the intrathecal dose may be injected through the epidural needle before it is removed and re-sited at a different interspace. Alternatively, the anesthesia provider may place a catheter...
in the subarachnoid space and administer continuous spinal analgesia for labor and delivery. This latter technique is particularly advantageous for patients at high risk for repeat dural puncture on a second attempt or in cases in which it may be difficult to enter either the epidural or subarachnoid space successfully at an alternative interspace (e.g., in obese women or in patients with abnormal anatomy of the lumbar spine). It is very important to append a label that clearly identifies the catheter as a spinal catheter to decrease the risk for injecting an epidural dose of local anesthetic into the subarachnoid space. The parturient and all providers on the labor and delivery unit, including nurses, midwives, and other anesthesia providers, must be made aware of the intrathecal catheter, and this information must be communicated during any hand-off of care to another provider. Particular care must be taken if the catheter is used to extend the block for cesarean delivery.

Re-siting the epidural catheter in a different interspace eliminates the problem of mistaking an intrathecal catheter for an epidural catheter. However, local anesthetic or opioid injected through the epidural catheter may pass through the dural puncture site and into the subarachnoid space, resulting in unexpectedly high neuroblockade. This complication is more likely to occur with the bolus injection of local anesthetic than with an epidural infusion of local anesthetic.

If dural puncture is not recognized until CSF is aspirated from the catheter, or if administration of the test dose results in spinal anesthesia, the anesthesia provider has the following two options: (1) replace the epidural catheter at an alternative interspace or (2) provide continuous spinal analgesia through the existing catheter.

### Respiratory Depression

The administration of opioids by any route entails risk for respiratory depression. Factors that affect the risk for respiratory depression after neuraxial opioid administration include the choice and dose of drug and its interaction with systemically administered opioids and other central nervous system depressants (see Chapter 13). The most important factor affecting the onset of respiratory depression is the lipid solubility of the drug. In general, if respiratory depression is going to occur, it will do so within 2 hours of the injection of a lipid-soluble opioid such as fentanyl or sufentanil. When a lipid-soluble opioid gains access to the CSF, it is quickly absorbed by lipophilic body tissues. Subsequent clearance and elimination are similar to those associated with intravenous injection of the same drug. Thus, with spinal or epidural injection of a lipid-soluble opioid, the “time window” for respiratory depression is short. Conversely, with a hydrophilic drug such as morphine, the onset of respiratory depression is delayed. Once a hydrophilic drug such as morphine enters the CSF, it tends to stay in the CSF. Rostral migration and absorption into the respiratory centers occur over several hours, so respiratory depression may not occur until 6 to 12 hours after injection of the drug (see Fig. 13.13).

The dose of opioid is a major determinant of the risk for respiratory depression. Herman et al. observed an increase in end-tidal CO\textsubscript{2} concentration with intrathecal fentanyl doses of 15 µg or higher. The time of maximum end-tidal CO\textsubscript{2} was approximately 30 minutes after the intrathecal injection. A risk factor for respiratory depression is previous parenteral opioid administration. Several reports have implicated prior intravenous opioid administration as a contributing factor to the respiratory arrest that occurred after intrathecal sufentanil 10 µg administration in laboring women. (This dose is higher than the currently recommended intrathecal dose range.) For this reason, we refrain from administering a bolus dose of epidural or spinal opioid to women who have recently received systemic opioid analgesia.

### Intravascular Injection of Local Anesthetic

The incidence of fatal local anesthetic systemic toxicity (LAST) appears to have declined in the past quarter century. In a prospective audit from the United Kingdom of more than 145,000 obstetric epidural procedures, the incidence of intravascular injection was 1 in 5000 (Table 23.10). Bupivacaine 0.75% is no longer used for epidural anesthesia in obstetric patients. In the United States, lidocaine or 2-chloroprocaine is most often used when a high-concentration local anesthetic is required for operative epidural anesthesia, but in other countries bupivacaine 0.5%, levobupivacaine 0.5% and ropivacaine 0.75% are often used; low concentrations of local anesthetic are now routinely used for labor analgesia. Nonetheless, LAST remains a serious potential complication during the administration of epidural anesthesia in obstetric patients.

Intravenous injection of a large dose of local anesthetic causes central nervous system symptoms (e.g., restlessness, dizziness, tinnitus, perioral paresthesia, difficulty speaking, seizures, loss of consciousness) (see Chapter 13). Cardiovascular effects may progress from increased blood pressure (as a result of sympathetic stimulation) to bradycardia, depressed ventricular function, and ventricular tachycardia and fibrillation. The extension of epidural labor analgesia to epidural

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular injection</td>
<td>1:5000</td>
<td>0.020 (0.014–0.029)</td>
</tr>
<tr>
<td>Intrathecal injection</td>
<td>1:2900</td>
<td>0.035 (0.027–0.046)</td>
</tr>
<tr>
<td>Subdural injection</td>
<td>1:4200</td>
<td>0.025 (0.017–0.033)</td>
</tr>
<tr>
<td>High/total spinal anesthesia</td>
<td>1:16,200</td>
<td>0.006 (0.003–0.012)</td>
</tr>
</tbody>
</table>

*Prospective data collection of 145,550 epidural procedures for obstetric patients in 14 maternity units in the South West Thames Region (United Kingdom) over a 17-year period (1987 to 2003).  
anesthesia for intrapartum cesarean delivery may be a particularly vulnerable risk period for LAST.\textsuperscript{556} Bupivacaine cardiotoxicity may be fatal in pregnant women.\textsuperscript{557}

Steps for the management of the unintentional intravascular injection of local anesthetic are listed in Box 23.8. They include treatment of convulsions, supporting oxygenation and ventilation, and initiating advanced cardiac life support, if indicated. Lidocaine should not be administered for the treatment of life-threatening ventricular arrhythmias. Early delivery of the infant should be considered, because it may improve the likelihood of successful resuscitation.

In its 2015 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, the American Heart Association suggested that it may be reasonable to administer lipid emulsion in cases of suspected LAST.\textsuperscript{558} Both the American Society of Regional Anesthesia and Pain Medicine\textsuperscript{559} and the Association of Anaesthetists of Great Britain and Ireland\textsuperscript{560} have incorporated the administration of lipid emulsion into their guidelines for managing LAST. At least one case report described the successful use of lipid emulsion for resuscitation of a parturient who developed LAST after the epidural injection of bupivacaine.\textsuperscript{561}

### High Neuroblockade and Total Spinal Anesthesia

An unexpectedly high level of anesthesia may result in one of several situations. High (or total) spinal blockade may occur after the unintentional and unrecognized injection of local anesthetic (via a needle or catheter) into either the subarachnoid or subdural space during the planned initiation of epidural analgesia/anesthesia. Alternatively, the epidural catheter may migrate into the subarachnoid or subdural space during the course of labor and delivery. Finally, high spinal blockade may result from an overdose of local anesthetic in the epidural space. Crawford\textsuperscript{553} reported 6 cases of high or total spinal anesthesia in a series of nearly 27,000 cases of lumbar epidural anesthesia administered during labor (an incidence of approximately 1 in 4500). Paech et al.\textsuperscript{559} reported 8 cases of unexpectedly high neuroblockade in a series of 10,995 epidural blocks in obstetric patients (an incidence of approximately 1 in 1400). Two patients required tracheal intubation and mechanical ventilation. Jenkins\textsuperscript{562} reported an incidence of 1 in 16,200 procedures (see Table 23.10). High spinal or epidural anesthesia contributed to 16% of anesthesia-related maternal deaths in the United States between 1997 and 2002.\textsuperscript{10}

Aspiration alone, particularly through a single-orifice catheter, is a not completely reliable method of excluding subarachnoid placement of the catheter. Administration of an appropriate test dose and careful assessment of the patient’s response to the test dose should minimize the chance of unintentional injection of a large dose of local anesthetic into the subarachnoid space.

High or total spinal anesthesia results in agitation, profound hypotension, dyspnea, the inability to speak, and loss of consciousness. Loss of consciousness usually results from hypoperfusion of the brain and brainstem, not from brain anesthesia. Evidence of spinal anesthesia may be apparent shortly after intrathecal injection of a local anesthetic, but the maximal spread may not be evident for several minutes. This delay underscores the need for the anesthesia provider to carefully assess the effects of both the test and therapeutic doses of local anesthetic. If total spinal anesthesia should occur, the anesthesia provider must be prepared to maintain oxygenation, ventilation, and circulation (Box 23.9). Immediate management consists of avoidance of aortocaval compression, ventilation with 100% oxygen, tracheal intubation, and administration of intravenous fluids and vasopressors to support the blood pressure as needed. The FHR should be monitored continuously.

Extensive neuroblockade may also result from subdural injection of a local anesthetic.\textsuperscript{563–565} A subdural injection may be difficult to diagnose because onset is later than that with an intrathecal injection and more closely resembles that associated with epidural neuroblockade.

The subdural space is a potential space between the dura mater and the arachnoid mater. A retrospective review of 2182 lumbar epidural injections for pain management found

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**BOX 23.8 Management of Local Anesthetic Systemic Toxicity**

- Stop injecting local anesthetic.
- Call for help.
- Position patient with left uterine displacement.
- Prepare for emergency delivery. Consider delivery of the infant if the mother is not resuscitated within several minutes because this may facilitate successful resuscitation of the mother.
- Consider 20% intravenous lipid emulsion administration at the first sign of LAST.\textsuperscript{9}
  - Bolus dose: 1.5 mL/kg over 2-3 min (approximately 100 mL)
  - Infusion: 200-250 mL over 15-20 min
  - Repeat bolus dose once or twice for persistent cardiovascular collapse.
  - Recommended maximum dose: 12 mL/kg
  - Administer 100% oxygen to maintain maternal oxygenation.
  - Use positive-pressure ventilation if necessary. Tracheal intubation will facilitate support of ventilation and help protect the airway, but do not delay administration of oxygen to intubate the trachea.
  - Stop the seizure with a benzodiazepine. Be aware that hypoxemia and acidosis develop rapidly during a seizure.
  - Alert the nearest facility capable of cardiopulmonary bypass.
  - Monitor maternal vital signs and fetal heart rate.
  - Support maternal blood pressure with fluids and vasopressors.
  - Initiate advanced cardiac life support if necessary, including modifications for pregnancy (see Chapter 54).
  - Avoid vasopressin, calcium entry-blocking agents, beta-adrenergic receptor antagonists, and local anesthetics.\textsuperscript{9}
  - Reduce individual epinephrine doses to less than 1 µg/kg.\textsuperscript{9}

Last, Local anesthetic systemic toxicity.

that clinical signs of subdural catheter placement occurred in approximately 0.82% of patients; the true incidence is not known, but may be as high as 10%. Subdural injection of local anesthetic typically results in unexpectedly high (but patchy) blockade with an onset time that is intermediate between that of spinal anesthesia and epidural anesthesia (i.e., 10 to 20 minutes) (Table 23.11). Cranial spread is more extensive than caudal spread of the local anesthetic, so sacral analgesia typically is absent. The block may involve the cranial nerves. (The subdural space, unlike the epidural space, extends intracranially.) Thus, apnea and unconsciousness can occur during a subdural block. Horner’s syndrome has been reported. A subdural block usually results in less intense motor blockade than the blockade that occurs with high or total spinal anesthesia. This difference may reflect the limited spread of the local anesthetic within the subdural space, which helps spare the anterior motor fibers. Subdural block results in less severe hypotension than that with high or total spinal anesthesia, most likely because subdural injection leads to less sympathetic blockade than spinal anesthesia. The unpredictable spread of local anesthetic, the slower onset of maximal spread (in comparison with spinal anesthesia), the patchy nature of the block, and the sacral sparing make it difficult to use a subdural catheter safely during labor and delivery. If it is suspected that a catheter is positioned within the subdural space, it should be replaced with an epidural catheter.

Unexpectedly high neuroblockade may result from the migration of an epidural catheter into the subdural or subarachnoid space. The mechanism by which a soft epidural catheter penetrates the dura or dura-arachnoid is unclear. Disposable epidural needles are sharp, and insertion of the needle into the epidural space may result in an unrecognized nick in the dura, which may create a site for delayed migration of the catheter into the subdural or subarachnoid space. Subdural or subarachnoid injection of local anesthetic also may occur if a multi-orifice catheter is used, and one orifice is located within the epidural space while another is located within the subdural or subarachnoid space. In this situation, the force of injection determines the ultimate destination of the local anesthetic. Thus, each bolus injection of local anesthetic should serve as a test dose. During the continuous infusion of a local anesthetic, a gradual increase in the level of anesthesia and intensity of motor blockade may indicate the intrathecal infusion of the local anesthetic solution.

**Extensive Motor Blockade**

Clinically significant motor block may occur after repeated bolus doses or after many hours of a continuous infusion of local anesthetic into the epidural space. The administration of bupivacaine with epinephrine may result in a greater likelihood of motor blockade than the administration of bupivacaine alone. Extensive motor blockade is often bothersome for the patient, and it may impair maternal expulsive efforts during the second stage of labor and increase the likelihood of instrumental vaginal delivery (see later discussion). Some obstetricians argue that pelvic floor relaxation prevents rotation of the fetal head and increases the likelihood of an abnormal position of the vertex at delivery.

If intense motor blockade develops during the continuous epidural infusion of local anesthetic, the infusion can be

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**TABLE 23.11 Clinical Features of Epidural, Subdural, and Spinal Blocks**

<table>
<thead>
<tr>
<th>Onset Time Spread</th>
<th>Epidural Block</th>
<th>Subdural Block</th>
<th>Spinal Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow</td>
<td>As expected</td>
<td>Intermediate</td>
<td>Rapid</td>
</tr>
<tr>
<td>Higher than expected; may extend intracranially, but sacral sparing is common</td>
<td>Intermediate between spinal and epidural, and dependent on the extent of the block</td>
<td>Higher than expected; may extend intracranially, and a sacral block is typically present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nature of Block</th>
<th>Motor Block</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental</td>
<td>Minimal</td>
<td>Less than spinal, and dependent on the extent of the block</td>
</tr>
<tr>
<td>Patchy</td>
<td>Minimal</td>
<td>Dense</td>
</tr>
<tr>
<td>Intermediate between spinal and epidural, and dependent on the extent of the block</td>
<td>Dense</td>
<td>Likely</td>
</tr>
</tbody>
</table>

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**BOX 23.9 Management of High and Total Spinal Anesthesia**

- High spinal anesthesia may occur several minutes after the unintentional intrathecal injection of local anesthetic or as a result of overdose of epidural local anesthetic. Communication with the patient is important. Agitation, dyspnea, difficulty speaking, and profound hypotension may herald the onset of total spinal anesthesia.
- Avoid aortocaval compression.
- Administer 100% oxygen.
- Provide positive-pressure ventilation, preferably through an endotracheal tube.
- Monitor maternal vital signs, electrocardiogram, and fetal heart rate.
- Support maternal circulation with intravenous fluids and vasopressors as needed. Do not hesitate to give epinephrine if needed.
- Maintain verbal communication with the mother, or administer a sedative-hypnotic (after treating any hypotension and hypoxemia) because total spinal anesthesia does not signal brain anesthesia. Patients may lose consciousness and stop breathing because of central nervous system hypoperfusion, not brain anesthesia.

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**TABLE 23.11 Clinical Features of Epidural, Subdural, and Spinal Blocks**

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<td>Dense</td>
<td>Likely</td>
</tr>
</tbody>
</table>
discontinued for a short period (e.g., 30 minutes). Subsequently, the infusion can be restarted at a reduced rate or with a more dilute solution of local anesthetic. Extensive motor blockade does not occur with administration of a very dilute solution of local anesthetic combined with an opioid.

**Prolonged Neuroblockade**

Rarely, the duration of neuraxial analgesia/anesthesia exceeds the time expected. Most cases of unexpectedly prolonged neuroblockade follow the epidural administration of a high concentration of local anesthetic with epinephrine. Abnormal neurologic findings after the administration of neuraxial anesthesia should prompt the anesthesia provider to look for evidence of peripheral nerve injury or an epidural hematoma (see Chapter 31). Factors that argue against the presence of an epidural hematoma include (1) the absence of back pain, (2) a unilateral block, and (3) regression (rather than progression) of the symptoms. Peripheral nerve injuries typically result in a neurologic deficit in the distribution of a specific peripheral nerve. Neurologic or neurosurgical consultation and immediate imaging studies should be obtained if there is any question about the etiology of prolonged anesthesia. Avoiding the use of a high concentration of local anesthetic should help minimize the incidence of prolonged neuroblockade during and after labor and vaginal delivery.

**Sensory Changes**

In one of the early studies of intrathecal opioid administration during labor, Cohen et al. observed sensory changes in women who received intrathecal sufentanil. Subsequent studies have demonstrated that these sensory changes do not result from a local anesthetic effect of sufentanil. Sensory changes do not predict the quality or duration of analgesia or the extent of hemodynamic change. Further, intrathecal sufentanil does not cause a sympathectomy. Wang et al. have provided the best explanation for these sensory changes. They showed that intrathecal opioids block the afferent information from A-delta and C fibers to the spinal cord but that efferent nerve impulses are unaffected. These sensory changes can be clinically significant, especially when they extend to the cervical dermatomes. In such cases, patients may feel that they cannot breathe or swallow, a sensation that can be quite distressing. Fortunately, neither intrathecal sufentanil nor fentanyl affects the efferent limb of the nervous system and so does not impair motor function. Affected patients should be reassured that respiratory efforts are not compromised and that these symptoms will subside in 30 to 60 minutes.

In addition to sensory changes, case reports have described mental status changes, aphasia, and automatisms after the intrathecal injection of fentanyl and sufentanil. These symptoms seem to be related to an opioid effect. In one case, the symptoms were partially reversed by naloxone.

**Back Pain**

Approximately 50% of women complain of back pain during pregnancy and the puerperium. The most significant risk factors for postpartum back pain are antepartum back pain and inability to reduce weight to prepregnancy levels. Early retrospective studies identified an association between epidural anesthesia and an increased risk for postpartum back pain. However, retrospective studies suffer not only from patient recall bias (i.e., patients with a problem are much more likely to complete and return the questionnaire) but also from selection bias in the epidural and nonepidural groups. Patients who select epidural analgesia for labor may have obstetric, orthopedic, social, or other unidentified factors that predispose them to postpartum back pain.

In an attempt to assess anesthetic factors that might contribute to postpartum backache (e.g., motor blockade), Russell et al. randomly assigned laboring women requesting epidural analgesia to receive either bupivacaine alone or bupivacaine plus an opioid. Despite the expected differences in motor blockade, the incidence of backache did not differ between the two anesthetic groups (bupivacaine alone, 39%; bupivacaine plus an opioid, 30%). In addition, the incidence of backache in both epidural groups was similar to that found in a nonrandomized control group of women who labored without epidural analgesia (31%).

Prospective reports have not shown a significant relationship between the use of epidural analgesia and long-term backache. Breen et al. observed no difference in the incidence of postpartum backache among women who delivered vaginally with or without epidural analgesia. A prospective Canadian study assessed the relationship between postpartum backache and patient-selected intrapartum analgesia. The rate of low back pain was greater in the epidural group (53%) than in the nonepidural group (43%) on the first postpartum day, but the rates were similar on postpartum day 7 and at 6 weeks and 1 year. These investigators suggested that the higher incidence of backache immediately after delivery may have resulted from tissue trauma during epidural needle placement. Finally, Loughnan et al. enrolled 310 women in a randomized controlled trial that compared epidural bupivacaine with systemic meperidine analgesia. The primary outcome was back pain 6 months after delivery. There was no difference between the two groups in the incidence of backache (epidural 48%, meperidine 50%). Similarly, another randomized controlled trial of epidural versus nonepidural analgesia found no difference in the incidence of backache at 3 and 12 months and several years after delivery.

In summary, prospective studies have consistently shown that no causal relationship exists between epidural analgesia and the development of long-term postpartum backache. Short-term backache (several days) may be related to local tissue trauma at the site of skin puncture.

**Pelvic Floor Injury**

Several studies have evaluated the possible effects of epidural analgesia on postpartum pelvic floor function. Retrospective studies have not identified an association between epidural analgesia and risk for perineal lacerations or pelvic floor dysfunction. For example, Loewenberg-Weisband et al. identified severe perineal trauma in 0.3% of 61,308 women in
a retrospective cohort trial. Epidural analgesia was not associated with an increased odds of perineal trauma (OR, 0.95; 95% CI, 0.69 to 1.29) after correcting for parity. A meta-analysis of epidural labor analgesia compared with nonepidural or no analgesia did not identify a difference in the risk for perineal trauma requiring suturing.5

Any factor that increases the likelihood of instrumental vaginal delivery might be expected to increase the risk for pelvic floor injury and subsequent pelvic floor dysfunction (see later discussion). However, to our knowledge, there is no evidence that epidural analgesia per se predisposes to pelvic floor injury.

**EFFECTS OF NEURAXIAL ANALGESIA ON THE PROGRESS OF LABOR**

Neuraxial analgesia during labor is associated with a prolonged labor and operative delivery. (The term *operative delivery* refers to both cesarean delivery and instrumental vaginal delivery [i.e., forceps delivery or vacuum extraction].) Controversy exists as to whether there is a cause-and-effect relationship between the use of these analgesic techniques and prolonged labor or operative delivery. The understanding of this subject has been limited by the difficulty of performing controlled trials in which parturients are randomly assigned to neuraxial analgesia or a control group. Ideally, if one wants to study the effect of neuraxial analgesia on the progress and outcome of labor, the control group would receive no analgesia. However, such a study is not ethical, and even if it were and women volunteered to participate in it, the crossover rate would probably be high and the data consequently would not be interpretable. Therefore, controlled trials have randomly assigned parturients to receive neuraxial analgesia or an alternative form of pain relief, usually systemic opioid analgesia. However, even when the control group receives some type of analgesia, the crossover rate may be high because the quality of neuraxial analgesia is markedly superior to that of all other modes of labor analgesia.388

The difficulty in performing and interpreting the results of labor analgesia trials was aptly described by Noble et al.,389 who assessed obstetric outcome in 245 patients randomly assigned to receive either epidural analgesia or “conventional” analgesia (i.e., meperidine, nitrous oxide, or no analgesia). The investigators made the following comments389:

Of 245 selected patients, 43 had to be removed from the trial after labour ensued….Most of the patients removed from the non-epidural group were apparently experiencing severe pain; they were usually primigravidae whose baby presented in the occipito-posterior position….The majority of patients removed from the epidural group were apparently normal and usually multigravidas; their labours were so rapid it was not possible to arrange for an epidural block.

In other words, patients at low risk for operative delivery were excluded from the epidural group, and patients at high risk were excluded from the nonepidural group. The investigators’ candid comments illustrate that, even when a prospective, randomized study is performed, it is difficult to maintain conditions that allow for the comparison of women at equal risk for abnormal labor and operative delivery.

Another concern is the external validity of these studies. Women who agree to participate in research trials may be inherently different from women who refuse to participate. Many women make a decision regarding labor analgesia well before the onset of labor and are unwilling to let chance randomization determine the type of labor analgesia. Thus, the study results may not be generalizable to the general obstetric population.

Ironically, the effect of systemic opioids on the progress and outcome of labor has not been well studied. Furthermore, there may be differences among the opioids.390 Finally, neuraxial analgesia is not a generic procedure. Conclusions about the effect of one technique on the progress of labor may not be applicable to other techniques (see later discussion).

Additional factors prevent rigorous scientific study of this issue. Ideally, a randomized controlled trial should be double-blinded. This is not possible for studies that compare neuraxial analgesia with another mode of analgesia, because of the marked difference in the quality of analgesia. Therefore, the potential for bias on the part of the parturient, nurses, and anesthesia and obstetric providers is substantial. Additionally, a number of factors are known to affect or to be associated with the progress and outcome of labor, including parity, artificial rupture of membranes, use of oxytocin, and payer status; these factors should be controlled in well-conducted studies.

One factor known to markedly influence the outcome of labor is the obstetric provider. Neuhoff et al.391 retrospectively reviewed the records of 607 nulliparous women at term gestation and compared the mode of delivery in “clinic” patients (whose care was given primarily by residents) and private patients (whose care was provided primarily by private obstetricians). Approximately 42% of patients received epidural analgesia during labor. Five percent of patients in the clinic group and 17% of patients in the private group underwent cesarean delivery (P < .001). More striking was the difference between groups in the incidence of cesarean delivery for dystocia (0.5% versus 13.7%, respectively; P < .001). Similarly, Guillemette and Fraser392 observed marked obstetrician variation in cesarean delivery rates, despite similarities in the use of oxytocin and epidural analgesia.

Several groups of investigators have noted that the timing of cesarean delivery conforms to a “circadian” rhythm.393,394 For example, investigators in Japan noted a delivery time rhythm in hospitals, but not birthing centers, suggesting that obstetric intervention, not biologic rhythm, partly determines the timing of delivery.395

Retrospective studies are difficult to interpret because they suffer from selection bias. In some cases, distinguishing between anesthesia administered for pain relief during labor and anesthesia administered in preparation for operative delivery is difficult. Moreover, women at higher risk for prolonged labor and operative delivery are more likely to
request and receive epidural analgesia during labor than women who have a rapid, uncomplicated labor. Wuitchik et al. observed a relationship between pain and cognitive activity during early labor and the subsequent progress of labor in 115 healthy nulliparous women. During the latent phase, higher levels of pain were predictive of longer latent and active phases of labor. Those women who reported “horrible” or “excruciating” pain during the latent phase were more than twice as likely to require instrumental delivery as women who only had “discomfort.” In addition, women who reported “distress” rather than “coping” had a fivefold higher incidence of abnormal FHR patterns and a fourfold higher requirement for assistance from pediatricians during neonatal resuscitation.

Greater pain intensity during labor appears to be a risk factor for operative delivery. This fact will significantly bias observational studies of labor analgesia because women with greater pain intensity request analgesia, specifically neuraxial analgesia, at a higher rate than women with less intense pain. Alexander et al. performed a secondary analysis of data from a randomized controlled trial in which one group of laboring women received patient-controlled intravenous meperidine analgesia. The rate of cesarean delivery for dystocia was 14% in women who self-administered 50 mg/h or more of meperidine, compared with 1.4% in women who self-administered less than 50 mg/h. In a retrospective study of factors that predict operative delivery in laboring women, Hess et al. found that the cesarean delivery rate in women who had significant breakthrough pain during low-dose bupivacaine/fentanyl epidural analgesia was more than twice as high as the rate in women with less breakthrough pain (odds ratio, 2.62; 95% CI, 2.01 to 3.43).

Taken together, these studies suggest that the early onset of severe pain and the requirement of high doses of analgesic agents predict higher risks for abnormal labor, FHR abnormalities, and operative delivery. These findings may explain the observed association between neuraxial analgesia and operative delivery.

**Cesarean Delivery Rate Randomized Controlled Trials**

A number of randomized controlled trials have studied the effect of neuraxial (primarily epidural) and systemic opioid (primarily meperidine) analgesia on the cesarean delivery rate. These trials differ in a number of ways, including (1) the population studied (e.g., nulliparous women or women of mixed parity); (2) onset of labor (spontaneous labor alone or a mix of spontaneous and induced labors); (3) type of neuraxial analgesia; (4) density of neuraxial analgesia; (5) route of administration of systemic analgesia (although all studies included meperidine with or without an adjuvant); (6) the crossover rate; and (7) management of labor (e.g., active management of labor, including electronic FHR monitoring, artificial rupture of membranes, and oxytocin infusion). All but one of these studies found no difference in the rate of cesarean delivery between women randomly assigned to receive either neuraxial or systemic opioid analgesia.

Four prospective, randomized trials were performed at the University of Texas Southwestern Medical Center, Parkland Hospital, in Dallas. This institution is unique among many others that have performed randomized trials, in that the population is composed largely of indigent women whose labor is managed by the same group of resident physicians and midwives, supervised by the same core group of attending obstetricians. In the first study, 1330 women of mixed parity were randomly assigned to receive either epidural bupivacaine/fentanyl or intravenous meperidine for labor analgesia. Approximately one-third of the women did not receive the assigned treatment. The cesarean delivery rates were 9.0% in women who received epidural analgesia and 3.9% in women who received intravenous meperidine. However, the investigators did not report an intention-to-treat analysis of these data; thus, it was unclear whether there was a higher incidence of cesarean delivery in the women randomly assigned to the epidural analgesia group. Subsequently, the investigators published a re-analysis of the data that included an intention-to-treat analysis (Table 23.12). The cesarean delivery rate in both groups was 6%. These analyses support the conclusion that women who choose epidural analgesia have an inherent risk factor(s) for cesarean delivery and that the administration of neuraxial analgesia per se does not alter this risk.

In an attempt to lower the rate of crossover by providing better analgesia to the control (meperidine) group, the Parkland Hospital investigators performed another study in which meperidine was administered by PCA. A significant number of women in both groups did not receive their assigned treatment, although the reason in all cases was rapid labor. Only 5 of 357 women randomly assigned to the

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**TABLE 23.12**

| Parkland Hospital Randomized Controlled Trial of Epidural Versus Systemic Opioid Analgesia and Rate of Cesarean Delivery: Actual Treatment Versus Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Cesarean Delivery Rate (%)</th>
<th>EPIDURAL ANALGESIA</th>
<th>SYSTEMIC OPIOID ANALGESIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup>In the systemic opioid group, 103 women requested and received epidural analgesia because opioid analgesia was inadequate. The initial analysis was published in 1995. The intention-to-treat analysis of the same data was published in 2000.

<sup>b</sup>The protocol violation rate was 35%.

<sup>c</sup>P < .05 compared with epidural analgesia group.

dural bupivacaine with fentanyl at the second request for protocol. An intention-to-treat analysis showed that there was no difference between groups in the rate of cesarean delivery (CSE 6%, systemic opioid 5.5%).

The studies comparing neuraxial with systemic opioid analgesia have been systematically reviewed in several meta-analyses.3,425 The latest meta-analysis covered outcomes for 8417 women randomized to receive neuraxial or no neuraxial analgesia. The number of women who had a cesarean delivery, the risk ratio, and 95% confidence interval (CI) of the risk ratio (fixed effect model) are shown for each study. For studies with no cesarean deliveries, the risk ratio could not be calculated. Control, nonepidural analgesia. n, number of events (cesarean delivery) in the neuraxial or non-neuraxial group; N, total number of subjects in the neuraxial or non-neuraxial group. The scale is logarithmic. (Modified from Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labor. Cochrane Database Syst Rev. 2011;CD000331.)

Fig. 23.8 Meta-analysis of cesarean delivery rate in women randomized to neuraxial or non-neuraxial labor analgesia. The number of women who had a cesarean delivery, the risk ratio, and 95% confidence interval (CI) of the risk ratio (fixed effect model) are shown for each study. For studies with no cesarean deliveries, the risk ratio could not be calculated. Control, nonepidural analgesia. n, number of events (cesarean delivery) in the neuraxial or non-neuraxial group; N, total number of subjects in the neuraxial or non-neuraxial group. The scale is logarithmic. (Modified from Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labor. Cochrane Database Syst Rev. 2011;CD000331.)

meperidine group crossed over to receive epidural analgesia. Using an intention-to-treat analysis, the investigators observed no difference between the groups in the incidence of cesarean delivery (4% in the epidural group and 5% in the PCIA group). There was no difference between the two groups in neonatal outcome, except that more neonates of women in the PCIA group received naloxone to reverse respiratory depression at birth.

Only one randomized trial has compared CSE and systemic opioid analgesia.404 In this large study (n = 1223), patients of mixed parity were randomly assigned to receive CSE analgesia (intrathecal sufentanil 10 μg, followed by epidural bupivacaine with fentanyl at the second request for analgesia) or intravenous meperidine (50 mg every hour on request). Approximately 60% of patients complied with the protocol. An intention-to-treat analysis showed that there was no difference between groups in the rate of cesarean delivery (CSE 6%, systemic opioid 5.5%).
dose-response effect. The COMET study randomly assigned more than 1000 parturients to one of three groups: (1) “high-dose” epidural analgesia (traditional epidural analgesia with bupivacaine 0.25%); (2) “low-dose” epidural analgesia (bupivacaine 0.1%/fentanyl 2 µg/mL bolus, followed by a continuous epidural infusion); and (3) “low-dose” CSE analgesia (intrathecal bupivacaine/fentanyl followed by intermittent boluses of epidural bupivacaine 0.1%/fentanyl 2 µg/mL).

There was no difference in cesarean delivery rates among groups (Fig. 23.9). Similarly, several other studies that compared traditional epidural analgesia (using bupivacaine 0.25%) and low-dose CSE techniques found no difference between groups in the cesarean delivery rate. The results of these studies suggest that “high-dose” neuraxial analgesia does not entail a higher risk for cesarean delivery than “low-dose” techniques; in other words, no dose-response effect has been observed.

There is no evidence that CSE analgesia influences the mode of delivery, compared with epidural analgesia alone. A meta-analysis that compared CSE with low-dose epidural analgesia included 15 trials with 1960 women; the risk ratio for cesarean delivery was 0.98 (95% CI, 0.82 to 1.16).

Impact Studies

Some physicians have questioned whether prospective, randomized studies provide an accurate representation of the effect of neuraxial analgesia on the mode of delivery in actual clinical practice. They have suggested the possibility that prospective studies may introduce a Hawthorne effect (which may be defined as the appearance or disappearance of a phenomenon on initiation of a study to confirm or exclude its existence). An alternative study design is to assess obstetric outcome immediately before and after a sentinel event, such as the introduction of an epidural analgesia service. The results of these studies may be generalizable to the general population because patients have not chosen to participate in a study. It also eliminates the problem of treatment group crossover because epidural analgesia was not available in the control period. One limitation of this study design is that it assumes that there were no other changes in obstetric management in the “after” period.

In 1999, Yancey et al. published an impact study using data from the Tripler Army Medical Center in Hawaii. Because of relative homogeneity in socioeconomic status, universal access to health care, and the availability of dedicated health care providers in the population served by this hospital, its rate of cesarean delivery may not be subject to influences common to other hospitals. Before 1993, the rate of epidural analgesia was less than 1% at Tripler Army Medical Center. In 1993, a policy change within the U.S. Department of Defense mandated on-demand availability of neuraxial labor analgesia in military hospitals. In nulliparous women in spontaneous labor with a singleton infant with a vertex presentation, the rate of epidural labor analgesia rose from less than 1% to approximately 80% in a 1-year period. The rate of cesarean delivery was unchanged during the same period (14.4% versus 12.1%, respectively; adjusted RR, 0.8; 95% CI, 0.6 to 1.2).

In another impact study, Impey et al. compared obstetric outcome for the first 1000 nulliparous women (term gestation, singleton fetus, cephalic presentation, spontaneous labor) who delivered at the National Maternity Hospital in Dublin in 1987 with the outcome for a similar group of women who delivered in 1992 and 1994. The epidural analgesia rate rose from 10% in 1987 to 45% in 1992 and 57% in 1994. In each of these 3 years, 82% of women underwent spontaneous vaginal delivery. The cesarean delivery rate was 4% in 1987, 5% in 1992, and 4% in 1994 (P = NS) (Fig. 23.10). The investigators concluded that the consistency of the operative delivery rates in each of 3 years with very different epidural rates suggests that epidural analgesia does not increase the cesarean delivery rate.

Socol et al. evaluated the impact of three initiatives to reduce the cesarean delivery rate in their hospital. First, they strongly encouraged a trial of labor and vaginal birth after cesarean delivery. Second, after the 1988 calendar year, they circulated data showing the cesarean delivery rate of every obstetrician to all obstetricians. Third, they recommended the active management of labor as the preferred method of labor management for term nulliparous women. The rates of total, primary, and repeat cesarean deliveries decreased from 27%, 18%, and 9% in 1986 to 17%, 11%, and 6%, respectively, in 1991 (P < .001 for all three comparisons). Meanwhile, the use of epidural analgesia rose from 28% in 1986 to 48% in 1991 (P < .001). There was no change in the incidence

Wassen et al.434 analyzed data from the Netherlands Perinatal Registry from 2000 to 2010. The final study population included more than 1.3 million women; among nulliparous women, the use of epidural analgesia tripled over the 10-year period, while the cesarean delivery rate increased by only 2.8% (the rate of instrumental vaginal delivery decreased by 3.3%). The authors concluded that epidural analgesia is not an important causal factor for operative deliveries.

In a meta-analysis, Segal et al.435 identified nine impact studies involving a total of 37,753 patients. These researchers found no increase in the rate of cesarean delivery with the increase in availability of epidural analgesia (Fig. 23.11). Thus, the before-after impact studies support the results of randomized controlled trials—namely, that neuraxial analgesia does not cause an increase in the cesarean delivery rate.

Several studies have assessed whether there is a relationship between an individual obstetrician’s cesarean delivery rate and the rate of epidural analgesia for his or her patients.436,437 For example, Lagrew and Adashek436 divided obstetricians into two groups according to whether their individual cesarean delivery rates were more than 15% (the control group) or less than 15% (the target group). Obstetricians in the target group used epidural analgesia more often than obstetricians in the control group. In other words, the target group of obstetricians was able to achieve a lower cesarean delivery rate despite their greater use of epidural analgesia.

**Timing of Initiation of Neuraxial Analgesia**

Review of observational data suggests an association between cesarean delivery and the initiation of neuraxial analgesia during early labor (often defined as a cervical dilation less than 4 to 5 cm).422,428,438 For example, in a retrospective study of 1917 nulliparous women, the rate of cesarean delivery was twice as high in women who received neuraxial analgesia at a cervical dilation less than 4 cm than in those in whom neuraxial analgesia was initiated at a cervical dilation of 4 cm or more (18.9% versus 8.9%, respectively).438 As a result of these data, for many years the ACOG suggested that women delay requesting epidural analgesia “when feasible, until the cervix is dilated to 4 to 5 cm.”439 However, as with the cause-and-effect question raised by the association of neuraxial labor analgesia and cesarean delivery, the question arises as to whether the early initiation of neuraxial labor analgesia causes a higher risk for cesarean delivery or whether the request for early labor analgesia is a marker for some other risk factor(s) for cesarean delivery.

A number of randomized controlled trials have addressed the question of whether initiation of neuraxial analgesia during early labor adversely affects the mode of delivery.18-22,440-442 All except one small study440 compared early labor neuraxial analgesia with systemic opioid analgesia, which was followed by neuraxial analgesia when cervical dilation reached 4 to 5 cm (the control group in the Luxman et al.440 study received no analgesia).

Wong et al.,19 and Ohel et al.39 reported randomized trials that compared early labor neuraxial analgesia with systemic opioid analgesia; the median cervical dilation at initiation of analgesia was 2 cm. There was no difference between the two groups in the rate of cesarean delivery or in the rate of instrumental vaginal delivery. The study protocols differed in that the treatment group in one study received CSE analgesia in early labor,19 whereas the treatment group in the second study
replicated these results. The researchers concluded that early initiation of neuraxial analgesia does not increase the rate of cesarean delivery (RR, 1.02; 95% CI, 0.96 to 1.08) (Fig. 23.12).

**Instrumental Vaginal Delivery Rate**

Observational data associate neuraxial labor analgesia with a higher rate of instrumental (forceps or vacuum extraction) vaginal delivery. The effect of neuraxial analgesia on mode of vaginal delivery has not been assessed as a primary outcome in randomized controlled trials, although it has been assessed as a secondary outcome in multiple trials. Interpretation of these results is clouded by the fact that most studies have not assessed the quality of analgesia during the second stage of labor. Further, most investigators did not define the criteria for the performance of instrumental vaginal delivery. In clinical practice, and in study interpretation, it is often difficult to distinguish “indicated” instrumental deliveries from elective instrumental deliveries. Indeed, we have observed that indications for instrumental vaginal delivery vary markedly among obstetricians. An obstetrician is more likely to perform an elective instrumental delivery in a patient with satisfactory anesthesia than in a patient without analgesia. In addition, most randomized controlled trials are conducted in teaching institutions that have an obligation to teach obstetric residents received epidural analgesia alone. The use of oxytocin augmentation was markedly different in the two studies (94% and 29%).

Subsequent to the publication of these studies, the ACOG published an updated Committee Opinion entitled *Analgesia and Cesarean Delivery Rates*. This revised opinion included the following statement:

*Neuraxial analgesia techniques are the most effective and least depressant treatments for labor pain. The American College of Obstetricians and Gynecologists previously recommended that practitioners delay initiating epidural analgesia in nulliparous women until the cervical dilation reached 4-5 cm. However, more recent studies have shown that epidural analgesia does not increase the risks of cesarean delivery. The choice of analgesic technique, agent, and dosage is based on many factors, including patient preference, medical status, and contraindications. The fear of unnecessary cesarean delivery should not influence the method of pain relief that women can choose during labor.*

Later randomized trials in nulliparous women in both spontaneous and induced labor, as well as a 2014 meta-analysis (nine randomized controlled trials; n = 15,752) replicated these results. The researchers concluded that early initiation of neuraxial analgesia does not increase the rate of cesarean delivery (RR, 1.02; 95% CI, 0.96 to 1.08) (Fig. 23.12).
In contrast to these studies, many of the impact studies observed no difference in the instrumental vaginal delivery rate between the control and study periods. For example, despite a rise in the epidural analgesia rate from 1% to almost 80% at Tripler Army Medical Center, the rate of instrumental vaginal delivery did not change (11.1% versus 11.9%). Similarly, despite a more than fivefold increase in the epidural analgesia rate at the National Maternity Hospital in Dublin (see earlier discussion), the instrumental vaginal delivery rate remained unchanged (see Fig. 23.10). A systematic review of seven impact studies involving more than 28,000 patients did not identify a difference in instrumental vaginal delivery rates between periods of low and periods of high epidural analgesia rates (mean change, 0.76%; 95% CI, −1.2 to 2.8).

Studies of early versus late initiation of neuraxial labor analgesia have not identified an increased risk for instrumental vaginal delivery in the early analgesia group. How to perform instrumental vaginal delivery. Instrumental vaginal deliveries performed for the purpose of teaching are more likely to be done in women with adequate analgesia. Multiple randomized, controlled studies comparing epidural analgesia with systemic opioid analgesia have assessed the rate of instrumental vaginal delivery as a secondary outcome variable. Most systematic reviews have concluded that epidural analgesia is associated with a higher risk for instrumental vaginal delivery than systemic analgesia. For example, in a 2011 meta-analysis of 23 studies (n = 7935), the risk ratio for instrumental vaginal delivery in women randomly assigned to receive epidural analgesia or nonepidural/no analgesia was 1.42 (95% CI, 1.28 to 1.57) (Fig. 23.13). Similarly, in the individual patient meta-analysis reported by Sharma et al., the adjusted odds ratio was 1.86 (95% CI, 1.43 to 2.40).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Epidural analgesia</th>
<th>Nonepidural</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bofill 1997</td>
<td>39/49</td>
<td>28/51</td>
<td>1.45 [1.09, 1.93]</td>
</tr>
<tr>
<td>Clark 1998</td>
<td>24/156</td>
<td>20/162</td>
<td>1.25 [0.72, 2.16]</td>
</tr>
<tr>
<td>Dickinson 2002</td>
<td>169/493</td>
<td>148/499</td>
<td>1.16 [0.96, 1.39]</td>
</tr>
<tr>
<td>El-Kerdawy 2010</td>
<td>3/15</td>
<td>0/15</td>
<td>7.00 [0.39, 124.83]</td>
</tr>
<tr>
<td>Evron 2008</td>
<td>3/148</td>
<td>1/44</td>
<td>0.89 [0.10, 8.36]</td>
</tr>
<tr>
<td>Gambling 1998</td>
<td>51/616</td>
<td>34/607</td>
<td>1.48 [0.97, 2.25]</td>
</tr>
<tr>
<td>Grandjean 1979</td>
<td>10/30</td>
<td>12/60</td>
<td>1.67 [0.81, 3.41]</td>
</tr>
<tr>
<td>Halpern 2004</td>
<td>36/124</td>
<td>25/118</td>
<td>1.37 [0.88, 2.14]</td>
</tr>
<tr>
<td>Head 2002</td>
<td>3/56</td>
<td>3/60</td>
<td>1.07 [0.23, 5.09]</td>
</tr>
<tr>
<td>Howell 2001</td>
<td>55/184</td>
<td>36/185</td>
<td>1.54 [1.06, 2.22]</td>
</tr>
<tr>
<td>Jain 2003</td>
<td>12/43</td>
<td>8/83</td>
<td>2.90 [1.28, 6.54]</td>
</tr>
<tr>
<td>Loughnan 2000</td>
<td>88/304</td>
<td>81/310</td>
<td>1.11 [0.86, 1.43]</td>
</tr>
<tr>
<td>Lucas 2001</td>
<td>51/372</td>
<td>27/366</td>
<td>1.86 [1.19, 2.90]</td>
</tr>
<tr>
<td>Muir 1996</td>
<td>0/28</td>
<td>0/22</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>Nafisi 2006</td>
<td>4/197</td>
<td>4/198</td>
<td>1.01 [0.25, 3.96]</td>
</tr>
<tr>
<td>Nikkola 1997</td>
<td>4/10</td>
<td>0/10</td>
<td>9.00 [0.55, 147.95]</td>
</tr>
<tr>
<td>Philipsen 1989</td>
<td>14/57</td>
<td>14/54</td>
<td>0.95 [0.50, 1.80]</td>
</tr>
<tr>
<td>Ramin 1995</td>
<td>41/432</td>
<td>13/437</td>
<td>3.19 [1.73, 5.87]</td>
</tr>
<tr>
<td>Sharma 1997</td>
<td>26/358</td>
<td>15/357</td>
<td>1.73 [0.93, 3.21]</td>
</tr>
<tr>
<td>Sharma 2002</td>
<td>26/226</td>
<td>7/233</td>
<td>3.83 [1.70, 8.64]</td>
</tr>
<tr>
<td>Thalme 1974</td>
<td>6/14</td>
<td>4/14</td>
<td>1.50 [0.54, 4.18]</td>
</tr>
<tr>
<td>Thorp 1993</td>
<td>9/48</td>
<td>5/45</td>
<td>1.69 [0.61, 4.66]</td>
</tr>
<tr>
<td>Volmanen 2008</td>
<td>1/21</td>
<td>4/24</td>
<td>0.29 [0.03, 2.36]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3981</td>
<td>3954</td>
<td>1.42 [1.28, 1.57]</td>
</tr>
</tbody>
</table>

Total events: 675 (Epidural analgesia), 489 (Nonepidural). Heterogeneity: Chi² = 33.55, df = 21 (P = .04); I² = 37%. Test for overall effect: Z = 6.72 (P < .00001). Test for subgroup differences: Not applicable.
Obstetricians and anesthesiologists have suggested that multiple factors (e.g., station and position of the fetal vertex, maternal pain and the urge to bear down, and neuraxial analgesia-induced motor blockade) may contribute to the outcome of the second stage of labor. The contribution of these factors to the mode of vaginal delivery, and their interactions, are not well understood, and these factors have not been well controlled in many studies.

Several studies have specifically assessed the effect of maintenance of neuraxial analgesia until delivery with regard to the duration and outcome of the second stage of labor. In a 2017 study from China, 400 women receiving epidural infusion of 0.08% ropivacaine with sufentanil 0.4 µg/mL for labor analgesia were randomized to continue the same infusion or to receive saline-placebo at the onset of the second stage of labor. The primary outcome—mean (± SD) duration of the second stage of labor—did not differ between groups (epidural group, 52 ± 27 minutes; placebo-control 51 ± 25 minutes), nor did the rate of instrumental vaginal delivery. More women in the placebo-control group had low satisfaction scores.

The effect of neuraxial analgesia on the outcome of the second stage of labor may be influenced by the density of neuraxial analgesia. High concentrations of epidural local anesthetic may cause maternal motor blockade, leading to relaxation of pelvic floor musculature, which in turn may interfere with fetal rotation during descent. Abdominal muscle relaxation may decrease the effectiveness of maternal expulsive efforts. The effects of specific analgesic techniques, concentration of local anesthetic, total dose of local anesthetic, and degree of motor blockade on the risk for instrumental vaginal delivery are overlapping and difficult to study. For example, some studies suggest that administration of epidural analgesia using higher concentrations of bupivacaine is associated with a higher risk for instrumental vaginal delivery compared with use of lower concentrations. In contrast, Collis et al. observed no difference in mode of delivery between women randomly assigned to receive either a high-dose or a low-dose neuraxial technique. The COMET investigators reported a lower rate of instrumental vaginal delivery in the two groups of women randomly assigned to receive either the low-dose epidural or CSE technique than in the group that received 0.25% bupivacaine (see earlier discussion and Fig. 23.9). However, the total bupivacaine dose in the traditional “high-dose” epidural group did not actually differ from that in the “low-dose” epidural group because the former was administered by intermittent injection and the latter by continuous infusion. In contrast, the total bupivacaine dose was significantly lower in the CSE group.

In a meta-analysis of 11 studies (n = 1145) comparing maintenance of epidural analgesia with high-concentration (defined as bupivacaine concentration greater than 0.1% or ropivacaine concentration greater than 0.17%) with low-concentration local anesthesia solutions, the odds of instrumental vaginal delivery were lower in the low-concentration group (OR, 0.70; 95% CI, 0.56 to 0.86), as was the duration of the second stage of labor. The odds of cesarean delivery did not differ. A 2017 meta-analysis compared parturients randomized to low-concentration epidural analgesia with nonepidural or no analgesia (earlier meta-analyses included studies using both high- and low-concentration solutions). There was no difference in the duration of the second stage of labor (mean difference, 5.7 minutes; 95% CI, –6.1 to 17.8) or the rate of instrumental vaginal delivery (RR, 1.52; 95% CI, 0.97 to 2.4), although the confidence intervals are wide. Finally, in a meta-analysis of studies that compared CSE and epidural analgesia, the instrumental vaginal delivery rate was lower in the CSE group than the traditional “high-dose” epidural analgesia group, but there was no difference between “low-dose” epidural and CSE analgesia. Taken together, these data suggest that the specific analgesia technique may influence the risk for instrumental vaginal delivery.

In general, the dose of bupivacaine is significantly lower if epidural analgesia is maintained with an intermittent bolus technique rather than a continuous infusion technique (see earlier discussion). Most investigators have noted a difference in motor blockade between the two techniques; higher total bupivacaine doses (i.e., continuous infusion techniques) are associated with a greater degree of motor blockade. However, the relationship between motor blockade and instrumental vaginal delivery is inconsistent. Smedstad and Morison reported a higher incidence of instrumental vaginal delivery when bupivacaine 0.25% was administered as a continuous epidural infusion than as intermittent bolus injections. In contrast, the COMET investigators observed no difference in the instrumental vaginal delivery rate in the two groups who received “low-dose” bupivacaine/fentanyl, one by infusion and the other by intermittent bolus. Similarly, in a meta-analysis of PCEA (without background infusion) compared with continuous epidural infusion analgesia, the dose of bupivacaine and degree of motor blockade were significantly lower in the PCEA group, but the rates of instrumental vaginal delivery did not differ.

It is possible that the inconsistent results can be explained by the actual absolute differences in bupivacaine dose and motor blockade. For example, the differences in dose and motor blockade may have clinically significant adverse effects on the outcome of the second stage of labor if bupivacaine 0.25% is compared with bupivacaine 0.125% but not if bupivacaine 0.125% is compared with bupivacaine 0.0625%. Many of the randomized controlled trials included in the meta-analysis that compared epidural with systemic opioid analgesia used concentrated solutions of bupivacaine for both the loading and infusion doses (e.g., bupivacaine 0.25% for the loading dose, bupivacaine 0.125% by continuous infusion for maintenance of analgesia).

Motor blockade may increase the risk for malrotation of the fetal vertex. Robinson et al. and Le Ray et al. observed a higher incidence of occiput malposition at delivery in patients who received epidural analgesia before engagement of the fetal head. In contrast, Yancey et al. and Sheiner et al. noted that the administration of on-demand epidural analgesia did not increase the frequency of malposition of the fetal head at delivery; the incidence of instrumental vaginal
delivery was not related to fetal station at initiation of analgesia. In a prospective cohort study using ultrasonography, Lieberman et al. reported that fetal position changed frequently during labor but that epidural analgesia was associated with a higher incidence of occiput posterior position at delivery (13% versus 3%, \( P < .002 \)). However, these results should be interpreted with caution as women were not randomly assigned to the treatment group. Factors that cause women to request analgesia when the fetal head is high may also be independent risk factors for instrumental vaginal delivery. A study from Italy in which ultrasonography was used to assess fetal head position found no association between use of early labor neuraxial analgesia and fetal head position at delivery.

In an editorial, Chestnut concluded that effective second-stage analgesia increases the risk for instrumental vaginal delivery. However, effective analgesia is a spectrum that ranges from complete absence of sensory input (dense analgesia) to perception of uterine contraction “pressure” without pain (less dense analgesia). Minimizing the risk for instrumental vaginal delivery while maximizing analgesia is both an art and a science and requires the attention of the anesthesia provider to the individual needs of the patient. A single analgesic technique or single dose/concentration of drug(s) is not likely to have optimal results for everyone. We believe the best technique for maintenance of analgesia incorporates a low-rate continuous infusion (4 to 8 mL/h) or PIEB, using a dilute solution of local anesthetic and opioid, with PCEA. Use of a dilute local anesthetic solution without PCEA leads to inadequate analgesia for many women. Increasing the infusion dose improves analgesia and reduces the workload for the anesthesia provider but will result in overly dense analgesia for some patients, thus potentially increasing the risk for instrumental vaginal delivery. In the future, new pump technology may allow closed-loop feedback anesthetic administration that will better tailor anesthetic dose to patient need.

Why should anesthesia providers give attention to the effects of analgesia on the method of vaginal delivery? Lack of effective maternal effort associated with inadequate progress of labor (descent of the fetus) is an indication for operative vaginal delivery. Studies suggest that vacuum extraction may be associated with a higher neonatal risk for cephalohematoma, subgaleal hemorrhage, and intraventricular hemorrhage than spontaneous vaginal, forceps, or cesarean delivery, whereas forceps delivery is associated with an increased risk for facial trauma. However, there is some evidence that these injuries may be attributed to the indication for delivery, rather than the specific delivery technique. There is no evidence of adverse long-term neonatal outcome with operative vaginal compared with spontaneous vaginal or cesarean delivery.

The risk for maternal trauma is also greater with operative vaginal delivery (e.g., third- and fourth-degree vaginal lacerations). Robinson et al. observed that epidural analgesia was associated with an increased rate of severe perineal trauma because of the more frequent use of instrumental vaginal delivery and episiotomy in nulliparous women who received epidural analgesia. In contrast, several large observational studies suggest that epidural analgesia is associated with a decreased risk for anal sphincter laceration in nulliparous women. Regardless of the presence or magnitude of the risks for maternal or neonatal injury, many women want to minimize the likelihood of operative delivery, and they perceive that a higher risk for instrumental vaginal delivery is undesirable. Of concern is a decline in the number of obstetricians skilled at operative vaginal delivery. The concern is that loss of these skills will lead to an increase in second-stage cesarean delivery rates.

### Duration of Labor

#### First Stage of Labor

The effect of neuraxial labor analgesia on the duration of the first stage of labor was addressed as a secondary outcome variable in many of the randomized controlled trials. A 2011 meta-analysis of 11 studies found no difference in the duration of the first stage of labor between women who were randomly assigned to receive epidural analgesia and those assigned to receive systemic opioid analgesia, although the confidence interval was wide, indicating significant heterogeneity among studies (Table 23.13). There was significant heterogeneity in the outcome because of the mixed parity of the patient populations and differences among studies in the definition of the duration of the first stage of labor. In contrast,

### TABLE 23.13 Meta-Analyses of Duration of First and Second Stages of Labor

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>First Stage of Labor</th>
<th>Second Stage of Labor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( P ) Value</td>
</tr>
<tr>
<td><strong>NEURAXIAL</strong> ( 95% ) CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anim-Somuah, 2011(^a)</td>
<td>2981(^b)</td>
<td>WMD 19 min (95% CI, –13 to 50)</td>
</tr>
<tr>
<td></td>
<td>4233(^a)</td>
<td>WMD 14 min (95% CI, 7–21)</td>
</tr>
<tr>
<td>Sharma, 2004(^c)</td>
<td>2703</td>
<td>8.1 ± 5 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 ± 56 min</td>
</tr>
</tbody>
</table>

\(^a\)First stage of labor.

\(^b\)Second stage of labor.

the individual meta-analysis of the Parkland Hospital data showed a significant prolongation of the first stage of labor (approximately 30 minutes) in nulliparous women who were randomly assigned to receive epidural analgesia.\textsuperscript{425}

Wong et al.\textsuperscript{19} and Ohel et al.\textsuperscript{33} assessed duration of labor as a secondary outcome in their randomized controlled trials of the initiation of neuraxial analgesia during early labor. Both groups of investigators determined that the duration of the first stage of labor, and thus consequently the overall duration of labor, were significantly shorter in women randomly assigned to receive early labor neuraxial analgesia than in those assigned to receive systemic opioid analgesia. In the Wong et al. study,\textsuperscript{19} the median difference in the overall duration of labor between the early and late neuraxial analgesia groups was 81 minutes (95% CI, 28 to 123).

Determining the duration of labor requires that investigators document start and end times. The definition of the start time varies among studies but is usually consistent between groups within a study. The end of the first stage of labor is defined as the time of full (10 cm) cervical dilation. This point can be determined only with manual cervical examination. Most studies do not mandate regular cervical examinations by study protocol, or if they do, the intervals are fairly long (e.g., 1 to 2 hours). Clinically, full cervical dilation is diagnosed when a cervical examination is performed because the patient complains of rectal pressure. It is likely that women with effective epidural analgesia will complain of rectal pressure at a later time (and lower fetal station) than women with systemic opioid analgesia. In other words, the patient may be fully dilated for a significant time before cervical examination verifies full cervical dilation. This difference serves to artificially prolong the duration of the first stage of labor in the epidural group, although it shortens the apparent duration of the second stage of labor.

Other factors may also influence the duration of the first stage of labor. Some clinicians have noted enhanced uterine activity in some patients for approximately 30 minutes after the initiation of neuraxial analgesia, whereas uterine activity appears to be reduced in other patients. Schellenberg\textsuperscript{466} suggested that aortocaval compression is responsible for the transient decrease in uterine activity that occurs after the administration of epidural analgesia in some patients. Cheek et al.\textsuperscript{467} noted that uterine activity decreased after the intravenous infusion of 1 L of crystalloid solution, but not after infusion of 0.5 L or maintenance fluid alone. Miller et al.\textsuperscript{468} hypothesized that a fluid bolus might inhibit antidiuretic hormone (vasopressin) release from the posterior pituitary gland. Because this organ also releases oxytocin, the production of that hormone might also be transiently suppressed; this possible decrease in oxytocin release may partially explain the transient changes in uterine contractility observed in association with epidural analgesia.

In a prospective but nonrandomized study, Rahm et al.\textsuperscript{469} observed that epidural analgesia (bupivacaine with sufentanil) was associated with lower plasma oxytocin levels at 60 minutes after initiation of analgesia than in healthy controls who did not receive epidural analgesia. Behrens et al.\textsuperscript{470} noted that epidural analgesia during the first stage of labor significantly reduced the release of prostaglandin F\textsubscript{2a} and "impede[d] the normal progressive increase in uterine activity." In contrast, Nielsen et al.\textsuperscript{471} measured upper and lower uterine segment intrauterine pressures for 50 minutes before and after the administration of epidural bupivacaine analgesia in 11 nulliparous women during spontaneous labor. No significant difference in the number of contractions before and after epidural analgesia was observed. There was greater intrauterine pressure in the upper uterine segment than in the lower segment (consistent with fundal dominance) both before and after initiation of epidural analgesia. Further, fundal dominance was higher after epidural analgesia than in the preanalgesia period.

Increased uterine activity after the initiation of neuraxial analgesia has been hypothesized to be an indirect effect of neuraxial analgesia (see later discussion).\textsuperscript{472} Initiation of neuraxial analgesia is associated with an acute decrease in the maternal plasma concentration of circulating epinephrine.\textsuperscript{4} Epinephrine is a tocolytic, and the acute decrease in maternal concentration may result in greater uterine activity. This may be an explanation for the salutary effect on the progress of labor that is observed in some women with dysfunctional labor after the initiation of neuraxial analgesia\textsuperscript{473} or in women who are extremely anxious.\textsuperscript{474}

The epidural administration of a local anesthetic with epinephrine is followed by systemic absorption of both drugs. Some physicians have expressed concern that the epinephrine may exert a systemic beta-adrenergic tocolytic effect and slow labor. Early studies, which used large doses of epinephrine, suggested that the caudal epidural administration of local anesthetic with epinephrine prolonged the first stage of labor and increased the number of patients who required oxytocin augmentation of labor.\textsuperscript{475} Subsequently, most studies have suggested that the addition of epinephrine 1.25 to 5 μg/mL (1:800,000 to 1:200,000) to the local anesthetic solution does not affect the progress of labor or method of delivery.\textsuperscript{469}

There is no evidence that the specific local anesthetic or opioid used for neuraxial analgesia directly or indirectly affects the duration of labor.\textsuperscript{85,477} In a randomized controlled trial, Tsen et al.\textsuperscript{478} observed a higher rate of cervical dilation in women who received CSE analgesia than in those who received epidural analgesia. However, randomized controlled trials that compared CSE and epidural analgesia have not found a difference in the duration of labor between the two techniques.\textsuperscript{434,426–428,479}

Evidence suggests that genetic polymorphism in the oxytocin receptor (OTXR), catechol-O-methyltransferase (COMT), and beta\textsubscript{2}-adrenergic receptor (ADRB2) genes affect the progress of labor.\textsuperscript{480,481} Whether these genotypes interact with neuraxial analgesia to affect the progress of labor requires further study with large numbers of parturients.

In summary, neuraxial analgesia appears to have a variable effect on the duration of the first stage of labor. It may shorten labor in some women and lengthen it in others. However, analgesia-related prolongation of the first stage of labor, if it
occurs, is short, has not been shown to have adverse maternal or neonatal effects, and is probably of minimal clinical significance.

**Second Stage of Labor**

There is little doubt that effective neuraxial analgesia prolongs the second stage of labor. Meta-analyses of randomized controlled trials that compared neuraxial with systemic opioid analgesia support this clinical observation (see Table 23.13). The mean duration of the second stage was 15 to 20 minutes longer in women randomly assigned to receive neuraxial analgesia than in women assigned to receive systemic opioid analgesia. In a retrospective cohort single-institution study of 42,268 women who delivered vaginally between 1979 and 2008, the 95th percentile length of the second stage of labor was 197 minutes (3.2 hours) in nulliparous women without epidural analgesia and 336 minutes (5.6 hours) in nulliparous women with epidural analgesia.

Historically, the ACOG has defined a prolonged second stage in nulliparous women as lasting more than 3 hours with neuraxial analgesia and more than 2 hours without neuraxial analgesia; for parous women, it is more than 2 hours in those with neuraxial analgesia and more than 1 hour in those without neuraxial analgesia. Zhang et al. performed a secondary analysis of data from the Consortium on Safe Labor, a large, multicenter study from 19 hospitals across the United States, to characterize the duration of labor in a contemporary cohort of American women. Data were abstracted for term parturients in spontaneous labor with a singleton gestation in the vertex presentation and with normal perineal status, (2) the mother is well hydrated and has adequate FHR monitoring confirms the absence of nonreassuring fetal status, (3) there is ongoing progress in the descent of the fetal head. In a small study, Gimovsky et al. randomized 78 nulliparous women to an extended care group (allowed at least 3 hours of second stage before facilitating delivery) or usual care group (allowed 2 hours of second stage before expediting delivery). All women received epidural analgesia. The cesarean delivery rate was 19.5% in the extended care group and 43.2% in the usual care group (RR, 0.45; 95% CI, 0.22 to 0.93). The operative vaginal delivery rate did not differ between groups.

A 2012 workshop was convened by the National Institute of Child Health and Human Development, the Society for Maternal-Fetal Medicine, and the ACOG, with the goal of recommending practices that prevent primary cesarean delivery. The group concluded that a cesarean delivery for second-stage arrest in nulliparous women with epidural analgesia should not be considered unless there is no progress (descent or rotation) for more than 4 hours (Box 23.10). Thus, the decision as to whether to perform an operative delivery in the second stage or allow continued observation should be made on the basis of clinical assessment of the woman and the fetus, and the skill and training of the obstetrician.

### BOX 23.10 Definition of Second-Stage Arrest

- **No progress (descent or rotation) for:**
  - Four hours or more in nulliparous women with epidural analgesia
  - Three hours or more in nulliparous women without epidural analgesia
  - Three hours or more in parous women with epidural analgesia
  - Two hours or more in parous women without epidural analgesia


---

**TABLE 23.14 Duration of Second Stage of Labor by Parity**

<table>
<thead>
<tr>
<th>Parity</th>
<th>Duration of Second Stage of Labor (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(n = 25,624)</td>
</tr>
<tr>
<td></td>
<td>Epidural analgesia</td>
</tr>
<tr>
<td></td>
<td>No epidural analgesia</td>
</tr>
<tr>
<td>1</td>
<td>(n = 16,755)</td>
</tr>
<tr>
<td></td>
<td>Epidemi al analgesia</td>
</tr>
<tr>
<td></td>
<td>No epidural analgesia</td>
</tr>
<tr>
<td>≥ 2</td>
<td>(n = 16,219)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity 0</th>
<th>Epidural analgesia</th>
<th>No epidural analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 (3.6)</td>
<td>0.6 (2.8)</td>
<td></td>
</tr>
</tbody>
</table>

Data are median (95th percentile) duration of the second stage of labor in spontaneous laboring women.

Second-stage management: immediate versus “delayed” pushing. Many women are asked to begin “pushing” as soon as full cervical dilation has been confirmed, regardless of the fetal station. Some practitioners have suggested that “delayed” pushing might result in less maternal exhaustion and better maternal and fetal outcomes. Several randomized studies have sought to determine whether immediate or delayed pushing for women with epidural analgesia during the second stage of labor affects labor duration and outcome. Data are conflicting. In a 2017 meta-analysis including 13 studies that compared early and delayed pushing in women with epidural analgesia, the authors judged that the evidence ranged from moderate to very low quality. Delayed pushing resulted in an increase in the rate of spontaneous vaginal delivery (RR, 1.07; 95% CI, 1.03 to 1.12; Fig. 23.14), and shorter duration of pushing at the expense of an increase in the total duration of the second stage of labor (mean difference 56 minutes). There was no difference in perineal trauma, neonatal intensive care unit admissions, or 5-minute Apgar scores. The authors concluded that the current evidence is insufficient and inconclusive to support any specific timing and type of pushing; further high-quality studies are necessary.

Although there do not appear to be any major advantages to delayed pushing, it does not seem reasonable to ask the mother to push from a high fetal station. It is common for anesthesia providers to be asked to decrease or discontinue neuraxial analgesia because the mother does not feel the urge to push when she is fully dilated. However, women with effective neuraxial analgesia do not feel the urge to push at a high fetal station. The density of neuraxial analgesia should not be decreased until the fetus has descended. If evaluation at this point determines that the mother still does not feel the urge to push, the maintenance dose may be reduced. Discontinuing the maintenance of analgesia is rarely indicated because analgesia/anesthesia may be difficult to reestablish if the need for operative delivery arises.

Third Stage
Rosaeg et al. retrospectively reviewed the outcomes of 7468 women who underwent vaginal delivery at their hospital between 1996 and 1999. Epidural analgesia was not associated with a prolonged third stage of labor. The duration of the third stage of labor was shorter in women who received epidural analgesia and subsequently required manual removal of the placenta. The researchers suggested that epidural analgesia

<table>
<thead>
<tr>
<th>Review: Pushing/bearing down methods for the second stage of labor</th>
<th>Comparison: 2 Analysis 2. Comparison 2: timing of pushing: delaying pushing versus immediate pushing (all women with epidural)</th>
<th>Outcome: 8 Spontaneous vaginal delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or subgroup</td>
<td>Delayed pushing</td>
<td>Immediate pushing</td>
</tr>
<tr>
<td>1 Nulliparous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick 2002</td>
<td>46/88</td>
<td>50/90</td>
</tr>
<tr>
<td>Fraser 2000b</td>
<td>769/963</td>
<td>718/926</td>
</tr>
<tr>
<td>Gillesby 2010</td>
<td>30/38</td>
<td>25/39</td>
</tr>
<tr>
<td>Goodfellow 1979</td>
<td>12/21</td>
<td>4/16</td>
</tr>
<tr>
<td>Hansen 2002</td>
<td>48/62</td>
<td>45/67</td>
</tr>
<tr>
<td>Kelly 2010</td>
<td>24/26</td>
<td>29/33</td>
</tr>
<tr>
<td>Maresh 1983</td>
<td>18/36</td>
<td>14/40</td>
</tr>
<tr>
<td>Mayberry 1999</td>
<td>58/81</td>
<td>46/72</td>
</tr>
<tr>
<td>Plunkett 2003</td>
<td>82/117</td>
<td>59/85</td>
</tr>
<tr>
<td>Simpson 2005</td>
<td>11/23</td>
<td>10/22</td>
</tr>
<tr>
<td>Vaus 1998</td>
<td>34/68</td>
<td>32/67</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1496</td>
<td>1457</td>
</tr>
<tr>
<td>Total events: 1132 (Delayed pushing), 1032 (Immediate pushing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 6.76, df = 10 (P = 0.75); I² = 0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.17 (P = 0.0015)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 23.14 Meta-analysis of delayed versus immediate pushing on the rate of spontaneous vaginal delivery in women with epidural analgesia. The size of the box at the point estimate for each study is proportional to the number of patients in the study. The diamond represents the point estimate of the pooled risk ratio, and the length of the diamond is proportional to the confidence interval. n, number of events in the treatment (delayed pushing) or control (immediate pushing) group; N, total number of patients in the treatment or control group. RR, risk ratio; CI, confidence interval. (Modified from Lemos A, Amorim MMR, Dornelas de Andrade A, et al. Pushing/bearing down methods for second stage labor. Cochrane Database Syst Rev. 2017;CD009124.)
“provided a ‘permissive’ role”—in other words, epidural analgesia likely facilitated and/or encouraged earlier intervention by the obstetrician.

Other Factors and Progress of Labor

Oxytocin

**Active management of labor** is a concept that consists of a disciplined, standardized labor management protocol that includes early amniotomy and oxytocin augmentation if the cervix fails to dilate at a minimum rate (usually 1 cm/hour in nulliparous women). Early studies suggested that this type of labor management decreased the rate of cesarean delivery. More recently, a 2013 meta-analysis that included 14 randomized controlled trials suggests that active management of labor may have little effect on the cesarean delivery rate.

Although randomized trials of neuraxial compared with systemic opioid analgesia have consistently found that neuraxial analgesia does not cause an increase in the rate of cesarean delivery (see earlier discussion), Kotaska et al. questioned the external validity of these trials because of oxytocin management. In a search of the medical literature, they identified 16 randomized controlled trials; 8 of the 16 trials included descriptions of labor management, and these trials were included in the analysis. Seven of the eight trials described active management of labor and found no difference in the mode of delivery between groups. Only one of eight trials described the use of low-dose oxytocin and reported a markedly higher rate of cesarean delivery in the neuraxial analgesia group. Kotaska et al. concluded that epidural analgesia in the setting of low-dose oxytocin probably increases the rate of cesarean delivery. The researchers were correct in stating that the role of oxytocin in neuraxial analgesia outcome studies has not been well controlled. However, their conclusion that epidural analgesia in the setting of low-dose oxytocin probably causes an increase in the rate of cesarean delivery is highly flawed because, in their analysis, the researchers did not include the eight studies that did not describe the management of labor. In all probability, the management of labor in these studies was not active (i.e., did not include high-dose oxytocin administration), or this would have been described.

In randomized controlled trials that compared the effects of neuraxial and systemic opioid analgesia on the outcome of labor, women who received neuraxial opioids had a higher rate of oxytocin augmentation. In a meta-analysis that included 13 randomized trials, the risk ratio was 1.19 (95% CI, 1.03 to 1.39). The reason(s) for this observation are not clear.

Randomized controlled trials that compared early and late initiation of neuraxial analgesia have used markedly different oxytocin protocols, yet all have concluded that early initiation of neuraxial analgesia does not have an adverse effect on the outcome of labor. In the study of early CSE analgesia by Wong et al., the rate of oxytocin use was high in both groups (approximately 93%). However, the maximum oxytocin infusion rate in the control (early systemic opioid) group was significantly higher than that in the early CSE group even though the median duration of labor was 81 minutes shorter in the CSE group. In the study of early epidural analgesia by Ohel et al., the rate of oxytocin use in both groups was much lower (approximately 29%); however, in the study by Wong et al., the duration of labor was significantly shorter in the early neuraxial analgesia group. Taken together, the results of these studies do not support the hypothesis that oxytocin played a major role in the outcomes.

**Ambulation**

Observational studies suggest that ambulation may be associated with less pain and a shorter duration of labor. However, randomized controlled trials that compared ambulation and bed rest during the first stage of labor in women with neuraxial analgesia have not demonstrated any advantages of ambulation with regard to the progress or outcome of labor. Nageotte et al. randomly assigned 505 nulliparous women to receive CSE analgesia either with or without ambulation. There was no difference between groups in the mode of delivery or duration of labor. These results agree with those of a meta-analysis of five randomized controlled trials involving 1161 women. In addition, there were no differences between groups in the use of oxytocin augmentation, satisfaction with analgesia, or Apgar scores. No adverse effects were reported. These results are similar to those of trials that compared ambulation and bed rest in women without neuraxial analgesia.

**EFFECTS OF NEURAXIAL ANALGESIA ON THE FETUS AND NEONATE**

Neuraxial analgesia may affect the fetus directly, indirectly, or both. First, systemic absorption of the anesthetic agents may be followed by transplacental transfer of the drug, which has a direct effect on the fetus. Second, the effects of neuraxial blockade on the mother may affect the fetus indirectly. Effects of local anesthetics and opioids on the fetus and neonate are discussed in detail in Chapter 13.

**Direct Effects**

Direct fetal effects include intrapartum drug effects on the FHR as well as possible respiratory depression after delivery. The determinants of maternal plasma drug concentration, transfer across the placenta, and effects on the neonate are discussed in Chapters 4 and 13. Determinants of maternal plasma drug concentration include dose, site of administration, metabolism and excretion of the drug, and the presence of adjuvants (e.g., epinephrine). Factors that influence placental transfer include maternal and fetal placental perfusion, the physicochemical characteristics of the drug, concentration of the free drug in maternal plasma, and permeability of the placenta. Most anesthetic and analgesic drugs, including local anesthetics and opioids, readily cross the placenta.

**Fetal Heart Rate**

Effects of local anesthetics and opioids on FHR may be direct and indirect (see earlier discussion); however, there is little evidence for a direct effect when these drugs are administered as components of neuraxial analgesia. Transient changes in FHR variability and periodic decelerations...
have been observed during epidural labor analgesia with bupivacaine and other local anesthetics.\textsuperscript{477,508,509} These FHR decelerations were not associated with maternal hypotension. However, Loftus et al.\textsuperscript{510} did not observe FHR decelerations in women who received epidural bupivacaine for elective cesarean delivery, despite the use of larger doses of bupivacaine and the occurrence of more extensive sympathetic blockade in comparison with epidural labor analgesia. Of interest, one study noted that the administration of either epidural bupivacaine or intrathecal sufentanil was followed by a similar incidence of FHR decelerations (23% and 22%, respectively) in laboring women.\textsuperscript{511} Other studies have not observed a higher incidence of FHR decelerations associated with epidural administration of bupivacaine during labor.\textsuperscript{512}

Further, the reports of FHR decelerations after bupivacaine did not demonstrate adverse neonatal outcome; thus, the significance of these decelerations is unclear. There are no published data on the relationship between the concentration of bupivacaine used for intrapartum epidural analgesia and the incidence of FHR decelerations. Altogether, these data suggest that epidural local anesthetics have minimal, if any, direct effect on FHR.

Similarly, neuraxial opioid administration has little direct effect on the FHR.\textsuperscript{106,513,514} In contrast, systemic meperidine analgesia was associated with a greater reduction of FHR variability and fewer FHR accelerations than epidural bupivacaine analgesia.\textsuperscript{515} Spinal administration of local anesthetics and opioids results in lower maternal plasma concentrations of drug(s) than epidural administration and is therefore even less likely to cause a direct fetal effect.

**Neonatal Depression**

Systemic absorption of local anesthetic or opioid may have neonatal effects. This occurs more often after the systemic administration of opioid for labor analgesia.\textsuperscript{19,516} The neonatal depressant effects of drugs administered to the mother in the intrapartum period are usually assessed with neurobehavioral testing. Unfortunately, these tests are quite subjective and lack specificity. Additionally, scientifically rigorous studies are lacking, and most of the local anesthetic studies were performed in the era when high-dose epidural analgesia was common; these observational studies found that local anesthetics administered as components of epidural analgesia were sometimes associated with minor, transient effects on neonatal behavior.\textsuperscript{85,477,517}

When given by continuous epidural infusion, epidural opioid administration rarely results in accumulation of the drug and subsequent neonatal respiratory depression.\textsuperscript{7} Bader et al.\textsuperscript{221} noted that a continuous epidural infusion of 0.125% bupivacaine with fentanyl 2 µg/mL over a period of 1 to 15 hours did not result in significant fetal drug accumulation or adverse neonatal effects (in this study, the maximal cumulative dose of fentanyl was 300 µg). Porter et al.\textsuperscript{222} reported no adverse effect of fentanyl on neurobehavioral scores or other indices of fetal welfare when patients received an epidural infusion of 0.0625% bupivacaine with or without fentanyl 2.5 µg/mL. The mean ± SD maternal dose of fentanyl was 183 ± 75 µg (range, 53 to 400 µg). Loftus et al.\textsuperscript{106} observed only a modest reduction in neuroadaptive capacity scores (NACS) at 24 hours in neonates whose mothers had received epidural fentanyl during labor; neonates exposed to sufentanil during labor had a somewhat higher NACS at 24 hours, and sufentanil was detected in the umbilical arterial blood in only one of nine samples. Vertommen et al.\textsuperscript{106} observed no difference in Apgar scores or NACS in neonates whose mothers were randomly assigned to receive epidural sufentanil (up to 30 µg) during the course of labor and a control group that did not receive sufentanil.\textsuperscript{106} Maternal sufentanil levels were below the sensitivity of the assay (0.1 ng/mL) after an epidural bolus of 10 µg.\textsuperscript{113}

Intrathecal administration of an opioid during labor would be expected to have even fewer direct effects on the fetus than epidural administration. Smaller doses of opioid are administered, and less drug is absorbed systemically.

**Indirect Effects**

The indirect fetal effects of epidural and intrathecal opioids may be more significant than the direct effects. Obviously, if the mother has severe respiratory depression and hypoxemia, fetal hypoxemia and hypoxia will follow. More common is the occurrence of fetal bradycardia after initiation of neuraxial analgesia. The presumed cause is that the rapid onset of analgesia results in decreased plasma concentrations of catecholamines.\textsuperscript{472} Epinephrine causes uterine relaxation by stimulating beta-1 adrenergic uterine receptors. A reduced circulating concentration of epinephrine may result in increased uterine tone. Because uteroplacental perfusion occurs during periods of uterine diastole (i.e., uterine relaxation), uterine tachysystole may result in decreased uteroplacental perfusion and fetal hypoxia.

Published observations suggest that uterine tachysystole and fetal bradycardia may follow the administration of either intrathecal or epidural analgesia during labor. Abrão et al.\textsuperscript{519} randomized 72 laboring women to receive either CSE or epidural analgesia, and they observed the incidence of FHR abnormalities (prolonged deceleration or bradycardia) and an elevation in uterine tone (defined as an increase of 10 mm Hg or more in basal uterine pressure). The incidences of FHR abnormalities (32% versus 6%), and FHR abnormalities combined with an increase in uterine pressure (27% versus 3%), were significantly higher in the CSE group than in the epidural group. However, a significant limitation of this study is that the outcomes were assessed for only 15 minutes after the initiation of analgesia and the analgesic techniques were not equipotent.\textsuperscript{520} The overall high incidence of FHR abnormalities noted in the study may have been caused by the initiation of analgesia in women in advanced labor.

Fortunately, fetal bradycardia after labor analgesia does not appear to increase the overall risk for adverse outcome. Albright and Forster\textsuperscript{221} retrospectively reviewed outcomes for 2560 women who delivered at their hospital between March

\textsuperscript{106,108,113,221,222,518}
1995 and April 1996. Approximately one-half of the patients received CSE analgesia (10 to 15 µg of intrathecal sufentanil), and the other half received either systemic opioids or no medication. There was no difference between the two groups in the incidence of emergency cesarean delivery (1.3% versus 1.4%, respectively).

Mardirosoff et al. performed a systematic review of reports of randomized comparisons of intrathecal opioid analgesia with any nonintrathecal opioid regimen in laboring women. The investigators noted that intrathecal opioid analgesia was associated with a significant increase in the risk for fetal bradycardia (OR, 1.8; 95% CI, 1.0 to 3.1). However, the risk for cesarean delivery for FHR abnormalities was similar in the two groups (6.0% versus 7.8%, respectively). Data are conflicting regarding an opioid dose-response for fetal bradycardia. Van de Velde et al. randomly assigned laboring women to one of the following three treatment regimens: intrathecal sufentanil 7.5 µg, intrathecal sufentanil 1.5 µg/bupivacaine 2.5 mg/epinephrine 2.5 µg, or epidural bupivacaine 12.5 mg/sufentanil 7.5 µg/epinephrine 12.5 µg. Although the incidence of FHR abnormalities was higher in the high-dose intrathecal sufentanil group, there was no difference among groups in the need for emergency cesarean delivery. Wong et al., in two separate studies, randomized multiparous women to receive intrathecal fentanyl 0, 5, 10, 15, 20, or 25 µg, or sufentanil 0, 2.5, 5, 7.5 or 10 µg, combined with bupivacaine 2.5 mg. There was no difference in the incidence of fetal bradycardia among groups. Abrão et al. noted an association with the extent of decrease in pain scores after the initiation of analgesia and the incidence of fetal bradycardia. These data suggest that the incidence of bradycardia is associated with the rate of onset of analgesia; faster onset of analgesia is associated with the incidence of fetal bradycardia. These data suggest that the rate of analgesia; faster onset of analgesia is associated with the rate of onset of fetal bradycardia (OR, 1.8; 95% CI, 1.0 to 3.1). However, maternal-fetal factors and obstetric management—not the use of neuraxial analgesia—are the most important determinants of the outcome of labor. Anesthesia providers should identify those methods of analgesia that provide the most effective pain relief without unduly increasing the risk for obstetric intervention. Operative delivery increases the risk for maternal morbidity and mortality and is more expensive than spontaneous vaginal delivery. Randomized trials suggest that the use of neuraxial analgesia does not increase the cesarean delivery rate but may adversely influence the instrumental vaginal delivery rate.

Further, neuraxial analgesia may occasionally, either directly or indirectly, have adverse—usually temporary—effects on the fetus.

Despite these risks, many women opt for neuraxial analgesia because no other method of labor analgesia provides its benefits (almost complete analgesia), and the risks are acceptably low. Even no analgesia may be more hazardous to some women than neuraxial analgesia (e.g., patients with an anticipated difficult airway or those at high risk for emergency cesarean delivery). Therefore, it is the duty of the anesthesia provider to provide appropriate (albeit not always total) pain relief during the first and second stages of labor. Analgesia should be tailored to the individual patient’s labor, medical condition, preferences, and goals. Most women strongly dislike dense motor blockade, and many prefer to maintain some sensation of uterine contractions and perineal pressure, especially during the second stage of labor. However, a few women may accept the probable increase in risk for instrumental vaginal delivery in exchange for dense analgesia.

A Practical Guide to Neuraxial Labor Analgesia

Initiation of Analgesia

Neuraxial labor analgesia may be initiated with either the intrathecal (CSE) or the epidural injection of analgesic/anesthetic agents. The decision regarding the specific technique and choice of drugs and doses is individualized for each parturient. Parity, stage and phase of labor, use of intravenous oxytocin, and the presence of any coexisting disease(s), as well as the status of the fetus, are all considered in the decision.

In healthy nulliparous women in early labor (less than 4 to 5 cm cervical dilation), my colleagues and I often initiate CSE analgesia with an intrathecal opioid alone (e.g., fentanyl 25 µg or sufentanil 5 µg), followed by placement of an epidural catheter and administration of a standard

CONCLUSIONS AND RECOMMENDATIONS

Philosophy of Labor Analgesia

An unacceptably high number of women involuntarily experience severe pain during labor. As noted by the ACOG, “There is no other circumstance where it is considered acceptable for a person to experience severe pain, amenable to safe intervention, while under a physician’s care.” Unfortunately, labor represents one of the few circumstances in which the provision of effective analgesia is alleged to interfere with the parturient’s and obstetrician’s goal (e.g., spontaneous vaginal delivery). Dense neuraxial anesthesia may adversely affect the progress of labor in some patients. Indeed, given the complicated neurohumoral and mechanical processes involved in childbirth, it would be unreasonable to expect that neuraxial blockade of the lower half of the body would not have an effect on this process, whether positive or negative. However, maternal-fetal factors and obstetric management—not the use of neuraxial analgesia—are the most important determinants of the outcome of labor. Anesthesia providers should identify those methods of analgesia that provide the most effective pain relief without unduly increasing the risk for obstetric intervention. Operative delivery increases the risk for maternal morbidity and mortality and is more expensive than spontaneous vaginal delivery. Randomized trials suggest that the use of neuraxial analgesia does not increase the cesarean delivery rate but may adversely influence the instrumental vaginal delivery rate.

Further, neuraxial analgesia may occasionally, either directly or indirectly, have adverse—usually temporary—effects on the fetus.

Despite these risks, many women opt for neuraxial analgesia because no other method of labor analgesia provides its benefits (almost complete analgesia), and the risks are acceptably low. Even no analgesia may be more hazardous to some women than neuraxial analgesia (e.g., patients with an anticipated difficult airway or those at high risk for emergency cesarean delivery). Therefore, it is the duty of the anesthesia provider to provide appropriate (albeit not always total) pain relief during the first and second stages of labor. Analgesia should be tailored to the individual patient’s labor, medical condition, preferences, and goals. Most women strongly dislike dense motor blockade, and many prefer to maintain some sensation of uterine contractions and perineal pressure, especially during the second stage of labor. However, a few women may accept the probable increase in risk for instrumental vaginal delivery in exchange for dense analgesia.
lidocaine 45 mg/epinephrine 15 µg epidural test dose. Some anesthesia providers initiate intrathecal analgesia with both an opioid and a local anesthetic. The addition of a local anesthetic is unnecessary for achieving complete spinal analgesia during early labor; it may increase the risk for hypotension and result in motor blockade in some patients, particularly if it is followed by injection of an epidural test dose that contains a local anesthetic. However, the intrathecal administration of both an opioid and a local anesthetic achieves a longer duration of analgesia and lower incidence and severity of pruritus than intrathecal injection of an opioid alone.

Alternatively, epidural analgesia can be initiated with injection of a low-concentration local anesthetic solution (bupivacaine 0.0625% to 0.125%) combined with an opioid (fentanyl 50 to 100 µg). The epidural catheter is sited and a standard epidural test dose is injected, followed by administration of 5 to 15 mL of the local anesthetic/opioid solution, injected in 5-mL increments. Ten to 15 mL provides satisfactory analgesia for most nulliparous women in early labor; injection of 20 mL may be necessary if a dilute solution (e.g., 0.0625% bupivacaine) is used. A smaller dose is necessary if administered after a standard test dose.

We typically give an epinephrine-containing test dose before initiation of epidural analgesia in laboring women. Some anesthesia providers elect to omit the epidural test dose when initiating epidural labor analgesia, particularly if a woman wishes to ambulate in early labor. The omission of the epidural test dose requires that the therapeutic dose of local anesthetic be injected slowly, incrementally, and cautiously, because the therapeutic dose functions as the test dose. These precautions should be followed with all bolus injections of local anesthetic through an epidural catheter.

For nulliparous women in the active phase of the first stage of labor, CSE analgesia is usually initiated with the intrathecal injection of an opioid combined with a local anesthetic (fentanyl 15 µg and bupivacaine 2.5 mg). Alternatively, epidural analgesia can be initiated with a local anesthetic (bupivacaine 0.125%) combined with an opioid (fentanyl 100 µg). Women in active labor may require a higher total volume of epidural local anesthetic solution (15 to 20 mL) than women in early labor (10 to 15 mL) as well as a higher local anesthetic concentration (e.g., 0.125% rather than 0.0625% bupivacaine).

Labor typically progresses at a faster rate in parous women, who often require a more rapid onset of analgesia and more extensive neuroblockade than nulliparous women when neuraxial analgesia is initiated at the same cervical dilation. Therefore, in healthy parous women CSE analgesia is usually initiated with an intrathecal opioid combined with a local anesthetic, regardless of the stage and phase of labor. Alternatively, epidural analgesia is initiated with bupivacaine 0.125% combined with fentanyl 100 µg.

CSE analgesia with both a local anesthetic and an opioid is particularly advantageous for parous women in the late active phase of the first stage of labor and in all women in whom neuraxial analgesia is initiated in the second stage of labor. Sacral neuroblockade is required for complete analgesia during the second stage of labor; this neuroblockade is difficult to accomplish in a timely fashion with an initial (de novo) lumbar epidural injection of analgesic/anesthetic agents. (For initiation of lumbar epidural anesthesia in late labor, the injection of a large volume [greater than or equal to 20 mL] of local anesthetic solution may be required to achieve sacral analgesia, and this injection often results in a mid- or high-thoracic neuroblockade that is more extensive than desired. Therefore, when initiating neuraxial analgesia in late labor, a CSE technique is preferred).

Maintenance epidural analgesia is typically initiated soon after the initiation of analgesia (within 15 to 30 minutes) rather than waiting for the neuroblockade to regress. There are several advantages to this technique. Most women experience seamless analgesia (i.e., there is no window of pain as the initial block regresses). The workload for the anesthesia provider is lessened, because he or she can set up and initiate the epidural infusion while monitoring the patient for hypotension after initiation of neuroblockade. Finally, an epidural bolus of local anesthetic is not required to reestablish or extend neuroblockade, possibly enhancing safety.

Analgesia is typically maintained with a dilute solution of an amide local anesthetic and an opioid, administered by continuous infusion or PIEB, combined with PCEA. My colleagues and I use PCEA because it allows patient titration of neuroblockade and entails less risk for breakthrough pain. Patient satisfaction is better, and the workload for the anesthesia provider is decreased. At our institution, the PCEA infusion pump parameters are the same for all laboring women, so there are fewer errors in pump setup. However, when a continuous infusion is used without PCEA to maintain analgesia, it may be necessary to titrate the continuous infusion rate to individual patient needs. For example, women in early labor require less drug to maintain analgesia (6 to 10 mL/h), whereas women in more advanced labor may require a higher infusion rate (8 to 15 mL/h). Similarly, a parous patient may require a higher infusion rate than a nulliparous patient, even though analgesia is initiated at the same stage of labor.

Some parturients experience breakthrough pain. After evaluating the nature of the pain, the extent of neuroblockade, and the progress of labor, we usually treat breakthrough pain with a bolus epidural injection of bupivacaine 0.125%, 10 to 15 mL, administered in 5-mL increments. The patient may benefit from additional instruction about the optimal use of PCEA. Occasionally, we may elect to use a more concentrated local anesthetic solution (e.g., bupivacaine 0.25%), particularly in the presence of an abnormal fetal position or dysfunctional labor. In this case, the concentration of the maintenance solution may also need to be increased.

This maintenance technique usually results in satisfactory perineal analgesia for delivery. Occasionally, women with epidural analgesia require additional (more dense) analgesia for delivery, particularly if an instrumental vaginal delivery is planned. In this case, we often administer 5 to 12 mL of 1% to
2% lidocaine or 2% to 3% 2-chloroprocaine. This usually results in satisfactory sacral anesthesia in a patient with pre-existing epidural labor analgesia.

There is no single correct way to provide neuraxial labor analgesia, although for particular patients and specific clinical conditions some methods may have advantages over others. Frequent communication among members of the anesthesia, obstetric, and nursing teams is essential to the safe and satisfactory provision of neuraxial labor analgesia. In addition, within each labor and delivery unit, consistency among anesthesia providers in their choice of techniques, specific drugs, and drug doses/concentrations is likely to result in fewer errors and higher satisfaction among other caregivers and patients.

**KEY POINTS**

- Neuraxial analgesia is the most effective form of intrapartum analgesia currently available.
- In most cases, maternal request for pain relief represents a sufficient indication for the administration of neuraxial analgesia.
- The safe administration of neuraxial analgesia requires a thorough (albeit directed) preanesthetic evaluation and the immediate availability of appropriate resuscitation equipment.
- Neuraxial labor analgesia is not a generic procedure. The procedure should be tailored to individual patient needs.
- The administration of the epidural test dose should allow the anesthesia provider to recognize most cases of unintentional intravascular or intrathecal placement of the epidural catheter. All therapeutic doses of local anesthetic should be administered incrementally.
- Bupivacaine is the local anesthetic most often used for epidural analgesia during labor in the United States. Ropivacaine and levobupivacaine are satisfactory alternatives. Most anesthesia providers reserve 2-chloroprocaine and lidocaine for cases that require the rapid extension of epidural analgesia for vaginal or cesarean delivery.
- The addition of a lipid-soluble opioid to a neuraxial local anesthetic allows the anesthesia provider to provide excellent analgesia while reducing the total dose of local anesthetic and minimizing the side effects of each agent. Perhaps the major advantage of this technique is that the severity of motor block can be minimized during labor.
- Intrathecal opioids alone may provide complete analgesia during the early first stage of labor. Epidural opioids without local anesthetic do not provide complete analgesia during labor.
- Administration of a local anesthetic (with or without an opioid) is necessary to provide complete neuraxial analgesia for the late first stage and the second stage of labor. Although a neuraxial local anesthetic alone can provide complete analgesia, the required dose is often associated with an undesirably dense degree of motor blockade.
- Hypotension is a common side effect of neuraxial analgesia. Prophylaxis and treatment involve the avoidance of aortocaval compression and the administration of a vasopressor as needed. The administration of an intravenous fluid “preload” does not significantly decrease the incidence of hypotension in euvolemic patients.
- Other potential side effects of neuraxial analgesia include pruritus, shivering, urinary retention, delayed gastric emptying, maternal fever, and fetal heart rate changes.
- Complications of neuraxial analgesia include inadequate analgesia, unintentional dural puncture, respiratory depression, unintentional intravenous injection, and extensive or total spinal anesthesia.
- The presence of severe pain during early labor—and/or an increase in local anesthetic/opioid dose requirement—may signal a higher risk for prolonged labor and operative delivery.
- Neuraxial labor analgesia does not result in a higher rate of cesarean delivery than systemic opioid analgesia.
- Initiation of neuraxial analgesia in early labor (cervical dilation less than 4 to 5 cm) does not increase the rate of cesarean delivery or prolong the duration of labor.
- Effective neuraxial analgesia likely results in a modest prolongation of the second stage of labor.
- Controversy exists as to whether there is a cause-and-effect relationship between neuraxial labor analgesia and risk for instrumental vaginal delivery. Dense neuroblockade (e.g., presence of significant motor blockade) and complete analgesia during the second stage of labor probably increase the rate of instrumental vaginal delivery. Use of a dilute solution of local anesthetic and opioid is less likely to adversely affect the progress of labor.
- Maternal-fetal factors and obstetric management—not the use of neuraxial analgesia—are the most important determinants of the cesarean delivery rate.

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Neuraxial analgesic techniques are the most flexible analgesic techniques available for obstetric patients. The anesthesia provider may use an epidural or spinal technique to provide effective analgesia during the first and/or second stage of labor. Subsequently, the epidural or spinal technique may be used to achieve anesthesia for either vaginal or cesarean delivery. Unfortunately, some maternal conditions (e.g., coagulopathy, severe thrombocytopenia) contraindicate the administration of neuraxial analgesia. Many parturients do not have access to neuraxial analgesia, and others do not want it. The purpose of this chapter is to discuss alternative regional analgesic techniques for labor and vaginal delivery.

**PARACERVICAL BLOCK**

During the first stage of labor, pain results primarily from dilation of the cervix and distention of the lower uterine segment and upper vagina. Pain impulses are transmitted from the upper vagina, cervix, and lower uterine segment by visceral afferent nerve fibers that join the sympathetic chain at L2 to L3 and enter the spinal cord at T10 to L1. Obstetricians may perform a paracervical block to provide analgesia during the first stage of labor, although the block is not discussed in the updated 2017 American College of Obstetricians and Gynecologists Practice Bulletin on Obstetric Analgesia and Anesthesia. The goal is to block transmission through the paracervical ganglion—which lies immediately lateral and posterior to the cervicouterine junction.

Paracervical block does not adversely affect the progress of labor. Further, it provides analgesia without the annoying sensory and motor blockade that may result from neuraxial analgesia. The paracervical technique does not block somatic sensory fibers from the lower vagina, vulva, and perineum. Thus, it does not relieve the pain caused by distention of these structures during the late first stage and second stage of labor. Experience suggests that paracervical block results in satisfactory analgesia during the first stage of labor in 50% to 75% of parturients. One study noted that paracervical block provided better analgesia in nulliparous women than in parous women, probably because paracervical block does not provide effective analgesia for the sudden and rapid descent of the presenting part that often occurs in parous women. In 2011, 2% to 7% of parturients in the United States received paracervical block during labor. The decline in the popularity of paracervical block results from both fear of fetal complications and the greater popularity and flexibility of neuraxial analgesic techniques.

Jensen et al. randomly assigned 117 nulliparous women to receive either bupivacaine paracervical block or intramuscular meperidine 75 mg. Women in the paracervical block group had significantly better analgesia than women in the meperidine group at 20, 40, and 60 minutes. During the first 60 minutes, pain relief was complete or acceptable in 78% of
the women in the paracervical block group but in only 31% of the women in the meperidine group. Two fetuses in the paracervical block group and one in the meperidine group had transient bradycardia. A total of 6 infants in the paracervical block group and 16 infants in the meperidine group ($P < .05$) had fetal/neonatal depression, which the investigators defined as an umbilical arterial blood pH of 7.15 or less and/or a 1-minute Apgar score of 7 or less. A 2012 Cochrane Review cited this study as evidence that paracervical block provides more effective analgesia during labor than intramuscular meperidine.

In a 2009 study, Junttila et al. randomly assigned 122 parous women to receive either bupivacaine paracervical block or single-shot spinal bupivacaine with sufentanil. Single-injection spinal analgesia was superior to that provided by paracervical block (Fig. 24.1), although paracervical block resulted in a pain score of 3 or less in 43% of the study subjects, and 51% of the women in the paracervical block group indicated that they would be happy to receive this method of analgesia during labor in a future pregnancy. There was no difference between the two groups in the incidence of fetal heart rate (FHR) abnormalities, and there were no cases of fetal bradycardia in either group.

Kangas-Saarela et al. compared neonatal neurobehavioral responses in 10 infants whose mothers received bupivacaine paracervical block with those in 12 infants whose mothers received no analgesia. The investigators performed paracervical block while each patient lay in a left lateral position, and they limited the depth of the injection into the vaginal mucosa to 3 mm or less. They observed no significant differences between groups in neurobehavioral responses at 3 hours, 1 day, 2 days, or 4 to 5 days after delivery. These investigators concluded that properly performed paracervical block does not adversely affect newborn infant behavior or neurologic function.

### Technique

Paracervical block is performed with the patient in a modified lithotomy position. The uterus should be displaced leftward during performance of the block; this displacement may be accomplished by placing a folded pillow beneath the patient’s right buttock. The physician uses a needle guide to define and limit the depth of the injection and to reduce the risk for vaginal or fetal injury. The physician introduces the needle and needle guide into the vagina with the left hand for the left side of the pelvis and with the right hand for the right side (Fig. 24.2). The needle is advanced through the vaginal mucosa to a depth of 2 to 3 mm. The physician should aspirate before each injection of local anesthetic. A total of 5 to 10 mL of local anesthetic, without epinephrine, is injected on each side.

Some obstetricians recommend giving incremental doses of local anesthetic on each side (e.g., 2.5 to 5 mL of local anesthetic) or single-shot spinal (intrathecal) injection of bupivacaine 2.5 mg and sufentanil 2.5 µg. Data are median pain scores with the 25th and 75th percentiles. PCB, paracervical block; SSS, single-shot spinal analgesia; $P_{t}$, P-time; $P_{g}$, P-groups; $P_{tg}$, P-time*group. $N_{SSS} = 56, 55, 54, 49, 37, 23, 5, 0$. $N_{PCB} = 56, 55, 49, 37, 23, 5, 0$. (From Junttila EK, Karjalainen PK, Ohtonen PP, et al. A comparison of paracervical block with single-shot spinal for labour analgesia in multiparous women: a randomized controlled trial. Int J Obstet Anesth. 2009;18:15–21.)

**Fig. 24.1** Pain scores over time before and after paracervical block (10 mL of 0.25% bupivacaine) or single-shot spinal (intrathecal) injection of bupivacaine 2.5 mg and sufentanil 2.5 µg. Data are median pain scores with the 25th and 75th percentiles. PCB, paracervical block; SSS, single-shot spinal analgesia; $P_{t}$, P-time; $P_{g}$, P-groups; $P_{tg}$, P-time*group. $N_{SSS} = 48, 44, 45, 36, 29, 15, 10$. $N_{PCB} = 56, 55, 54, 49, 37, 23, 5, 0$. (From Abouleish E. Pain Control in Obstetrics. New York, NY: JB Lippincott; 1977:344.)

**Fig. 24.2** Technique of paracervical block. Notice the position of the hand and fingers in relation to the cervix and fetal head. No undue pressure is applied at the vaginal fornix by the fingers or the needle guide, and the needle is inserted to a shallow depth. (Redrawn from Abouleish E. Pain Control in Obstetrics. New York, NY: JB Lippincott; 1977:344.)
anesthetic between the 3-o’clock and 4-o’clock positions, followed by 2.5 to 5 mL between the 4-o’clock and 5-o’clock positions.\textsuperscript{6,10,11}

After injecting the local anesthetic in either the left or right lateral vaginal fornix, the physician should wait 5 to 10 minutes and observe the FHR before injecting the local anesthetic on the other side.\textsuperscript{11} Some obstetricians do not endorse this recommendation. Van Dorsten et al.\textsuperscript{12} randomly assigned 42 healthy parturients at term to either of two methods of paracervical block. The study group experienced a 10-minute interval between injections of local anesthetic on the left and right sides of the vagina. The control group had almost simultaneous injections on the left and right sides. No cases of fetal bradycardia occurred in either group. The investigators concluded that patient selection and lateral positioning after the block have a more important role in the prevention of post-paracervical block fetal bradycardia than spacing the injections of local anesthetic. However, because they studied only 42 patients and had no cases of fetal bradycardia in either group, they could not exclude the possibility that incremental injection might result in a lower incidence of fetal bradycardia in a larger series of patients.

**Choice of Local Anesthetic**

The physician should administer small volumes of a dilute solution of local anesthetic. There is no reason to inject more than 10 mL of local anesthetic on each side. Further, there is no indication for the use of concentrated solutions, such as 2% lidocaine, 0.5% bupivacaine, or 3% 2-chloroprocaine. Nieminen and Puolakka\textsuperscript{13} observed that paracervical block with 10 mL of 0.125% bupivacaine (5 mL on each side) provided analgesia similar to that provided by 10 mL of 0.25% bupivacaine.

The choice of local anesthetic is controversial. The North American manufacturers of bupivacaine have stated that bupivacaine is contraindicated for the performance of paracervical block. In contrast, Scandinavian obstetricians have used bupivacaine for this procedure. Bupivacaine has greater cardiotoxicity than other local anesthetic agents, and some investigators have suggested that its use leads to a higher incidence of fetal bradycardia or adverse outcome than use of other local anesthetics for paracervical block. In a review of 50 cases of perinatal death associated with paracervical block, the 2-chloroprocaine group, compared with 5 of 31 fetuses in the lidocaine group (\(P = .14\)), LeFevre\textsuperscript{18} retrospectively observed that fetal bradycardia occurred after 2 (6%) of 33 paracervical blocks performed with 2-chloroprocaine versus 44 (12%) of 361 paracervical blocks performed with mepivacaine (\(P = .29\)).

2-Chloroprocaine undergoes rapid enzymatic hydrolysis. Thus it has the shortest intravascular half-life among the local anesthetics used clinically. This rapid metabolism seems advantageous in the event of unintentional intravascular or fetal injection. Philipson et al.\textsuperscript{17} performed paracervical block with 10 mL of 1% 2-chloroprocaine in 16 healthy parturients. At delivery, only trace concentrations of 2-chloroprocaine were detected in one (6%) of the maternal blood samples and four (25%) of the umbilical cord venous blood samples. The investigators concluded:\textsuperscript{17}

> In all of the studies of paracervical block with 2-chloroprocaine, there were no cases in which the abnormal fetal heart rate patterns were associated with depressed neonates. This is in contrast to the studies with amide local anesthetics and may be explained by the rapid enzymatic inactivation of 2-chloroprocaine.

Some obstetricians dislike 2-chloroprocaine because of its relatively short duration of action. However, in one study the mean duration of analgesia was 40 minutes after paracervical administration of either 2-chloroprocaine or lidocaine.\textsuperscript{16} A 2012 Cochrane Review concluded that the choice of local anesthetic agent did not affect maternal satisfaction with pain relief after paracervical block.\textsuperscript{5}

**Maternal Complications**

Maternal complications of paracervical block are uncommon but may be serious (Box 24.1).\textsuperscript{19–22} Local anesthetic systemic toxicity may result from direct intravascular injection or rapid systemic absorption of the local anesthetic. Postpartum neuropathy may follow direct sacral plexus trauma, or it may result from hemotoma formation. Retropsoal and subgluteal abscesses are rare but may result in maternal morbidity or mortality.\textsuperscript{23,22}

**BOX 24.1 Maternal Complications of Paracervical Block**

- Vasovagal syncope
- Laceration of the vaginal mucosa
- Local anesthetic systemic toxicity
- Parametrial hematoma
- Postpartum neuropathy
- Paracervical, retropsoal, or subgluteal abscess
Fetal Complications

In some cases, fetal injury results from direct injection of local anesthetic into the fetal scalp during paracervical block. Fetal scalp injection of 10 or 20 mL of local anesthetic undoubtedly causes local anesthetic systemic toxicity, which may result in fetal death. Fetal scalp injection seems more likely to occur when the obstetrician performs paracervical block in the presence of advanced (i.e., > 8 cm) cervical dilation.

Bradycardia is the most common fetal complication. Fetal bradycardia typically develops within 2 to 10 minutes after the injection of local anesthetic. Most cases resolve within 5 to 10 minutes, but some cases of bradycardia persist for as long as 30 minutes. Published studies have noted an incidence of bradycardia that varies between 0% and 70%. These figures represent extremes on either side of the true incidence of this complication. Some studies have overstated the problem by defining bradycardia as a baseline FHR of less than 120 bpm. A baseline FHR of 110 bpm does not necessarily indicate fetal compromise. Experienced obstetricians clearly do not encounter clinically significant fetal bradycardia after 70% of their paracervical blocks. It is equally clear that the incidence of clinically significant fetal bradycardia is not zero, and it is difficult to teach this technique without placing some fetuses at risk.

Shnider et al. reported that fetal bradycardia occurred after 24% of 845 paracervical blocks administered to 705 patients with either 1% mepivacaine, 1% lidocaine, or 1% propitocaine (prilocaine). Neonatal depression occurred significantly more often in infants who had FHR changes after paracervical block than in a control group or in a group of infants with no FHR changes after paracervical block. In contrast, Carlsson et al. performed 523 paracervical blocks with 0.125% or 0.25% bupivacaine in 469 women. Of the total, nine (1.9%) fetuses had bradycardia, but at delivery all nine of the newborns had a 5-minute Apgar score of 9 or 10.

Goins observed fetal bradycardia in 24 (13%) of 182 patients who received paracervical block with 20 mL of 1% mepivacaine. He compared neonatal outcome for these patients with neonatal outcome for 343 patients who received other analgesic/anesthetic techniques. There was a slightly higher incidence of low Apgar scores at 1 minute and 5 minutes in the paracervical block group, but the difference was not statistically significant. LeFevre observed fetal bradycardia after 46 (11%) of 408 paracervical blocks. Fetal bradycardia was more common in those patients with a nonreassuring FHR tracing before the performance of paracervical block.

In a review of four randomized controlled trials published between 1975 and 2000, Rosen estimated that the incidence of post-paracervical block fetal bradycardia is 15%. More recently, Volmanen et al. reviewed four studies of paracervical block that had adequate sample size (n > 200), used the superficial injection technique, and administered 0.125% or 0.25% bupivacaine. Among the 1361 patients in these four studies, the incidence of fetal bradycardia was 2.2%. The observed episodes of fetal bradycardia were transient and did not require emergency cesarean delivery.

Etiology of Fetal Bradycardia

The etiology of fetal bradycardia after paracervical block is unclear. Investigators have offered at least four theories that might explain the etiology of fetal bradycardia, as discussed here.

**Reflex bradycardia.** Manipulation of the fetal head, the uterus, or the uterine blood vessels during performance of the block may cause reflex fetal bradycardia.

**Direct fetal central nervous system and myocardial depression.** The performance of paracervical block results in the injection of large volumes of local anesthetic close to the uteroplacental circulation. Local anesthetic rapidly crosses the placenta and may cause fetal central nervous system (CNS) depression, myocardial depression, and/or umbilical vasoconstriction. Puolakka et al. observed that the most common abnormality after paracervical block was the disappearance of FHR accelerations. They speculated that FHR changes result from rapid transplacental passage of local anesthetic into the fetal circulation, followed by a direct toxic effect of the local anesthetic on the FHR regulatory centers.

Some investigators have suggested that fetal bradycardia results from a direct toxic effect of the local anesthetic on the fetal heart. Shnider et al. reported that in four cases of fetal bradycardia, mepivacaine concentrations in fetal scalp blood were higher than peak concentrations in maternal arterial blood. Asling et al. made similar observations in six of seven cases of fetal bradycardia. They suggested that local anesthetic reaches the fetus by a more direct route than maternal systemic absorption, and they speculated that high fetal concentrations of local anesthetic result from local anesthetic diffusion across the uterine arteries. This would lead to local anesthetic concentrations in intervillous blood that are higher than concentrations in maternal brachial arterial blood. High fetal concentrations would then occur from the passive diffusion of local anesthetic across the placenta.

High fetal concentrations of local anesthetic also may result from fetal acidosis and ion trapping. Local anesthetics are weak bases, and if acidosis develops in a fetus, increasing amounts of local anesthetic will be trapped in the fetal circulation. It is also possible that the obstetrician may directly inject local anesthetic into uterine blood vessels.

Most studies have noted that local anesthetic concentrations in the fetus are consistently lower than those in the mother after paracervical block. Freeman et al. injected 300 mg of mepivacaine directly into the scalp of two anencephalic fetuses. The QRS complex widened, the PR interval lengthened, and both fetuses died, but fetal bradycardia did not occur before fetal death. In contrast, the investigators observed no widening of the QRS complex or lengthening of the PR interval in normal fetuses demonstrating bradycardia after paracervical block. Rather, the fetal electrocardiogram (ECG)
changes were consistent with sinoatrial node suppression with a wandering atrial pacemaker. The investigators concluded that a mechanism other than direct fetal myocardial depression is responsible for fetal bradycardia after paracervical block.

**Increased uterine activity.** Increased uterine activity results in decreased uteroplacental perfusion. Fishburne et al.\(^{39}\) noted that direct uterine arterial injection of bupivacaine consistently caused a significant increase in uterine tone in gravid ewes. Uterine arterial injection of 2-chloroprocaine did not affect myometrial tone, whereas injection of lidocaine had an intermediate effect.

Myometrial injection of a local anesthetic also may cause greater uterine activity. Morishima et al.\(^{40}\) performed paracervical block with either lidocaine or 2-chloroprocaine in pregnant baboons with normal and acidotic fetuses. A transient increase in uterine activity and a significant reduction in uterine blood flow occurred after paracervical block in 73% of the mothers. Approximately 33% of the normal fetuses and all of the acidic fetuses had bradycardia after paracervical block. The acidic fetuses had more severe bradycardia, greater hypoxemia, and slower recovery of oxygenation compared with fetuses that were well oxygenated before paracervical block. The researchers concluded that post-paracervical block fetal bradycardia is in part a result of greater uterine activity, diminished uteroplacental perfusion, and decreased oxygen delivery to the fetus. They also concluded that paracervical block should be avoided in the presence of fetal compromise.

**Uterine and/or umbilical artery vasoconstriction.** The deposition of local anesthetic in close proximity to the uterine arteries may cause uterine artery vasoconstriction, with a subsequent drop in uteroplacental perfusion. At least two studies noted that lidocaine and mepivacaine caused vasoconstriction of human uterine arteries in vitro.\(^{41,42}\) (These studies were performed before recognition of the importance of intact endothelium during investigation of vascular smooth muscle response.) Similarly, Norén et al.\(^{43,44}\) noted that bupivacaine caused concentration-dependent contraction of uterine arterial smooth muscle from rats and pregnant women. The calcium entry-blocking drugs verapamil and nifedipine decreased the vascular smooth muscle contraction caused by bupivacaine. The researchers concluded that the use of bupivacaine for paracervical block may cause uterine artery vasoconstriction, especially when the bupivacaine is injected close to the uterine arteries. Further, they suggested that the administration of a calcium entry-blocking drug may successfully eliminate this vasoconstrictive effect of bupivacaine. (The researchers did not mention whether they preserved, removed, or even observed the presence of the vascular endothelium. The presence of vascular endothelium may alter the response of vascular smooth muscle to local anesthetics.\(^{45}\)

Greiss et al.\(^{46}\) observed that intra-aortic injection of lidocaine or mepivacaine led to decreased uterine blood flow in gravid ewes. Similarly, Fishburne et al.\(^{39}\) noted that direct uterine arterial injection of lidocaine, bupivacaine, or 2-chloroprocaine reduced uterine blood flow in gravid ewes. They concluded that only paracervical block "would be expected to produce the high, sustained uterine arterial concentrations of anesthetic drugs that cause the significant reductions in uterine blood flow which we now feel are the etiology of fetal bradycardia."\(^{39}\) In a later study, Manninen et al.\(^{47}\) observed that paracervical injection of 10 mL of 0.25% bupivacaine led to an increase in the uterine artery pulsatility index—an estimate of uterine vascular resistance—in healthy nulliparous women, suggesting that paracervical block may result in uterine artery vasoconstriction.

In contrast, Puolakka et al.\(^{48}\) used \(^{133}\)Xe to measure intervillous blood flow before and after the performance of paracervical block with 10 mL of 0.25% bupivacaine in 10 parturients. They observed no decrease in mean intervillous blood flow in these patients. Further, they noted minimal change in intervillous blood flow in the three patients who had fetal bradycardia after paracervical block. Using Doppler ultrasonography, Räsänen and Jouppila\(^{49}\) observed no significant change in either uterine or umbilical artery pulsatility index after the performance of paracervical block with 10 mL of 0.25% bupivacaine in 12 healthy parturients. However, fetal bradycardia occurred in two patients, and in those two cases, a marked increase in umbilical artery pulsatility index occurred.

Baxi et al.\(^{50}\) performed paracervical block with 20 mL of 1% lidocaine in 10 pregnant women. They observed a decrease in fetal transcutaneous \(\text{Po}_2\) 5 minutes after injecting lidocaine in each of the 10 patients. There was a maximum decline in transcutaneous \(\text{Po}_2\) at 11.5 minutes, and transcutaneous \(\text{Po}_2\) returned to baseline by approximately 31 minutes. Some of the patients had increased uterine activity after paracervical block. In contrast, Jacobs et al.\(^{51}\) observed a consistent, sustained decrease in fetal transcutaneous \(\text{Po}_2\) after only 1 of 10 paracervical blocks performed with 10 mL of 0.25% bupivacaine. These investigators attributed their good results to the following precautions: (1) performance of paracervical block only in healthy mothers with normal pregnancies; (2) administration of a small dose of bupivacaine; (3) a limited depth of injection; (4) administration of bupivacaine in four incremental injections (i.e., two injections on each side); and (5) use of the left lateral position immediately after performance of the block. In a later study, Kaita et al.\(^{52}\) observed that paracervical injection of 10 mL of 0.25% bupivacaine in 10 healthy parturients resulted in a slight (clinically insignificant) increase in fetal \(\text{Sao}_2\) as measured by fetal pulse oximetry.

**Summary**

Most observers currently believe that post-paracervical block bradycardia results from reduced uteroplacental and/or fetoplacental perfusion. Reduction in uteroplacental perfusion may occur because of increased uterine activity and/or a direct vasoconstrictive effect of the local anesthetic. Likewise, decreased umbilical cord blood flow may result from increased uterine activity and/or umbilical cord vasoconstriction. Regardless of the etiology, the severity and duration of
fetal bradycardia correlate with the incidence of fetal acidosis and subsequent neonatal depression. Freeman et al.\(^{39}\) reported a significant drop in pH and a rise in base deficit only in fetuses with bradycardia of longer than 10 minutes’ duration. In an observational study of paracervical block and nalbuphine analgesia during labor, Levy et al.\(^{40}\) observed no association between paracervical block and low umbilical arterial blood pH at delivery.

**Physician Complications**

The performance of paracervical block requires the physician to make several blind needle punctures within the vagina. The needle guide does not consistently protect the physician from a needle-stick injury. Thus, the performance of paracervical block may entail the risk for physician exposure to hepatitis C virus (HCV), human immunodeficiency virus (HIV), or another infectious agent.

**Recommendations**

It is difficult for us to offer enthusiasm for the performance of paracervical block in contemporary obstetric practice. Nonetheless, paracervical block may be an appropriate technique in circumstances in which neuraxial analgesia is contraindicated or unavailable. The following recommendations seem reasonable:

1. Perform paracervical block only in healthy parturients at term who have no evidence of uteroplacental insufficiency or fetal compromise.
2. Continuously monitor the FHR and uterine activity before, during, and after performance of paracervical block. Perform paracervical block only in patients with a reassuring FHR tracing. An obvious exception would be a patient whose fetus has an anomaly incompatible with life (e.g., anencephaly).
3. Do not perform paracervical block when the cervix is dilated 8 cm or more.
4. Establish intravenous access before performing paracervical block.
5. Maintain left uterine displacement during and after performance of the block.
6. Limit the depth of injection to approximately 3 mm.
7. Aspirate before each injection of local anesthetic.
8. After injecting the local anesthetic on one side, wait 5 to 10 minutes and observe the FHR before injecting the local anesthetic on the other side.
9. Administer small volumes of a dilute solution of local anesthetic; 2-chloroprocaine is the agent of choice.
10. Avoid the administration of epinephrine-containing local anesthetic solutions.
11. Monitor the mother’s blood pressure and watch for signs of local anesthetic systemic toxicity after performance of the block. Maintain normal maternal blood pressure.
12. If fetal bradycardia should occur, try to achieve fetal resuscitation \textit{in utero}. Discontinue oxytocin, administer supplemental oxygen, and ensure that the patient is on her left side. Perform operative delivery if the fetal bradycardia persists beyond 10 minutes.

**LUMBAR SYMPATHETIC BLOCK**

In 1933, Cleland\(^{53}\) demonstrated that lower uterine and cervical visceral afferent sensory fibers join the sympathetic chain at L2 to L3. Subsequently, lumbar sympathetic block was used as an effective—if not popular—method of first-stage analgesia in some hospitals.\(^{54-57}\) Like paracervical block, paravertebral lumbar sympathetic block interrupts the transmission of pain impulses from the cervix and lower uterine segment to the spinal cord. Lumbar sympathetic block provides analgesia during the first stage of labor but does not relieve pain during the second stage. It provides analgesia comparable to that provided by paracervical block but with less risk for fetal bradycardia.

Lumbar sympathetic block may have a favorable effect on the progress of labor. Hunter\(^{58}\) reported that lumbar sympathetic block accelerated labor in 20 of 39 patients with a normal uterine contractile pattern before performance of the block. (Indeed, some of the patients in that study had a 5- to 15-minute period of uterine tachysystole after the block.) Further, he observed that lumbar sympathetic block converted an abnormal uterine contractile pattern to a normal pattern in 14 of 19 patients. He concluded that lumbar sympathetic block represents “one of the most reliable methods reported to actively convert an abnormal labor pattern to a normal pattern.”\(^{59}\) In a later study, Leighton et al.\(^{60}\) randomly assigned 39 healthy nulliparous women at term to receive either epidural analgesia or lumbar sympathetic block. The women who received lumbar sympathetic block had a more rapid rate of cervical dilation during the first 2 hours of analgesia, a shorter second stage of labor, and a nonsignificant trend toward a lower incidence of cesarean delivery for dystocia. However, there was no difference between the groups in the rate of cervical dilation during the active phase of the first stage of labor.

Anesthesiologists may successfully perform lumbar sympathetic block when a history of previous back surgery precludes the successful administration of epidural analgesia.\(^{60}\) Some anesthesiologists offer lumbar sympathetic block to prepared childbirth enthusiasts who desire first-stage analgesia without any motor block or loss of perineal sensation. Meguiar and Wheeler\(^{61}\) stated that the primary usefulness of lumbar sympathetic block is “in cases where continuous lumbar epidural analgesia is refused or contraindicated.” They administered 20 mL of 0.5% bupivacaine with 1:200,000 epinephrine to 40 nulliparous women. Among these women, 38 experienced good analgesia, and 28 delivered before resolution of the block. Pain recurred before delivery in the remaining 12 women; the mean ± SD duration of analgesia was 283 ± 103 minutes among these patients.\(^{51}\) Leighton et al.\(^{60}\) administered the same dose of bupivacaine, but they observed a shorter duration of analgesia than that observed by Meguiar and Wheeler.\(^{61}\)

During the past three decades, lumbar sympathetic block has all but disappeared from obstetric anesthesia practice in the United States, for several reasons. Most anesthesiologists minimize motor block during epidural analgesia by...
giving a dilute solution of local anesthetic, with or without an opioid. For those few patients who want to retain full perineal sensation, anesthesiologists may give an opioid alone, either intrathecally or epidurally. Thus, there are few patients for whom lumbar sympathetic block holds unique advantages. Further, the procedure often is painful, and few anesthesiologists have acquired and maintained proficiency in performing lumbar sympathetic block in obstetric patients.

Lumbar sympathetic block remains an attractive technique in a small number of patients.60 Alternatively, two reports have described the performance of bilateral lower thoracic paravertebral block in five laboring women in whom epidural analgesia was contraindicated.62,63 As anesthesiologists gain greater proficiency with thoracic paravertebral block for patients undergoing breast surgery, perhaps this technique will be used more often in parturients for whom neuraxial analgesia is contraindicated.

**Technique**

With the patient in the sitting position, a 10-cm, 22-gauge needle is used to identify the transverse process on one side of the second lumbar vertebra. The needle is then withdrawn, redirected, and advanced another 5 cm so that the tip of the needle is at the anterolateral surface of the vertebral column, just anterior to the medial attachment of the psoas muscle (Fig. 24.3). It is possible to place the needle within a blood vessel or the subarachnoid space; thus, the anesthesiologist must aspirate before injecting the local anesthetic. Two 5-mL increments of a dilute solution of local anesthetic (with or without epinephrine) are then injected, and the procedure is repeated on the opposite side of the vertebral column.

**Complications**

Modest hypotension occurs in 5% to 15% of patients.58,59,61 The risk for hypotension may be reduced by giving 500 mL of lactated Ringer’s solution intravenously before performing the block. Less common maternal complications are local anesthetic systemic toxicity, total spinal anesthesia, retroperitoneal hematoma, Horner’s syndrome,64 and post-dural puncture headache.65

Fetal complications are unlikely unless hypotension or increased uterine activity results in decreased uteroplacental perfusion.

**PUDENDAL NERVE BLOCK**

During the second stage of labor, pain results from distention of the lower vagina, vulva, and perineum. The pudendal nerve, which includes somatic nerve fibers from the anterior primary divisions of the second, third, and fourth sacral nerves, represents the primary source of sensory innervation for the lower vagina, vulva, and perineum. The pudendal nerve also provides motor innervation to the perineal muscles and to the external anal sphincter.

In 1916, King66 reported the use of pudendal nerve block for vaginal delivery. This procedure did not become popular
until 1953 and 1954, when Klink and Kohl described the anatomy and reported modified techniques. Obstetricians often perform pudendal nerve block in patients without epidural or spinal analgesia. The goal is to block the pudendal nerve distal to its formation by the anterior divisions of S2 to S4 but proximal to its division into its terminal branches (i.e., dorsal nerve of the clitoris, perineal nerve, and inferior hemorrhoidal nerve). Pudendal nerve block may provide satisfactory anesthesia for spontaneous vaginal delivery and perhaps for outlet-forceps delivery, but it provides inadequate anesthesia for mid-forceps delivery, postpartum examination and repair of the upper vagina and cervix, and manual exploration of the uterine cavity.

### Efficacy and Timing

The efficacy of pudendal nerve block varies according to the training and experience of the obstetrician. Many obstetric trainees receive little or no formal training in performance of pudendal block. A 2013 audit of 57 obstetricians in the United Kingdom revealed that the majority of participants were unable to correctly identify the ideal point of injection and were unaware of the lag time required for the onset of effective anesthesia. It is not surprising that unilateral or bilateral failure is common. Thus, obstetricians typically perform simultaneous infiltration of the perineum, especially if the performance of pudendal nerve block is delayed until delivery. Scudamore and Yates reported bilateral success rates of approximately 50% after use of the transvaginal route and of approximately 25% after use of the transperineal route. They concluded:

> The term “pudendal block” is often a misnomer…. If this limitation were more widely appreciated, then many mothers would be spared the unnecessary pain which is caused when relatively complicated procedures are attempted under inadequate anesthesia.

In the United States, performance of pudendal nerve block typically occurs immediately before delivery. This practice reflects obstetrician concern that perineal anesthesia prolongs the second stage of labor. Early performance of the procedure allows time for successful neuroblockade to occur. Subsequently the obstetrician may repeat the block on one or both sides if it should fail, provided that the maximum safe dose of local anesthetic is not exceeded. European obstetricians seem more willing to perform pudendal nerve block at the onset of the second stage of labor. Langhoff-Roos and Lindmark administered pudendal nerve block before or just after complete cervical dilation in 551 (64%) of 865 women. In a nonrandomized study, Zador et al. evaluated obstetric outcome in 24 patients who received pudendal nerve block when the cervix was completely dilated and in 24 patients who did not receive pudendal block. Pudendal nerve block slightly prolonged the second stage of labor, but it did not increase the incidence of instrumental vaginal delivery.

It is barbaric to withhold analgesia during the second stage of labor. Obstetricians need not delay the administration of pudendal nerve block until delivery. Rather, for those patients without epidural or spinal analgesia, it seems appropriate to perform pudendal nerve block when the patient complains of vaginal and perineal pain. A 2004 study suggested that pudendal nerve block does not provide reliable analgesia during the second stage of labor but has greater efficacy for episiotomy and repair. In a randomized, double-blind, placebo-controlled study, Aissaoui et al. observed that unilateral, nerve stimulator-guided pudendal nerve block with ropivacaine was associated with decreased pain and less need for supplemenal analgesia during the first 48 hours after performance of mediolateral episiotomy at vaginal delivery.

### Technique

The transvaginal approach is more popular than the transperineal approach in the United States. The obstetrician uses a needle guide (either the Iowa trumpet or the Kobak needle guide) to prevent injury to the vagina and fetus. In contrast to the technique for paracervical block, the needle must protrude 1.0 to 1.5 cm beyond the needle guide to allow adequate penetration for injection of the local anesthetic. The obstetrician introduces the needle and needle guide into the vagina with the left hand for the left side of the pelvis and with the right hand for the right side (Fig. 24.4). The needle is introduced through the vaginal mucosa and sacrospinous ligament, just medial and posterior to the ischial spine. The pudendal artery lies in close proximity to the pudendal nerve; thus, the obstetrician must aspirate before and during the injection of local anesthetic. The obstetrician typically injects 7 to 10 mL of local anesthetic solution on each side. (Some obstetricians inject 3 mL of local anesthetic just above the ischial spine on each side.) The obstetrician should pay attention to the total dose of local anesthetic given, especially when repetitive pudendal nerve blocks or both pudendal nerve block and perineal infiltration are performed.

![Fig. 24.4 Local infiltration of the pudendal nerve. Transvaginal technique showing the needle extended beyond the needle guard and passing through the sacrospinous ligament (S) to reach the pudendal nerve (N). (From Cunningham FG, MacDonald PC, Gant NF, et al. *Williams Obstetrics.* 20th ed. Stamford, CT: Appleton & Lange; 1997:389.)](image)
**Choice of Local Anesthetic**

Rapid maternal absorption of the local anesthetic occurs after the performance of pudendal nerve block. Zador et al. detected measurable concentrations of lidocaine in maternal venous and fetal scalp capillary blood samples within 5 minutes of the injection of 20 mL of 1% lidocaine. They detected peak concentrations between 10 and 20 minutes after injection. Kuhnert et al. reported that after pudendal nerve block, neonatal urine concentrations of lidocaine and its metabolites were similar to those measured in neonatal urine after epidural administration of lidocaine.

Some physicians favor the administration of 2-chloroprocaine. Its rapid onset of action provides an advantage when pudendal nerve block is performed immediately before delivery. Its rapid metabolism and short intravascular half-life lower the likelihood of maternal or fetal systemic toxicity. 2-Chloroprocaine has the disadvantage of a short duration of action. However, if the obstetrician performs pudendal nerve block with 2-chloroprocaine at the onset of the second stage of labor, the block can be repeated as needed. When the block is performed immediately before delivery, the brief duration of action of 2-chloroprocaine is not a disadvantage for the experienced obstetrician.

Merkow et al. evaluated neonatal neurobehavior in infants whose mothers received 30 mL of 0.5% bupivacaine, 1% mepivacaine, or 3% 2-chloroprocaine for pudendal nerve block and perineal infiltration before delivery. Neonatal response to pinprick at 4 hours was better in the mepivacaine group; otherwise, there were no significant differences among groups in neurobehavioral scores at 4 and 24 hours after delivery.

Regardless of the choice of local anesthetic, there is no indication for the administration of a concentrated solution. For example, it is unnecessary, and perhaps dangerous, to give 0.5% bupivacaine, 2% lidocaine, or 3% 2-chloroprocaine. Rather, the obstetrician should use 2% 2-chloroprocaine or 1% lidocaine.

Some obstetricians contend that the addition of epinephrine to the local anesthetic solution improves the quality of pudendal nerve block. Langhoff-Roos and Lindmark reported a randomized, double-blind study of 865 patients who received pudendal nerve block with 16 mL of 1% mepivacaine, 1% mepivacaine with epinephrine, or 0.25% bupivacaine. Mepivacaine with epinephrine provided effective anesthesia more often and also caused a greater “loss of the urge to bear down” than did the other two local anesthetic solutions. However, there was no significant difference among groups in the duration of the second stage of labor or the incidence of instrumental vaginal delivery. Schierup et al. randomly assigned 151 patients to receive pudendal nerve block with 20 mL of 1% mepivacaine either with or without epinephrine. The addition of epinephrine did not improve the quality of anesthesia, but it slightly prolonged the interval between pudendal nerve block administration and delivery. Maternal venous blood mepivacaine concentrations were slightly higher in the no-epinephrine group, but there was no difference between groups in umbilical cord blood concentrations of mepivacaine.

**Complications**

Maternal complications of pudendal nerve block are uncommon but may be serious (Box 24.2). Local anesthetic systemic toxicity may result from either direct intravascular injection or systemic absorption of an excessive dose of local anesthetic. Toxicity may occur if the obstetrician exceeds the safe dose of local anesthetic during repetitive injections performed to obtain a successful block. Vaginal, ischiorectal, and retroperitoneal hematomas may result from trauma to the pudendal artery. These hematomas are typically small and rarely require operative intervention. Subgluteal and retropsoal abscesses are rare but can result in significant morbidity or mortality.

Fetal complications are rare. The primary fetal complications result from fetal trauma and/or direct fetal injection of local anesthetic. Pages et al. reported three cases of neonatal lidocaine intoxication following maternal pudendal nerve block before delivery. Two infants required mechanical ventilation, and lidocaine was detected in the serum of two infants, but all three infants had complete recovery.

As with paracervical block, the performance of pudendal nerve block requires the obstetrician to make several blind needle punctures within the vagina. The needle guide does not uniformly protect the physician from a needle-stick injury. Thus, performance of pudendal nerve block may entail a risk for physician exposure to HCV, HIV, or another infectious agent.

**PERINEAL INFILTRATION**

Perineal infiltration is perhaps the most common local anesthetic technique used for vaginal delivery. Given the frequent failure of pudendal nerve block, obstetricians often perform pudendal nerve block and perineal infiltration simultaneously. Perineal infiltration also may be required in patients with incomplete neuraxial anesthesia. The obstetrician injects several milliliters of local anesthetic solution into the posterior fourchette. There are no large nerve fibers to be blocked, so the onset of anesthesia is rapid. However, perineal infiltration provides anesthesia only for episiotomy and repair. Anesthesia is often inadequate even for these limited procedures. Moreover, perineal infiltration provides no muscle relaxation. In a prospective randomized trial, perineal infiltration of saline-placebo provided postpartum analgesia that was equivalent to that provided by infiltration of either ropivacaine or lidocaine in women who underwent mediolateral episiotomy at vaginal delivery.
Choice of Local Anesthetic

Philipson et al. evaluated the pharmacokinetics of lidocaine after perineal infiltration. They gave 1% or 2% lidocaine without epinephrine during the crowning phase of the second stage of labor in 15 healthy parturients. The mean ± SD dose of lidocaine was 79 ± 3 mg, and the mean drug-to-delivery interval was 7.8 ± 7.0 minutes. The investigators detected lidocaine in maternal plasma as early as 1 minute after injection. Peak maternal plasma concentrations of lidocaine occurred between 3 and 15 minutes after injection. Despite the administration of small doses of lidocaine and the short drug-to-delivery intervals, there was rapid placental transfer of significant amounts of lidocaine. The mean fetal-to-maternal lidocaine concentration ratio of 1.32 was significantly higher than the ratio reported after administration of lidocaine for paracervical block, pudendal nerve block, or epidural anesthesia for vaginal or cesarean delivery. There was a significant correlation between the fetal-to-maternal lidocaine concentration ratio and the length of the second stage of labor. These investigators speculated that fetal tissue acidosis increased the fetal-to-maternal lidocaine ratio after perineal infiltration in this study. Finally, they noted the persistence of lidocaine and its pharmacologically active metabolites for at least 48 hours after delivery.

Subsequently, Philipson et al. evaluated the placental transfer of 2-chloroprocaine after perineal administration of 1% or 2% 2-chloroprocaine to 17 women shortly before delivery. The mean ± SD dose of 2-chloroprocaine was 81.8 ± 27.0 mg, and the mean drug-to-delivery interval was 6.7 ± 4.3 minutes. Perineal infiltration of 2-chloroprocaine provided adequate anesthesia for episiotomy repair except in two patients who required additional local anesthetic for repair of fourth-degree lacerations. The investigators did not detect 2-chloroprocaine in maternal plasma after infiltration or at delivery. Further, they detected 2-chloroprocaine at delivery in only one umbilical cord venous blood sample and no 2-chloroprocaine in neonatal plasma. In contrast, they consistently detected the drug’s metabolite, chloroaminobenzoic acid, in maternal plasma, umbilical cord venous plasma, and neonatal urine. The fetal-to-maternal ratio of chloroaminobenzoic acid (0.80) was similar to that reported after the administration of 2-chloroprocaine for paracervical block and epidural anesthesia for cesarean delivery. The investigators suggested that very little, if any, unchanged 2-chloroprocaine reaches the fetus after perineal infiltration. They concluded that 2-chloroprocaine may be preferable to lidocaine for antepartum perineal infiltration.

Complications

The obstetrician must take care to avoid injecting the local anesthetic into the fetal scalp. Kim et al. reported a case of newborn lidocaine toxicity after maternal perineal infiltration of 6 mL of 1% lidocaine before vaginal delivery. Similarly, De Praeter et al. reported a case of lidocaine toxicity in a newborn whose mother received perineal infiltration with 10 mL of 2% lidocaine 4 minutes before delivery. In both cases, the infants were initially vigorous but required endotracheal intubation 15 minutes after delivery. No lidocaine was detected in umbilical cord blood, but neonatal blood samples revealed concentrations of 14 µg/mL at 2 hours and 13.8 µg/mL at 6.5 hours. Small scalp puncture wounds suggested that the lidocaine toxicity resulted from direct fetal scalp injection. Pignotti et al. reported two cases of neonatal local anesthetic toxicity. In one case, lidocaine and prilocaine cream had been applied to the maternal perineum. In the second case, 10 mL of 2% mepivacaine had been injected into the perineum. The obstetrician must take care to avoid injecting the local anesthetic into the fetal scalp. Kim et al. suggested that the presence of a molded head in the occiput posterior position may predispose to unintentional direct injection of the fetal scalp. These cases support the recommendation for use of 2-chloroprocaine for perineal infiltration.

**KEY POINTS**

- Paracervical block and lumbar sympathetic block may provide effective analgesia for the first stage of labor. Neither technique relieves pain during the second stage.
- Fetal bradycardia is the most worrisome complication of paracervical block.
- Paracervical block is contraindicated in patients with uteroplacental insufficiency or preexisting fetal compromise.
- For patients without epidural or spinal analgesia, it is appropriate to perform pudendal nerve block when the patient complains of pelvic floor pain.
- Pudendal nerve block may provide satisfactory anesthesia for spontaneous vaginal delivery and outlet-forceps delivery, but it provides inadequate anesthesia for mid-forceps delivery, postpartum repair of the cervix, and manual exploration of the uterine cavity.
- Perineal infiltration provides anesthesia only for episiotomy and repair.
- It is unnecessary—and perhaps dangerous—to give concentrated solutions of local anesthetic for paracervical block, pudendal nerve block, or perineal infiltration.
- Some cases of fetal injury result from direct fetal scalp injection of local anesthetic during attempted paracervical block, pudendal nerve block, or perineal infiltration.
- 2-Chloroprocaine is most likely the safest choice of local anesthetic for paracervical block, pudendal nerve block, and perineal infiltration.
- The performance of either paracervical block or pudendal nerve block requires the obstetrician to make several blind needle punctures within the vagina. Thus, there is a risk for physician needle-stick injury during the performance of either procedure.
REFERENCES


CHAPTER 24 Alternative Regional Analgesic Techniques for Labor and Vaginal Delivery

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Many women choose tubal sterilization for permanent contraception. Of the approximately 700,000 cases performed annually in the United States, data from 1995-2006 found that half were performed postpartum and half as ambulatory interval procedures.\(^1\) Although the interval sterilization rate has declined by 12% in the United States, the postpartum sterilization rate remains stable, and postpartum sterilization is performed after 8% to 9% of all live births.\(^1\) The considerations and controversies regarding the administration of anesthesia for postpartum tubal sterilization are discussed in this chapter.

**American Society of Anesthesiologists Guidelines**

The American Society of Anesthesiologists (ASA) has published Practice Guidelines for Obstetric Anesthesia,\(^2\) which includes a discussion of postpartum tubal ligation (see Appendix B). The Task Force recommendations can be summarized as follows:

1. Before a postpartum tubal ligation, the patient should have no oral intake of solid foods within 6 to 8 hours of the surgery, depending on the type of food ingested (e.g., fat content).

2. Consider aspiration prophylaxis.

3. Both the timing of the procedure and the decision to use a specific anesthetic technique (i.e., neuraxial versus general) should be individualized, based on anesthetic and obstetric risk factors (e.g., blood loss at delivery), and patient preferences.

4. Consider selecting neuraxial techniques in preference to general anesthesia for most postpartum tubal ligations.

5. Be aware that gastric emptying will be delayed in patients who have received opioids during labor.

6. Be aware that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals.

7. If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, do not attempt the procedure at a time when it might compromise other aspects of patient care on the labor and delivery unit.

**Surgical Considerations**

Tubal sterilization can be performed satisfactorily at any time, but the early postpartum period has several advantages for women who have had an uncomplicated vaginal delivery.\(^3\) The patient avoids the cost and inconvenience of a second hospital visit. The uterine fundus remains near the umbilicus for several days postpartum, which allows easy access to the fallopian tubes via a mini-laparotomy. Mini-laparotomy and laparoscopy have similar rates of serious complications (e.g., bowel laceration, vascular injury), although postpartum tubal ligation is associated with lower failure rates than interval laparoscopic tubal ligation.\(^4\) Finally, costs may be lower with postpartum mini-laparotomy.

There are at least two potential disadvantages to immediate postpartum sterilization. First, parous women are at increased risk for uterine atony and postpartum hemorrhage. This risk decreases substantially 12 hours after delivery. Second, immediate surgery results in sterilization before assessment of the newborn is complete. Postpartum tubal ligation is not wise if the patient is ambivalent regarding permanent sterilization. However, women who undergo postpartum sterilization have a similar probability of regret.
Several techniques are used for postpartum tubal sterilization (Fig. 25.1). Puerperal sterilization has a failure rate that is lower than many interval procedures, and the failure rate is lowest (approximately 0.75%) if some form of tubal resection occurs. With the Irving procedure, the obstetrician buries the cut ends of the tubes in the myometrium and mesosalpinx. This technique is least likely to fail, but it requires more extensive exposure and increases the risk for hemorrhage. The Pomeroy procedure is simplest. The surgeon ligates a loop of oviduct and excises the loop above the suture. With the Parkland procedure, the obstetrician ligates the tube proximally and distally and then excises the mid-segment. The last two methods are most commonly performed during postpartum tubal ligations. Regardless of the technique, the obstetrician should document that the fimbriae are present to preclude ligation of another structure such as the round ligament. The excised portions typically are sent to a pathologist for verification. Recently, surgical technique has changed and instead of performing a tubal ligation for sterilization some surgeons are recommending a salpingectomy because bilateral salpingectomy reduces the incidence of ovarian cancer to a greater degree than tubal ligation, and it adds only approximately 10 minutes to the procedure without additional complications.

**NONMEDICAL ISSUES**

Nonmedical issues affect decisions regarding the timing of tubal sterilization. The obstetrician must obtain and document informed consent for surgery. Tubal ligation should be considered an irreversible procedure. Therefore, most obstetricians require a discussion with the patient before labor and delivery. Physicians should be aware of state laws or insurance regulations that may require a specific interval between obtaining consent and performance of sterilization procedures. Regulations often do not allow the woman to give consent while in labor or immediately after delivery. For example, the Medicaid reimbursement program includes the following requirements for sterilization:

- The patient must be at least 21 years of age and mentally competent when consent is obtained.
- Informed consent may not be obtained while the patient is in labor or during childbirth.
- Consent may not be obtained while the patient is undergoing an abortion or under the influence of alcohol or other substances.
- A total of 30 days must pass between the date the consent is signed and the date the procedure is performed. (Exceptions to the 30-day waiting period can be made for preterm delivery or emergency abdominal surgery.)
- Consent is valid for only 180 days.

An ethical analysis of the Medicaid sterilization consent regulations notes: “…the regulations are ethically flawed: by preventing women from accessing needed family planning services, the Medicaid consent rules violate the standards of beneficence and non-maleficence; by treating publically insured women differently from privately insured women, they fail the justice standard; and by placing constraints on women’s free choice of contraceptive methods, they run afoul of the autonomy standard.”

In some cases the obstetrician may schedule a patient for a postpartum tubal sterilization because of a fear that the patient will not return for interval tubal sterilization 6 weeks after delivery. Concerns regarding patient compliance should not prompt the performance of postpartum tubal sterilization in patients with significant medical or obstetric complications. However, women who request postpartum tubal sterilization but do not receive it are more likely to become
pregnant within 1 year of delivery (46.7%) than are women who did not request the procedure (22.3%).

The American College of Obstetricians and Gynecologists (ACOG) has stated that given the consequences of a missed procedure and the limited time frame in which it may be performed, postpartum sterilization should be considered an urgent surgical procedure. They also stated that obstetrician-gynecologists should identify and eliminate barriers that restrict access to postpartum sterilization. The ACOG concluded that obstetrician-gynecologists should be champions or patient advocates for postpartum sterilization in their respective hospitals and help to coordinate administration and health care staff in streamlining access to the procedure. Increasing access and availability of postpartum sterilization may not only directly improve outcomes for women desiring the procedure, but may decrease overall costs to the health care system.

PREOPERATIVE EVALUATION

The patient scheduled for postpartum tubal sterilization requires a thorough preoperative evaluation, and a reevaluation should be performed even if the patient is known to the anesthesia provider as a result of the provision of labor analgesia. A cursory evaluation should not be performed simply because the patient is young and healthy. Patients with preeclampsia may safely receive neuraxial or general anesthesia for postpartum tubal sterilization provided that there is no evidence of pulmonary edema, oliguria, or thrombocytopenia.

Physicians and nurses often underestimates blood loss during delivery. Excessive blood loss from uterine atony is not uncommon in parous women. Orthostatic changes in blood pressure and heart rate should be excluded, especially if an immediate postpartum procedure is to be performed. At the University of Colorado, for surgery performed the day after delivery, the patient’s hematocrit is determined several hours after delivery (to allow for equilibration) and compared with the antepartum measurement. A hematocrit is not obtained before an immediate postpartum tubal sterilization (performed less than 8 hours after delivery), provided that the antepartum hematocrit was acceptable, there are no orthostatic vital sign changes, and there was no evidence of excessive blood loss during delivery.

No absolute value of hematocrit requires a delay of surgery, but physical signs of hemodynamic instability or laboratory evidence of excessive blood loss should prompt postponement of the procedure until 6 to 8 weeks postpartum. Fever may signal presence of endometritis or uterine tract infection and may also require postponement of surgery until a later date. Finally, the condition of the neonate should be confirmed before surgery to exclude any unexpected problems.

Mothers may be concerned that medications administered during surgery might affect their ability to breast-feed or that these medications might harm the newborn. Any drug present in the mother’s blood will be present in breast milk, with the concentration dependent on factors such as protein binding, lipid solubility, and degree of ionization. Typically, the amount of drug present in breast milk is small. Opioids, barbiturates, and propofol administered during anesthesia are excreted in insignificant amounts. (See Chapter 14 for a detailed discussion of interactions between drugs and breast-feeding.)

RISK FOR ASPIRATION

Historically, anesthesiologists have considered maternal aspiration the major risk associated with anesthesia for postpartum tubal sterilization, although the evidence for this is scant and conflicting. A review of anesthesia-related maternal mortality found no maternal deaths associated with aspiration during postpartum tubal ligation, despite tracking deaths for an entire year after delivery. A review of serious complications related to obstetric anesthesia sponsored by the Society for Obstetric Anesthesia and Perinatology also did not identify any cases of maternal death related to aspiration during postpartum tubal ligation. However, several factors may place the pregnant woman at increased risk for aspiration. Some but not all of these factors are resolved at delivery. The placenta is the primary site of progesterone production, and progesterone concentrations fall rapidly after delivery of the placenta (Fig. 25.2). Typically, progesterone concentrations decline within 2 hours of delivery; and by 24 hours postpartum, progesterone concentrations are similar to those found during the luteal phase of the menstrual cycle.

Two important questions to address during the preanesthetic evaluation are (1) What is the duration of the fast for solids? (2) Were parenteral opioids administered during labor?

Gastric Emptying

Several studies have assessed gastric emptying in pregnant and postpartum women. O’Sullivan et al. used an epigastric impedance technique to compare gastric emptying times for solids and liquids in women during the third trimester of pregnancy, in women during the first hour postpartum, and in nonpregnant controls. The investigators observed that the overall rate of gastric emptying was lower in the postpartum patients than in the pregnant or nonpregnant patients. However, when patients who had received parenteral opioids in labor were separated from those who had not, rates of gastric emptying for women who had not received opioids were similar to those for nonpregnant controls. The investigators concluded that the rate of gastric emptying in postpartum women is delayed only if opioids have been administered during labor.

Other studies have used the acetaminophen (paracetamol) absorption technique to assess gastric emptying. Gin et al. studied women on the first and third days after delivery and at 6 weeks postpartum. They found comparable times to peak concentration of acetaminophen in all three groups. They concluded that gastric emptying was no different in the immediate postpartum period than 6 weeks later, and they
recommended that “the approach to prophylaxis against acid aspiration should be more consistent between nonpregnant and postpartum patients.”

Sandhar et al.\textsuperscript{21} used applied potential tomography to measure gastric emptying in 10 patients at term gestation, 2 to 3 days postpartum, and 6 weeks postpartum. The 6-week measurement served as each woman’s control value. All measurements were made after administration of an H\textsubscript{2}-receptor antagonist. The times to 50% emptying after ingestion of 400 mL of water were not different among the three periods of testing (Fig. 25.3).

Wong et al.\textsuperscript{22} assessed gastric emptying in nonlaboring pregnant women at term gestation, after ingestion of either 50 or 300 mL of water, by using two techniques: (1) serial assessment of acetaminophen absorption and (2) use of ultrasonography to determine gastric antrum cross-sectional areas. Gastric emptying was significantly faster after ingestion of 300 mL of water, consistent with the observation that a liquid meal may actually accelerate gastric emptying. Repeating the study in obese women showed similar results.\textsuperscript{23} Kubli et al.\textsuperscript{24} compared the effects of isotonic “sport drinks” versus water on residual gastric volume in women in early labor. Women who received isotonic sport drinks had similar gastric volumes and a similar incidence of vomiting as compared with those who received water, but the ingestion of sport drinks prevented the increase in ketone production that occurred in the control (water) group.

In contrast, Jayaram et al.\textsuperscript{25} found that 39% of women presenting for postpartum tubal ligation had solid food particles in the stomach, as demonstrated by ultrasonography, but they did not find solid food particles in a control group of nonpregnant women presenting for gynecologic surgery. They also found that 4 hours after a standardized meal in women not scheduled for surgery, 95% of postpartum women—compared with only 19% of nonpregnant subjects—still had solid food particles in the stomach. Prior administration of an opioid did not seem to be a risk factor in this study. Scrutton et al.\textsuperscript{26} randomized 94 women presenting in early labor to receive either a light diet or water only during labor. The mothers who ate a light diet had significantly larger gastric antrum cross-sectional areas (determined by ultrasonography) and were twice as likely to vomit at or around delivery as those who had water only. Also, the volumes vomited were significantly larger in the women who ate a light diet.
During the preoperative assessment of any woman scheduled for postpartum tubal sterilization, the anesthesia provider should determine when the patient last consumed solids and whether opioids were administered by any route. Systemic absorption of an opioid occurs after epidural administration. However, published studies have provided conflicting results regarding the effect of epidural opioid administration on gastric emptying. Wright et al.\textsuperscript{27} observed that epidural administration of 10 mL of 0.375% bupivacaine with fentanyl 100 µg caused a modest prolongation of gastric emptying during labor when compared with epidural administration of bupivacaine alone. However, Kelly et al.\textsuperscript{28} found that intrathecal, but not epidural, fentanyl delayed gastric emptying.

In summary, the preponderance of evidence suggests that (1) administration of an opioid during labor increases the likelihood of delayed gastric emptying during the early postpartum period; (2) gastric emptying of solids is delayed during labor and in the immediate postpartum period in all parturients; and (3) gastric emptying of clear liquids is probably not delayed unless parenteral opioids were administered.

**Gastric Volume and pH**

There is little evidence that postpartum women are at greater risk for sequelae if aspiration occurs than patients undergoing elective surgery, based solely on pregnancy-induced changes in gastric pH and volume. The conventional wisdom is that a gastric volume of more than 25 mL and a gastric pH of less than 2.5 are risk factors for aspiration pneumonia. Côté\textsuperscript{29} noted that this dogma was derived from unpublished animal studies and that it assumes that every milliliter of gastric fluid is directed into the trachea. A marked disparity exists between the incidence of patients labeled “at risk” and the incidence of patients with clinically significant aspiration pneumonia.

Blouw et al.\textsuperscript{30} measured gastric volume and pH in nonpregnant women undergoing gynecologic surgery and postpartum women 9 to 42 hours after delivery. They found no significant difference between the groups. Approximately 75% of women in both groups had a gastric pH of less than 2.5. When the combination of volume and pH was used to determine the risk for aspiration, 64% of the control patients but only 33% of postpartum patients were at risk. The researchers concluded that 8 hours after delivery, postpartum patients are not at greater risk than nonpregnant patients undergoing elective surgery. They did not examine patients earlier than 8 hours after delivery. In addition, they observed that a large number of patients in both groups are at risk based on their gastric volumes and pH.

James et al.\textsuperscript{31} attempted to determine the “safe” interval after delivery. They compared gastric pH and gastric volume in postpartum women 1 to 8 hours, 9 to 23 hours, and 24 to 45 hours after delivery with a control group of nonpregnant women undergoing elective surgery. There were no significant differences in either parameter between the group of patients undergoing elective surgery and any of the postpartum groups (Table 25.1). Approximately 60% of all patients were considered “at risk” for aspiration pneumonitis. The investigators concluded that there was no difference in the risk for sequelae if aspiration should occur, but they speculated that hormonal changes or mechanical factors might make aspiration more likely during the postpartum period.

Finally, Lam et al.\textsuperscript{32} administered 150 mL of water to 50 women 2 to 3 hours before tubal ligation that was performed 1 to 5 days postpartum. Another 50 postpartum and 50 nonpregnant women fasted after midnight. The authors found no differences in gastric pH or volume among the postpartum-water group, the postpartum-fasted group, and the group of nonpregnant controls undergoing elective surgery.

**Gastroesophageal Reflux**

Women in the third trimester of pregnancy have decreased lower esophageal barrier pressures as compared with nonpregnant controls.\textsuperscript{33} Those with symptoms of heartburn have even lower pressures and a higher incidence of gastric reflux. Vanner and Goodman\textsuperscript{34} asked parturients to swallow a pH electrode to measure lower esophageal pH at term and on the second postpartum day. Patients were placed in four positions: supine with tilt, left lateral, right lateral, and lithotomy, and were then asked to perform a Valsalva and other maneuvers to promote reflux. A total of 17 of 25 patients had reflux at term, whereas only 5 of 25 had reflux after delivery. The investigators concluded that the incidence of reflux returns toward normal by the second day after delivery. However, this conclusion is arguable given the fact that they did not determine normal by defining the incidence of reflux before or 6 to 8 weeks after pregnancy.

**Summary of Aspiration Risk**

No data indicate that the postpartum patient’s safety is enhanced by delaying surgery or is compromised by proceeding with surgery immediately after delivery. This situation has led to confusion and inconsistency in the development of policies for the performance of postpartum tubal sterilization.\textsuperscript{35} No particular waiting interval guarantees that the postpartum patient is free of risk for aspiration. It is probably

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**TABLE 25.1 Gastric Volume and pH at Intervals after Delivery**

<table>
<thead>
<tr>
<th>Volume</th>
<th>pH &lt; 2.5 (%)</th>
<th>At Risk* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 25 mL (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (1–8 h)</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>Group 2 (9–23 h)</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Group 3 (24–45 h)</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>Group 4 (control)</td>
<td>67</td>
<td>80</td>
</tr>
</tbody>
</table>

*Gastric contents with pH < 2.5 and volume > 25 mL.

prudent to use some form of aspiration prophylaxis in all patients undergoing postpartum tubal sterilization. However, significant aspiration pneumonitis is so rare that it will be difficult to document cost-effectiveness and decreased rates of morbidity and mortality from the use of these measures. H$_2$-receptor antagonists and antacids do not reduce the possibility of regurgitation and aspiration, but they may make the consequences less severe. Metoclopramide (a prokinetic agent) may decrease the incidence of reflux by increasing lower esophageal sphincter tone and hastening gastric emptying.\textsuperscript{35} None of these medications can guarantee that gastric contents will not enter the lungs. Aspiration is best prevented by an experienced anesthesia provider using careful airway management or by use of a neuraxial anesthetic technique.

Performance of an immediate postpartum tubal sterilization (within 8 hours of delivery) may decrease both length of hospital stay and hospital costs. In this era of health care cost containment, any decision to postpone surgery that requires an extra day of hospitalization must be evaluated carefully. Anesthesia providers and obstetricians have questioned the need to wait 8 or more hours after delivery if gastric emptying time and gastric volume and pH are no different in the postpartum patient from those in nonpregnant women. Possible reasons to consider an 8-hour delay are as follows. First, women may remain at increased risk for gastroesophageal reflux immediately after delivery. Second, delays in gastric emptying due to the antepartum administration of opioids will resolve during this period. Third, an 8-hour delay allows the administration of aspiration prophylaxis drugs, although they might also be given during labor. Fourth, maximal hemodynamic stress and potential instability occur immediately postpartum when central blood volume suddenly increases because of contraction of the evacuated uterus, relief of aortocaval compression, and loss of the low-resistance placental circuit; indeed, the patient with cardiovascular disease is at greatest risk for hemodynamic decompensation immediately postpartum. Fifth, if there are concerns about excessive blood loss at delivery, an 8-hour delay allows the physician to assess serial hemodynamic measurements (including the presence or absence of orthostatic changes), obtain an equilibrated postpartum hematocrit, and, if necessary, restore intravascular volume. Sixth, delay allows a more thorough evaluation of the infant. Finally, delay allows the woman more time to assess her decision. However, it is important to remember that women who request postpartum tubal sterilization but do not receive it before discharge from the hospital are twice as likely to become pregnant within 1 year of delivery than women who did not request the procedure.\textsuperscript{11} The ACOG has stated that given the consequences of a missed procedure, postpartum sterilization should be considered an urgent surgical procedure.\textsuperscript{12}

At the University of Colorado, we follow standard NPO guidelines (i.e., no solid foods for 6 to 8 hours [depending on fat content] and no clear liquids for 2 hours) before postpartum tubal sterilization. NPO policies for postpartum tubal sterilization should not differ from those used for elective surgery in the main operating rooms. Immediate postpartum tubal sterilization may be performed in patients who have a functioning epidural catheter in place. These patients are given an H$_2$-receptor antagonist and metoclopramide intravenously during labor or immediately after delivery, and a clear (nonparticulate) antacid is administered just before taking the patient to the operating room. In other patients who do not want (or are unable to receive) epidural analgesia for labor, similar precautions are used. This is an elective procedure, and patients should not have consumed solid food for 6 to 8 hours preoperatively. Before surgery, estimated blood loss is reviewed and orthostatic vital signs may be assessed. Most of these patients (without preexisting epidural analgesia) receive spinal anesthesia for postpartum tubal sterilization. However if the patient strongly prefers, general anesthesia can be provided using rapid-sequence induction with cricoid pressure.

**ANESTHETIC MANAGEMENT**

Local, general, or neuraxial anesthesia may be used successfully for postpartum tubal sterilization. Physiology remains altered in the postpartum patient and requires some modification in anesthetic technique. It seems reasonable to give all postpartum patients some form of aspiration prophylaxis.\textsuperscript{3} This may include a clear (nonparticulate) antacid, an H$_2$-receptor antagonist, and/or metoclopramide to increase lower esophageal sphincter tone and hasten gastric emptying. Metoclopramide also may prevent emesis during and after surgery. Patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes mellitus) warrant prophylaxis with all three classes of drugs. Tubal sterilization does not require administration of preoperative antibiotics.\textsuperscript{36}

**Local Anesthesia**

Local anesthesia is used for more than 75% of tubal sterilizations worldwide, although neuraxial anesthesia is most often administered for postpartum tubal sterilization in the United States.\textsuperscript{3} Several reports have documented the efficacy and safety of local anesthesia for postpartum or laparoscopic tubal ligation in the hospital operating room or a free-standing outpatient facility. Cruikshank et al.\textsuperscript{37} described the use of intraperitoneal lidocaine for postpartum tubal ligation. After intravenous administration of diazepam, lidocaine 100 mg was used to infiltrate the skin and subcutaneous tissue. The peritoneum was entered, and 400 mg of lidocaine (80 mL of 0.5% solution) was instilled into the peritoneal cavity. A Pomeroy tubal ligation was performed 5 minutes later. All patients had complete peritoneal anesthesia, and all patients stated they would have the same procedure again. None recalled any pain or discomfort 24 hours later. There were no signs of lidocaine toxicity in any patient, and the maximum lidocaine blood level obtained was 5.3 µg/mL (the toxic blood level is generally considered greater than 5 µg/mL). Surgeons rated the conditions excellent. This study was published in 1973, when anesthesiologists may or may not have been involved and before ASA monitoring standards such as pulse oximetry existed.
Poindexter et al. 38 described almost 3000 laparoscopic tubal sterilization procedures performed with local anesthesia in an ambulatory surgical facility. After intravenous sedation with midazolam (5 to 10 mg) and fentanyl (50 to 100 μg), the skin was infiltrated with 10 mL of 0.5% bupivacaine. After insertion of the trocar, the abdomen was insufflated with nitrous oxide. Each tube was sprayed with 5 mL of 0.5% bupivacaine, and a Silastic ring was applied. Patients were discharged home after approximately 1 hour in the postanesthesia care unit. The authors reported a technical failure rate of 0.14% and no unintended laparotomies or intraoperative complications. They reported that this technique reduced surgical time by 33% and cost by 68% to 85% when compared with general anesthesia. The investigators presented no data regarding patient satisfaction, and they made no comment on the use of pulse oximetry or blood pressure monitors. Four percent of patients, however, required oxygen therapy for “adequate tissue perfusion.” This study was done in the 1980s, before many ambulatory surgery facilities had institutional guidelines for sedation.

General Anesthesia

Much of the impetus for performing sterilization procedures under local anesthesia came from two reports in 1983 indicating that morbidity and mortality were much higher when general anesthesia was used. It is important to realize that these reports preceded the mandatory use of pulse oximetry and capnography and do not reflect modern anesthesia care. The first report involved 3500 interval (not postpartum) laparoscopic tubal sterilizations at nine university medical centers. 39 Among all patients, the risk for intraoperative or postoperative complications was 1.75%, but the risk was five times higher with general anesthesia than with local anesthesia. (In this report, local anesthesia included local, epidural, and spinal anesthesia.) The reason(s) for the difference was unclear. In the second report, the U.S. Centers for Disease Control and Prevention examined deaths attributed to tubal sterilization procedures from 1977 to 1981. 40 Both immediate postpartum laparotomies and interval laparoscopic procedures were included. Of the 29 deaths, 11 followed complications of general anesthesia and were caused by hypventilation or cardiorespiratory arrest. Aspiration was not reported as a cause of death. Of the six patients whose deaths were definitely attributed to hypventilation, none had undergone tracheal intubation. Five of the 11 deaths attributed to general anesthesia occurred during postpartum laparotomy. Of these, only one woman had undergone tracheal intubation; all others underwent mask ventilation. The investigators concluded, “It appears that for tubal sterilization, like abortion, the greatest risk for death is that associated with the anesthesia used during the procedure.”

In the 35 years since those reports, appropriate airway management with tracheal intubation has become standard practice. Thorough adherence to ASA standards for basic anesthesia monitoring (including use of pulse oximetry and capnography to monitor oxygenation and ventilation) should help reduce morbidity and mortality associated with general anesthesia. At the University of Colorado, rapid-sequence induction (with cricoid pressure) is performed and all patients undergo tracheal intubation during administration of general anesthesia for postpartum tubal sterilization.

Volatile anesthetic agents cause uterine relaxation and could potentially increase the risk for postpartum hemorrhage if administered to women in the immediate postpartum period. Therefore, the question arises as to whether the anesthesia provider should use an inhalation or an intravenous technique to maintain general anesthesia for postpartum tubal sterilization. Marx et al. 41 measured postpartum uterine activity and the response to oxytocin with different concentrations of halothane or enflurane (Fig. 25.4). Impairment of spontaneous uterine activity occurred at 0.5 minimum alveolar concentration (MAC) of both agents, and loss of the response to oxytocin occurred near 1 MAC. Spontaneous contractions reappeared when anesthetic concentrations were reduced below these levels. Parous women are at risk for postpartum uterine atony, and administration of a high concentration of a volatile halogenated agent may precipitate postpartum hemorrhage.

Two studies have determined the MAC of isoflurane during the postpartum period. Chan and Gin 42 found a positive correlation between MAC and the length of time after delivery, with nonpregnant values achieved by 72 hours postpartum. Zhou et al. 43 determined that the MAC of isoflurane was approximately 0.75% in the first 12 hours postpartum and 1.04% in patients who were 12 to 24 hours postpartum. No significant difference in MAC existed between the latter group and a control group of nonpregnant gynecologic patients. Together these results demonstrate that the reduced MAC observed during pregnancy persists for a variable period between 12 and 36 hours postpartum.

Propofol has advantages (e.g., rapid awakening, decreased incidence of emesis) that make it attractive as an induction agent for short sterilization procedures. When propofol was used for induction and maintenance of anesthesia for cesarean delivery, breast milk samples obtained at 4 and 8 hours postpartum had a low concentration of the drug, which suggested a negligible newborn exposure to propofol. 44 Use of sodium thiopental for induction of anesthesia also results in negligible newborn exposure during subsequent breast-feeding.

Alterations occur in the activity of both depolarizing and nondepolarizing muscle relaxants during the postpartum period. Evans and Wroe 45 described the changes in plasma cholinesterase activity during pregnancy. A rapid decline in activity occurred during the first trimester. This low level of activity was maintained until delivery and was followed by an even lower level of activity during the first week postpartum. Ganga et al. 46 found that a lower dose of succinylcholine was required to achieve 80% twitch suppression in postpartum women than in nonpregnant women. Time to recovery also was prolonged and correlated with lower cholinesterase activity in the postpartum patients. Leighton et al. 47 studied four groups of patients: nonpregnant, nonpregnant using oral contraceptives, term pregnant, and postpartum women.
Cholinesterase activity was significantly lower in both term pregnant and postpartum women. Recovery time was 25% longer in the postpartum patients than in other groups (685 seconds versus approximately 500 seconds). Although a 3-minute prolongation of paralysis may not seem clinically significant, it could be important if airway difficulties occur. Metoclopramide prolongs neuromuscular block with succinylcholine by 135% to 228% because of its inhibition of plasma cholinesterase. Ranitidine does not affect either plasma cholinesterase activity or the duration of action of succinylcholine.

Several studies have evaluated the use of the nondepolarizing muscle relaxants rocuronium, mivacurium, vecuronium, atracurium, and cisatracurium in postpartum patients. Rocuronium’s duration of action is prolonged by approximately 25% in postpartum patients, and mivacurium’s duration of action is prolonged by approximately 20%. In postpartum patients, the duration of action of vecuronium is prolonged by more than 50%. In contrast, the duration of action for atracurium is unchanged and that of cisatracurium is significantly shorter in the postpartum period. Prolongation of neuromuscular block could be clinically significant during a short procedure. Khuenl-Brady et al. suggested that a relative decrease in hepatic blood flow and/or competition between vecuronium and steroid hormones for hepatic uptake may interfere with the hepatic clearance of vecuronium in postpartum women. Alternatively, Gin et al. concluded that the duration of action for rocuronium is not prolonged in postpartum women if lean body mass—rather than total body weight—is used to calculate dose. These researchers speculated that the prolonged duration noted earlier might be explained by relative drug overdose if the dose of rocuronium is based on the patient’s temporarily increased body weight. Sugammadex has been used to reverse neuromuscular blockade with rocuronium after cesarean delivery, and it can be used to reverse neuromuscular blockade after postpartum tubal sterilization as well. Data from adult patients having abdominal surgery showed that sugammadex reversal, when compared to reversal with neostigmine, shortened the time until the patient was ready for discharge from the operating room and eliminated residual neuromuscular blockade in the PACU.
Neuraxial Anesthesia

Spinal and epidural anesthesia both provide excellent operating conditions for postpartum tubal sterilization. Airway obstruction, hypventilation, and aspiration are much less likely during and after neuraxial anesthesia. A sensory level of T4 is needed to block visceral pain during exposure and manipulation of the fallopian tubes. The choice between spinal and epidural anesthesia is a matter of personal preference for the patient and the anesthesia provider.

Epidural Anesthesia

When the performance of postpartum tubal sterilization is anticipated in a parous patient, I encourage administration of epidural analgesia for labor and delivery. The epidural anesthetic can be extended for immediate postpartum tubal sterilization if appropriate. I avoid administration of parenteral opioids during labor if immediate postpartum tubal sterilization is planned. Immediate postpartum tubal sterilization may save the patient the cost and inconvenience of an extra day in the hospital, allow her to eat shortly after delivery (and surgery), and enable her to avoid the apprehension of undergoing a surgical procedure the following day. The avoidance of opioids helps maintain normal gastric emptying, which should decrease any risk for aspiration during postpartum surgery. If the patient is stable and personnel are available, the procedure may be performed soon after delivery. The obstetrician must exclude excessive intrapartum blood loss and document that the patient has given informed consent. The patient should also be asked whether the epidural catheter provided adequate analgesia for her delivery. A catheter that was inadequate for labor analgesia is unlikely to provide adequate surgical anesthesia.

At the time the patient is moved to the operating room, an epidural test dose is given to rule out intrathecal or intravascular migration of the epidural catheter, and the sensory level is extended with a concentration of local anesthetic suitable for surgical anesthesia. A short-acting local anesthetic (e.g., 3% 2-chloroprocaine) is usually appropriate because the procedure is short in duration. An alternative choice is 2% lidocaine with epinephrine 1:200,000, although this may prolong her PACU stay while the block resolves. The addition of 100 μg epidural fentanyl may also improve the quality of the block. Appropriate sedative drugs also may be given, if the patient requests.

If surgery is not performed immediately after delivery, the catheter may be left in place for later postpartum tubal sterilization. Several studies have evaluated the efficacy of using a previously placed epidural catheter for a tubal ligation performed several hours after delivery. Vincent and Reid found that the mean delivery-to-surgery interval was shorter in those patients who had adequate epidural anesthesia than in those without adequate anesthesia (10.6 versus 14.8 hours). The chance of successful epidural anesthesia was greatest if the catheter was used within 4 hours of delivery. In contrast, Lawlor et al. reported an 87% success rate using an indwelling epidural catheter for postpartum tubal ligation, and they observed no difference in the catheter placement-to-surgery interval between the successful epidural and failed epidural groups (21.4 versus 20.5 hours). In this study, each epidural catheter was threaded 4 to 7.5 cm into the epidural space. Similarly, Goodman and Dumas reported an overall success rate of 92% with the use of an indwelling epidural catheter for postpartum tubal ligation. The success rate was 93% among patients who underwent surgery less than 24 hours after delivery but only 80% among the 10 patients who underwent surgery more than 24 hours after delivery (Fig. 25.6).

Spinal Anesthesia

Spinal anesthesia for postpartum tubal sterilization has several advantages over epidural anesthesia. Epidural anesthesia requires the use of a large volume of concentrated local anesthetic and thereby introduces the risk for intravascular injection and cardiotoxicity. Epidural anesthesia also is time-consuming; the induction of epidural anesthesia may require more time than the tubal sterilization itself. Spinal anesthesia is simple to perform, is rapid in onset, and provides dense sensory and motor block. In one study, spinal anesthesia for postpartum tubal ligation was associated with lower professional fees and operating room charges than attempted reactivation of an epidural catheter placed during labor. There is no need to reinject a catheter intraoperatively for a short procedure such as postpartum tubal sterilization, and...
Intrathecal lidocaine requirements were similar in pregnant and postpartum patients, even though plasma and CSF progesterone concentrations were lower in the postpartum women. The authors suggested “that a minimum level of progesterone in the CSF and/or plasma is necessary for this heightened local anesthetic activity” associated with progesterone. Together these studies suggest that local anesthetic requirements return to nonpregnant requirements 12 to 36 hours after delivery.\textsuperscript{64–66}

Huffnagle et al.\textsuperscript{67} gave hyperbaric intrathecal lidocaine 75 mg to postpartum women to determine whether age, weight, height, body mass index, vertebral column length, or time from delivery to placement of the block correlated with the spread of sensory block. Only patient height had a weak positive correlation, and it accounted for less than 15% of the variance in height of the block. Because of the large variation in the spread of sensory block among patients of the same height, the investigators concluded that there was little use in adjusting the dose of local anesthetic on the basis of height.

Many anesthesia providers have discontinued the use of hyperbaric lidocaine for spinal anesthesia because of concern about transient neurologic symptoms or transient radicular irritation, but obstetric patients may be at lower risk for this complication. A prospective nonrandomized study of 303 obstetric patients who received spinal anesthesia during a 9-month period observed a 0% incidence of transient radicular irritation (95% confidence interval 0% to 4.5%).\textsuperscript{68} Patients underwent a variety of procedures, including cesarean delivery, postpartum tubal ligation, cerclage, and other cases. The number of patients was too small to determine the true incidence of transient radicular irritation in obstetric patients, but the investigators concluded that the true incidence is likely less than 5%. In a randomized controlled trial, Philip et al.\textsuperscript{69} compared spinal administration of hyperbaric 5% lidocaine with that of hyperbaric 0.75% bupivacaine for postpartum tubal ligation. They observed a 3% incidence of transient neurologic symptoms with the use of lidocaine, compared with a 7% incidence with bupivacaine, a nonsignificant difference. In an editorial accompanying their report, Schneider and Birnbach\textsuperscript{70} acknowledged that “there are no very short-acting hyperbaric spinal local anesthetics that have taken the place of lidocaine for these short procedures and many believe that spinal bupivacaine lasts too long to be a reasonable choice of anesthetic for a procedure that will last less than 20 minutes.” However, they concluded, “Because pregnant patients represent a population that lies to the extreme in terms of the criteria for safety and lack of morbidity, we believe that for the present, there is still insufficient safety evidence to suggest that spinal hyperbaric 5% lidocaine be routinely used in obstetrics.” At the University of Colorado, some anesthesia providers use 5% lidocaine because of its short duration of action, whereas others prefer to avoid spinal lidocaine despite the low risk for transient neurologic symptoms in obstetric patients.

Postpartum women seem to be at lower risk for hypotension during spinal anesthesia than pregnant women, and

### TABLE 25.2 Risk for Post–Dural Puncture Headache after Spinal and Epidural Anesthesia in Obstetric Patients

<table>
<thead>
<tr>
<th>Needle Used\textsuperscript{*}</th>
<th>Number of Anesthetics</th>
<th>Incidence of PDPH (%)</th>
<th>Patients with PDPH Who Required Epidural Blood Patch (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quincke 26-gauge</td>
<td>2256</td>
<td>5.2</td>
<td>33</td>
</tr>
<tr>
<td>Quincke 27-gauge</td>
<td>852</td>
<td>2.7</td>
<td>39</td>
</tr>
<tr>
<td>Whitacre 25-gauge</td>
<td>1000</td>
<td>1.2</td>
<td>13</td>
</tr>
<tr>
<td>Epidural 17-gauge</td>
<td>21,578</td>
<td>1.3</td>
<td>75</td>
</tr>
</tbody>
</table>

\textsuperscript{*}There was a significant difference in the incidence of post–dural puncture headache between the 26-gauge Quincke needle and the epidural needle (\(P < .05\)), but not between the Whitacre needle or the 25-gauge Quincke needle and the epidural needle.


PDPH, Post–dural puncture headache.

Quincke needles have a cutting bevel. Whitacre needles have a pencil-point tip.

there is no need for prolonged postoperative analgesia. The risk for post–dural puncture headache is low if a small-gauge (25- or 27-gauge) pencil-point or noncutting spinal needle is used. Indeed, some studies have suggested that the incidence of post–dural puncture headache in obstetric patients is no different after spinal anesthesia with a 25-gauge Whitacre needle from that after planned epidural anesthesia (Table 25.2).

Local anesthetic requirements for spinal and epidural anesthesia are decreased during pregnancy, but studies have demonstrated a return to nonpregnant requirements by 36 hours postpartum. Assali and Prystowsky\textsuperscript{64} demonstrated a return to nonpregnant requirements by 36 to 48 hours postpartum. Abouleish\textsuperscript{65} prospectively compared the dose of spinal bupivacaine required for cesarean delivery with that required for postpartum tubal ligation. He noted that 30% more bupivacaine was required to achieve a T4 dermatomal level in women who were 8 to 24 hours postpartum. The reason for the rapid decrease in sensitivity to local anesthetics is unclear but may be related to the rapid fall in progesterone levels after delivery of the placenta.

Datta et al.\textsuperscript{66} examined plasma and cerebrospinal fluid (CSF) progesterone concentrations and spinal lidocaine requirements in nonpregnant, term pregnant, and postpartum women 12 to 18 hours after delivery. Plasma progesterone levels in pregnant women were 60 times higher than in nonpregnant women but only seven times higher than those in postpartum women. CSF progesterone concentrations were eight times higher in term pregnant women and three times higher in postpartum women than in nonpregnant women. Assali and Prystowsky\textsuperscript{64} demonstrated a return to nonpregnant requirements by 36
maintenance of uteroplacental perfusion is not a concern after delivery. Abouleish\textsuperscript{65} gave ephedrine to correct maternal hypotension in 83% of pregnant women who received spinal bupivacaine anesthesia for cesarean delivery. In contrast, only 7% of postpartum women who received spinal anesthesia for tubal ligation required ephedrine. An autotransfusion of blood occurs immediately after delivery. The greater intravascular volume and the lack of aortocaval compression may help protect postpartum patients from hypotension during spinal anesthesia. Sharma et al.\textsuperscript{71} compared the use of crystalloid with the use of 6% hetastarch for the prevention of hypotension during spinal anesthesia for postpartum tubal ligation. They observed a 52% incidence of hypotension in the crystalloid group and a 16% incidence in the hetastarch group. However, they acknowledged that the greater expense of colloid, as well as the risk for an allergic reaction, might not be justifiable. Suelto et al.\textsuperscript{72} compared normotensive and hypertensive patients receiving hyperbaric lidocaine for postpartum tubal ligation and found no difference in the use or dose of ephedrine for treatment of hypotension.

Preservative-free intrathecal meperidine can be used as an alternative to local anesthetic for postpartum tubal sterilization. The typical dose is 1 mg per kilogram prepregnant weight (50 to 80 mg) for cesarean delivery or tubal sterilization. With an onset time of 3 to 5 minutes and a duration of 30 to 60 minutes, intrathecal meperidine compares favorably with 5% lidocaine. In a study that compared intrathecal lidocaine 70 mg with intrathecal meperidine 60 mg for postpartum tubal ligation, patients who received meperidine had more pruritus but longer postoperative analgesia (448 versus 83 minutes, respectively).\textsuperscript{73} There was no difference between groups in rates of nausea, hemoglobin desaturation, or patient satisfaction. Intrathecal meperidine may be an alternative to lidocaine or bupivacaine for postpartum tubal sterilization.

**Box 25.1** summarizes anesthetic management for postpartum tubal sterilization.

**POSTOPERATIVE ANALGESIA**

Postpartum tubal sterilization produces modest postoperative pain of short duration. Patients may receive one dose of parenteral opioid postoperatively, followed by oral analgesics. Optimal analgesia encourages early ambulation, interaction with the newborn, and early discharge from the hospital. An oral nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen may be given to supplement other analgesics. When epinephrine 0.2 mg was added to lidocaine with fentanyl 10 \( \mu \)g for spinal anesthesia, the duration of complete and effective analgesia was prolonged and the incidence of pruritus was decreased, but the time to complete motor recovery was also prolonged.\textsuperscript{74} Habib et al.\textsuperscript{75} reported that adding intrathecal morphine 0.05 mg to intrathecal bupivacaine and fentanyl for postpartum tubal ligation resulted in less intense pain at rest and with movement at 4 hours after surgery than with saline control. However, patients who received morphine had more vomiting and pruritus. Despite side effects, patients who received morphine were significantly more satisfied. Similarly, Marcus et al.\textsuperscript{76} found that epidural morphine 2 mg provided better analgesia without increasing the need to treat side effects, in comparison with a regimen of oral opioids and NSAIDs without epidural morphine. Although effective, spinal and epidural morphine analgesia should be used with caution because these patients could be

**Box 25.1 Anesthetic Management for Postpartum Tubal Sterilization**

**Management During Labor**
- Encourage use of epidural analgesia.
- Avoid administration of parenteral opioids.
- Keep patient on nil per os (NPO) status except for clear liquids.
- Give aspiration prophylaxis if the procedure is to be performed immediately after delivery.

**Timing of Surgery**
- Consider performing surgery immediately postpartum if the patient is hemodynamically stable and has received aspiration prophylaxis.
- An epidural catheter placed for labor may provide more reliable anesthesia if used within 10 hours of delivery.

**General Anesthesia**
- Perform a rapid-sequence induction with cricoid pressure.
- Intubate the trachea and control ventilation.
- Avoid high concentrations (greater than 0.5 minimum alveolar concentration [MAC]) of a volatile anesthetic agent.
- Monitor neuromuscular blockade if a nondepolarizing muscle relaxant is used.

**Epidural Anesthesia**
- Requires a T4 sensory level of anesthesia.
- After a negative test dose result, consider using 3% 2-chloroprocaine unless a longer procedure is planned.
- If a catheter placed during labor is used, beware of a higher risk for failure if the delivery-to-surgery interval is prolonged more than 10 hours.
- Give fentanyl 50 to 100 \( \mu \)g via the epidural catheter for intraoperative and postoperative analgesia.

**Spinal Anesthesia**
- Requires a T4 sensory level of anesthesia.
- It is the preferred technique for delayed postpartum tubal sterilization, or for immediate surgery in patients who did not have epidural labor analgesia, or in whom epidural analgesia during labor and delivery was ineffective.
- Use a small-gauge, noncutting, pencil-point spinal needle.
- Give lidocaine 75 mg with fentanyl 10 to 25 \( \mu \)g or bupivacaine 10 to 12 mg with fentanyl 10 to 25 \( \mu \)g.

**Postoperative Pain Management**
- Consider infiltration of the skin and the mesosalpinx with bupivacaine.
- Administer a nonsteroidal anti-inflammatory drug such as ketorolac or ibuprofen perioperatively.
- Begin oral analgesics before complete block regression after spinal or epidural anesthesia.
discharged within hours after postpartum tubal sterilization, before the risk for delayed respiratory depression has lapsed. The method of postoperative analgesia chosen should not delay patient discharge because of side effects or the need for postoperative respiratory monitoring.

Local anesthetic infiltration of the mesosalpinx with bupivacaine or topical application of a local anesthetic to the fallopian tubes significantly decreases opioid requirements postoperatively. These are simple, rapid techniques that can be used by the obstetrician. A systematic review and meta-analysis of the application of topical or injectable local anesthetic during laparoscopic tubal ligation found that use of local anesthetic decreased pain substantially for up to 8 hours after surgery. NSAIDs also improve postoperative pain control. The manufacturer of ketorolac has stated that ketorolac is contraindicated in nursing mothers because of the possible adverse effects of prostaglandin synthetase inhibitors including ductal closure and gastrointestinal bleeding on neonates. In contrast, the American Academy of Pediatrics considers NSAIDs to be compatible with breast-feeding.

**KEY POINTS**

- Postpartum tubal sterilization is an elective procedure. No data indicate that the postpartum patient’s safety is enhanced by a delay of surgery or compromised by the performance of tubal sterilization immediately after delivery.
- Postpartum tubal sterilization (versus interval laparoscopic tubal sterilization) offers several advantages including convenience for the patient and technical simplicity for the surgeon.
- Postpartum patients do not have lower gastric pH or higher gastric volumes than nonpregnant patients undergoing elective surgery. Some studies suggest that gastric emptying is delayed postpartum only if the patient has received opioid analgesics during labor.
- The incidence of gastroesophageal reflux returns toward normal by the second postpartum day.
- Modern anesthetic drugs do not appear in breast milk in amounts that affect the newborn.
- The duration of succinylcholine-, rocuronium-, mivacurium-, and vecuronium-induced neuromuscular blockade is prolonged during the postpartum period. In contrast, the duration of action for atracurium is unchanged and that of cisatracurium is shorter.
- An epidural catheter placed for labor may be used for postpartum tubal sterilization, but the risk for failure to provide adequate surgical anesthesia may be greater if surgery is delayed more than 10 hours after delivery.
- Spinal anesthesia is preferred for delayed postpartum tubal sterilization (greater than 10 hours after delivery), regardless of whether an epidural catheter was placed for labor analgesia.
- The local anesthetic dose for spinal anesthesia returns to nonpregnant requirements by 12 to 36 hours postpartum.
- Postoperative multimodal analgesia including local anesthetic infiltration improves maternal mobilization and infant bonding and may facilitate earlier hospital discharge.

**REFERENCES**


HISTORY

Cesarean delivery is defined as the birth of an infant through incisions in the abdomen (laparotomy) and uterus (hysterotomy). Although the technique is commonly associated with the birth of the Roman Emperor Julius Caesar, medical historians question this possibility, given his birth in an era (100 BC) when such operations were invariably fatal and the acknowledged presence of Caesar’s mother in his later life.1

Morbidity and mortality, most often associated with hemorrhage and infection, limited the use of cesarean delivery until the 20th century, when advances in aseptic, surgical, and anesthetic techniques improved the safety for both mother and baby. Today, cesarean delivery is the most common major surgical procedure performed worldwide, with an estimated 23 million procedures performed each year.2 However, the rate of cesarean delivery varies dramatically by country, ranging from 0.6% (South Sudan) to 56% (Brazil) of all deliveries (Fig. 26.1).3 Maternal, obstetric, fetal, medicolegal, health-system, and social factors are largely responsible for this variability, resulting in significant differences in cesarean delivery rates even among individual obstetricians and institutions (Box 26.1).4 A recent analysis suggested that the optimal cesarean delivery rate for minimizing neonatal and maternal morbidity is 19%.2
delivery in a subsequent pregnancy. A trial of labor after cesarean (TOLAC), which if successful is called a vaginal birth after cesarean (VBAC), is an alternative option; validated algorithms for predicting the probability of successful VBAC have been developed. A trial of labor after cesarean (TOLAC), which if successful is called a vaginal birth after cesarean (VBAC), is an alternative option; validated algorithms for predicting the probability of successful VBAC have been developed.6 Similar to cesarean delivery rates, VBAC rates vary substantially among countries with a reported range of 9% (United States) to 55% (Netherlands) (see Chapter 19).7

**OPERATIVE TECHNIQUE**

The technical aspects of performing a cesarean delivery are comparable worldwide, with minor variations. A midline vertical abdominal incision allows rapid access and greater surgical exposure; however, the horizontal suprapubic (Pfannensti) incision offers better cosmesis and wound strength. Similarly, a low transverse uterine incision, compared with a vertical incision, allows for a lower incidence of uterine dehiscence or rupture in subsequent pregnancies, as well as a reduction in the risks for infection, blood loss, and bowel and omental adhesions. Vertical uterine incisions are most often used in the following situations: (1) if the lower uterine segment is underdeveloped (typically before 34 weeks’ gestation), (2) for delivery of a preterm infant in a woman who has not labored, and (3) in selected patients with multiple gestation and/or malpresentation. In some cases, a vertical uterine

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**BOX 26.1 Factors Contributing to the Increasing Cesarean Delivery Rate**

**Maternal**
- Increasing proportion of deliveries in nulliparous women
- Delayed childbearing and increasing maternal age
- Increasing prevalence of obesity

**Obstetric**
- Increasing use of labor induction
- Fewer vaginal breech deliveries
- Fewer instrumental vaginal deliveries
- Fewer attempts at trial of labor after cesarean delivery
- Increasing availability of cesarean delivery in developing nations

**Fetal**
- Increasing incidence of fetal macrosomia
- Increasing incidence of multiple gestation
- Ex utero intrapartum treatment (EXIT) procedures

**Practice Environment**
- Concern for malpractice litigation
- Increased use of electronic fetal heart rate monitoring
- Concern for pelvic floor injury associated with vaginal birth
- Desire for scheduled procedures (convenience)

**BOX 26.2 Indications for Cesarean Delivery**

**Maternal**
- Antepartum or intrapartum hemorrhage
- Arrest of labor
- Breech presentation
- Chorioamnionitis
- Deteriorating maternal condition (e.g., severe preeclampsia)
- Dystocia
- Failure of induction of labor
- Genital herpes (active lesions)
- High-order multiple gestation (or twin gestation in which twin A has a breech presentation)
- Maternal request
- Placenta previa
- Placental abruption
- Previous myomectomy
- Prior classic uterine incision
- Uterine rupture

**Fetal**
- Breech presentation or other malpresentation
- Fetal intolerance of labor
- Suspected macrosomia
- Nonreassuring fetal status
- Prolapsed umbilical cord

**Obstetrician**
- Desire to avoid difficult forceps or vacuum delivery

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**INDICATIONS**

An elective (scheduled) cesarean delivery can be performed for obstetric or medical indications or at the request of a patient, and it is typically planned and performed before the onset of labor. A cesarean delivery performed during labor for a planned vaginal delivery can also occur for a wide range of maternal and fetal indications but may need to be conducted in an urgent or emergent manner. The most common reasons for a primary cesarean are labor arrest (34%), nonreassuring fetal heart rate (FHR) tracing (23%), malpresentation (e.g., breech) (17%), and multiple gestation (7%) (Box 26.2). A prior cesarean delivery does not necessitate cesarean delivery in a subsequent pregnancy. A trial of labor after cesarean (TOLAC), which if successful is called a vaginal birth after cesarean (VBAC), is an alternative option; validated algorithms for predicting the probability of successful VBAC have been developed. Similar to cesarean delivery rates, VBAC rates vary substantially among countries with a reported range of 9% (United States) to 55% (Netherlands) (see Chapter 19).
incision is performed high on the anterior uterine wall (i.e., classical incision), especially in the patient with a low-lying anterior placenta previa or when a cesarean hysterectomy is planned.

Uterine exteriorization following delivery facilitates visualization and repair of the uterine incision, particularly when the incision has been extended laterally. Although the effect of exteriorization on blood loss and febrile morbidity remains controversial, higher rates of intraoperative nausea, emesis, and venous air embolism as well as postoperative pain have been reported.9,10

**MORBIDITY AND MORTALITY**

Complications of cesarean delivery include hemorrhage, infection, thromboembolism, ureteral and bladder injury, abdominal pain, and increased risk for abnormal placentation and uterine rupture in subsequent pregnancies (Box 26.3). Maternal morbidity and mortality vary widely from country to country (see Chapter 39). In most developed nations, the rate of maternal death associated with all cesarean deliveries remains higher than that associated with vaginal deliveries, although this is in large measure attributable to the underlying conditions that necessitate cesarean delivery (Table 26.1).12,13 Planned cesarean delivery also appears to be associated with a higher risk for many measures of maternal morbidity compared with planned vaginal delivery, although the absolute differences in risk are small.14 Neonatal morbidity, in particular respiratory system morbidity, is greater with elective cesarean delivery than with vaginal delivery.15 Performance of cesarean delivery also places the mother at higher risk for morbidity (and perhaps mortality) in subsequent pregnancies and cesarean deliveries.16

**PREVENTION OF CESAREAN DELIVERY**

Neuraxial labor analgesia was earlier thought to increase the cesarean delivery rate compared with nonmedicated labor or other analgesic techniques; however, randomized controlled trials indicate that neuraxial analgesia is not associated with a higher cesarean delivery rate than systemic opioid analgesia

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### TABLE 26.1 Relationship between Route of Delivery and Maternal Death

<table>
<thead>
<tr>
<th>Delivery Type</th>
<th>Number of Procedures</th>
<th>Number of Deaths</th>
<th>Frequency of Death (per 100,000 Procedures)</th>
<th>Causal Relationship of Delivery Route with Maternal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>1,003,173</td>
<td>17</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>Primary cesarean</td>
<td>282,632</td>
<td>46</td>
<td>16.3</td>
<td>7</td>
</tr>
<tr>
<td>Repeat cesarean</td>
<td>175,465</td>
<td>12</td>
<td>6.8</td>
<td>2</td>
</tr>
<tr>
<td>Total cesarean</td>
<td>458,097</td>
<td>58</td>
<td>12.7</td>
<td>9</td>
</tr>
<tr>
<td>Not delivered/dilation and curettage</td>
<td>NA</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>1,461,270</td>
<td>95</td>
<td>6.5[1]</td>
<td>11</td>
</tr>
</tbody>
</table>

NA, not applicable.

*Association relationships:* For vaginal birth versus total cesarean, vaginal birth versus primary cesarean, and vaginal birth versus repeat cesarean, \( P < .001 \). For primary cesarean versus repeat cesarean, \( P = .01 \).

*Causal relationships:* For vaginal birth versus total cesarean and vaginal birth versus primary cesarean, \( P < .001 \). For vaginal birth versus repeat cesarean, \( P = .12 \). For primary cesarean versus repeat cesarean, \( P = .50 \). For vaginal birth versus primary, repeat, and total cesarean delivery, excluding pulmonary embolism deaths preventable with universal prophylaxis, \( P = .07 \), \( P = .38 \), and \( P = .08 \), respectively.

of uterine tachysystole. Moreover, the combined spinal-epidural (CSE) technique for labor analgesia, despite its association with fetal bradycardia, does not result in an increase in the total cesarean delivery rate. Some cesarean deliveries may be avoided through the provision of (1) adequate labor analgesia, including analgesia for trial of labor after cesarean delivery and instrumental vaginal delivery; (2) analgesia for external cephalic version (see Chapter 34); and (3) intrauterine resuscitation, including pharmacologic uterine relaxation in cases of uterine tachysystole.

**Maternal Labor Analgesia**

The National Institutes of Health State-of-the-Science statement on cesarean delivery on maternal request emphatically concluded that "maternal request for cesarean delivery should not be motivated by unavailability of effective [labor] pain management." While most hospitals in the United States now offer labor analgesia, this is not necessarily the case in many parts of the world, and studies suggest that the introduction of epidural analgesia may be an effective approach to decrease the cesarean delivery rate in these settings.

Adequate maternal analgesia and perineal relaxation are also important for instrumental (forceps, vacuum) vaginal deliveries. Neuraxial techniques can optimize anesthetic conditions for these obstetric procedures (see Chapter 23).

**External Cephalic Version**

Singleton breech presentations occur in 3% to 4% of term pregnancies. The Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists (ACOG) caution against a vaginal breech delivery, given poorer neonatal outcomes compared with planned cesarean delivery. External cephalic version (ECV), a procedure by which manual external pressure is applied to the maternal abdomen to change the fetal presentation from breech to cephalic, remains a viable option. ECV is usually performed between 36 and 39 weeks’ gestation (see Chapter 34).

Meta-analyses of available trial data support the finding that neuraxial analgesia or anesthesia increases the success rate of attempted ECV. Moreover, these studies show that the use of neuraxial blockade does not appear to compromise maternal and fetal safety, and specifically it does not increase the risk for fetal bradycardia, placental abruption, or fetal death.

**Intrauterine Resuscitation**

Evidence of intrapartum fetal compromise (nonreassuring fetal status) should prompt the obstetric team (including obstetric, anesthesia, and nursing providers) to attempt intrauterine resuscitation (Box 26.4). These actions include changing maternal position to relieve aortocaval compression, administering vasopressors and intravenous fluid to treat maternal hypotension, discontinuing exogenous oxytocin administration, and, in cases of uterine tachysystole, administration of a tocolytic agent such as terbutaline or nitroglycerin (see Chapter 8).

**Box 26.4 Obstetric Management of Nonreassuring Fetal Status**

- Optimize maternal position:
  - To avoid or relieve aortocaval compression.
  - To relieve umbilical cord compression.
- Administer supplemental oxygen.
- Maintain maternal circulation:
  - Perform rapid intravenous administration of a non–dextrose-containing balanced salt solution.
  - Treat hypotension with either ephedrine or phenylephrine.
- Discontinue oxytocin.
- Consider administration of a tocolytic agent for treatment of uterine tachysystole.

**PREPARATION FOR ANESTHESIA**

The anesthetic management of cesarean delivery may depend in part on the obstetric indications for operative delivery. The anesthesia provider should consider the patient’s medical, surgical, and obstetric history, the presence or absence of labor, the urgency of the delivery, and the resources available in preparing for a cesarean delivery.

**Preanesthetic Evaluation**

All women admitted for labor and delivery are potential candidates for the emergency administration of anesthesia, and an anesthesia provider ideally should evaluate every woman shortly after admission. Optimally, for high-risk patients, preanesthesia consultation should occur in the late second or early third trimester, even if a vaginal delivery is planned. This practice offers the opportunity to provide patients with information, solicit further consultations, optimize medical conditions, and discuss plans and preparations for the upcoming delivery. Early communication among the members of the multidisciplinary team is encouraged. In some cases, the urgent nature of the situation allows limited time for evaluation before induction of anesthesia and commencement of surgery; nonetheless, essential information must be obtained and risks and benefits of alternative anesthetic management decisions should be considered.

A focused preanesthetic history and physical examination includes (1) a review of maternal health and anesthetic history, relevant obstetric history, allergies, and baseline blood pressure and heart rate measurements; and (2) performance of an airway, heart, and lung examination consistent with the American Society of Anesthesiologists (ASA) guidelines (see Appendix B).

**Blood Products**

Peripartum hemorrhage remains a leading cause of maternal mortality worldwide (see Chapters 37 and 39). There is little difference in blood loss between an uncomplicated elective cesarean delivery and an uncomplicated planned vaginal birth; however, a cesarean delivery performed during labor or in the setting of abnormal placenta is associated with
greater blood loss. Risk factors for peripartum hemorrhage are listed in Box 26.5.

Preparation for obstetric hemorrhage includes (1) reviewing the patient’s history for anemia or risk factors for hemorrhage; (2) consulting with the obstetric team regarding the presence of risk factors; (3) reviewing reports of ultrasonographic or magnetic resonance images of placentation; (4) obtaining a blood sample for a type and screen or cross-match; (5) contacting the blood bank to ensure the availability of blood products; (6) obtaining and checking the necessary equipment (blood filters and warmers, infusion pumps and tubing, compatible fluids and medications, and standard clinical laboratory collection tubes); and (7) consulting with a blood bank pathologist, hematologist, and/or interventional radiologist in selected cases (Box 26.6).

Currently, there is a lack of consensus as to which patients require a blood type and screen and which patients require a cross-match. The maternal history (previous transfusion, existence of known red blood cell antibodies) and anticipated hemorrhagic complications, as well as local institutional policies, should guide decision-making. In certain high-risk cases (e.g., suspected placenta accreta), blood products (e.g., 2 to 4 units of packed red blood cells) should be physically present near or in the operating room before making the surgical incision, if possible.

**Monitoring**

Attention should be given to the availability and proper functioning of equipment and monitors for the provision of

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**BOX 26.5 Selected Risk Factors for Peripartum Hemorrhage**

- Abnormal placentation
- Advanced maternal age
- Anticoagulation
- Bleeding disorder
- Chorioamnionitis
- Fetal demise
- Fetal malpresentation
- General anesthesia
- Increased parity/grand multiparity
- Instrumental vaginal delivery
- Internal trauma (e.g., curretage, internal version)
- Oxytocin augmentation of labor
- Placental abruption
- Precipitous delivery
- Preecampsia
- Premature rupture of membranes
- Previous uterine surgery (e.g., cesarean delivery, myomectomy)
- Prolonged labor
- Retained placenta
- Tocolytic therapy
- Trauma
- Uterine distention (e.g., macrosomia, multiple gestation, polyhydramnios)
- Uterine leiomyoma

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**BOX 26.6 Suggested Resources for Obstetric Anesthesia**

**Monitors**

- Electrocardiogram
- Noninvasive blood pressure
- Pulse oximetry
- Capnography
- Oxygen and volatile agent analyzers
- Ventilator (with appropriate pressure and disconnection sensors/alarms)
- Peripheral nerve stimulator

**For Hemorrhage**

- Large-bore intravenous catheters
- Fluid warmer
- Forced-air body warmer
- Availability of blood bank resources
- Equipment for infusing intravenous fluids and blood products rapidly (e.g., hand-squeezed fluid chambers, hand-inflated pressure bags, automatic infusion devices)
- Availability of interventional radiology service

**For Routine Airway Management**

- Laryngoscope and assorted blades
- Videolaryngoscope
- Oral airways of assorted sizes
- Endotracheal tubes of assorted sizes (6.5 and 7.0 mm) with stylets
- Oxygen source
- Suction source with tubing and catheters
- Self-inflating bag and mask for positive-pressure ventilation
- Medications for blood pressure support, hypnosis, and muscle relaxation

**For Difficult Airway Management**

- Rigid laryngoscope blades of alternative design and size from those routinely used
- Supraglottic airway devices (e.g., laryngeal mask airway)
- Endotracheal tube guides (e.g., semirigid stylets with or without hollow cores for jet ventilation, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube)
- Retrograde intubation equipment
- At least one device suitable for emergency nonsurgical airway ventilation (e.g., hollow jet ventilation stylet with a transtracheal jet ventilator; supraglottic airway device, such as a Combitube [Sheridan Catheter Corporation, Argyle, NY] or intubating LMA [Fastrach LMA, LMA North America, San Diego, CA])
- Fiberoptic intubation equipment
- Equipment suitable for emergency surgical airway access (e.g., cricothyrotomy)
- Topical anesthetics and vasoconstrictors

Modified from the American Society of Anesthesiologists; Society for Obstetric Anesthesia and Perinatology. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. *Anesthesiology.* 2016;124:270–300. (The full practice guidelines are published as Appendix B, found at the end of this textbook.)
anesthesia and the management of potential complications (e.g., failed tracheal intubation, cardiopulmonary arrest). Equipment should be checked on a daily basis and serviced at recommended intervals. The equipment and facilities available in the labor and delivery operating room suite should be comparable to those available in the main operating room.

The ASA standards for basic monitoring apply to the provision of anesthesia for all patients. Within obstetrics, basic monitoring consists of maternal pulse oximetry, electrocardiography (ECG), and noninvasive blood pressure monitoring, as well as FHR monitoring.

ECG abnormalities are often observed in late pregnancy and are believed to be caused by hyperdynamic circulation, circulating catecholamines, and/or altered estrogen and progesterone concentration ratios (see Chapter 2). During cesarean delivery with neuraxial anesthesia, ECG changes have a reported frequency of 25% to 60%; in this setting, administration of droperidol, ondansetron, and oxytocin may be associated with prolongation of the QTc interval, and oxytocin administration may be associated with ST-segment depression. The significance of these ECG findings as an indicator of cardiac pathology remains unclear, because only a small minority of parturients experience myocardial ischemia as measured by elevated serum cardiac troponin levels or echocardiographic wall motion abnormalities. The placement of five ECG leads improves the sensitivity of detecting ischemic events; combining leads II, V₆, and V₃ resulted in a sensitivity of 96% for detecting ST-segment changes in a nonobstetric population. In a prospective study of 254 healthy women undergoing cesarean delivery with spinal anesthesia, Shen et al. determined the incidence of first- and second-degree atrioventricular block (3.5% for each), severe bradycardia (< 50 bpm; 6.7%), and multiple premature ventricular contractions (1.2%). The investigators speculated that a relative increase in parasympathetic activity occurred as a result of spinal blockade of cardiac sympathetic activity. Most of the dysrhythmias were transient and resolved spontaneously.

Processed electroencephalogram monitors used to indicate the depth of anesthesia have received only limited evaluation in women undergoing cesarean delivery. Whether routine use of these monitors can reduce the incidence of intraoperative awareness during general anesthesia for cesarean delivery is unclear (see later discussion).

An indwelling urinary catheter is used in almost all women undergoing cesarean delivery. A urinary catheter helps avoid overdistention of the bladder during and after surgery. In cases associated with hypovolemia and/or oliguria, or anticipated significant blood loss, a collection system that allows precise measurement of urine volume is helpful.

The FHR is often assessed by a qualified individual before and after administration of anesthesia. However, data are insufficient to determine the value of FHR monitoring before elective cesarean delivery in patients without risk factors. Our practice is to monitor FHR until the abdominal skin preparation for cesarean delivery has begun.

In some cases of emergency cesarean delivery, a previously placed fetal scalp (or buttock) ECG electrode can be used to monitor the FHR before, during, and after the initiation of anesthesia. Typically, the fetal scalp electrode is removed when the surgical drapes are applied to the abdomen, but in some cases the scalp electrode may be left in place until just before delivery, when the circulating nurse reaches under the drapes to disconnect the electrode. Continuous FHR monitoring is useful in this setting for at least three reasons. First, the FHR abnormality often resolves; in some cases, the obstetrician will then elect to forgo the performance of a cesarean delivery. In other cases, the obstetrician may continue with plans to perform a cesarean delivery, but continuous FHR monitoring may facilitate the administration of neuraxial anesthesia. For example, an improved FHR tracing allows time for extension of epidural anesthesia or administration of spinal anesthesia. Second, continuous FHR monitoring may guide management in cases of failed tracheal intubation. If intubation fails and there is no evidence of fetal compromise, both the anesthesia provider and the obstetrician will have greater confidence in a decision to awaken the patient and proceed with an alternative anesthetic technique. By contrast, if there is evidence of ongoing fetal compromise, the anesthesia provider may decide to provide general anesthesia by means of a face mask or supraglottic airway, and the obstetrician may proceed with cesarean delivery (see Chapter 29). Third, intraoperative FHR monitoring allows the obstetrician to modify the surgical technique according to the urgency of delivery.

Invasive monitoring (e.g., arterial catheter), noninvasive cardiac output monitoring, or echocardiography may be indicated for individual patients at high risk for cardiopulmonary compromise.

**Equipment**

Labor and delivery units may be adjacent to or remote from the main operating rooms. In some facilities, the unit is located on a separate floor but shares a common operating room facility (used for other surgical procedures), whereas in others it is a geographically separate, self-contained unit with its own operating room facilities. Regardless of location, the equipment, facilities, and support personnel available in the labor and delivery operating room should be comparable to those available in the main operating room. In addition, personnel and equipment should be available to care for obstetric patients recovering from major neuraxial or general anesthesia.

Resources for the conduct and support of neuraxial anesthesia and general anesthesia should include those necessary

*Outside the operating room, and before the onset of labor, maternal blood pressure is ideally measured (using an appropriately sized cuff with a bladder length that is 80% and a width that is at least 46% of the arm circumference) after a rest period of 10 minutes or more, with the pregnant woman sitting or lying on her left side with her arm at the level of the right atrium. The onset (phase 1) and disappearance (phase 5) of Korotkoff sounds correspond to systolic and diastolic pressures, respectively.*
for the basic delivery of anesthesia and airway management as well as those required to manage complications (e.g., failed tracheal intubation). The immediate availability of these resources is particularly important, given the frequency and urgency of anesthesia care. Consideration should be given to having some of the equipment and supplies immediately available in one location or in a cart (e.g., difficult airway cart, massive hemorrhage cart, malignant hyperthermia box) specifically located on the labor and delivery unit. Equipment and supplies should be checked on a frequent and regular basis. Securing special-situation equipment and supplies in a cart with a single-use breakthrough plastic tie helps ensure that the cart is kept in a fully stocked state.

**Aspiration Prophylaxis**

The patient should be asked about oral intake, although insufficient evidence exists regarding the relationship between recent ingestion and subsequent aspiration pneumonitis (see Chapter 28). Gastric emptying of clear liquids during pregnancy occurs relatively quickly; the residual content of the stomach (as measured by ultrasonographic assessment of the cross-sectional area of the gastric antrum 60 minutes after the ingestion of 300 mL of water) does not appear to be different from baseline fasting levels in either lean or obese nonlaboring pregnant women. Moreover, when measured by serial gastric ultrasonographic examinations and acetaminophen (paracetamol) absorption, the gastric emptying half-time of 300 mL of water is shorter than that of 50 mL of water in healthy, nonlaboring, nonobese pregnant women (24 ± 6 versus 33 ± 8 minutes, respectively).

The healthy patient undergoing elective cesarean delivery may drink modest amounts of clear liquids up to 2 hours before induction of anesthesia. Examples of clear liquids are water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sport drinks. The volume of liquid ingested is less important than the absence of particulate matter. Patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway) or laboring patients at increased risk for cesarean delivery (e.g., nonreassuring FHR pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

Ingestion of solid foods should be avoided in laboring patients and patients undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal sterilization). A fasting period for solids of 6 to 8 hours, depending on the fat content of the food, has been recommended.

A reduction in gastric content acidity and volume is believed to decrease the risk for damage to the respiratory epithelium if aspiration should occur. Oral administration of a nonparticulate antacid (0.3 M sodium citrate, pH 8.4) causes the mean gastric pH to increase to greater than 6 for 1 hour; it does not affect gastric volume. Histamine-2 (H2)-receptor antagonists (e.g., ranitidine, famotidine), proton pump inhibitors (e.g., omeprazole), and metoclopramide reduce gastric acid secretion and volume but require at least 30 to 40 minutes to exert their effects. A systematic review of interventions used to reduce the risk for aspiration pneumonitis in women undergoing cesarean delivery found a significant reduction in the risk for gastric pH less than 2.5 with antacids (relative risk [RR], 0.17; 95% confidence interval [CI], 0.09 to 0.32), H2-receptor antagonists (RR, 0.09; 95% CI, 0.05 to 0.18), and proton-pump inhibitors (RR, 0.26; 95% CI, 0.14 to 0.46), compared with no treatment or placebo. The combined use of an antacid and an H2-receptor antagonist was found to be more effective in reducing pH less than 2.5 than administration of placebo or an antacid alone. However, in a randomized evaluation, sodium citrate was associated with a higher incidence and severity of nausea than an H2-receptor antagonist (famotidine), suggesting that a H2-receptor antagonist may be the preferred agent in selected patients. Metoclopramide is a promotility agent that hastens gastric emptying, increases lower esophageal sphincter tone, and decreases nausea and vomiting. Before surgical procedures, the timely administration of a nonparticulate antacid, an H2-receptor antagonist, and metoclopramide should be considered, especially for nonelective procedures.

**Prophylactic Antibiotics**

Prophylactic antibiotic administration results in a 60% decrease in the incidence of endometritis, a 25% to 65% decrease in the incidence of wound infection, and fewer episodes of fever and urinary tract infections for both elective (nonlaboring) and nonelective (laboring) cesarean deliveries. The ACOG has recommended the prophylactic administration of a narrow-spectrum antibiotic, such as a first-generation cephalosporin, within 1 hour of the start of cesarean delivery.

Antibiotics with efficacy against gram-positive, gram-negative, and some anaerobic bacteria are commonly used for prophylaxis for cesarean delivery. Appropriate coverage includes intravenous ampicillin 2 g, cefazolin 1 g, or ceftriaxone 1 g. Appropriate antibiotic coverage should last for 3 to 4 hours; therefore, ampicillin may be less appropriate owing to a shorter half-life than the cephalosporins. In parturients with a significant allergy to beta-lactam antibiotics (e.g., history of anaphylaxis, angioedema, respiratory distress, or urticaria), intravenous clindamycin with gentamicin is a reasonable alternative.

Because of the greater volume of distribution, higher doses of antibiotics may be considered in women with a body mass index (BMI) greater than 30 kg/m² or an absolute weight greater than 120 kg. After administration of cephalosporin 2 g, Pezvner et al. observed that the minimum inhibitory tissue concentration for gram-negative rods was not achieved at the time of skin incision or closure in 20% of obese women and 33% of morbidly obese women.

A 2016 randomized controlled trial addressed whether surgical site infection prophylaxis should be broadened to cover species commonly associated with postcesarean infection (e.g., ureaplasma). Women undergoing cesarean delivery after labor or rupture of membranes were randomized to receive standard antibiotics with or without the addition of azithromycin (500 mg). Although the addition of azithromycin decreased the prevalence of the composite infection endpoint...
by one-half (6.1% versus 12.0%), almost three-fourths of the trial participants were obese, raising concern that the standard antibiotics may have been underdosed.55 The 2018 ACOG guidelines suggest that prophylactic azithromycin administration may be considered for nonelective cesarean delivery.52

In the past, prophylactic antibiotics were typically administered after umbilical cord clamping because of concern that fetal antibiotic exposure might mask a nascent infection and/or increase the likelihood of a neonatal sepsis evaluation. However, a meta-analysis demonstrated that preincision antibiotic prophylaxis reduces the incidence of postcesarean endometritis and total maternal infectious morbidity, without evidence of adverse neonatal effects.56 Thus, current guidelines recommend administration of prophylactic antibiotics within 60 minutes before the start of the cesarean delivery.52

**Aseptic Technique**

In the early 19th century, Ignác Semmelweis observed that puerperal fever, known as “childbed fever,” was most likely transmitted when the first stage of labor was prolonged and multiple individuals performed vaginal examinations with contaminated hands. Since that time, the practice of hand hygiene has caused a significant reduction in maternal and neonatal infectious morbidity.

The immunologic changes of pregnancy may impair clearance of infections.57 Epidural abscess and meningitis have been reported as complications of neuraxial procedures in obstetric patients (see Chapter 31). As a consequence, obstetric anesthesia providers should always give careful attention to aseptic technique, especially during performance of a neuraxial procedure. Proper sterile technique for neuraxial procedures includes wearing a face mask, performing hand hygiene, and donning sterile gloves (see Chapter 12).58 Attention should also be given to the careful preparation of anesthetic drugs during administration of either general or neuraxial anesthesia. An increasing number of institutions are using premixed solutions of local anesthetic and opioid (prepared under aseptic conditions in a hospital or compounding pharmacy) to limit breaches in aseptic technique during the administration of neuraxial anesthesia.

**Intravenous Access and Fluid Management**

The establishment of functional intravenous access is of critical importance to the successful outcome of many clinical situations in obstetric anesthesia practice. According to the Hagen-Poiseuille equation, the infusion rate of fluid through a catheter is directly related to the pressure gradient of the fluid and the fourth power of the catheter’s radius, and inversely related to the viscosity of the fluid and the catheter’s length. Because the size of the catheter, more than the size of the vein, dictates the flow rate, the use of a short, large-diameter catheter (e.g., 16- or 18-gauge) is associated with the best flow.59

In general, a smaller but functional catheter is more important than a larger catheter that is unreliable or requires frequent manipulation. Smaller catheters may be acceptable in an emergency; volume and blood resuscitation can be satisfactorily achieved using 20- and 22-gauge catheters (without evidence of greater red blood cell destruction) with the use of dilution, pressurization, or both.60 However, in situations when more rapid resuscitation is needed, especially when large blood loss is anticipated, or administration of multiple blood products is required, the anesthesia provider may choose to insert a central venous catheter.

Although the administration of intravenous fluids may decrease the incidence of neuraxial anesthesia-associated hypotension, initiation of anesthesia should not be delayed to administer a fixed volume of fluid,28 particularly in the case of an emergency cesarean delivery, in which the life and health of the mother and the infant are best preserved with timely delivery. Vasopressors can be used for both prophylaxis and treatment of hypotension. The type of fluid (crystalloid, colloid) and the volume, rate, and timing of administration are relevant factors in the prevention and treatment of hypotension.61,62 In most situations, a balanced salt solution such as lactated Ringer’s solution is acceptable. Blood products are most often administered with normal saline. Crystalloid or colloid solutions that contain calcium or glucose should not be administered with blood products, owing to the risks for clotting (caused by reversal of the citrate anticoagulant) and clumping of red blood cells, respectively.

Traditionally, approximately 1 L of crystalloid solution has been administered intravenously (as “prehydration” or “preload”) to prevent or reduce the incidence and severity of hypotension during neuraxial anesthesia for cesarean delivery. However, prehydration, even with large volumes (30 mL/kg), is minimally effective in preventing neuraxial anesthesia-induced hypotension. Although an initial study found that administering crystalloid solution at the time of the intrathecal injection (“co-load”) was more efficacious than prehydration in preventing hypotension,63 later studies did not support this finding, likely because the infusion rate was too slow.64 Colloid, administered before or at the time of the intrathecal injection, is more effective than crystalloid for preventing hypotension.65 Colloid administered before the intrathecal injection (preload) is equally efficacious as commencing administration at the time of injection (co-load).66 In healthy patients, we rapidly administer approximately 1 L of crystalloid starting at the time of initiation of neuraxial anesthesia. For patients at high risk for hypotension or the consequences of hypotension, colloid may be administered before or at the time of initiation of neuraxial blockade.67 Hypotension despite fluid administration is treated with vasopressors (see later discussion).

**Supplemental Medications for Anxiety**

The administration of benzodiazepines, even low doses (e.g., midazolam 0.02 mg/kg), may result in amnesia.68,69 as a consequence, benzodiazepines are typically avoided during awake cesarean delivery. However, on occasion, particularly in women with severe anxiety or undergoing an emergency cesarean delivery, the use of low doses of intravenous midazolam or an opioid may facilitate performance of a neuraxial technique, awake tracheal intubation, or the induction of general anesthesia. Anxiolytics may also assist in mitigating the feelings of distress during the birthing experience, which
may lessen the risk for developing posttraumatic stress dis-
order. The use of low doses of sedative or anxiolytic agents has minimal to no neonatal effects. In a trial of healthy women randomized to receive intravenous midazolam (0.02 mg/kg) and fentanyl (1 µg/kg) or saline before administration of spinal anesthesia for cesarean delivery, no differences in neonatal Apgar scores, neurobehavioral scores, or oxygen saturation were observed between the two treatment groups.69

Positioning

After 20 weeks’ gestation, most practitioners position patients with left uterine displacement to minimize aortocaval compression. The supine hypotension syndrome, which is caused by compression of the aorta and inferior vena cava by the gravid uterus, can manifest as pallor, tachycardia, sweating, nausea, hypotension, and dizziness.70,71 Uteroplacental blood flow is compromised by decreased venous return and cardiac output, increased uterine venous pressure, and compression of the aorta or common iliac arteries.72

The full lateral position minimizes aortocaval compression but does not allow performance of cesarean delivery. Fifteen degrees of left lateral tilt (left uterine displacement) has been proposed to significantly reduce the adverse hemodynamic consequences of the supine position, although both the aorta and inferior vena cava may remain partially compressed.73 However, most anesthesia providers overestimate the degree of lateral tilt. These elements may explain the results of a 2013 systematic review that concluded that left compared with right lateral tilt was associated with some maternal and fetal benefit, but outcomes were not dramatically different among different positions.74 Overall, data were insufficient to prove or disprove the benefits of tilting or flexing the operating room table or using wedges or mechanical displacers during positioning for cesarean delivery.74

Whether left uterine displacement is necessary in the context of patients receiving a co-load of fluid and a prophylactic phenylephrine infusion at the time of induction of spinal anesthesia has been questioned.75 In healthy, term women undergoing elective cesarean delivery, there was no difference in neonatal acid-base status in women randomized to the supine position versus left uterine displacement, despite mean maternal cardiac output being lower in the supine group.75 The trial excluded women at increased risk for aortocaval compression (e.g., polyhydramnios, multiple gestation, obesity) or women with impaired placental perfusion (e.g., fetal growth restriction, preeclampsia). Given these limitations, and the apparent absence of adverse maternal or fetal effects with lateral uterine displacement, the routine use of this technique should not be abandoned.76 Anesthesia providers should recognize that (1) susceptibility to aortocaval compression varies among individuals,77 (2) visual estimates of lateral tilt may be in error,78 and (3) in symptomatic women, increasing the extent of left uterine displacement may be beneficial. Lateral tilt should be used in all women in mid- to late pregnancy after the administration of neuraxial or general anesthesia, with greater tilt used when feasible if aortocaval compression is suspected as the cause for maternal or fetal compromise.79

The use of a slight (10 degrees) head-up position may help reduce the incidence of hypotension after initiation of hyperbaric spinal anesthesia.80 A 30-degree head-up position significantly increases functional residual capacity compared with the supine position in term parturients, although this effect diminishes with increasing BMI.81 In morbidly obese patients receiving general anesthesia, a 25-degree head-up position may be particularly useful to improve denitrogenation and glottic view during direct laryngoscopy; this position can be accomplished with blankets or commercially available devices (see Chapters 29 and 49). If blankets are used to create the ramp position, they should be stacked rather than interlaced, to allow for rapid removal and readjustment of the head and neck position if necessary. The ideal position aligns the external auditory meatus and the sternal notch in a horizontal plane; this position (1) aligns the oral, pharyngeal, and tracheal axes (“sniffing position”) and (2) facilitates insertion of the laryngoscope blade (see Fig. 29.7).82

Theoretically, the Trendelenburg (head-down) position may augment venous return and increase cardiac output. The value of this approach in preventing hypotension during neuraxial anesthesia has been questioned.74 After the initiation of hyperbaric spinal anesthesia, the Trendelenburg position has been reported to result in more cephalad spread of anesthesia in one study83 but not in others.85,86 However, this position had no effect on the incidence of hypotension after administration of hyperbaric spinal anesthesia.84,86

The optimal patient position for initiation of neuraxial anesthesia may depend on clinical circumstances and the preferences and skills of the anesthesia provider (see Chapter 12). Whether the use of the lateral or the sitting position is best for routine initiation of neuraxial anesthesia is controversial.87,88 Advocates of the lateral position cite a reduction of vagal reflexes, which can result in dizziness, diaphoresis, pallor, bradycardia, and hypotension.89 Moreover, the lateral position may allow better uteroplacental blood flow than the sitting position,90 but this is controversial.91 The lateral position may also be associated with a small increase in maternal cardiac index, stroke volume index, heart rate, and systolic blood pressure compared with the sitting or supine positions.92 Further, in a randomized controlled trial, the severity
and duration of hypotension were greater in women randomly assigned to receive CSE anesthesia (hyperbaric spinal bupivacaine with fentanyl) in the sitting position than the lateral position, despite no differences in the level of sensory blockade.93

Some parturients find the lateral position more comfortable during administration of neuraxial anesthesia, whereas others find the sitting position more comfortable.94 Moreover, because uterine compression of the vena cava diverts blood into the epidural venous plexus,95 the use of the lateral position can reduce hydrostatic pressure and engorgement of the epidural venous plexus.96 Studies suggest that epidural catheter placement in the lateral recumbent head-down position results in lower risk for lumbar epidural venous plexus cannulation than the sitting or the lateral recumbent horizontal position in both obese and nonobese parturients.97,98

Magnetic resonance imaging and computed tomography studies show that the cross-sectional area and the anteroposterior diameter of the dural sac at the level of the L3–L4, L4–L5, and L5–S1 interspaces are significantly influenced by posture.99 Lumbar cerebrospinal fluid (CSF) pressure is lower and dural sac cross-sectional area smaller in the recumbent compared with the upright position. Theoretically, the lateral position may be of value during advancement of an epidural needle because it minimizes the prominence of the dural sac. By contrast, a bulging dural sac might be preferable during administration of spinal or CSE anesthesia. Bulging of the lumbar dural sac—particularly in the sitting position—may decrease the force required to create a dural puncture with a Tuohy epidural needle, but this possibility is unproven.

The sitting position also has some advantages, including easier landmark recognition in obese parturients and ease of positioning patients in a symmetrical position (the spine is often rotated in the lateral position because the bottom shoulder is fixed).88 Given that there is no evidence that one position is universally better than the other, patient position for initiating neuraxial anesthesia is largely a matter of practitioner preference. However, anesthesia providers should be facile with the placement of needles for neuraxial techniques in both the sitting and lateral positions, because the sitting position should not be used in some situations (e.g., umbilical cord prolapse, footling breech presentation).87

### Supplemental Oxygen

The routine administration of supplemental oxygen during elective cesarean delivery with neuraxial anesthesia is controversial. It became a common practice following the seminal report by Fox and Houle100 that demonstrated improved oxygenation, better umbilical cord blood acid-base measurements, and less time to sustained respiration in the neonate, when mothers undergoing cesarean delivery with neuraxial anesthesia breathed 100% oxygen instead of air for at least 10 minutes. However, later evidence suggested that routine oxygen administration may be unnecessary, ineffective101 and possibly detrimental.102 A 2016 meta-analysis of randomized trials performed in low-risk women undergoing elective cesarean delivery found that the administration of supplemental oxygen compared with room air was associated with higher maternal oxygen saturation, maternal $\text{Pa}_2$, umbilical vein $\text{Po}_2$, and umbilical artery $\text{Po}_2$, but no differences in 1- and 5-minute Apgar scores.103

The use of a fractional inspired concentration of oxygen ($\text{FiO}_2$) of 0.35 to 0.4 (which cannot be obtained by using a nasal cannula or a simple face mask with a flow rate less than 6 L/min104) does not improve fetal oxygenation during labor or elective cesarean delivery. Although respiratory function can deteriorate in parturients receiving neuraxial anesthesia,105,106 maternal or fetal hypoxemia does not normally occur when parturients breathe room air.106 An $\text{FiO}_2$ of 0.6 in nonlaboring women undergoing elective cesarean delivery with spinal anesthesia increases the umbilical venous oxygen content by only 12%; an increase in oxygen content is not observed when the uterine incision-to-delivery (U-D) interval exceeds 180 seconds.107

Supplemental oxygen may have detrimental effects.102 High levels of maternal $\text{FiO}_2$, are necessary for significant maternal-fetal oxygen transfer, but also result in the formation of reactive oxygen species and subsequent peroxidation of lipids, alteration of cellular enzymatic functions, and destruction of genetic material.108 Known to extend ischemia-reperfusion injury, deplete antioxidants, and suppress immune function,109 free radicals have also been implicated in the pathogenesis of disorders related to prematurity, including neonatal retinopathy, bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage.

Nonetheless, the emergency cesarean delivery of the compromised fetus should include maternal oxygen administration of high $\text{FiO}_2$, particularly in the setting of uterine contractions, which can exacerbate fetal compromise; in these situations, supplemental oxygen may reduce the severity of fetal hyperoxia with limited oxygen free-radical effects.109 Term (but not preterm) fetuses may be able to withstand the adverse effects of these reactive oxygen species through a compensatory increase in antioxidants during labor.110,111 Antioxidants, the defense against reactive oxygen species, consist of enzymatic inactivators (superoxide dismutase, catalase, peroxidase) and scavengers (ascorbate, glutathione, transferrin, lactoferrin, ceruloplasmin). The activity of these compensatory mechanisms and their relationship to gestational age and labor suggest that the highest risk for ischemia-reperfusion injury occurs in preterm fetuses before the onset of labor.102,111

The a use of high $\text{FiO}_2$ (greater than 0.6) improves oxygen transfer to hypoxic fetuses for a limited period (approximately 10 minutes); beyond this time, continued hyperoxia, especially in the setting of restored perfusion, increases reactive oxygen species, placental vasoconstriction, and fetal acidosis.112,113 A lower $\text{FiO}_2$ may be of benefit in some situations. Of interest, when asphyxiated infants are immediately resuscitated at birth with air instead of 100% oxygen, better short-term outcomes have been observed114,115; this finding may be a result of the shift in the balance between beneficial oxygenation and detrimental free radicals.

All women who are at risk for requiring general anesthesia for emergency cesarean delivery should receive an $\text{FiO}_2$ of 1.0
after transfer to the operating table to simultaneously promote maternal oxygenation and denitrogenation; denitrogenation significantly reduces the risk for maternal hypoxemia during apnea before tracheal intubation.

Although the value of supplemental oxygen use during elective cesarean delivery with neuraxial anesthesia of a non-compromised fetus is questionable, some obstetric anesthesia providers place nasal cannulae or a mask to monitor ventilation using expired carbon dioxide analysis.

**ANESTHETIC TECHNIQUE**

Providing anesthesia to the parturient is a dynamic, multistep process (Table 26.2). The most appropriate anesthetic technique for cesarean delivery depends on maternal, fetal, and obstetric factors (Table 26.3). The urgency and anticipated duration of the operation play an important role in the selection of an anesthetic technique. A standardized four-grade classification system may be used to communicate the degree of urgency among providers (Table 26.4). Using such a classification system also facilitates comparing data and outcomes among providers and institutions.

In cases of dire fetal compromise, the anesthesia provider may need to perform a preanesthetic evaluation simultaneously with other tasks (i.e., establishing intravenous access and placing a blood pressure cuff, pulse oximeter probe, and ECG electrodes). Regardless of the urgency, the anesthesia provider should not compromise maternal safety by failing to obtain critical information about previous medical and anesthetic history, allergies, and the airway. Effective communication with the obstetric team is critical to establish the degree of urgency, which helps guide decisions regarding anesthetic management. Further, contemporary standards for patient safety require that all members of the surgical team participate in a preoperative “time-out” to verify (1) the correct patient identity, position, and operative site; (2) agreement on the procedure to be performed; and (3) the availability of special equipment, if needed.

In cases of emergency cesarean delivery, the emotional needs of the mother and father are also important. Parental distress commonly occurs in this setting, and the anesthesia provider is often the best person to give reassurance. All members of the obstetric care team should remember that chaos does not need to accompany urgency.

**Neuraxial versus General Anesthesia**

Overall, neuraxial (epidural, spinal, CSE) techniques are the preferred method of providing anesthesia for cesarean delivery; specific benefits and risks of each technique dictate the eventual choice. In contemporary practice, neuraxial anesthesia is administered to some patients who would have received general anesthesia in the past. Umbilical cord prolapse, placenta previa, and preeclampsia with severe features are no longer considered absolute indications for general anesthesia. For example, in some cases a prolapsed umbilical cord can be decompressed, and if fetal status is reassuring, a neuraxial technique can be used. In an analysis of obstetric anesthesia trends in the United States between 1981 and 2012, a progressive increase was noted in the use of neuraxial anesthesia, especially spinal anesthesia, for both elective and emergency cesarean deliveries. Neuraxial anesthesia is now used for more than 95% of elective cesarean deliveries and 80% of emergent cesarean deliveries in the United States. Similar increases have occurred in other developed as well as developing countries.

The greater use of neuraxial anesthesia for cesarean delivery has been attributed to several factors, including (1) the growing use of epidural techniques for labor analgesia, (2) an awareness of the possibility that an in situ epidural catheter may decrease the necessity for general anesthesia in an urgent situation, (3) improvement in the quality of neuraxial anesthesia with the addition of an opioid to the local anesthetic, (4) appreciation of the risks of airway complications during general anesthesia in parturients, (5) the desire for limited neonatal drug transfer, and (6) the ability of the mother to remain awake to experience childbirth and to have a support person present in the operating room. Spinal anesthesia is considered an appropriate technique even in the most urgent settings; in a tertiary care institution with an average of 9500 cesarean deliveries annually, neuraxial anesthesia was used in more than 99% of cesarean deliveries over a 6-year period.

In the setting of a category 1 (immediate threat to life of woman or fetus) cesarean delivery, Kinsella et al. described a “rapid-sequence spinal” technique, by which skin preparation, spinal drug combinations, and the spinal technique were simplified; the median time from positioning until satisfactory neuroblockade was 8 minutes (interquartile range [IQR] 7 to 8, range 6 to 8).

Maternal mortality following general anesthesia has been a primary motivator for the transition toward greater use of neuraxial anesthesia for cesarean delivery. A study compared the anesthesia-related maternal mortality rate from 1979 to 1984 with that for the period from 1985 to 1990 in the United States. The estimated case-fatality risk ratio for general versus neuraxial anesthesia was as high as 16.7 in the years 1985 to 1990; however, a similar analysis by the same group of investigators found a nonsignificant risk ratio of 1.7 in the years 1991 to 2002. This shift may reflect technological advances in the devices available for airway management and their widespread dissemination (e.g., supraglottic airways, fiberoptic bronchoscopes). Of interest, these data may overstate the relative risk associated with general anesthesia, because this method of anesthesia is used principally when neuraxial anesthetic techniques are contraindicated for medical reasons or time constraints.

The type of maternal morbidity differs with the use of neuraxial anesthetic techniques and general anesthesia. A systematic review of randomized and quasi-randomized controlled trials comparing major maternal and neonatal outcomes with the use of neuraxial anesthesia and general anesthesia for cesarean delivery found less maternal blood loss and shivering but more nausea in the neuraxial anesthesia group. The intraoperative “perception” of pain was greater in the neuraxial group, but the time elapsed before the first...
TABLE 26.2 Provision of Anesthesia for Cesarean Delivery

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<tr>
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<td>“Sniffing” position if general anesthesia is planned</td>
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<td>Rarely provides satisfactory anesthesia as a primary technique</td>
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</tbody>
</table>

*Procedures, techniques, and drugs may need to be modified for individual patients and circumstances.

*Evidence suggests that administration of prophylactic antibiotics before incision (rather than after cord clamping) reduces the incidence of postcesarean endometritis and total maternal infectious morbidity.52
TABLE 26.3  Selection of Anesthetic Technique for Cesarean Delivery

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>Comments/Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For Neuraxial Anesthesia</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Maternal desire to witness birth and/or avoid general anesthesia</td>
<td>Most common maternal preference</td>
</tr>
<tr>
<td>Risk factors for difficult airway or aspiration</td>
<td>Physical examination predicts possible difficult airway</td>
</tr>
<tr>
<td></td>
<td>History of difficult tracheal intubation</td>
</tr>
<tr>
<td></td>
<td>High body mass index (obesity)</td>
</tr>
<tr>
<td></td>
<td>History of gastroesophageal reflux (common in pregnancy)</td>
</tr>
<tr>
<td>Presence of comorbid conditions</td>
<td>Malignant hyperthermia history</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>General anesthesia intolerance or failure</td>
<td>History of significant side effects with general anesthesia</td>
</tr>
<tr>
<td>Other benefits</td>
<td>Attempted general anesthesia with failed intubation; patient awakened</td>
</tr>
<tr>
<td></td>
<td>Plan for neuraxial analgesia after surgery</td>
</tr>
<tr>
<td></td>
<td>Less fetal drug exposure</td>
</tr>
<tr>
<td></td>
<td>Less blood loss</td>
</tr>
<tr>
<td></td>
<td>Allows presence of husband or support person</td>
</tr>
<tr>
<td><strong>For General Anesthesia</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Maternal refusal or failure to cooperate with neuraxial technique</td>
<td>Strong maternal preference, in the absence of factors that predict a difficult airway</td>
</tr>
<tr>
<td></td>
<td>Severe psychiatric disorder</td>
</tr>
<tr>
<td></td>
<td>Severe developmental delay</td>
</tr>
<tr>
<td></td>
<td>Severe emotional immaturity or lability</td>
</tr>
<tr>
<td>Presence of comorbid conditions that contraindicate a neuraxial technique</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Local infection at neuraxial insertion site</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Severe uncorrected hypovolemia (e.g., hemorrhage from placenta previa or uterine rupture)</td>
</tr>
<tr>
<td></td>
<td>Intracranial mass with increased intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Known allergy to local anesthetic (rare)</td>
</tr>
<tr>
<td>Insufficient time to induce neuraxial anesthesia for urgent delivery</td>
<td>Umbilical cord prolapse with persistent fetal bradycardia</td>
</tr>
<tr>
<td>Failure of neuraxial technique</td>
<td>Multiple needle placement failures</td>
</tr>
<tr>
<td></td>
<td>Missed spinal segments</td>
</tr>
<tr>
<td></td>
<td>Persistent intraoperative pain that is not treated successfully</td>
</tr>
<tr>
<td>Fetal issues</td>
<td>Planned ex utero intrapartum treatment (EXIT) procedure</td>
</tr>
</tbody>
</table>

<sup>a</sup>Many indications for or contraindications to specific anesthesia techniques are relative, and the choice of anesthetic must be tailored to individual circumstances.

TABLE 26.4  Classification for Urgency of Cesarean Delivery

<table>
<thead>
<tr>
<th>Grade</th>
<th>Label</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Emergency</td>
<td>Immediate threat to life of mother or fetus</td>
<td>Prolonged fetal bradycardia</td>
</tr>
<tr>
<td>2</td>
<td>Urgent</td>
<td>Maternal or fetal compromise that is not immediately life-threatening</td>
<td>Deep variable decelerations with cervical dilation of 3 cm</td>
</tr>
<tr>
<td>3</td>
<td>Scheduled</td>
<td>Needing early delivery but no maternal or fetal compromise</td>
<td>Ruptured membranes with previously undiagnosed breech presentation</td>
</tr>
<tr>
<td>4</td>
<td>Elective</td>
<td>At a time to suit the mother and delivery team</td>
<td>Elective repeat cesarean delivery</td>
</tr>
</tbody>
</table>


Postoperative request for analgesia was longer. Prospective audits of post-cesarean delivery outcomes have indicated that in the first postoperative week, patients who received neuraxial anesthesia had less pain, gastrointestinal stasis, coughing, fever, and depression and were able to breast-feed and ambulate more quickly than patients who received general anesthesia.126

Neonatal outcomes associated with maternal anesthetic selection require further study. Apgar and neonatal neurobehavioral scores are relatively insensitive measures of neonatal well-being, and umbilical cord blood gas and pH measurements may reflect the reason for the cesarean delivery rather than differences in the effect of the anesthetic technique on fetal/neonatal well-being. In a meta-analysis, lower umbilical...
cord blood pH measurements were associated with spinal, but not epidural, anesthesia compared with general anesthesia. However, the study included both randomized and nonrandomized trials and both elective and nonelective procedures, and most trials were conducted in an era when ephedrine was used to support maternal blood pressure (see later discussion). In a systematic review of randomized trials in which the indication for cesarean delivery was not urgent, no differences in umbilical cord arterial blood pH measurements were found among general and neuraxial anesthetic techniques.

Overview of Neuraxial Anesthetic Techniques

Table 26.5 outlines the advantages and disadvantages of the various neuraxial anesthetic techniques for cesarean delivery. With all neuraxial techniques, an adequate sensory level of anesthesia is necessary to minimize maternal pain and avoid the urgent need for administration of general anesthesia. Because motor nerve fibers are typically larger and more difficult to block, the complete absence of hip flexion and ankle dorsiflexion most likely indicates that a functional sensory and sympathetic block is also present in a similar (primarily lumbosacral) distribution. However, because afferent nerves innervating abdominal and pelvic organs accompany sympathetic fibers that ascend and descend in the sympathetic trunk (T5 to L1), a sensory block that extends rostrally from the sacral dermatomes to T4 should be the goal for cesarean delivery anesthesia.

The manner in which the level of sensory blockade is assessed has implications for the success of a neuraxial technique. The different methods of assessing the extent of sensory blockade (i.e., sensation to light touch, pinprick, cold) may indicate levels of blockade that differ by several spinal segments. A prospective study of 102 women undergoing cesarean delivery with spinal anesthesia indicated that although sensory blockade to light touch differed from sensory blockade to pinprick or cold sensation by 0 to 11 spinal segments, no constant relationship among these levels could be determined. The investigators concluded that a T6 blockade to touch would likely provide a pain-free cesarean delivery for most women.

Sensory examination should move caudad to cephalad in the mid-axillary line on the lower extremities but can be performed in the mid-clavicular line on the torso. The time at which an adequate block is achieved, as well as the cephalad level of the block and the presence of surgical anesthesia of the lower abdomen, should be documented on the anesthetic record.

Because the undersurface of the diaphragm (C3 to C5) and the vagus nerve may be stimulated by surgical manipulation during cesarean delivery, maternal discomfort (including shoulder pain) and other symptoms (e.g., nausea and vomiting) may occur despite a T4 level of blockade. Neuraxial or systemic opioids help prevent or alleviate these symptoms (see later discussion).

<table>
<thead>
<tr>
<th>Neuraxial Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural</td>
<td>No dural puncture required</td>
<td>Slow onset of anesthesia</td>
</tr>
<tr>
<td></td>
<td>Can use in situ catheter placed for earlier administration of labor analgesia</td>
<td>Larger drug doses required than for spinal techniques:</td>
</tr>
<tr>
<td></td>
<td>Ability to titrate extent of sensory blockade</td>
<td>• Greater risk for maternal local anesthetic systemic toxicity</td>
</tr>
<tr>
<td></td>
<td>Continuous intraoperative anesthesia</td>
<td>• Greater fetal drug exposure</td>
</tr>
<tr>
<td></td>
<td>Continuous postoperative analgesia</td>
<td>Delayed verification of functioning epidural catheter</td>
</tr>
<tr>
<td>Combined spinal-epidural</td>
<td>May be technically easier than spinal anesthesia in obese patients</td>
<td>Low doses of local anesthetic and opioid</td>
</tr>
<tr>
<td></td>
<td>Rapid onset of dense lumbosacral and thoracic anesthesia</td>
<td>Rapid onset of dense lumbosacral and thoracic anesthesia</td>
</tr>
<tr>
<td></td>
<td>Ability to titrate extent of sensory blockade</td>
<td>Continuous intraoperative anesthesia</td>
</tr>
<tr>
<td></td>
<td>Continuous postoperative analgesia</td>
<td></td>
</tr>
<tr>
<td>Continuous spinal</td>
<td>Low doses of local anesthetic and opioid</td>
<td>Large dural puncture increases risk for post-dural puncture headache</td>
</tr>
<tr>
<td></td>
<td>Rapid onset of dense anesthesia</td>
<td>Possibility of overdose and total spinal anesthesia</td>
</tr>
<tr>
<td></td>
<td>Ability to titrate extent of sensory blockade</td>
<td>if the spinal catheter is mistaken for an epidural catheter</td>
</tr>
<tr>
<td></td>
<td>Continuous intraoperative anesthesia</td>
<td>Limited duration of anesthesia</td>
</tr>
<tr>
<td>Single-shot spinal</td>
<td>Technically simple</td>
<td>Limited ability to titrate extent of sensory blockade</td>
</tr>
<tr>
<td></td>
<td>Low doses of local anesthetic and opioid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid onset of dense lumbosacral and thoracic anesthesia</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 26.5  Advantages and Disadvantages of Neuraxial Anesthetic Techniques for Cesarean Delivery
Spinal Anesthesia

Spinal anesthesia is a simple and reliable technique that allows visual confirmation of correct needle placement (by visualization of CSF) and is technically easier to perform than an epidural technique. Spinal anesthesia provides rapid onset of dense neuroblockade that is typically more profound than that provided with an epidural technique, resulting in a reduced need for supplemental intravenous analgesics or conversion to general anesthesia.\(^{130,131}\) Only a small amount of local anesthetic is needed to establish functional spinal blockade; therefore, spinal anesthesia is associated with negligible maternal risk for systemic local anesthetic toxicity and with minimal drug transfer to the fetus. Given these advantages, spinal anesthesia is the most commonly used anesthetic technique for cesarean delivery in the developed world.\(^{19}\) Spinal anesthesia is also associated with predictable and relatively prompt recovery that enables patients to quickly transition through the postanesthesia care unit (PACU); in some settings, such a recovery may result in a cost savings to the institution.\(^{130}\)

Spinal anesthesia is usually administered as a single-injection procedure (“single-shot” technique) through a noncutting, pencil-point needle that is 24-gauge or smaller. A number of different needle designs are available (see Chapter 12); the size and design of the needle tip affect the incidence and severity of post–dural puncture headache (see Chapter 30).

The spinal technique should be performed at the L3–L4 interspace or below (see Chapter 12). This space is used to avoid the potential for spinal cord trauma; although the spinal cord ends at L1 in most adults, it extends to the L2–L3 interspace in a small minority (see Chapter 31). Additionally, anesthesia providers often misidentify the location of the needle insertion site on the spinal column, and the needle is more frequently introduced at a higher level than intended.

On occasion, a continuous spinal anesthetic technique is used, particularly in the setting of an unintentional dural puncture with an epidural needle. Intentional continuous spinal anesthesia may be desirable in certain settings, when the reliability of a spinal technique and the ability to precisely titrate the initiation and duration of anesthesia are strongly desired (e.g., a morbidly obese patient with a difficult airway). Continuous spinal anesthesia may be administered through purpose-intended spinal catheters or through an “epidural catheter” that is sited in the subarachnoid space through an epidural needle that is advanced into the subarachnoid space (see Chapter 12).

Local Anesthetic Agents

The choice of local anesthetic agent (and adjuvants) used to provide spinal anesthesia depends on the expected duration of the surgery, the postoperative analgesia plan, and the preferences of the anesthesia provider. For cesarean delivery, the local anesthetic agent of choice is typically bupivacaine (Table 26.6). In the United States, spinal bupivacaine is formulated as a 0.75% solution in dextrose 8.25%; in other countries use of 0.5% concentration is common. Intrathecal administration of bupivacaine results in a dense block of long duration.

The dose of intrathecal bupivacaine that has been successfully used for cesarean delivery ranges from 4.5 to 15 mg. In general, pregnant patients require smaller doses of spinal local anesthetic than nonpregnant patients. Reasons include (1) a smaller CSF volume in pregnancy, (2) cephalad movement of hyperbaric local anesthetic in the supine pregnant patient, and (3) greater sensitivity of nerve fibers to the local anesthetic during pregnancy.\(^{132}\) Overall, the mass of local anesthetic, rather than the concentration or volume, is thought to influence the spread of the resulting blockade; however, the specific influence of the dose/concentration and baricity on the efficacy of the block is controversial. The necessary dose may be influenced by other factors, such as co-administration of neuraxial opioids and surgical technique. (Exteriorization of the uterus during closure of the uterus is more stimulating than closure in situ.)

A dose-finding study in 48 women undergoing cesarean delivery demonstrated that the effective dose for 95% of recipients (ED\(_{95}\)) for plain bupivacaine with fentanyl 10 µg and morphine 0.2 mg was 13 mg; the effective dose for 50% of recipients (ED\(_{50}\)) was 7.25 mg.\(^{134}\) However, other studies have suggested that lower doses can be used successfully. Low doses of hyperbaric or plain bupivacaine (9 mg with

### Table 26.6 Drugs Used for Spinal Anesthesia for Cesarean Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Anesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>60–80 mg</td>
<td>45–75</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>7.5–15 mg</td>
<td>60–120</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>7.5–15 mg</td>
<td>60–120</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>15–25 mg</td>
<td>60–120</td>
</tr>
</tbody>
</table>

| **Opioids**     |            |                |
| Fentanyl       | 10–25 µg   | 180–240        |
| Sufentanil     | 2.5–5 µg   | 180–240        |
| Morphine       | 100–200 µg | 720–1440       |
| Hydromorphone  | 60–75 µg (0.060–0.075 mg) | 720–875 |
| Meperidine\(^{a}\) | 60–70 mg   | 60             |

| **Adjuvant Drugs** |            |                |
| Epinephrine\(^{a}\) | 100–200 µg | (0.1–0.2 mg)   |

\(^{a}\)For the local anesthetics, the duration is defined as the time to two-segment regression. For the opioids, the duration is defined as the period of analgesia (or time to first request for a supplemental analgesic drug).

\(^{b}\)Meperidine has both local anesthetic and opioid properties and can provide surgical anesthesia without the addition of a local anesthetic. The dose indicated represents meperidine used without a local anesthetic.

\(^{c}\)The addition of epinephrine may augment the duration of local anesthetics by 15 to 20 minutes.
fentanyl 20 µg, 135 6.6 mg with sufentanil 3.3 µg136) have been demonstrated to provide adequate spinal anesthesia for most patients; whether hyperbaric or plain bupivacaine provides better anesthesia remains unclear. Reducing the dose of plain bupivacaine from 10 to 5 mg has been observed to decrease the incidence of hypotension and nausea; however, these findings were obscured by the variable use of opioids in the low-dose group. 137 Finally, in a comparison of plain bupivacaine 4.5 mg with hyperbaric bupivacaine 12 mg (both with fentanyl 50 µg and morphine 0.2 mg), similar cephalad sensory levels (C8), incidence of hypotension (approximately 75%), side effects, and patient satisfaction scores were found with the two approaches.138 Five of 27 (19%) patients in the bupivacaine 4.5-mg group and 1 of 25 (4%) patients in the bupivacaine 12-mg group required supplemental analgesia; no conversion to general anesthesia occurred. Altogether, while these data indicate that lower anesthetic doses can be used, whether they should be used is controversial. The anesthesia provider should consider whether adjuvant drugs will be used and whether the risks of giving supplemental analgesia or conversion to general anesthesia that are associated with low doses of bupivacaine outweigh the potential benefits (i.e., less hypotension, faster recovery).

For a single-shot spinal technique, most clinicians use a dose of bupivacaine between 10 and 15 mg, in combination with an opioid. Studies of hyperbaric bupivacaine (12 to 15 mg) have determined that the patient's age, height, weight, body mass, and vertebral column length do not affect the resulting neuraxial blockade.139,140 The use of the larger dose (15 mg) results in a longer duration of surgical anesthesia; however, cervical sensory blockade is achieved more frequently (Fig. 26.2). In patients with extremes of height (less than 5 feet [152 cm], or greater than 6 feet [183 cm]), some anesthesia providers alter the dose of local anesthetic. The baricity of the local anesthetic does affect the extent of spread of blockade. When the cephalad spread of hyperbaric local anesthetic is desired, the patient can be placed in a slight head-down position.

Ropivacaine is approximately 40% less potent than bupivacaine after spinal injection in nonpregnant individuals.141 In a dose-finding study of 72 patients undergoing elective cesarean delivery with CSE anesthesia randomly assigned to receive plain ropivacaine 10, 15, 20, or 25 mg,142 the ED50 and ED90 were determined to be 16.7 mg and 26.8 mg, respectively. Subsequently, the same investigators demonstrated that hyperbaric spinal ropivacaine 25 mg produced a more rapid block with faster recovery and fewer requirements for supplemental epidural anesthesia than the same dose of plain ropivacaine in women undergoing cesarean delivery with spinal anesthesia.143

The value of ropivacaine compared with bupivacaine for spinal anesthesia, however, is doubtful. Given the low doses, there is minimal, if any, reduction in risk for local anesthetic systemic toxicity. Further, it is not clear whether ropivacaine produces spinal anesthesia of similar quality to that provided by bupivacaine. An assessment of plain spinal ropivacaine 0.5% versus bupivacaine 0.5%, both administered with morphine 0.15 mg, found that ropivacaine was associated with a slower onset, less hypotension, and faster recovery.144 Similarly, spinal levobupivacaine may not be as effective as bupivacaine. A randomized trial assigned 90 parturients to receive plain ropivacaine 8 mg, levobupivacaine 8 mg, or ropivacaine 12 mg (all with sufentanil 2.5 µg); effective anesthesia was achieved in 97%, 80%, and 87% of patients, respectively.145 The duration of levobupivacaine and ropivacaine sensory and motor blockade was shorter than that with bupivacaine.146 The U.S. Food and Drug Administration (FDA) has not approved ropivacaine or levobupivacaine for intrathecal administration. Thus, in the United States, bupivacaine remains the predominant agent for spinal anesthesia for cesarean delivery.

Hyperbaric spinal lidocaine or mepivacaine (60 to 80 mg) may be used when the obstetrician can reliably perform cesarean delivery in less than 45 minutes. The use of hyperbaric lidocaine for spinal anesthesia remains controversial because of concerns about transient neurologic symptoms (see Chapter 31).

**Adjuvant Agents**

Adjuvant medications contribute to spinal anesthesia by different mechanisms from those of local anesthetics. For cesarean delivery, adjuvant agents improve the quality of intraoperative anesthesia, prolong postoperative analgesia, and reduce the dose, and therefore the side effects, of local anesthetics. Opioids, dextrose, and epinephrine are commonly used adjuvants; neostigmine and clonidine are two agents undergoing clinical investigation.

Opioids have been observed to improve intraoperative and postoperative comfort for patients undergoing spinal anesthesia for cesarean delivery. Intraoperatively, this effect can be observed through a reduction in local anesthetic drug doses and the need for analgesic supplementation. In a systematic review of intraoperative and postoperative analgesic efficacy...
and adverse effects of intrathecal opioids, 24% of patients undergoing cesarean delivery with spinal hyperbaric bupivacaine alone required supplemental intraoperative analgesia compared with 4% who also received intrathecal opioids.146 Opioids augment the quality and prolong the duration of local anesthetic–induced blockade, an effect most likely modulated by A-delta (pinprick) and C (cold) nerve fibers; muscle function (A-alpha nerve fibers) does not appear to be affected.147 The mechanism for the opioid-induced prolongation of sensory block remains unclear but may include modulation of sensory input at the spinal and supraspinal level as well as an alteration of consciousness of peripheral sensations.148

An additional advantage of intrathecal opioid administration is its salutary effect on the incidence of intraoperative nausea and vomiting. During periods of visceral stimulation (i.e., exteriorization of the uterus and fascial stimulation during closure), patients often complain of nausea. The addition of spinal fentanyl in doses of 10 to 25 µg to lidocaine or bupivacaine decreases the incidence of nausea and/or vomiting during cesarean delivery.149,150

Clinicians commonly add both a lipid- and water-soluble opioid to the local anesthetic for spinal anesthesia for cesarean delivery. This practice takes advantage of the fast onset of the lipid-soluble agent and the prolonged duration of the water-soluble agent (Fig. 26.3) (see Chapter 13). However, there is some evidence that the administration of a lipid-soluble agent (e.g., fentanyl, sufentanil) with a water-soluble agent (e.g., morphine) leads to acute spinal opioid tolerance. In a study of 60 patients undergoing cesarean delivery, there was no difference in intravenous patient-controlled analgesia morphine consumption within the first 6 hours in patients randomized to receive spinal fentanyl 25 µg or saline added to plain bupivacaine 10 mg.151 However, between 6 and 23 hours, there was a 63% increase in morphine use in the group that received fentanyl.151 In another a study of 40 women undergoing cesarean delivery using intrathecal fentanyl (0, 5, 10, or 25 µg) combined with hyperbaric bupivacaine 12 mg and morphine 0.2 mg, higher postoperative pain scores were observed in the patients who received fentanyl, but no differences were observed among groups in postoperative intravenous patient-controlled analgesia morphine consumption.152 Women who did not receive fentanyl had a higher incidence of intraoperative nausea and vomiting, suggesting that fentanyl is an important adjunct for intraoperative anesthesia.152 In general, we believe the improvement of intraoperative analgesia outweighs the potential for acute opioid tolerance. We therefore recommend the administration of both a lipid- and a water-soluble opioid when spinal anesthesia is administered for cesarean delivery.

The optimal dose of spinal opioids is influenced by the type, dose, and baricity of the accompanying local anesthetic and the presence of other adjuvants. In a systematic review and meta-analysis of studies examining the use of spinal fentanyl (2.5 to 60 µg) to augment spinal anesthesia for cesarean delivery, studies were pooled into two groups based on spinal fentanyl dose (15 to 35 µg and 40 to 60 µg)146; no difference between groups in the need for supplemental intraoperative analgesia was observed. Postoperative pruritus, nausea, and vomiting were significantly lower with administration of doses less than 35 µg, although no meaningful postoperative analgesia was produced at these doses. Spinal doses of fentanyl 10 to 25 µg are commonly used for cesarean delivery anesthesia (see Table 26.6).146,153

Spinal sufentanil 2.5 to 20 µg has been used with bupivacaine for cesarean delivery. A study of 37 parturients undergoing elective cesarean delivery with sufentanil (0, 10, 15, or 20 µg) added to hyperbaric bupivacaine 10.5 mg found better quality and longer duration of analgesia in all sufentanil groups than in the control group; Apgar scores, umbilical cord blood gas measurements, and Early Neonatal Neurobehavioral Scale (ENNS) scores were similar among groups.154 No cases of respiratory depression occurred. A randomized study assigned parturients to receive hyperbaric bupivacaine 12.5 mg with sufentanil (0, 2.5, 5, or 7.5 µg).155 Analgesia lasted longer with sufentanil 5 and 7.5 µg, and pruritus and somnolence were more pronounced with 7.5 µg. Thus, there appears to be little justification for giving a dose of sufentanil greater than 5 µg in this setting.

Preservative-free morphine, hydromorphone, and diamorphine can improve intraoperative comfort of parturients during cesarean delivery; however, these drugs are primarily used for providing prolonged (12 to 24 hours) postcesarean analgesia (see Chapter 27). Spinal morphine has a latency of 30 to 60 minutes for onset of analgesia,156 and it produces significant analgesia with acceptable side-effect profiles when given in doses ranging from 0.05 to 0.25 mg. In a dose-response study of morphine added to hyperbaric bupivacaine 12.75 mg, morphine 0.1 mg provided analgesia comparable to that provided by doses as high as 0.5 mg.157 The incidence of pruritus, but not nausea and vomiting, appeared to be dose-related. A more recent study that randomized patients to morphine 0.05, 0.10, or 0.15 mg combined with hyperbaric bupivacaine 12 mg and fentanyl 15 µg, and intravenous ketoroloc, found no difference in measures of analgesia among the three groups; pruritus was more common at doses

![Fig. 26.3 Schematic illustration of the pharmacokinetic and pharmacodynamic activities resulting from the neuraxial administration of a lipid-soluble opioid (e.g., fentanyl) and a water-soluble opioid (e.g., morphine) for analgesia. The transition point varies according to the opioid drugs and doses administered. For most commonly used opioids, this transition point occurs in the postoperative period.](image-url)
of 0.10 and 0.15 mg than 0.05 mg.\textsuperscript{158} Hydromorphone, while used less commonly than morphine, also appears to provide effective postcesarean analgesia, with an intrathecal potency ratio of 2:1 compared with morphine.\textsuperscript{159}

Intrathecal diamorphine is used in the United Kingdom for postoperative analgesia. It is metabolized to the two active compounds 6-acetyl morphine and morphine. Diamorphine is more lipophilic than morphine, enabling a rapid onset (6 to 9 minutes, similar to fentanyl) but a potentially shorter duration of action.\textsuperscript{160} In a study of intrathecal diamorphine 0.4 mg combined with bupivacaine 12.5 mg, the intraoperative supplementation rate was less than 5%; however, the incidence of nausea and vomiting was 56%, and the incidence of pruritus was 80%.\textsuperscript{161}

Neuraxial administration of water-soluble opioids such as morphine may be associated with delayed respiratory depression (6 to 18 hours after administration) (see Chapter 27). Postoperative monitoring protocols should observe for respiratory depression, which although infrequent, can lead to mortality, particularly in high-risk patients (e.g., those with sleep apnea or obesity).\textsuperscript{164,162} The respiratory depressant effects of many opioids, including morphine and diamorphine, outlast the antagonism provided by naloxone (approximately 90 minutes).\textsuperscript{162}

Spinal local anesthetics are often prepared in dextrose to make the agents hyperbaric. For example, commercially available hyperbaric bupivacaine contains 8.25% dextrose (82.5 mg/mL). The amount of dextrose required to make a meaningful clinical difference in a spinal technique with local anesthetic agents has not been well characterized. Baricity is defined as the ratio of the density of the local anesthetic solution to the density of CSF measured at the same temperature. The density of CSF is lower in women than in men, particularly during pregnancy and the immediate postpartum period;\textsuperscript{164} even so, CSF density is significantly greater than that of local anesthetics and opioids in the absence of dextrose.\textsuperscript{163}

The intrathecal administration of an alpha-adrenergic agonist (e.g., epinephrine, clonidine) increases the density of sensory and motor blockade and may prolong the duration of blockade as well as contribute to postcesarean analgesia. A randomized trial involving 63 women undergoing elective cesarean delivery showed that intrathecal epinephrine 0.1 to 0.2 mg, when combined with hyperbaric bupivacaine, improved the quality of intraoperative analgesia and prolonged both sensory and motor blockade by approximately 15% compared with bupivacaine alone.\textsuperscript{165} However, another study found that the addition of epinephrine 0.3 mg to hyperbaric bupivacaine 12.5 mg for elective cesarean delivery increased the incidence of nausea.\textsuperscript{166}

Spinal clonidine, in doses of 60 to 150 µg, improves intraoperative analgesia, decreases shivering, and reduces peri-incisional hyperalgesia in women undergoing cesarean delivery; however, it has been associated with hypotension and sedation.\textsuperscript{167} This agent is not used commonly in the United States, although it may be considered in specific circumstances (e.g., when patients are expected to be tolerant to the effects of neuraxial opioid analgesia). The FDA has issued a “black box” warning against its use in obstetric patients because of concern for hypotension.

In women undergoing cesarean delivery, spinal neostigmine in doses up to 100 µg significantly reduced postoperative pain with no effect on FHR or Apgar scores. However, multiple studies have demonstrated a high incidence of nausea and emesis associated with intrathecal neostigmine, which may be refractory to treatment with antiemetic agents.\textsuperscript{168–170} This side effect significantly limits its clinical use.

At many institutions, the spinal agents and doses are standardized so that consistent results are obtained during the provision of spinal anesthesia for cesarean delivery. Such standardization enables the anesthesia, obstetric, and nursing staff to anticipate predictable onset and recovery characteristics and respond to physiologic responses that are outside the norm. Standardization of drugs and doses may also result in fewer errors. At our institution, spinal anesthesia for cesarean delivery is provided with 0.75% hyperbaric bupivacaine 12 mg, fentanyl 10 µg, and morphine 0.1 mg. Intrathecal opioids are drawn in a tuberculin or insulin syringe to insure measurement accuracy. Another common practice is the administration of 0.75% hyperbaric bupivacaine 12 mg, fentanyl 15 µg, and morphine 0.15 mg.

**Epidural Anesthesia**

The use of epidural anesthesia for nonelective cesarean delivery has increased, primarily because of the greater use of epidural analgesia during labor. However, the use of epidural anesthesia is less common for elective cesarean delivery when an epidural catheter is not already in situ (e.g., for labor analgesia), in part because the resulting block is less reliable than that with spinal anesthesia. Initiation of CSE anesthesia offers both rapid onset and reliable spinal anesthesia coupled with the ability to augment or prolong the blockade through the epidural catheter (e.g., cases that are high-order repeat cesarean deliveries, have greater risk for hemorrhage, or include tubal sterilization or additional procedures).

Epidural local anesthetic and opioid doses are generally 5 to 10 times greater than doses given intrathecally; this difference results from the requirement for penetration of nerve roots as they traverse the epidural space, the greater capacity of the epidural space, and the presence of the epidural venous plexus, which becomes progressively more engorged during pregnancy. Greater systemic absorption of anesthetic agents occurs with epidural anesthesia than with spinal anesthesia, and the risk for local anesthetic systemic toxicity is a real possibility with local anesthetic injection for epidural anesthesia, but not for spinal anesthesia.

Possible advantages of the epidural technique include a slower onset of sympathetic blockade; this may allow compensatory mechanisms to attenuate the severity of hypotension. This approach has utility in the care of patients with severe cardiac disease for whom even transient hypotension may be poorly tolerated. A catheter-based technique also allows titration of the level, density, and duration of anesthesia. Continuous postcesarean analgesia can be provided through an epidural catheter.
TABLE 26.7 Drugs Used for Epidural Anesthesia for Cesarean Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range*</th>
<th>Duration (min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Anesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine 2% with epinephrine 5 µg/mL</td>
<td>300–500 mg</td>
<td>75–100</td>
</tr>
<tr>
<td>2-Chloroprocaine 3%</td>
<td>450–750 mg</td>
<td>40–50</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>75–125 mg</td>
<td>120–180</td>
</tr>
<tr>
<td>Ropivacaine 0.5%</td>
<td>75–125 mg</td>
<td>120–180</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50–100 µg</td>
<td>120–240</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10–20 µg</td>
<td>120–240</td>
</tr>
<tr>
<td>Morphine</td>
<td>3–4 mg</td>
<td>720–1440</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.6–1.5 mg</td>
<td>780–1090</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50–75 mg</td>
<td>240–720</td>
</tr>
</tbody>
</table>

*Both the mass and volume of local anesthetic affect the extent and quality of anesthesia. The usual volume of local anesthetic solution administered into the epidural space at the indicated concentrations is 15 to 25 mL. More mass/volume is required for initiating epidural anesthesia de novo; conversely, less is required if epidural labor analgesia is being extended to surgical anesthesia.

*bFor the local anesthetics, the duration is defined as the time to two-segment regression. For the opioids, the duration is defined as the period of analgesia (or time to first request for a supplemental analgesic drug).

Local Anesthetic Agents

The most common local anesthetic used in the United States for the initiation and maintenance of epidural anesthesia for cesarean delivery is 2% lidocaine with epinephrine (Table 26.7). The epidural administration of lidocaine in concentrations less than 2%, or without the addition of epinephrine (which augments the analgesia through alpha-adrenergic receptor blockade), may result in anesthesia that is inadequate for surgery.172

The epidural administration of a 3% solution of 2-chloroprocaine has the most rapid onset and the shortest duration of action of available local anesthetics. These characteristics make it an excellent choice for emergency cesarean delivery (see later discussion) because the dose is administered rapidly, and even if unintentional intravenous administration of drug were to occur, the sequelae are likely to be less severe than the similar administration of an amide local anesthetic agent. Administration of 2-chloroprocaine has been associated with neurologic sequelae, possibly associated with the antioxidant sodium bisulfite, and paralumbar muscle spasms and pain, believed to be a result of calcium chelation by the preservative EDTA. Current preparations of 2-chloroprocaine do not contain an antioxidant or a preservative (see Chapter 13). Epidural administration of 2-chloroprocaine may be associated with a rapid onset of hypotension and an apparent reduction in the clinical efficacy of subsequently administered epidural opioids (see Chapter 13).173 The pharmacokinetic characteristics of the drug likely play a role. The analgesic effect of epidural morphine administered 30 minutes before 2-chloroprocaine does not appear to be mitigated; however, administration of morphine before 2-chloroprocaine in the setting of emergency cesarean delivery is not possible.173 These considerations limit the use of 2-chloroprocaine to those situations in which the rapid onset of anesthesia is paramount.

Surgical anesthesia can be produced with epidural administration of 0.5% bupivacaine; however, the slow onset of neuroblockade and the risk for cardiovascular sequelae from unintentional intravascular injection (or systemic absorption) have limited the contemporary use of this agent in the United States. (The risk for cardiovascular sequelae resulted in a proscription against the epidural administration of 0.75% bupivacaine in obstetric patients by the FDA.) The single-isomer, levorotatory local anesthetics 0.5% to 0.75% ropivacaine and 0.3% levobupivacaine may be preferable to racemic bupivacaine because of their better safety profiles and earlier recovery, although a significant portion of the improved safety profile is caused by the lower potency of these agents (0.5% bupivacaine is more potent than 0.5% levobupivacaine or 0.5% ropivacaine).175 A randomized controlled trial of 60 patients compared 30 mL of epidural 0.5% levobupivacaine with racemic 0.5% bupivacaine in women undergoing elective cesarean delivery; no differences in the block onset or resolution, signal-averaged ECG results, complications, or maternal and fetal plasma pharmacokinetic profiles between the treatment groups was found.176 Another study involving 62 patients undergoing cesarean delivery with epidural anesthesia reported no difference in onset, spread, or duration of sensory block in women who received 25 mL of 0.5% levobupivacaine or 0.5% racemic bupivacaine, although levobupivacaine produced lower limb motor blockade of longer duration and less intensity. Finally, a study of 60 patients demonstrated that the onset, duration, and regression of sensory blockade with 0.5% ropivacaine was similar to that provided by 0.5% bupivacaine, although a faster onset and longer duration of motor blockade was observed with bupivacaine.178 The free concentrations of ropivacaine were approximately twice those of bupivacaine in both maternal and neonatal blood at delivery; however, these measurements were less than the concentrations shown to be toxic in animals.

Adjuvant Agents

As with spinal anesthesia, adjuvant medications are used for their intrinsic analgesic properties and to reduce the dose and side effects of local anesthetic agents. The use of epidural adjuvants can improve the quality of intraoperative anesthesia and result in less motor blockade as well as enhance postoperative analgesia (see Chapter 27).

Although some anesthesia providers administer an epidural opioid with the initial therapeutic dose of local anesthetic, others delay opioid administration until after the umbilical cord is clamped to prevent transfer of opioid to the fetus. The onset of analgesia is dictated by complex pharmacokinetics; however, the lipid-soluble opioids (e.g., fentanyl, sufentanil) have more rapid onset and more rapid clearance than the water-soluble opioids (e.g. morphine).179
The administration of epidural fentanyl (50 to 100 µg) results in activity at both spinal and supraspinal sites of action,\textsuperscript{180} improves the intraoperative quality of anesthesia during cesarean delivery,\textsuperscript{181,182} and does not appear to adversely affect the neonate.\textsuperscript{183} The optimal dose of epidural fentanyl has not been determined for patients undergoing cesarean delivery; however, in an experimental pain study in nonpregnant patients, there was an analgesic effect at the segmental level of injection for epidural fentanyl 100 µg, but not 50 µg.\textsuperscript{184}

Epidural sufentanil (10 to 20 µg) added to 0.5% bupivacaine with epinephrine 5 µg/mL, provides significantly better intraoperative anesthesia and longer postoperative analgesia than bupivacaine and epinephrine alone, with minimal maternal side effects and no adverse neonatal effects.\textsuperscript{185} Epidural sufentanil is approximately five times more potent than epidural fentanyl, but when equipotent doses are administered, no differences between the agents in onset, quality, or duration of analgesia have been observed.\textsuperscript{186,187}

Epidural administration of the hydrophilic drug morphine provides prolonged postcesarean analgesia. A dose-response study of epidural morphine (1.25, 2.5, 3.75, and 5 mg) found 3.75 mg to be an optimal dose beyond which postcesarean analgesia (as measured by patient-controlled analgesia morphine demands) was no better.\textsuperscript{188} Extended-release epidural morphine 10 mg provides better postoperative analgesia than epidural morphine 4 mg, with no differences in nausea, pruritus, or sedation scores.\textsuperscript{189}

Epidural hydromorphone is sometimes used as an alternative to morphine. Doses between 0.6 and 1.5 mg are commonly used. Studies suggest a similar analgesic effect and side-effect profile compared with epidural morphine analgesia, although the duration of analgesia may be slightly shorter.\textsuperscript{190,192}

Epidural diamorphine (2.5 to 3 mg) is commonly used in the United Kingdom for providing prolonged postcesarean analgesia.\textsuperscript{193} Optimal dose-finding studies of epidural diamorphine have not been performed; however, the duration and quality of analgesia from epidural diamorphine 3 mg appears to similar to that provided by spinal diamorphine 0.3 mg, with significantly less pruritus.\textsuperscript{194}

Epidural clonidine (75 to 200 µg) combined with morphine or fentanyl reduces the requirement for postcesarean morphine analgesia.\textsuperscript{195} The effect of co-administering clonidine and fentanyl appears to be additive rather than synergistic in producing postcesarean analgesia. Common side effects include hypotension and sedation. Currently, epidural clonidine has only one specific neuraxial indication in the United States (intractable cancer pain), and the package insert has a “black box” warning from the FDA stating that “epidural clonidine is not recommended for obstetrical, postpartum and perioperative pain management.”

Epidural neostigmine produces a modest amount of postcesarean analgesia when given after umbilical cord clamping. A dose-finding study investigated the administration of 75, 150, or 300 µg of epidural neostigmine in women undergoing elective cesarean delivery.\textsuperscript{196} An increase in intraoperative shivering and sedation was observed in the 300-µg group only; a dose-independent reduction in postoperative pain and sedation was observed in all groups.

**Epinephrine** may be added to the local anesthetic agent to minimize systemic absorption and peak blood level of the local anesthetic, increase the density of sensory and motor blockade, and prolong the duration of anesthesia.\textsuperscript{171,197,198} The pharmacokinetic effects of epinephrine co-administered with an opioid vary with the opioid and the sampling site. In the lumbar epidural space, epinephrine lengthened the mean residence time of morphine but shortened that of fentanyl and sufentanil.\textsuperscript{199}

The epidural administration of epinephrine in preeclamptic women is controversial (see Chapter 35).\textsuperscript{200} Animal and clinical studies suggest that epidural epinephrine 0.1 mg does not decrease uterine blood flow in normotensive pregnancies.\textsuperscript{201,202} By contrast, in hypertensive women, the addition of epidural epinephrine 5 µg/mL (1:200,000) to bupivacaine significantly reduced uteroplacental blood flow; however, this did not affect umbilical arterial blood flow or pH measurements at delivery.\textsuperscript{204}

When combined with local anesthetic for epidural anesthesia, the usual epinephrine concentration is 2.5 or 5 µg/mL (i.e., 1:400,000 or 1:200,000). The addition of epinephrine to a solution of plain local anesthetic just before administration results in a solution that has a higher pH than commercially prepared epinephrine-containing products, which use (low-pH) antioxidants to preserve the efficacy of the epinephrine (see Chapter 13). Thus, use of freshly prepared solutions hastens the onset of anesthesia.

The addition of sodium bicarbonate results in a solution with more local anesthetic molecules in a non-ionized state, which hastens the onset and augments the quality of the local anesthetic blockade, particularly if sodium bicarbonate is added to a low-pH solution (see later discussion).

**Combined Spinal-Epidural Anesthesia**

The CSE technique incorporates the rapid and predictable onset of spinal blockade with the ability to augment anesthesia by injection of additional drug through the epidural catheter.\textsuperscript{205,206} In 1981, Brownridge\textsuperscript{207} reported the first use of the CSE technique for cesarean delivery through separate spinal and epidural needles introduced at different interspaces. Carrie and O’Sullivan\textsuperscript{206} subsequently described the needle-through-needle technique via a single interspace for cesarean delivery; this has become the more popular technique. Compared with a conventional epidural anesthetic technique for cesarean delivery, the advantages of the CSE technique include faster onset and lower pain scores at delivery.\textsuperscript{207}

Additional advantages of the CSE technique include (1) use of the epidural needle as an introducer for a longer spinal needle when attempts with a traditional introducer and spinal needle have failed and (2) use of a spinal needle (and return of CSF through the needle) to “confirm” the correct positioning of the epidural needle in the epidural space. The CSE technique also allows use of a low dose of local anesthetic to
initiate spinal anesthesia (associated with a lower incidence of hypotension), followed by use of the epidural catheter to extend intraoperative anesthesia or provide postoperative analgesia.

Conventional spinal doses (e.g., 12 mg) of hyperbaric bupivacaine are most often used to provide CSE anesthesia for cesarean delivery; however, a satisfactory block has been reported with plain bupivacaine drug doses as low as 4.5 mg.\(^{189}\) Although the use of lower doses of local anesthetic is enabled by the presence of the epidural catheter (because additional agents can be administered if discomfort occurs), the block achieved with the CSE technique may be inherently different from the block achieved with a single-shot spinal technique with the same dose(s) of medication. One study, in which men undergoing surgery were positioned in the right lateral position for initiation of neuraxial anesthesia, demonstrated that the median effective doses of intrathecal hyperbaric bupivacaine (to achieve a T6 sensory level of anesthesia for 60 minutes) for the CSE and spinal techniques were 9.2 mg and 11.4 mg, respectively.\(^{208}\) The investigators speculated that the use of the loss-of-resistance to air (during introduction of the epidural needle) resulted in a reduction in lumbar CSF volume and a subsequently higher sensory blockade. Similarly, in another study that initiated neuraxial analgesia with intrathecal bupivacaine 10 mg in parturients undergoing elective cesarean delivery, median sensory levels were C6 and T3 with the CSE and spinal techniques, respectively.\(^{209}\) The CSE technique was performed with loss-of-resistance to air (2 mL); however, after administration of the spinal medications, the epidural catheter was not inserted. The investigators speculated that the loss of negative pressure in the epidural space created by the introduction of the epidural needle was responsible for the observed differences. However, when investigators from the same institution performed the same anesthetic techniques for cesarean delivery in laboring women, no differences in the block characteristics were observed.\(^{210}\) The reasons for these differences are unclear.

The sequential CSE technique uses a lower dose of spinal bupivacaine (7.5 to 10 mg) followed by incremental injection of local anesthetic through the epidural catheter to achieve a T4 level of anesthesia.\(^{211,212}\) The purported advantage of this approach is a lower incidence of hypotension. In a study involving 42 patients comparing sequential CSE anesthesia using 1.5 mL of 0.5% of hyperbaric bupivacaine (followed by extension with fractionated doses of 0.5% bupivacaine administered through the epidural catheter as needed) versus single-shot spinal anesthesia using 2.5 mL of 0.5% of hyperbaric bupivacaine, more gradual onset of hypotension and a lower initial sensory level was observed with the CSE compared with the single-shot spinal technique (T7 and T4, respectively).\(^{212}\) The sequential CSE technique may be of particular advantage in high-risk parturients (e.g., significant cardiac disease) in whom avoidance of severe hypotension can be vitally important.

Another CSE technique is the extradural volume extension (EVE) technique.\(^{211,213}\) Intrathecal administration of a small dose of local anesthetic is followed by the administration of saline through the epidural catheter. Studies have observed a higher cephalad spread of one to four dermatomal segments associated with the use of this technique, presumably because of thecal compression.\(^{211}\) However, the effect of EVE may depend on the initial dose and baricity of local anesthetic, the time interval between spinal and epidural injection, the volume of epidural saline, and the outcomes measured, as several studies have failed to find a difference in sensory blockade using this technique.\(^{211,214}\)

Potential drawbacks of CSE techniques include an untested epidural catheter and hypotension. Administering the CSE technique in the sitting position may result in greater severity and duration of hypotension than the left lateral decubitus position.\(^{93}\) The hypotension may be related to the delay in moving the patient from the sitting to the supine (with leftward tilt) position.

### Extension of Epidural Labor Analgesia

The extension of epidural labor analgesia to surgical anesthesia sufficient for cesarean delivery can be accomplished with several local anesthetic agents. The selection of agent often depends on the urgency of the case. Extension of epidural analgesia can be initiated as preparations are being made to move the patient from the labor room to the operating room. Whether an in situ epidural catheter should be used for an extension attempt depends on several factors, including the quality of the existing labor analgesia. If obtaining satisfactory epidural labor analgesia has been problematic (e.g., one-sided or “patchy” analgesia), replacing the catheter or using a spinal or CSE technique may be a better method to attain rapid and effective anesthesia. A systematic review and meta-analysis found that the incidence of failed conversion of labor analgesia to cesarean delivery anesthesia is greater when an increasing number of epidural boluses have been required to produce sufficient labor analgesia, a greater urgency for cesarean delivery exists, and a nonobstetric anesthesiologist is managing the case.\(^{215}\)

Specific local anesthetic and adjuvant solutions may influence whether the quality and level of epidural anesthesia is adequate for cesarean delivery. A meta-analysis of 11 randomized controlled trials examining the type of local anesthetic used to “top-up” epidural labor analgesia for emergency cesarean delivery\(^{216}\) compared 0.5% bupivacaine or levobupivacaine, lidocaine with epinephrine (with and without fentanyl), and 0.75% ropivacaine. The pooled analysis suggested that lidocaine with epinephrine resulted in the fastest onset of sensory block; the addition of fentanyl further hastened block onset, but not quality as measured by the need for intraoperative supplementation. Compared with bupivacaine, ropivacaine was associated with a lower need for intraoperative supplementation, and lidocaine demonstrated a trend toward lower need. The epidural administration of 2% lidocaine with freshly added epinephrine 5 µg/mL was compared with 3% 2-chloroprocaine in a randomized trial involving 40 women undergoing elective cesarean delivery.\(^{217}\) This study observed no significant difference in the onset of anesthesia between the two groups, although the study was likely underpowered; the
median onset was 8 minutes (range of 4 to 13 minutes) in the 2-chloroprocaine group and 5 minutes (range of 2 to 22 minutes) in the lidocaine group. However, given the time taken to prepare the lidocaine with epinephrine solution, the investigators concluded that use of a pre-prepared solution, such as 2-chloroprocaine, may be preferred.

Alkalinization of the local anesthetic solution not only increases the speed of onset but also improves the quality and prolongs the duration of neuroblockade. Alkalinization shifts more of the local anesthetic molecules to the non-ionized, lipid-soluble form, which allows the local anesthetic to pass more easily through the lipophilic neuronal membrane. Although this phenomenon can be demonstrated for all local anesthetics, alkalinization is most often performed with local anesthetic agents of short and medium duration (e.g., 2-chloroprocaine, lidocaine). Typically, 1 mL of 8.4% sodium bicarbonate (1 mEq/mL) is added to 10 mL of lidocaine or 2-chloroprocaine. Longer-acting agents (e.g., bupivacaine, ropivacaine, levobupivacaine) easily precipitate with the addition of sodium bicarbonate. Precipitation occurs with the addition of less than 0.2 mEq of bicarbonate to 20 mL of 0.5% bupivacaine. Alkalinization exerts the greatest effect when it is freshly mixed with the local anesthetic solution; however, the mixture is relatively stable.

The addition of sodium bicarbonate to local anesthetics has been demonstrated to result in a clinically significant reduction in the time until an adequate anesthetic level is obtained (Fig. 26.4). In a randomized trial, 40 women with functioning epidural labor analgesia received a 3-mL epidural test dose of 2% lidocaine with epinephrine, followed by 12 mL of premixed 2% lidocaine with epinephrine 5 µg/mL (1:200,000) and fentanyl 75 µg with 1.2 mL of 8.4% sodium bicarbonate or saline. The mean times to attain a T6 anesthesia level with and without bicarbonate were 5.2 minutes and 9.7 minutes, respectively.

Extension of a T10 level of analgesia to a T4 level of anesthesia typically requires a volume of 15 to 20 mL of local anesthetic with one or more adjuvants. At our institution, the extension of epidural labor analgesia begins with assessment of the quality of analgesia. For emergency cesarean delivery, we initiate the extension of epidural anesthesia in the labor room by giving 10 mL of alkalinized 2% lidocaine (with epinephrine) or 3% 2-chloroprocaine. The sensory blockade is assessed after transfer of the patient to the operating room; if the blockade is bilateral and moving in a cephalad direction, an additional 5 to 10 mL is administered to bring the sensory level to T4. The use of this fractionated dosing schedule offers several advantages, including (1) greater hemodynamic stability during patient transfer; (2) assessment of the evolving sensory level before administration of the full dose of local anesthetic; (3) minimization of dural sac compression (by a large volume epidural injection), which enables a less difficult and safer conversion to spinal anesthesia if extension of epidural anesthesia is not successful (see later discussion); and (4) early sensory blockade at the incision site, so that surgery can be initiated in emergency cases before establishment of a full T4 sensory level.

The extension of epidural analgesia to epidural anesthesia in the labor room is controversial. Some anesthesia providers delay epidural administration of additional local anesthetic until the patient has arrived in the operating room. However, this practice may increase the risk for failed epidural anesthesia, necessitating the induction of general anesthesia with its attendant risks (see later discussion).

**General Anesthesia**

Although neuraxial techniques are typically preferred when anesthesia is provided for cesarean delivery, there are some clinical situations in which the administration of general anesthesia is considered the most appropriate option (see Table 26.3). In addition, general anesthesia offers an advantage in cases in which uterine relaxation would be beneficial (e.g., cesarean delivery as part of an ex utero intrapartum treatment [EXIT] procedure).

The basic elements for preparation and care of the obstetric patient undergoing cesarean delivery apply to the patient undergoing general anesthesia (Box 26.7, see Table 26.2). The preanesthetic evaluation should focus on assessment of physical characteristics (e.g., airway) and comorbidities. The consent process should feature the risks associated with airway management, aspiration, and awareness. The importance of a careful airway evaluation cannot be overemphasized (see Chapter 29); pregnancy-induced changes in the upper airway may be exacerbated during labor. Acoustic reflectometry shows that soft tissue mucosal edema in both the oral (incisor teeth to oropharyngeal junction) and pharyngeal (oropharyngeal junction to the glottis) tissue...
anesthesia-related causes of maternal death. If the airway is guarded, pulmonary aspiration of gastric contents remains leading to complete tracheal intubation, failed ventilation, and oxygenation, and increases during labor. If the antacid may be particularly important in the emergent situation when metoclopramide and ranitidine have not had the necessary time to exert their pharmacologic effects. If the patient has airway characteristics that herald difficult intubation, consideration should be given to the placement of a neuraxial catheter during early labor, even if it is not used to provide labor analgesia.

**Preparation**

All pregnant patients requiring surgical anesthesia should be considered at risk for pulmonary aspiration of gastric contents (see Chapter 28). Attempts should be made to minimize both the risk for maternal aspiration and the risk for pulmonary injury if aspiration occurs. Fasting policies should be shared with all members of the obstetric care team. We administer metoclopramide 10 mg and ranitidine 50 mg intravenously between 30 and 60 minutes before induction of general anesthesia, when possible, to diminish gastric volume and gastric acid secretion, respectively. A clear, nonparticulate antacid (sodium citrate 30 mL) should also be administered within 30 minutes of surgery to neutralize gastric acid. The antacid may be particularly important in the emergent situation when metoclopramide and ranitidine have not had the necessary time to exert their pharmacologic effects.

If the patient has airway characteristics that herald difficult mask ventilation or intubation, consideration should be given to performing an awake tracheal intubation (see Chapter 29). Preparations include administering an antisympathectomy (e.g., glycopyrrolate), judicious sedation (e.g., midazolam), and topical airway anesthesia (e.g., aerosolized lidocaine or benzocaine). Glosopharyngeal and laryngeal nerve blocks may also be considered, although these should be avoided in patients at excess risk for bleeding (e.g., Hemolysis, Elevated Liver enzymes and Low Platelet count [HELLP] syndrome).

**BOX 26.7 Steps for Initiating General Anesthesia for Cesarean Delivery**

1. Discuss the operative plan with the multidisciplinary team.
2. Perform preanesthetic assessment, and obtain informed consent.
3. Prepare necessary medications and equipment.
4. Place patient supine with left uterine displacement.
5. Secure 16- or 18-gauge intravenous access. Send blood specimen for baseline laboratory measurements; consider type and screen (or cross-match) if risk factors for peripartum hemorrhage are present.
6. Give metoclopramide 10 mg and/or ranitidine 50 mg intravenously more than 30 minutes before induction, if possible.
7. Give a nonparticulate antacid orally less than 30 minutes before induction.
8. Administer antibiotic prophylaxis (with 60 minutes before incision).
9. Initiate monitoring.
10. Perform a team “time-out” to verify patient identity, position, and operative site; procedure to be performed; and availability of special equipment, if needed.
11. Provide 100% oxygen with a tight-fitting face mask for 3 minutes or longer, when possible, for denitrogenation/preevacuation. Otherwise, instruct the patient to take four to eight vital-capacity breaths immediately before induction of anesthesia.
12. After the abdomen has been prepared and operative drapes are in place, verify that the surgeon and assistant are ready to begin surgery.
13. Initiate rapid-sequence induction:
   a. Cricoid pressure 10 N while awake; increase to 30 N after loss of consciousness.
   b. Thiopental 4 to 6 mg/kg or propofol 2 to 2.8 mg/kg and succinylcholine 1 to 1.5 mg/kg; wait 30 to 40 seconds.
15. Provide maintenance of anesthesia:
   a. Use isoflurane, sevoflurane, or desflurane (approximately 1 MAC) in 100% oxygen or oxygen/nitrous oxide (up to 50%).
   b. Treat hypotension (e.g., phenylephrine, ephedrine).
   c. If additional muscle relaxant (e.g., rocuronium, vecuronium) is necessary, titrate dose according to response to peripheral nerve stimulator.
17. Administer a bolus and/or a continuous infusion of oxytocin; consider other uterotonic agents (e.g., methylergonovine, 15-methyl prostaglandin Fα) if uterine tone is inadequate. Monitor blood loss, and respond as necessary.
18. Adjust maintenance technique after delivery of the infant:
   a. Administer a reduced concentration of a volatile halogenated agent (0.5 to 0.75 MAC).
   b. Supplement anesthesia with nitrous oxide and an intravenous opioid.
   c. Give attention to risk for awareness and recall. Consider administration of a benzodiazepine (e.g., midazolam).
19. Perform tracheal extubation when neuromuscular blockade is fully reversed and the patient is awake and responds to commands.
20. Evaluate postoperative issues (e.g., pain, nausea).
The patient should be placed supine with left uterine displacement. The head, neck, and shoulders should be optimally positioned for airway management (i.e., the sniffing position) (see Fig. 29.7). Routine monitoring should be established, including ECG, pulse oximetry, blood pressure, and capnography. Preoxygenation (denitrogenation) with 100% oxygen should be performed to delay the onset of hypoxemia during apnea; this hypoxemia occurs more rapidly because of the pregnancy-induced decrease in functional residual capacity and increase in oxygen consumption. In a computer simulation of the respiratory and cardiovascular systems during pregnancy, the presence of labor, high BMI, and sepsis further accelerated oxyhemoglobin desaturation during apnea; by contrast, multiple gestation and hemorrhage appeared to have minimal effects. Ideally, preoxygenation is accomplished by 3 minutes of tidal-volume breathing with a tight-fitting face mask. Although four maximal deep breaths over 30 seconds with an Fio2 of 1.0 can achieve a similar PaO2, the same protection against rapid oxyhemoglobin desaturation is not afforded, owing to differences in tissue and venous compartment oxygen reserves. The method of eight deep breaths over 1 minute appears to provide better protection from oxyhemoglobin desaturation during apnea than the four deep breaths over 30-second method.

In contrast to most surgical procedures, the patient’s abdomen is prepared and draped before induction of general anesthesia to minimize fetal exposure to general anesthesia. After the surgical drapes have been applied and the operating personnel are ready at the bedside, the surgeon should be instructed to delay the incision until the anesthesia provider confirms correct placement of the endotracheal tube and gives verbal instructions to proceed with surgery.

Induction
A rapid-sequence induction is initiated with denitrogenation/preoxygenation followed by administration of an induction agent, paralysis, and cricoid pressure. Mask ventilation is traditionally not performed, because when it is applied without the application of cricoid pressure and with pressures greater than 20 cm H2O, insufflation of the stomach can occur (see Chapter 29). Some guidelines have suggested modification of the rapid-sequence induction to include gentle, low-pressure (Pmax 20 cm H₂O) mask ventilation to confirm that ventilation is possible and to maximize oxygen reserve while awaiting induction and paralysis. Whether rapid-sequence induction with or without modification should be employed, particularly in an appropriately fasted, nonlabored patient presenting for elective cesarean delivery, has been questioned. Further, the value of cricoid pressure has been challenged owing to (1) physiologic evidence demonstrating that cricoid pressure reduces lower esophageal sphincter pressure, (2) anatomic investigations showing an inability to completely occlude the esophagus, (3) a lack of clinical outcome data that confirm that cricoid pressure reduces the incidence of aspiration, and (4) the frequent misapplication of the technique itself. The technique for cricoid pressure begins with an assistant applying 10 newtons (N) of force, 1 N being the unit of force required to accelerate a mass of 1 kg by 1 m/s² (force cannot be represented by mass alone, but as a practical guide to the amount of force to apply, 10 N is approximately equivalent to the downward force exerted by a weight of 1 kg). Following loss of consciousness, the amount of force is increased to 30 N. Application of the full amount of force while the patient is still awake can provoke active retching and regurgitation. In some cases, cricoid pressure may be briefly released to enable a successful intubation; not infrequently the benefit of release outweighs the risk for regurgitation. Cricoid pressure should then be reapplied until the correct endotracheal tube position is confirmed.

Historically, thiopental (4 to 6 mg/kg) has been the most frequently used induction agent. Because of recent lack of availability, it is now rarely used in the United States, although it is still used in other countries. Propofol (2 to 2.8 mg/kg) is now commonly used to induce general anesthesia for cesarean delivery. Propofol, in a dose sufficient for induction and to prevent maternal awareness (2.5 mg/kg), may depress the infant more than thiopental. In the presence of hemodynamic instability, ketamine (1 to 1.5 mg/kg) or etomidate (0.3 mg/kg) should be substituted for propofol. Paralysis is achieved by succinylcholine (1 to 1.5 mg/kg) in 30 to 40 seconds. Administration of a defasciculating dose of a nondepolarizing muscle relaxant is not recommended, because it may delay the onset of neuromuscular blockade with succinylcholine. Pregnancy appears to be associated with less severe succinylcholine-induced fasciculations and muscle pain.

Rocuronium (1 mg/kg) may provide intubating conditions similar to those provided with succinylcholine (1 mg/kg) for cesarean delivery and is a suitable alternative in situations in which succinylcholine should be avoided (e.g., malignant hyperthermia, myotonic dystrophy, spastic paraparesis). Some recent data suggest its use in cesarean delivery may be associated with a lower frequency of myalgia compared with succinylcholine. The use of a priming preinduction dose of a nondepolarizing muscle relaxant is not recommended during pregnancy, because it may result in complete paralysis and increase the risk for aspiration.

Enhanced activity of nondepolarizing agents may also be observed in patients receiving magnesium sulfate (e.g., for seizure prophylaxis in women with preeclampsia or for fetal neuroprotection).

Sugammadex, a modified gamma-cyclodextrin, has been demonstrated to be effective in providing rapid recovery (a train-of-four ratio of greater than 0.9) without recurarization from moderate and profound rocuronium-induced neuromuscular blockade in parturients undergoing cesarean delivery.

A small-diameter cuffed endotracheal tube (i.e., 6.5 or 7.0 mm) should be used during pregnancy; the use of a videolaryngoscopy device (e.g., C-MAC, Glidescope), a flexible stylet within the endotracheal tube, and a bougie on standby, allows a “first and best” attempt at tracheal intubation. Tissue trauma and airway edema may occur with repeated attempts at intubation. Correct endotracheal tube placement should be confirmed by checking for a normal
capnographic tracing. Auscultation should be performed to rule out inadvertent endobronchial intubation. The anesthesia provider should also observe ongoing evidence of adequate maternal oxyhemoglobin saturation as well as bilateral thoracic movement and breath sounds. If there is doubt, fiberoptic bronchoscopy can confirm the correct placement of the endotracheal tube in the trachea. If incorrect endotracheal tube placement is promptly recognized, extubation (with continued cricoid pressure) will often allow another attempt without the need for additional muscle relaxant. Anticipation of a difficult endotracheal intubation, or a failed intubation attempt, should invoke the difficult airway algorithm and a call for assistance (see Chapter 29). Options include (1) allowing the patient to awaken, (2) using alternative techniques to place an endotracheal tube, and (3) using alternative airway devices. Emergency airway equipment should be immediately available in all obstetric operating rooms.28

Some authors suggest that a supraglottic airway device (e.g., laryngeal mask airway [LMA]) can be used routinely for cesarean delivery performed under general anesthesia. One series reported clinically effective airway management with a classic LMA which was placed successfully on the first attempt in 98% of 1067 healthy parturients undergoing elective cesarean delivery with general anesthesia.287 Cricoid pressure was maintained throughout the cesarean delivery, and no adverse sequelae occurred. Utilizing an LMA with a higher seal pressure than a classic LMA and a built-in gastric draining tube, another study reported successful placement of the airway in 98% of 3000 healthy parturients undergoing elective cesarean delivery; they observed only one case of regurgitation without aspiration.286 Cricoid pressure was not maintained after confirmation of successful airway placement. In both of these studies, patients were excluded if they had symptoms of gastroesophageal reflux, known/predicted difficult airway, and a prepregnancy BMI greater than 30 kg/m2. As supraglottic airway devices do not prevent pulmonary soiling with gastric contents as efficiently as an endotracheal tube, and high morbidity rate is associated with aspiration, we do not routinely use these devices for cesarean delivery. However, any device that can facilitate ventilation should be used as a life-saving device in situations of failed intubation. A number of variations to the classic LMA have been developed that may facilitate airway management in specific situations (see Chapter 29).

**Maintenance**

The goals for anesthetic maintenance include (1) adequate maternal and fetal oxygenation, with maintenance of normocapnia for pregnancy; (2) appropriate depth of anesthesia to promote maternal comfort and a quiescent surgical field and to prevent awareness and recall; (3) minimal effects on uterine tone after delivery; and (4) minimal adverse effects on the neonate. These goals can be accomplished using inhalational anesthesia or, less commonly, total intravenous anesthesia.

Fetal oxygenation appears maximal when a maternal Fio2 of 1.0 is used225; however, in the absence of fetal compromise, an Fio2 of 0.3 appears to provide sufficient oxygenation while minimizing the production of oxygen free radicals (see earlier discussion). Although the use of a higher Fio2 can increase maternal arterial and umbilical venous blood oxygen content, this action has not been observed to result in differences in 1- or 5-minute Apgar or neurobehavioral scores.238,239 As a consequence, in the absence of fetal compromise, inspired oxygen concentrations should be guided by pulse oximetry rather than provision of an arbitrarily set level of Fio2.

Maternal ventilation should maintain normocapnia, which at term gestation is a PaCO2 of 30 to 32 mm Hg (4.0 to 4.3 kPa). Excessive ventilation can cause uteroplacental vasoconstriction and a leftward shift of the oxyhemoglobin dissociation curve, which may result in compromised fetal oxygenation.240 On the other hand, hypercapnia can lead to maternal tachycardia and is also undesirable. Initially, high fresh-gas flows should be used to ensure an adequate end-tidal concentration of the volatile halogenated agent. No specific volatile halogenated agent has been demonstrated to be superior to another. The anesthetic requirements for volatile halogenated agents are diminished 25% to 40% during pregnancy.241 A bispectral index measurement less than 60 typically requires more than 0.75 minimum alveolar concentration (MAC) of a volatile halogenated agent combined with 50% nitrous oxide and has been suggested to prevent intraoperative awareness and recall in parturients undergoing general anesthesia;242; however, this target bispectral index value requires further study in pregnant women. Several studies suggest the need for lower volatile agent requirements to maintain a target bispectral index value in women with prior labor compared with women without prior labor243,244; these results could not be explained by differences in plasma concentrations of progesterone, prolactin, or cortisol.244

In clinical practice, approximately 1.0 MAC of a volatile halogenated agent is typically administered between tracheal intubation and delivery. Halogenated agents cause dose-dependent depression of uterine contractility,242,245,246 which may lead to greater blood loss after delivery.247 Therefore, the concentration of the volatile agent is reduced to 0.5 to 0.75 MAC after delivery. Nitrous oxide 50% in oxygen is often added to reduce the required concentration of volatile agent, thereby mitigating adverse effects on uterine tone; intravenous propofol or ketamine can also be administered to maintain an appropriate depth of anesthesia. The administration of a benzodiazepine (e.g., midazolam) after delivery may reduce the risk for maternal awareness.

Intravenous opioids are often withheld until after delivery to minimize the potential for neonatal respiratory depression; however, there may be circumstances in which maternal hemodynamic stability or blunting of responses to airway manipulation and surgical stimulation favor the administration of opioids during the induction of general anesthesia. The rapid onset and efficacy of intravenous lipid-soluble agents (e.g., remifentanil, fentanyl, alfentanil) make them ideal for mitigating the responses to laryngoscopy and intubation.248 Intraoperatively, the prolonged activity of watersoluble agents (e.g., morphine, hydromorphone) can be
useful to minimize volatile anesthetic use and for the provi-
sion of intraoperative and postoperative analgesia (see
Chapter 27).

Given the pregnancy-induced stretching of the abdomi-
nal wall, additional neuromuscular blockade may not be nece-
sary in the parturient who has an adequate depth of anesthe-
sia (with administration of both a volatile agent and an
opioid). A small dose of a short-acting nondepolarizing agent
(or an infusion of succinylcholine) may be administered, with
maternal response monitored with a peripheral nerve stimu-
lator, if additional muscle relaxation is indicated.

General anesthetic agents can redistribute from the neo-
natal fat to the central circulation and lead to secondary depres-
sion of neonatal ventilatory effort; thus, the presence of a
pediatrician (or another neonatal provider) is advisable until
a normal ventilatory pattern is observed. Although differen-
tes in maternal and umbilical artery acid–base status have
been observed in women who underwent elective general
anesthesia compared with epidural anesthesia for cesarean
delivery, similar neonatal outcomes were demonstrated.

Similarly, epidemiologic data suggest that brief exposure to
general anesthetics at the time of cesarean delivery is not
associated with an increase for abnormal neonatal neuro-
development and later learning difficulties.

**Emergence and Tracheal Exubtation**

When the patient awakens, tracheal extubation should be
performed with the patient in a semi-recumbent position.
The patient should demonstrate purposeful response to
verbal commands and return of protective airway reflexes
before tracheal extubation. In a review of anesthesia-related
maternal deaths between 1985 and 2003 in the state of Michi-
gan, deaths associated with hypoventilation or airway
obstruction did not occur at induction and tracheal intuba-
tion but rather during emergence, extubation, or recovery
from anesthesia. Risk factors associated with mortality were
obesity and African-American race, which may have delayed
the visual recognition of cyanosis; medical management and
medication issues were also identified. The ASA Practice
Guidelines for Postanesthetic Care suggest that pulse oximetry
is associated with early detection of hypoxemia; the guidelines
recommend periodic assessment of airway patency, respira-
tory rate, and oxygen saturation during emergence and
recovery. If repeated airway manipulation, massive hemor-
 rhage, or emergency hysterectomy has occurred, delayed
extubation and/or transfer to an intensive care unit (ICU)
should be considered.

**Pharmacology**

**Thiopental.** Historically, the barbiturates (e.g., thiopental
[thiopentonel], methohexital, thiamylal) have been the induc-
tion agents most commonly used for cesarean delivery.
Extensive published data have confirmed the safety and effi-
cacy of thiopental for induction of anesthesia in patients
undergoing cesarean delivery at various gestational ages.
Thiopental 4 to 6 mg/kg provides a rapid and reliable induc-
tion of anesthesia. As a negative inotrope and vasodilator,
thiopental can cause decreased cardiac output and blood
pressure, which may result in significant hypotension in
hypovolemic patients. Some investigators have attempted to
minimize this effect by using a lower dose of thiopental in
combination with ketamine or propofol, with varying success.

Thiopental rapidly crosses the placenta. In 11 healthy
subjects who underwent induction of general anesthesia
with thiopental, the mean umbilical vein-to-maternal vein
(UV/MV) ratio was 1.08 with an induction-to-delivery (I-D)
time interval that ranged from 8 to 22 minutes. Similarly,
the fetal-to-maternal concentration ratios after a single thiopental dose exposure
in other studies in term infants exhibited a range of 0.43
to 0.96. The equilibration of thiopental occurs relatively
rapidly in the fetus; however, fetal brain concentrations rarely
exceed the threshold required for neonatal depression. With
a maternal induction dose of 4 mg/kg, umbilical vein con-
centrations of thiopental are well below the arterial plasma
concentrations necessary to produce anesthesia in adults.
However, with large induction doses (8 mg/kg), thiopental
can produce significant neonatal depression.

Several theories have been proposed to explain the clinical
occurrence of an unconscious mother but an awake neonate:
(1) preferential uptake of thiopental by the fetal liver, which
is the first organ perfused by blood coming from the umbil-
cal vein; (2) the higher relative water content of the fetal
brain; (3) rapid redistribution of the drug into the maternal
tissues, which causes a rapid reduction in the maternal-to-
fetal concentration gradient; (4) nonhomogeneity of blood
flow in the intervillous space; and (5) progressive dilution by
admixture with the various components of the fetal circula-
tion. Because of this rapid equilibration of thiopental and
the low fetal brain concentration of thiopental, there is no
advantage in delaying delivery until thiopental concentra-
tions decline. There is no evidence that thiopental causes
adverse fetal effects when the incision-to-delivery interval is
prolonged.

**Propofol.** Propofol is an intravenous induction agent with
a rapid onset, rapid recovery, and favorable side-effect profile,
which includes a low incidence of nausea and vomiting.
Induction with propofol can result in pain on injection and a
reduction in maternal blood pressure and cardiac output.
The pharmacokinetics of propofol are similar in pregnant
and nonpregnant women, except for a more rapid clearance
observed during pregnancy, which may partially reflect drug
removal through blood loss and the delivery of the infant and
placenta.

When given as an intravenous bolus, by continuous infu-
sion, or both, propofol rapidly crosses the placenta and results
in an UV/MV ratio of approximately 0.7. In an in vitro
human placenta study, propofol produced vasodilation of
fetal placental blood vessels and decreased the effect of various
vasoconstrictors, most likely through the inhibition of
calcium influx through the smooth muscle sarcolemma; lipid
emulsion, the propofol carrier solution, was not responsible
for these effects. One randomized trial of women undergoing
cesarean delivery with general anesthesia reported signifi-
cantly lower Apgar and neurobehavioral scores in neonates
delivered of mothers who received propofol compared with thiopental; however, this finding was not replicated in a more recent randomized trial. Other studies have found no effect of propofol on neurobehavioral scores or the time to sustained spontaneous respiration with an induction bolus dose of propofol 2.5 mg/kg or with infusion doses less than 6 mg/kg/h. However, higher doses of propofol (9 mg/kg/h) have been correlated with a low Neurologic and Adaptive Capacity Score (NACS).

Compared with thiopental, propofol results in a greater incidence of maternal hypotension, which may more effectively attenuate the response to laryngoscopy and tracheal intubation at the risk for reduced uteroplacental blood flow. Care must be given to closely monitor maternal blood pressure following induction with propofol and, if needed, supporting the blood pressure with vasopressors. Maternal heart rate needs to also be carefully monitored; one report noted a transient but severe episode of maternal bradycardia after administration of propofol followed by succinylcholine for rapid-sequence induction. This effect has also been demonstrated in pregnant ewes; one animal experienced severe bradycardia that led to a sinus arrest.

In a study of nonpregnant women, the interaction of propofol and ketamine was found to be additive at hypnotic and anesthetic endpoints; the cardiostimulant effects of ketamine appear to offset the cardiodepressant effects of propofol.

Ketamine. The sympathomimetic properties of ketamine make it an ideal induction agent in the setting of an urgent cesarean delivery in a patient with hypotension or an acute exacerbation of asthma. Ketamine is an analgesic, hypnotic, and amnestic agent associated with minimal respiratory depression; it is often used to supplement a neuraxial technique that may not be providing optimal anesthesia. Maternal awareness may still occur after an induction dose of ketamine 1 to 1.5 mg/kg, but the incidence is lower than with thiopental 4 mg/kg or a mixture of ketamine 0.5 mg/kg and thiopental 2 mg/kg. The incidence of maternal awareness can also be diminished with the co-administration of a benzodiazepine.

When used to maintain general anesthesia with 50% nitrous oxide in oxygen for cesarean delivery, a continuous infusion of ketamine (70 µg/kg/min) was followed by a higher incidence of factual recall and postoperative pain than seen with a volatile anesthetic technique, suggesting this approach is not preferred for the maintenance of anesthesia. Whether ketamine, given as a bolus or infusion initiated after infant delivery, can provide postcesarean analgesia and pain modulation remains controversial (see later discussion). One study found that patients who received ketamine 1 mg/kg for induction had lower postoperative morphine consumption than patients who received thiopental 4 mg/kg (anesthesia was maintained with nitrous oxide and isoflurane).

Etidomate. Etidomate is an intravenous induction agent that produces rapid onset of anesthesia with minimal effects on cardiorespiratory function. This property makes it ideal for parturients who are hemodynamically unstable or who would not tolerate hemodynamic aberrations (e.g., patients with severe cardiac disease). With an induction dose of 0.2 to 0.3 mg/kg, etidomate undergoes rapid hydrolysis, thereby allowing rapid recovery. Intravenous administration of etidomate may cause pain and involuntary muscle movements in unpremedicated patients; etidomate is also associated with nausea and vomiting, potential activation of seizures in patients with an epileptogenic foci, and an impaired glucocorticoid response to stress.

Etidomate crosses the placenta rapidly; however, large variations in the UV/MV ratio (0.04 to 0.5) have been reported. An induction dose of etidomate 0.3 mg/kg was associated with better neonatal acid-base measurements and overall clinical condition than with thiopental 3.5 mg/kg. A transient (less than 6 hours) reduction in neonatal cortisol production has been observed when an induction dose of
etomidate is used for cesarean delivery; however, the clinical relevance of this finding is unclear.

**Midazolam.** Midazolam is a short-acting, water-soluble benzodiazepine that has few adverse hemodynamic effects and provides hypnosis and amnesia. It is commonly used as a premedicant before anesthesia but also can be used as an induction agent for cesarean delivery, although there are few indications for this purpose (e.g., when there are relative or absolute contraindications to the use of other agents). Data suggest that compared with thiopental, midazolam (at a dose of 0.2 mg/kg) for induction of anesthesia results in a higher incidence of low Apgar scores and longer time to spontaneous respiration, as well as lower neurobehavioral scores, body temperature, general body tone, and arm recoil. However, these differences are short lived and do not persist beyond 4 hours after delivery.

**Muscle relaxants.** Muscle relaxants are commonly used before delivery to provide optimal tracheal intubation and operating conditions. Most muscle relaxants are highly ionized with low lipid solubility; thus, they do not undergo appreciable metabolism before delivery to provide optimal tracheal intubation and operating conditions. Most muscle relaxants are highly ionized with low lipid solubility; thus, they do not undergo significant placental transfer. The depolarizing agent succinylcholine (suxamethonium) at a dose of 1 to 1.5 mg/kg is the muscle relaxant of choice for most parturients undergoing rapid-sequence induction of general anesthesia. Maternal administration provides adequate intubating conditions within approximately 45 seconds of intravenous administration. Succinylcholine is highly ionized and water-soluble, and only small amounts cross the placenta. Although high doses of succinylcholine (2 to 3 mg/kg) can result in detectable levels in umbilical cord blood, very large doses (10 mg/kg) are required for placental transfer sufficient to cause neonatal muscle weakness.

Succinylcholine is rapidly metabolized by plasma pseudocholinesterase, the concentration of which is decreased during pregnancy; however, in most patients this effect is offset by the pregnancy-induced increase in volume of distribution. Thus, recovery from succinylcholine is not prolonged, unless the patient has extremely low levels of pseudocholinesterase or atypical pseudocholinesterase. The administration of metoclopramide may also prolong succinylcholine-induced neuromuscular blockade, perhaps by inhibiting plasma pseudocholinesterase; this effect is rarely (if ever) clinically significant. The return of neuromuscular function should be confirmed before additional doses of muscle relaxant are given.

**Rocuronium** is a suitable alternative to succinylcholine when a nondepolarizing agent is preferred for rapid-sequence induction (e.g., history of malignant hyperthermia), particularly with the option of rapid reversal using sugammadex (16 mg/kg). According to one study, rocuronium (0.6 mg/kg) can provide good to excellent intubating conditions in pregnant women after a mean interval of 79 seconds and maximal intubating conditions in 98 seconds. Another study demonstrated that rocuronium 1.2 mg/kg resulted in an onset of paralysis similar to that provided by succinylcholine (55 seconds), but it had a significantly longer clinical duration of action. Rocuronium does not appear to adversely affect Apgar scores, acid-base measurements, time to sustained respiration, or neurobehavioral scores.

Although the onset of action is slower than that of rocuronium, vecuronium 0.1 mg/kg is another alternative to succinylcholine. However, its onset of action is significantly slower than succinylcholine, even after a priming dose is administered. The mean duration of action of vecuronium is significantly longer in peripartum patients compared with nonpregnant controls. Vecuronium crosses the placenta in small amounts; however, neonatal outcome, as assessed by Apagar scores and NACS, does not appear to be adversely affected.

**Atracurium** is a less desirable agent for rapid-sequence induction because the high dose required for a rapid onset of action may result in significant histamine release, which may cause hypotension. Cisatracurium does not have these undesirable side effects, but its relatively slow onset makes it less optimal than other alternatives.

Regardless of the choice of agent, laryngoscopy and tracheal intubation should not be attempted until adequate muscle relaxation has occurred. The use of a nerve stimulator allows an objective assessment of the onset and duration of the neuromuscular blockade. Residual neuromuscular blockade can be reversed with neostigmine (with atropine or glycopyrrolate) or sugammadex. To diminish the risk for aspiration, the anesthesia provider should confirm that the patient responds appropriately to verbal commands before tracheal extubation.

**Nitrous oxide.** Nitrous oxide is an inhalational agent commonly used for cesarean delivery because of its minimal effects on maternal blood pressure and uterine tone. The use of nitrous oxide allows for a reduction in the concentration of the volatile halogenated agent (high concentrations of a volatile halogenated agent decrease uterine tone). Administration of 50% to 67% nitrous oxide in oxygen without another anesthetic agent does not provide complete anesthesia and can result in maternal awareness in 12% to 26% of cases. Nitrous oxide is transferred rapidly across the placenta, where fetal tissue uptake reduces the fetal arterial concentration for the first 20 minutes. In an evaluation of the relationship between duration of exposure to nitrous oxide 67% and the resulting umbilical vein-to-maternal artery nitrous oxide concentration ratios, the observed ratios differed according to duration of exposure, as follows: 2 to 9 minutes (0.37), 9 to 14 minutes (0.61), and 14 to 50 minutes (0.70). Apagar scores at 1 minute inversely correlated with duration of anesthesia, an effect observed in other studies. The use of a lower concentration (e.g., 50%) of nitrous oxide may reduce but not eliminate these neonatal effects. A randomized trial of parturients undergoing general anesthesia compared 100% oxygen with 50% nitrous oxide in oxygen, both supplemented by isoflurane (1.5 MAC for the first 5 minutes and 1.0 MAC thereafter). Neonates exposed to nitrous oxide required more resuscitation, although no significant differences were observed in Apagar scores.
**Volatile halogenated agents.** Volatile halogenated agents are the most commonly used agents for maintaining general anesthesia for cesarean delivery. Volatile halogenated agents produce central nervous system and cardiovascular effects in a dose-dependent manner; of particular concern for the obstetric patient are the resulting decreases in blood pressure (which may result in reduced uterine blood flow) and uterine tone. The uptake and delivery of a volatile halogenated agent is determined by inspired partial pressure, blood flow, and the blood/gas/tissue partition coefficient. The alveolar partial pressure of volatile agents during pregnancy follows known patterns of equilibration; the following commonly used agents are listed in order of more rapid to slower equilibration: desflurane, sevoflurane, and isoflurane. Volatile halogenated agents cross the placenta rapidly and equilibrate quickly with fetal tissues. Neonatal depression may occur. This is typically not a clinical issue when volatile anesthetic agents are used for emergency cesarean delivery, because the delivery usually occurs before much of the volatile agent crosses the placenta (particularly if uteroplacental insufficiency is the reason for emergency delivery). Volatile halogenated agents cause dose-dependent depression of uterine contractility. These effects may influence maternal blood loss after delivery.

Lower concentrations of volatile halogenated agents are required during pregnancy, with an approximately 30% reduction in MAC compared with nonpregnant women. These findings were correlated with an increase in progesterone level. Animal models demonstrate that long-term administration of progesterone is associated with a reduction in MAC. This reduction in MAC persists for 24 to 36 hours postpartum, with a gradual return to normal values by 72 hours.

**Opioids.** All opioids, particularly those with high lipid solubility (e.g., remifentanil, fentanyl, sufentanil), readily pass through the placenta to the fetus. Consequently, the administration of opioids is usually avoided until after delivery to reduce the risk for neonatal depression. However, the hemodynamic stability provided by opioids during airway manipulation and surgery may be valuable in select settings, particularly in the presence of maternal cardiac disease, neurologic conditions, and preeclampsia or hypertension.

The administration of remifentanil has been observed to mitigate the hemodynamic responses to tracheal intubation and surgery but can result in significant neonatal depression. Even with the administration of relatively low doses of remifentanil (0.5 µg/kg bolus followed by 0.15 µg/kg/min continuous infusion until peritoneal incision), Apgar scores and umbilical cord blood pH measurements were observed to be lower in the infants exposed to remifentanil than in the infants whose mothers received fentanyl 5 µg/kg after delivery; some neonates exposed to remifentanil required tracheal intubation.

The highly lipid-soluble agent fentanyl rapidly crosses the placenta. Fentanyl is 60% to 80% protein bound; thus, approximately one-third is available for transfer across the placenta. Despite its low lipid solubility, morphine has a UV/MV blood concentration ratio of 0.96 at 5 minutes; this rate of equilibration and the production of active metabolites are relevant considerations in the use and timing of intravenous morphine administration.

**Meperidine (pethidine)** is highly lipid soluble and is 50% to 70% protein bound; maternal administration results in a mean UV/MV blood concentration ratio of 0.75. The production of the active metabolite normeperidine, which can accumulate in both the mother and neonate and result in respiratory and neurobehavioral alterations, limits the use of meperidine as a principal analgesic agent during cesarean delivery; however, after delivery of the neonate, an intravenous dose of 12.5 to 25 mg is useful for treatment of shivering in the mother.

Maternal respiratory depression, as well as nausea and emesis during the intraoperative and postoperative periods, represent significant concerns in parturients given intravenous opioids.

**Local Anesthesia**

As a method used primarily for supplementation of neuraxial anesthesia, the infiltration of local anesthesia can also be used to facilitate an emergency cesarean delivery. This technique has been well described and is used predominantly in low-resource settings, where contemporary anesthesia techniques may not be readily available. Few contemporary obstetricians are familiar or proficient with this technique in developed countries.

The success of local infiltration depends on the obstetrician making a midline abdominal incision, avoiding use of retractors, and not exteriorizing the uterus. In settings in which an anesthesia provider might not be readily available, the obstetrician might begin surgery with the aid of local infiltration; after delivery of the infant, the achievement of temporary hemostasis, and the arrival of the anesthesia provider, surgery may be completed once general anesthesia has been induced.

Local infiltration is performed in sequential steps as the operation progresses (Box 26.8). The use of 0.5% lidocaine with epinephrine is recommended; the use of a more concentrated solution may result in local anesthetic systemic toxicity. A 25-gauge spinal needle is used to make the intracutaneous injection; the needle is inserted just below the umbilicus and is directed in the midline toward the symphysis pubis. Approximately 10 mL of local anesthetic is required to create a skin wheal that extends from the symphysis pubis to the umbilicus. The subcutaneous injection is also performed for the full length of the planned incision with 10 to 20 mL of local anesthetic. Ideally, the obstetrician should then wait for 3 to 4 minutes to allow the local anesthetic agent to exert its effect before making the skin incision.

A vertical skin incision is made between the umbilicus and the symphysis pubis and is extended down to the rectus fascia. The obstetrician then infiltrates local anesthetic into the rectus fascia and rectus muscles by making three to five laterally directed injections on each side. The needle should be passed between the rectus sheath and the transversus
muscle at an angle of 10 to 15 degrees and a depth of 3 to 5 cm; aspiration is performed, and 2 to 3 mL of local anesthetic is injected at each site with an additional 1 mL injected with needle withdrawal. The obstetrician should also make oblique injections at the upper and lower poles of the incision. The local anesthetic will spread freely in the rectus sheath, but it takes 4 to 5 minutes for anesthesia to be complete. The suprapubic area must also be generously infiltrated to ensure blockade of the branches of the iliohypogastric nerve. The disadvantage of the rectus sheath block is the large volume (40 to 50 mL) of local anesthetic required; a less effective alternative that requires less volume and time is to raise a longitudinal paramedian wheal in the rectus fascia on each side of the midline and to infiltrate the suprapubic region.

The obstetrician then extends the incision through the rectus sheath, and the peritoneum is grasped with forceps clamps. If the patient has pain, the parietal peritoneum may be infiltrated with 5 to 10 mL of local anesthetic and then incised. The visceral peritoneum overlying the area of the uterine incision is injected with 10 mL of local anesthetic and is then incised and reflected appropriately. Paracervical infiltration with 5 to 10 mL of local anesthetic may block pain impulses from the uterus and cervix. A uterine incision is made, and the infant is delivered. The surgeon must avoid forceful retraction and blunt dissection of tissue planes, and uterine manipulation should be kept to a minimum. A support person at the head of the table who can provide coaching and reassurance to the mother is invaluable.

The major disadvantages of local infiltration anesthesia are patient discomfort and the potential for local anesthetic systemic toxicity, given that as much as 100 mL of local anesthetic solution is required. The risk for local anesthetic systemic toxicity may be especially problematic in the absence of a skilled anesthesia provider to assist with maternal resuscitation. Another disadvantage is the amount of time required for maximal anesthesia to develop; maternal discomfort often accompanies an urgent delivery performed with this form of anesthesia. Finally, local infiltration does not provide satisfactory operating conditions in the event of a surgical complication (e.g., uterine laceration, broad ligament hematoma).

Cesarean delivery with use of local infiltration, if successful, has the advantages of preserving maternal cardiovascular stability and a patent airway while allowing the initiation of surgery in emergency cases. However, the technique is frequently associated with incomplete maternal anesthesia, which subsequently presents significant management issues, because the surgical procedure has commenced, positioning options are limited, and the consequences of the operative procedure (e.g., hemorrhage) may require immediate attention.

Additional peripheral nerve blockade techniques (e.g., transversus abdominis plane blockade) may successfully augment local anesthesia infiltration; however, the degree to which the maternal experience is enhanced and the timing required to place these blocks deserve further investigation.

### RECOVERY FROM ANESTHESIA

Cesarean delivery is a major abdominal surgical procedure with significant anatomic, physiologic, and hormonal sequelae, even when it is performed electively without complications in a healthy parturient. The risk for adverse outcomes is greater in the presence of significant maternal comorbidity or in the setting of surgical complications (e.g., massive blood loss, cesarean hysterectomy).

A study at a single, tertiary care center found that the majority of patients who received neuraxial anesthesia for cesarean delivery could meet revised discharge criteria (i.e., presence of a normal level of consciousness, stable vital signs, adequate analgesia, and ability to flex the knees) within 60 minutes, which could shorten the average duration of PACU stay and result in cost savings. However, 26% to 36% of patients remained in the PACU for up to 180 minutes because of pain, sedation, nausea and vomiting, pruritus, prolonged neuroblockade, and/or drug treatment. In addition, 16% to 22% remained in the PACU for up to 210 minutes for cardiovascular (e.g., bleeding, hypertension, hypotension, tachycardia) or respiratory events. Moreover, the study did not include the most seriously ill or highest-risk patients, who were transferred directly to an ICU.

The 2001 National Sentinel Caesarean Section Audit in the United Kingdom reported that 10% of women undergoing cesarean delivery required admission to a high-dependency unit. Moreover, 3.5% of these women required subsequent transfer to an ICU. Preexisting comorbid conditions accounted for the majority (80%) of these ICU admissions; a smaller fraction were caused by the medical emergency (e.g., uterine rupture, placental abruption) that prompted the cesarean delivery. Although ICU admission is uncommon in obstetric patients, it occurs more frequently (approximately 9 per 1000 patients) after cesarean delivery; the risk for ICU admission following cesarean delivery is greater in patients with high BMI.
Of concern, inadequate postoperative care has been cited as a recurring factor in maternal deaths (see Chapter 39). The ASA Practice Guidelines for Obstetric Anesthesia state that “appropriate equipment and personnel should be available to care for obstetric patients recovering from neuraxial or general anesthesia.” Similarly, the National Obstetric Anesthetic Service Guidelines from the United Kingdom state that postoperative care of the patient undergoing cesarean delivery should meet the same standard of care as required for any postoperative patient. 

There is increasing interest in enhanced recovery after surgery (ERAS) protocols for women who have undergone cesarean delivery. Further study is required to identify the components of the protocols that actually enhance recovery. Common components in current protocols include excellent analgesia combined with early ambulation, oral intake, and removal of urinary catheters.

**Oral Intake**

A systematic review of six randomized clinical trials comparing early with delayed oral intake of fluid and food after cesarean delivery found that the early oral consumption (within 4 to 8 hours) was associated with a shorter time to return of bowel sounds and a shorter hospital stay. No differences were reported in nausea and vomiting, abdominal distention, time to bowel activity, paralytic ileus, or need for analgesia. Guidelines from the National Institute for Health and Clinical Excellence (NICE) state that “women who are recovering well and who do not have complications … can eat and drink when they feel hungry or thirsty.”

**Removal of Urinary Catheter**

There are no differences in the incidence of urinary retention after general anesthesia and epidural anesthesia following cesarean delivery. Risk factors for postpartum urinary retention after cesarean delivery include the use of postoperative opioid analgesia (particularly when given via an epidural catheter), multiple gestation, and a low BMI. Most urinary catheters are removed either immediately after cesarean delivery or within 24 hours; there are no differences between these two options in regard to postoperative urinary retention, dysuria, urgency, fever, positive microscopy, or length of hospital stay; immediate removal does appear to decrease the risk for urinary infection and lead to earlier ambulation. In obstetric patients, the return of bladder sensation of fullness after neuraxial techniques appears to be a function of time, rather than urinary volume. The return of bladder sensation after spinal anesthesia for cesarean delivery (with hyperbaric bupivacaine and fentanyl) takes longer (mean of 374 minutes [IQR 172 to 692]) than return of sensation after patient-controlled epidural analgesia for vaginal delivery (mean of 234 minutes [IQR 95 to 382]).

**Postoperative Assessment and Discharge**

The anesthesia provider should assess for recovery of motor and sensory function if a neuraxial technique was administered. Women should be reassured that breast-feeding is safe, even after general anesthesia, and that postoperative analgesics have a favorable safety profile. Early mobility and ambulation should be encouraged.

**ANESTHETIC COMPLICATIONS**

**Awareness and Recall**

Cesarean delivery is a high-risk procedure for the occurrence of intraoperative awareness, defined as the spontaneous postoperative recall of an event that occurred during general anesthesia. The following factors contribute to the risk for maternal awareness during cesarean delivery: (1) the avoidance of sedative premedication, (2) the deliberate use of a low concentration of a volatile halogenated agent, (3) the use of muscle relaxants, (4) the reduction in dose of anesthetic agents during hypotension or hemorrhage, (5) the presence of partial neuraxial blockade in parturients requiring conversion to general anesthesia after failed neuraxial anesthesia, and (6) the (mistaken) assumption that high baseline sympathetic tone is responsible for intraoperative tachycardia in parturients.

Concern for neonatal depression and uterine atony associated with volatile halogenated agents has led to administration of relatively low doses of these agents. Administration of a barbiturate induction agent followed by nitrous oxide 50% in oxygen resulted in maternal awareness in 12% to 26% of cases. Using an isolated forearm technique, King et al. assessed 30 women undergoing cesarean delivery with thiopental 250 mg, succinylcholine infusion, and 0.5% halothane in 50% nitrous oxide; the majority of patients signaled pain in the first minute. The incidence of recall with this anesthetic regimen was approximately 1%. The use of higher concentrations of a volatile halogenated agent has subsequently become a more common practice, leading to an incidence of maternal awareness of approximately 0.26%. However, the result of increasing the depth of maternal anesthesia is that neonates born to women who receive general anesthesia tend to have lower Apgar and neurobehavioral scores, particularly when the incision-to-delivery interval exceeds 8 minutes.

The optimal doses and concentrations of anesthetic agents to prevent awareness remain unclear, in part because of the difficulty in assessing awareness. Studies have evaluated several tools for assessment of depth of maternal anesthesia, including the electroencephalogram, brainstem auditory evoked potentials, and the bispectral index. The bispectral index is an empirically derived electroencephalographic parameter in which values less than 60 are suggested to predict a low probability of intraoperative recall and awareness. With each of these monitoring devices, the threshold for awareness will need further validation, particularly during pregnancy; some data suggest that these types of monitors are not reliable for monitoring anesthesia depth in the setting of cesarean delivery. Moreover, many of these devices are not suitable for use for the emergency conditions under which most general anesthetics for cesarean delivery are administered.
Although pregnancy diminishes anesthetic requirements by 25% to 40%, administration of 0.5 MAC of a volatile halogenated agent may not reliably provide adequate depth of anesthesia to prevent maternal awareness. Some commentators recommend larger doses of induction agents than are administered to nonpregnant patients (e.g., thiopental 5 to 7 mg/kg instead of 3 to 4 mg/kg), an end-tidal volatile anesthetic concentration greater than 0.8 MAC, the highest concentration of nitrous oxide compatible with appropriate oxygenation, and the administration of an opioid and a benzodiazepine after delivery. Intravenous induction or infusion techniques that may reduce the risk for maternal awareness include the administration of repeat doses of induction agents, the use of ketamine, or a combination of these. Midazolam 0.075 mg/kg provides 30 to 60 minutes of anterograde amnesia when given to women undergoing elective cesarean delivery under epidural anesthesia. Propofol exhibits an amnestic effect that is not dependent on the degree of sedation; however, the effect is significantly less than that with midazolam.

The psychological morbidity associated with awareness should not be underestimated. Further investigations into the anesthetic regimens and monitoring necessary to prevent awareness and recall in pregnant women undergoing operative procedures are needed. These studies should incorporate the growing data on gender- and pregnancy-related differences in pharmacokinetics and pharmacodynamics of drugs used for anesthesia.

Paradoxically, the issue of recall is not limited to the administration of general anesthesia. In women undergoing cesarean delivery with a neuraxial technique who desire treatment for anxiety, the administration of anxiolytic or hypnotic agents may result in a lack of recall of delivery, which is typically undesirable.

**Dyspnea**

After the initiation of neuraxial anesthesia, the patient may complain of dyspnea. The most common cause of this complaint is hypotension (causing hypoperfusion of the brainstem); therefore, the complaint of difficulty in breathing should prompt immediate assessment of blood pressure and treatment, if appropriate. Other causes of dyspnea are blunting of thoracic proprioception, partial blockade of abdominal and intercostal muscles, and the recumbent position, which increases the pressure of the abdominal contents against the diaphragm. The sensation of dyspnea appears related to the cephalad extent of the sensory blockade and may be mitigated by using a low-dose hyperbaric spinal bupivacaine technique in women undergoing cesarean delivery.

Despite these changes, significant respiratory compromise is unlikely, primarily because the neuraxial blockade rarely affects the cervical nerves that control the diaphragm. A study examining the pulmonary effects of various spinal regimens including bupivacaine 10 mg, ropivacaine 20 mg, and levobupivacaine 10 mg, all with fentanyl 15 µg, in women undergoing cesarean delivery reported small reductions in the functional vital capacity (3 to 6%) and peak expiratory flow rate (6 to 13%). However, the findings had no apparent clinical significance, were similar for all local anesthetics, and did not differ for sensory blockade that extended higher, versus no higher, than the T4 dermatome.

If the patient loses the ability to vocalize, demonstrate a strong hand grip, and/or maintain normal oxyhemoglobin saturation (e.g., symptoms suggestive of high spinal anesthesia), a rapid-sequence induction of anesthesia with cricoid pressure and placement of an endotracheal tube should be performed to maintain ventilation and prevent aspiration of gastric contents.

**Hypotension**

Hypotension is a common sequela of neuraxial anesthesia and, if severe and sustained, may lead to impairment of uteroplacental perfusion and result in fetal hypoxia, acidosis, and neonatal depression or injury. Severe maternal hypotension can also have adverse maternal outcomes, including altered consciousness, pulmonary aspiration, apnea, and cardiac arrest.

Although not universally accepted, most investigators accept the following definitions for maternal hypotension: (1) a decrease in systolic blood pressure of more than 20% to 30% from baseline measurements or (2) a systolic blood pressure lower than 100 mm Hg. Neuraxial anesthetic techniques produce hypotension through blockade of sympathetic nerve fibers, which control vascular smooth muscle tone. Several studies using noninvasive measures of cardiac output have demonstrated that cardiac output commonly increases after spinal anesthesia, even in the presence of a phenylephrine infusion and fluid administration. These studies emphasize that spinal anesthesia–induced hypotension is principally related to a marked decrease in systemic vascular resistance, rather than decreased cardiac output. The rate and extent of the sympathetic involvement, and subsequently the severity of hypotension, are determined by the onset and extent of the neuraxial blockade; hypotension may be less common with epidural anesthesia than with spinal anesthesia because of the slower onset of neuroblockade and the earlier recognition and treatment.

**Risk Factors for Hypotension**

A number of studies have attempted to identify pregnant women at increased risk for development of hypotension. Of interest, women with severe preeclampsia or in established labor appear less likely to experience hypotension during administration of spinal anesthesia for cesarean delivery (see Chapter 35).

Studies using a modified orthostatic challenge (i.e., “tilt test”) have been unable to establish a correlation in the observed change in orthostatic blood pressure or heart rate with hypotension after spinal anesthesia. However, the investigators have found that patients with a baseline heart rate higher than 90 bpm had a 83% chance (positive predictive value) of experiencing marked hypotension (decrease in blood pressure greater than 30%), whereas patients with a baseline heart rate lower than 90 bpm had a 75% chance.
(negative predictive value) of not experiencing marked hypotension.\textsuperscript{348}

One study found that the response of pregnant women to a preoperative supine stress test (i.e., placing the patient in the supine position to potentially cause aortocaval compression) predicts the occurrence of symptomatic hypotension, the need for ephedrine, and a decrease in systolic blood pressure below 80 mm Hg during administration of spinal anesthesia for cesarean delivery.\textsuperscript{349} The supine stress test was considered positive if it was associated with (1) an increase in maternal heart rate greater than 10 bpm, (2) a decrease in systolic blood pressure of more than 15 mm Hg, or (3) signs and symptoms related to the supine position (e.g., nausea, dizziness). These investigators found that the preoperative stress test had a sensitivity of 69% and a specificity of 92% in identifying women who would have symptomatic hypotension.

Investigators have used other methods, including assessment of heart rate variability\textsuperscript{350,351} and noninvasive measurements of systemic vascular resistance (e.g., thoracic impedance\textsuperscript{352}) in an attempt to identify parturients at risk for neuraxial anesthesia–induced hypotension for cesarean delivery. To date, predicting which parturients will have hypotension after neuraxial anesthesia for cesarean delivery has not proven clinically feasible and will likely require more sophisticated studies that employ a number of different methodologies. Such prediction is likely to be challenging given the myriad of factors that control the autonomic, physiologic, and hormonal changes and hemodynamic responses that occur during pregnancy.

**Prevention of Hypotension**

A number of strategies can mitigate hypotension after spinal anesthesia for cesarean delivery, including fluid administration, vasopressor administration, lower local anesthetic doses, leg elevation or wrapping, and left uterine displacement.

The use of intravenous fluid to prevent hypotension can be manipulated by (1) timing of administration, either before (preload) or coincident with (co-load) the intrathecal injection; and/or (2) type of fluid, either crystalloid or colloid. Rate of fluid administration may also play a role. Crystalloid preload is minimally effective, even when volumes as great as 30 mL/kg are infused.\textsuperscript{62} By contrast, colloid preload consistently reduces the incidence and severity of hypotension. A randomized trial of 36 healthy women undergoing elective cesarean delivery compared the administration of 1500 mL of lactated Ringer’s solution and 500 mL and 1000 mL of hydroxyethyl starch solution (HES) 6% before spinal anesthesia for cesarean delivery.\textsuperscript{353} The frequency of hypotension (systolic blood pressure less than 100 mm Hg and less than 80% of baseline) was 75%, 58%, and 17%, respectively. Significant increases in intravascular volume and cardiac output, as measured by indocyanine green spectrophotometry, were observed in the HES groups (Fig. 26.5). At 30 minutes, 100% of the HES volume, versus 28% of the lactated Ringer’s volume, remained within the intravascular space.

Whether crystalloid fluid is given as a preload or co-load does not appear to affect the frequency of hypotension. A meta-analysis of randomized trials comparing crystalloid preload to co-load did not find a difference in the incidence of hypotension.\textsuperscript{64} Similarly, no difference in the incidence of hypotension is observed with a colloid preload versus co-load, likely reflecting the intravascular dwell time of colloid.\textsuperscript{64}

Both preload and co-load administration of colloid are more effective than co-load administration of crystalloid in mitigating hypotension.\textsuperscript{341} However, the cost and associated pruritus, mild coagulation abnormalities, and potential for an allergic reaction to colloid starch solutions, particularly with first-generation agents, have tempered their widespread use. Possible fetal and neonatal effects related to the type and timing of maternal fluid administration deserve further investigation; for example, the rapid administration of 1500 to 2000 mL of fluid can release atrial natriuretic peptide, which may result in vasodilation and reduced sensitivity to vasoconstrictors.\textsuperscript{354}

Our current practice is to administer rapid crystalloid co-load (approximately 15 mL/kg) to healthy parturients undergoing elective cesarean delivery with spinal anesthesia. Parturients at high risk for hypotension (e.g., history of supine hypotension syndrome) or at high risk for the adverse consequences of hypotension (e.g., hypertrophic cardiomyopathy) receive colloid preload (500 mL).

**Vasopressor agents**, including ephedrine and phenylephrine, can be titrated to maintain maternal blood pressure and have been observed to be more effective than crystalloid solution or placebo in preventing spinal anesthesia–induced hypotension. In a meta-analysis, Lee et al.\textsuperscript{355} concluded that ephedrine was superior to placebo in the prevention of spinal anesthesia–induced hypotension for women undergoing cesarean delivery. Although greater doses of ephedrine provided more effective prophylaxis, hypotension was still observed and reactive hypertension and umbilical artery metabolic acidosis were more common with higher doses.
Traditionally, ephedrine was used to prevent and treat the hypotension associated with neuraxial anesthesia because of fear that pure alpha-adrenergic agonists would decrease uterine blood flow. However, phenylephrine is greater or equally efficacious to ephedrine for the prevention and treatment of hypotension, and it is less likely to depress umbilical arterial blood pH and base excess. Phenylephrine crosses the placenta less than ephedrine, presumably, ephedrine contributes to stimulation of fetal metabolism, resulting in lower pH and base excess than phenylephrine.

There is some controversy as to whether vaspressors should be administered as a continuous infusion or bolus, particularly for the prevention of hypotension. When administered as an infusion, phenylephrine infusion rates of 25 to 100 µg/min are usually used to prevent hypotension. However, the number of interventions to maintain systolic blood pressure within 20% of baseline are lower for phenylephrine infusions of 25 and 50 µg/min than for infusions of 75 and 100 µg/min because of the number of interventions required to treat hypertension with the higher doses. Using an up-down sequential allocation study design, the effective phenylephrine bolus dose for preventing hypotension in 95% of patients (ED95) was estimated at 159 µg (95% CI, 122 to 371 µg). Reflex decreases in heart rate and reductions in cardiac output may occur with phenylephrine; however, this does not appear to affect umbilical cord blood gas values or Apgar scores in uncompromised infants delivered electively.

One study demonstrated a salutary effect of a prophylactic infusion of ephedrine combined with phenylephrine compared with infusion of ephedrine alone. However, another study comparing infusions of different ephedrine-to-phenylephrine ratios found that as the proportion of ephedrine increased, the incidence of hypotension and nausea/vomiting also increased, whereas umbilical cord blood pH and base excess decreased.

The titration of vasopressor infusions may require frequent infusion rate adjustments, and this mode of administration may be considered by some to be more cumbersome than bolus administration of the same agents. Thus, some clinicians prefer to administer a bolus dose of vasopressor to prevent or treat hypotension. Various ratios of ephedrine combined with phenylephrine, administered as a bolus, have been tested, but investigators have been unable to identify a combination that reliably prevented hypotension yet avoided hypertension. Methods under investigation include a closed-loop feedback computer-controlled infusion of phenylephrine for maintaining blood pressure during spinal anesthesia.

The combination of fluid and vasopressor administration may be the most effective regimen to prevent hypotension. In a study by Ngan Kee et al., the incidence of spinal anesthesia–associated hypotension was almost zero (1.9%) in the group randomized to receive a rapid crystalloid co-load combined with a prophylactic phenylephrine infusion (beginning at 100 µg/min); the incidence of hypotension was 28% in the women who received phenylephrine without the co-load. No difference in neonatal outcome was observed between groups.

The initial studies comparing ephedrine to phenylephrine enrolled healthy women undergoing elective cesarean delivery. In a randomized trial comparing ephedrine to phenylephrine in women with preeclampsia undergoing cesarean delivery with spinal anesthesia, there was no difference in umbilical artery pH between prophylactic phenylephrine and ephedrine infusions.

Several studies have investigated prophylactic norepinephrine for the prevention of spinal anesthesia–induced hypotension. In a randomized controlled trial of computer-controlled infusions of norepinephrine compared with phenylephrine in women with spinal anesthesia undergoing cesarean delivery, women who received norepinephrine had higher cardiac output (primary outcome) and a lower incidence of bradycardia, with similar neonatal outcomes. The median (IQR) norepinephrine infusion rate was 2.35 µg/min (1.95 to 2.90). Further study of the safety of norepinephrine for this purpose is indicated.

The use of lower doses of spinal local anesthetic is associated with a lower incidence of hypotension, particularly when high and low doses are compared (e.g., hyperbaric bupivacaine 6.5 mg versus 9.5 mg, or 3.75 mg versus 9 mg; and plain bupivacaine 5 mg versus 10 mg combined with fentanyl 25 µg). However, the desire to use a low dose of spinal local anesthetic (e.g., bupivacaine less than or equal to 8 mg) should be tempered by the potential for an increased requirement for intraoperative supplemental analgesia or conversion to general anesthesia. The optimal local anesthetic dose is likely influenced by a number of factors, including technical factors (e.g., precision of dose, spinal level of injection, concomitant opioid use, positioning of patient during and after the block), and other factors (e.g., genetic sensitivity, patient expectations, differences in operative technique); these factors are often not controlled in studies of local anesthetic dose. Anesthesia providers who administer an intermediate or low dose of local anesthetic should consider the use of a catheter-based technique (continuous spinal or CSE anesthesia), given the frequent need (up to 40%) for supplemental administration of additional local anesthetic through the catheter.

Physical methods to prevent hypotension include the use of lower limb compression bandages or pneumatic compression devices, which have demonstrated some success and may assist in preventing thromboembolic complications.

**Treatment of Hypotension**

The ideal treatment of hypotension would be reliable, titratable, easy to use, and devoid of maternal and fetal side effects. Almost 45 years ago, ephedrine, a mixed alpha- and beta-adrenergic receptor agonist, emerged as the leading choice for the treatment of hypotension on the basis of studies demonstrating its efficacy and apparent superiority (over other agents) in protecting and/or restoring uterine blood flow in gravid ewes and other pregnant animal models. By contrast, other agents, including metaraminol and phenylephrine, while restoring maternal blood pressure, were associated with a decrease in uterine artery blood flow and fetal pH.
Contemporary animal studies have provided a mechanistic understanding of these effects. During pregnancy, vasopressors appear to constrict the femoral artery more than the uterine artery, which increases blood pressure and protects uterine blood flow. This differential pressor effect is greater for ephedrine than for metaraminol. A second mechanism appears to be the up-regulation of nitric oxide synthase (NOS) in the uterine artery during pregnancy. The presence of NOS potentially makes this artery less sensitive to vasopressors; this effect may be further augmented by ephedrine, a drug observed to independently cause the release of NOS.

In a quantitative systematic review, Lee et al. noted that the use of ephedrine for treatment of maternal hypotension during administration of spinal anesthesia for cesarean delivery was associated with lower umbilical cord blood pH measurements than the use of phenylephrine. This surprising clinical result (which differs from results in animal studies) may reflect interspecies differences in vascular smooth muscle physiology, control of blood flow, and drug metabolism. This finding may also reflect the fetal effects of ephedrine administered to the mother. Cooper et al. subtracted the umbilical vein PCO2 from the umbilical artery PCO2 to calculate an index that reflected fetal CO2 generation; the index was higher, reflecting a higher metabolic production of CO2, in newborns whose mothers received ephedrine. Ngan Kee et al. observed that the greater depression of fetal pH and base excess with ephedrine compared with phenylephrine appears related to its ability to cross the placenta to a greater extent, undergo less early metabolism or redistribution in the fetus, and consequently produce greater fetal concentrations of lactate, glucose, and catecholamines.

A randomized trial compared phenylephrine and ephedrine for the treatment of hypotension in women with preeclampsia undergoing cesarean delivery with spinal anesthesia. There were no differences between groups in umbilical artery and vein base excess values or Apgar scores. The NICE guidelines state that phenylephrine and ephedrine are equally effective as vasopressors. Given the efficacy of phenylephrine in the treatment of hypotension and the better umbilical cord blood acid-base measurements associated with its use in healthy patients, and its lack of harm in women with preeclampsia, many anesthesia providers now use phenylephrine as a first-line agent for the prevention and treatment of maternal hypotension. Regardless of the vasopressor agent selected to treat hypotension, therapy should be administered as soon as the blood pressure begins to decrease, rather than after the occurrence of clinically significant hypotension. In addition, vasopressor administration strategies can optimize maternal, and potentially fetal, hemodynamics and well-being by maintaining blood pressure near baseline, instead of lower target goals such as 80% or 90% of baseline measurements. Ephedrine is usually administered intravenously in bolus doses of 5 to 10 mg. Phenylephrine may be administered intravenously in bolus doses of 50 to 100 µg or by continuous infusion beginning at 25 to 50 µg/min, with titration to maintain maternal arterial blood pressure at or near baseline and avoidance of maternal bradycardia. Administration of ephedrine may lead to tachycardia, as well as tachyphylaxis. By contrast, phenylephrine may result in reflex maternal bradycardia, which, if treated with an anticholinergic agent in the absence of hypotension, may result in significant hypertension.

Failure of Neuraxial Blockade

“Failed” neuraxial anesthesia can be defined as neuroblockade insufficient in extent, density, or duration to provide anesthesia for cesarean delivery. Four to 13 percent of epidural anesthetics and 0.5% to 4% of spinal anesthetics fail to provide sufficient anesthesia for the initiation or completion of cesarean delivery. Epidural techniques are more often associated with failure, given that the catheter is often placed during early labor, and over time the catheter may migrate out of the epidural space. Factors that correlate with failed extension of labor epidural anesthesia for cesarean delivery include a higher number of bolus doses for the provision of labor analgesia (i.e., treatment of breakthrough pain), patient characteristics (e.g., obesity, distance from the skin to the epidural space), and the time elapsed between placement of the epidural catheter and cesarean delivery.

The causes of failure of neuraxial techniques include anatomic, technical, and obstetric factors. Steps to reduce the likelihood of epidural block failure include meticulous attention to technical detail, the administration of a solution that contains both a local anesthetic and an opioid, and a better understanding of the characteristics of epidural versus spinal blockade. Moreover, the patient should be prepared to expect the sensation of deep pressure and movement yet be reassured that reports of discomfort or pain will be addressed promptly. Initiation of surgery should be delayed until adequate thoracic and sacral sensory blockade have been achieved; on rare occasions, in the setting of an urgent procedure for which a developing epidural block is present at T10 but has yet to achieve a T4 level, surgery can commence with the understanding that adjuvant treatments or alternative forms of anesthesia may be required.

Evaluation of intraoperative pain requires (1) determination of the location and extent of discomfort, (2) evaluation of the sensory level of anesthesia, (3) assessment of the current status of the surgery (e.g., incision, delivery, uterine repair, skin closure), and (4) assessment of the presence of confounding factors (e.g., hemorrhage, anxiety). Shoulder pain can originate from irritation of the diaphragm (usually by amniotic fluid or blood) and is mediated by the phrenic nerve (C3 to C5); prolonged abduction and extension of the arms can also cause discomfort. Additional discomfort can occur from visceral stimulation such as uterine manipulation, which often involves the greater splanchnic nerve (T5 to T10). Alternatively, the extent of the block may be adequate but the density of neuroblockade of the large nerve fibers in the lumbosacral plexus may be inadequate. Inadequate anesthesia can result from regression of the block from a cephalad or caudad direction. Management of breakthrough pain should begin with acknowledgement of the patient’s discomfort and
consideration of the fetal (e.g., presence of nonreassuring fetal status), surgical (e.g., ongoing or anticipation of prolonged surgery), and anesthetic (e.g., maternal airway examination, BMI) implications, as well as the anesthesia provider’s experience. Emergent or ongoing surgery may require administration of general anesthesia. If no block exists, the surgery has not begun, and time allows, neuraxial anesthesia can be repeated; whether an epidural or spinal technique is attempted depends on the previously mentioned factors. If an inadequate, partial block exists in an elective situation, either the surgery can be postponed (to allow resolution of the partial block) or a second neuraxial technique may be performed with caution.

The disadvantages of replacing a failed neuraxial block with epidural anesthesia include (1) the potential for local anesthetic systemic toxicity (particularly after epidural administration of a large dose of local anesthetic for the initial attempt), (2) the time required to establish an adequate block, and (3) the unpredictable reliability and quality of the resulting block. As a consequence, many practitioners intent on replacing a failed epidural technique suggest the cautious use of a technique with an intrathecal component (i.e., spinal, CSE, or continuous spinal technique). The performance of a spinal technique in the setting of a partial but failed epidural or spinal anesthetic technique is controversial. In this setting, intrathecal administration of a standard intrathecal dose of bupivacaine may result in a high spinal block. Radiographic evidence suggests that the dural sac is compressed by prior epidural drug administration. Thus, when performing a spinal anesthetic technique after failed epidural or spinal anesthesia, the anesthesia provider should consider (1) using a different interspace to avoid possible anatomic distortions (e.g., from the loss of resistance to saline or previous needle passes) or abnormalities; (2) reducing the dose of bupivacaine (with the chosen dose depending on the extent of existing neuroblockade); (3) placing the patient in a semi-sitting (Fowler’s) position to limit cephalad spread of the local anesthetic; (4) using a CSE technique with a small intrathecal dose of local anesthetic, and, if necessary, titrating the sensory level with additional drugs administered through the epidural catheter; and/or (5) intentionally placing a catheter into the intrathecal space for administration of continuous spinal anesthesia. This last strategy may be especially useful in obese patients in whom the technical difficulty of the neuraxial approach may otherwise limit success.

If discomfort is reported after the start of surgery, it is often helpful to ask the surgeons to halt the operation while an assessment is made. If an epidural catheter is in place, an alkanalized local anesthetic with an opioid (e.g., 3% 2-chloroprocaine with fentanyl) should be administered. The density of epidural anesthesia may be improved by “repainting the fence.” An additional dose of local anesthetic (20% to 30% of the initial dose [e.g., 4 to 7 mL]) is administered approximately 20 minutes after the initial dose. This second dose serves to improve the density of neuroblockade without extending the sensory level. Some anesthesia providers routinely administer this supplemental dose, without waiting for a patient’s complaint of breakthrough pain.

Intravenous administration of an opioid (e.g., fentanyl), inhalation of nitrous oxide (40% to 50% in oxygen), or intravenous anxiolysis (midazolam) may be helpful for the treatment of breakthrough pain. Severe pain may require intravenous ketamine in 5- to 10-mg increments. However, care should be taken, because the administration of multiple agents can result in significant sedation, loss of consciousness, and the presence of psychomimetic and amnestic effects. The obstetrician can infiltrate the wound or instill the peritoneal cavity with local anesthetic. In some instances, the induction of general anesthesia with tracheal intubation is necessary.

If the anesthesia provider anticipates that the duration of the surgical procedure will be longer than the predicted duration of epidural or CSE anesthesia, additional local anesthetic (with or without an opioid) should be administered before anticipated regression of neuroblockade (see Table 26.7). The usual dose to maintain neuroblockade is one-third to one-half of the initial dose.

High Neuraxial Blockade

It is not uncommon for the parturient to report mild dyspnea or reduced ability to cough, especially if the neuraxial blockade has achieved a T2 sensory level. If impaired phonation, unconsciousness, respiratory depression, or significant impairment of ventilation occurs, general anesthesia should be induced. High neuraxial blockade may also result in cardiovascular sequelae, including bradycardia and hypotension. An easy method to diagnose clinically significant high neuraxial blockade is to ask the patient to make a fist (“squeeze your fingers”). A weak hand grasp indicates high thoracic and cervical motor blockade.

High neuraxial block can be caused by several mechanisms, including an exaggerated spread of spinal or epidural drugs and unintentional intrathecal or subdural administration of an “epidural dose” of local anesthetic. The rapid epidural administration of a large volume of local anesthetic solution in the presence of a large-bore dural puncture (e.g., after a “wet tap”) may also result in high neuroblockade.

Nausea and Vomiting

Nausea and vomiting are regulated by the chemoreceptor trigger zone and the vomiting center, which are located in the area postrema and the medullary lateral reticular formation, respectively. The vomiting center receives impulses from the vagal sensory fibers in the gastrointestinal tract, the semicircular canals and ampullae (labyrinth) of the inner ear, higher cortical centers, the chemoreceptor trigger zone, and intracranial pressure receptors. Impulses from these structures are influenced by dopaminergic, muscarinic, tryptaminergic, histaminic, and opioid receptors, which are subsequently the targets for antiemetic agents. Efferent impulses from the vomiting center are transmitted through the vagus, phrenic, and spinal nerves to the abdominal muscles, which causes the physical act of vomiting.
Preoperative Nausea and Vomiting

Nausea and vomiting may occur separately or in combination and are not uncommon during pregnancy. A number of metabolic, endocrine, and anatomic changes have been implicated in the genesis of gestational nausea and vomiting, including human chorionic gonadotropin, estrogen, progestrone, prostaglandins, and immune system dysregulation. When vomiting is sufficiently severe to produce weight loss, dehydration, acidosis from starvation, alkalosis from loss of hydrochloric acid in vomitus, and hypokalemia, it is referred to as hyperemesis gravidarum (see Chapter 16). This disorder most commonly occurs in early pregnancy, but as many as 10% of pregnant women have nausea and vomiting that persist beyond 22 weeks’ gestation. Severe and persistent hyperemesis may result in maternal and fetal morbidity. The presence of delayed gastric emptying during labor and administration of opioids are risk factors for nausea and vomiting before cesarean delivery.

Intraoperative Nausea and Vomiting

Intraoperative nausea and vomiting associated with cesarean delivery can be variable in incidence and presentation, depending on preexisting symptoms, anesthetic and obstetric techniques, and preventive and therapeutic measures. The incidence of nausea may be as high as 80%, particularly when the anesthesia provider specifically assesses for the presence of intraoperative symptoms; symptoms occur frequently with exteriorization of the uterus. Anesthetic causes of intraoperative nausea and vomiting include hypotension and increased vagal activity; nonanesthetic causes include surgical stimuli, bleeding, medications (e.g., uterotonics, antibiotics), and motion at the end of surgery. Many of these elements occur simultaneously.

Hypotension is among the most common sequelae associated with the administration of neuraxial anesthesia. Centrally, hypotension may lead to cerebral and brainstem hypoperfusion, which results in stimulation of the medullary vomiting center. Peripherally, hypotension may cause gut ischemia with release of emetogenic substances (e.g., serotonin) from the intestine. Strict maintenance of intraoperative blood pressure can reduce the occurrence of emesis; Datta et al. observed that the incidence of intraoperative nausea and vomiting was 66% when the blood pressure decreased more than 30% from baseline, but was less than 10% when blood pressure was maintained at baseline with ephedrine. Similarly, Ngan Kee et al. demonstrated progressive increases in intraoperative nausea and vomiting during spinal anesthesia for cesarean delivery when blood pressure control with an infusion of phenylephrine was less aggressive; the incidence of nausea and vomiting was 4% when blood pressure control targeted 100% of baseline, 16% for 90% of baseline, and 40% for 80% of baseline.

Uterotonic agents may also contribute to intraoperative nausea and vomiting. Ergot alkaloids (e.g., methylergonovine maleate) may cause nausea and vomiting by interacting with dopaminergic and serotonergic receptors. Oxytocin causes nausea and vomiting primarily as a result of the hypotension produced through release of nitric oxide and atrial natriuretic peptide. A 29% incidence of nausea and a 9% incidence of vomiting have been reported with an intravenous bolus of oxytocin 5 units during elective cesarean delivery with neuraxial anesthesia. Administration of 15-methyl prostaglandin F2α causes nausea through the stimulation of smooth muscles of the gastrointestinal tract; a 10% incidence of nausea and vomiting has been observed after administration of 250 µg intramuscularly. Likewise, misoprostol is associated with a high risk for nausea and vomiting.

Surgical stimuli, including exteriorization of the uterus, intra-abdominal manipulation, and peritoneal traction, can cause visceral pain and subsequent nausea through the stimulation of vagal fibers and activation of the vomiting center. Despite high levels of thoracic sensory block obtained for cesarean delivery anesthesia, visceral pain may still occur, particularly after the neuraxial administration of a local anesthetic without opioid. The administration of neuraxial opioids reduces visceral pain–induced nausea and vomiting. Neuraxial fentanyl both improves the quality of neuraxial anesthesia and decreases intraoperative nausea; the minimal effective intrathecal and epidural doses are 6.25 µg and 50 µg, respectively.

Postoperative Nausea and Vomiting

Risk factors for postoperative nausea and vomiting have not been specifically studied in obstetric patients; however, studies have identified risk factors in nonobstetric patients receiving general or neuraxial anesthesia (Box 26.9). A multicenter observational study identified the following four highly predictive factors for postoperative nausea and vomiting in nonobstetric patients after general anesthesia, which may have relevance in the pregnant population: (1) female sex, (2) history of motion sickness or postoperative nausea and vomiting, (3) nonsmoking status, and (4) the use of perioperative opioids.

<table>
<thead>
<tr>
<th>Box 26.9</th>
<th>Risk Factors for Nausea and Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Anesthesia–Related Factors</td>
<td>- Female sex&lt;br&gt;- History of motion sickness or postoperative nausea and vomiting&lt;br&gt;- Nonsmoking status&lt;br&gt;- Use of perioperative opioids</td>
</tr>
<tr>
<td>Spinal Anesthesia–Related Factors</td>
<td>- Block height of T5 or higher&lt;br&gt;- History of motion sickness&lt;br&gt;- Hypotension&lt;br&gt;- Omission of neuraxial opioids</td>
</tr>
</tbody>
</table>

opioids. The incidence of postoperative nausea and vomiting was 10% if the patient had no risk factors, 21% for one, 39% for two, 61% for three, and 79% for four. A subset of pregnant women may have a lower threshold for nausea and vomiting associated with motion. Changes in position and transfer to and on the stretcher may stimulate afferent neural pathways that trigger emesis. Because the histamine-1 (H1) and muscarinic cholinergic pathways play primary roles in this response, antihistamine and anticholinergic agents should be considered first-line treatments. Postoperative nausea and vomiting may be related to postoperative ileus, which in turn is influenced by the effect of opioids on the gastrointestinal tract, the activation of the sympathetic nervous system, the occurrence of intestinal wall inflammation, and the presence of volume overload or edema.

Prophylaxis and Treatment of Nausea and Vomiting

Preventing maternal hypotension may be the best means of preventing nausea and vomiting (see earlier). Several options exist for the pharmacologic prophylaxis of nausea and vomiting, and several different classes of drugs are available (Table 26.8). Although various algorithms have been developed to prevent postoperative nausea and vomiting, primarily targeting the nonpregnant patient population, none has been universally successful. However, the prophylactic use of these agents either before or after umbilical cord clamping during cesarean delivery with neuraxial anesthesia has been demonstrated to be highly effective. Balki and Carvalho suggested an algorithm consisting of metoclopramide as a first-line agent, dimenhydrinate (a combination of diphenhydramine and 8-chlorotheophylline) as a second-line agent, and ondansetron or granisetron as a third-line agent. Multimodal therapies may eventually prove the most effective, as has been demonstrated in nonpregnant patients.

**Metoclopramide** is the agent most frequently given, owing to its favorable prokinetic effects. Common side effects include dizziness, drowsiness, and fatigue; rarer side effects include extrapyramidal reactions and acute dystonias. A meta-analysis of 11 studies of 702 patients undergoing cesarean delivery found that intravenous metoclopramide 10 mg compared with placebo, administered before neuraxial blockade, resulted in a significant reduction in intraoperative nausea (RR, 0.27; 95% CI, 0.16 to 0.45) and vomiting (RR, 0.14; 95% CI, 0.03 to 0.56). This approach was more effective than administering the metoclopramide after delivery, although administration after delivery also resulted in a significant reduction in perioperative nausea and vomiting. Early postoperative nausea (RR, 0.47; 95% CI, 0.26 to 0.87) and vomiting (RR, 0.45; 95% CI, 0.21 to 0.93) were also reduced with metoclopramide.

**Ondansetron** has been found to be more effective than placebo for the prevention of intraoperative nausea and vomiting during cesarean delivery with spinal anesthesia. A study that compared ondansetron 4 mg to metoclopramide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Drug Dose</th>
<th>Optimal or Recommended Timing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>4–8 mg IV</td>
<td>Unknown</td>
<td>Unknown for patients undergoing cesarean delivery</td>
<td>Delayed onset of action; used infrequently in patients undergoing cesarean delivery</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>25–50 mg IV</td>
<td>Unknown</td>
<td>Unknown for patients undergoing cesarean delivery</td>
<td>Antihistamine</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>12.5 mg IV</td>
<td>After umbilical cord clamping</td>
<td>Serotonin antagonist; not effective in the single published randomized controlled trial</td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.625–1.25 mg IV</td>
<td>End of surgery</td>
<td>Butyrophenone with a package insert that contains an FDA “black box” warning regarding prolongation of corrected QT interval on electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0.5 mg/kg IM</td>
<td>End of surgery</td>
<td>Vasopressor</td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td>40 µg/kg IV</td>
<td>After umbilical cord clamping</td>
<td>Serotonin antagonist</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg IV</td>
<td>Before surgery or after umbilical cord clamping</td>
<td>Benzamide</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg IV</td>
<td>After umbilical cord clamping</td>
<td>Serotonin antagonist</td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1.5-mg transdermal patch</td>
<td>Unknown</td>
<td>Muscarinic antagonist</td>
<td></td>
</tr>
</tbody>
</table>

IM, Intramuscularly; IV, intravenously.

*If nausea and vomiting occur despite prophylaxis, the anesthesia provider should consider administration of a drug from a different pharmacologic class. There is no evidence that a second administration of the same drug within 6 hours provides additional benefit.

*Studies in nonobstetric patients suggest that administration of dexamethasone at induction of anesthesia results in better efficacy, but the optimal timing in obstetric patients is unclear.

*Has not been studied in patients undergoing cesarean delivery with neuraxial anesthesia; however, this drug has proved effective for prophylaxis of postoperative nausea and vomiting in studies of nonobstetric patients after administration of general anesthesia.
10 mg administered after umbilical cord clamping found ondansetron to be more effective in preventing nausea (26% versus 51%) but not vomiting (15% versus 18%). A systematic review concluded that the use of a serotonin receptor antagonist (e.g., ondansetron, granisetron) in women undergoing neuraxial anesthesia for cesarean delivery was associated with a reduction in intraoperative nausea (but not vomiting) and postoperative nausea and vomiting, compared with placebo. Furthermore, serotonin receptor antagonists were found to be more effective in reducing postoperative nausea than dopamine receptor antagonists (e.g., metoclopramide, droperidol). Some studies have suggested that the administration of ondansetron decreases the incidence of bradycardia and hypotension following spinal anesthesia, potentially by blocking the Bezold-Jarisch reflex (which is mediated by 5-HT3 serotonin receptors). However, the strength of the evidence for this effect has been questioned.

Animal toxicology studies suggest that the epidural administration of ondansetron may be safe. In a study of 80 women undergoing elective cesarean delivery with CSE anesthesia, the incidence of postoperative nausea was lower in women randomized to receive an epidural infusion of ondansetron than in women who received an intravenous infusion (8 mg over 48 hours) at both 24 and 48 hours. However, future investigations are needed to validate the safety of the neuraxial administration of ondansetron before this route of administration can be recommended.

A 2012 meta-analysis of aggregated data suggests that a single intravenous dose of dexamethasone 5 to 10 mg (but not 2.5 mg) compared with placebo reduces the incidence of postoperative nausea (23% versus 41%, respectively) and vomiting (20% versus 36%, respectively) in women who received neuraxial morphine for cesarean delivery. In a subgroup analysis, the authors identified a lower incidence of postoperative nausea and vomiting in women who received epidural morphine; however, they were unable to draw definitive conclusions regarding the effect of dexamethasone on postoperative nausea and vomiting in women who received spinal morphine because of the small sample size. In a later study, women randomized to receive preincision dexamethasone 10 mg after spinal anesthesia with bupivacaine and morphine 0.06 mg had a lower 24-hour cumulative incidence of both nausea and vomiting compared with a control group.

Administration of a transdermal scopolamine 1.5-mg patch after umbilical cord clamping was shown to be as effective as ondansetron 4 mg in the prevention of nausea and vomiting after cesarean delivery with spinal anesthesia (bupivacaine 12 mg with fentanyl 10 µg and morphine 0.2 mg); compared with placebo, both drugs resulted in a reduction in the incidence of postoperative emesis from approximately 60% to approximately 40%. The use of scopolamine may be limited by side effects, particularly dry mouth and blurry vision. The results of a systematic review suggest that the use of an anticholinergic agent (e.g., scopolamine, glycopyrrolate) in women undergoing neuraxial anesthesia for cesarean delivery results in a significant reduction in intraoperative nausea but not vomiting.

Alternative therapies may play a role in preventing or treating perioperative nausea and vomiting. Several studies have found a favorable effect of acupressure on the P6 acupoint (on the anterior aspect of the wrist). After spinal anesthesia for cesarean delivery, acupressure has been observed to result in a lower incidence of nausea (36% and 15%, respectively) and vomiting (17% and 9%, respectively), compared with placebo. Two systematic reviews of randomized controlled trials involving a total of 649 women undergoing neuraxial anesthesia for cesarean delivery concluded that despite heterogeneity in the data, P6 stimulation (compared with placebo) appears to reduce intraoperative nausea but not intraoperative vomiting or postoperative nausea or vomiting.

One study found that the administration of supplemental oxygen (Fio2 of 0.7) between umbilical cord clamping and the end of cesarean delivery with neuraxial anesthesia was not associated with a lower incidence of nausea and vomiting than the administration of room air. This finding is consistent with the results of a meta-analysis of randomized controlled trials in the nonobstetric population; there was no difference in the incidence of nausea and vomiting with the use of supplemental oxygen (Fio2 of 0.8) compared with the use of lower oxygen concentrations (Fio2 of 0.3 to 0.4).

A systematic review suggests that the administration of subhypnotic doses of propofol (0.5 to 1.5 mg/kg/h) for the reduction of intraoperative and postoperative nausea and vomiting in women undergoing neuraxial anesthesia for cesarean delivery is more effective than placebo; however, there are insufficient data to compare this method with other therapies.

**Perioperative Pain**

In contrast to surveys performed in the general surgical patient population, in which patients have revealed a primary concern for postoperative nausea and vomiting, a survey performed in obstetric patients during their expectant parent class indicated that pain during and after cesarean delivery was their greatest concern. Inadequate neuraxial anesthesia leading to pain during labor or cesarean delivery was the most frequent “damaging event” in obstetric claims (31%) against the National Health Service in the United Kingdom from 1995 to 2007.

A preoperative discussion about pain and discomfort can help allay patient concerns. The anesthesia provider should (1) explain that there may be some deep pressure, pain, or discomfort during cesarean delivery performed with a neuraxial technique; (2) reassure the patient that the anesthesia provider will be present throughout the operation to administer additional analgesics or general anesthesia if necessary; (3) ensure and document adequacy of neuraxial blockade before the start of surgery; (4) communicate with the patient frequently during the procedure, specifically about pain or discomfort; and (5) treat pain when it arises, in agreement with the patient’s wishes. During the postoperative visit, the anesthesia provider should address any concerns that may have arisen during or after surgery.
The anesthetic technique for the cesarean delivery may be altered because of postoperative pain management considerations. For example, an epidural catheter–based technique may be optimal for the patient with a significant pain history (e.g., sickle cell vaso-occlusive crises, chronic pain syndromes, opioid use disorder) so that the epidural catheter may be used for postoperative pain management.

By directly activating spinal and supraspinal opioid receptors, epidurally and spinally administered opioids blunt nociceptive input and produce analgesia of greater intensity than parenterally or intramuscularly administered doses. A number of opioids have been used in the epidural and spinal spaces; however, morphine has emerged as the leading agent for postcesarean analgesia, owing to its long duration of action and low cost (see Chapter 27). When morphine is administered intrathecally or epidurally, doses of 0.1 mg and 3.75 mg, respectively, appear to provide optimal analgesia after cesarean delivery.157,188 Higher doses slightly prolong analgesia, but result in a markedly higher risk for pruritus and vomiting.110 Neuraxial morphine has a peak analgesic effect at 60 to 90 minutes but continues to provide effective analgesia for up to 24 hours.188 Thus, intrathecal morphine is often co-administered with the local anesthetic and lipid-soluble opioid administered for spinal anesthesia, and epidural morphine is administered intraoperatorically, after the umbilical cord is clamped, to allow sufficient time for the onset of epidural morphine analgesia before the regression of epidural analgesia.

The local anesthetic selected for epidural anesthesia may influence postoperative analgesia. The epidural administration of 2-chloroprocaine has been observed to adversely affect the subsequent efficacy of epidural morphine analgesia,411 although this remains a matter of some dispute.173,412 The mechanism for this potential interaction remains unknown; however, the use of 2-chloroprocaine should be limited to emergency situations in which rapid augmentation of epidural anesthesia is desired (see earlier discussion).

Adverse effects of neuraxial morphine include pruritus, nausea and vomiting, urinary retention, and delayed respiratory depression. Frequent evaluations (hourly for the first 12 hours, and then every 2 hours for another 12 hours) should be conducted.413 Postpartum women who are morbidly obese or have preexisting respiratory issues (sleep apnea) are at greater risk for respiratory depression.414

Postoperative pain has at least two components, somatic and visceral. A multimodal approach with different agents (e.g., ketamine) and techniques (e.g., tissue infiltration, peritoneal spraying, transversus abdominis plane [TAP] block) provides the most effective postcesarean analgesia (see Chapter 27). The administration of nonsteroidal anti-inflammatory drugs has been associated with potential adverse effects (platelet dysfunction, uterine atony), and some investigators have expressed concern related to neonatal exposure through breast milk. However, the American Academy of Pediatrics415 has stated that ibuprofen and ketorolac are compatible with breast-feeding. Unless specifically contraindicated, nonsteroidal anti-inflammatory drugs are a usual component of multimodal postoperative analgesia.

### Table 26.9: Agents for Prevention or Treatment of Pruritus in Women Undergoing Cesarean Delivery

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug and Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid antagonists</td>
<td>Naloxone infusion</td>
<td>May reverse analgesia</td>
</tr>
<tr>
<td></td>
<td>1–2 µg/kg/h IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–9 mg PO</td>
<td></td>
</tr>
<tr>
<td>Opioid agonist/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypnotic agent</td>
<td>Propofol</td>
<td>Subhypnotic dose with conflicting evidence</td>
</tr>
<tr>
<td></td>
<td>10–20 mg IV</td>
<td>regarding efficacy in treating pruritus</td>
</tr>
<tr>
<td>Serotonin antagonist</td>
<td>Ondansetron 0.1 mg/kg IV</td>
<td>Conflicting evidence regarding efficacy in treating pruritus</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>Droperidol 1.25 mg IV</td>
<td>Package insert contains an FDA “black box”</td>
</tr>
</tbody>
</table>

- IV, intravenously; PO, orally.
Dexamethasone in doses of 2.5 to 10 mg has not been found to reduce the incidence of pruritus associated with neuraxial morphine in women undergoing cesarean delivery.\(^{401}\) Although opioid receptor antagonists, such as naltrexone and naloxone, and partial agonist/antagonists, such as nalbuphine, are currently the most effective treatments for pruritus, a single dose or continuous intravenous infusion of any of these agents may reverse analgesia. Because the primary mechanism of opioid-induced pruritus appears unrelated to histamine release, antihistamines seldom represent a viable treatment option, although some benefit may be derived from the accompanying sedative qualities of these agents.

**Hypothermia and Shivering**

Perioperative hypothermia and shivering are commonly observed in women undergoing cesarean delivery, with a reported incidence of 66% and 85%, respectively.\(^{419,420}\) Hypothermia has been associated with a number of adverse outcomes in nonpregnant surgical patients, including wound infection, coagulopathy, increased blood and transfusion requirements, increased oxygen consumption, decreased metabolism, and prolonged recovery.\(^{421}\) In a systematic evaluation of randomized trials of normothermic and mildly hypothermic (34° C to 36° C) nonpregnant surgical patients, Rajagopalan et al.\(^{422}\) observed that even hypothermia less than 1° C below normal body temperature was associated with a 16% increase in blood loss (95% CI, 4% to 26%) and a 22% increase in risk for transfusion (95% CI, 3% to 37%).

Normally, core body temperature is tightly regulated within a narrow range of 36° C to 37° C. During pregnancy, despite an increase in maternal basal metabolic rate and energy released by the developing fetal and uteroplacental unit, maternal core temperature decreases, reaching a nadir at 12 weeks postpartum (36.4° C).\(^{423}\) Major causes of hypothermia during cesarean delivery are most likely related to core-to-periphery heat redistribution caused by diminished vasoconstriction and shivering, particularly after neuraxial blockade, and impairment of centrally mediated thermoregulatory control.\(^{421}\)

The onset and severity of hypothermia and shivering are associated with the patient’s baseline thermal status, the perioperative environment, and the anesthetic technique and agents selected. A study showed that spinal anesthesia reduced the initial core temperature of patients undergoing cesarean delivery more rapidly than epidural anesthesia, but the overall incidence of shivering was similar. However, the severity of shivering was significantly less in the spinal group, possibly through the induction of a lower shivering threshold or the inhibition of thermoregulatory control as a function of the number of blocked dermatomes.\(^{424}\)

The effect of neuraxial opioids on thermoregulation and shivering in patients undergoing cesarean delivery is not fully understood. Intravenously administered meperidine 12.5 to 25 mg is one of the most effective antishivering drugs and is unique among opioids in producing this effect at doses not typically associated with respiratory depression. The mechanism of this effect does not appear to be related to \(\kappa\)-opioid receptor activity or inhibition of cholinergic receptors; instead, central \(\alpha_2\)-adrenergic receptor stimulation may be involved.\(^{425}\) The \(\alpha_2\)-adrenergic receptor agonists clonidine (150 µg) and dexmedetomidine (0.5 µg/kg) are effective antishivering agents that can lower the shivering threshold,\(^{425}\) although both agents may have limited use during pregnancy because of the potential to cause sedation, bradycardia, and hypotension.

Other modalities have been used to prevent and treat hypothermia and shivering. Preoperative patient warming using forced air has been shown to reduce the incidence of perioperative and postoperative core hypothermia and shivering in patients undergoing cesarean delivery with epidural anesthesia.\(^{426}\) In contrast, a subsequent study found that perioperative forced-air warming did not prevent maternal hypothermia after cesarean delivery with spinal anesthesia.\(^{419}\) The ambient operating room temperature has also been shown to impact the risk for hypothermia. One study showed that increasing the set temperature from 20° C (67° F) to 23° C (73° F) resulted in significant reduction in maternal hypothermia on arrival in the postoperative care area.\(^{427}\) Lower limb wrapping has been observed to have no effect on the incidence of hypothermia or shivering.\(^{428}\)

**OBSTETRIC COMPLICATIONS**

**Postpartum Hemorrhage**

A leading cause of maternal and fetal morbidity and mortality worldwide, mild to moderate obstetric hemorrhage can be masked by pregnancy-related physiologic changes. Underestimation of blood loss and inadequacy of resuscitation are common problems (see Chapter 37).

Failure of the uterus to contract (uterine atony) after delivery accounts for most cases of postpartum hemorrhage and remains a leading cause of postpartum hysterectomy and blood transfusion. Each minute, 600 to 700 mL of blood flows through the placental intervillous spaces; thus, obstetric hemorrhage can rapidly result in maternal shock. Uterine atony occurs more commonly after cesarean delivery than after vaginal delivery, perhaps as a reflection of the condition(s) that prompted the cesarean delivery or possibly because surgery disrupts the normal postpartum response to uterotonics hormons and pharmacologic agents. Risk factors for uterine atony include (1) high parity, (2) an overdistended uterus (multiple gestation, macrosomia, polyhydramnios), (3) prolonged labor (augmented by oxytocin), (4) chorioamnionitis, (5) abnormalities in placentation (placenta accreta, increta, or percreta), (6) retained placental tissue, (7) mechanical barriers to effective contraction (e.g., fibroids, uterine anomalies), and (8) poor perfusion of the uterine myometrium (e.g., hypotension).

Initial efforts to control uterine atony include uterine massage and exogenous oxytocin administration. Postpartum oxytocin is administered in a wide range of doses, methods, and timing patterns (e.g., before or after delivery of the placenta),\(^{429}\) although small doses of oxytocin are
sufficient to produce adequate uterine contraction after cesarean delivery in most women. The effective bolus dose necessary for adequate uterine tone in 90% (ED₉₀) of non-laboring women undergoing cesarean delivery oxytocin is 0.35 unit⁴²⁹; in laboring women who have received approximately 10 hours of oxytocin augmentation, the ED₉₀ is 2.99 units.⁴³¹ The ED₉₀ of an oxytocin infusion in elective cesarean delivery patients is estimated to be 0.29 unit/min (95% CI, 0.15 to 0.43).⁴³² Women undergoing intrapartum cesarean delivery after exposure to exogenous oxytocin during labor require higher infusion rates (ED₉₀ 0.74 units/min, 95% CI, 0.56 to 0.93).⁴³³

Women receiving oxytocin augmentation for labor have greater blood loss despite higher oxytocin doses; this appears to originate from signal attenuation and desensitization of the oxytocin receptors in a time- and concentration-dependent manner.⁴³⁴–⁴³⁷ Continued high-dose oxytocin exposure in the postpartum period can lead to acute receptor desensitization and render the myometrium less responsive to additional oxytocin but not to other uterotonic agents.⁴³⁷ Pregnancy causes a 180-fold increase in the concentration of oxytocin receptors, with a significant proportion of this increase occurring just before the onset of labor³⁸⁸; this change in receptor number may have relevance to parturients who are delivering preterm infants.

A randomized trial including 60 women undergoing elective cesarean delivery compared a “rule of 3’s” (oxytocin 3 units, 3-minute evaluation intervals, 3 total doses, and oxytocin 3 units/h for maintenance) protocol for the administration of oxytocin after delivery with a “wide-open” infusion of oxytocin (30 units in 500 mL of normal saline).³⁹³ In the “rule of 3’s” approach, oxytocin 3 units is given as a slow bolus or as an infusion (30 units oxytocin in 500 mL of normal saline [50 mL]), at a rate no faster than over a period of 15 seconds. Uterine tone is reassessed again at 3 and 6 minutes; if inadequate, an additional dose of oxytocin 3 units is given. If uterine atony persists after three total doses of oxytocin, other uterotonic agents should be employed (see later discussion). The trial demonstrated that the “rule of 3’s” algorithm results in lower oxytocin doses when compared with continuous-infusion oxytocin in women undergoing elective cesarean delivery, without changing measures of uterine tone, maternal hemodynamics, or blood loss.⁴³⁹

The specific timing of the initial dose of oxytocin varies by individual practitioner; insufficient data are available to determine whether oxytocin administration immediately on emergence of the infant’s shoulder or body or after placental delivery makes a difference in overall blood loss during cesarean delivery. The optimal duration of oxytocin after delivery is not known. After the establishment of adequate uterine tone, an infusion of 3 units/h for up to 5 hours has been recommended.²⁹

The administration of oxytocin as a rapid intravenous bolus causes hypotension and may result in cardiovascular collapse; patients with preeclampsia may have an unpredictable hemodynamic response to oxytocin administration (e.g., decrease in cardiac output).⁴⁴² Oxytocin has a direct relaxing effect on vascular smooth muscle, which leads to decreased systemic vascular resistance, hypotension, and tachycardia.⁴⁴³ Tachycardia also may result from a direct effect on specific oxytocin receptors in the myocardium and subsequently result in alterations in atrioventricular conduction and myocardial repolarization.⁴⁴⁴–⁴⁴⁶ Chest pain and signs suggestive of myocardial ischemia and anaphylaxis may occur. Owing to the structural similarity of oxytocin to vasopressin, water intoxication may occur and, when severe, can lead to hyponatremia, confusion, convulsions, and coma.

If oxytocin proves ineffective, the administration of second-line uterotonics, including methylergonovine, carbo-prost, and/or misoprostol, should be considered. The ergot alkaloid derivative methylergonovine (0.2 mg) may be given intramuscularly to enhance uterine tone; onset time is within 10 minutes, and the effect persists for 3 to 6 hours. Intravenous administration (in small divided doses) should be performed only with great caution, because intense vasoconstriction may lead to acute hypertension, seizures, cerebrovascular accident, retinal detachment, and myocardial arrest; this possibility is of special concern in patients with preeclampsia or cardiac disease. Methylergonovine also has additive hemodynamic effects when given with sympathomimetic agents, such as ephedrine and phenylephrine. Nausea and vomiting are common side effects, which most likely reflect a direct central nervous system effect. The co-administration of oxytocin and ergometrine has been demonstrated to improve uterine contractions (as measured by the requirement for additional uterotonic agents) compared with the administration of oxytocin alone; however, the estimated blood loss was not different between groups, and nausea and vomiting were more prevalent with the oxytocin-ergometrine combination.⁴⁴⁵

Carboprost (analogue of 15-methyl prostaglandin F₂₅) causes a dose-dependent increase in the force and frequency of uterine contractions. The initial recommended dose is 250 µg given intramuscularly; this dose can be repeated if necessary at 15- to 90-minute intervals up to a maximum of eight doses.⁴⁴⁶ Whether carboprost is more effective than oxytocin is controversial;⁴⁴⁷ however, it clearly has a role in the treatment of refractory uterine atony.⁴⁴⁸ In approximately 20% of women, the following side effects occur (listed in descending order of frequency): diarrhea, hypertension, vomiting, fever, flushing, and tachycardia.⁴⁴⁸ Bronchospasm, pulmonary vasoconstriction, and oxyhemoglobin desaturation may also occur. Observational data suggest that methylergonovine is more effective than carboprost as a second-line uterotonic in preventing hemorrhage-related morbidity.⁴⁴⁹

Rectal or sublingual administration of prostaglandin E₁ (misoprostol) is a uterotonic agent with a rapid onset of action. A systematic review of prophylactic misoprostol (given orally or sublingually in doses ranging from 400 to 800 µg) administered for active management of the third stage of labor concluded that it is more effective than placebo in preventing severe postpartum hemorrhage but less effective than conventional injectable uterotonic agents.⁴⁵⁰ Several
large studies have assessed misoprostol’s role when given as an adjunct to standard uterotonics. In these studies, the administration of misoprostol was no more effective than placebo, but was associated with high rates of side effects, including hyperthermia, severe shivering, and gastrointestinal symptoms. There may be a prophylactic role for this drug in low-resource settings where oxytocin is not available, but its utility in high-resource settings as a second-line uterotonic is likely limited.

**Preparation for Blood Loss**

When risk factors for hemorrhage are identified, several preparatory steps can be considered. Iron supplementation and use of recombinant human erythropoietin are effective therapies for producing red blood cells, particularly in patients with preexisting anemia, renal failure, and/or reasons for preoperative donation of autologous blood. Antepartum erythropoietin administration may be of value in pregnant women at high risk for hemorrhage or who refuse blood products (e.g., Jehovah's Witnesses); however, additional investigation is needed to determine the optimal dosing, goals of therapy, and side-effect profiles. Hypertension, a problem associated with the use of erythropoietin in patients with renal failure, is a relevant concern during pregnancy. Although normal pregnancy is associated with a twofold to fourfold increase in maternal erythropoietin levels, isolated studies of the effect of erythropoietin on placental vessels suggest that dose-dependent vasoconstriction occurs. Observation of high erythropoietin levels in hypertensive and preeclamptic parturients has fueled speculation that erythropoietin participates in the humoral mechanisms responsible for preeclampsia and fetal growth restriction. However, whether treatment with erythropoietin increases the risk for these complications remains unclear, and the safety data that have accumulated to date are reassuring. A hyperglycosylated analogue of recombinant human erythropoietin (darbepoetin) has a threefold longer terminal half-life and results in a more rapid and greater erythropoietic response than recombinant human erythropoietin.

The efficacy of preoperative autologous blood donation is limited by the maximum life span of stored blood; collection can start no sooner than 6 weeks before a planned delivery, with an average unit collection interval of 3 to 7 days. This method may be of some use in a woman with maternal antibodies to red blood cell antigens. The technique seems safe but has limited applicability and efficacy in obstetric patients (see Chapter 37).

**Acute normovolemic hemodilution** has the advantage of reducing the risk for administrative errors and bacterial contamination and allowing the infusion of whole blood replete with functional coagulation factors and platelets. This technique may reduce the need for transfusion in selected patients, and it may be acceptable to Jehovah’s Witness patients at increased risk for blood loss during cesarean delivery.

The use of intraoperative red blood cell salvage in obstetric patients is gaining greater acceptance. In the past, obstetric anesthesia providers have expressed concern that intraoperative cell salvage might precipitate amniotic fluid embolism. Data now suggest a very low risk for amniotic fluid contamination when a leucocyte depletion filter is employed. However, the cell salvage process does not remove all fetal red blood cells and hemoglobin, and maternal isoimmunization may occur. Intraoperative cell salvage may be used to prevent morbidity and mortality in parturients who refuse homologous blood or in cases of intractable hemorrhage that may overwhelm blood bank supplies (see Chapter 37).

**Response to Blood Loss**

Underestimation of blood loss and inadequate resuscitation are common problems in the management of obstetric hemorrhage. Rapid volume replacement is more important for maintaining tissue perfusion and oxygenation than the type of administered fluid. Colloids and blood products should be considered early, along with a request for assistance, establishment of a second large-bore intravenous catheter, and use of pressurized transfusion equipment. Many institutions require performance of a blood type and screen for parturients at high risk for hemorrhage undergoing a trial of labor for a planned vaginal delivery and in all parturients undergoing cesarean delivery. The immediate availability of two to four units of cross-matched packed red blood cells should be considered when the potential for significant blood loss appears imminent, such as in women with suspected placenta accreta. In situations in which the need for emergency blood transfusion precedes the availability of cross-matched blood, type-specific (or type O, Rh-negative blood) should be administered. All institutions should have an obstetric massive transfusion protocol in place. Continued blood loss and hemodynamic instability despite transfusion of packed red blood cells is often an indication for placement of an arterial line and invasive central venous pressure monitoring; however, restoration of circulating volume takes precedence. Urine output, heart rate, blood pressure, and transthoracic or transesophageal echocardiography (TEE or TEE) assessments can assist in the rapid evaluation of the adequacy of volume resuscitation.

Fortunately, most pregnant women are healthy and tolerate modest blood loss well. Concerns about uteroplacental perfusion and fetal oxygenation are no longer present after delivery of the infant. The ASA Task Force on Perioperative Blood Management states that red blood cell transfusion for hemoglobin concentrations between 6 and 10 g/dL should be based on potential or actual ongoing bleeding, intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve. It is important to note that in the setting of acute blood loss, the measured hemoglobin may not accurately reflect the degree of loss. The hemorrhaging patient should be monitored for the development of coagulopathy. Coagulopathy should be treated with the appropriate blood products or factor concentrates. Transfusion of platelets is not indicated unless the platelet count is less than 100,000/mm³ (unless platelet dysfunction and microvascular bleeding are present), and replacement of fibrinogen is not indicated unless the fibrinogen concentration is less than...
150 to 200 mg/dL in the presence of microvascular bleeding. However, a decrease in fibrinogen concentrations may serve as an early predictor of the severity of obstetric hemorrhage (baseline fibrinogen concentration is higher in pregnancy).463

The prophylactic placement of intravascular balloon occlusion catheters can facilitate the timely control of obstetric bleeding in some parturients at high risk for hemorrhage.464 Harnett et al.465 have recommended the placement of an epidural catheter before an intravascular balloon catheter for the following reasons: (1) once the balloon catheter is placed, flexion of the hips (during positioning for a neuraxial anesthetic technique) is discouraged, because it may result in balloon dislodgement or occlusion and subsequent thrombosis; (2) epidural anesthesia seems preferable to the use of local anesthesia with sedation for balloon catheter placement; (3) during balloon catheter placement, small amounts of heparin are sometimes used, and it seems preferable to have the epidural catheter in place before anticoagulation; and (4) should untoward events (e.g., fetal compromise, vessel rupture) occur during the procedure, the epidural catheter allows for rapid extension of anesthesia for cesarean delivery. With prior planning, operative procedures, including cesarean delivery, can be performed successfully under neuraxial anesthesia in the interventional radiology suite.465

When uterine bleeding occurs postpartum, the use of uterine tamponade balloon catheters has been demonstrated to tamponade and potentially treat intrauterine sources of bleeding and allow time to correct coagulopathy.466 Commercially available balloon catheters designed specifically for uterine tamponade allow for uterine cavity drainage, with variable success in function and ability to identify ongoing, significant bleeding.466 The balloons are often left in place for 24 to 48 hours, along with a vaginal pack and continued antibiotic administration. Distention of the uterus causes discomfort, and pain relief should be provided, either with systemic agents or epidural analgesia if a catheter is in situ. We typically provide continuous epidural analgesia, or patient-controlled epidural analgesia, with a dilute solution of local anesthetic and a lipid-soluble opioid, similar to that used for labor analgesia. The epidural catheter, regardless if used for analgesia, is typically kept in place until the uterine balloon is deflated to allow for rapid transition to surgical anesthesia if necessary.

Obstetric Hysterectomy

The incidence of cesarean hysterectomy and emergency postpartum hysterectomy ranges from 0.03% to 0.33% in different hospital settings and countries.467 Over a 14-year period in the United States, the rate of peripartum hysterectomy per 100,000 deliveries increased from 71.6 (1994 to 1995) to 82.6 (2006 to 2007); this increased rate was associated with an increased rate of hysterectomy for abnormal placentation (e.g., placenta previa, placenta accreta) from 32.9 to 40.5, and an increased rate of hysterectomy for uterine atony from 11.2 to 25.9 per 100,000 deliveries.468 Increasing rates of cesarean delivery, failed trial of labor, infection, intrauterine fetal death, and disseminated intravascular coagulation are other factors associated with cesarean hysterectomy. Improvements in ultrasonography, color flow Doppler ultrasonography, and magnetic resonance imaging have allowed earlier identification of women with placenta accreta; however, limitations in diagnostic sensitivity and specificity exist.469

Cesarean hysterectomy is considered a high-risk procedure owing to the vascularity and size of the uterus and the distorted anatomic relationships. Bladder and ureteral injuries are common. Before performance of hysterectomy, various conservative medical and surgical treatment modalities may be attempted (see Chapter 37). The ligation or embolization of major and collateral uterine vessels with the assistance of an interventional radiologist is becoming more common, particularly in tertiary care settings.464

The amount of blood loss depends in part on whether the hysterectomy is elective or an emergency. In a prospective review of all obstetric hysterectomies performed at five university hospitals (1984 to 1987), Chestnut et al.470 found an average blood loss of 1319 mL and 2526 mL in 25 elective and 21 emergency cases, respectively, with an average replacement of 1.6 units and 6.6 units of blood, respectively. In a more recent study, Briery et al.471 performed a multicenter retrospective review of operative and postoperative outcomes in 30 elective and 35 emergency cesarean hysterectomies; the mean (± SD) blood loss for elective and emergency cases was 1963 ± 1180 mL and 2597 ± 1369 mL, with 33% and 66% of the patients requiring blood transfusion, respectively.

The anesthesia provider should consult with the obstetric team to discuss risk factors and the planned course of management. Preparations for the management of potentially massive blood loss should be made, which may include the placement of an epidural catheter and prophylactic intravascular balloon catheters (see earlier discussion). An elective cesarean hysterectomy, or a cesarean delivery in which the patient is at high risk for emergency hysterectomy, is not a contraindication to a neuraxial anesthetic technique, although a catheter-based technique is recommended. Moreover, the occurrence of an emergency cesarean hysterectomy does not always necessitate immediate conversion to general anesthesia. Consideration should be given to (1) maternal history (e.g., number of prior abdominal operative procedures, which may lead to more scarring and adhesions); (2) the presence of risk factors (e.g., extent of placentation abnormality, coagulation status); (3) the potential difficulty of conversion to general anesthesia if required (e.g., presence of difficult airway, level of assistance available); (4) the desires and experience of the obstetric team; and (5) the desires of the patient. Chestnut et al.470 observed in their review that none of the 12 patients who received continuous epidural anesthesia for cesarean delivery (8 patients from the elective group and 4 from the emergency group) required intraoperative induction of general anesthesia for hysterectomy. In addition, there was no evidence that epidural anesthesia significantly affected blood loss, crystalloid replacement, or requirement for transfusion. In women with suspected placenta percreta at high risk for major blood loss, some anesthesiologists favor administration of neuraxial anesthesia for cesarean delivery.
of the infant, followed by administration of general anesthesia (to secure the airway) after delivery, before hysterectomy begins.

Given the morbidity and mortality associated with a peripartum hysterectomy, particularly if it is accompanied by significant blood loss, postoperative observation of the patient in a critical care setting should be considered. An investigation using nationwide administrative data compared women who underwent a peripartum hysterectomy \( (n = 4967) \) with women who had a nonobstetric hysterectomy \( (n = 578,179) \): women in the peripartum hysterectomy group were nine and five times more likely to have bladder and ureteral injuries, respectively, and they had greater rates of reoperation, postoperative hemorrhage, wound complications, and venous thromboembolism. Perioperative cardio-vascular, pulmonary, gastrointestinal, renal, and infectious morbidities were also higher for women who had peripartum hysterectomy. In addition, women undergoing peripartum hysterectomy had a higher rate of blood transfusion (46% versus 4%), a longer hospital stay, and a higher rate of perioperative mortality.\(^{472}\)

**Thromboembolic Events**

Thromboembolic events constitute a major reason for peripartum maternal mortality, and risks for the development of pregnancy-associated thrombosis include an operative delivery, physiologic changes of pregnancy, and medical history and comorbidities (e.g., obesity, hemoglobinopathies, hypertension, smoking).\(^{473}\) The risk for venous thromboembolism appears highest in the first postpartum week.\(^{473}\) A number of prophylactic interventions have been evaluated; however, the trials have been small and unable to provide robust results.\(^{474}\) Recommended thromboprophylaxis measures include hydration, early mobilization, pneumatic compression devices, and, in high-risk patients, pharmacologic prophylaxis (see Chapter 38).

### KEY POINTS

- Cesarean delivery is the most common major surgical procedure performed in many developed countries. The rate of cesarean delivery is increasing worldwide.
- Some cesarean deliveries might be avoided through the provision of satisfactory neuraxial analgesia for labor (including a trial of labor after cesarean delivery), instrumental vaginal delivery, and external cephalic version.
- Gastric emptying is unchanged during pregnancy. The parturient without complications may drink modest amounts of clear liquids up to 2 hours before induction of anesthesia for elective cesarean delivery. The fasting period for solids should be 6 to 8 hours. Slower digestion is observed for foods with high fat content, during labor, and with the administration of opioid analgesic agents.
- An \( H_2 \)-receptor antagonist or a proton-pump inhibitor may be given intravenously to increase gastric fluid pH, and intravenous metoclopramide may be given to both accelerate gastric emptying and increase lower esophageal sphincter tone. If possible, these agents should be administered more than 30 minutes before induction of anesthesia. Oral sodium citrate, which also increases gastric fluid pH, should be administered less than 30 minutes before induction.
- Antibiotic prophylaxis, administered within 60 minutes before abdominal incision, decreases the risk for maternal infectious complications after cesarean delivery.
- Although the use of intravenous fluids may reduce the frequency of maternal hypotension, initiation of neuraxial anesthesia should not be delayed to administer a fixed volume of fluid.
- The value of supplemental maternal oxygen during neuraxial anesthesia for the elective cesarean delivery of a noncompromised fetus is questionable.
- Left uterine displacement should be applied during cesarean delivery, regardless of the anesthetic technique.
- Umbilical cord prolapse (without fetal bradycardia), placenta previa, and severe preeclampsia (in a patient with an acceptable platelet count) are not absolute indications for general anesthesia.
- Among women receiving general anesthesia for cesarean delivery, maternal deaths associated with hypoventilation or airway obstruction are occurring with greater frequency during emergence, tracheal extubation, or recovery, rather than during induction and tracheal intubation; attention to airway and ventilation management should focus on both of these critical time periods.
- The combined spinal-epidural technique offers the benefits of both spinal and epidural anesthesia while minimizing the disadvantages of either technique alone. Advantages include the fast onset of dense anesthesia with a small dose of local anesthetic and the ability to provide prolonged anesthesia and continuous postoperative analgesia.
- Alkalization of the local anesthetic solution not only increases the speed of onset but also improves the quality and prolongs the duration of neuroblockade. Administration of 3% 2-chloroprocaine with 8.4% sodium bicarbonate (10 mL of 2-chloroprocaine mixed with 1 mL [1 mEq] of bicarbonate) produces the fastest onset of epidural anesthesia.
- The application of cricoid pressure to prevent passive regurgitation during induction of general anesthesia is controversial. If used, pressure should be initiated with a force of 10 N on the cricoid cartilage and increased to 30 N once the patient loses consciousness.
- When choosing the concentration of a volatile halogenated agent to maintain general anesthesia, the anesthesia provider must consider the uterine relaxation caused by these agents as well as the reduced MAC of pregnancy and the potential for maternal awareness.
• Either phenylephrine or ephedrine may be used for the prevention and treatment of maternal hypotension during neuraxial or general anesthesia for cesarean delivery. Phenylephrine appears to exert less metabolic effect on the fetus and results in higher umbilical arterial blood pH at delivery compared with ephedrine.

• Underestimation of blood loss and inadequate intravascular volume resuscitation during peripartum hemorrhage are common occurrences that contribute to maternal morbidity and mortality.

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Postoperative Analgesia

Ronald B. George, MD, FRCPC, Brendan Carvalho, MBBCh, FRCA, MDCH, Alexander Butwick, MBBS, FRCA, MS, Pamela Flood, MD

The cesarean delivery rate in the United States and around the world has steadily increased as a result of changing patterns in obstetric practice.\(^1\) Recent data indicate that more than 1 million cesarean deliveries are now performed annually in the United States.\(^2\) With cesarean delivery accounting for 32% of all deliveries in the United States, strategies for reducing adverse postcesarean maternal outcomes, including postoperative pain, have important clinical and public health implications.\(^2\)

Pain is a potential harm that can occur during and after any surgical procedure. Inadequately treated pain can cause numerous undesirable physiologic and psychologic consequences in women undergoing cesarean delivery, including impaired recovery, persistent and chronic pain, and increased cost.\(^3\)-\(^5\)

PAIN AFTER CESAREAN DELIVERY

Management of postoperative pain is frequently substandard, with 30% to 80% of patients experiencing moderate to severe postoperative pain.\(^6\)-\(^8\) Pain following cesarean delivery may be equivalent to that reported after a hysterectomy.\(^9\) Postoperative pain results from direct tissue trauma and subsequent inflammation. Local and systemic inflammatory cytokines act to sensitize the peripheral nerves and enhance pain perception.\(^10\) Inflammation likely plays a particularly significant role in pain after delivery because inflammatory cytokines are increased as a part of the normal labor and delivery process.\(^11,12\)

After cesarean delivery, wound cytokine concentration is positively correlated with analgesic drug consumption.\(^13\) The range of pain reported after cesarean delivery is greater than that after vaginal delivery, but the pain burden and duration are remarkably similar (Fig. 27.1).\(^5,14\) A sample of expectant mothers attending birthing classes identified pain during and after cesarean delivery as their most important concern (Table 27.1).\(^15\) Measuring pain intensity and satisfaction with simple tools has not met the goals of preventing and treating moderate and severe pain.\(^4,8,14-18\)

Severe acute postoperative pain is one of the most prominent factors associated with chronic postoperative pain.\(^3,5,19-21\) Some studies suggest that the use of perioperative neuraxial blockade may prevent central sensitization and chronic pain.\(^22,23\) Additional mechanistic and clinical research is needed to improve our understanding of persistent pain after cesarean delivery (see Chapter 42). Multimodal pharmacologic and nonpharmacologic treatment for pain is the optimal approach and should be offered whenever feasible and medically indicated.

SYSTEMIC ANALGESIA

Opioid Analgesia

In the United States, most women who undergo cesarean delivery with neuraxial anesthesia receive neuraxial opioids for postoperative analgesia. However, many women require systemic analgesia to augment neuraxial therapy, and some
women are unable to receive neuraxial anesthesia. In the United States it is common practice to prescribe oral opioids on discharge from the hospital, although this is not common practice in other parts of the world.\textsuperscript{24}

### Choice of Opioid

Factors that affect the choice of opioid are speed of onset, duration of action, overall efficacy, and the type and frequency of side effects. If side effects prevent adequate analgesia, other opioids or nonopioid adjuvants should be used. Patient preferences based on past experiences and desired analgesia should also be considered.\textsuperscript{25}

Historically, meperidine (pethidine) has been a popular opioid for postoperative analgesia. However, the American College of Obstetricians and Gynecologists (ACOG)\textsuperscript{26} and the American Pain Society\textsuperscript{27} have discouraged the use of meperidine in obstetric patients because of the accumulation of normeperidine in the neonate and its subsequent effect on neurobehavioral scores. Table 27.2 shows commonly used alternatives to meperidine with equianalgesic doses.

### Intravenous Patient-Controlled Analgesia

Intramuscular and subcutaneous opioids are inexpensive, easy to administer, and associated with a long history of safety but are not commonly used in the United States because of the need for repeated painful injections, delayed (and sometimes erratic) absorption of drug, and an inconsistent analgesic response caused by variation in plasma opioid concentration. Intravenous patient-controlled analgesia (PCA) allows patients to control their own pain management by self-administering small doses of intravenous opioids. A

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**TABLE 27.1 Women’s Ranking and Relative Value of Potential Anesthesia Outcomes Assessed before Cesarean Delivery**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rank\textsuperscript{a}</th>
<th>Relative Value\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during cesarean delivery</td>
<td>8.4 ± 2.2</td>
<td>27 ± 18</td>
</tr>
<tr>
<td>Pain after cesarean delivery</td>
<td>8.3 ± 1.8</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.8 ± 1.5</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8 ± 1.7</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>Cramping</td>
<td>6.0 ± 1.9</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>Itching</td>
<td>5.6 ± 2.1</td>
<td>9 ± 8</td>
</tr>
<tr>
<td>Shivering</td>
<td>4.6 ± 1.7</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.1 ± 1.9</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.9 ± 1.4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation.

\textsuperscript{a}Rank = 1 to 10 from the most desirable (1) to the least desirable (10) outcome.

\textsuperscript{b}Relative value = dollar value patients would pay to avoid an outcome (e.g., they would pay $27 of a theoretical $100 to avoid pain during cesarean delivery).


**TABLE 27.2 Opioid Equianalgesic Doses**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral (mg)</th>
<th>Subcutaneous/Intravenous (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 (mg)</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 (mg)</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20 (mg)</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 (mg)</td>
<td>1.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>NA</td>
<td>0.1 (100 µg)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 (mg)</td>
<td>1</td>
</tr>
</tbody>
</table>

A 25-µg/h transdermal patch is equianalgesic to ≈50 mg of oral morphine per day.

NA, Not applicable.


**Fig. 27.1** Pain trajectory after vaginal and cesarean delivery. Dotted lines represent pain reports from individual subjects, and solid white line is a moving average. Shaded area covers the range from the 5th to 95th percentile of the data. NRS, verbal numerical rating scale from 0 to 10, with 0 = no pain and 10 = worst pain imaginable. (From Komatsu R, Carvalho B, Flood PD. Recovery after nulliparous birth: a detailed analysis of pain analgesia and recovery of function. Anesthesiology. 2017;127:684–694.)
2015 meta-analysis concluded that PCA is often preferred by patients compared with nurse-administered analgesia on request, and PCA was shown to provide better pain control and increased patient satisfaction compared with non–patient-controlled methods. The American Society of Anesthesiologists (ASA) Task Force for Acute Pain Management in the Perioperative Setting recommended that “these modalities [epidural or intrathecal opioids, systemic opioid PCA, and peripheral regional techniques] should be used in preference to intramuscular opioids ordered ‘as needed.’”

The American Pain Society has recommended the use of intravenous opioid PCA when parenteral administration of analgesics is necessary and the oral route is not available.

PCA has been used via the intravenous and epidural routes after cesarean delivery. A study that compared intravenous and epidural PCA using fentanyl reported higher pain scores and greater fentanyl consumption with the intravenous route, although patient satisfaction was similar in the two groups. In another study that compared intravenous versus epidural PCA using hydromorphone, drug requirement was 3- to 4-fold higher in the intravenous group; the two groups had similar pain and sedation scores, but patients in the intravenous group reported more frequent drowsiness and less pruritus. Studies that compared intravenous morphine PCA to single-shot epidural morphine administration for postcesarean analgesia showed that analgesia and patient satisfaction were better and sedation was less with epidural morphine, although the incidence of pruritus was higher.

**Side Effects and Safety Considerations**

The goal of opioid administration is to achieve maximum analgesia with minimal side effects. It is important to monitor the respiratory rate and sedation level before giving an additional dose or adjusting the PCA bolus dose. Patients with comorbidities such as hepatic or renal dysfunction (e.g., occurring with severe preeclampsia), morbid obesity, and/or obstructive sleep apnea are particularly susceptible to the respiratory depressant effects of opioids; these patients may need special alterations to pain management, especially the use of multimodal analgesia (see later discussion).

Health care professionals who prescribe PCA should (1) be able to evaluate candidates for PCA (e.g., mental state, level of consciousness, patient understanding); (2) know drug selection criteria, dosing schedules, lockout periods, and infusion devices; (3) be able to provide patient education on pain management and the use of PCA; (4) understand when to alter PCA settings and when to give or withhold additional (rescue) doses of medications; and (5) be able to respond to side effects and adverse events. Observational studies of nonobstetric cohorts have reported an incidence of respiratory depression with intravenous PCA of 0% to 11.5%, which is equivalent to or higher than that reported for neuraxial opioids.

In December 2004, The Joint Commission issued a Sentinel Event Alert on PCA “by proxy” (i.e., when other individuals, including family members, become involved in drug administration by PCA). The Joint Commission acknowledged that PCA is a safe and effective method of controlling pain when used as prescribed; however, serious adverse events, including oversedation, respiratory depression, and death, can result when analgesia is delivered “by proxy.” The Joint Commission made the following recommendations: (1) develop criteria for selecting appropriate candidates for PCA, (2) carefully monitor patients, (3) teach patients and family members about the proper use of PCA and the dangers of others pressing the button for the patient, (4) alert staff to the dangers of administering a dose outside a prescribed protocol, and (5) consider placing warning tags on all PCA delivery pendants stating “only the patient should press this button.” The PCA settings (drug, demand dose, lockout interval, 4-hour limit, and the rate of continuous infusion, if used) are documented on a flow sheet, and any changes in PCA settings clearly documented.

**Infusion Pump Settings**

Programmable PCA parameters include drug choice, bolus dose, maximum dose, and lockout interval (Table 27.3).
Owen et al.\textsuperscript{43–45} performed several PCA investigations in patients undergoing abdominal surgery. In an assessment of PCA morphine demand bolus doses (0.5, 1, or 2 mg with a 5-minute lockout interval), more patients in the 0.5-mg group had inadequate pain relief, whereas those in the 2-mg group had more side effects, including respiratory depression (respiratory rate less than 10 breaths/min).\textsuperscript{45} These outcomes correlated with the total dose of self-administered morphine. Although the role of the lockout interval was not addressed in this study, the investigators suggested that inadequate analgesia could be produced by lockout intervals that are too long or demand doses that are too small. By contrast, larger doses or shorter lockout intervals might lead to more opioid-related side effects.

Although patients who experience inadequate analgesia would be expected to make more PCA demands, this is often not the case.\textsuperscript{45} Patients may be afraid to administer too much opioid or anticipate more severe side effects. Additionally, it has been suggested that patients are discouraged by an inadequate analgesic effect or they may expect a delayed response.\textsuperscript{45}

Continuous basal (background) infusions are not necessary in opioid-naive women.\textsuperscript{35} The American Pain Society does not recommend routine use of basal infusions of opioid in opioid-naive patients; most evidence does not demonstrate improved analgesia compared with patients who receive no basal infusion.\textsuperscript{30} Basal infusions of opioids are associated with an increased incidence of nausea and vomiting, and some studies have shown an increased risk for respiratory depression.\textsuperscript{30} Parker et al.\textsuperscript{46} compared a group receiving an intravenous PCA morphine regimen (bolus dose 2 mg) with a group receiving the same intravenous PCA regimen and a nighttime continuous infusion (1 mg/h). There were no differences between groups in postoperative pain, sleep pattern, demand or delivered bolus dose per hour, opioid consumption, or recovery from surgery. The use of a continuous infusion resulted in six errors during the programming of the device. Three patients required discontinuation of the continuous infusion because of significant oxyhemoglobin desaturation.\textsuperscript{46} The ASA Task Force on Acute Pain Management concluded that special caution should be taken when a continuous infusion is used because of the potential for adverse effects from opioid accumulation.\textsuperscript{79}

During PCA, the ratio of patient demands to delivered bolus doses appears to be a good measure of analgesia and is strongly correlated with pain scores.\textsuperscript{47} A high ratio likely reflects patient misunderstanding or inadequate analgesia; a ratio close to 1 signifies adequate pain relief. Analgesia may be improved by an increase in the bolus dose, a shorter lockout interval, or a change of opioid.

Because of the significant morbidity associated with high doses of opioids, use of these drugs should invoke the application of algorithms for pain assessment, management, and monitoring. Acute postoperative pain is limited in duration; therefore, a plan should be devised for the transition from intravenous opioids to oral analgesic agents when the patient’s pain is controlled and she is able to take medication by mouth.

**Oral Opioid Analgesia**

Some investigators have advocated the use of oral analgesics rather than intravenous PCA as there is seldom a requirement for a prolonged fasting period after cesarean delivery.\textsuperscript{46–51} Most evidence suggests intravenous administration of opioids is not superior to oral opioids for postoperative analgesia.\textsuperscript{30} In fact, patients randomized to oral oxycodone experienced less pain, nausea, and drowsiness 6 hours after cesarean delivery compared with those who received intravenous PCA morphine.\textsuperscript{31} Dieterich et al.\textsuperscript{42} found intravenous PCA and oral opioids provided similar degrees of satisfaction and pain scores after cesarean delivery. Therefore, when tolerated, oral administration of opioids may be the preferred route of administration. Advantages of this approach are cost savings, facilitation of early mobility, and, perhaps, greater patient satisfaction. Long-acting oral opioids are not recommended in the immediate postoperative period.\textsuperscript{35}

**Multimodal Analgesia**

Multimodal analgesia balances the effectiveness of individual analgesics, maximizing their efficacy while attempting to minimize side effects. The rationale of multimodal analgesia is the optimization of additive or synergistic effects of different modes of analgesia or drug classes, while reducing the dose and minimizing the side effects of individual drugs with different mechanisms of action.\textsuperscript{35} Although analgesic efficacy is the primary goal, important secondary goals include minimizing transfer of drugs to breast milk and reducing maternal side effects that may interfere with breastfeeding or infant care. Various combinations of opioids, nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen (paracetamol), and local anesthetics are among drugs that have been used with varying degrees of success.\textsuperscript{54–56} Several studies have demonstrated superior analgesia when oral analgesics are administered at a predetermined fixed interval rather than on demand.\textsuperscript{48,57}

**Acetaminophen**

Acetaminophen is used extensively for postoperative analgesia and provides an opioid-sparing effect of approximately 10% to 20%.\textsuperscript{58–60} A 2012 meta-analysis identified four randomized controlled trials evaluating acetaminophen and its effect on opioid consumption after major surgery; only one study included obstetric patients.\textsuperscript{61} The meta-analysis showed that acetaminophen was less effective than NSAIDs for decreasing opioid consumption and postoperative nausea and vomiting (PONV).\textsuperscript{62} A comparison of intravenous acetaminophen with oral ibuprofen in postcesarean patients found similar pain scores, opioid consumption, and patient satisfaction.\textsuperscript{62} The combination of NSAIDs and acetaminophen has been shown to be synergistic in human experimental pain studies.\textsuperscript{63–65}

In 2009, the U.S. Food and Drug Administration (FDA) lowered the recommended maximum daily dose of acetaminophen from 4000 mg to 3250 mg because of concern for toxicity.\textsuperscript{66} Avoiding opioid/acetaminophen combination medication is recommended to decrease unnecessary opioid use and avoid exceeding recommended maximum doses of...
acetaminophen. The change forced the replacement of combination oral opioid-acetaminophen analgesics with scheduled acetaminophen and as-needed opioids for postcesarean analgesia. Valentine et al. performed a retrospective medical record review of women who underwent cesarean delivery before and after a change in clinical practice at their institution. All patients in their study received spinal anesthesia containing intrathecal morphine 0.2 mg and scheduled NSAIDs for 48 h postoperatively. After the change, the women received oral acetaminophen 650 mg every 6 h for 48 h postoperatively with oral oxycodone administered as needed for breakthrough pain. The scheduled acetaminophen cohort used less opioid than the historical as-needed cohort in the first 48 hours (Fig. 27.2).

Intravenous acetaminophen has gained popularity, with earlier and higher plasma and cerebrospinal fluid levels compared with more slowly absorbed oral acetaminophen. However, in patients with a functioning gastrointestinal system, there is no documented analgesic advantage of intravenous versus oral administration.

**Nonsteroidal Antiinflammatory Drugs**

NSAIDs suppress inflammation by inhibition of the cyclooxygenase (COX) enzymes and are a key component of multimodal analgesia. They are effective for perineal pain after vaginal delivery and postcesarean abdominal pain; when co-administered with opioids, they produce a 30% to 50% opioid-sparing effect that can reduce opioid-related side effects. A 2016 systematic review and meta-analysis showed that the use of NSAIDs resulted in lower pain scores up to 24 hours postoperatively, less opioid consumption, and less sedation after cesarean delivery. Fixed-interval dosing of NSAIDs provides more effective analgesia and results in better patient satisfaction than on-demand dosing.

**Ibuprofen** is one of the most widely used NSAIDs that is available without prescription. Because it nonselectively inhibits COX-1 and COX-2 isoenzymes, in addition to its anti-inflammatory, analgesic, and antipyretic properties, ibuprofen also inhibits platelet adhesion and causes renal artery vasoconstriction and gastrointestinal irritation. Therefore, NSAID use in patients at risk for hemorrhage and renal failure warrants caution. Nonetheless, in most parturients without risk factors for hemorrhage or renal failure, use of NSAIDs is considered safe. Because of limited transfer to breast milk, NSAIDs are particularly beneficial for lactating mothers. In a small study (oral ibuprofen 400 mg every 6 hours for 24 hours), less than 1 mg of ibuprofen was excreted in breast milk in a 36-hour period. Many centers administer 600 to 800 mg every 6 to 8 hours as a standard dose. Ibuprofen is approved as a therapeutic drug for children and therefore is considered compatible with breast-feeding.

Oral naproxen 500 mg every 12 hours has been shown to reduce incisional pain compared with placebo and decrease opioid consumption (Fig. 27.3).

**Diclofenac** has also been extensively studied; rectal suppositories (100 mg twice a day) decreased morphine consumption (14 mg versus 22 mg in 32 hours) compared with placebo after cesarean delivery. A single rectal dose of diclofenac 100 mg prolonged the mean time to first analgesic administration by more than 5 hours in patients who received intrathecal morphine. Patients who received intrathecal morphine doses as small as 0.025 mg required no rescue analgesic when intramuscular diclofenac 75 mg was administered every 8 hours. Munishankar et al. randomized patients who received spinal anesthesia with bupivacaine and fentanyl to receive one of three analgesic modalities:

![Fig. 27.2](image1.png)  
*Fig. 27.2 Opioid use in milligram intravenous morphine equivalents after cesarean delivery in 24-hour increments in patients who received scheduled acetaminophen with as-needed opioid (dark bars) versus patients who received as-needed combination opioid-acetaminophen (light bars). Data are mean (bar) and standard deviation (whisker). *Significant difference between groups (*P* < .001). (Redrawn from Valentine AR, Carvalho B, Lazo TA, Riley ET. Sched-uled acetaminophen with as-needed opioids compared to as-needed acetaminophen plus opioids for post-cesarean pain management. *Int J Obstet Anesth.* 2015;24:210–216.)

![Fig. 27.3](image2.png)  
*Fig. 27.3 Effect of naproxen on requirement for oral codeine after cesarean delivery: oral codeine use in milligram equivalents (expressed as mean) over time by group. (From Angle PJ, Halbourn SH, Leighton BL, et al. A randomized controlled trial examining the effect of naproxen on analgesia during the second day after cesarean delivery. *Anesth Analg.* 2002;95:741–745.)
acetaminophen, diclofenac, or diclofenac and acetaminophen. Women who received both diclofenac and acetaminophen required less morphine than those who received acetaminophen alone (Fig. 27.4).78

Lowder et al.79 showed that ketorolac decreased pain scores at 2, 3, 4, 6, 12, and 24 hours after cesarean delivery and also decreased opioid consumption. Ketorolac previously had a “black box” warning that it was “contraindicated in nursing mothers,” but current recommendations are to use it with caution. The American Academy of Pediatrics (AAP) considers NSAIDs safe for nursing mothers.80 Use of NSAIDs in pregnant and breast-feeding women is discussed in detail in Chapter 14.

Cyclooxygenase-2-Selective Inhibitors

COX-2–selective inhibitors have a potential benefit compared with traditional nonselective NSAIDs in that they have minimal effects on platelet adhesion and thus are less likely to interfere with blood clot formation and contribute to hemorrhage. This category of NSAIDs has similar analgesic effectiveness and opioid dose-sparing to traditional NSAIDs in nonobstetric settings.81 However, in the setting of cesarean delivery, they do not appear to be as effective as NSAIDs.82,83 Additionally, concerns about the potential to increase the risk for cardiovascular and thrombotic events, combined with the baseline elevated risk for these events during pregnancy and postpartum, have prevented COX-2 inhibitors from playing a major role in postpartum analgesia. Celecoxib is the only widely available COX-2–selective inhibitor in the United States. The breast milk content of parecoxib and its primary active metabolite valdecoxib was very low, and neonatal neurologic and adaptive scores were normal, after a single 40-mg intravenous dose following cesarean delivery.84

Alpha2-Adrenergic Receptor Agonists

Alpha2-adrenergic receptor agonists have been used for the treatment of acute and chronic pain in nonobstetric patients.85 Intravenous dexmedetomidine has been used as an adjunct to opioids as a component of general anesthesia for cesarean delivery.86 Dexmedetomidine is excreted in breast milk in extremely small concentrations; the relative infant dose was 0.034%.87 Neuraxial clonidine has been used for labor analgesia but is not commonly used for postcesarean analgesia. The epidural formulation of clonidine carries a “black box” warning from the FDA because of the incidence of hypotension at higher intrathecal doses.88

Magnesium Sulfate

Peripartum magnesium sulfate therapy is used for tocolysis for preterm labor, seizure prophylaxis in women with pre eclampsia, and fetal neuroprotection in women at risk for preterm delivery.89 A 2013 meta-analysis of trials of intravenous magnesium for the treatment of acute postoperative pain after nonobstetric surgery performed with general anesthesia concluded that magnesium sulfate administration resulted in a small reduction in postoperative pain scores and a substantial reduction in opioid use, although the incidence of nausea and vomiting was not reduced.90 The use of intravenous magnesium as an adjunct to postcesarean analgesia has not been rigorously studied.

Gabapentin

Gabapentin is an anticonvulsant that has analgesic properties, particularly in the setting of neuropathic pain. It has been extensively studied in the management of chronic pain and for postoperative analgesia where it is associated with more rapid opioid cessation.91 However, its role in opioid-naïve patients after cesarean delivery is less clear. As part of a multimodal analgesic regimen in patients undergoing cesarean delivery, a preoperative dose of oral gabapentin 600 mg was associated with lower pain scores with movement and at rest; however, the incidence of sedation was greater in the gabapentin group than in the placebo group (19% versus 0%).92 In a follow-up study, two doses of gabapentin (300 mg and 600 mg) were compared with placebo in the hope of finding an efficacious dose associated with less sedation. Unfortunately, the trial failed to show efficacy in either gabapentin group.93 These results were confirmed by Monks et al.94 in a randomized trial comparing perioperative gabapentin (600 mg preoperatively followed by 200 mg every 8 hours for 2 days) with placebo when added to a multimodal postcesarean analgesic regimen. Gabapentin produced a clinically insignificant improvement in analgesia (difference in 100-mm visual analog scale pain score on movement −7 mm, 95% confidence interval [CI] −13 to 0; P = .047) after cesarean delivery but was associated with a higher incidence of sedation.

Gabapentin may play a role in postcesarean analgesia in patients with chronic pain and those with opioid tolerance.
Ketamine and Dextromethorphan

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has analgesic properties and may play a role in the treatment of acute postoperative pain and prevention or reversal of central sensitization. An evaluation of low-dose ketamine for postcesarean analgesia compared intravenous ketamine 0.15 mg/kg, intrathecal fentanyl 10 μg, and placebo. The study demonstrated prolonged duration of analgesia in both the fentanyl and ketamine groups compared with the placebo group (time to first analgesic request 145 minutes in the placebo group, 165 minutes in the fentanyl group, 199 minutes in the ketamine group). Ketamine was superior to fentanyl and placebo for reducing pain scores at 90 and 180 minutes, and reducing analgesic requirements in the first 24 hours, but not in the second 24 hours, after cesarean delivery. In a setting in which intrathecal opioids were not available, the administration of intravenous ketamine 0.15 mg/kg immediately following bupivacaine spinal anesthesia resulted in better postoperative analgesia and reduced analgesic requirements compared with saline-placebo. In contrast, in another study in which women undergoing cesarean delivery were randomized to receive intrathecal ketamine 10 mg or placebo shortly after delivery as part of a multimodal regimen of intrathecal morphine and regular NSAID administration, the authors were unable to demonstrate a difference in breakthrough pain, time to first analgesic request, or cumulative rescue analgesic requirements. However, pain scores were lower in the ketamine group 2 weeks after the surgery.

A 2015 systematic literature review and meta-analysis included seven studies of ketamine use during spinal anesthesia and five during general anesthesia. Intravenous ketamine in the setting of spinal anesthesia delayed the time to first opioid request and reduced pain after cesarean delivery with no differences in the incidence of nausea, vomiting, pruritus, and psychomimetic effects.

NEURAXIAL ANALGESIA

Efficacy and Benefits of Neuraxial Analgesia

Most cesarean deliveries in the developed world are performed with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural [CSE] techniques). This allows the administration of neuraxial drugs for postoperative analgesia.

Neuraxial opioid administration currently represents the “gold standard” for providing effective postcesarean analgesia. A 2010 systematic review found that a single dose of epidural morphine provides better analgesia than parenteral opioids after cesarean delivery. A meta-analysis of studies involving a broad population of patients undergoing a variety of surgical procedures confirmed that opioids delivered by either patient-controlled epidural analgesia (PCEA) or continuous epidural infusion (CEI) provide postoperative pain relief that is superior to that provided by intravenous PCA. Similar results have been reported in studies comparing intrathecal and epidural opioid administration with intravenous opioid PCA or intramuscular opioid administration after cesarean delivery (Fig. 27.5).

Neuraxial opioids also provide superior postcesarean analgesia compared with non-neuraxial regional techniques (e.g., transversus abdominis plane block), local wound infiltration, and oral analgesics (e.g., NSAIDs and opioids). Although neuraxial analgesia offers important benefits in optimizing postoperative analgesia, multimodal analgesic strategies augment the analgesic effect of neuraxial opioids.

Most commonly, neuraxial opioid analgesia serves as the central component of multimodal analgesia. Although analgesia is superior, some opioid-related side effects (e.g., pruritus) are more common after neuraxial opioid administration. Both higher and lower maternal satisfaction scores have been reported with neuraxial compared with systemic opioid analgesia. This variability in reported maternal satisfaction scores may be influenced by how patients judge analgesic quality against the presence and severity of side effects (e.g., pruritus, nausea and vomiting). Depending on individual priorities, women given a choice will choose lower intrathecal morphine if they wish...
to avoid side effects or choose higher doses if they wish to optimize postcesarean delivery analgesia.25 Neuraxial techniques may confer other benefits in addition to better postoperative analgesia, including increased functional ability, earlier ambulation, and earlier return of bowel function.114–118 Other potential benefits include a lower incidence of pulmonary infection and pulmonary embolism, fewer cardiovascular and coagulation disturbances, and a reduction in inflammatory and stress-induced responses to surgery.114–116 Although a wealth of data from clinical studies and meta-analyses have shown a reduction in postoperative pain, there is less consistent evidence linking neuraxial anesthesia with a reduction in postoperative morbidity and mortality.114,119

Surgical trauma and postoperative immobility are associated with an increased risk for postoperative deep vein thrombosis and pulmonary embolism. The incidence of obstetric thromboembolism has increased 72% during hospitalizations for childbirth between 1998 and 2009.120 Risk factors for thromboembolism, including obesity, advanced maternal age, and major medical comorbidities, are increasingly common in the obstetric population.121–123 In theory, early ambulation and avoidance of prolonged immobility may reduce the risk for postpartum deep vein thrombosis and pulmonary embolism. Effective postoperative analgesia can reduce pain on movement, thereby facilitating deep breathing, coughing, and early ambulation. These beneficial effects may lead to a reduction in the incidence of pulmonary complications (i.e., atelectasis, pneumonia) after cesarean delivery.

Neuraxial analgesic techniques may be particularly useful for reducing perioperative morbidity in high-risk obstetric patients. Women with severe preeclampsia, cardiovascular disease, and morbid obesity may benefit from the reduction in cardiovascular stress and improved pulmonary function associated with effective postcesarean analgesia.124,125 Investigators have found that CEI of a solution of opioid and dilute local anesthetic attenuates coagulation abnormalities, hemodynamic fluctuation, and stress hormone responses in nonpregnant patients.126–128 Some studies suggest that opioid-based PCEA may improve postoperative outcome.129–131 Patients treated with PCEA meperidine after cesarean delivery ambulated more quickly and experienced an earlier return of gastrointestinal function compared with similar patients who received intravenous meperidine PCA.129 However, continuous postoperative neuraxial analgesia techniques also have disadvantages, including reduced mobility because of infusion pumps, more complicated management of postoperative thromboprophylaxis, and increased nursing workload.132

**Neuraxial Opioids**

The discovery that opioid receptors are localized within discrete areas of the spinal cord (laminae I, II, and V of the dorsal horn) suggested that exogenous opioids could be administered into the neuraxis to produce antinociception. Opioids administered to superficial layers of the dorsal horn produce selective analgesia of prolonged duration without affecting motor function, sympathetic tone, or proprioception.133 In 1979, Wang et al.134 published the first report of intrathecal morphine administration in humans that was followed shortly thereafter by a report of intrathecal meperidine. Intrathecal morphine (0.5 to 1 mg) produced complete pain relief for 12 to 24 hours in six of eight patients suffering from intractable cancer pain, with no evidence of sedation, respiratory depression, or impairment of motor function.134 Subsequently, researchers and clinicians have validated the analgesic efficacy of neuraxial opioids.

**Central Nervous System Penetration**

Opioids administered epidurally must penetrate the dura, pia, and arachnoid membranes to reach the dorsal horn and activate the spinal opioid receptors. The arachnoid layer is the primary barrier to drug transfer into the spinal cord.135 Drug movement through this layer is passive and depends on the physicochemical properties of the opioid (see Chapter 13). Drugs penetrating this arachnoid layer must first move into a lipid bilayer membrane, then traverse the hydrophilic cell, and finally partition into other cell membranes before entering the cerebrospinal fluid (CSF). Opioids that are highly lipid soluble (e.g., sufentanil, fentanyl) can easily pass through the hydrophobic cell membrane. However, these drugs have difficulty crossing through the hydrophilic cellular fluid. In contrast, drugs that are less lipid soluble (e.g., morphine) have a greater challenge crossing the cell membrane, but can easily traverse the cell interior. Thus, opioid penetration of the arachnoid mater is dependent on the drug’s lipid solubility.136 Highly lipid-soluble drugs have poor CSF bioavailability because of (1) poor penetration through the arachnoid layer, (2) rapid absorption and sequestration by epidural fat, and (3) rapid uptake by epidural veins.

Some investigators have questioned the neuraxial specificity of lipophilic opioids given epidurally and have suggested that the primary analgesic effect occurs via vascular uptake, systemic absorption, and redistribution of the drug to supraspinal sites.137–142 Earlier studies suggested that parenteral fentanyl provides analgesia equivalent to that provided by epidural fentanyl,142,143 but more recent evidence suggests that epidural fentanyl provides analgesia via a spinal mechanism.144–146 Cohen et al.,147 comparing a continuous infusion of intravenous fentanyl with epidural fentanyl after cesarean delivery, reported improved analgesia and less supplemental analgesic consumption despite lower plasma fentanyl levels with epidural administration. The difference may relate to speed of administration. There is evidence that bolus administration of lipophilic opioids has both spinal and supraspinal effects.144–146,148 Sadurni et al.148 randomized 30 patients undergoing abdominal surgery to receive intraoperative analgesia with boluses of fentanyl administered by either the thoracic epidural or intravenous route; patients who received epidural fentanyl required lower intraoperative fentanyl doses compared with those who received it by the intravenous route, suggesting that epidural fentanyl has a spinal as well as supraspinal effect. Additionally, after the administration of an epidural bolus of sufentanil
50 µg in a dog model, CSF concentration of sufentanil was 140 times greater than that found in plasma, and the amount detected in cisternal CSF was only 5% of that measured in lumbar CSF. Intrathecal administration allows for a predominantly spinal location of action. Intrathecal administration of morphine has been observed after epidural administration, indicating a predominantly spinal location of action. Intrathecal administration allows for injection of the drug directly into the CSF. This is a more efficient method of delivering opioid to spinal cord receptors than epidural or parenteral administration. A bolus dose of intrathecal morphine 0.5 mg resulted in a CSF concentration higher than 10,000 ng/mL, with barely detectable plasma concentrations.

**Distribution and Movement of Opioids within the Central Nervous System**

The movement and distribution of opioids within the central nervous system (CNS) follows specific patterns. Movement in the spinal cord is such that lipophilic agents (e.g., fentanyl) are taken up by the white matter with much greater affinity than hydrophilic agents (e.g., morphine), and less drug will reach the gray matter of the dorsal horn. Within the epidural space (and subsequently epidural fat or veins), lipophilic agents are more likely to be absorbed and transported from the epidural space to the systemic circulation. Rostral spread in the CSF is determined by CSF drug bioavailability and the drug concentration gradient; hydrophilic opioids (e.g., morphine) are associated with more rostral spread.

Although opioid dose, volume of injectate, and degree of ionization are important variables, lipid solubility plays a key role in determining the onset of analgesia, the dermatomal spread, and the duration of activity (Table 27.4). Highly lipophilic opioids penetrate the spinal cord more rapidly and have a quicker onset of action than more water-soluble agents. The duration of activity is affected by the rate of clearance of the drug from the sites of action. Lipid-soluble opioids are rapidly absorbed from the epidural space, whereas hydrophilic agents remain in the CSF and spinal tissues for a longer time.

**Epidural Opioids**

The provision of cesarean delivery anesthesia using an epidural catheter (placed during labor or as part of a CSE technique) has prompted an extensive evaluation of epidural opioids to facilitate postoperative analgesia (Table 27.5).

### Morphine

Preservative-free morphine received FDA approval for neuraxial administration in 1984, and subsequently epidural morphine administration has been widely investigated and extensively used. Epidural administration of morphine provides postcesarean analgesia superior to that provided by intravenous or intramuscular morphine. A meta-analysis concluded that epidural morphine administration prolongs the time to first analgesic request, decreases pain scores, and reduces postoperative analgesic requests during the first 24 hours after cesarean delivery compared with systemic opioid administration. However, epidural morphine administration is associated with an increased risk for pruritus (relative risk [RR], 2.7; 95% CI, 2.1 to 3.6) and nausea (RR, 2.0; 95% CI, 1.2 to 3.3) compared with systemic opioid administration.

**Onset and duration.** After epidural administration, plasma morphine concentration is similar to that observed after intramuscular injection. Epidural morphine has a relatively

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**TABLE 27.4 Spinal Opioid Physiochemistry and Pharmacodynamics**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Molecular Weight</th>
<th>Lipid Solubility</th>
<th>Parenteral Potency</th>
<th>pKa</th>
<th>µ-Opioid Receptor Affinity</th>
<th>Dissociation Kinetics</th>
<th>Potency Gain (Epidural versus IV or SC)</th>
<th>Onset of Analgesia</th>
<th>Duration of Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>285</td>
<td>0.7</td>
<td>1</td>
<td>7.9</td>
<td>Moderate</td>
<td>Slow</td>
<td>10</td>
<td>Delayed</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Meperidine</td>
<td>247</td>
<td>39</td>
<td>0.1</td>
<td>8.5</td>
<td>Moderate</td>
<td>Moderate</td>
<td>2–3</td>
<td>Rapid</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Methadone</td>
<td>309</td>
<td>116</td>
<td>2</td>
<td>9.3</td>
<td>High</td>
<td>Slow</td>
<td>2–3</td>
<td>Rapid</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>285</td>
<td>1.28</td>
<td>10</td>
<td></td>
<td>High</td>
<td>Slow</td>
<td>5</td>
<td>Rapid</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>417</td>
<td>129</td>
<td>25</td>
<td>6.5</td>
<td>High</td>
<td>Very rapid</td>
<td>1–2</td>
<td>Very rapid</td>
<td>Short</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>336</td>
<td>717</td>
<td>80</td>
<td>8.4</td>
<td>High</td>
<td>Rapid</td>
<td>1–2</td>
<td>Very rapid</td>
<td>Short</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>386</td>
<td>2842</td>
<td>800</td>
<td>8.0</td>
<td>Very high</td>
<td>Moderate</td>
<td>1–1.5</td>
<td>Very rapid</td>
<td>Short</td>
</tr>
</tbody>
</table>

IV, Intravenous; SC, subcutaneous.

*octanol-water partition coefficient at pH 7.4.
TABLE 27.5  Epidural Opioids for Cesarean Delivery

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Dose</th>
<th>Onset (min)</th>
<th>Peak Effect (min)</th>
<th>Duration (h)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>2–4 mg</td>
<td>30–60</td>
<td>60–90</td>
<td>12–24</td>
<td>Long duration</td>
<td>Delayed onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Side-effect profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potential for delayed respiratory depression</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50–100 µg</td>
<td>5</td>
<td>20</td>
<td>2–3</td>
<td>Rapid onset</td>
<td>Short duration</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10–25 µg</td>
<td>5</td>
<td>15–20</td>
<td>2–4</td>
<td>Rapid onset</td>
<td>Short duration</td>
</tr>
<tr>
<td>Meperidine</td>
<td>25–50 mg</td>
<td>15</td>
<td>30</td>
<td>4–6</td>
<td>Rapid onset</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.4–1 mg</td>
<td>15</td>
<td>45–60</td>
<td>10–20</td>
<td>Intermediate onset and duration</td>
<td>Side-effect profile similar to that of morphine</td>
</tr>
<tr>
<td>Morphine/fentanyl</td>
<td>3 mg/50 µg</td>
<td>10</td>
<td>15</td>
<td>12–24</td>
<td>Rapid onset</td>
<td>Fewer side effects than morphine 5-mg dose</td>
</tr>
<tr>
<td>Morphine/sufentanil</td>
<td>3 mg/10 µg</td>
<td>5</td>
<td>15</td>
<td>12–24</td>
<td>Rapid onset</td>
<td>Fewer side effects than morphine 5-mg dose</td>
</tr>
</tbody>
</table>

The volume of the diluent does not appear to affect the pharmacokinetics or clinical activity of epidural morphine. The quality and duration of analgesia, the need for supplemental analgesics, and the incidence of side effects were similar when epidural morphine 4 mg was administered with 2, 10, and 20 mL of sterile saline.165

**Single-dose epidural regimens to optimize postcesarean analgesia and minimize opioid-related side effects.** In a prospective dose-response study, Palmer et al.164 observed that postcesarean analgesia (assessed by need for supplemental intravenous morphine by PCA) improved as the dose of epidural morphine increased from 0 to 3.75 mg. A further increase in dose (to 5 mg) did not significantly improve analgesia or reduce the amount of supplemental intravenous morphine used in the first 24 postoperative hours (Fig. 27.6).164 Chumpathong et al.161 did not observe any difference in pain relief, patient satisfaction, or side effects in women receiving epidural morphine 2.5 mg, 3 mg, or 4 mg for postcesarean analgesia. Rosen et al.162 found that epidural morphine 5 mg and 7.5 mg provided similar analgesic efficacy, but a 2-mg dose provided ineffective analgesia. Fuller et al.163 recommended epidural morphine 3 mg after a large retrospective study of epidural morphine in doses ranging from 2 to 5 mg for postcesarean analgesia.

In contemporary clinical practice, doses of epidural morphine 2 to 4 mg are most commonly used. Lower doses may not provide effective analgesia, and women may require additional supplemental analgesia,163,164 whereas higher doses may increase opioid-related side effects without improving analgesia. Singh et al.166 conducted a randomized, noninferiority trial in which all women received scheduled

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**Fig. 27.6** Random allocation dose-response trial of epidural morphine 0.0, 1.25, 2.5, 3.75, and 5.0 mg for postcesarean delivery analgesia. Breakthrough pain as assessed by total 24-hour patient-controlled analgesia (PCA) morphine use. Data are mean ± 95% confidence interval. Groups were significantly different \( (P < .001) \). *Group 0.0 mg was significantly different from groups 2.5, 3.75, and 5.0 mg. **Group 1.25 mg was significantly different from groups 3.75 and 5.0 mg. (From Palmer CM, Nogami WM, Van Maren G, Alves DM. Postcesarean epidural morphine: a dose-response study. Anesth Analg. 2000;90:887–891.)
ketroloac and acetaminophen as well as epidural morphine. Morphine 1.5 mg was noninferior to 3 mg for postcesarean delivery analgesia. They found no difference in 24-hour opioid consumption between the 1.5-mg and 3-mg epidural morphine groups.166 Thus, lower epidural morphine doses may be appropriate when multimodal analgesia is used and minimizing side effects is a priority.

**Epidural versus intrathecal administration.** A number of studies have compared the analgesic efficacy of epidural and intrathecal administration of opioids. Sarvela et al.167 compared epidural morphine 3 mg with intrathecal morphine 0.1 mg and 0.2 mg; the two routes of administration provided postcesarean analgesia with similar efficacy and equal duration. Duale et al.168 observed modest improvements in pain scores and lower morphine consumption with epidural morphine 2 mg than with intrathecal morphine 0.075 mg. In both studies, the incidence of side effects (e.g., sedation, pruritus, nausea and vomiting) was not different between the epidural and intrathecal routes.167,168 A meta-analysis concluded that both epidural and intrathecal techniques provide effective postcesarean analgesia; neither technique is superior in terms of analgesic efficacy.169 However, intrathecal administration results in less systemic drug exposure and less potential fetal drug exposure and has a faster onset of action than epidural administration of morphine. Profound sedation and respiratory depression requiring opioid reversal and intensive care monitoring has been reported after unintentional subdural or intrathecal administration of a dose intended for epidural administration.170 If a CSE anesthetic is planned, intrathecal administration of the opioid may be preferable.

**Fentanyl**

Fentanyl is not approved by the FDA for neuraxial administration, but it is very commonly administered for short-term analgesia. Commercial preparations of fentanyl contain no preservative, are suitable for epidural or intrathecal administration, and have an excellent safety record. Grass et al.171 reported that the 50% and 95% effective doses (ED50 and ED95, respectively) of epidural fentanyl to reduce postcesarean pain scores to less than 10 mm (using a 100-mm visual analog scale) were 33 µg and 92 µg, respectively. An epidural fentanyl dose of 1 µg/kg has also been suggested to optimize intraoperative analgesia.172 In clinical practice, doses of 50 to 100 µg are given alone or in combination with epidural morphine.

The slow onset of action of morphine limits its ability to provide optimal intraoperative analgesia, and more lipophilic opioids (e.g., fentanyl) with a faster onset of analgesia are more appropriate for supplementation of intraoperative anesthesia (see Table 27.4).173,174 Although single-dose epidural fentanyl improves intraoperative anesthesia, no meaningful postoperative pain relief occurs beyond 4 hours.174 Duration is variable and dose dependent.175,176 A dose-response study of epidural fentanyl 25, 50, 100, and 200 µg, administered at the time of first complaint of postoperative pain following epidural anesthesia (lidocaine with epinephrine), found that the duration of analgesia ranged from 1 to 2 hours.171 Local anesthetics may have a synergistic effect with epidurally administered opioids. The concurrent administration of local anesthetic reduces epidural fentanyl dose requirements after cesarean delivery.177 Epidural fentanyl, administered either as a single dose or as a continuous or patient-controlled infusion, generally has fewer side effects than epidural morphine.181,175,176 Some investigators have suggested that the administration of epidural fentanyl before incision may provide preemptive analgesia that improves postoperative analgesia.172

**Sufentanil**

Epidural sufentanil is a lipid-soluble opioid that provides a rapid onset of effective postcesarean analgesia. The potency ratio of epidural sufentanil to epidural fentanyl is approximately 5:1.171 No differences in onset, quality, or duration of analgesia were found after epidural administration of equivalent analgesic doses of sufentanil and fentanyl.171 Like fentanyl, epidural sufentanil does not provide postoperative analgesia of significant duration. Rosen et al.178 compared epidural morphine 5 mg with epidural sufentanil 30, 45, or 60 µg. Although most patients who received sufentanil reported pain relief within 15 minutes, the duration of analgesia was 4 to 5 hours, in contrast to 26 hours of analgesia with epidural morphine.175 The duration of analgesia is dose-dependent; an epidural bolus of sufentanil 25 µg produced less than 2 hours of analgesia, whereas 60 µg provided 5 hours of pain relief.171,178

**Meperidine**

Epidural meperidine has local anesthetic properties, and it has been used for postcesarean analgesia. Two clinical trials compared the safety and efficacy of epidural meperidine 50 mg and intramuscular meperidine 100 mg administered to patients after cesarean delivery.179,180 Epidural meperidine provided a faster onset of analgesia with a duration (2 to 4 hours) similar to that provided by intramuscular meperidine. Paech181 evaluated the quality of analgesia and side effects produced by a single epidural bolus of meperidine 50 mg or fentanyl 100 µg. The onset of pain relief was slightly faster with fentanyl; however, the duration of analgesia was longer with meperidine. Ngan Kee et al.182,183 compared different doses of epidural meperidine (12.5, 25, 50, 75, and 100 mg) as well as varying volumes of diluent. They concluded that meperidine 25 mg diluted in 5 mL of saline was superior to 12.5 mg and that doses greater than 50 mg offered no improvement in the quality or duration of analgesia. Studies that have compared a single bolus dose of epidural or intrathecal morphine with PCEA meperidine have reported superior analgesia with morphine, but with a higher incidence of opioid-related side effects such as nausea, pruritus, and sedation.184,185

**Other Epidural Opioids**

Hydromorphone is a hydroxylated derivative of morphine with a lipid solubility intermediate between that of morphine.
and meperidine.\textsuperscript{186} The quality of epidural hydromorphone analgesia after cesarean delivery appears to be similar to that observed with epidural morphine; however, its onset is faster and its duration shorter.\textsuperscript{187–189} Evidence suggests a potency ratio of 3:1 to 5:1 between epidural morphine and epidural hydromorphone.\textsuperscript{186} Chestnut et al.\textsuperscript{189} evaluated postcesarean analgesia with epidural hydromorphone 1 mg. Most patients reported good or excellent pain relief, and the mean time to first request for supplemental analgesia was 13 hours. Dougherty et al.\textsuperscript{187} reported that epidural hydromorphone 1.5 mg provided 18 hours of postcesarean analgesia and that the duration was prolonged to 24 hours with the addition of ephedrine. Henderson et al.\textsuperscript{188} observed 19 hours of postcesarean analgesia with epidural hydromorphone 1 mg. The incidence of pruritus was high in the two latter studies.\textsuperscript{187,188} Halpern et al.\textsuperscript{190} found no overall differences in quality of postcesarean analgesia or severity of side effects between patients who received epidural hydromorphone 0.6 mg or epidural morphine 3 mg. A meta-analysis suggested that epidural morphine and hydromorphone provide analgesia with similar efficacy and side effects when given for the treatment of acute or chronic pain.\textsuperscript{191}

**Diamorphine** (heroin) is a lipid-soluble diacetylated derivative of morphine that is commonly administered neuraxially in the United Kingdom.\textsuperscript{192} The lipid solubility of diamorphine provides rapid-onset analgesia, and its principal metabolite (morphine) facilitates prolonged duration of analgesia, although less than that of morphine. Roulston et al.\textsuperscript{193} found that epidural diamorphine 2.5 mg provided postcesarean analgesia for 16 hours. Other investigators have found a duration of postcesarean analgesia of 6 to 12 hours after epidural diamorphine 5 mg.\textsuperscript{194–196} In the United Kingdom, the National Institute for Health and Care Excellence (NICE) suggests a dose of epidural diamorphine of 2.5 to 5 mg for postcesarean analgesia.\textsuperscript{197}

**Epidural Opioid Combinations**

Theoretically, the epidural administration of a lipophilic opioid combined with morphine should provide analgesia of rapid onset and prolonged duration. The use of lipophilic opioids administered intrathecally (e.g., fentanyl 15 µg) or epidurally (e.g., fentanyl 100 µg) in combination with epidural morphine 3.5 mg improves intraoperative anesthesia and reduces nausea and vomiting during cesarean delivery.\textsuperscript{198,199} Some investigators have expressed concern that opioid interactions might reduce analgesic efficacy after epidural administration and that neuraxial fentanyl might initiate acute tolerance or affect the pharmacokinetic and receptor-binding characteristics of morphine. However, these concerns have not been confirmed in subsequent studies.\textsuperscript{199,200} Epidural fentanyl, administered immediately after delivery of the infant, improved the quality of intraoperative analgesia without worsening epidural morphine analgesia after cesarean delivery.\textsuperscript{199}

Studies of combined epidural morphine and sufentanil have produced mixed results. Dottrens et al.\textsuperscript{201} compared a single epidural dose of either morphine 4 mg, sufentanil 50 µg, or morphine 2 mg with sufentanil 25 µg. The addition of sufentanil to epidural morphine provided a more rapid onset and similar duration of postcesarean analgesia than morphine alone.\textsuperscript{201} In another study, morphine alone or in combination with sufentanil provided analgesia of longer duration than sufentanil alone. Sinatra et al.\textsuperscript{202} were unable to show any potentiation when epidural sufentanil 30 µg was added to morphine 3 mg, and the duration of this combination was shorter than that of epidural morphine 5 mg alone.

**Patient-Controlled Epidural Analgesia (PCEA)**

The use of continuous epidural analgesia is a popular means of providing postoperative analgesia in patients undergoing thoracic or upper abdominal surgery. Better analgesia at rest and with movement has been reported in reviews of studies that compared epidural analgesia with intravenous PCA after nonobstetric surgery.\textsuperscript{203–205} A systematic review of studies comparing PCEA, CEI, and intravenous PCA suggested that CEI provides better analgesia than PCA and PCEA in nonobstetric patients.\textsuperscript{104} However, marked heterogeneity among studies prevented definitive conclusions.

PCEA is less frequently used for analgesia after cesarean delivery compared with single-dose epidural morphine. Fanshawe\textsuperscript{203} compared PCEA meperidine with single-dose epidural morphine. Postoperative pain scores were better with epidural morphine at 6, 8, and 24 hours.\textsuperscript{206} However, lipophilic opioids have been widely evaluated for PCEA after cesarean delivery (Table 27.6) and can be used when requirement for long-lasting analgesia is anticipated.\textsuperscript{204,205} Epidural morphine’s prolonged latency and risk for delayed respiratory depression make it a less safe option for continuous epidural infusion. Previous investigations have compared meperidine PCEA with other routes of parenteral administration (PCA, intramuscular). Paech et al.\textsuperscript{206} performed a crossover study comparing PCEA with intravenous PCA meperidine after cesarean delivery; patients were randomly assigned to either PCEA or intravenous PCA for 12 hours before crossing over to the other route of drug administration for the next 12 hours. The PCEA and PCA meperidine protocols in this study were identical (20-mg bolus, 5-minute lockout). Patients receiving meperidine PCEA had lower pain scores at rest and with coughing than patients receiving intravenous PCA. Ngan Kee et al.\textsuperscript{21} observed that PCEA (fentanyl or meperidine) regimens were associated with lower pain scores compared with the respective PCA regimens. Goh et al.\textsuperscript{207} observed similar analgesic profiles among patients receiving fentanyl and meperidine PCEA, but noted more favorable side-effect profiles and better patient satisfaction among patients receiving meperidine PCEA.

Cooper et al.\textsuperscript{130} postulated that the combination of epidural fentanyl with local anesthetic (fentanyl 2 µg/mL with 0.05% bupivacaine) would provide better analgesia than that provided by a single-drug PCEA regimen (fentanyl 4 µg/mL or 0.1% bupivacaine). The combination drug regimen was associated with lower pain scores at rest and significantly lower total drug requirements. However, no significant differences in pain scores during coughing were reported among
### TABLE 27.6 Comparative Studies Investigating Opioid-Containing, Patient-Controlled Epidural Analgesia Regimens for Postcesarean Analgesia

<table>
<thead>
<tr>
<th>Comparison(s)</th>
<th>PCEA Dosing Regimen</th>
<th>Pain Scores</th>
<th>Mean Total 24-h Opioid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCEA versus Intramuscular Opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine PCEA versus meperidine IM (100 mg, q3–4 h) (^{29})</td>
<td>B = 10 mg LO = 20 min BI = 10 mg/h</td>
<td>PCEA group lower VAS score (3–24 h)</td>
<td>625 mg versus 485 mg (PCEA versus IM; (P &lt; .05))</td>
</tr>
<tr>
<td><strong>PCEA versus Epidural Opioid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine PCEA versus epidural morphine (\text{B} = 4 \text{mg})^{203}</td>
<td>B = 15 mg LO = 10 min No BI</td>
<td>VAS score lower at 2 h; higher at 8, 10, 24 h in PCEA group No differences in pain outcome measurements</td>
<td>PCEA = 192 mg (NA for epidural morphine) PCEA = 680 µg</td>
</tr>
<tr>
<td>Fentanyl PCEA versus epidural morphine (\text{B} = 3 \text{mg})^{204}</td>
<td>B = 50 µg LO = 5 min (max 100 µg/h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCEA versus PCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine PCEA versus meperidine PCA (\text{B} = 20 \text{mg}; \text{LO} = 5 \text{min})^{206}</td>
<td>B = 20 mg LO = 5 min No BI</td>
<td>PCEA lower VAS score (2–24 h)</td>
<td>NA</td>
</tr>
<tr>
<td>Meperidine PCEA versus PCA; fentanyl PCEA versus PCA (4 groups: cross-over study)^{31}</td>
<td>Meperidine PCEA/PCA: B = 20 mg LO = 6 min No BI Fentanyl PCEA/PCA: B = 40 µg LO = 6 min No BI</td>
<td>Meperidine PCEA versus PCA: lower VAS score Meperidine versus fentanyl: no difference in VAS score (PCEA and PCA)</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone PCEA versus PCA (\text{B} = 0.15 \text{mg}; \text{LO} = 10 \text{min})^{32}</td>
<td>Hydromorphone PCEA: Loading dose = 0.225–0.9 mg B = 0.15 mg LO = 30 min</td>
<td>No differences in pain VAS score</td>
<td>PCEA 1.8–2.1 mg versus PCA 7.6 mg</td>
</tr>
<tr>
<td><strong>PCEA versus PCEA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine PCEA versus fentanyl PCEA^{207}</td>
<td>Meperidine PCEA: B = 25 mg LO = 20 min No BI Fentanyl PCEA: B = 50 µg LO = 20 min</td>
<td>No differences in pain VAS score</td>
<td>NA</td>
</tr>
<tr>
<td>Three groups^{10}: Bupivacaine 0.1% PCEA Fentanyl PCEA 4 µg/mL Bupivacaine 0.1% + fentanyl PCEA 4 µg/mL</td>
<td>All PCEA regimens: B = 5 mL LO = 10 min</td>
<td>No differences in pain VAS score on coughing</td>
<td>NA</td>
</tr>
<tr>
<td>Four groups^{13}: Hydromorphone PCEA Hydromorphone PCEA + BI Hydromorphone + 0.08% bupivacaine PCEA Hydromorphone + 0.08% bupivacaine PCEA + combination BI</td>
<td>All PCEA regimens: B = 2 mL LO = 30 min Hydromorphone BI = 0.0375 mg/h Combination BI = hydromorphone 0.0375 mg/h + bupivacaine 0.04 mg/h</td>
<td>No differences in pain VAS score</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continued
found between the two treatment groups. In a follow-up study, these investigators assessed hydromorphone PCEA, with and without a background infusion, and hydromorphone combined with 0.08% bupivacaine, with and without a background infusion.²⁰⁹ No differences in pain scores, PCEA usage, or 24-hour PCEA requirements were noted, and the combination of hydromorphone-bupivacaine PCEA with a background infusion was associated with a greater degree of lower extremity numbness and weakness.

Cohen et al.²⁰⁶ compared fentanyl 2 μg/mL and sufentanil 0.8 μg/mL PCEA with 0.01% bupivacaine and epinephrine 0.5 μg/mL after cesarean delivery. Pain scores and side effects (nausea, pruritus, and sedation) were similar in the two groups; however, vomiting occurred more commonly in the sufentanil group. Vercauteren et al.²⁰⁹ compared sufentanil PCEA (bolus 5 μg, lockout 10 minutes) with an identical PCEA regimen accompanied by a background infusion of sufentanil 4 μg/h.²⁰⁹ Pain was lower at 6 hours in the group receiving PCEA with a background infusion, but no other differences in analgesia were reported between 6 and 24 hours. It is not surprising that the overall incidence and severity of sedation were higher in the background infusion group that received considerably more sufentanil.

Although CEI or PCEA can provide satisfactory postoperative analgesia, these techniques may diminish maternal satisfaction as a result of local anesthetic–induced motor block in lower limbs and the lack of physical independence from infusion devices in the postpartum period. They increase cost and potentially increase the risk for catheter-related complications (e.g., hematoma, infection) in comparison with single-dose administration of neuraxial morphine.¹⁰¹,¹²⁰ Neuraxial morphine may facilitate early discharge after elective cesarean deliveries, a strategy suggested by the NICE guidelines, which state that “women who are recovering well, are apyrexial and do not have complications following cesarean should be offered early discharge.”¹⁹⁷

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**TABLE 27.6 Comparative Studies Investigating Opioid-Containing, Patient-Controlled Epidural Analgesia Regimens for Postcesarean Analgesia—cont’d**

<table>
<thead>
<tr>
<th>Comparison(s)²⁰⁶:</th>
<th>PCEA Dosing Regimen</th>
<th>Pain Scores</th>
<th>Mean Total 24-h Opioid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four groups²⁰⁶:</td>
<td>All PCEA regimens:</td>
<td>Ropivacaine 0.025%</td>
<td>NA</td>
</tr>
<tr>
<td>Ropivacaine 0.025%</td>
<td>BI = 10 mL/h</td>
<td>group reported lower</td>
<td>VAS score</td>
</tr>
<tr>
<td>Ropivacaine 0.05%</td>
<td>B = 4 mL</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ropivacaine 0.1%</td>
<td>LO = 10 min</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ropivacaine 0.2%</td>
<td>BI = 16 mL/h</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>(All PCEA solutions contained fentanyl 3.0 μg/mL + epinephrine 0.5 μg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil PCEA 0.8 μg/mL versus fentanyl PCEA 2 μg/mL²⁰⁸</td>
<td>All PCEA regimens:</td>
<td>No differences in pain</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BI = 10 mL/h</td>
<td>VAS score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B = 3 mL</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LO = 15 min</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BI = 16 mL/h</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* B, Bolus; BI, background infusion; IM, intramuscular injection; LO, lockout interval; NA, data not available; PCEA, intravenous patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; VAS, visual analog scale.
* Superscript numbers indicate chapter references.
* Both groups received 0.01% bupivacaine + epinephrine 0.5 μg/mL.

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**Fig. 27.7** Randomized trial of postcesarean delivery patient-controlled epidural analgesia (PCEA) with fentanyl 4 μg/mL, 0.1% bupivacaine, or both fentanyl 2 μg/mL and 0.05% bupivacaine. Pain scores during coughing on a 100-mm visual analog scale. Median score (bars) and interquartile range (whiskers) for groups who received epidural bupivacaine (dark blue bars), fentanyl (medium blue bars), and bupivacaine plus fentanyl (light blue bars). There were no differences in scores among the three groups. (From Cooper DW, Ryall DM, McHardy FE, et al. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. *Br J Anaesth.* 1996;76:611–615.)
Extended-Release Epidural Morphine

Extended-release epidural morphine (EREM) is an FDA-approved drug that delivers standard morphine sulfate via DepoFoam (Pacira Pharmaceuticals, Inc., San Diego, CA). DepoFoam is a drug-delivery system composed of multivesicular lipid particles containing nonconcentric aqueous chambers that encapsulate the active drug. These naturally occurring lipids are broken down by erosion and reorganization, resulting in a sustained release of morphine for up to 48 hours after epidural administration of a single dose.212,214

After treatment with EREM, lower pain scores and lower requirement for supplemental analgesia over 48 hours were reported compared with standard epidural morphine.160,215 Supplemental analgesia consumption was reduced by 60% in women who received a single dose of EREM 10 mg compared with standard epidural morphine 4 mg after cesarean delivery.160 However, caution is required as pooled data from EREM studies for nonobstetric surgery suggest that EREM is associated with more opioid-related side effects, especially with higher doses, including a significantly higher risk for respiratory depression compared with intravenous opioid PCA (odds ratio [OR], 5.8; 95% CI, 1.1 to 31.9; \( P = .04 \)).212,216,217

Use of EREM requires extended monitoring for respiratory depression (48 hours compared with 24 hours with standard epidural morphine).216 Unintentional intrathecal EREM administration has the potential to result in profound and prolonged opioid-related side effects, although a case report of unintentional intrathecal administration of a standard dose of EREM did not result in significant side effects or respiratory depression.219

Caution should be exercised when the administration of EREM follows the use of any epidural local anesthetic. A 2011 study found that epidural lidocaine administration (20 to 35 mL) for cesarean delivery, administered 1 hour before EREM administration, increased peak venous blood morphine levels and increased the incidence of vomiting, use of supplemental oxygen, and hypotension, compared with a control group that did not receive epidural lidocaine.228 However, Gambling et al.221 demonstrated no differences in the pharmacokinetic and pharmacodynamic profiles of EREM when administered 15, 30, and 60 minutes after epidural bupivacaine 0.25%. Any analgesic advantage must be weighed against the potential risk for serious side effects associated with EREM administration. The role of EREM for postcesarean analgesia remains unclear.

Intrathecal Opioids

Spinal anesthesia has become the preferred anesthetic technique for patients undergoing elective cesarean delivery in the United States and the United Kingdom.100-102 Intrathecal opioids are commonly administered with a local anesthetic to improve intraoperative anesthesia and postoperative analgesia (Table 27.7).

Morphine

The potency differences between intrathecal and epidural opioids account for the smaller doses of intrathecal opioid used for cesarean delivery. Intrathecal morphine 0.075 to 0.2 mg is equivalent to epidural morphine 2 to 3 mg.167,168 The analgesic efficacy, duration of action, and side-effect profile of intrathecal morphine are similar to that of epidural morphine (see earlier discussion).167,168,222

**Onset and duration.** Intrathecal morphine administration may result in a faster onset of analgesia than epidural morphine, but 60 to 90 minutes are still required for the drug to achieve a peak effect. The duration of analgesia is similar to the duration after epidural administration (14 to 36 hours).4 A systematic review and meta-analysis found that the median time to first analgesic request after cesarean delivery was 27 hours (range, 11 to 29 hours) after intrathecal morphine administration.113 The duration of analgesia is dose-dependent.113,223,226 A 2016 meta-analysis comparing low-dose (0.05 to 0.1 mg) and high-dose (>0.1 to 0.25 mg) intrathecal morphine found mean time to first analgesic request was longer (mean difference, 4.5 hours; 95% CI, 1.8 to 7.1; \( P = .0008 \)) for the high-dose group compared with the low-dose group.226

**Dose.** Several studies have attempted to determine the optimal dose of intrathecal morphine for postcesarean analgesia. Palmer et al.227 compared postcesarean intravenous PCA morphine use after doses of intrathecal morphine ranging from 0.025 to 0.5 mg. The investigators found no

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**TABLE 27.7** Intrathecal Opioids for Cesarean Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset (min)</th>
<th>Peak Effect (min)</th>
<th>Duration (h)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.05–0.2 mg (50–200 µg)</td>
<td>30–60</td>
<td>60–90</td>
<td>14–36</td>
<td>Long duration</td>
<td>Side-effect profile Potential for delayed respiratory depression</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10–25 µg</td>
<td>5</td>
<td>10</td>
<td>2–3</td>
<td>Rapid onset</td>
<td>Minimal postoperative analgesia Short duration Pruritus</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2.5–5 µg</td>
<td>5</td>
<td>10</td>
<td>2–4</td>
<td>Rapid onset</td>
<td>Minimal postoperative analgesia Short duration Pruritus</td>
</tr>
<tr>
<td>Meperidine</td>
<td>10 mg</td>
<td>10–15</td>
<td>15–20</td>
<td>4–5</td>
<td>Rapid onset</td>
<td>Minimal postoperative analgesia Nausea and vomiting</td>
</tr>
</tbody>
</table>
significant difference in PCA morphine use with morphine doses greater than 0.075 mg.227 They concluded that there was little justification for using a dose of intrathecal morphine higher than 0.1 mg. Milner et al.228 noted that intrathecal morphine 0.1 mg and 0.2 mg produced comparable analgesia but that the lower dose led to less nausea and vomiting. Yang et al.229 found that intrathecal morphine 0.1 mg provided similar postcesarean analgesia with fewer side effects in comparison with 0.25 mg. Uchiyama et al.230 performed a dose-response study with intrathecal morphine 0, 0.05, 0.1, and 0.2 mg. They observed that 0.1 mg and 0.2 mg provided comparable and effective postcesarean analgesia for 28 hours. The 0.05-mg dose was less effective, and the incidence of side effects was greater with the 0.2-mg dose; therefore, the investigators concluded that intrathecal morphine 0.1 mg is the optimal dose for postcesarean analgesia.230 Berger et al.231 compared 0.05, 0.1, and 0.15 mg of intrathecal morphine in women who received multimodal analgesia with intravenous ketorolac; all doses provided similar analgesia after cesarean delivery. There were no differences in 24-hour morphine consumption or reported pain or nausea scores, but pruritus scores were lower at 6 and 12 hours in the 0.05-mg group. A retrospective study reported that intrathecal morphine 0.2 mg provided better analgesia than 0.1 mg but with the “trade-off” of increased nausea.232 Girgin et al.233 reported no differences in analgesia with intrathecal morphine doses ranging from 0.1 to 0.4 mg; however, pruritus was increased with higher morphine doses.

Sultan et al.226 completed a meta-analysis to determine whether low-dose (0.05 to 0.1 mg) intrathecal morphine provides comparable duration and quality of analgesia with fewer side effects than a high-dose (greater than 0.1 to 0.25 mg). Pain scores at 12 hours and morphine consumption at 24 hours were not significantly different, but duration of analgesia was longer with the higher doses. The incidence of opioid-related side effects, including nausea or vomiting (OR 0.4; 95% CI, 0.3 to 0.7)) and pruritus (OR 0.3; 95% CI, 0.2 to 0.6) were lower in the low-dose group.226 Thus, there is a trade-off with incidence of side effects and duration of analgesia.

Studies have compared the analgesic efficacy and side-effect profile of intrathecal morphine with those of PCEA after cesarean delivery. Intrathecal morphine 0.15 mg compared with PCEA with 0.06% bupivacaine and sufentanil 1 µg/mL provided superior analgesia and fewer side effects.210 Paech et al.215 compared intrathecal morphine 0.2 mg with PCEA meperidine for postcesarean analgesia. Patients in the morphine group reported lower pain scores offset by a higher incidence of pruritus, nausea, and drowsiness. In another study in which intrathecal morphine (0, 0.05, and 0.1 mg) was combined with CEI (0.2% ropivacaine at 6 mL/h), inclusion of intrathecal morphine improved postcesarean analgesia compared with placebo.234

In summary, the intrathecal administration of a small dose of morphine (0.05 to 0.2 mg) provides effective analgesia for 14 to 36 hours after cesarean delivery. Higher doses (greater than 0.1 mg) may slightly increase the duration of analgesia but are associated with increasing side effects and limited improvement in analgesic quality in the average patient. Because of the variability in patient response to intrathecal morphine, some patients treated with low doses may experience inadequate postoperative analgesia and/or opioid-related side effects. Thus, the use of low-dose intrathecal morphine as a component of multimodal analgesia may provide optimal analgesia with a low risk for side effects.

The relationship between patients’ expectations for pain after a cesarean delivery and their analgesic needs requires more study. Carvalho et al.235 investigated the relationship between patients’ choice for their dose of intrathecal morphine and postcesarean pain scores and opioid use. Patients were randomly assigned to a choice of 0.1 or 0.2 mg of intrathecal morphine or no choice. Women assigned a choice were read a standardized script that discussed the trade-off of pain relief with increased risk for the most common intrathecal morphine side effects (nausea, vomiting, and pruritus).25 Participants who requested the larger dose of intrathecal morphine required more supplemental opioids and reported more pain with movement regardless of the intrathecal morphine dose they actually received.25 Thus, patients may correctly anticipate a greater postoperative opioid need. Using a higher dose of intrathecal morphine in patients predicted to be at risk for high acute postpartum pain after cesarean delivery may result in less acute postoperative pain.25,235 Shared decision-making, involvement of both the patient and her anesthesia provider in a sharing of information to build a consensus about preferred dose, and reaching an agreement about which dose to use may result in improved analgesia.236

**Fentanyl**

Intrathecal fentanyl improves intraoperative anesthesia (especially during uterine exteriorization), reduces intraoperative nausea and vomiting, decreases local anesthetic dose requirement, and provides a better postoperative transition to other pain medications during recovery from spinal anesthesia for cesarean delivery.237–240 However, intrathecal fentanyl provides a limited duration of postoperative analgesia, with a median time to first request for additional analgesia of 4 hours (range, 2 to 13 hours).113 A study that compared intrathecal morphine 0.1 mg with fentanyl 25 µg found that morphine provided better and longer postoperative analgesia after cesarean delivery.241

The analgesic effects, duration of analgesia, and side effects after intrathecal fentanyl are dose-related.113,237,238 Belzarena237 found that intrathecal fentanyl provided analgesia for a duration of 305 to 787 minutes (with 0.25 µg/kg and 0.75 µg/kg, respectively). However, patients who received the higher dose experienced decreased respiratory rate and a high incidence of side effects (e.g., pruritus, nausea). Dahlgren et al.238 reported that intrathecal fentanyl 10 µg added to bupivacaine increased the mean time of effective analgesia from 121 minutes to 181 minutes. Similarly, Wilwerth et al.242 added intrathecal fentanyl 25 µg to bupivacaine and intrathecal morphine with a resultant median duration of analgesia of
187 minutes (interquartile range [IQR], 151 to 230 minutes). Hunt et al. compared a range of intrathecal fentanyl doses (2.5 to 50 µg) in combination with intrathecal bupivacaine for cesarean delivery. Intrathecal fentanyl doses larger than 6.25 µg were associated with better intraoperative anesthesia and a longer time to first request for additional analgesia than administration of bupivacaine alone (72 minutes versus 192 minutes, respectively). Chu et al. found that fentanyl doses of 12.5 to 15 µg were required to increase the duration of effective analgesia.

In summary, intrathecal fentanyl optimizes intraoperative anesthesia and provides immediate postoperative analgesia. However, intrathecal fentanyl (10 to 25 µg) provides a limited duration of postcesarean analgesia (2 to 4 hours) and does not decrease subsequent postoperative analgesic requirements.

**Sufentanil**

Sufentanil has a fast onset of action, which may improve intraoperative anesthesia and reduce the dose of local anesthetic required for cesarean anesthesia. However, its pharmacokinetic properties limit the duration of effective postoperative analgesia after intrathecal administration. Courtney et al. found that intrathecal sufentanil 10, 15, or 20 µg resulted in a mean duration of postcesarean analgesia of approximately 3 hours. More than 90% of patients reported pruritus, but only one patient required treatment. Dahlgren et al. compared the safety and efficacy of the co-administration of sufentanil 2.5 or 5 µg, fentanyl 10 µg, or placebo with hyperbaric bupivacaine 12.5 mg for cesarean delivery. The duration of effective analgesia was longer with inclusion of the opioids, particularly in the sufentanil groups; sufentanil 5 µg provided the longest duration of analgesia but also had the highest incidence of pruritus. Patients receiving intrathecal sufentanil had lower requirements for intraoperative antiemetics and postoperative intravenous morphine rescue. Intrathecal sufentanil 7.5 µg did not provide more effective postoperative analgesia than that observed in the 5-µg group, and the incidence of pruritus was higher. Karaman et al. found that intrathecal sufentanil 5 µg delayed the time to first analgesic request to 6 hours, compared with 20 hours for intrathecal morphine 0.2 mg. A study that compared intrathecal fentanyl 20 µg and sufentanil 2.5 µg added to bupivacaine for cesarean delivery found no difference in the quality of intraoperative and postoperative analgesia, as well as no difference in the frequency of nausea and pruritus between the two opioid groups. Wilwerth et al. added intrathecal fentanyl 25 µg, sufentanil 2.5 µg, or sufentanil 5 µg to hyperbaric bupivacaine 10 mg. Effective analgesia was defined as time from spinal injection to first intravenous morphine administered. Duration of analgesia was longer with sufentanil 2.5 µg (214 minutes) and 5 µg (236 minutes) compared with fentanyl 25 µg (187 minutes). The incidence of pruritus and PONV was similar among groups. In summary, intrathecal sufentanil, similar to fentanyl, enhances intraoperative anesthesia but has limited postoperative analgesia. It has a ceiling dose of 5 µg, and the likelihood of pruritus increases with higher doses.

**Other Intrathecal Opioids**

Intrathecal meperidine reduces the intensity of pain associated with the regression of spinal anesthesia and provides postoperative analgesia of intermediate duration (4 to 5 hours). Yu et al. found that the addition of meperidine 10 mg to hyperbaric bupivacaine 10 mg prolonged the mean duration of postcesarean analgesia (234 minutes in the meperidine group versus 125 minutes in the placebo group). However, the incidence of intraoperative nausea and vomiting was greater in the meperidine group. A dose of 7.5 mg added to bupivacaine 10 mg also prolonged postoperative analgesia for 257 ± 112 minutes (mean ± SD) compared with a saline group (161 ± 65 min).

Unlike other opioids, meperidine possesses local anesthetic qualities in addition to µ-opioid receptor agonism. Some anesthesia providers have administered a higher intrathecal meperidine dose (1 mg/kg) as the sole anesthetic agent for cesarean delivery under spinal anesthesia. However, surgical anesthesia was unreliable, with a short mean (± SD) anesthetic duration of 41 ± 15 minutes.

Diamorphine has physicochemical properties that are of value in providing intrathecal analgesia as well as epidural analgesia. A high lipophilicity (octanol-water coefficient, 280) results in a rapid onset of analgesia, and diamorphine’s active metabolite (morphine) provides prolonged duration of analgesia. The more rapid onset of diamorphine is an advantage in the provision of intraoperative as well as postoperative analgesia. Saravanan et al. concluded that the ED₅₀ for intrathecal diamorphine to prevent intraoperative discomfort was 0.4 mg when combined with hyperbaric bupivacaine 12.5 mg.

Kelly et al. compared intrathecal diamorphine 0.125, 0.25, and 0.375 mg for postcesarean analgesia. The 0.25-mg and 0.375-mg doses provided effective analgesia; the incidence of both vomiting and pruritus was dose related. Stacey et al. reported that the duration of analgesia was dose-dependent and found that intrathecal diamorphine 1 mg provided 10 hours of postcesarean analgesia, compared with 7 hours for 0.5 mg. A dose-response study using intrathecal diamorphine 0.1, 0.2, or 0.3 mg reported a dose-dependent enhancement of analgesia and an increase in pruritus. Husaini and Russell observed that intrathecal diamorphine 0.2 mg and intrathecal morphine 0.2 mg provided similar postcesarean analgesia as assessed by rescue postoperative intravenous PCA morphine requirements. However, the patients who received intrathecal morphine had a higher incidence of pruritus and drowsiness. Hallworth et al. reported that intrathecal diamorphine 0.25 mg produced the same duration and quality of postcesarean analgesia as epidural diamorphine 5 mg, with less nausea and vomiting.

Diamorphine is commonly used in the United Kingdom, but it is not available for clinical use in the United States and Canada. In the United Kingdom, the NICE suggests an intrathecal diamorphine dose of 0.3 to 0.4 mg for postcesarean analgesia.

Intrathecal hydromorphone has been used to provide analgesia following cesarean delivery as an alternative to...
morphine. The use of intrathecal hydromorphone has increased with shortages of intrathecal morphine in the United States. Two retrospective studies found an analgesic advantage in favor of intrathecal morphine. Marroquin et al. \(^{261}\) retrospectively compared intrathecal morphine 0.2 mg or epidural morphine 3 mg with intrathecal hydromorphone 60 µg or epidural hydromorphone 0.6 mg. Time to first opioid request was 17 to 21 hours with neuraxial morphine compared with 13 to 15 hours for neuraxial hydromorphone. \(^{261}\) Beatty et al. \(^{262}\) compared intrathecal morphine 0.1 mg with intrathecal hydromorphone 40 µg and found 24-hour supplemental opioid use favored intrathecal morphine (8 mg versus 33 mg). The side effects of intrathecal morphine and hydromorphone are similar. \(^{261,262}\)

The optimal intrathecal hydromorphone dose has not been fully elucidated. Using an up-down sequential allocation method, Lynde\(^{263}\) estimated that the ED\(_{50}\) of intrathecal hydromorphone was 4.6 µg. In a dose-response study, Sviggum et al. \(^{264}\) randomized 80 participants to intrathecal morphine or intrathecal hydromorphone using a biased-coin, up-down sequential allocation method to assign dose. The effective dose (ED\(_{50}\)) for achieving a numeric pain score (0 to 10 scale) less than or equal to 3 for a duration of 12 hours was 75 µg for intrathecal hydromorphone compared with 150 µg for intrathecal morphine. \(^{261}\) Further research will need to help refine the optimal dose of intrathecal hydromorphone for postcesarean analgesia.

**Intrathecal Opioid Combinations**

Intrathecal administration of morphine in combination with a lipophilic opioid (e.g., fentanyl, sufentanil) may offer some advantages, similar to their combination in the epidural space. Intrathecal morphine has a delayed onset; therefore, the co-administration of lipophilic opioids may serve to improve intraoperative anesthesia and reduce the intensity of pain associated with the regression of spinal anesthesia in the postanesthesia care unit. Chung et al. \(^{265}\) found that the combination of intrathecal meperidine 10 mg and morphine 0.15 mg provided better intraoperative analgesia, less need for supplemental analgesia, and greater satisfaction than intrathecal morphine alone following cesarean delivery. Intrathecal sufentanil 5 µg co-administered with morphine 0.15 mg provided better and longer pain relief than intrathecal sufentanil plus a single injection of subcutaneous morphine; however, a higher incidence of side effects, such as nausea and vomiting, was observed with intrathecal morphine. \(^{266}\)

Some investigators have suggested that intrathecal morphine may be less effective when concurrently administered with intrathecal fentanyl, suggesting acute spinal opioid tolerance. \(^{267}\) This claim is controversial, and study results are inconsistent. Cooper et al. \(^{267}\) reported that patients who received intrathecal fentanyl 25 µg with bupivacaine had higher postoperative intravenous morphine PCA requirements than patients who received bupivacaine alone. By contrast, Sibilla et al. \(^{267}\) found that the intrathecal combination of fentanyl 25 µg and morphine 0.1 mg provided similar postoperative analgesia to that provided by intrathecal morphine alone. Carvalho et al. \(^{268}\) found no difference in postoperative analgesia requirements but small increases in postoperative pain scores with the addition of increasing doses of intrathecal fentanyl (5, 10, or 25 µg) to intrathecal morphine 0.2 mg for cesarean delivery. The authors suggested that intrathecal fentanyl may induce subtle acute tolerance to intrathecal morphine. The clinical significance of this finding is unclear, however, especially because of widespread evidence that intrathecal lipid-soluble opioids decrease the incidence of *intraoperative* visceral pain and nausea. Many anesthesia providers currently administer both intrathecal morphine and fentanyl with a local anesthetic for spinal anesthesia for cesarean delivery (see Chapter 26). \(^{101}\) The co-administration of intrathecal fentanyl does *not* appear to significantly compromise the postoperative analgesia provided by intrathecal morphine.

Despite the administration of neuraxial opioid analgesia, the quality and duration of analgesia after cesarean delivery is often incomplete. Thus, neuraxial opioid analgesia is rarely the sole analgesic technique used for postcesarean analgesia. Rather, neuraxial opioids should be considered as part of a multimodal analgesic approach for the treatment of postcesarean pain. \(^{104,106,118}\)

**Side Effects of Neuraxial Opioids**

Careful evaluation of the potential adverse effects of neuraxial pharmacologic agents is important before making the decision to administer these drugs. In obstetric patients, adverse maternal effects as well as potential neonatal effects should be considered.

**Maternal Safety**

Neurotoxicity (safety) studies suggest that morphine, fentanyl, sufentanil, hydromorphone, meperidine, clonidine, and neostigmine are safe for neuraxial administration. \(^{269-272}\) Morphine and clonidine are approved by the FDA for neuraxial administration. Although unlicensed for neuraxial administration, fentanyl and sufentanil have been used for many years without evidence of neurotoxicity. Studies in sheep have reported potential neurotoxicity with intrathecal butorphanol. \(^{273}\) Culebras et al. \(^{274}\) reported potential toxic interactions with the co-administration of nalbuphine and local anesthetic. However, Rawal et al. \(^{273}\) evaluated the behavioral and histopathologic effects of butorphanol, sufentanil, and nalbuphine after intrathecal administration in sheep and found that nalbuphine caused the least evidence of neural tissue damage.

Clinicians should avoid neuraxial administration of any agent before adequate evaluation for potential neurotoxicity has been completed. \(^{275-277}\) Drugs and diluents that are proven safe for parenteral use may have adverse effects when administered intrathecally. Despite these valid concerns, a number of opioid analgesics, including fentanyl and sufentanil, have been administered intrathecally to healthy obstetric patients without prior adequate investigation of their safety profile in animal and clinical volunteer studies. \(^{277}\)
Preservatives added to many commercial preparations may be hazardous if administered to the neuraxis. Examples are sodium (meta)bisulfite and disodium ethylenediaminetetraacetic acid (EDTA), which are known to incite inflammatory and fibrotic changes in pia-arachnoid and spinal tissue after intrathecal administration. Deoxycorticosterone has been shown to cause neuropathologic changes in the dog spinal cord. Similarly, glycinic, a neurotransmitter, is added as a preservative to remifentanil preparations and is specifically contraindicated for neuraxial injection.

Neonatal Effects
All opioids have the potential for placental transfer and neonatal effects. Minimal neonatal effects have been found after the administration of epidural morphine 2 to 7.5 mg for cesarean delivery. This is not surprising given the slow increase in plasma concentration after epidural administration and active transport of morphine out of the blood brain barrier and placenta by P-glycoproteins. Some clinicians prefer to administer neuraxial opioids after umbilical cord clamping to avoid placental transfer, although it is minimal. Lipophilic opioids are associated with faster systemic uptake; if indicated (e.g., for treatment of intraoperative pain before delivery), the smallest necessary dose should be administered. Courtney et al. found that intrathecal sufentanil (10, 15, or 20 μg) did not affect neonatal outcome as assessed by umbilical cord blood gas measurements and Apgar and neurobehavioral scores. Smaller doses of intrathecal opioids are associated with less neonatal drug transfer than epidural or intravenous opioid administration.

Respiratory Depression
Neuraxial opioids can depress the respiratory center in the brainstem via direct and/or indirect mechanisms. Respiratory depression after neuraxial morphine administration is biphasic. Early respiratory depression can occur 30 to 90 minutes after epidural morphine administration owing to systemic vascular absorption from the epidural space, whereas delayed respiratory depression can occur 6 to 18 hours after epidural or intrathecal morphine administration owing to rostral spread in CSF and slow penetration into the brainstem. In contrast, lipophilic opioids do not cause delayed respiratory depression but may cause early respiratory depression, typically within 30 minutes, because of vascular uptake and rostral spread in CSF and, potentially, direct transit in epidural veins.

Although rare, perioperative opioid–induced respiratory depression can lead to death or permanent brain damage. The incidence of respiratory depression after neuraxial morphine administration in obstetric patients is very low, with reported ranges from 0% to 0.9%. The Serious Complication Repository (SCORE) project of the Society for Obstetric Anesthesia and Perinatology (SOAP) systematically tracked complications related to obstetric anesthesia between 2004 and 2009. Among 90,795 reported cases of neuraxial anesthesia for cesarean delivery, no cases of respiratory arrest secondary to neuraxial opioid administration were reported.

No studies in the obstetric setting have reported serious morbidity, although some patients have required naloxone administration for treatment of respiratory depression. Early reports suggested that intrathecal morphine was more likely to cause delayed respiratory depression than epidural morphine. However, this likely reflected the relatively high intrathecal morphine doses (1 to 10 mg) used in early clinical studies. Subsequently, lower doses of intrathecal morphine have been found to provide effective analgesia with a low risk for clinically significant respiratory depression. No maternal deaths attributable to maternal neuraxial opioid administration were reported in the 2013-2015 Confidential Enquiries report from the United Kingdom. In a retrospective study of 5036 postpartum women who received low-dose neuraxial morphine for cesarean delivery, no instances of respiratory depression were identified (defined as clinically relevant episodes of respiratory depression requiring naloxone administration or a rapid-response team call). Thus, clinicians have concluded that the analgesic benefits derived from neuraxial opioids outweigh the risks associated with respiratory depression in most patients. The incidence of respiratory depression associated with systemic (intravenous or intramuscular) opioids is likely to be equivalent or higher than that observed with neuraxial opioids.

There are very few case reports of respiratory depression after neuraxial administration of a lipophilic agent in the obstetric setting. In one report, respiratory depression occurred 25 minutes after spinal anesthesia with intrathecal fentanyl 15 μg and required reversal with naloxone. Respiratory depression has been described after administration of epidural fentanyl 90 to 100 μg for cesarean delivery. Cohen et al. reported that epidural sufentanil 30 to 50 μg depressed the ventilatory response to CO₂ after cesarean delivery. Although overt respiratory depression did not occur, the highest sedation scores and depression of CO₂ response occurred 45 minutes after administration. Another group reported that epidural fentanyl 100 μg or sufentanil 10 to 50 μg added to lidocaine for cesarean delivery caused significant changes in respiratory rate and end-tidal CO₂ but no adverse clinical events.

Historically, respiratory depression was more common because patients received greater doses of neuraxial opioid than those currently used in modern practice. For cesarean delivery, neuraxial morphine appears to have a limit or “ceiling” in analgesic efficacy. More specifically, effective doses of intrathecal and epidural morphine are 0.075 to 0.2 mg and 2 to 4 mg, respectively, in opioid-naïve patients. Sultan et al. performed a systematic review of studies of low-dose compared with high-dose intrathecal morphine administered for postoperative analgesia following elective cesarean delivery; there were no reported episodes of respiratory depression. Thus, avoiding high doses of neuraxial morphine may improve safety without compromising analgesia.

Monitoring and Detection of Respiratory Depression
Guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid
administration have been published by the American Society of Anesthesiologists (ASA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA). These guidelines do not specifically address obstetric patients and are likely overly prescriptive given the low risk for clinically significant neuraxial opioid–induced respiratory depression with conventional dosing in this patient population. The SOAP has commissioned a consensus statement (planned publication in 2019) to provide recommendations specifically for the obstetric population following cesarean delivery.

All patients who receive neuraxial opioids should be monitored for adequacy of ventilation, oxygenation, and level of consciousness. Opioid effects on respiration include reduced minute ventilation (decrease in respiratory rate, tidal volume, or both) and decreased response to hypoxemia and changes in PaCO₂. Nearly two-thirds of cases of respiratory depression following general anesthesia in the Anesthesia Closed Claims Project database reported somnolence was present, but not addressed, before the respiratory depression event. Vigilant nursing care and hourly assessments of respiratory effort, respiratory rate, and somnolence are probably adequate for low-risk patients who receive neuraxial opioid analgesia. Continuous pulse oximetry, although appropriate for obstetric patients with risk factors for respiratory depression such as obesity, may be unnecessary in healthy patients receiving low doses of neuraxial opioid (e.g., intrathecal morphine ≤ 0.2 mg, epidural morphine ≤ 4 mg). Greater surveillance and ventilation monitoring (e.g., capnography) may be warranted in patients at high risk for respiratory depression who are receiving supplemental oxygen; the monitoring of patients at high-risk for respiratory depression merits further study.

The duration of respiratory monitoring corresponds to the expected duration of action of the administered opioid. The onset of respiratory depression after neuraxial opioids is variable and has been reported to range from 2 to 12 hours. CO₂ responsiveness is depressed for up to 24 hours after the administration of epidural morphine 5 mg. The ASA recommends that respiratory monitoring after neuraxial administration of morphine should occur at least every hour for the first 12 hours and then every 2 hours for the next 12 hours.

Early-onset respiratory depression associated with lipophilic opioids usually occurs within 30 minutes of administration and is likely to occur in a high-visibility, controlled setting (e.g., operating or labor room). The ASA and ASRA recommend that respiratory monitoring after administration of neuraxial fentanyl should continue for a minimum of 2 hours.

Nausea and Vomiting

Nausea and vomiting are common complaints after cesarean delivery, and the causes are likely multifactorial. Neuraxial opioids increase the risk for PONV after cesarean delivery in a non–dose-dependent manner via rostral spread of opioid in the CSF to the brainstem or from vascular uptake and delivery to the vomiting center and chemoreceptor trigger zone. Palmer et al. found no difference in PONV between intrathecal morphine (0.025 to 0.5 mg) and placebo, nor a relationship between PONV and morphine dose. A similar study by the same group found no difference in the severity of PONV in patients receiving increasing doses of epidural morphine (1.25 to 5 mg). However, neither study was adequately powered to investigate absence of PONV as a primary outcome measure. Many studies have investigated different regimens to reduce PONV in patients receiving neuraxial opioids for cesarean delivery, but these studies did not standardize PONV outcome measures and did not stratify patients according to risk for PONV. In a blinded study assessing PONV as a secondary outcome after intrathecal morphine 0.1 and 0.2 mg, an increased incidence and severity of nausea was identified in the high-dose group.

Single antiemetic agents. Older antiemetics, such as metoclopramide and droperidol, have been used to prevent or treat neuraxial opioid–induced emesis in the obstetric setting. Metoclopramide antagonizes dopamine receptors in the chemoreceptor trigger zone. It is often administered preoperatively owing to its favorable gut prokinetic properties, and it is associated with a reduction in rates of intraoperative nausea and vomiting (IONV) and PONV in patients receiving spinal anesthesia. In a meta-analysis of studies that assessed efficacy of antiemetic prophylaxis, metoclopramide was associated with a reduced incidence of IONV and early PONV compared with placebo.

The use of a transdermal scopolamine patch may also lower the incidence of PONV after cesarean delivery. A transdermal scopolamine patch (1.5 mg) provided efficacy similar to that provided by ondansetron 4 mg in reducing emesis among parturients receiving spinal anesthesia (incidence of 40% and 42%, respectively, versus 59% in the control group). However, transdermal scopolamine has a latency period of 3 to 4 hours, and side effects, including dry mouth, visual disturbances, dizziness, and agitation, are common.

Serotonin (5-HT₃) receptor antagonists have been used for both prophylaxis and treatment of PONV. These drugs bind to 5-HT₃ receptors in the chemoreceptor trigger zone and at vagal afferents in the gastrointestinal tract. Prophylactic administration of ondansetron 4 to 8 mg has been shown to have a better antiemetic profile in the first 24 hours after intrathecal and epidural opioid administration compared with placebo (Fig. 27.8). A meta-analysis of six trials found that the use of 5-HT₃ receptor antagonists reduced the incidence of PONV and the need for rescue antiemetic treatment in women who received intrathecal opioids for cesarean delivery.

Corticosteroid receptors have been identified in areas important to the signal processing of nausea and vomiting, including the nucleus of the solitary tract, the nucleus of raphe, and the area postrema. Tzeng et al. reported that intravenous dexamethasone 8 mg and droperidol 1.25 mg provided similar efficacy in the prevention of PONV. Wang et al. suggested that dexamethasone 5 mg is the minimum effective dose for preventing PONV. In both studies, patients received epidural morphine 3 mg. In a 2012 study...
meta-analysis of studies of obstetric and gynecologic patients who received neuraxial morphine, prophylactic dexamethasone (2.5 to 10 mg) was associated with a reduced risk for PONV and need for antiemetic rescue therapy compared with placebo. Administration of cyclizine 50 mg has been reported to be associated with fewer episodes of PONV (0 to 12 hours after cesarean delivery) than administration of dexamethasone 8 mg after intrathecal opioid (fentanyl and morphine) administration.

**Combination antiemetic regimens.** Administration of drugs acting at two different receptor sites may improve antiemetic efficacy through additivity or synergism. Drug combinations may also facilitate a concomitant reduction in drug doses limiting individual side effects. Wu et al. reported lower rates of PONV after intrathecal morphine administration with use of a combination of dexamethasone 8 mg and droperidol 0.625 mg than with use of dexamethasone 8 mg or droperidol 1.25 mg alone. In a multicenter study, Habib et al. randomized women to one of three groups: placebo, metoclopramide 10 mg plus placebo, or a combination of metoclopramide 10 mg plus ondansetron 4 mg. Spinal anesthesia–induced hypotension was managed prophylactically with a phenylephrine infusion to maintain the systolic blood pressure within 20% of baseline or greater than 90 mm Hg. The combination of metoclopramide and ondansetron reduced IONV and PONV compared with placebo.

**Nonpharmacologic techniques.** Several studies have investigated the prophylactic use of acupressure (using wrist bands with a plastic bead placed bilaterally on the P6 [HG-6] acupoint) for reducing PONV after neuraxial anesthesia for cesarean delivery. A meta-analysis of six studies (649 patients) that assessed the effect of P6 stimulation versus placebo to reduce IONV and PONV revealed inconsistent results, thereby limiting any definitive conclusions regarding the efficacy of this intervention. Based on very limited evidence in patients having cesarean delivery, supplemental oxygen and generous intravenous fluid administration do not appear to reduce IONV or PONV.

**Pruritus**

Pruritus is a common side effect of neuraxial opioid administration in obstetric patients. In a retrospective review of 4880 patients undergoing cesarean delivery who received epidural morphine 2 to 5 mg, pruritus was reported by 58% of patients. However, a sample of patients who received spinal anesthesia for cesarean delivery ranked pain, nausea, and vomiting as more undesirable than pruritus (see Table 27.1). The incidence and severity of pruritus are likely influenced by the opioid dose, route of administration (more common after intrathecal administration), and method of assessment. The incidence of pruritus after intrathecal morphine is as high as 70% to 90%, with approximately 25% to 40% of patients requesting treatment.

Pruritus may manifest in the dermatomal distribution of neuraxial opioid spread as well as nonspecific areas of the head and neck; specific symptoms and severity vary among patients. Opioid-induced histamine release from mast cells does not appear to be the causative mechanism for pruritus after neuraxial opioid administration. Plasma opioid and histamine levels are clinically insignificant at the time of symptom presentation (3 to 6 hours after intraspinal morphine administration). At present, the mechanisms of spinal and epidural opioid–induced pruritus remain unclear. Postulated theories include (1) direct or indirect excitatory effects on central µ-opioid receptors; (2) cephalad migration of the opioid within the CSF to the trigeminal nucleus (which contains the subnucleus caudalis, integrates facial sensory input, and exhibits high opioid receptor density); (3) excitatory effects on dorsal or ventral horn neurons; and (4) other mechanisms (e.g., effects on dopamine-2 [D2] receptors, prostaglandin system, serotonin 5-HT3 receptors, and CNS gamma-aminobutyric acid [GABA] and glycine receptors). Pregnant patients may be more susceptible as a result of estrogen interaction with opioid receptors.

The incidence of moderate-to-severe pruritus with epidural morphine administered for postcesarean analgesia has been reported to be lower in patients homozygous for the G118G polymorphism in the µ-opioid receptor gene (OPRM1) than in patients with the A118G or A118A genotype (incidence 5%, 42%, and 53%, respectively). In a study of 63 women undergoing elective cesarean delivery with spinal anesthesia with morphine 0.1 mg, Pettini et al. reported an incidence of pruritus of 50% in patients homozygous for the G118G polymorphism and 82% in patients with the A118G or A118A genotype.
There is little consensus regarding the prevention and treatment of neuraxial opioid–induced pruritus after cesarean delivery. Further, there are currently no validated or consistent methods for assessing pruritus, which limits the analysis of data from studies investigating the efficacy of antipruritic regimens.

Studies comparing opioid antagonists for the treatment of pruritus have demonstrated mixed results. Nalbuphine (5 mg) significantly reduced the severity of pruritus after epidural morphine, and fewer patients required additional treatment of persistent pruritus. Smaller doses of nalbuphine (2 to 3 mg) adequately treat moderate-to-severe pruritus after intrathecal morphine administration. Wu et al. found that butorphanol 1 mg followed by an infusion of 0.2 mg/h was associated with reduced pruritus compared with a saline-control group in patients who received intrathecal morphine.

Prophylactic treatment with opioid antagonists has also been investigated as a method of reducing the incidence of opioid-induced pruritus. Morgan et al. reported that pretreatment with intravenous nalbuphine (20 mg at skin closure) with subsequent postoperative administration (20 mg in divided doses) was ineffective in reducing pruritus in patients receiving epidural morphine. Similarly, pretreatment with subcutaneous naloxone (0.4 mg) did not reduce the incidence of pruritus in patients receiving intrathecal fentanyl and morphine for elective cesarean delivery. This is not surprising given the short half-life of naloxone. However, naloxone and nalbuphine administered via patient-controlled bolus doses with a continuous background infusion have been found to reduce the incidence of pruritus after cesarean delivery in patients who received epidural morphine 5 mg.

The long-acting oral opioid antagonist naltrexone reduced pruritus compared with placebo after cesarean delivery in patients who received epidural or intrathecal morphine. Paech et al. compared methylnaltrexone, a peripherally acting µ-opioid receptor antagonist developed to antagonize the peripheral side effects of opioids while preserving centrally mediated analgesia, with placebo. Women undergoing elective cesarean delivery under spinal anesthesia with intrathecal morphine 0.1 mg were randomized to receive subcutaneous methylnaltrexone 12 mg or placebo after delivery. The incidence and severity of pruritus were not statistically different between groups, although the study may have been underpowered to identify a small effect. Pentazocine, a κ-opioid receptor agonist and partial µ-opioid receptor agonist, may be a useful drug for treating opioid-induced pruritus. Hirabayashi et al. randomized women scheduled for cesarean delivery with spinal anesthesia containing fentanyl 10 µg and morphine 0.1 mg to receive pentazocine 15 mg or saline-placebo. Pentazocine reduced the overall incidence of pruritus within the first 24 hours compared with saline.

The effects of neuraxially administered opioid antagonists have also been investigated. Jeon et al. reported less pruritus in patients who received epidural naloxone (1.2 mg over 48 hours) with epidural 0.1% bupivacaine and morphine (6 mg over 48 hours) than in patients in a control group. Similarly, Culebras et al. investigated the effects of three different doses of intrathecal nalbuphine (0.2, 0.8, and 1.6 mg) and found a significantly lower incidence of pruritus in all of the nalbuphine groups compared with a control group that received intrathecal morphine without nalbuphine. However, the duration of analgesia was shorter among patients in the nalbuphine groups. It is not clear whether an optimal dose of µ-opioid receptor antagonists can be found that prevents pruritus without reducing analgesia. These drugs are not approved for administration into the neuraxial canal.

Propofol has been reported to relieve pruritus caused by neuraxial opioids in nonobstetric patients after a single 10-mg bolus dose and after a 10-mg bolus dose followed by a 30 mg/24 h infusion. The mechanism of the antipruritic effect of propofol is unknown, and these results have not been replicated in obstetric patients who received subhypnotic doses of propofol (10 to 20 mg) for treatment of intrathecal morphine–induced pruritus. A comparative study demonstrated that intravenous nalbuphine 3 mg is superior to propofol 20 mg for treating pruritus after administration of intrathecal morphine.

Stimulation of 5-HT₃ receptors found in the dorsal horn of the spinal cord and in the nucleus of the spinal tract of the trigeminal nerve in the medulla may occur after subarachnoid opioid administration. A meta-analysis of studies of surgical patients receiving neuraxial opioids concluded that prophylaxis with a 5-HT₃ antagonist results in a reduced risk for postoperative pruritus compared with placebo (OR, 0.44; 95% CI, 0.29 to 0.68). Intravenous ondansetron 4 to 8 mg has been shown to be more effective than placebo for reducing the incidence of postcesarean pruritus after intrathecal administration of morphine 0.15 to 0.2 mg. However, other studies that compared ondansetron 8 mg with placebo found no significant reduction in pruritus after intrathecal administration of morphine (0.1 to 0.2 mg) alone or in combination with a lipophilic opioid (sufentanil or fentanyl). The lack of antipruritic effect in these studies may be caused by the peak effect of ondansetron occurring sooner (15 minutes after intravenous administration) than that of intrathecal morphine. The antipruritic effects associated with ondansetron may depend on the dose, lipophilicity, and duration of action of the intrathecal opioid. Siddik-Sayyid et al. found no significant differences in the incidence or severity of pruritus among patients who received granisetron 3 mg or ondansetron 8 mg or saline. In contrast, Tan et al. observed that the severity of pruritus was reduced at 8 and 24 hours after cesarean delivery in patients who received granisetron 3 mg compared with those who received ondansetron 8 mg.

George et al. reported a meta-analysis of studies of women who received spinal anesthesia with morphine for cesarean delivery; prophylactic administration of a 5-HT₃ antagonist did not reduce the risk for pruritus compared with the placebo control group. However, administration of a 5-HT₃ antagonist reduced the severity of pruritus and the need for rescue treatment compared with placebo.
Heterogeneity and small sample sizes in the studies included in this systematic review limited detailed analysis of the efficacy of prophylactic administration of a 5-HT₃ antagonist.

Few studies have assessed the *therapeutic* effect of 5-HT₃ antagonists for managing postcesarean pruritus induced by neuraxial opioids. In one study, ondansetron 4 mg had a high rate of success for the treatment of moderate-to-severe pruritus compared with placebo (80% and 36%, respectively).³⁵⁷

Historically, antihistamines have been a popular first choice for treatment of pruritus. However, the efficacy of these agents has been questioned in patients receiving neuraxial opioids, as histamine release is not the mechanism of pruritus. Alhashemi et al.³⁵⁸ demonstrated that diphenhydramine was less effective than nalbuphine (higher itching scores and more treatment failures) after administration of intrathecal morphine 0.2 mg. Yeh et al.³⁵¹ found that the incidence of pruritus was comparable among patients receiving diphenhydramine 30 mg and placebo (80% and 85%, respectively); however, both groups had a higher incidence of pruritus than did a group that received ondansetron 0.1 mg/kg (25%). In contrast, Siddik-Sayyid et al.³⁵⁹ found that the therapeutic success rates for ondansetron 4 mg and diphenhydramine 25 mg were identical (70% for each drug), with similar recurrence rates in successfully treated patients (28% versus 35%, respectively). Differences in study methodology and antihistamine-induced sedation may explain the inconsistent antipruritic effect of diphenhydramine observed in these studies.

**Urinary Retention**

The mechanisms by which neuraxial opioids affect specific components of micturition (urge sensation, detrusor and sphincter function) are also not fully understood, although spinal and supraspinal sites of action are likely to be involved. Kuipers et al.³⁶⁰ performed urodynamic studies in healthy male volunteers who received intrathecal sufentanil and morphine. Both opioids caused dose-dependent decreases in detrusor contractility and the urgency to void. Volunteers receiving intrathecal sufentanil had earlier recovery of lower urinary tract function than those receiving intrathecal morphine.³⁶⁰ Intrathecal local anesthetics (bupivacaine and lidocaine) have also been shown to ablate detrusor contractility and urge sensation until the dermatomal block regresses to S2 to S3, with no partial recovery until this regression has occurred.³⁶¹

Evron et al.³⁶² performed an observational study investigating the urinary effects of epidural morphine and methadone in 120 women undergoing cesarean delivery. Not surprisingly given the longer duration of action, difficulty in micturition and need for bladder catheterization were greater in the morphine group (58%) compared with the methadone group (3%).³⁶² A similar study by Liang et al.³⁶³ reported a higher incidence of postcesarean urinary retention and urinary catheterization (22%) among patients receiving epidural morphine compared with other analgesia modalities (PCEA with ropivacaine-fentanyl [7%] and intramuscular meperidine [3%]). In a study of male volunteers, naloxone reversed the impact of neuraxial morphine on urodynamic function.³⁶⁴

To avoid impairment of bladder/detrusor function, urinary catheterization should be considered if voiding has not occurred within 6 hours.³⁶⁵ Risk factors for postcesarean urinary retention include low body mass index, multiparity, emergency cesarean delivery, prolonged operation time, perineal injury, and postoperative analgesia.³⁶⁶–³⁶⁸ Transient postpartum voiding difficulty is not detrimental to urinary function and does not subsequently lead to voiding difficulties.³⁶⁷ Reversal with systemic naloxone may be considered in problematic cases.

**Neuraxial Nonopioid Analgesic Adjuvants**

The addition of neuraxial nonopioid adjuvants to local anesthetic agents may improve the quality of both intraoperative anesthesia and postcesarean analgesia. Nonopioid neuraxial adjuvants have different sites and mechanisms of actions, and interactions between neuraxial opioids and nonopioid adjuvants may be additive or synergistic. Potential advantages of neuraxial drug combinations include a reduction in dose of individual drugs (with subsequent reductions in dose-dependent side effects), in particular a reduction in postoperative opioid requirements and opioid-related side effects.³⁶⁹

**Alpha₂-Adrenergic Receptor Agonists**

Alpha₂-adrenergic receptor agonists bind to presynaptic and postsynaptic alpha₂-adrenergic receptors at peripheral, spinal (dorsal horn), and brainstem sites. Epidural and intrathecal alpha₂-adrenergic receptor agonists provide analgesia by activating the descending noradrenergic system.³⁷⁰,³⁷¹ This process subsequently leads to norepinephrine release, which in turn modulates pain processing in the dorsal horn by inhibiting the release of substance P and increasing acetylcholine levels to produce analgesia.³⁷²,³⁷³ Clonidine, an alpha₂-adrenergic receptor agonist, provides a more potent analgesic response with fewer side effects when administered neuraxially than systemically. Clonidine also potentiates sensory and motor block when administered with epidural local anesthetics and acts additively or synergistically with intraspinal opioids.³⁶⁰,³⁷³ In combination with an intrathecal local anesthetic, intrathecal clonidine may also prolong the regression of sensory block, improve postoperative analgesia, and decrease intraoperative pain.³⁷⁴ However, a combination of intrathecal clonidine and local anesthetic may also increase the risk for hypotension in a non–dose-dependent manner.³⁷⁴ Pregnancy may enhance the analgesic effects of alpha₂-adrenergic receptor agonists, thus making them particularly valuable in this setting.

Mendez et al.³⁷⁶ compared the analgesic efficacy of low-dose epidural clonidine (400-µg bolus) versus high-dose clonidine (800-µg bolus), followed by epidural infusion at 10 or 20 µg/h after cesarean delivery. They observed short-lived, dose-dependent analgesia and sedation, and prolonged motor block, which might lead to delays in the discharge of patients from the postanesthesia care unit. Huntoon et al.³⁷⁷ reported similar postcesarean analgesia in patients receiving epidural clonidine 400 or 800 µg after epidural bupivacaine anesthesia.
Several studies have investigated epidural clonidine in combination with epidural opioids for optimizing postcesarean analgesia. An isobolographic evaluation of epidural clonidine (in doses ranging from 50 to 400 µg) with fentanyl (15 to 135 µg) demonstrated additivity but not synergism between clonidine and fentanyl in patients recovering from cesarean delivery. However, marked variability in drug response and failure of high doses to produce complete analgesia limited the validity of dose-response and ED50 analyses. Capogna et al. observed that the addition of clonidine 75 to 150 µg to epidural morphine 2 mg lengthened the duration of postcesarean analgesia without increasing the incidence of side effects.

A number of studies have evaluated the potential role of intrathecal clonidine for postcesarean analgesia. Ginosar et al. administered intrathecal clonidine (0 to 100 µg) to healthy volunteers to assess the analgesic effect of doses below 100 µg; analgesia to experimental heat pain was detected for doses greater than 25 µg. Van Tuijl et al. assessed postcesarean analgesia in patients who received intrathecal clonidine 75 µg combined with bupivacaine compared with intrathecal bupivacaine alone. Early postoperative analgesia (for 1 to 2 hours) was improved in patients who received clonidine; however, no difference was found in 24-hour morphine consumption between the groups, likely reflecting the short duration of action of a bolus dose of clonidine.

Interaction studies of intrathecal opioids combined with clonidine have investigated the contribution of each drug to analgesia and side effects. Benhamou et al. evaluated postcesarean analgesic outcomes in patients who received hyperbaric bupivacaine alone, or bupivacaine and clonidine 75 µg, or bupivacaine with clonidine and fentanyl 12.5 µg. Patients who received the bupivacaine-clonidine-fentanyl combination reported less intraoperative pain and more prolonged postcesarean analgesia (time to first analgesic request 215 minutes) than those receiving bupivacaine-clonidine and bupivacaine alone (183 and 137 minutes, respectively). However, higher rates of pruritus and sedation were reported for the bupivacaine-clonidine-fentanyl group. Paech et al. performed a six-arm study assessing postcesarean analgesia after intrathecal bupivacaine 12.5 mg with fentanyl 15 µg and one of the following regimens: clonidine 150 µg; morphine 0.1 mg; and morphine 0.1 mg with clonidine 30, 60, 90, or 150 µg. They concluded that the morphine-clonidine regimens provided optimal analgesia with lower pain scores at rest and with coughing in the first 4 hours. The minimum effective intrathecal dose of clonidine was 30 to 60 µg combined with bupivacaine, fentanyl 15 µg, and morphine 0.1 mg. However, an increase in intraoperative sedation was observed in all groups receiving clonidine.

Lavand’homme et al. compared anti-hyperalgesic effects in patients receiving intrathecal clonidine 150 µg with bupivacaine, clonidine 75 µg with bupivacaine-sufentanil, or bupivacaine-sufentanil. The bupivacaine-clonidine 150-µg group had a smaller area of peri-incisional hyperalgesia and a lower incidence of hyperalgesia compared with the other study groups. However, no between-group differences were observed in postoperative morphine consumption or in pain scores before and after discharge. Carvalho et al. randomized 195 women to receive intrathecal hyperbaric bupivacaine with morphine 0.05 mg, morphine 0.1 mg, or morphine 0.05 mg combined with clonidine 75 µg for surgical anesthesia. Pain intensity at rest or while coughing did not differ among groups. During recovery, the incidences of hypertension, bradycardia, and sedation were similar among groups.

Crespo et al. performed a systematic review of trials comparing intrathecal clonidine as an adjuvant to local anesthetics with or without additional opioids in women undergoing cesarean delivery. They evaluated outcomes related to efficacy of clonidine as an intrathecal adjuvant, including duration of analgesia and motor block. Clonidine prolonged the duration of sensory block by 128 minutes and motor block by 45 minutes while also increasing sedation compared with intrathecal blocks without clonidine.

In summary, neuraxial clonidine may offer a small improvement in postcesarean analgesia in addition to that provided by neuraxial morphine. Epidural clonidine (150 to 800 µg) may prolong postcesarean analgesia when given in combination with epidural opioids. Intrathecal clonidine (75 to 450 µg) has modest efficacy and a relatively short duration of action. Ongoing concern about the adverse side-effect profile of epidural and intrathecal clonidine—notably sedation and hypotension—limit the neuraxial administration of this agent in most patients undergoing cesarean delivery. Additionally, in the United States, epidural clonidine has a “black box” warning stating that it is not recommended for obstetric, postpartum, or perioperative pain management because of the risk for hypotension and bradycardia that were identified after high doses. In selected cases, the anesthesia provider may conclude that the potential benefits outweigh the risks.

Dexmedetomidine is a highly selective alpha2-adrenergic receptor agonist that provides some analgesic effects mediated at the spinal level. Its systemic administration is widespread in anesthesia and critical care; however, its use in peripheral nerve blocks and neuraxial anesthesia is off-label. In one of the few studies evaluating neuraxial dexmedetomidine, 80 healthy women were randomly assigned to a control group (intrathecal hyperbaric bupivacaine 5 mg and an epidural mixture of 10-mL plain bupivacaine 0.25% and fentanyl 50 µg) or a study group who received the same drugs with the addition of epidural dexmedetomidine (0.5 µg/kg). The dexmedetomidine group required less intraoperative and postoperative fentanyl than the control group (4/40 and 18/40,
respectively). There was no difference between the groups in block characteristics or sedation. In the only study of intrathecal dexametomidine for cesarean anesthesia, Qi et al. compared bupivacaine 10 mg, bupivacaine 10 mg combined with dexametomidine 5 µg, and bupivacaine 10 mg combined with morphine 0.1 mg. Sensory blockade was longer in the dexametomidine groups than in other groups. Intrathecal dexametomidine provided similar analgesia and less pruritus and shivering compared with morphine.

**Epinephrine** has a direct analgesic effect by activating alpha2-adrenergic receptors and may potentiate local anesthetics by inducing local vasoconstriction through alpha2-adrenergic activation, resulting in slower drug clearance. A number of clinical studies have investigated epinephrine as a spinal or epidural adjunct. Robertson et al. reported that epidural epinephrine 25 µg prolonged the duration of analgesia with epidural fentanyl 100 µg but increased the incidence of pruritus. Similar prolongation of analgesia has been observed when epinephrine (5 to 30 µg/mL) was combined with epidural diamorphine or sufentanil; however, the incidence of side effects (including vomiting that required treatment) was also increased. In contrast, McMorland et al. did not replicate this finding, although their study was not powered to demonstrate noninferiority. Importantly, studies of the addition of epidural epinephrine (5 µg/mL) to 2% lidocaine or 0.5% bupivacaine have not demonstrated any detrimental effects of epinephrine on umbilical artery blood-flow velocity waveforms, uteroplacental or fetal vascular resistance, fetal myocardial function, or fetal heart rate or neonatal outcomes.

The use of intrathecal epinephrine as an adjuvant to local anesthetics, with or without opioids, has been evaluated in several studies. The addition of epinephrine 200 µg to hyperbaric spinal bupivacaine improved perioperative analgesia but was associated with a longer duration of residual sensory and motor block. In a separate study, a combined intrathecal regimen of epinephrine 200 µg with morphine 0.2 mg improved intra- and postoperative analgesia compared with intrathecal morphine 0.2 mg alone. Zakowski et al. found earlier and higher peak plasma bupivacaine concentrations with the addition of spinal epinephrine 200 µg to spinal bupivacaine in patients undergoing cesarean delivery. In contrast, plasma levels of morphine were approximately 66% lower in the epinephrine group than in the control group. The investigators concluded that the enhanced efficacy of intrathecal bupivacaine combined with morphine and epinephrine was not caused by vasoconstriction alone.

In summary, the use of epidural epinephrine (2.5 to 30 µg/mL) seems to prolong the duration of analgesia with epidural opioids but may increase side effects. The use of intrathecal epinephrine 200 µg does seem to enhance neuraxial opioid analgesia but is associated with prolonged sensory and motor block.

**Neostigmine**

By interfering with the breakdown of acetylcholine, neostigmine indirectly stimulates spinal nicotinic and muscarinic receptors and the release of nitric oxide. As both nicotinic and muscarinic receptors are important to central and peripheral pain transmission, the resulting analgesia may be caused by central and/or peripheral alterations in pain modulation and transmission. Initial studies of intrathecal neostigmine in animals and human volunteers have demonstrated analgesic effects without neurotoxic effects. However, despite producing dose-dependent analgesia, intrathecal neostigmine results in nausea that is particularly resistant to traditional antiemetic treatment, and therefore the use of intrathecal neostigmine is generally not recommended.

Kaya et al. assessed the analgesic efficacy of epidural neostigmine administration after cesarean delivery. A CSE technique was employed with intrathecal bupivacaine 8 mg and fentanyl 10 µg, and patients subsequently received epidural neostigmine doses of 75, 150, or 300 µg after delivery. The investigators reported modest, short-lived, and dose-independent reductions in postoperative pain in the neostigmine groups. No differences among groups in 24-hour morphine consumption after surgery were observed. The use of epidural neostigmine is not currently recommended for routine use until additional studies substantiate clinically significant postcesarean analgesic benefits with fewer side effects compared with alternatives. Data regarding the maternal and fetal safety profile of epidural neostigmine are reassuring.

**N-Methyl-D-Aspartate Receptor Antagonists**

**Ketamine.** Limited data exist regarding the role of neuraxial ketamine in the provision of postcesarean analgesia. Anesthetic and subanesthetic doses of ketamine have analgesic properties via noncompetitive antagonism of NMDA receptors. In patients undergoing cesarean delivery randomly assigned to receive intrathecal bupivacaine alone or in combination with S(+) ketamine 0.05 mg/kg or fentanyl 25 µg, significantly prolonged and better quality analgesia was observed in the fentanyl group. It is unclear whether the S(+) or R(−) isomers of ketamine have analgesic advantages over the racemate. No published studies have evaluated perioperative epidural ketamine administration in patients undergoing cesarean delivery. At this time neuraxial use cannot be recommended for patients undergoing cesarean delivery because there is a lack of data regarding the safety of neuraxial administration.

**Magnesium.** Magnesium is a noncompetitive antagonist of the NMDA receptor and may alter pain signaling by preventing central sensitization after nociceptive stimulation. Magnesium blocks NMDA ion channels in a voltage-dependent manner. Studies investigating intrathecal or epidural magnesium have shown variable analgesic effects after cesarean delivery. Sun et al. compared the postcesarean analgesic profile of four different epidural solutions administered in the perioperative period. All patients received 0.1% bupivacaine 10 mL with one of the following: morphine 1.5 mg, magnesium 500 mg, morphine 1.5 mg and magnesium 500 mg, or placebo. Patients who received magnesium and morphine had lower postoperative pain scores at...
rest and with movement, an increased time to first analgesic request, and increased satisfaction at 24 hours after surgery compared with women who received only one drug or placebo. Albrecht et al.406 reviewed 18 trials (including some trials in women undergoing cesarean delivery) of the efficacy and safety of neuraxial magnesium sulfate for postoperative analgesia. They observed an overall increase in the interval to first analgesic request (mean difference of 40 minutes after intrathecal administration and 110 minutes after epidural administration). However, only four trials assessed neurologic complications, and the authors concluded that there were not enough patients \( (n = 140) \) to evaluate the risk for neurologic complications.

**Intrathecal** magnesium sulfate 50 mg prolonged the duration of spinal anesthesia and improved postoperative analgesia in patients undergoing nonobstetric surgery with bupivacaine and fentanyl spinal anesthesia.407, 408 In women undergoing cesarean delivery, no difference in the first request for postcesarean analgesia was found among patients who were randomized to receive intrathecal magnesium sulfate 50 mg compared with placebo (median time, 100 minutes versus 105 minutes, respectively), and patients who received intrathecal fentanyl 25 µg had a longer time to first request for analgesia (132 minutes) compared with the magnesium group.409

In summary, neuraxial administration of magnesium may have a favorable analgesic effect in patients after cesarean delivery. However, more research, including dose-response studies and comparison with systemic administration, are needed to more formally assess the analgesic efficacy of epidural and intrathecal magnesium.

**Experimental Agents**

In the future, newer agents and adjuvants may enhance postoperative pain management strategies in patients receiving neuraxial anesthesia for cesarean delivery. **Adenosine** (and adenosine analogues) have been proposed to have antinociceptive activity related to activation of spinal adenosine A₁ receptors.410 However, studies have not demonstrated improved analgesia with intrathecal adenosine administration in patients undergoing hysterectomy411, 412 or for labor analgesia.413

A direct relationship may exist between central potassium channel activity and antinociception. Several animal studies have investigated **potassium channel activators** (nicorandil, sildenafil) administered by the intrathecal414 or epidural415 route. Neuraxial administration of these drugs has not been studied in humans.

A meta-analysis of studies that assessed the clinical benefit and side effects of intrathecal **midazolam** in obstetric and nonobstetric patients suggested a favorable pharmacologic profile.416 Intrathecal midazolam was associated with improved analgesia and a reduced risk for PONV. After cesarean delivery, patients who received intrathecal midazolam 2 mg (without neuraxial opioids) had prolonged postoperative analgesia, reduced requirement for rescue analgesic, and lower pain scores for 6 hours after surgery compared with patients who received either intrathecal midazolam 1 mg or no midazolam.417 Dodawad et al.418 randomly assigned 60 women with pregnancy-induced hypertension undergoing cesarean delivery to receive intrathecal bupivacaine 10 mg (control group) or bupivacaine combined with midazolam 2 mg (study group). Postoperative analgesia was longer in the midazolam group than in the control group (202 minutes and 358 minutes, respectively). It is unknown whether intrathecal midazolam has any benefit compared with intrathecal morphine or in addition to morphine.

Several neuraxially administered drugs have been shown to produce antinociceptive effects by altering calcium channel conductance in the spinal cord. Intrathecal **gabapentin** reduced incision-induced allodynia in rats,419, 420 and epidural **verapamil** lowered postoperative opioid consumption after lower abdominal surgery.421 **Ziconotide**, a neuronal N-type-selective voltage-sensitive calcium entry–blocking agent, has been shown to have analgesic effects after intrathecal administration in chronic pain patients.422

Before recommendations can be made about the potential use of new adjunct agents, neurotoxicity studies are necessary to ensure these agents’ safety for neuraxial administration. In addition, studies assessing analgesic efficacy, side effects, and toxicity must demonstrate that these agents result in significant improvement over the neuraxial local anesthetic and opioid regimens currently used in clinical practice.

**NON-NEURAXIAL REGIONAL ANALGESIC TECHNIQUES**

**Abdominal Fascial Sheath Blocks**

The transversus abdominis plane (TAP) block and quadratus lumborum block (QLB) are regional anesthetic techniques in which local anesthetic is injected between fascial sheaths of the abdominal musculature. In clinical practice, the blocks are usually performed using ultrasonography to verify correct needle position and site of injection. In the TAP block, infiltration is between the internal oblique and the transversus abdominis muscle layers (Fig. 27.9), and in the QLB (Fig. 27.10), infiltration is adjacent to the anterolateral aspect of the quadratus lumborum muscle. Both techniques block the plexus of nerves supplying the anterior abdominal wall. Some have suggested the possibility that the QLB may have greater efficacy than the TAP block because of spread of the local anesthetic solution beyond the muscle fascia into an interfascial plane close to the paravertebral space.423 Chin et al.424 provide a detailed review of the anatomy of abdominal wall blocks.

Three systematic reviews and meta-analyses of TAP blocks for postcesarean analgesia have been completed. Mishrikiy et al.425 reviewed the efficacy of TAP blocks after cesarean delivery with primary outcomes of pain intensity scores and opioid consumption at 24 hours. Nine studies compared TAP blocks with inactive controls, seven of them done in combination with spinal anesthesia for cesarean delivery. In women who did not receive intrathecal morphine, TAP blocks...
reduced opioid consumption (mean difference, −20.2 mg morphine equivalents [95% CI, −33.7 to −6.8]) and opioid-related side effects. In patients who received intrathecal morphine, there was no difference between TAP blocks and inactive controls in pain scores at 24 hours, and the impact on opioid consumption was inconclusive. Three studies directly compared TAP blocks with intrathecal morphine, two with 0.1 mg and one with 0.2 mg. Intrathecal morphine provided lower pain scores on movement (mean difference, 0.98 [95% CI, 0.06 to 1.91]) and reduced 24-hour opioid consumption (mean difference, −8.4 mg morphine equivalents [95% CI, 1.7 to 15.1]). A limitation of the meta-analysis was the significant heterogeneity among studies. Champaneria et al. completed a subsequent meta-analysis with additional studies; they confirmed the conclusion that TAP blocks are effective but do not confer additional analgesia when intrathecal morphine is included as part of a multimodal analgesia regimen.

The QLB is an abdominal fascial block similar to the TAP block, but with potential for more diffuse analgesia because the point of injection is more posterior. QLB 1, 2, and 3 are all described based on location of local anesthetic administration relative to the quadratus lumborum muscle; consensus on the best approach is lacking. Local anesthetic is infiltrated into the space between the quadratus lumborum muscle and the medial layer of the thoracolumbar fascia; the solution may spread to the paravertebral space. Blanco et al. reported a randomized placebo-controlled trial of QLB after cesarean delivery; 25 women who did not receive neuraxial morphine received a QLB with 0.125% bupivacaine 0.2 mL/kg, and outcomes were compared with 25 women who received a placebo block with saline. Patients in the QLB group used less morphine at 6 and 12 hours postoperatively; the difference was not significant at 24 hours (median dose, 11 mg [IQR 5 to 18] and 19 mg [IQR 11 to 36], respectively; $P = .11$). Similarly, Blanco et al. compared the QLB and the TAP block in women scheduled for elective cesarean delivery under spinal anesthesia with bupivacaine and fentanyl. Women in the QLB group used less morphine than those in the TAP block group with no difference in pain scores between groups. Future research will likely shed light on whether the QLB adds benefit to current multimodal analgesia practices and whether the analgesia it provides is superior to that of intrathecal morphine after cesarean delivery.
who had spinal anesthesia for elective cesarean delivery (this dose corresponds to 20 mL of 0.5% ropivacaine on each side for an 80-kg patient). The mean (± SD) peak plasma ropivacaine concentration 30 minutes after injection was 1.82 ± 0.69 µg/mL. Although this concentration is below the reported threshold for LAST (2.2 µg/mL), 12 of 30 patients had peak concentration measurements above this threshold (maximum, 3.76 µg/mL), and 3 patients had symptoms of mild LAST (perioral tingling, metallic taste). Similarly, Trabelsi et al. demonstrated that bilateral TAP blocks with bupivacaine 100 mg (total dose) led to plasma concentrations above the reported toxic threshold in 3 of 17 women; plasma bupivacaine concentration above the threshold value persisted for as long as 90 minutes. The addition of epinephrine to the local anesthetic solution decreases local anesthetic peak plasma concentration. Clinically significant LAST (seizures) has been reported following TAP block in obstetric patients. The concentration of local anesthetic (ropivacaine, bupivacaine, levobupivacaine) has ranged from 0.125% to 0.5% for QLB and TAP blocks. A 2018 meta-analysis comparing high (greater than 50 mg) versus low doses (less than or equal to 50-mg bupivacaine equivalents per side) for TAP block in women undergoing cesarean delivery found no difference in opioid consumption, time to first analgesia, pain scores, or satisfaction between doses. Given current reports, we suggest that a local anesthetic dose less than 2.5 mg/kg should be used and that patients should be observed for LAST for at least 30 minutes after these blocks are performed.

Current data support the conclusion that abdominal fascial sheath blocks may represent a reasonable alternative for patients who are unable to receive neuraxial morphine, and they may serve as a rescue technique in special cases. However, they are not superior to neuraxial opioid analgesia–based multimodal techniques, which remain the gold standard for postcesarean analgesia. Additionally, because analgesia from TAP blocks may be comparable to that provided by simple wound infiltration or a continuous wound infiltration catheter (see later discussion), the value of TAP blocks in postcesarean analgesia remains unclear.

Complications of the blocks are infrequent and include local anesthetic systemic toxicity (LAST) from systemic absorption of local anesthetic or intravascular injection, and bowel perforation. The described potential benefit of the QLB, spread to the paravertebral space, may also result in unintended motor blockade. Wikner described a patient with hip flexion and knee extension weakness leading to unplanned overnight admission following QLB with 20 mL of 0.25% levobupivacaine for a laparoscopic gynecologic procedure. Presumably, paravertebral spread to the lumbar spinal nerves led to weakness of the psoas and quadriceps muscles.

The relationships between local anesthetic dose, volume, concentration, and response have not been well studied, and consensus on the optimal volume and concentration of local anesthetic for single-shot abdominal fascial plane blocks is lacking. Griffiths et al. performed bilateral TAP blocks with a total ropivacaine dose of 2.5 mg/kg (diluted with 0.9% saline to a total volume of 40 mL) in women who had spinal anesthesia for elective cesarean delivery (this dose corresponds to 20 mL of 0.5% ropivacaine on each side for an 80-kg patient). The mean (± SD) peak plasma ropivacaine concentration 30 minutes after injection was 1.82 ± 0.69 µg/mL. Although this concentration is below the reported threshold for LAST (2.2 µg/mL), 12 of 30 patients had peak concentration measurements above this threshold (maximum, 3.76 µg/mL), and 3 patients had symptoms of mild LAST (perioral tingling, metallic taste). Similarly, Trabelsi et al. demonstrated that bilateral TAP blocks with bupivacaine 100 mg (total dose) led to plasma concentrations above the reported toxic threshold in 3 of 17 women; plasma bupivacaine concentration above the threshold value persisted for as long as 90 minutes. The addition of epinephrine to the local anesthetic solution decreases local anesthetic peak plasma concentration. Clinically significant LAST (seizures) has been reported following TAP block in obstetric patients.

The concentration of local anesthetic (ropivacaine, bupivacaine, levobupivacaine) has ranged from 0.125% to 0.5% for QLB and TAP blocks. A 2018 meta-analysis comparing high (greater than 50 mg) versus low doses (less than or equal to 50-mg bupivacaine equivalents per side) for TAP block in women undergoing cesarean delivery found no difference in opioid consumption, time to first analgesia, pain scores, or satisfaction between doses. Given current reports, we suggest that a local anesthetic dose less than 2.5 mg/kg should be used and that patients should be observed for LAST for at least 30 minutes after these blocks are performed.
Wound Infusion Catheters

Wound infusion of local anesthetic provides effective analgesia after cesarean delivery. However, whether wound infusion provides additional analgesia beyond that provided by neuraxial morphine is not clear. In a study comparing pain control provided by wound infusion or epidural levobupivacaine, the epidural group had less pain in the first 4 hours, but pain control did not differ between groups thereafter.441 There was no difference between groups in opioid consumption.441 In another study comparing intrathecal morphine analgesia and wound infusion with ropivacaine or saline, more oxycodone was required in the ropivacaine wound infusion group than in the intrathecal morphine group during the first 24 hours (48 mg versus 26 mg; P = .004); there was no difference in oxycodone use between the ropivacaine wound infusion and saline-control groups.442 Carvalho et al.443 compared wound infusion with bupivacaine alone to bupivacaine combined with ketorolac in patients who had received intrathecal morphine. The addition of ketorolac was associated with a decrease in pain scores and opioid consumption, and lower concentrations of inflammatory mediators were collected from the wound.443 Lalmand et al.444 randomly allocated patients undergoing elective cesarean delivery into three groups: control, intrathecal morphine, and wound catheter infusion. All patients received spinal anesthesia with bupivacaine and sufentanil, and a multiorifice catheter was inserted into the wound. The control group received saline intrathecally and through the catheter, the morphine group received intrathecal morphine 0.1 mg and saline infusion through the wound catheter, and the catheter group received intrathecal saline and 0.2% ropivacaine infused through the catheter (15-mL bolus followed by a 10-mL/h infusion). Intrathecal morphine and 0.2% ropivacaine wound infusion increased the time to the first oral morphine request and reduced morphine consumption compared with placebo. The wound infusion was not superior to intrathecal morphine 0.1 mg for analgesia and had a similar side-effect profile.444

Some of the differences in outcomes among these studies may be because of differences in catheter-insertion technique, local anesthetic concentration, and rate of infusion. Taken together, current evidence does not support the superiority of local anesthetic wound infusion over neuraxial opioid administration, although there may be additive benefit in some circumstances.

Continuous wound infusion below the fascia has been shown to be more effective in reducing postcesarean morphine consumption compared with infusion above the fascia.445 Klasen et al.446 evaluated a multimodal analgesic regimen for cesarean delivery and found no difference between a TAP block and continuous subfascial wound infiltration. Although some centers use wound-infusion catheters, the additional cost of the pump and some minor inconveniences, such as wound leakage, may have discouraged widespread use.

Ilioinguinal-Iliohypogastric Block

Ilioinguinal-iliohypogastric nerve block is useful for postoperative analgesia after lower abdominal surgery. Similar to a TAP block, the block can be performed with ultrasonographic guidance. Evidence is inconsistent as to whether ilioinguinal-iliohypogastric blocks improve analgesia provided by neuraxial morphine.447,448 In a study in women who did not receive neuraxial morphine, women who received multilevel ilioinguinal-iliohypogastric blocks used less systemic opioid, although no difference in opioid-related side effects was observed.449

Subcutaneous Infiltration of Local Anesthetics

Subcutaneous local wound infiltration is a relatively simple component of multimodal postoperative analgesia. In a study of patients who did not receive neuraxial morphine for postcesarean analgesia, infiltration of 0.25% bupivacaine with epinephrine (40 mL) before wound closure was associated with decreased opioid requirements in the first 12 hours compared with saline placebo.450 In the absence of intrathecal morphine, wound infiltration may confer similar analgesia to bilateral TAP blocks following cesarean delivery with spinal anesthesia.451,452 Simavli et al.453 randomized patients who had general anesthesia for cesarean delivery to receive bupivacaine-soaked absorbable gelatin sponges or placebo, placed in the wound. Pain scores were lower in the sponge group compared with the control group, and fewer patients required rescue opioid. Adesope et al.454 conducted a systematic review of randomized trials to assess the efficacy of local anesthetic wound infiltration in women undergoing cesarean delivery. Wound infiltration reduced opioid consumption at 24 hours (morphine equivalent −9.7 mg) but had no clinical effect on pain scores and did not reduce opioid-related side effects.454

**KEY POINTS**

- Cesarean deliveries account for nearly one-third of all deliveries in the United States; therefore, strategies for reducing adverse postcesarean maternal outcomes, including postoperative pain, have important clinical and public health implications.
- Effective postoperative analgesia confers many physiologic and psychological benefits and may improve maternal and neonatal outcomes after cesarean delivery.
- Optimal postcesarean analgesia consists of a multidisciplinary approach that should involve physicians, nurses, pharmacists, and other health care providers.
- Multimodal techniques provide efficient postcesarean analgesia by acting on different pain pathways to maximize analgesia while limiting side effects.
- Neuraxial morphine administration currently represents the “gold standard” for providing effective postcesarean...
analgesia and is the most important component of multimodal analgesia.

- Morphine has the longest duration of action among available neuraxial opioids, and neuraxial administration of opioids provides better postoperative pain relief than systemic administration.
- In clinical practice, single-dose epidural (2 to 4 mg) or intrathecal (0.075 to 0.2 mg) morphine administration is most commonly administered for postcesarean analgesia. Higher doses may increase opioid-related side effects without improving analgesia.
- Nonopioid neuraxial adjuncts (e.g., α₂-adrenergic receptor agonists, anticholinesterases) may be considered as alternatives to, or combined with, neuraxial opioids. However, these adjuncts are associated with modest analgesic benefits, and the risk for spinal neurotoxicity associated with many of these drugs remains to be determined.

- Opioids are the most common systemic medications administered for postcesarean analgesia. Adverse effects associated with opioids, which often limit their use, include respiratory depression, sedation, constipation, nausea and vomiting, urinary retention, and pruritus.
- Oral analgesic adjuvants (acetaminophen, NSAIDs) should be prescribed at a fixed interval, rather than on patient request.
- Abdominal fascial sheath blocks may represent a reasonable alternative for patients who are unable to receive neuraxial morphine, or they may be used as a rescue technique in selected cases.
- Local wound instillation may be considered in addition to neuraxial morphine, acetaminophen, and NSAIDs to provide further multimodal analgesia.

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Aspiration: Risk, Prophylaxis, and Treatment

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HISTORY

In 1848, Sir James Simpson first suggested aspiration as a cause of death during anesthesia. Hannah Greener, a 15-year-old given chloroform for a toenail extraction, became cyanotic and “sputtered” during the anesthetic. A “rattling in her throat” then developed, and she soon died. Her physician administered water and brandy by mouth. Simpson contended that it was the aspiration of water and brandy, and not the adverse effects from the chloroform, that caused her death. In 1940, Hall published a report of 15 cases of aspiration, 14 of which occurred in mothers receiving inhalation anesthesia for a vaginal or cesarean delivery. Among the 14 obstetric cases, 5 mothers died.

Subsequently, Curtis Mendelson, in a landmark paper, reported a series of animal experiments that clearly described the clinical course and pathology of pulmonary acid aspiration. In the same paper, Mendelson audited 44,016 deliveries at the New York Lying-In Hospital between 1932 and 1945. He identified 66 (0.15%) cases of aspiration, of which the aspirated material was recorded in 45 cases; 40 mothers aspirated liquid, and 5 aspirated solid food. Importantly, no mothers died from aspirated liquid, but 2 mothers died from asphyxiation caused by the aspiration of solid food. At this time general anesthesia usually involved the inhalation of ether, often as Mendelson observed, by “a new and inexperienced intern.” Mendelson therefore advocated (1) the withholding of food during labor, (2) the greater use of regional anesthesia, (3) the administration of antacids, (4) the emptying of the stomach before administration of general anesthesia, and (5) the competent administration of general anesthesia. This advice became the foundation of obstetric anesthesia practice during subsequent decades.

INCIDENCE, MORBIDITY, AND MORTALITY

Maternal mortality from pulmonary aspiration of gastric contents has declined to almost negligible levels in the past 3 decades (Fig. 28.1). This decline can probably be attributed to the following factors: (1) the greater use of neuraxial anesthesia; (2) the use of antacids, histamine-2 (H2) receptor antagonists, and/or proton-pump inhibitors; (3) the use of rapid-sequence induction of general anesthesia; (4) an improvement in the training of anesthesia providers; and (5) the establishment and enforcement of nil per os (NPO) policies. Arguably, the common use of neuraxial analgesic/anesthetic techniques, both during labor and for cesarean delivery, is the single most important factor in this
remarkable decline in maternal mortality from pulmonary aspiration.

The reported incidence of aspiration pneumonitis depends on the criteria used for making the diagnosis. The relative risk for aspiration in pregnant versus nonpregnant women can best be estimated from comparisons within single-study populations. Olsson et al. reported an overall incidence of aspiration of 1 in 2131 in the general population undergoing anesthesia and 1 in 661 in women undergoing cesarean delivery (i.e., a threefold higher aspiration risk). In two other surveys related to aspiration (one a retrospective review of 172,334 consecutive patients undergoing general anesthesia and the other a review of 133 cases of aspiration from the Australian Anaesthetic Incident Monitoring Study [AIMS]), there were no cases of pulmonary aspiration in women undergoing either elective or emergency cesarean delivery. However, in the latter two studies, emergency surgery was a significant predisposing factor for aspiration; this finding may be relevant for the practice of obstetric anesthesia, given that many obstetric surgical procedures are performed on an urgent or emergency basis. The AIMS study also implicated obesity as a significant risk factor for aspiration.

Morbidity and mortality associated with aspiration vary according to (1) the physical status of the patient, (2) the type and volume of aspirate, (3) the therapy administered, and (4) the criteria used for making the diagnosis. Since 1952, organizations in the United Kingdom have published detailed triennial reports on all maternal deaths. Data from these reports, now administered by the body Mothers and Babies—Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK), indicate that death from pulmonary aspiration in obstetrics is vanishingly rare (see Fig. 28.1). In the MBRRACE-UK reports from 2009 to 2015, there were no reported maternal deaths from aspiration. Prior reports from 1994 to 2008 identified three maternal deaths from aspiration; one was an obese parturient, the second was a mother anesthetized 3 days after delivery, and the third was a woman with a placenta previa who required an emergency cesarean delivery after eating a full meal and aspirated on emergence from general anesthesia. Although the number of general anesthetics administered to parturients during this 20-year period (1994 to 2014) is not known, there were approximately 13.8 million deliveries, indicating that the mortality rate from aspiration was less than 1 in 4.6 million deliveries.

Data on pulmonary aspiration in obstetrics in the United States are less comprehensive. The Serious Complication Registry (SCORE) from the Society for Obstetric Anesthesia and Perinatology review of 307,000 deliveries from 30 U.S. centers between 2004 and 2009 reported a failed tracheal intubation rate of 1 in 533, but no related cases of pulmonary aspiration. Data from the U.S. Centers for Disease Control and Prevention’s Pregnancy Mortality Surveillance System suggest that before 1990, aspiration was the most common cause of anesthesia-related maternal death in the United States. It was calculated that at that time there were 17 deaths related to general anesthesia for every 1 death related to regional anesthesia, although it is not clear from these data what proportion of deaths are attributable to aspiration. By the early 1990s, this ratio had improved to 6 to 1. By 2002, death rates for both general and regional anesthesia were similar, likely due in part to a decrease in the risk for aspiration in cases in which general anesthesia was employed.

However, mortality statistics are generally a poor predictor of maternal morbidity; several studies have indicated that perioperative aspiration is associated with important morbidity in obstetric patients; thus all possible measures must be taken to prevent pulmonary aspiration in obstetric patients.

**GASTROESOPHAGEAL ANATOMY AND PHYSIOLOGY**

**Esophagus**

In adults, the esophagus is approximately 25 cm long and the esophagogastric junction is approximately 40 cm from
the incisor teeth. In humans, the proximal one-third of the esophagus is composed of striated muscle, but the distal end contains only smooth muscle. Muscular sphincters at both ends are normally closed. The cricopharyngeal or upper esophageal sphincter prevents the entry of air into the esophagus during respiration, and the gastroesophageal or lower esophageal sphincter prevents the reflux of gastric contents. The lower esophageal sphincter is characterized anatomically and manometrically as a 3-cm zone of specialized muscle that maintains tonic activity. The end-expiratory pressure in the sphincter is 8 to 20 mm Hg above the end-expiratory gastric pressure. The lower esophageal sphincter is kept in place by the phrenoesophageal ligament, which inserts into the esophagus approximately 3 cm above the diaphragmatic opening (Fig. 28.2). The lower esophageal sphincter is not always closed; transient relaxations occur that account for the gastroesophageal reflux that healthy subjects experience.

**Gastrointestinal Motility**

Differences in fasting and fed patterns of gut motility are firmly established. During fasting, the main component of peristalsis is the migrating motor complex (MMC). Each MMC cycle lasts 90 to 120 minutes and comprises four phases: Phase I has little or no electrical spike activity and thus no measurable contractions; phase II has intermittent spike activity; phase III has spikes of large amplitude and is associated with strong contractile activity; and phase IV is a brief period of intermittent activity leading back to phase I. The MMC first appears in the lower esophageal sphincter and stomach, followed by the duodenum, and finally the terminal ileum, at which time a new cycle begins in the lower esophageal sphincter and stomach. The phase of the MMC at the time of administration of certain drugs can affect absorption and thereby the onset of therapeutic effect. Eating abolishes the MMC and induces a pattern of intermittent spike activity that appears similar to that in phase II. The duration of the fed pattern is determined both by the calorie content and the type of nutrients in the meal.

The stomach, through the processes of receptive relaxation and gastric accommodation, can accept 1.0 to 1.5 L of food before intragastric pressure begins to increase. The contraction waves that propel food into the small intestine begin in the antrum. The pylorus closes midway through the contraction wave, allowing some fluid to exit into the duodenum but causing the remaining fluid to move retrograde toward the body of the stomach. The jet of fluid that exits the pylorus contains primarily liquid and fine particles. Large particles that lag behind are caught in the retrograde flow of fluid, which assists in their disintegration. Therefore, the manner by which individual components of a meal pass through the
Gastric Secretion

In one day, the stomach produces as much as 1500 mL of highly acidic fluid containing the proteolytic enzyme pepsin. Normal individuals can produce a peak acid output of 38 mmol/h. Acid is secreted at a low basal rate of approximately 10% of maximal output, even when the stomach is empty. There is diurnal variation in this basal rate of gastric acid secretion, with the lowest and highest outputs occurring in the morning and evening, respectively.

The stomach lining has two types of glands: pyloric and oxyntic. The pyloric glands contain chief cells, which secrete pepsinogen, the precursor for pepsin. The oxyntic glands contain the oxyntic cells, which secrete hydrochloric acid. Water molecules and carbon dioxide in the oxyntic cells combine to form carbonic acid, which dissociates into hydrogen ions and bicarbonate. The bicarbonate leaves the cell for the bloodstream, and the hydrogen ions are actively exchanged for potassium ions in the canaliculi connecting with the lumen of the oxyntic gland. The secretions of the oxyntic cell can contain a hydrochloric acid concentration as great as 160 mmol/L (pH 0.8). Proton-pump inhibitors (PPIs) block the hydrogen ion pump on the canaliculi to decrease acid production.

The pylorus contains G cells, which secrete gastrin into the bloodstream when stimulated by the vagus nerve, stomach distention, tactile stimuli, or chemical stimuli (e.g., amino acids, certain peptides). Gastrin binds to gastrin receptors on the oxyntic cell to stimulate the secretion of hydrochloric acid. Acetylcholine binds to muscarinic (M3) receptors on the oxyntic cell to cause an increase in intracellular calcium ion concentration, which results in hydrochloric acid secretion. Histamine potentiates the effects of both acetylcholine and gastrin by combining with H2 receptors on the oxyntic cell to increase the intracellular cyclic adenosine monophosphate concentration, leading to a dramatic increase in the production of acid. H2-receptor antagonists (e.g., ranitidine, famotidine) prevent histamine’s potentiation of acid production (Fig. 28.3).

Ingestion of Food

When a meal is eaten, the mechanisms that control the secretion of gastric juice and the motility and emptying of the stomach interact in a complex manner to coordinate the functions of the stomach. The response to eating is divided into three phases: cephalic, gastric, and intestinal. Chewing, tasting, and smelling cause an increase in the vagal stimulation of the stomach, which in turn increases gastric acid production. This represents the cephalic phase of digestion. In this phase, gastric acid output increases to approximately 55% of peak output. The gastric phase begins with the release of gastrin. Gastric acid secretion depends on antral distention, vagal activity, gastrin concentration, and the composition of the meal. Gastric acid secretion during a mixed-composition meal increases to approximately 80% of peak acid output. The intestinal phase begins with the movement of food into the small intestine and is largely inhibitory. Hormones (e.g., gastrin, cholecystokinin, secretin) and an enterogastric reflex further modulate gastric acid secretion and motility depending on the composition and volume of the food in the duodenum. This inhibition of gastric emptying by food in the duodenum enables the duodenal contents to be processed before more material is delivered from the stomach.

After the ingestion of a meal, gastric emptying depends on (1) the premeal volume, (2) the volume ingested, (3) the composition of the meal, (4) the size of the solids, (5) the amount of gastric secretion, (6) the physical characteristics of the stomach contents entering the duodenum, and (7) patient position. A mixture of liquids and solids passes through the stomach much more slowly than liquids alone. Gastric emptying is slowed by high lipid content, high caloric load, and large particle size. Thus, predicting an exact time for the passage of liquids and solids through the stomach is very difficult. For non-nutrient liquids (e.g., normal saline), the gastric volume decreases exponentially with respect to time.

In one study, 90% of a 150-mL saline meal given to fasting adults in the sitting position passed through the stomach in a median time of 14 minutes; however, in adults in the left lateral position, the median time for gastric emptying was 28 minutes. In a subject eating a 400-mL meal of steak, bread, and vanilla ice cream, 800 mL of gastric juice was produced.
Effects of Pregnancy on Gastric Function

Gastroesophageal reflux, resulting in heartburn, is a common complication of late pregnancy. Pregnancy compromises the integrity of the lower esophageal sphincter; it alters the anatomic relationship of the esophagus to the diaphragm and stomach, raises intragastric pressure, and in some women limits the ability of the lower esophageal sphincter to increase its tone. Progesterone, which relaxes smooth muscle, probably accounts for the inability of the lower esophageal sphincter to increase its tone. Lower esophageal pH monitoring has shown a higher incidence of reflux in pregnant women at term, even in those who are asymptomatic, than in nonpregnant controls. Therefore, at term gestation the pregnant woman who requires anesthesia should be regarded as having an incompetent lower esophageal sphincter. These physiologic changes return to their prepregnancy levels by 48 hours after delivery.

Serial studies assessing gastric acidity during pregnancy have proved difficult to perform because they require repeated placement of nasogastric tubes. However, in the most comprehensive study of gastric acid secretion during pregnancy, basal and histamine-augmented gastric acid secretion was measured in 10 controls and 30 pregnant women equally distributed throughout the three trimesters of pregnancy. No significant differences in basal gastric acid secretion were seen between the pregnant and nonpregnant women.

A variety of techniques have been used to study gastric emptying during pregnancy and labor (Table 28.1). Overall, the data suggest that pregnancy does not significantly alter the rate of gastric emptying. In addition, gastric emptying has not been found to be delayed in either obese or nonobese term pregnant women who ingested 300 mL of water after an overnight fast. However, management of obese parturients should take into account the possible presence of other associated problems in this group of patients (e.g., hiatal hernia or difficult airway). Gastric emptying appears to be normal in early labor but becomes delayed as labor advances; the cause is uncertain. Pain is known to delay gastric emptying, but even when labor pain is abolished with epidural analgesia using a local anesthetic alone, the delay still occurs. Parenteral opioids cause a significant delay in gastric emptying, as do bolus doses of epidural and intrathecal opioids. Continuous epidural infusion of low-dose local anesthetic with fentanyl does not appear to delay gastric emptying until the total dose of fentanyl exceeds 100 µg. The plasma concentration of the gastrointestinal hormone motilin is decreased during pregnancy. Studies have shown either no change or an increase in the plasma concentration of gastrin.

RISK FACTORS FOR ASPIRATION PNEUMONITIS

Mendelson divided aspiration pneumonitis into two types: liquid and solid. Whereas the aspiration of solids could result in asphyxiation, Mendelson demonstrated that the sequelae from the aspiration of liquids were more severe clinically and pathologically when the liquid was highly acidic. His observations, together with the results from other investigations, suggest that the morbidity and mortality of aspiration depend on the following three variables: (1) the chemical nature of the aspirate, (2) the physical nature of the aspirate, and (3) the volume of the aspirate. Aspirates with a pH less than 2.5 cause a granulocytic reaction that continues beyond the acute phase. Aspiration of particulate material can yield a clinical picture with severity equal to or greater than that caused by the aspiration of acidic liquid. Aspiration of small volumes of neutral liquid results in a very low rate of mortality. However, aspiration of large volumes of neutral liquid results in a high mortality rate, presumably as a result of the disruption of surfactant by the large volume of liquid or from a mechanism similar to that seen in “near drowning.”

Historically, anesthesia providers have considered a nonparticulate gastric fluid with a pH less than 2.5 and a gastric volume greater than 25 mL (i.e., 0.4 mL/kg) as risk factors for aspiration pneumonitis. No human study has directly answered this question.
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<td>&lt; 100 µg: no delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 100 µg: delay</td>
</tr>
<tr>
<td></td>
<td>Kelly et al. (1997)</td>
<td>Labor with neuraxial bolus: (1) epidural bupivacaine 0.375%; (2) epidural bupivacaine 0.25% + fentanyl 50 µg; (3) intrathecal bupivacaine 2.5 mg + fentanyl 25 µg</td>
<td>Epidural fentanyl: no delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intrathecal fentanyl: delay</td>
</tr>
</tbody>
</table>
different volumes of an acidic tracheal aspirate. Death was seen with aspirate volumes of 0.8 mL/kg and 1.0 mL/kg but not with volumes of 0.4 mL/kg and 0.6 mL/kg. Similarly, Plourde and Hardy refuted the assumption that all the gastric contents would be aspirated and demonstrated that gastric volumes of 0.4 mL/kg did not increase the risk for aspiration. Hence the gastric volume that puts a patient at risk for aspiration pneumonitis has not been determined. However, a reasonable goal of prophylactic therapy would be a gastric pH greater than 2.5 and a gastric volume as low as possible.

**PATHOPHYSIOLOGY**

Aspiration pneumonitis (Mendelson’s syndrome) describes a chemical injury to the tracheobronchial tree and alveoli caused by the inhalation of sterile acidic gastric contents, whereas aspiration pneumonia may be regarded as an infectious process of the respiratory tract caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria. Aspiration of gastric contents could therefore result in acid injury to the lung with or without bacterial and particulate matter–related effects.

Aspiration of acidic liquid injures the alveolar epithelium and results in an alveolar exudate composed of edema, albumin, fibrin, cellular debris, and red blood cells whereas the aspiration of neutral, nonparticulate liquid leads to an alveolar exudate with minimal damage to the alveoli. The phospholipid and apoprotein composition of surfactant changes, exerting a negative effect on its surface-active properties. This effect leads to an increase in intra-alveolar water and protein content and a loss of lung volume, resulting in a decrease in pulmonary compliance and intrapulmonary shunting of blood. The cellular debris and bronchial denuding cause bronchial obstruction. The exudative pulmonary edema, bronchial obstruction, reduced lung compliance, and shunting result in hypoxemia, increased pulmonary vascular resistance, and increased work of breathing. After the direct acid-mediated injury of the respiratory tract, an intense inflammatory response ensues from macrophage activation and secretion of cytokines (e.g., interleukins [IL]-1, IL-6, IL-8, etc.)

- **Table 28.1:** Studies of Gastric Emptying during Pregnancy and Labor—cont’d

<table>
<thead>
<tr>
<th>Method of Assessment</th>
<th>Study</th>
<th>Study Period and Subjects</th>
<th>Gastric Emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time ultrasonography</td>
<td>Carp et al. (1992)³⁸</td>
<td>Nonpregnant controls, third trimester</td>
<td>No delay</td>
</tr>
<tr>
<td>Real-time ultrasonography</td>
<td>Chiloiro et al. (2001)³⁷</td>
<td>Serial study in 11 women: first and third trimesters, 4–6 months postpartum</td>
<td>No delay</td>
</tr>
<tr>
<td>Real-time ultrasonography and acetaminophen absorption</td>
<td>Wong et al. (2002)³⁹</td>
<td>Third trimester</td>
<td>50-mL or 300-mL water: no delay</td>
</tr>
<tr>
<td>Real-time ultrasonography and acetaminophen absorption</td>
<td>Wong et al. (2002)³⁹</td>
<td>Cross-over study</td>
<td>Faster gastric emptying with 300 mL</td>
</tr>
<tr>
<td>Real-time ultrasonography and acetaminophen absorption</td>
<td>Wong et al. (2007)³⁷</td>
<td>10 obese parturients</td>
<td>50-mL or 300-mL water: no delay</td>
</tr>
</tbody>
</table>

**Fig. 28.5** Relationship between acidity and PaO₂. In this study, 4 mL/kg of fluid of varying pH was instilled into the tracheas of dogs. The severity of the hypoxemia correlated with the pH of the aspirate. A maximal decrease in PaO₂ occurred with aspirates with a pH of less than 2.5. B, baseline. (From Awe WC, Fletcher WS, Jacob SW. The pathophysiology of aspiration pneumonitis. Surgery. 1966;60: 232–239.)
IL-8, and IL-10, and tumor necrosis factor-alpha (TNF-α). These inflammatory mediators lead to the chemotaxis, accumulation, and activation of neutrophils in the alveolar exudate, up-regulation of adhesion molecules within the pulmonary vasculature, and activation of the complement pathways. The neutrophils subsequently release oxidants, proteases, leukotrienes, and other proinflammatory molecules. Amplification of these inflammatory processes may result in the development of acute lung injury or acute respiratory distress syndrome (ARDS) (Fig. 28.6).²⁴-²⁶

The acidic contents of the stomach prevent the growth of bacteria under normal conditions. However, gastric contents may become colonized with pathogenic gram-negative bacteria in patients receiving antacid therapy (e.g., proton-pump inhibitor or H₂-receptor antagonist) or patients with gastroparesis or intestinal obstruction. The bacterial content adds to the inflammatory response to acid aspiration.²⁷

Aspiration of particulate matter in the supine position most commonly involves injury to the posterior segments of the upper lobes and the apical segments of the lower lobes, whereas aspiration in the semirecumbent or upright position typically leads to injury to the lower lobes. The right lower lobe is the most common site of aspiration injury because the right mainstem bronchus has larger and more vertical architecture compared with the left mainstem bronchus. Obstruction of the bronchi or bronchioles results in bronchial denudation and collapse of the bronchopulmonary segments. Persistent or unresolved collapse can lead to lung abscesses and cavitation.²⁷

After the acute period, the process resolves through the proliferation and differentiation of surviving type II pneumocytes in the alveolar epithelial cells.²⁵,²⁶ The type II pneumocytes actively transport sodium out of the alveolus, and water follows passively. Soluble proteins are removed by paracellular diffusion and endocytosis, and insoluble proteins are removed by macrophages. Neutrophils are removed by programmed cell death and subsequent phagocytosis by macrophages. Type II pneumocytes gradually restore the normal composition of the surfactant. In a subset of patients with ARDS, the injury progresses to a fibrosing alveolitis—an accumulation of mesenchymal cells, their products, and new blood vessels.

Bronchospasm and disruption of surfactant likely account for the slight decrease in PaO₂ and increase in shunting that are observed.²⁹ Aspiration of large solid particles may cause atelectasis by obstructing large airways.³ Aspiration of smaller particulate matter causes an exudative neutrophilic response at the level of the bronchioles and alveolar ducts; the clinical picture is similar after the aspiration of acidic liquid.⁸⁸,⁶⁹

**CLINICAL COURSE**

In most cases of aspiration during anesthesia, the anesthesia provider witnesses regurgitation of gastric contents into the hypopharynx. Patients who aspirate while breathing spontaneously have a brief period of breath-holding followed by tachypnea, tachycardia, and a slight respiratory acidosis. Significant aspiration always results in some hypoxemia caused by greater shunting and, frequently, bronchospasm.

An abnormality on a chest radiograph can be seen in 85% to 90% of patients who aspirate gastric contents.²⁸ Because these chest radiographic findings may lag behind clinical signs by as much as 12 to 24 hours, the initial radiograph may appear normal.²² In mild cases, alveolar infiltrates are seen in the dependent portions of the lungs. Severe aspiration results in diffuse bilateral infiltrates without signs of heart failure (i.e., without engorged pulmonary vasculature and/or enlarged cardiac silhouette) (Fig. 28.7). These symptoms and signs may progress to satisfy the Berlin Definition for ARDS; the criteria are as follows²⁹:

- **Clinical:** within 1 week of known clinical insult
- **Chest imaging:** bilateral opacities not explained by effusions
- **Biochemical:** PaO₂/FiO₂ ratio less than 300 with continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) greater than 5 cm H₂O
- **Origin of pulmonary edema:** not explained by cardiac failure or fluid overload

**TREATMENT**

**Management of Aspiration**

Management principles include (1) tracheal suction; (2) rigid bronchoscopy in cases of aspiration of large, solid particles; and (3) management of hypoxemia with CPAP in nonintubated patients. Treatments that lack evidence to support their use are the administration of corticosteroids, routine use of prophylactic antibiotics, and lung lavage with saline and bicarbonate.²²

**Initial Management**

Suction of the upper airway followed by tracheal intubation and suction of the primary bronchi with a soft suction catheter is indicated for the initial management. Fiberoptic bronchoscopy can be useful for evaluating the extent of aspiration and whether solid particles are present, and for the removal of liquid contents. Rigid bronchoscopy is useful for removing large food particles that cause airway obstruction. Lung lavage with saline or bicarbonate does not reduce the parenchymal damage caused by acid aspiration and can worsen preexisting hypoxemia.²²

**Antibiotics**

Prophylactic antibiotics are not efficacious for aspiration and may lead to the development of infection with resistant organisms. Infection is not a component of acute pulmonary aspiration of sterile gastric contents.²² Antibiotics should be administered only in the presence of clinical findings that suggest infection (e.g., fever, worsening infiltrates on chest radiographs, leukocytosis, positive result of Gram stain of sputum, clinical deterioration).

In patients who are intubated, a nonbronchoscopic bronchoalveolar lavage sample can be sent for laboratory analysis. Tracheal sputum samples may be insufficient to identify a
Aspiration: Risk, Prophylaxis, and Treatment

Interstitium
- Necrotic or apoptotic type I cell
- Red cell
- Endothelial cell
- Type II cell
- Fibroblast
- Surfactant layer
- Alveolar macrophage
- Alveolar air space
- Type I cell

Red cell
Fibroblast
Neutrophil
Protein-rich edema fluid
Hyaline membrane
Migrating neutrophil
Activated neutrophil
Platelets
Fibrin
Proteases
IL-8
IL-6,
IL-10
MIF
TNF-α
Oxidants
Leukotrienes
PAF
Procollagen
Inactivated surfactant
Activated neutrophil
Fibroblast
Cellular debris
Alveolar macrophage
Alveolar air space
Swollen, injured endothelial cells
Widened edematous interstitium
Inactivated surfactant
Unresolved fibrin depositions
Fibrin-rich hyaline membranes
The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant and, together with unresolved fibrin depositions, fibrin-rich hyaline membranes are formed.

bacterial pathogen, and some authorities recommend sampling of the lower respiratory tract with a protected specimen brush. 

Empirical antibiotic therapy is appropriate in patients with suspected bacterial colonization of gastric contents. The “at risk” group includes patients who have gastroparesis or bowel obstruction and those who are receiving antacid therapy. The use of PPIs and H$_2$-receptor antagonists is common in late pregnancy, given the prevalence of gastroesophageal reflux disease. Reduced gastric acidity from long-term antacid therapy increases the incidence of community-acquired and ventilation-associated pneumonia. But it is uncertain whether parturients on long-term acid-suppression therapy are at higher risk for developing bacterial pneumonia after aspiration. Nonetheless, empirical antibiotic therapy is also appropriate for parturients on long-term antacid therapy and for those with aspiration pneumonitis that fails to resolve within 48 hours. The choice of antibiotic depends on the observed local patterns of antibiotic resistance. The target pathogens are gram-positive organisms (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*) and some gram-negative organisms (e.g., *Haemophilus influenzae*, *Escherichia coli*, Enterobacteriaceae) when the diagnosis is made less than 48 hours after hospital admission (i.e., community-acquired pneumonia). *Pseudomonas aeruginosa* is a common pathogen in cases of nosocomial (hospital-acquired) aspiration pneumonia. Anaerobes are no longer believed to be present in the majority of cases. Pharmacologic therapy should be altered when specific pathogens and their antibiotic sensitivities are determined.

**Treatment of Hypoxemia**

Exudation of fluid into the alveoli, decreased surface activity of surfactant, and atelectasis all result in intrapulmonary shunting and hypoxemia. The administration of CPAP in patients breathing spontaneously or the administration of PEEP in patients undergoing mechanical ventilation restores functional residual capacity, reduces pulmonary shunting, and reverses hypoxemia. Supplemental oxygen should be given as required.

**Corticosteroids**

Despite decades-long use of corticosteroids in the management of aspiration pneumonitis, animal and human studies have failed to demonstrate a beneficial effect on pulmonary function, lung injury, alveolar-capillary permeability, or clinical outcomes after acid aspiration. Thus, the administration of corticosteroids for aspiration pneumonitis is not recommended.

**Management of Respiratory Failure**

Aspiration of gastric contents can result in activation of inflammatory intrapulmonary pathways consistent with the pathophysiology observed in ARDS. The basic tenets of management of ARDS include the use of “lung-protective” ventilation strategies, the judicious management of fluids, and the application of basic critical care algorithms. The management of severe ARDS and hypoxemia resistant to conventional management involves the use of rescue therapies (e.g., prone positioning, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation) usually used in the critical care setting and thus will not form part of this overview. The following section outlines the basic principles in immediate management and stabilization. Readers are referred to extensive reviews of management of ARDS for further information.

**Mechanical Ventilation**

The key principles governing mechanical ventilation in ARDS involve limiting the inspiratory plateau pressure to 30 cm H$_2$O and providing the lowest effective tidal volume to prevent alveolar overdistention and tidal (cyclic) recruitment-derecruitment. Such lung-protective strategies correlated with improved outcomes in a prospective multicenter trial of the management of ARDS in which the use of low tidal volumes and plateau pressure (6 mL/kg and 30 cm H$_2$O or less) was compared with traditional ventilation strategy (12 mL/kg and 50 cm H$_2$O or less). Patients in the lower tidal volume group had a 22% reduction in mortality and an increase in ventilator-free days. Current recommendations for the treatment of ARDS include mechanical ventilation that minimizes ventilator-induced lung injury (low target tidal volume [6 mL/kg], plateau pressure less than 30 cm H$_2$O, prone positioning for severe ARDS, and higher PEEP in moderate and severe ARDS). In addition, guidelines from new evidence support the use of high-frequency oscillatory ventilation for those with severe hypoxemia and limiting extracorporeal membrane oxygenation to a subset of patients who have defined dead space and static lung compliance values.

**Positive End-Expiratory Pressure**

PEEP is a recommended component of the initial ventilatory support in the setting of ARDS. A randomized clinical trial of
ARDS (n = 549) compared the effects of low and intermediate PEEP levels set according to predetermined combinations of PEEP and FiO₂ in the setting of a lung-protective mechanical ventilation strategy. There were no significant differences in hospital mortality (24.9% versus 27.5%, respectively) or days to unassisted breathing (14.5 days versus 13.8 days, respectively) between the two groups. However, the role of comparatively higher levels of PEEP in protective ventilation strategies for ARDS is far from clear. An experimental model for acute lung injury from acid aspiration demonstrated that the titration of PEEP improved arterial oxygenation but was associated with lung inflammation as evidenced by histopathologic evaluation. This study supports the concept of best PEEP as a compromise between alveolar recruitment, lung inflammation, and hyperinflation. Current PEEP strategies focus on degree of recruitability of the lungs, given the finding that higher PEEP benefits patients with high recruitability (severe lung injury), while the injurious effects of high PEEP outweigh the benefit in those with low recruitability (mild lung injury).

Fluid Management

In a 2 × 2 factorial trial design, the ARDS Clinical Trials Network Research Group evaluated the use of a conservative versus liberal fluid strategy and the value of guiding this intervention with central venous pressure or pulmonary artery occlusion pressure measurements. The group that received conservative fluid management, whether guided by central venous pressure and/or pulmonary capillary occlusion pressure measurements, had much lower net fluid balance, better lung function, and a shorter duration of mechanical ventilation and intensive care unit stay. Further, there appeared to be no increase in the incidence or duration of shock or need for dialysis in the conservative fluid management arm of the trial. A 2017 meta-analysis comparing conservative and liberal fluid resuscitation strategies found increased ventilator-free days and decreased intensive care unit stay among patients managed with conservative fluid strategies. Thus, early management of ARDS (after initial resuscitation) focuses on limiting iatrogenic insult with conservative fluid management.

Basic Critical Care Algorithms

To minimize the risk for sepsis, central venous catheters and other invasive hemodynamic monitors should be removed as early as is clinically feasible. Aseptic precautions should be used during care, and infections should be treated with antibiotics specific to the bacterial pathogen. Whether tight and rigorous glycemic control should be employed is controversial. Occasional withdrawal of sedation and the use of propofol for gastrointestinal bleeding and thromboembolic events are currently considered the standard of care in any critically ill patient (see Chapter 54). Corticosteroids

Recovery from ARDS depends on the functional resolution of the underlying pulmonary disorder, which may follow one of two courses: (1) rapid improvement in lung function with an uncomplicated recovery or (2) slow improvements in lung function, oxygenation, and ventilation with prolonged weaning and recovery.

The corticosteroid controversy in ARDS in the context of aspiration is still unresolved. Although a 2009 systematic review suggested potential benefit from corticosteroids, their use did not appear to improve lung function or recovery in patients with ARDS in two of the well-conducted randomized clinical trials and may be associated with longer-term side effects. To further add to the controversy, a 2007 randomized controlled trial reported an improvement in outcomes in patients with ARDS randomized to receive a methylprednisolone infusion versus placebo. Most recently, a 2014 meta-analysis including 1474 patients in 18 studies showed no impact of corticosteroid therapy on mortality. While there was no specific analysis of cases of ARDS from aspiration-related lung injury, corticosteroid therapy increased mortality in a subgroup of patients with influenza-related ARDS. At the current time, data do not support the routine use of corticosteroids in ARDS for the attenuation of lung injury after pulmonary aspiration.

PROPHYLAXIS

The risk for aspiration is extremely low when gastric emptying is normal and patients, including parturients, are appropriately fasted. Factors predisposing to regurgitation, particularly in obstetrics, include emergency surgery, difficult/failed tracheal intubation, light anesthesia, and gastroesophageal reflux. The risk for failed intubation is 3 to 11 times greater in pregnant patients than in nonpregnant patients, reported as 1 in 250 at the end of a 17-year audit in the United Kingdom (1978 to 1994) and as 1 in 232 in an 8-year audit in the United States (2006 to 2013) (see Chapter 29). Airway edema, breast enlargement, obesity, and the high rate of emergency surgery can all contribute to the risk for failed tracheal intubation in pregnant women. Aspiration pneumonitis is often associated with difficult or failed intubation during the induction of general anesthesia. In a survey conducted by the Society for Obstetric Anesthesia and Perinatology, intubation was recorded as difficult in 14 of 19 cases of aspiration in which tracheal intubation was required. Moreover, Warner et al. reported that the risk for aspiration during emergence from anesthesia was almost as high as that during induction of anesthesia. Thus, prophylactic regimens must provide protection during both induction of, and emergence from, general anesthesia. Although the risk for aspiration during elective, as opposed to emergency, surgery under general anesthesia is very low, parturients undergoing cesarean delivery or other surgical procedures should receive pharmacologic prophylaxis.

Because the incidence of aspiration pneumonitis is low, the efficacy of prophylactic regimens is measured by their ability to alter gastric pH and volume. In 30% to 43% of pregnant women, the fasting gastric volume is greater than 25 mL and the gastric fluid pH is less than 2.5. However,
the percentage of term parturients at risk may not differ from that of patients undergoing elective abortion, postpartum sterilization, or gynecologic surgery (Table 28.2). Decreased lower esophageal sphincter tone and a higher risk for difficult tracheal intubation are the primary factors that increase the risk for aspiration during pregnancy and the immediate postpartum period, and these are the factors that mandate the need for pharmacologic prophylaxis.

**Preoperative Oral Fluid Administration**

Multiple studies have described no increase in gastric volume or acidity after the oral administration of 150 mL of fluid (e.g., coffee, tea, water, other clear liquids, orange juice without pulp) in nonpregnant adults 2 hours before elective surgery. The patients in these studies all fasted overnight and were expected to have a low gastric volume when the test meal was given. Lewis and Crawford noted that allowing women undergoing elective cesarean delivery to consume a meal of both tea and toast 2 to 4 hours preoperatively increased gastric volume and decreased gastric pH compared to a fasted control group. Consumption of tea without toast resulted in an increase in gastric volume, but it did not alter gastric pH. Particulate material was aspirated from the stomachs of 2 of the 11 patients who consumed both tea and toast. The investigators did not state the volume of tea consumed by these patients.

When gastric emptying of both 50 mL and 300 mL of water was assessed in nonlaboring term parturients, the gastric emptying half-time for 300 mL was significantly shorter than that for 50 mL. When a similar study was conducted in obese nonlaboring term parturients (mean ±SD prepregnancy body mass index 41 ± 9 kg/m²), the gastric emptying time for 300 mL was not longer than that for 50 mL. The latter finding suggests that the American Society of Anesthesiologists (ASA) Guidelines for Obstetric Anesthesia, which state that “the uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia” could also be applied to healthy, obese pregnant women presenting for elective surgery. However, factors other than the rate of gastric emptying can influence the rate of pulmonary aspiration, particularly in obese subjects. Obesity is associated with a higher incidence of gastroesophageal reflux and difficult airway management (both intraoperatively and postoperatively) (see Chapter 49). Moreover, the cesarean delivery rate is higher and the success rate of trial of labor after cesarean delivery is lower in obese parturients.

**Choice of Anesthesia**

The Obstetric Anesthesia Work Force Survey demonstrated that general anesthesia was used for less than 5% of elective cesarean procedures by 2011. Two sequential analyses performed at a large tertiary care obstetric facility showed that the use of general anesthesia for cesarean delivery decreased from 7.2% to 3.6% from 1990 to 1995, with a further decline from 1% to 0.8% from 2000 to 2005. One maternal death resulted from a failed tracheal intubation in the first cohort, with no reported anesthesia-related mortality during the second study period. Hawkins et al. reported 67 maternal deaths resulting from complications of general anesthesia and 33 maternal deaths resulting from complications of neuraxial anesthesia in the United States during the years 1979 to 1990. Approximately 73% of general anesthesia–related maternal deaths were caused by airway difficulty, primarily failed intubation and/or aspiration. In contrast, data from the more recent period spanning the years 1997 to 2002 indicate that the mortality rates for cesarean delivery are similar for general and regional anesthesia. Studies reviewing failed tracheal intubation during the periods 1993 to 1998 and 1999 to 2003 in the United Kingdom showed that, while the rate of failed intubation during this period had not declined, there were no deaths from this potentially fatal complication. Although this relative change in maternal mortality from the complications of general anesthesia is very encouraging, other factors such as the worldwide obesity epidemic have increased the challenges presented to anesthesia providers, particularly with respect to emergency operative deliveries. Therefore, techniques for preventing pulmonary aspiration of gastric contents will remain or even become increasingly pertinent to clinical practice.

**Antacids**

The ASA Practice Guidelines for Obstetric Anesthesia state: “Before surgical procedures (e.g., cesarean delivery and postpartum tubal ligation), consider timely administration of nonparticulate antacids, H₂-receptor antagonist, and/or metoclopramide for aspiration prophylaxis.” Particulate antacids should not be used as prophylaxis because when aspirated they cause pulmonary shunting and hypoxemia of magnitude similar to that caused by acid aspiration and

<table>
<thead>
<tr>
<th>Population</th>
<th>pH &lt; 2.5</th>
<th>Volume &gt; 25 mL</th>
<th>pH &lt; 2.5 and Volume &gt; 25 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>57–80</td>
<td>51–54</td>
<td>31–43</td>
</tr>
<tr>
<td>Nonpregnant</td>
<td>75–95</td>
<td>45–67</td>
<td>45–60</td>
</tr>
<tr>
<td>Postpartum</td>
<td>54–93</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Children</td>
<td>93–100</td>
<td>64–78</td>
<td>64–77</td>
</tr>
<tr>
<td>Obese, nonpregnant</td>
<td>88</td>
<td>86</td>
<td>75</td>
</tr>
</tbody>
</table>
Histamine-2 Receptor Antagonists

The ASA Task Force on Obstetric Anesthesia concluded that H₂-receptor antagonists are efficacious in reducing gastric acidity and volume. H₂-receptor antagonists block histamine receptors on the oxyntic cell and thus diminish gastric acid production, leading to a slight reduction in gastric volume in the fasting patient. When given intravenously, an H₂-receptor antagonist begins to take effect in as little as 30 minutes. When the same study was repeated in laboring women, the mean time that the pH remained greater than 3.0 was 57 minutes in subjects who had received no analgesia and 166 minutes in those who had received meperidine. Nonparticulate antacids should be administered within 20 minutes of the induction of general anesthesia, particularly if the procedure is an emergency and there is insufficient time for a co-administered H₂-receptor antagonist to be effective.

Cimetidine (given in doses of 200 to 400 mg intravenously or orally) reduces gastric acidity within 60 to 90 minutes. Therapeutic plasma concentrations are sustained for approximately 4 hours. Cimetidine may decrease the rate of plasma clearance of certain drugs, including some local anesthetics (e.g., lidocaine), by binding to the cytochrome P450 system in the hepatocyte and by reducing hepatic blood flow. Cimetidine crosses the placenta, but this does not appear to have harmful effects. Because arrhythmias and cardiac arrest have been reported with the rapid intravenous administration of cimetidine, a slow rate of intravenous administration or the oral route of administration is recommended. The use of cimetidine in obstetric anesthesia has largely been replaced by the use of other H₂-receptor antagonists.

Ranitidine, a chemically substituted amino-alkyl furan, has been evaluated after the administration of an intravenous or intramuscular dose of 50 to 100 mg or an oral dose of 150 mg. These studies have noted that the administration of ranitidine results in a gastric pH greater than 2.5 within 1 hour and sustained therapeutic concentrations for approximately 8 hours. Ranitidine does not have any major interaction with the cytochrome P450 system and does not alter plasma concentrations of lidocaine or bupivacaine after their epidural administration.

Nizatidine (given in doses of 150 to 300 mg orally) and famotidine (given in doses of 20 to 40 mg orally or intravenously) are alternative H₂-receptor antagonists. Both have a duration of action greater than 10 hours and do not interfere with the metabolism of other drugs by the cytochrome P450 system.

Proton-Pump Inhibitors

Omeprazole (20 to 40 mg orally) and lansoprazole (15 to 30 mg orally) are substituted benzimidazoles that inhibit the hydrogen ion pump on the gastric surface of the oxyntic cell. Purported advantages of PPIs are a long duration of action, low toxicity, and the potential for low maternal and fetal blood concentrations at the time of delivery. However, a meta-analysis has indicated that premedication with ranitidine is more effective than PPIs in reducing the volume of gastric secretion and increasing gastric pH.

Metoclopramide

Metoclopramide is a procainamide derivative that is a peripheral cholinergic agonist and a central dopamine receptor antagonist. An intravenous dose of metoclopramide 10 mg increases lower esophageal sphincter tone and reduces gastric volume by increasing gastric peristalsis. Metoclopramide can have a significant effect on gastric volume in as little as 15 minutes. Unfortunately, prior administration of an opioid or atropine antagonizes the effect of metoclopramide. Extrapyramidal effects are a major potential side effect of metoclopramide. Metoclopramide crosses the placenta, but no significant effects on the fetus or neonate have been reported.

A systematic review of antacid prophylaxis concluded that there was no evidence to support the routine administration of drugs to women in normal labor to reduce the incidence of pulmonary aspiration or Mendelson’s syndrome. This conclusion reflects the low incidence of pulmonary aspiration of gastric contents and the absence of high-quality studies of antacid prophylaxis, rather than the presence of studies demonstrating negative results; the review cited only three studies, published in 1971, 1980, and 1984. One study assessed the use of metoclopramide and perphenazine in women receiving meperidine in labor, and the other two studies focused on the use of particulate antacids. An audit of acid aspiration prophylaxis during labor in the United Kingdom showed a decreasing number of institutions with policies to administer routine antacid prophylaxis to all laboring women. However, many institutions attempted to identify women at high risk for an emergency cesarean delivery, to whom they gave oral ranitidine 150 mg at 6-hour intervals throughout labor. An audit of French obstetric units revealed that at least one medication to prevent gastric content aspiration was used in every patient in 93% of institutions before cesarean delivery, but the frequency of
prophylaxis administration for laboring parturients was not assessed.\textsuperscript{139}

**Combination Prophylaxis Therapy**

A systematic review of interventions for reducing the risk for aspiration pneumonitis in women who received general anesthesia for cesarean delivery (22 studies) showed that each assessed therapy, including antacids, H\textsubscript{2}-receptor antagonists, and PPIs, achieved significant reduction of intragastric pH below 2.5.\textsuperscript{144} H\textsubscript{2}-receptor antagonists showed superior gastric acid pH reduction compared with PPIs at the time of tracheal intubation. Compared with placebo or with antacids alone, the combined use of antacids and H\textsubscript{2}-receptor antagonists yielded a significantly greater reduction in intragastric pH.

**Sellick Maneuver and Induction of Anesthesia**

Sellick demonstrated that the occlusion of the esophagus by cricoid pressure in cadavers prevented the flow of barium from the stomach to the pharynx.\textsuperscript{141} He also reported the successful use of this maneuver in 26 cases to prevent the passive regurgitation of gastric contents into the airway. For proper application of cricoid pressure, the head should be fully extended; it may help to have a trained assistant place a hand behind the patient’s neck, so that the cervical vertebrae and esophagus are brought forward, making it easier to occlude the latter. The trained assistant should place the thumb and middle finger on either side of the cricoid cartilage; no more than light pressure should be applied while the patient is awake, to prevent coughing, straining, retching, and esophageal rupture. After denitrogenation (preoxygenation) and administration of induction drugs, an increasingly firm downward pressure is applied to the cricoid cartilage as loss of consciousness occurs. Full application of cricoid pressure requires a force of 30 newtons (N), 1 N being the force required to accelerate a mass of 1 kg by 1 m/s\textsuperscript{2}. As a practical clinical guide to the amount of force to apply, 10 N is approximately equivalent to the downward force exerted by a mass of 1 kg. Vanner and Pryle\textsuperscript{142} demonstrated that 30 N of cricoid force prevented regurgitation of saline in cadavers with esophageal pressures as high as 40 mm Hg. The research team recommended a modest cricoid force (10 N) before loss of consciousness, increasing to 30 N after loss of consciousness; their data suggested that such pressure should be sufficient to prevent passive regurgitation of esophageal contents during induction of general anesthesia in most patients.\textsuperscript{143} Cricoid pressure is maintained until the endotracheal tube cuff is inflated and correct endotracheal tube position is confirmed.

The value of cricoid pressure has been questioned. A study employing magnetic resonance imaging of 22 healthy volunteers of both genders noted that the resting position of the esophagus was lateral relative to the cricoid cartilage in 53% of the subjects without cricoid pressure and in 91% with cricoid pressure.\textsuperscript{144} In addition, cricoid pressure displaced the esophagus relative to its initial resting position to the left and right in 68% and 21% of the subjects, respectively. The authors suggested that cricoid pressure may lead to airway displacement and an inability to reliably produce midline esophageal compression; these factors could limit the protective effect of the maneuver against passive reflux and make the intubation process more difficult. However, Rice et al.\textsuperscript{145} challenged these conclusions in a subsequent magnetic resonance imaging study investigating the efficacy of cricoid pressure. They demonstrated that the hypopharynx, rather than the esophagus, lies behind the cricoid cartilage (Fig. 28.8). The relationship of the cricoid and laryngeal cartilages is constant and is maintained by their connecting ligaments and muscles. Because the cricoid cartilage and postcricoid hypopharynx are constantly related, they will behave as a unit when compressed against the cervical spine. The investigators contended that the sealing of the hypopharynx is therefore independent of the position of the esophagus, and the actual position of the esophagus is irrelevant to the successful application of cricoid pressure.

When the technique of rapid-sequence induction of anesthesia with tracheal intubation was first described in detail, it was recommended that the trunk be elevated 30 degrees to prevent reflux and aspiration.\textsuperscript{146} Hignett et al.\textsuperscript{147} demonstrated that the functional residual capacity of healthy term parturients was increased in the 30-degree head-up position compared with the supine position. Moreover, in the 30-degree head-up position, the esophageal pressure is lower and thus the force applied to the cricoid could be reduced to 20 N\textsuperscript{148}; this reduction in force may reduce the incidence of airway problems, because these problems are often proportional to the force applied.\textsuperscript{149} Further work is required to determine whether the increase in functional residual capacity in the 30-degree head-up position prolongs the time to oxyhemoglobin desaturation during the apnea phase of rapid-sequence induction and whether this position should be routinely adopted for induction of general anesthesia in obstetric patients.

Should the incorrect application of cricoid pressure distort the laryngeal inlet and cause difficulty with laryngoscopy and/or intubation, the cricoid pressure should be promptly released.

**RECOMMENDATIONS FOR CESAREAN DELIVERY**

When possible, all mothers should be encouraged to have neuraxial anesthesia for cesarean delivery. Awake fiberoptic intubation should be considered for parturients with a potentially difficult airway who require general anesthesia. For elective cesarean delivery, a suitable antacid regimen may include the oral or intravenous administration of an H\textsubscript{2}-receptor antagonist (e.g., famotidine 20 mg) 60 to 120 minutes before the induction of anesthesia and oral sodium citrate 30 mL within 30 minutes before surgery. Some practitioners also give metoclopramide 10 mg orally at the same time as the H\textsubscript{2}-receptor antagonist or intravenously at least 15 minutes before the induction of anesthesia.

For emergency cesarean delivery under general anesthesia, 30 mL of sodium citrate should be administered...
Aspiration: Risk, Prophylaxis, and Treatment

Gastric Ultrasonography

Real-time assessment of gastric contents through the use of gastric ultrasonography may have clinical utility for cases in which nonfasted parturients require urgent cesarean delivery. The use of gastric ultrasonography to assess peripartum aspiration risk and guide anesthetic management has evolved since its first reported use in studies of gastric emptying during pregnancy. The gastric antrum can be visualized in a sagittal plane between the liver anteriorly and the pancreas posteriorly and the antral cross-sectional area (CSA) can be measured. Two mathematical models have been reported to predict gastric volume based on antral CSA. Additionally, a qualitative 3-point grading system, which assesses gastric antrum contents in both the supine and right lateral decubitus (RLD) positions, has been described; grade 0 antrum is defined as the absence of fluid content in

Fig. 28.8 Axial magnetic resonance images in the sniffing position, without (A) and with (B) cricoid pressure. (A) Postcricoid hypopharynx (arrow) and the cricoid cartilage skin marker (arrowhead) placed by the anesthesiologist before imaging. (B) Example of postcricoid hypopharynx compression (arrow) lateral to the vertebral body with cricoid pressure. In this image, the postcricoid hypopharynx is compressed against the longus colli muscle group (arrowhead). (D) Image 2 cm inferior to the cricoid ring distinctly shows the cervical esophagus (arrow) lateral to the vertebral body. In (B) and (C) the anesthesiologist’s thumb and index finger can be seen pushing on the cricoid cartilage. The axial image chosen for each study (A to C) was the image at the most inferior level of the cricoid cartilage. (From Rice MJ, Mancuso AA, Gibbs C, et al. Cricoid pressure results in compression of the postcricoid hypopharynx: the esophageal position is irrelevant. Anesth Analg. 2009;109:1546–1552.)

just after transfer of the patient to the operating room. This timing is important because sodium citrate has a relatively short duration of action, except in those mothers in whom gastric emptying has been delayed by the administration of an opioid. In addition, ranitidine 50 mg (or famotidine 20 mg or omeprazole 40 mg) and metoclopramide 10 mg should be given intravenously when time allows. Administration of these drugs may not reduce gastric volume or acidity at the time of tracheal intubation but will decrease the risk for aspiration at the time of extubation. For further protection against aspiration upon emergence from general anesthesia, an orogastric tube can be utilized to empty the stomach contents before extubation. Some units administer an H2-receptor antagonist orally every 6 hours during labor to all mothers considered to be at risk for an operative delivery.

The evidence that H2-receptor antagonists or PPIs reduce maternal morbidity and mortality has not been conclusively demonstrated; however, increasing the pH and reducing the volume of gastric contents should assist in limiting damage if pulmonary aspiration occurs. The use of cricoid pressure as part of a rapid-sequence induction technique remains standard practice.

Gastric Ultrasonography

Real-time assessment of gastric contents through the use of gastric ultrasonography may have clinical utility for cases in which nonfasted parturients require urgent cesarean delivery. The use of gastric ultrasonography to assess peripartum aspiration risk and guide anesthetic management has evolved since its first reported use in studies of gastric emptying during pregnancy. The gastric antrum can be visualized in a sagittal plane between the liver anteriorly and the pancreas posteriorly and the antral cross-sectional area (CSA) can be measured. Two mathematical models have been reported to predict gastric volume based on antral CSA. Additionally, a qualitative 3-point grading system, which assesses gastric antrum contents in both the supine and right lateral decubitus (RLD) positions, has been described; grade 0 antrum is defined as the absence of fluid content in
both the supine and RLD positions, grade 1 antrum is defined as the observation of fluid in only the RLD position, and grade 2 antrum if fluid is observed in both positions. The upper 95th percentile limit of antral CSA for fasting term, nonlaboring pregnant women in this study was 10.3 cm² in the RLD position. In a randomized controlled trial with blinded assessors, fasted third-trimester pregnant women ingested apple juice, 0 mL, 50 mL, 100 mL, 200 mL, 300 mL, or 400 mL; antral CSA measures correlated well with ingested volume.154 Further studies are warranted to validate the use of gastric ultrasonography for assessment of aspiration risk and anesthetic management for obstetric patients. Ultrasonographic detection of delayed gastric emptying or full stomach may serve as a trigger to avoid the use of general anesthesia or prompt administration of prophylactic neutralizing and promotility agents.

**ORAL INTAKE DURING LABOR**

Women in the third trimester of pregnancy exhibit a state of “accelerated starvation” if denied food and drink.155 Fasting results in the production of ketones, primarily beta-hydroxybutyrate and acetoacetic acid, and the nonesterified fatty acids from which they are derived. These changes are exacerbated by the metabolic demands of labor and delivery. Consequently, some obstetricians and nurse-midwives have suggested that maternal oral intake policies should be liberalized during labor.156 It is argued that allowing mothers to eat and drink during labor prevents ketosis and dehydration and subsequently improves obstetric outcome. The widespread use of neuraxial analgesia has resulted in a reduction in the use of systemic opioids for labor analgesia113; thus, fewer women may be at risk for opioid-induced delays in gastric emptying (with its inherent potential for aspiration). This trend has increased the demand to liberalize NPO policies during labor.157

A randomized study examined the effect of a light diet on the maternal metabolic profile, the residual gastric volume, and the outcome of labor.158 Women presenting in early, uncomplicated labor at term were stratified by parity and randomized to receive a light diet or water only. Women who consumed a light diet did not have the increase in beta-hydroxybutyrate and nonesterified acid levels seen in the mothers who consumed water only. However, the gastric volumes as measured by ultrasonography were significantly larger in those who had eaten. Thus, mothers who consume a light diet during labor could be at greater risk for aspiration if general anesthesia is required. The same study design was used in another group of women, but isotonic “sports drinks” were administered instead of solid food; these drinks reduced ketosis without increasing intragastric volume.

O’Sullivan et al.160 evaluated the effect of food intake during labor on obstetric outcomes in a randomized controlled study. A total of 2443 low-risk nulliparous women in labor were randomly assigned to either an “eating” or a “water only” group. Intention-to-treat analysis was performed. No significant differences were found in (1) the normal vaginal delivery rate, (2) the instrumental vaginal delivery rate, (3) the cesarean delivery rate, or (4) the incidence of vomiting (Fig. 28.9). Similarly, there was no difference between groups in the duration of labor; the geometric mean (GM) labor duration was 597 minutes in the “eating” group and 612 minutes in the “water only” group (ratio of GM, 0.975; 95% confidence interval, 0.927 to 1.025).

Maternal death from Mendelson’s syndrome is now extremely rare, and its decline probably owes more to the widespread use of neuraxial anesthesia than to NPO policies. Rigid NPO policies are therefore no longer appropriate on the labor and delivery unit, and women should be allowed to alleviate thirst during labor by consuming ice chips and clear fluids (e.g., isotonic sports drinks, fruit juices without pulp, black tea, and coffee). In some high-risk pregnancies, it will remain appropriate to maintain hydration by the intravenous route, and such cases must be managed individually. The American College of Obstetricians and Gynecologists (ACOG) has stated that adherence to a predetermined fasting period before nonelective surgical procedures (i.e., cesarean delivery) is not possible.161 They therefore conclude, along with the American Society of Anesthesiologists (ASA) and the Society for Obstetric Anesthesia and Perinatology, that solid food should be avoided in laboring patients.70,161 European guidelines also discourage women from eating solid food during labor. However the European guidelines acknowledge the low incidence of aspiration in obstetrics and therefore state that low-risk women could consume low residue foods (biscuits, toast, cereals) during labor.162 To date, countries with a more liberal attitude to eating during labor (e.g., the Netherlands, the United Kingdom, Australia) have not witnessed a higher incidence of maternal deaths from pulmonary aspiration. Further audit, research, and observation are required to fully inform the guidelines for oral intake during labor.

![Fig. 28.9](image-url) The effect of eating during labor on maternal obstetric outcome. CD, cesarean delivery; IVD, instrumental vaginal delivery; NVD, normal vaginal delivery. (Based on data from O’Sullivan G, Liu B, Hart D, et al. Effect of food intake during labour on obstetric outcome: randomised controlled trial. BMJ. 2009;338:b784.)
During anesthetic residual labor.

REFERENCES

- Preoperative
- The
- Reduced

include an H₂-receptor antagonist. Fast from solid food. Preoperative antacid prophylaxis may be given to administration of an H₂-receptor antagonist (or a proton pump inhibitor) and metoclopramide. These drugs may be administered after the induction of anesthesia if time does not permit their administration before induction.

- Hypoxemia

Mechanical ventilation with positive end-expiratory pressure is the most effective treatment for severe hypoxemia. “Lung-protective” ventilation strategies (i.e., lower tidal volumes and inspiratory pressures) should be employed.

- The oral intake of clear fluids may be allowed during labor.
- Eating during labor results in larger residual gastric volumes. Eating during labor does not improve obstetric outcomes.

KEY POINTS

- Airway problems associated with the use of general anesthesia are a common cause of anesthesia-related maternal deaths.
- Reduced lower esophageal sphincter tone and a higher risk for difficult tracheal intubation are the primary factors that increase the risk for aspiration during pregnancy and the immediate postpartum period.
- Although pulmonary aspiration of gastric contents is rare in contemporary obstetric anesthesia practice, fatal aspiration may occur during cesarean delivery, during difficult or failed tracheal intubation, or after extubation.
- The most effective way to decrease the risk for aspiration is to avoid the administration of general anesthesia.
- The mother undergoing elective cesarean delivery should fast from solid food. Preoperative antacid prophylaxis may include an H₂-receptor antagonist.
- Preoperative prophylaxis before emergency cesarean delivery under general anesthesia should include a nonparticulate antacid. A clear antacid is preferred because aspiration of a particulate antacid results in pulmonary parenchymal damage similar to the damage that occurs after the aspiration of gastric acid. Strong consideration should also be given to administration of an H₂-receptor antagonist (or a proton pump inhibitor) and metoclopramide. These drugs may be administered after the induction of anesthesia if time does not permit their administration before induction.
- Hypoxemia is the hallmark of aspiration pneumonitis. Mechanical ventilation with positive end-expiratory pressure is the most effective treatment for severe hypoxemia. “Lung-protective” ventilation strategies (i.e., lower tidal volumes and inspiratory pressures) should be employed.
- The oral intake of clear fluids may be allowed during labor.
- Eating during labor results in larger residual gastric volumes. Eating during labor does not improve obstetric outcomes.

REFERENCES


The Difficult Airway: Risk, Assessment, Prophylaxis, and Management

Robin Russell, MBBS, MD, FRCA

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RISK

Definitions

A difficult airway can be defined in several ways. A practitioner may be said to encounter a difficult airway when he or she experiences difficulty providing adequate maintenance or protection of the airway that leads to hypoxemia or soiling of the tracheobronchial tree. This definition includes difficulty in providing ventilation via a face mask or supraglottic airway (e.g., laryngeal mask airway [LMA]) or tracheal intubation. The American Society of Anesthesiologists (ASA) Task Force on Management of a Difficult Airway defines a difficult airway as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with face mask ventilation of the upper airway, difficulty with tracheal intubation, or both. 2

The prevalence of difficult face mask ventilation is dependent on the definition. In one study, 3% of 1502 non-pregnant patients experienced difficulty in face mask ventilation, which was defined as an oxyhemoglobin saturation value less than 92%. A multivariate analysis identified five independent risk factors for difficult face mask ventilation: (1) age older than 55 years, (2) body mass index (BMI) greater than 26 kg/m2, (3) presence of a beard, (4) lack of teeth, and (5) a history of snoring. Impossible face mask ventilation, defined as an inability to exchange air during bag-and-mask ventilation despite multiple providers, airway adjuncts, and neuromuscular blockade, was reported in 77 of 50,000 (0.15%) nonobstetric anesthetic procedures. 4 Independent predictors of impossible face mask ventilation were previous neck irradiation, male sex, diagnosis of sleep apnea, and a Mallampati class III or IV (see later discussion). 5 Difficult laryngeal mask ventilation may be defined as the inability within three attempts of device insertion to produce expired tidal volumes more than 7 mL/kg (leak pressure greater than 15 to 20 cm H2O). 6 In a study of 11,910 nonobstetric patients, 7 the incidence of difficult laryngeal mask ventilation was 0.19%.

Although failed tracheal intubation may appear to be a tangible endpoint, its definition is not standardized. Various
definitions have been used, ranging from tracheal intubation not accomplished with a single dose of succinylcholine to simply an inability to intubate during general anesthesia. Such variation inevitably leads to a difference in the reported rate of failed intubation. Defining difficult tracheal intubation is even more complex. Difficulty may be encountered because of failure to visualize the glottis (difficult laryngoscopy) or due to an anatomic laryngeal or tracheal abnormality. Difficulty has been variously defined by (1) the time taken to intubate, (2) the number of attempts, (3) the view at laryngoscopy, and (4) the requirement for special equipment.

Although a dramatic decrease in the number of anesthesia-related deaths has been reported in the UK Confidential Enquiries into Maternal Deaths over the past 40 years, complications from general anesthesia, primarily complications of airway management, continue to be a leading cause of anesthesia-related maternal mortality. Similarly, data from the United States have demonstrated a higher case-fatality rate with general anesthesia compared with neuraxial anesthesia. Although the development of national guidelines has resulted in a more systematic approach to the management of the difficult airway, deaths directly resulting from anesthesia still occur owing to failures in ventilation, tracheal intubation, or airway management following extubation. Despite widespread use of neuraxial anesthesia for operative delivery, general anesthesia may still be required in emergency situations, if neuraxial anesthesia is contraindicated or patients refuse it, or, most commonly, if neuraxial anesthesia fails to provide adequate anesthesia.

Incidence and Epidemiology
The incidence of failed intubation in obstetrics has long been considered to be approximately 1 in 250 to 300 (Table 29.1). A 2015 systematic review including data from published studies, abstracts, and databases reported a failed intubation rate at cesarean delivery of 1 in 433. The incidence of failed intubation for all obstetric procedures was slightly higher at 1 in 390, which likely reflects intubation difficulties resulting from airway swelling following crystalloid resuscitation in postpartum hemorrhage. The authors noted no increase in incidence from 1985 to 2014. However, there was significant heterogeneity among reports. Importantly, the authors highlighted the perceived emphasis on the need to achieve tracheal intubation. This emphasis (see later discussion) may encourage repeated efforts with their accompanying risk for morbidity.

Regardless, the failed intubation rate in obstetric patients is approximately 8 times higher than estimates of the rate in nonobstetric surgical populations. A number of reasons have been proposed to explain the increased difficulty with obstetric airway management. Significant physiologic and anatomic changes of pregnancy (see later discussion) affect the airway, oxygenation, and metabolism. The majority of obstetric general anesthetics are administered for emergency deliveries, often during off-hours; these anesthetic procedures may be conducted by inexperienced anesthesia providers with less proficiency in difficult airway management. Excessive cricoid pressure applied by a poorly trained assistant can worsen the glottic view at laryngoscopy, as can positioning parturient with left lateral tilt. With a decrease in the number of cesarean deliveries performed under general anesthesia, trainees have fewer opportunities to become familiar with challenges of the obstetric difficult airway. Changes in anesthesia training, notably the reduction in trainee working hours and the advent of supraglottic airway (SGA) devices, mean that laryngoscopy and intubation are now less commonly performed than previously. Therefore, the skills required to manage a challenging tracheal intubation are less likely to have been gained before working on the labor and delivery unit without direct supervision.

Changes in maternal demographics, most notably an increase in the prevalence of maternal obesity, may increase the risk for complications from general anesthesia, especially when performed for emergency procedures. Obese women are at increased risk for obstetric interventions requiring anesthesia and are at increased risk for failed neuraxial anesthesia, necessitating the use of general anesthesia for emergency delivery (see Chapter 49). Difficulty with intubation has been reported to occur in 15.5% of the nonobstetric obese population. A large Danish cohort study of more than 90,000 nonobstetric patients found that a BMI greater than 35 kg/m² was a significant risk factor for difficult intubation (odds ratio [OR], 1.34); BMI was a more accurate predictor of difficult intubation than weight alone. Data collected from one UK region from 1993 to 1998 identified 26 parturients with failed intubation at cesarean delivery; the mean BMI was 33.1 kg/m². Poor head and neck positioning at induction of anesthesia, inappropriately applied cricoid pressure, macromastia, shorter interval from start of apnea until significant oxygen desaturation, and operator anxiety may be responsible for a higher incidence of difficult airway management in obese patients. In contrast to some experts, others have questioned whether the rate of difficult and failed intubation is increasing.

### TABLE 29.1 The Incidence of Failed Intubation in Obstetrics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Number</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyons</td>
<td>1985</td>
<td>UK</td>
<td>2331</td>
<td>1:291</td>
</tr>
<tr>
<td>Samssoon</td>
<td>1987</td>
<td>UK</td>
<td>1980</td>
<td>1:280</td>
</tr>
<tr>
<td>Rocke</td>
<td>1992</td>
<td>South Africa</td>
<td>1500</td>
<td>1:750</td>
</tr>
<tr>
<td>Hawthorne</td>
<td>1996</td>
<td>UK</td>
<td>5802</td>
<td>1:250</td>
</tr>
<tr>
<td>Barnardo</td>
<td>2000</td>
<td>UK</td>
<td>8970</td>
<td>1:249</td>
</tr>
<tr>
<td>Rahman</td>
<td>2005</td>
<td>UK</td>
<td>4768</td>
<td>1:238</td>
</tr>
<tr>
<td>Saravanakumar</td>
<td>2006</td>
<td>UK</td>
<td>5968</td>
<td>1:543</td>
</tr>
<tr>
<td>McDonnell</td>
<td>2008</td>
<td>Australia</td>
<td>1095</td>
<td>1:274</td>
</tr>
<tr>
<td>Djabatey</td>
<td>2009</td>
<td>UK</td>
<td>3430</td>
<td>0</td>
</tr>
<tr>
<td>Bullough</td>
<td>2009</td>
<td>UK</td>
<td>19,762</td>
<td>1:309</td>
</tr>
<tr>
<td>McKeen</td>
<td>2011</td>
<td>Canada</td>
<td>2633</td>
<td>1:1300</td>
</tr>
<tr>
<td>Quinn</td>
<td>2013</td>
<td>UK</td>
<td>12,800</td>
<td>1:224</td>
</tr>
<tr>
<td>D’Angelo</td>
<td>2014</td>
<td>US</td>
<td>5332</td>
<td>1:533</td>
</tr>
</tbody>
</table>
in obstetric anesthesia practice. A more liberal attitude toward the use of general anesthesia has been suggested to lead to greater familiarity with maternal airway management and subsequent reduced rates of difficulty. Other explanations include increased use of neuraxial blocks in those with predicted airway difficulty, focused training with a bougie as a tracheal tube guide, senior specialist–level involvement, and increasing use of video laryngoscopy and fiberoptic intubation.

Certainly the presence of experienced anesthesia staff during induction of general anesthesia is recommended and should reduce the morbidity and mortality, and perhaps the frequency, of difficulty with airway management. It is hoped that the introduction and widespread acceptance of simulation training in obstetrics will lead to improvement in staff performance during critical events such as difficult airway management (see Chapter 11). A need for situational awareness and recognition of the risk for fixation error, especially when dealing with emergency airway issues, was highlighted in a recent edition of the UK Confidential Enquiries into Maternal Deaths.

**Maternal Morbidity and Mortality**

For many years the UK Confidential Enquiries into Maternal Deaths have reported thromboembolism, hypertensive disease, hemorrhage, and infection as the leading direct causes of maternal mortality. In the report covering the 2012 to 2014 triennium, pregnancy-related mortality from anesthetic causes was the 11th most common cause, accounting for 1% of maternal deaths. In the United States between 1991 and 2002, 1.6% of maternal deaths were related to complications of anesthesia care, representing a 59% reduction in anesthesia-related mortality compared with data from 1979 to 1990. Experience from both countries demonstrates dramatic improvements in anesthesia-related maternal mortality in the past three decades. This improvement likely reflects the tremendous efforts by national anesthesia organizations in defining standards of care that lead to improved maternal safety.

Compared with neuraxial anesthesia, general anesthesia is associated with a greater risk for maternal mortality (Table 29.2; see also Chapter 39). Using data from the Centers for Disease Control and Prevention (CDC), the estimated case-fatality risk ratio for general anesthesia compared with neuraxial anesthesia was 16.7 between 1985 and 1990. However, the estimated risk ratio for the period between 1997 and 2002 was only 1.7 (95% CI, 0.6 to 4.6, \( P = 0.2 \)). Improvements in monitoring and rescue airway equipment, and the publication of algorithms for difficult airway management may account for the reduction in mortality from general anesthesia. The case-fatality risk for general anesthesia from the earlier period may have overstated the relative risk because the accuracy of data was questionable and it is likely that general anesthesia was used for more complex cases for which mortality was expected to be greater. Unfortunately, maternal deaths directly attributable to general anesthesia are still reported. Although protocols for the management of a difficult airway are now ubiquitous, they are not always followed.

Hypoventilation and airway obstruction after extubation are now increasingly recognized as causes of maternal mortality. In Michigan between 1983 and 2003, eight maternal deaths were believed to be related to anesthesia care; all deaths occurred during emergence from general anesthesia or the recovery period, and six of the eight patients were obese. System errors in which the care of the patient did not meet recognized standards were identified in five of the eight cases. These errors included inadequate supervision by an anesthesiologist and lapses in postoperative monitoring.

**Physiologic and Anatomic Changes in Pregnancy**

Of the multitude of anatomic and physiologic changes that occur in pregnancy (see Chapter 2), some have a significant effect on the degree of difficulty of laryngoscopy and tracheal intubation (Box 29.1).

**Airway Edema**

Fluid retention makes the tissues of the head and neck less compliant and may lead to narrowing of the upper airway,

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### TABLE 29.2 Case-Fatality Rates and Risk Ratios of Anesthesia-Related Mortality during Cesarean Delivery in the United States: 1979 to 2002

<table>
<thead>
<tr>
<th>Year Range</th>
<th>CASE-FATALITY RATES*</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Anesthesia</td>
<td>Neuraxial Anesthesia</td>
<td></td>
</tr>
<tr>
<td>1979–1984</td>
<td>20.0</td>
<td>8.6</td>
</tr>
<tr>
<td>1985–1990</td>
<td>32.3</td>
<td>1.9</td>
</tr>
<tr>
<td>1991–1996</td>
<td>16.8</td>
<td>2.5</td>
</tr>
<tr>
<td>1997–2002</td>
<td>6.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*Deaths per million anesthetics.

The Difficult Airway: Risk, Assessment, Prophylaxis, and Management

However, the effects of topical agents on both the prevention of epistaxis and maternal hemodynamic parameters and uteroplacental perfusion must be evaluated, and the relative risk associated with this procedure should be assessed on an individual basis.

Respiratory and Metabolic Changes

As pregnancy progresses, the gravid uterus increasingly encroaches on the diaphragm and lung volumes are reduced. By term, expiratory reserve volume decreases by 25% and residual volume decreases by 15%, resulting in a 20% reduction in functional residual capacity (FRC). This decrease is more marked in the supine than in the upright position, and in the obese than in the lean patient. Closing volume is unchanged in pregnancy, but the decrease in FRC results in airway closure in 50% of women in the supine position.50 Metabolic requirements for oxygen increase by nearly 60% during pregnancy, predominantly because of fetal demands. Oxygen requirement is further increased during labor (see Chapter 2). These changes make pregnant women more likely to become hypoxemic during periods of apnea such as during the induction of general anesthesia.51 Therefore, adequate denitrogenation (so-called preoxygenation—replacing nitrogen in the FRC with oxygen) is vital to delay the onset of hypoxemia during periods of apnea (see later discussion).

Preoxygenation and the rate of hemoglobin desaturation have been investigated by computer modeling.34,52,53 In these models, labor, morbid obesity, and sepsis all hasten preoxygenation; however, desaturation also occurs more rapidly in the moderately ill and the obese (Fig. 29.1). Importantly, the time to life-threatening hypoxemia is significantly shorter especially in the supine position. Nasal congestion, snoring, and voice changes all occur more frequently in advanced pregnancy.43 A 34% increase in Mallampati class IV scores44 from the first to the third trimester of pregnancy has been observed (see later discussion).45 Difficulty with intubation has been shown to be more than 11 times more common in pregnant and postpartum women with Mallampati class IV than class I scores.12

Although changes in the airway develop gradually during pregnancy, more acute changes may be observed during labor. Mallampati class scores deteriorate during labor.46,67 Decreases in upper airway volume during labor have been demonstrated by acoustic reflectometry.46 The volume of both the oral component of the airway (from the incisors to the oropharyngeal junction) and the pharyngeal component (from the oropharyngeal junction to the glottis) are decreased, presumably as a result of increasing soft tissue edema. Airway narrowing may be more significant in women with preeclampsia. The airway edema that has been observed during labor may be exacerbated by expulsive efforts during the second stage of labor,48 after extubation after cesarean delivery,12 or by fluid resuscitation for obstetric hemorrhage. It is therefore prudent to reevaluate the airway before induction of general anesthesia rather than rely solely on a prelabor assessment.46

Nasal capillary engorgement during pregnancy increases the risk for epistaxis after nasal instrumentation and has led many practitioners to believe that nasal intubation is relatively contraindicated in pregnancy. In a 2011 review, Arendt et al.49 challenged this opinion, suggesting that nasal fiberoptic intubation is acceptable after careful and appropriate preparation of the nasal mucosa with topical vasoconstrictors. However, the effects of topical agents on both the prevention of epistaxis and maternal hemodynamic parameters and uteroplacental perfusion must be evaluated, and the relative risk associated with this procedure should be assessed on an individual basis.

**Fig. 29.1** Time course of SaO₂ during apnea in pregnant (horizontal hatching) and nonpregnant (vertical hatching) virtual subjects predicted to tolerate short, average, and long periods of apnea. Heavy lines represent average subjects. (a) Pregnant subjects, no preoxygenation; (b) nonpregnant subjects, no preoxygenation; (c) pregnant subjects, 99% complete denitrogenation; (d) nonpregnant subjects, 99% complete denitrogenation. (From McClelland SH, Bogod DG, Hardman JG. Apnoea in pregnancy: an investigation using physiological modelling. *Anaesthesia*. 2008;63:264–269.)
than that for recovery from paralysis from succinylcholine. Increasing BMI is associated with more than that for recovery from paralysis from succinylcholine. Alternatively, if rocuronium is used instead of succinylcholine and ventilation and oxygenation are impossible, emergency reversal of neuromuscular blockade with sugammadex 16 mg/kg is recommended. Using physiologic simulations in 40-year-old male patients in three BMI categories, Naguib et al. demonstrated that sugammadex reversal of neuromuscular function with rocuronium 1.2 mg/kg was faster than spontaneous recovery of ventilation after succinylcholine 1 mg/kg. However, ventilatory depression leading to a significant fall in oxygen saturation was more likely in obese subjects. Studies of emergency sugammadex reversal in obstetric patients are currently lacking.

**Weight Gain**

During pregnancy, most women gain 10 to 15 kg (22 to 33 lb) or more due to increases in fat deposition, blood and interstitial fluid volume, and uterine and fetal mass. High BMI is associated with difficulty in mask ventilation and tracheal intubation and with a greater risk for requiring emergency cesarean delivery. Increasing BMI is associated with more rapid oxygen desaturation during apnea during the induction of general anesthesia.

**Breast Enlargement**

Breast enlargement during pregnancy may impede intubation by interfering with correct placement of the laryngoscope blade and laryngoscopic manipulation to improve visualization of the larynx. Various strategies can minimize this problem, the most important of which is optimizing the patient’s position. With both arms abducted, breast tissue falls away from the chest. Ensuring that the patient is in the ideal intubating position (see later discussion and Chapter 49) further facilitates laryngoscope blade insertion; a short-handled laryngoscope is recommended. The handle can be directed toward the shoulder on insertion of the blade and then redirected once the blade is in the oropharynx.

**Full Dentition**

Full dentition is typically present in young pregnant women and can interfere with direct laryngoscopy, particularly if the maxillary incisors are protruding or the thyromental distance is small.

**Gastroesophageal Changes**

Pregnancy-induced changes in the gastroesophageal system do not per se make laryngoscopy and intubation more difficult. However, owing to the increased risk for regurgitation and aspiration from the second trimester onward (see Chapters 2 and 28), rapid-sequence induction of general anesthesia is advocated for almost all parturients, thus potentially increasing the risk for difficult airway management. Antacid prophylaxis is therefore mandatory if surgical intervention is required.

**AIRWAY ASSESSMENT**

Preanesthetic assessment of the airway is necessary before both general and neuraxial anesthesia, so that plans for airway management can be made in advance. A variety of bedside tests have been used, either singularly or in combination, to predict the airway difficulty. The validity of many tests has been questioned, and it is useful to consider how these assessments have been investigated. First, airway difficulty, the outcome, must be defined. A number of definitions have been used (see earlier discussion), including difficulty or failure with ventilation (with or without an SGA) or intubation. Second, various predictive factors that are associated with difficult airway management have been tested on different sample populations of patients.

For an assessment to be useful, it must be both sensitive (i.e., correctly identify those whose tracheas are difficult to intubate) and specific (i.e., correctly identify those whose tracheas are easy to intubate). Despite having both reasonably high sensitivity and specificity, many predictive tests have limited use in the clinical environment because failed intubation is rare; the number of false-positive tests (those predicted to be difficult that are not) will always be significantly higher than the number of true-positive tests (those predicted to be difficult that are). The positive predictive value (ratio of true-positive tests to the total number of positive tests) for individual difficult airway tests is typically less than 50%; that is, fewer than one-half of the procedures predicted to be difficult will actually be difficult. Despite these shortcomings in difficult airway prediction, airway assessment is a vital part of anesthetic management. Combining difficult airway tests can raise the index of suspicion for difficulty with airway management. Preanesthetic assessment allows the consideration of potential airway problems and the creation of a stepwise plan for dealing with difficulties should they arise.

**Cormack and Lehane Grade**

Cormack and Lehane devised a glottic view grading system in 1984. The purpose of the system was to grade the glottic view obtained with direct laryngoscopy and use the grade as a means of training for general anesthesia in the obstetric patient. Therefore, the Cormack and Lehane grade is not a preoperative assessment tool but rather a classification method to describe the relative difficulty with subsequent tracheal intubation. The original description includes four grades of laryngoscopy (Fig. 29.2):

- Grade 1: Full view of glottis
- Grade 2: Partial view of glottis or arytenoids
- Grade 3: Only epiglottis visible
- Grade 4: Neither glottis nor epiglottis visible

Subsequent modifications have been proposed. Grade 2 may be divided into 2A (part of vocal cords visible) and 2B (only arytenoids or very posterior origin of vocal cords visible). Further, Grade 3 may be divided into those in whom the epiglottis is visible and is able to be lifted, such as with a gum elastic bougie (Grade 3A), and those in which the epiglottis is visible but not able to be lifted (Grade...
Increasing difficulty with intubation is to be expected with each progressive grade of the Cormack and Lehane classification.

Because of the widespread acceptance of the Cormack and Lehane grading system, some useful information can be gained by reviewing the anesthetic records of patients who have a previous history of direct laryngoscopy; the Cormack and Lehane glottic view grade is often documented. However, prior reports should be treated with caution because grades given in the nonpregnant state will likely differ from those determined during pregnancy, and the potential for interobserver and intraobserver variability exists.

**Mallampati Class**

In 1985 Mallampati et al. described a three-point scale of the oropharyngeal view of the open mouth based on concealment of the faunal pillars, soft palate, and uvula by the base of the tongue; the more the view was obscured, the greater the difficulty with laryngoscopy and intubation. Samsoon and Young later modified the scoring system into a four-point scale (Fig. 29.3):

- **Class I:** visualization of soft palate, uvula, and tonsillar pillars
- **Class II:** visualization of soft palate and base of uvula
- **Class III:** visualization of soft palate only
- **Class IV:** visualization of hard palate only

The test should be performed with the patient sitting upright with her head in the neutral position. The patient is instructed to open her mouth as wide as possible and protrude her tongue as far as possible without phonation. Increasing difficulty with laryngoscopy and tracheal intubation has been demonstrated with greater Mallampati scores in both obstetric and nonobstetric populations.

Mallampati scores are frequently used as part of an assessment to predict difficult intubation. It is important to remember that scores change during pregnancy and during labor. When used as the sole predictor of a difficult airway, the incidence of both significant false-positive and false-negative results is high. This poor predictive value may be explained by the use of phonation, poor patient positioning, involuntary arching of the tongue, and interobserver variability in interpretation. A meta-analysis of the Mallampati score concluded that the test had limited accuracy for predicting a difficult airway and was not a useful screening test. Consequently, the Mallampati score is best used in combination with other tests.

**Thyromental Distance**

During laryngoscopy, the tongue is normally pushed into the mandibular space. The thyromental distance, the distance from the tip of the chin to the notch of the thyroid cartilage, can be used to estimate the size of this space and, therefore, whether the tongue can easily be displaced to facilitate laryngoscopy. In the absence of other abnormalities, if the thyromental distance is more than 6.5 cm and the horizontal mandibular length more than 9 cm, intubation should proceed without difficulty. A thyromental distance of less than 6 cm suggests an increased risk for difficulty. However, lack of detail in various studies regarding precisely how the thyromental distance was measured (whether it was performed from the inner or outer border of the mandible) make interpretation of this test difficult.

Anatomically, if the mandibular space is small and unable to accommodate the tissues displaced by the laryngoscope blade, few alterations will improve the line of vision during direct laryngoscopy. When the mandibular space is small, the larynx lies relatively anterior and the tongue must be pulled forward maximally and compressed to expose the larynx.
Anesthetic Complications

**Atlanto-Occipital Joint Extension**

Extension of the atlanto-occipital joint is necessary for the patient to be in the ideal intubating position in which the oral, pharyngeal, and laryngeal axes are aligned (see later discussion). Movement can be assessed with the patient seated with the head and neck in the neutral position facing forward and then with the joint maximally extended (Fig. 29.4). Normal extension should be 35 degrees or more; difficulty with intubation can be expected when joint movement is decreased. The accuracy of this assessment is subject to interobserver variability, making its role in routine airway assessment questionable.

**Mandibular Protrusion**

The patient’s ability to extend the mandibular teeth anteriorly beyond the line of the maxillary teeth may predict adequate visualization of the larynx during direct laryngoscopy. In the mandibular protrusion test, patients are asked to protrude their mandible as far as possible (Fig. 29.5); one of three classes is assigned:

- **Class A:** The lower incisors can be protruded anterior to the upper incisors
- **Class B:** The lower incisors can be brought edge to edge with the upper incisors
- **Class C:** The lower incisors cannot be brought edge to edge with the upper incisors

Class A is a good predictor of a good glottic view with direct laryngoscopy, whereas class C is associated with poor glottic view.

The upper lip bite test (ULBT) is similar to mandibular protrusion. In class I, the lower incisors can bite the upper lip above the vermilion border (i.e., the normally sharp demarcation between the lip and the adjacent normal skin); in class II, the lower incisors can bite the upper lip below the vermilion border; and in class III, the lower incisors cannot bite the upper lip. The ULBT has been shown to be a better predictor than a Mallampati score for predicting ease with laryngoscopy and intubation. The ULBT cannot be assessed in edentulous patients.

**Other Assessments**

Sternomental distance has been suggested to predict difficult laryngoscopy. This distance is measured between the chin and sternum with the head fully extended on the neck and the mouth closed. Unfortunately, the assessment has extremely weak predictive power, and consequently it has largely been abandoned.
Limited mouth opening impedes the introduction of a laryngoscope blade as well as other airway devices; an interincisor distance of less than 5 cm may predict difficult intubation. Mouth opening of less than two fingerbreadths has been shown to reduce the prevalence of easy intubation from 95% to 62%. Mouth opening also is influenced by cervical spine movement; if movement is limited, mouth opening may also be restricted. Protruding maxillary incisors, a single maxillary incisor, and missing maxillary incisors have been shown to be predictive of difficult intubation in obstetric patients.

Comorbidities, including those not related to pregnancy, may influence airway management and should be considered before anticipated airway management. Most notably, maternal obesity is associated with an increased incidence of airway problems (see earlier discussion). Similarly, difficulties in airway management should be anticipated in patients with severe preeclampsia.

Multivariable Assessments

Individual tests are poorly predictive of airway difficulty; therefore, investigators have combined assessments in an effort to improve specificity. Wilson et al. assessed five risk factors (weight, head and neck movement, jaw movement, presence or absence of a receding mandible, prominent teeth). Each variable was scored from 0 to 2, giving a Wilson risk sum. Although 75% of cases of difficult laryngoscopy could be predicted, 12% were falsely predicted to be difficult. Subsequent work using the Wilson risk sum found a positive predictive value of only 9%, and consequently it is now rarely used in clinical practice.

Frerk demonstrated that a combination of the Mallampati score and thyromental distance was more predictive than either test alone; the combined assessment had a sensitivity of 81% and a specificity of 98% in predicting a difficult airway. However, owing to the rarity of difficult intubation, the positive predictive value was only 64%. Realizing that there was an absence of a clear description and agreement as to the method of performing individual tests, Lewis et al. assessed different methods of grading the oropharyngeal view and the mandibular space as predictors of difficult laryngoscopy. Twenty-four different oropharyngeal assessments were considered using two body positions, three head positions, and two tongue positions, each with and without phonation. Similarly, the mandibular space was measured in 24 ways using two body positions, three head positions, and two distal and two proximal endpoints. The results were subject to logistic regression analysis. Although most difficult intubations could be predicted, one-half of those that were anticipated to be difficult were ultimately found to be easy, even with the most predictive combination of tests.

Tse et al. combined the angle at full head extension (in an upright position, the angle made by a line joining the ear tragus [apex] and the corner of the mouth to a line parallel to the floor [horizontal]), thyromental distance, and Mallampati classification in an attempt to predict difficult intubation in a general surgery population. Although these tests were likely to identify easy intubations, they had low sensitivity for predicting those in whom intubation was difficult.

In a study of 400 pregnant women scheduled for elective cesarean delivery, Honarmand and Safavi evaluated Mallampati class score, ratio of height to thyromental distance, and the ULBT, both in isolation and combination. A total of 8.75% of patients had a Cormack and Lehane grade 3 or 4 laryngoscopic view; the ratio of height to thyromental distance was the best predictor of this outcome.

Recommendations

The thoroughness of the airway assessment often depends on the urgency with which surgery needs to be performed. For emergency procedures, relatively little time is available; thus it is prudent to assess all women in the labor and delivery suite soon after their arrival, focusing on those with the greatest risk for intervention. However, changes in assessment during the course of labor must be anticipated, and reevaluation before inducing anesthesia is vital to the safe care of these patients.

The assessment should attempt to identify the patients who will be difficult to ventilate and whose tracheas will be difficult to intubate. It should start with a history to detect factors that may indicate the presence of a difficult airway, as well as the potential risk for pulmonary aspiration. Examination of previous anesthetic records, if available, may indicate problems with ventilation or intubation. The presence of comorbidities such as obesity and preeclampsia should be considered. The ASA Practice Guidelines for Management of the Difficult Airway list 11 airway examination components that can be assessed (Table 29.3), acknowledging the absence of a single test that can reliably predict who is likely to present difficulty with airway management. Consequently, a combination of assessments is generally considered preferable.

Performing and documenting mouth opening, the Mallampati class, atlanto-occipital mobility, thyromental distance, and mandibular protrusion may be performed relatively quickly and should identify most patients who will present difficulties with airway management. The preanesthesia evaluation should seek to identify risk factors for difficulty with mask ventilation, laryngoscopy, airway device insertion (including intubation), and performance of a surgical airway. When risk factors are identified, appropriate plans for airway management, such as the ready availability of additional equipment and personnel (e.g., individuals experienced with airway management and the creation of a surgical airway) should be made. The proposed plan should consider that the administration of a neuraxial anesthetic technique may be the safest option for both mother and infant, even in the presence of nonreassuring fetal status. The plan must also include alternatives for situations in which the initial plan is not possible. The use of ultrasonography to identify the cricothyroid membrane before the induction of general anesthesia may improve landmark identification should emergency surgical (front-of-neck) access be required to rescue failed intubation. The risks and benefits of various alternatives should be discussed with the patient and the obstetric, neonatal,
Prophylaxis

Neuraxial Labor Analgesia

The widespread acceptance and use of neuraxial analgesic and anesthetic techniques for obstetric patients has significantly reduced the need for general anesthesia and airway manipulation. In obstetric patients in whom difficulty in airway management or neuraxial technique administration is anticipated or when risk factors for an urgent or emergent cesarean delivery are present, early or prophylactic placement of an epidural catheter should be encouraged. A prophylactic epidural catheter is one that is placed and tested with a small dose of local anesthetic; analgesia is not established until active labor begins, the patient requests analgesia, and/or an epidural catheter serves to verify that the catheter remains in position in the epidural space, facilitating timely extension of anesthesia if necessary.

Unfortunately, labor analgesia cannot always be successfully converted to surgical anesthesia for an operative delivery; reported failure rates are as high as 8%. A 2012 meta-analysis demonstrated the need for conversion to general anesthesia in 5% of women who receive epidural analgesia in labor77; higher failure rates are observed among women requiring more provider interventions for inadequate epidural labor analgesia, in settings of need for urgent delivery, and when an anesthesiologist without specialty training or experience in obstetric anesthesia is providing care. Consequently, women receiving labor epidural analgesia must be evaluated at regular intervals; if analgesia is inadequate, re-siting the epidural catheter must be considered. A meta-analysis of studies comparing different local anesthetics for conversion of epidural analgesia to anesthesia found that lidocaine with epinephrine has a faster onset than bupivacaine, levobupivacaine, or ropivacaine. The addition of bicarbonate to chloroprocaine or lidocaine with epinephrine further hastens the onset of local anesthetic action (see Chapter 26).

In situations in which conversion of epidural analgesia to anesthesia is not possible, general anesthesia may still be avoided if time permits the initiation of spinal or combined spinal-epidural anesthesia. However, care should be taken when administering a spinal anesthetic after a failed epidural top-up dose of local anesthetic, because cases of high and total spinal anesthesia have been reported in this setting (see Chapter 26). An airway management plan must always be in place, even if the primary plan is for the administration of neuraxial anesthesia.

Fasting and Antacid Prophylaxis

All obstetric patients requiring surgical anesthesia are at risk for pulmonary aspiration of gastric contents, particularly if airway difficulties are encountered (see Chapter 28). Because conversion from neuraxial to general anesthesia may be required either before or during surgery, strategies must be adopted to minimize this risk. The ASA and the American College of Obstetricians and Gynecologists (ACOG) recommendations allow modest amounts of clear liquid with uncomplicated labor, but they recommend the avoidance of solid foods in laboring women. Clear liquids and solids are allowed up to 2 hours and 6 to 8 hours, respectively, before an elective operative procedure. However, more liberal policies on oral intake in labor have become increasingly widespread as maternal death from aspiration becomes less

### TABLE 29.3 Components of Preoperative Airway Examination

<table>
<thead>
<tr>
<th>Airway Examination Component</th>
<th>Nonreassuring Findings</th>
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<tbody>
<tr>
<td>1. Length of upper incisors</td>
<td>Relatively long</td>
</tr>
<tr>
<td>2. Relation of maxillary and mandibular incisors during normal jaw closure</td>
<td>Prominent overbite (maxillary incisors anterior to mandibular incisors)</td>
</tr>
<tr>
<td>3. Relation of maxillary and mandibular incisors during voluntary protrusion</td>
<td>Patient cannot bring mandibular incisors anterior to maxillary incisors</td>
</tr>
<tr>
<td>4. Interincisor distance</td>
<td>Less than 3 cm</td>
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<tr>
<td>5. Visibility of uvula</td>
<td>Not visible when tongue protruded with patient sitting (e.g., Mallampati class &gt; II)</td>
</tr>
<tr>
<td>6. Shape of palate</td>
<td>Highly arched or very narrow</td>
</tr>
<tr>
<td>7. Compliance of mandibular space</td>
<td>Stiff, indurated, occupied by mass, or nonresilient</td>
</tr>
<tr>
<td>8. Thyromental distance</td>
<td>Less than three ordinary fingerbreadths</td>
</tr>
<tr>
<td>9. Length of neck</td>
<td>Short</td>
</tr>
<tr>
<td>10. Thickness of neck</td>
<td>Thick</td>
</tr>
<tr>
<td>11. Range of motion of head and neck</td>
<td>Patient cannot touch tip of chin to chest or cannot extend neck</td>
</tr>
</tbody>
</table>

common. The UK National Institute for Health and Clinical Excellence suggests that women be allowed to drink isotonic fluids in labor and eat a light diet unless they develop risk factors that make general anesthesia more likely.\(^8^1\) Consequently, all laboring women should be assessed and oral intake restricted if surgical intervention appears likely.

Once surgical intervention is required, antacids such as intravenous histamine-2 (\(H_2\))-receptor antagonists or proton-pump inhibitors should be administered, if not already given, in case general anesthesia is necessary. However, these drugs take up to 30 minutes to become effective. If emergency general anesthesia is required, oral administration of a nonparticulate antacid such as sodium citrate is used to increase the pH of gastric contents. A dose of sodium citrate (0.3 molar) 30 mL is effective for approximately 30 minutes and should be administered shortly before the induction of general anesthesia.\(^8^2\)

Metoclopramide promotes gastric emptying and increases lower esophageal sphincter tone, although its efficacy is decreased by concurrent use of opioids. It may be given orally in labor or intravenously before general anesthesia.

A number of deaths from presumed aspiration after tracheal extubation have been reported in the UK Confidential Enquiries into Maternal Deaths.\(^3^6\) Previous reports have recommended that when general anesthesia is administered to a woman with a potentially full stomach, consideration should be given to passing an “in and out” orogastric tube before extubation.

**Patient Positioning**

The optimal view during laryngoscopy, which yields the best chance for successful intubation, requires appropriate patient positioning. The sniffing position, with 35 degrees of neck flexion and 15 degrees of head extension, has been considered the ideal position for facilitating a view of the glottis by aligning the oral, pharyngeal, and laryngeal axes (Fig. 29.6).\(^8^3\) Although use of the sniffing position has recently been questioned, most studies find it superior to other positions. The correct use of the sniffing position requires that the external auditory meatus and sternum are in horizontal alignment. Some video laryngoscopes (see later discussion) do not require the patient’s head and neck to be in the sniffing position for successful device use.

For obese patients, a ramped position is preferable (Fig. 29.7). The anteroposterior chest diameter is increased in obese patients, making 35 degrees of neck flexion unachievable in the supine position. Consequently, the shoulders and upper torso need to be raised; this position can be achieved with the use of blankets or pillows, or one of the many commercially available, wedge-shaped positioning cushions.

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\(^{8^1}\) UK National Institute for Health and Clinical Excellence.

\(^{8^2}\) UK Confidential Enquiries into Maternal Deaths.

Optimal elevation is verified by checking that the external auditory meatus and sternoclavicular joint are in horizontal alignment. Elevating the back of the operating table by 25 degrees may make laryngoscopy easier and also aids preoxygenation (see later discussion). The operating room table should be elevated to a height at which the laryngoscopist is most comfortable, with space at the head of the bed to accommodate access for the anesthesia team and necessary equipment.

Left uterine displacement to minimize aortocaval compression should be maintained during preparation for, and induction of, general anesthesia. This may be achieved by tilting the operating table or by placing a wedge under the right hip.

**Denitrogenation (Preoxygenation)**

In pregnancy, the decrease in FRC and increase in oxygen requirement result in rapid oxygen desaturation during periods of apnea (e.g., during induction of general anesthesia). The FRC is the primary reservoir for oxygen during apnea. Therefore, effective denitrogenation, or preoxygenation, of the FRC is vital to delay the onset of hypoxemia.

The standard technique for preoxygenation has been to breathe 100% oxygen through a tight-fitting face mask at normal tidal volumes for 3 to 5 minutes. Given the urgent nature of obstetric general anesthesia, attention has focused on whether several maximal deep breaths over a shorter period can be as effective. Chiron et al. compared a traditional 3-minute technique with either eight deep breaths over 1 minute (8 DB/1 min) or four deep breaths over 30 seconds (4 DB/30 sec). By monitoring with end-tidal fractional oxygen concentration (F\text{ET}O\text{2}), which is probably the best marker of lung denitrogenation, the authors found that 3 minutes of tidal volumes and the 8 DB/1 min technique were more effective than the 4 DB/30 sec technique. They suggested using the 8 DB/1 min technique in the setting of emergency obstetric anesthesia.

The use of maximal deep breaths to achieve denitrogenation may cause maternal hypocarbia and, therefore, should be limited to situations in which time does not allow normal tidal volume breathing of 100% oxygen to maximize oxygen storage in tissue and vascular body compartments. Indeed, during apnea, the time to desaturation depends on (1) the amount of oxygen stored in the lungs, tissue, and blood; (2) the mixed venous oxyhemoglobin saturation; and (3) the presence of intrapulmonary shunting.

A tight-fitting face mask is necessary to prevent air entrainment, which reduces the efficiency of preoxygenation. With normal tidal volume breathing, preoxygenation is best achieved with oxygen flow rates in excess of 10 L/min for 3 minutes, although this may still be inadequate due to air entrainment; some authors suggest F\text{ET}O\text{2} should be greater than 0.8 before anesthesia is induced. A 20-degree to 30-degree head-up tilt increases the FRC and delays the time to desaturation, especially in obese patients.

There has been recent interest in the use of the transnasal humidified rapid-insufflation ventilator exchange (THRIVE) technique. Using flow rates of up to 70 L/min of oxygen, desaturation was not observed despite a mean apnea time of 248 seconds in nonobstetric patients undergoing rapid-sequence induction. Computer modeling of the effects of high-flow nasal oxygen in the pregnant patient has shown that with an F\text{IO}2 of 1.0 and a patent airway, apnea times in excess of 30 minutes can be achieved without maternal desaturation to less than 90%. However, the authors cautioned against long apnea times due to a significant increase in PaCO2 and a fall in pH. Further work is required to determine the role of THRIVE in obstetric airway management.

**Rapid-Sequence Induction and Cricoid Pressure**

In an attempt to minimize the risk for aspiration, rapid-sequence induction has become the standard technique for induction of obstetric general anesthesia. It usually consists of preoxygenation, rapid intravenous injection of a predetermined dose of induction agent followed immediately by succinylcholine administration, application of cricoid pressure, and avoidance of positive-pressure ventilation before tracheal intubation with a cuffed endotracheal tube (ETT). The relative urgency of intubation, in a patient in whom ventilation is avoided, may increase the likelihood of failure.

Although in widespread use, the conduct of rapid-sequence induction is not uniform. Induction agents should provide rapid loss of consciousness with minimal hemodynamic instability while improving the quality of intubating conditions. Although no longer available in the United States, thiopental has traditionally been the induction agent of choice for obstetric general anesthesia. When used with succinylcholine, it provides intubating conditions that are as good or better than other agents. An additional advantage is that it can be reconstituted and stored for future use. Furthermore, some evidence suggests that, compared with propofol, thiopental leads to less maternal hypotension and fewer detrimental effects on the neonate. Propofol, however, appears to offer better intubating conditions when combined with rocuronium; compared with thiopental in nonobstetric patients, visualization of the vocal cords was significantly more likely with propofol. Its superiority to thiopental is most likely related to its greater ability to suppress pharyngeal and laryngeal reflexes. However, when succinylcholine is used, the choice of induction agent has no significant effect on intubating conditions. With thiopental increasingly difficult to obtain, the popularity of propofol continues to increase (see Chapter 26).

Opioids have traditionally not been part of rapid-sequence induction because of concerns about respiratory depression should intubation fail. Moreover, in the obstetric population, the potential for neonatal depression is greater if opioids are used because of rapid placental transfer of these drugs. In nonobstetric patients, the addition of opioids produces better intubating conditions when combined with rocuronium; this improvement has not been demonstrated with succinylcholine.

Succinylcholine is associated with a number of undesirable side effects, most notably a prolonged duration of action
in patients with cholinesterase deficiency and a trigger for malignant hyperthermia and anaphylaxis. However, because of its rapid onset, succinylcholine has traditionally been the muscle relaxant of choice for rapid-sequence induction of anesthesia in obstetric patients. Despite reduced levels of plasma pseudocholinesterase in pregnancy, the duration of action of succinylcholine remains clinically unchanged in the obstetric patient.96 The ideal dose of succinylcholine, traditionally 1 mg/kg, remains controversial97; when combined with opioids in nonobstetric patients, succinylcholine 1 mg/kg fails to produce good intubating conditions at 1 minute in up to 8% of cases.98 Naguib et al.99 found that succinylcholine doses as high as 2 mg/kg still do not guarantee excellent intubating conditions in all patients; however, the authors found little extra benefit from using doses above 1.5 mg/kg. In a study of succinylcholine in nonobstetric obese patients,99 a dose of 1 mg/kg total body weight was found to provide more predictable laryngoscopic conditions than 1 mg/kg ideal or lean body weight.

The potential disadvantage of increasing the succinylcholine dose is delayed return of spontaneous respiration; return of spontaneous ventilation is vital should intubation not be achieved. Reducing the succinylcholine dose to 0.5 mg/kg does not appear to compromise intubating conditions, at least when administered in the nonobstetric population with propofol and fentanyl; the lower dose slightly shortens the recovery time.100 In pregnancy, however, the reduced maternal FRC and greater oxygen demands make significant desaturation likely before the return of spontaneous respiration, no matter the succinylcholine dose. Because opioids are not commonly administered at induction, continued use of succinylcholine 1 to 1.5 mg/kg is recommended.

The side-effect profile of succinylcholine has resulted in consideration of alternative muscle relaxants for the rapid-sequence technique. Rocuronium is often used when succinylcholine is contraindicated. In a study of 240 women undergoing rapid-sequence induction of general anesthesia for cesarean delivery,101 rocuronium did not prolong time to tracheal intubation, and provided less resistance to laryngoscopy and a lower incidence of postoperative myalgia than succinylcholine. However, its prolonged duration of action is a significant concern when failure to ventilate or intubate occurs. Sugammadex, with its ability to rapidly reverse the effects of rocuronium, may address this concern (see earlier discussion). When used with propofol for rapid-sequence induction, results of a 2015 meta-analysis102 indicated that succinylcholine (1 mg/kg or greater) produced superior intubating conditions than rocuronium (0.6 to 0.7 mg/kg) (relative risk [RR], 0.86; 95% CI, 0.81 to 0.92). No significant difference was observed between the two agents when a larger dose of rocuronium (1.2 mg/kg) was used.102 Therefore, succinylcholine currently remains the preferred muscle relaxant for use in rapid-sequence induction of anesthesia.

Cricoid pressure as a method to decrease pulmonary aspiration during induction of anesthesia was first described in 1961.103 Interest in the technique was promoted by the reports of deaths due to aspiration under general anesthesia.104 Although the effectiveness of cricoid pressure in preventing pulmonary aspiration of gastric contents has recently been challenged,105,106 it is frequently used during the induction of obstetric general anesthesia (see Chapters 26 and 28). However, the use of cricoid pressure can adversely affect the ease of ventilation, laryngoscopy, and intubation. In a comparison of cricoid pressure with 20 N, 30 N, and 44 N of force, increasing pressure was more likely to lead to cricoid deformity and esophageal occlusion, particularly in women.107 Difficulty with ventilation is less likely when 30 N is applied (currently accepted practice) than with 44 N (the previously suggested optimum value).108 When correctly applied, with an increase in force from 10 N to 30 N with the induction of general anesthesia, there is little evidence of harm. However, when difficulty with intubation or ventilation arises, pressure may need to be reduced or released (see later discussion).

Although the cricoid pressure technique originally described by Sellick109 was a one-handed technique, the placement of a second hand behind the patient’s neck to prevent excessive neck flexion has been observed to provide a superior laryngoscopic view.109 However, it should also be remembered that the two-handed cricoid pressure technique does not allow the anesthetic assistant to assist with other procedures, such as holding additional equipment necessary for difficult airway management.

**MANAGEMENT**

**Planning**

The approach to the difficult airway in the obstetric patient depends on the situation as well as the skill set of the anesthesia provider. A suggested approach for management of obstetric patients with an anticipated difficult airway is outlined in Fig. 29.8. After an initial assessment of the patient, an airway management plan should be created and shared with the patient and other members of the multidisciplinary team. In extreme cases, anesthesia considerations may influence the mode and timing of delivery. Despite a thorough airway assessment and management plan, unanticipated or unrecognized airway issues and complications may arise; alternative algorithms and equipment should be readily available to ensure oxygenation and ventilation. Emergence and extubation should also be planned in advance. Lack of forethought and planning can lead to poor decision-making in crisis situations.

**Neuraxial Anesthesia**

The value of establishing and confirming a functional epidural catheter during labor in patients with an anticipated difficult airway has been described (see earlier discussion). A neuraxial anesthetic technique may also be preferable in patients with an anticipated difficult airway undergoing urgent or elective cesarean delivery. The choice of anesthetic technique (e.g., single-shot spinal, combined spinal-epidural, epidural, continuous spinal techniques) depends on the circumstances and preferences of the anesthesia provider.
Awake intubation can be performed with a number of airway management devices, but the flexible fiberoptic bronchoscope offers unique advantages (Box 29.2). Proper planning and execution, with attention to detail, are key to patient cooperation and a high success rate. Appropriate equipment must be readily available, and experienced assistance is desirable. It is useful to have two anesthesia providers: one to perform the endoscopy and another to monitor the patient. Pulse oximetry, capnography, continuous electrocardiography, and blood pressure monitoring are mandatory. The level of conscious sedation must be constantly monitored to obtain the desired level for the procedure (see later discussion). Supplemental oxygen should be administered.
An unhurried, thorough explanation of the technique to the patient helps allay anxiety. Pharmacologic premedication should include prophylaxis for pulmonary aspiration and an antisyndromal as such as intravenous glycopyrrolate 0.2 mg. A dry mouth improves topical oral anesthesia by ensuring better contact between the local anesthetic and the mucosa. Secretions may also cause internal reflection from the light source and distort the fiberoptic view. Performing the procedure with the patient in the upright, rather than supine, position minimizes airway obstruction and aortocaval occlusion, enhances drainage of secretions, and allows better acceptance of topical anesthesia by the patient.

**Conscious Sedation**

The term *awake intubation* is a misnomer because in practice most patients receive some form of sedation to relieve anxiety, produce amnesia, and reduce pain and discomfort during the procedure. Moderate sedation/analgesia, also termed *conscious sedation*, is a drug-induced depression of consciousness during which the patient can respond purposefully to verbal or tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. An overdose of the sedative/hypnotic or analgesic drugs can result in airway obstruction, hypoxemia, and cardiorespiratory depression; maintenance of continuous verbal contact is the optimal method for avoiding oversedation.

The choice of drugs to produce conscious sedation depends on the preference and experience of the anesthesia provider. Small boluses of intravenous midazolam (0.5 to 1 mg) and fentanyl (25 to 50 µg) are usually adequate, the use of a propofol infusion has also been described. Remifentanil may confer some advantages over fentanyl in providing rapid onset, more precise titration with the ability to use an infusion, and rapid metabolism and dissipation of effects; decreased respiratory rate or apnea may be quickly reversed by stopping the infusion. Remifentanil infusion rates between 0.05 and 0.175 µg/kg/min have been used for awake fiberoptic intubation in nonobstetric patients; target-controlled infusions of remifentanil, with or without propofol, can also provide ideal conditions. The use of intravenous dexmedetomidine infusion to facilitate awake fiberoptic intubation at cesarean delivery has also been described.

Neonatal effects of the drugs used for sedation are usually minimal; however, the neonatologist should be informed of the drugs administered to the mother before delivery.

**Topical Anesthesia**

Providing adequate topical anesthesia of the upper respiratory tract is one of the most critical elements of successful awake fiberoptic intubation. Local anesthetic agents can be used in two basic ways to provide topical upper airway anesthesia: direct application to the mucosa or the injection for laryngeal nerve blocks. Topical application of local anesthetic is the most commonly used technique owing to its ease and effectiveness. There are a number of techniques. For example, the patient can be asked to gargle and slowly swallow viscous lidocaine (2% or 4%), or lidocaine (2%, 4%, or 10%) can be aerosolized and sprayed onto the tongue and oropharynx. A number of commercially available devices, which are produced in a variety of shapes and sizes, can aerosolize and spray local anesthetic solutions in a jetlike stream. The Mackenzie technique uses an intravenous cannula with an injection port (e.g., 20- or 18-gauge) connected to oxygen tubing via a three-way connector (Fig. 29.9). Administration of local

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**Fig. 29.9** Topical airway anesthesia. The MacKenzie technique uses a 20-gauge intravenous cannula with an injection port connected to oxygen tubing via a three-way tap to produce a jetlike spray of local anesthetic administered from a syringe connected to the cannula with the oxygen flowing at 2 L/min.
anesthetic from a syringe through the connector, with the oxygen flowing at 2 L/min, creates a jetlike spray.\textsuperscript{121} An additional method uses a nebulizer mask or mouthpiece, with 4% lidocaine (4 to 6 mL) placed in the nebulizer bowl and connected to an oxygen source at a flow rate of 8 L/min. This method is easy to administer, noninvasive, and comfortable for the patient, with minimal or absent coughing. Each of these techniques may be insufficient as a single entity and may be combined with other methods, including instillation of local anesthetic through the working channel of the fiberoptic bronchoscope channel.

The “spray as you go” (SAYGO) technique uses the working channel of the fiberoptic bronchoscope to instill local anesthetic onto the mucous membranes of the airway. The working channel of an intubating fiberoptic bronchoscope, such as the Olympus LF-2 (Olympus America Inc., Centre Valley, PA), is 600 mm long and 1.5 mm in diameter. If a small syringe is directly attached to the working channel port and the solution is merely injected, the local anesthetic is likely to stay in the channel rather than be sprayed onto the mucosa. This problem can be overcome by placing an epidural catheter through the working channel; using a Luer-Lok connector for the epidural catheter allows a direct and tight connection with the local anesthetic syringe and avoids leakage. The local anesthetic agent is drawn up in a 2-mL syringe and “dripped” on the mucus membranes; this instillation can be better targeted if the distal tip of the epidural catheter is allowed to protrude approximately 1 cm from the tip of the fiberoptic bronchoscope.

Nerve Blocks

The nerve supply to the upper airway is derived from branches of cranial nerves V, VII, IX, and X. The lingual branch of the glossopharyngeal nerve (IX), which innervates the submucosal pressure receptors at the base of the tongue, can be blocked with the bilateral administration of 1% lidocaine (2 mL) just under the mucosa at the base of the anterior tonsillar pillars. The value or necessity of this block during performance of awake intubation in obstetric patients is controversial.\textsuperscript{122} Laryngeal and tracheal sensation can be minimized with blockade of the superior laryngeal nerve and transtracheal administration of lidocaine, respectively. Blockade of the superior laryngeal nerve may be performed by locating the greater cornu of the hyoid bone, advancing a small-bore needle until the bone is contacted, walking the needle off the edge of the bone into the thyrohyoid membrane, and injecting 1% lidocaine, approximately 3 mL. The injection is then repeated on the other side of the neck.

Historically, nerve blocks were an essential part of preparing the upper airway; today, meticulous topical application is easier to perform, less invasive, and provides effective intubating conditions. A technique for topical anesthesia for oral awake fiberoptic intubation is described in Box 29.3.

Airway Anesthesia and Risk for Aspiration

Some anesthesia providers are concerned that local anesthesia of the larynx might obtund the reflexes for protecting the airway. An early study found that an unprotected glottis might result from translaryngeal block.\textsuperscript{123} Local anesthetic solutions can spread to the superior aspect of the vocal cords after a translaryngeal block.\textsuperscript{124} However, in a series of 129 patients, both the translaryngeal injection and SAYGO techniques were effective and safe, with no evidence of regurgitation or aspiration in any patient.\textsuperscript{125} It has been suggested that topical anesthesia of the larynx does not impair voluntary motor function of the vocal cords, such as coughing on request,\textsuperscript{126} thus allowing the patient to protect her airway. The SAYGO technique may be preferred because the interval between topical anesthesia and endoscopy is minimal and if gastric reflux occurs during endoscopy it can be visualized and the gastric juice aspirated through the fiberoptic bronchoscope. The key to minimizing the risk for aspiration, however, is avoidance of oversedation. Nonetheless, administration of aspiration prophylaxis is advised, and the patient should be monitored for possible reflex or emesis.

Fiberoptic Intubation

Fiberoptic laryngoscopy can be performed orally or nasally, but the oral route is more common because of the engagement of the nasal mucosa and the potential for epistaxis. However, in very specific situations (i.e., when the oral aperture is insufficient to allow fiberoptic bronchoscope passage), the nasal route can be successfully used in the obstetric patient with careful topical preparation of the nasal mucosa with agents that provide anesthesia and vasoconstriction.\textsuperscript{127} A common impediment to successful fiberoptic laryngoscopy is being able to easily advance the ETT into the correct position. Guiding the ETT over the fiberoptic bronchoscope is a “blind” procedure. The ETT most commonly arrests at the right arytenoid cartilage.\textsuperscript{127} In a review of the causes, incidence, and solutions to this issue, Asai and Shingu\textsuperscript{128}
and highly motivated patient may tolerate the procedure surprisingly well. Awake intubation also has been described using indirect or video laryngoscopes (see later discussion), but their role in awake intubation in the obstetric setting has yet to be determined. Other techniques for awake intubation, such as blind-nasal intubation and retrograde intubation, are performed infrequently in obstetric patients.

**Video Laryngoscopy**

Since the introduction of the Bullard laryngoscope in the late 1980s, a number of rigid indirect-optical laryngoscopes have been developed. Frequently referred to as video laryngoscopes because of a video camera eye positioned near the tip of the blade, these devices capture an image of the glottis in real time and transmit it to a video screen. Video laryngoscopes offer several advantages over conventional direct laryngoscopy (Box 29.4). To obtain a good view of the glottis with a direct laryngoscope, a line of sight from the oral opening to the glottis must be obtained by neck flexion and head extension (see earlier discussion). With video laryngoscopes, a direct line of sight to the glottis is unnecessary. In patients with an anteriorly positioned larynx, an assistant is frequently required to apply pressure on the thyroid cartilage to move the larynx posteriorly and improve the view; with the use of a

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**Fig. 29.10** Endotracheal tube tips. *Left,* The tip of a conventional endotracheal tube. *Right,* The tip of an endotracheal tube used with an intubating laryngeal mask airway (LMA). The Huber tip of the intubating LMA endotracheal tube is less likely to impinge on other structures, thus increasing the success of advancement and correct placement in the trachea.

**Box 29.4 Advantages and Disadvantages of Video Laryngoscopes**

**Advantages**

- Improvement in Cormack and Lehane grade 1–2 view
- Fewer failed intubations in anticipated and simulated difficult airways
- Reduced requirement for bougie and external laryngeal manipulation
- Utility as a rescue technique in patients with a difficult airway
- Assistant can view glottis and facilitate view with external glottic manipulation
- Useful teaching tool
- Possible advantage in patients with cervical spine pathology because of less need to manipulate neck
- Reduced risk for dental trauma because less force is required to align axes
- Increased rates of successful tracheal intubation for inexperienced providers

**Disadvantages**

- Various models with different characteristics requiring different positioning
- Limited data comparing efficacy of different models
- Learning required to become familiar with technique
- Difficulty passing endotracheal tube despite good glottic view
- Increased rate of successful intubation only in those familiar with technique
- Adequate mouth opening required
- Possibly increased time to achieve intubation

video laryngoscope, the assistant may watch the screen image to directly witness the effect of the pressure.

A 2016 systematic review,\textsuperscript{131} which included more than 7000 adult patients, found significantly fewer failed intubations when a video laryngoscope was used (OR 0.35) compared with direct laryngoscopy, and fewer failed intubations in both anticipated (OR 0.28) and simulated (OR 0.18) difficult airways. However, in patients not predicted to have a difficult airway, no significant reduction in failed intubation rate was observed. Of note, laryngeal or airway trauma was reduced when a video laryngoscope was used. Due to the high level of statistical heterogeneity, the authors did not present data on the time taken to achieve tracheal intubation.

Video laryngoscopes may be classified into three categories (Fig. 29.11)\textsuperscript{132}:

1. **Macintosh type** (e.g., C-MAC, Karl Storz Endoscopy, Tuttingen, Germany). These devices have a Macintosh-type blade and an insertion method similar to that used with conventional laryngoscopy. The glottis is visualized either directly or on the video screen. In the setting of anticipated difficult airway, the success rate is generally higher with these devices than with direct laryngoscopy, but external pressure and an ETT introducer are more frequently required.\textsuperscript{133}

2. **Anatomically shaped without a tube guide** (e.g., GlideScope video laryngoscope, Verathon Inc., Bothell, WA; McGrath video laryngoscope, LMA North America, San Diego, CA). The curved shape of the blade allows a view of the glottis without flexing or extending the head and neck; however, directing the ETT toward the glottis may be difficult, resulting in trauma. Several reports have described pharyngeal and palatal injury with use of the GlideScope.\textsuperscript{134,135} Injury is more likely when the GlideScope or ETT is inserted blindly through the mouth, when a rigid stylet is used, and when undue force is employed during ETT insertion.

3. **Anatomically shaped blade with tube guide** (e.g., Airtraq, King Systems Corporation, Noblesville, IN; The Airway Scope AWS-S100, Hoya-Pentax, Tokyo, Japan). The tip of the tube is captured on the video screen even before the device is inserted, and hence its location can be continuously confirmed during the entire course of intubation. Palatal injury has also been reported with the Pentax Airway Scope.\textsuperscript{136}

Although there are a number of studies comparing different video laryngoscopes in normal airways,\textsuperscript{137–139} there are few studies that compare the use of different video laryngoscopes in patients with an anticipated difficult airway.\textsuperscript{140,141} Furthermore, it is not known whether the preoperative assessments used to predict difficult direct laryngoscopy are valid predictors of difficult video laryngoscopy. Additional investigation is necessary to compare various devices and to ascertain whether specific devices or device types are better for specific airway conditions.

Evidence of benefit of video laryngoscopy in the obstetric population is limited.\textsuperscript{132} Arici et al.\textsuperscript{142} performed a randomized study comparing the McGrath Series 5 with a Macintosh blade in 80 women undergoing cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt.

Dhonneur et al.\textsuperscript{143} reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt. Dhonneur et al.\textsuperscript{143} reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt. Dhonneur et al.\textsuperscript{143} reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt. Dhonneur et al.\textsuperscript{143} reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt. Dhonneur et al.\textsuperscript{143} reported the successful use of a difficult airway algorithm in which the Airtraq device was used in parturients as a rescue device if tracheal intubation failed after 2 minutes of direct laryngoscopy. During a 6-month period, 69 parturients underwent emergency cesarean delivery with general anesthesia. Video laryngoscopy resulted in a significantly better view of the glottic opening but a longer apnea interval. All intubation attempts were successful on the first attempt.
intubation (95% CI, 92% to 99%). Video laryngoscopy with a GlideScope resulted in 18 of 18 successful intubations on the first attempt (95% CI, 81% to 100%) and a successful intubation in the patient with the failed direct laryngoscopy. Of note, the patients whose tracheas were intubated with the video laryngoscope were more likely to require urgent or emergency surgery and/or have predictors of difficult direct laryngoscopy than the patients whose tracheas were intubated using direct laryngoscopy.

Video laryngoscopy has become increasing popular in anesthesia care,\(^\text{145}\) as evidence demonstrating their potential advantages continues to be published. Literature in the obstetric population is, however, relatively sparse, although extrapolation of studies in nonpregnant patients, especially the obese, would suggest use of video laryngoscopy is of benefit. Moreover, the 2015 Obstetric Anaesthetists’ Association (OAA)/Difficult Airway Society (DAS) guidelines for the management of failed intubation state that a video laryngoscope should be immediately available for all obstetric general anesthesia.

**Awake Tracheostomy or Surgery Standby**

It is possible to perform an awake tracheostomy with local anesthesia, a technique that may be required in some situations in which airway management is anticipated to be extremely difficult and dangerous.\(^\text{146}\) In some cases, particularly if there is a known airway pathologic process, it is prudent to request that a surgical team proficient in emergency surgical airway management be immediately available before the induction of anesthesia for cesarean delivery.

**Local Anesthesia for Cesarean Delivery**

Rarely, the infiltration of local anesthesia may be used as a primary anesthetic technique for emergency cesarean delivery in the patient with an anticipated difficult airway. This technique, which has been well described, is most often used in developing countries, where contemporary anesthetic techniques may not be readily available (see Chapter 26).\(^\text{147}\) Few obstetricians today are familiar or proficient with this technique, but some resident training programs still provide instruction on its use.\(^\text{64}\) A large volume (i.e., 75 to 100 mL) of a dilute local anesthetic solution, such as 0.5% lidocaine or 1% prilocaine, is often required.\(^\text{148}\) Administration of such a large volume entails a risk for systemic local anesthetic toxicity. Mei et al.\(^\text{149}\) described four cases in which cesarean delivery was performed with bilateral transversus abdominis plane (TAP) block and ilioinguinal-iliohypogastric (IIIH) nerve blocks using 0.5% ropivacaine 40 mL.

In some cases, it is possible to perform the entire surgical procedure with local infiltration, provided the obstetrician makes a midline abdominal incision, makes minimal use of retractors, and does not exteriorize the uterus. Alternatively, the obstetrician might begin surgery and deliver the infant with the aid of local infiltration. Temporary hemostasis may be achieved until the airway is secured and then surgery completed after the induction of general anesthesia.\(^\text{147}\)

Cesarean delivery performed with local infiltration, if successful, has the advantages of preserving maternal hemodynamic stability and a patent airway while allowing emergency delivery of the infant. However, the technique requires a skilled and patient obstetrician; it may not be suitable when emergency delivery is necessary. Maternal anesthesia is typically incomplete and often inadequate, a fact that subsequently presents significant management issues, given that the abdomen has been opened, positioning options are limited, and the consequences of the surgical procedure such as hemorrhage may require immediate attention.

**THE UNANTICIPATED DIFFICULT AIRWAY**

**Obstetric Anesthesia Failed Intubation Guidelines**

Despite attempts to adequately assess parturients preoperatively, cases of unanticipated difficulty with airway management do occur. Therefore, the anesthesia provider and the entire operating team should have a plan to manage unanticipated difficulties in airway management before administering general anesthesia to obstetric patients. Until recently, guidelines on difficult airway management specifically for the obstetric patient have not been available. New guidelines have been developed that reflect the unique and often difficult conflict in which safe management of the mother may threaten the life of the fetus and vice versa. In 2013, Law et al.\(^\text{150}\) published recommendations on difficult airway management which contained a section on the obstetric patient. Subsequently, in 2015, the OAA and DAS published guidelines on the management of difficult and failed intubation in obstetrics.\(^\text{9}\) These guidelines are divided into three algorithms and two tables: the master algorithm is shown in Fig. 29.12.

**Algorithm 1** covers safe obstetric general anesthesia practice, emphasizing the need for planning and preparation. The algorithm includes preoperative assessment of mother and fetus, multidisciplinary team planning, performance of a rapid-sequence induction, and up to three attempts at laryngoscopy. Before induction of anesthesia, the anesthesia provider and obstetrician should discuss whether to awaken the woman or continue with surgery if tracheal intubation is not possible. Patient position should be optimized, effective preoxygenation performed (see earlier discussion), and appropriate doses of drugs administered. If the first attempt at laryngoscopy produces a poor view of the larynx, consideration should be given to reducing or removing cricoid pressure, external laryngeal manipulation, head repositioning, and the use of a bougie. If this fails to improve the view, the guidelines recommend gentle face mask ventilation. For a second attempt at laryngoscopy, consideration should be given to using an alternative laryngoscope and removing cricoid pressure. If this is also unsuccessful, a third attempt should only be attempted by an experienced colleague.

**Algorithm 2** summarizes the initial management of an obstetric failed intubation. Failure to intubate is communicated to the operating room team who should summon help. The priority at this stage is to maintain maternal oxygenation. This may be achieved by insertion of an SGA, preferably a...
Anesthetic Complications

second-generation device with a gastric drain (see later discussion) with cricoid pressure removed during insertion; or by face mask, with or without an oropharyngeal airway. If oxygenation is possible, a decision must then be made regarding whether to proceed with surgery. However, if oxygenation is not possible, Algorithm 3 should be followed. This final algorithm provides details of management of a “can’t intubate, can’t oxygenate” scenario. The situation should be declared to all members of the operating room team, and specialist help (e.g., otolaryngologist, trauma surgeon, intensivist) should be summoned. Laryngospasm should be excluded and neuromuscular block ensured; 100% oxygen should be administered. Front-of-neck access (see later discussion), with either a needle or surgical cricothyroidotomy may be necessary. If successful, a decision is made on whether to proceed with cesarean delivery. If front-of-neck access fails to restore oxygenation, maternal advanced life support and perimortem cesarean delivery may be required.

Table 1 of the OAA/DAS algorithm (Fig. 29.13) provides a structure of individual factors that should aid in the decision of whether to proceed with surgery. Several factors (maternal and fetal condition, experience of the anesthesia provider, maternal obesity, anticipated surgical difficulty, aspiration risk, and possible alternative anesthetic techniques) should be addressed before induction of anesthesia. Two factors (availability of airway devices, presence of ventilation and airway hazards) are assessed after failed intubation. Although some criteria may suggest proceeding and others waking, the final decision depends on the anesthesia provider’s judgment. If the mother and fetus are not in immediate jeopardy, the safest course is to awaken the mother. Once this is accomplished, other anesthetic options, such as an awake intubation or a neuraxial anesthetic technique, should be considered. The risk associated with proceeding with surgery in this scenario represents an elective commitment to the possibility of mask airway failure, the requirement of additional airway manipulation, risk for aspiration, and progression to a “cannot oxygenate” scenario.

If the situation is immediately life-threatening to the mother secondary to hemorrhage (e.g., uterine rupture, placental abruption), it may be necessary to proceed with cesarean delivery to optimize outcome for both the mother and

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**Figure 29.12** Obstetric Anaesthetists’ Association and Difficult Airway Society master algorithm for the management of difficult and failed tracheal intubation in obstetrics. CICO, Can’t intubate, can’t oxygenate; Pmax, maximal inflation pressure. (From Mushambi MC, Kinsella SM, Popat M, et al. Obstetric Anaesthetists’ Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia. 2015;70:1286–1306, with permission from Obstetric Anaesthetists’ Association/Difficult Airway Society.)
infant. Significant angst and controversy often accompany decision-making in the management of a stable mother with evidence of life-threatening fetal compromise, such as fetal bradycardia as a result of a prolapsed umbilical cord. In such cases, if mask ventilation is easy and adequate, the risk-benefit ratio of proceeding with an unsecured airway and an increased risk for aspiration should be weighed against the benefits of prompt delivery of the infant. In cases in which the maternal risk for aspiration is considered low and mask ventilation is easy, it may be reasonable to continue mask ventilation and avoid further intubation attempts. It is unclear whether continued mask ventilation or repeated intubation attempts represent the greater risk to the mother; even insertion of an SGA may further traumatize the airway or precipitate regurgitation.

The anesthesia provider should carefully consider the maternal risks of proceeding with cesarean delivery in a mother with an unsecured and unprotected airway, especially if no urgency exists and/or mask ventilation is difficult. Some obstetric anesthesiologists argue that even a nonreassuring (but not life-threatening) fetal heart rate tracing does not always justify proceeding with cesarean delivery under general anesthesia in a patient with an unsecured airway. Alternatively, in some of these cases, proceeding with cesarean delivery via mask ventilation or with an SGA may be a better option than awakening the patient, especially in those in whom neuraxial techniques are contraindicated. In these cases, the importance of communication between the obstetric and anesthesia teams cannot be overemphasized.

Table 2 from the OAA/DAS guidelines (Fig. 29.14) provides information on management after a failed intubation with information on awakening the patient and proceeding with surgery. If the patient is to be awakened, oxygenation should be maintained and cricoid pressure continued unless it impedes ventilation. The patient is positioned head-up or in the left-lateral position, and, if necessary, neuromuscular blockade is reversed. Further airway difficulty should be anticipated. Once awake, the urgency for delivery should be reviewed and alternative anesthetic options considered. In situations in which surgery is to proceed, anesthesia needs to be maintained with consideration of controlled or spontaneous ventilation. Aspiration risk should be minimized by maintaining cricoid pressure, emptying the stomach, minimizing fundal pressure, and administering antacids. Surgery
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should be performed by the senior obstetrician and the neonatal team informed of the failed tracheal intubation attempt. If uterine tone is poor, propofol may be substituted for volatile agents to maintain anesthesia. Throughout surgery, the anesthetist must anticipate further airway problems.

The publication of the OAA/DAS guidelines and the associated narrative review are welcome additions to the armamentarium of the obstetric anesthesia provider. These important documents address problems specific to the obstetric patient; an accompanying editorial by Preston highlights some important management features. The emphasis is now on oxygenation rather than ventilation, with bag-and-mask ventilation no longer forbidden. The decision to awaken the patient and perform another technique is often a difficult one. Kinsella et al. concluded that there has been increasing willingness to continue with general anesthesia rather than awakening the patient over the last 40 years. Hopefully, with routine preinduction discussion and with the guidance offered in Table 1 of the OAA/DAS guidelines, this decision will be more informed. Finally, front-of-neck access (attaining a surgical airway) is not an easy rescue technique and one that is unfamiliar to many obstetric anesthesia providers. If it is to be recommended, obstetric anesthesia providers will need to master this skill.

**Laryngeal Mask Airway**

The LMA is arguably the SGA with which anesthesia providers are most familiar. The introduction of the LMA into anesthetic practice was a significant advance in airway management that resulted in major alterations to the difficult airway algorithms of the ASA and other societies. Insertion of an LMA in an obstetric patient who can easily be ventilated by face mask is controversial, because little additional ventilation benefit is obtained and placement can induce vomiting and aspiration in this setting. However, in any situation in which conventional face mask ventilation is difficult or impossible, an SGA is the rescue device of choice.

The LMA has many advantages, most notably its ease of use and a very high initial success rate. Moreover, the LMA need not be perfectly positioned over the larynx to allow adequate ventilation. When assessed by flexible fiberoptic endoscopy, radiography, and magnetic resonance imaging,
placement of the LMA around the larynx is variable\textsuperscript{152}; however, 94% to 99% of patients with an LMA have little or no difficulty with ventilation.

In a prospective study, an LMA was inserted by experienced users in 1067 healthy parturients undergoing elective cesarean delivery under general anesthesia.\textsuperscript{153} The investigators demonstrated that a clinically effective and acceptable airway was obtained on the first attempt in 98% of patients and on the second or third attempt in an additional 1%. Fewer than 1% of patients required tracheal intubation for failure to obtain satisfactory LMA placement within 90 seconds, or for an \( \text{SpO}_2 \) less than 94%, or an end-tidal \( \text{CO}_2 \) greater than 45 mm Hg. Moreover, the airway management (which was accomplished with the LMA, maintenance of cricoid pressure until delivery, and mechanical tidal-volume ventilation of 8 to 12 mL/kg) was associated with no episodes of hypoxemia (\( \text{SpO}_2 \) less than 90%), regurgitation, aspiration, laryngospasm, bronchospasm, or gastric insufflation. The investigators concluded that, in experienced hands, an LMA is effective and “probably safe” for ventilation and the administration of a volatile anesthetic agent for general anesthesia in selected healthy patients undergoing elective cesarean delivery.

Many case reports have described the use of an LMA as a rescue device for obstetric patients in whom conventional methods of securing the airway have failed. In a national case control study performed in the UK from 2007 to 2009, 39 of 57 patients with a failed intubation were managed with a classic LMA.\textsuperscript{21}

An LMA may also act as a conduit for intubation; however, passage of an ETT without visualization has a low success rate.\textsuperscript{154} By contrast, fiberoptic-guided intubation through the LMA has a success rate that has approached 100% in some studies.\textsuperscript{152}

Despite these benefits, the LMA has been associated with the following disadvantages: (1) placement can induce vomiting; (2) aspiration of gastric contents is not prevented; (3) improper positioning can lead to gastric insufflation; (4) multiple insertion attempts may be required for correct placement, which may result in airway trauma; and (5) use of positive-pressure ventilation may be limited. In 0.4% to 0.6% of patients with normal airway findings, the placement of an LMA leads to inadequate ventilation\textsuperscript{152}; reasons for this outcome have been reported to include (1) backfolding of the distal cuff, (2) occlusion of the glottis by the distal cuff, (3) complete downfolding of the epiglottis, and (4) 90- to 180-degree rotation of the mask around its long axis.

Most of the data just cited pertain to the use of the original classic LMA; several variations in LMA design have since become available. Updated designs that have been found to be useful in difficult airway management of parturients are the ProSeal LMA (LMA North America, San Diego, CA, USA) and the Fastrach LMA (LMA North America, San Diego, CA, USA). The ProSeal LMA has a specialized high-volume/low-pressure cuff that allows the device to achieve a better fit over the glottis than a classic LMA (Fig. 29.15).\textsuperscript{157} This design allows the use of higher ventilation pressures (up to 30 to 40 cm H\textsubscript{2}O) with less air leakage around the cuff and a lower risk for air entry into the stomach. The ProSeal LMA also contains a specialized drainage conduit that bypasses the bowl of the LMA and prevents gastric fluid from entering the glottic area. A gastric tube can be passed down this drainage lumen to assist in emptying the stomach contents.

Cook et al.\textsuperscript{158} randomly assigned 180 nonparalyzed, nonpregnant anesthetized patients to airway management with a ProSeal or classic LMA. The ProSeal more reliably allowed positive-pressure ventilation than the classic LMA. Halaseh et al.\textsuperscript{159} described the use of the ProSeal LMA in 3000 patients undergoing cesarean delivery who had fasted for more than 4 hours and were not thought to have a difficult airway. They established an “effective” airway on the first attempt in 2992 (99.7%) women, with only 8 patients (0.3%) requiring a change to a different LMA size. None of the patients required tracheal intubation, and only one patient experienced regurgitation of gastric contents into the mouth.\textsuperscript{159} Minor side effects such as sore throat occurred in 21 patients (0.7%). Case reports have described the successful use of the ProSeal LMA after failed intubation in obstetric patients.\textsuperscript{160-162}

A disadvantage of use of the ProSeal LMA in an emergency is that it requires practice and experience to use correctly. High rates of successful first-pass insertion can be achieved by loading the drainage conduit with a lubricated gum elastic bougie\textsuperscript{163} or orogastric tube\textsuperscript{164} and using direct laryngoscopy to position the conduit in the esophagus, and then railroad- ing the ProSeal LMA into position. Given its complexity, this technique may not be appropriate when inserting an LMA to rescue failed intubation. A disposable, single-use version of the ProSeal LMA—the LMA Supreme—has a rigid design that facilitates high rates of successful first-pass insertion. Yao et al.\textsuperscript{165} described the successful use of the LMA Supreme in 700 nonobese women undergoing cesarean delivery under general anesthesia.
Anesthetic Complications

Arytenoid cartilage
Epiglottis
Cricoid cartilage
Thyroid cartilage

Fig. 29.16 Intubating laryngeal mask airway (LMA). This device features a more rigid J-shaped design than the conventional LMA to facilitate the alignment of the mask over the glottic opening and better accommodate a special soft-tipped tracheal tube for blind intubation (see Fig. 29.10).

Fig. 29.17 The position of the laryngeal mask airway (LMA) with and without cricoid pressure. The blue-shaded area indicates the distal part of the LMA that occupies the hypopharynx. The dashed lines indicate anatomic correlation. 1, Posterior view of the larynx. 2, Lateral view of the larynx. 3, Position of the tip of the LMA when cricoid pressure is applied. When cricoid pressure is applied before placement, the LMA, in theory, might be wedged in the hypopharynx but is more likely to occupy the space behind the arytenoid cartilages. The LMA is positioned at least 2 cm more proximal than usual. 4, Position of the LMA when no cricoid pressure is applied. When the LMA is placed correctly, the distal tip is at the distal end of C5 (fifth cervical vertebral), and the distal part of the LMA should fully occupy the hypopharynx and the pharyngeal space behind both the arytenoid and cricoid cartilages. (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)

general anesthesia. Both the ProSeal LMA and LMA Supreme have a large esophageal drain that decreases the size of the airway conduit, and thereby impedes direct passage of an ETT. Further, intubating conduits (e.g., fiberoptic scope) are difficult to insert through the LMA Supreme due to its rigid design.

Although designed specifically to facilitate blind tracheal intubation, the Fastrach or intubating LMA can also be combined with fiberoptic bronchoscopy (Fig. 29.16). Both reusable and disposable versions are available; unlike the Proseal LMA and LMA Supreme, neither has a gastric drainage conduit. When properly placed, the intubating LMA allows ventilation similar to that of the original LMA; however, a more rigid J-shaped design improves the alignment of the mask over the glottic opening and better accommodates a special soft-tipped tracheal tube for blind intubation (see Fig. 29.10). This special silicone ETT minimizes the risk for airway trauma and is available in diameter sizes 6.0 to 8.0 mm. In addition, the intubating LMA has an epiglottis elevator bar at its distal end that acts to lift the epiglottis anteriorly as the ETT exits the intubating LMA into the glottis. When a fiberoptic bronchoscope is used with an intubating LMA, the ETT should be advanced far enough to partially elevate the epiglottis elevator bar to assist the passage of the fiberoptic bronchoscope into the trachea. The successful use of the intubating LMA during a failed intubation at emergency cesarean delivery has been reported.

Laryngeal Mask Airway and Cricoid Pressure

With the possible exception of the ProSeal, an LMA does not protect against pulmonary aspiration of gastric contents, and its placement may precipitate regurgitation in a lightly anesthetized patient. Therefore, it is generally recommended that continuous cricoid pressure be maintained after the placement of an LMA in obstetric patients. Although a correctly placed LMA does not appear to compromise the effectiveness of cricoid pressure, the use of cricoid pressure can inhibit proper insertion of the LMA and, in some cases, may make correct insertion impossible (Fig. 29.17). The application of cricoid pressure can prevent the tip of the LMA from fully occupying the hypopharynx behind the arytenoid and cricoid cartilages. Therefore, if difficulty with insertion of an LMA is encountered during an obstetric airway emergency, consideration should be given to releasing cricoid pressure temporarily while a second attempt is made at insertion. The risk for hypoxemia after failed LMA placement is most likely greater than the small risk for aspiration due to the temporary release of cricoid pressure. Once the LMA is in place, cricoid pressure can be reapplied. However, in some patients, reaplication of cricoid pressure may decrease tidal volumes during positive-pressure ventilation through an LMA. In such cases, a reduction in cricoid pressure typically allows adequate ventilation.

Laryngeal Mask Airway as a Conduit for Intubation

Intubation through an LMA can be achieved blindly, especially with an intubating LMA, or with the assistance of a fiberoptic bronchoscope. Before starting this maneuver, the risks and benefits of an intubation attempt must be weighed. Intubation attempts should never supersede or compromise active ventilation; however, in certain situations, such as a patient at significant risk for aspiration or if ventilation is...
marginal, securing the airway with an ETT may take precedence. The use of a fiberoptic bronchoscope through an LMA has been reported to be nearly 100% successful in achieving intubation. A 6-mm ID cuffed ETT may be passed over the fiberoptic bronchoscope and through the shaft of a size 3 or 4 classic or intubating LMA; of note, a nasal RAE tube (Nellcor, Boulder, CO) is a suitable match for this purpose, owing to its adequate length and widespread availability. A 7-mm ID cuffed ETT may be passed in a similar manner through the shaft of a size 5 classic or intubating LMA.

When a fiberoptic bronchoscope is passed through an LMA, the bronchoscope should be introduced through the self-sealing diaphragm of an elbow adapter attached to the ETT and the airway circuit to allow continuous ventilation. The space available for ventilation around a 4-mm outer diameter (OD) fiberoptic bronchoscope placed within a 6-mm ID ETT is equivalent to that available with a 4.5-mm ID tube. Alternatively, a two-stage method can be employed, in which a fiberoptic bronchoscope is placed through the lumen of an Aintree Intubation Catheter (Cook Critical Care, Bloomington, IN) and the stem of a size 3 or 4 LMA. With the LMA in the oropharynx, the fiberoptic bronchoscope and Aintree Catheter are advanced through the vocal cords, the fiberoptic bronchoscope withdrawn, and then an ETT is guided over the Aintree Catheter.

There are no studies assessing the success rate of these advanced techniques that use the LMA as a conduit for tracheal intubation; however, these techniques take time and skill and should be performed by anesthesia providers experienced in their use.

Laryngeal Tube and Esophageal-Tracheal Combitube

The laryngeal tube (VBM Medizintechnik GmbH, Sulz, Germany) is another SGA device. Laryngeal tubes are manufactured from either silicone or polyvinylchloride (PVC) and have ventilation apertures between a proximal oropharyngeal cuff and a distal esophageal cuff. The laryngeal tube is inserted into the oropharynx until resistance is met, which should result in positioning of the ventilation apertures directly above the glottic opening. These devices are reported to provide seal pressures similar to those with the ProSeal LMA (40 cm H₂O) and insertion times and success rates comparable to those of the LMA. The Laryngeal Tube-S (LTS) contains a second lumen that can be used for drainage of the stomach. The LTS has been used successfully after a failed intubation and ventilation in a patient undergoing emergency cesarean delivery.

The esophageal-tracheal Combitube (ETC) (Sheridan Catheter Corporation, Argyle, NY) is a twin-lumen plastic tube with an outer diameter of 13 mm. One lumen has an open distal end and thus resembles a tracheal tube (i.e. the tracheal lumen), and the other (esophageal) lumen has a closed distal end. The ETC has a 100-mL proximal pharyngeal balloon; when the ETC is correctly positioned, the pharyngeal balloon fills the space between the tongue base and soft palate. When inflated, the proximal balloon seals the oral and nasal cavities. Distal to the pharyngeal balloon, but proximal to the level of the larynx, are eight perforations in the esophageal lumen. A smaller 15-mL distal cuff, similar to that on an ETT, seals either the esophagus or trachea when inflated. The ETC is inserted, with or without the aid of a laryngoscope, but its insertion does not require visualization of the larynx. Indeed, in the usual clinical context, the larynx cannot be visualized. The ETC enters the esophagus 96% of the time, allowing ventilation through the esophageal lumen perforations. If the ETC enters the trachea, the patient’s lungs can be ventilated directly through the tracheal lumen. Therefore, regardless of whether the distal end of the ETC enters the trachea or esophagus, the anesthesia provider can ventilate the lungs, assuming correct identification of which lumen should be used for ventilation.

The ETC allows adequate ventilation while preventing aspiration of gastric contents. If the distal end of the ETC enters the esophagus, the ETC can assist in removing gastric fluids through suction applied to the “tracheal” lumen. When long-term ventilation is anticipated or required, the ETC should be exchanged for an ETT.

Use of the ETC in the out-of-hospital setting has been associated with a notable incidence of serious complications, including upper airway bleeding, esophageal laceration and perforation, and mediastinitis. Although a lower incidence of serious complications would be expected in the more controlled operating room environment with an anesthesia provider using a laryngoscope to facilitate placement, the stiffness and the anterior curvature of the ETC, as well as the potential for balloon overinflation, still represent potential sources of airway and esophageal injury.

Cannula and Surgical Cricothyrotomy

The anesthesia provider must diagnose the failure of face mask and alternative devices to oxygenate and ventilate the patient and decide that direct tracheal access is necessary. A delay in performing cricothyrotomy results in greater morbidity and mortality than complications resulting from the attempt. Three techniques for cricothyrotomy are available:

1. Narrow-bore cricothyrotomy using a purpose-designed cannula less than 2-mm ID (e.g., Ravussin; VBM Medizintechnik GmbH, Sulz, Germany)
2. Wide-bore cricothyrotomy using a purpose-designed cannula greater than 4-mm ID (e.g., QuickTrach; VBM Medizintechnik GmbH, Sulz, Germany)
3. Surgical cricothyrotomy using a scalpel to enable placement of a small (less than 6-mm ID) standard tracheal or tracheostomy tube

Narrow-bore cannula cricothyrotomy requires the use of a high-pressure ventilation source (e.g., Manujet) for transtracheal jet ventilation (TTJV). The other two techniques use standard ventilation circuits. Most TTJV systems have an in-line regulator that allows the delivery pressure between 0 and 50 psi. A minimum pressure of 20 to 30 psi is required in the majority of patients to inflate the chest and provide appropriate tidal volumes and minute ventilation. During TTJV, it is critical that the operator allow time for exhalation.
of inspired gas to avoid hyperinflation of the lungs, potential air trapping, and barotrauma.\textsuperscript{188–190} Exhalation can be facilitated by keeping the airway patent by some means (e.g., nasal/oral airway, jaw thrust, LMA). There are numerous reports of the use of TTJV as a means to prevent hypoxemia during life-threatening airway emergencies\textsuperscript{190–192} and as a temporizing measure before a more definitive surgical airway can be established.

Although cannula cricothyrotomy is faster and carries significantly fewer risks, its success rate is much lower than that of surgical cricothyrotomy.\textsuperscript{112,186} Freerk and Cook reported failure in 12 of 19 emergency narrow-bore cricothyroidotomies and three failures out of seven with wide-bore cricothyroidotomies. Skill fade associated with increased length of time since training is likely to have a more significant impact on outcome than choice of device.\textsuperscript{186} The choice of technique can therefore be determined by local protocols. As highlighted by Preston,\textsuperscript{151} the anesthesia provider should evaluate and practice various airway techniques to maximize success during an emergency. The role of ultrasound in locating the cricothyroid membrane has recently received attention\textsuperscript{193}; further research is required to assess its benefit in emergency front-of-neck access.

**EXTUBATION OF THE PATIENT WITH A DIFFICULT AIRWAY**

**General Principles**

Tracheal extubation is a critical step during emergence from general anesthesia. Airway condition at the time of tracheal extubation may be less favorable than at induction of anesthesia. The patient’s disease process (e.g., preeclampsia) may contribute to worsening airway edema, as do fluid and blood products that have been administered during the procedure. Comorbidities, such as obesity and obstructive sleep apnea, may contribute to an increased risk for airway compromise after extubation of the trachea. Although the majority of extubations occur without incident, a number of serious adverse events, including hypoxic brain injury, can occur during emergence from general anesthesia and tracheal extubation or in the postoperative period.\textsuperscript{152,194}

After publication of the ASA guidelines for management of the difficult airway,\textsuperscript{1} a statistically significant reduction in airway claims arising from injury at induction of anesthesia was observed.\textsuperscript{195} However, the number of claims arising from intraoperative events and those at extubation and during recovery has not changed. Death and brain injury occur more commonly after extubation and during recovery than during induction of anesthesia.\textsuperscript{195} Not surprisingly, extubation problems are more common in obese patients and in those with obstructive sleep apnea.\textsuperscript{195} In the fourth National Audit Project (NAP4) of the Royal College of Anaesthetists and DAS, major airway complications in patients receiving anesthesia occurred during emergence or recovery in approximately one-third of the reported cases.\textsuperscript{112}

Extubation is an elective procedure that should always have a management strategy.\textsuperscript{196–198} The goals of extubation management are to ensure uninterrupted oxygen delivery, avoid airway stimulation, and allow ventilation and possibly reintubation with minimum difficulty and delay should extubation fail. The DAS Extubation Guidelines\textsuperscript{10} describe a four-step approach to the safe management of tracheal extubation:

- **Step 1: Plan extubation**
- **Step 2: Prepare for extubation**
- **Step 3: Perform extubation**
- **Step 4: Postextubation care: recovery and follow-up**

The planning and preparation steps allow the anesthesia provider to stratify risk and categorize the patient as either at low risk or at risk for extubation complications. A fasted patient with an uncomplicated airway is at low risk, whereas a patient at risk for aspiration in whom the ability to oxygenate and reintubate is potentially difficult is at risk.\textsuperscript{10} By definition, all obstetric patients fall into the “at-risk” group owing to the risk for pulmonary aspiration.\textsuperscript{10} A crucial decision is to determine whether it is safe to extubate the trachea or to postpone the extubation. Unfortunately, studies attempting to identify risk factors that can reliably predict difficulty with extubation, performed almost entirely in the critical care population, have been inconclusive.\textsuperscript{199} The leak test, in which the ETT cuff is deflated, the proximal end of the tube is occluded, and the patient is evaluated to determine if she can spontaneously ventilate around the tube, has not been uniformly demonstrated to predict success with extubation.\textsuperscript{200}

If the surgical procedure was long, or massive bleeding and significant fluid replacement has occurred, consideration should be given to transferring the patient to the intensive care unit and delaying tracheal extubation. The decision to remove the ETT should follow a full assessment of the patient (i.e., ability to follow commands, appropriate level of consciousness, recovery from neuromuscular blockade). The head of the bed can be elevated or the patient positioned on her left side. Patients for whom oxygenation and/or reintubation is predicted to be difficult may benefit from the insertion of an airway exchange catheter before tracheal extubation (see later discussion).

**Airway Exchange Catheters**

In situations in which the patient appears ready for extubation but concerns exist regarding potential difficulty with—and/or need for—reintubation (e.g., difficult intubation), establishing continuous airway access may be of benefit; such access can be achieved with an airway-exchange catheter (AEC) inserted through the ETT before extubation.\textsuperscript{201–204} There are many commercially available AECs: the Cook AEC (Cook Critical Care, Bloomington, IN) is a long, thin, hollow tube made from semirigid thermostable polyurethane. It has a blunt end with distal terminal and side holes; it is radiopaque and has length markings on its outer surface. The catheter is supplied with a removable 15-mm connector that is compatible with anesthetic circuits for oxygenation and Luer-Lok connectors for use with high-pressure source (jet) ventilation. AECs are available in various sizes; the most appropriate sizes for extubation are of sufficient length.
(e.g., 83 cm) and diameter (e.g., 11- to 14-gauge) to remain between the vocal cords while removing and/or reinserting an ETT. These catheters are compatible with tracheal tubes of internal diameters greater than 5 and 4 mm, respectively. Successful reintubation can be enhanced by the use of a smaller tracheal tube and rotation of the ETT 90 degrees during insertion to facilitate passage of the bevel through the vocal cords.  

Mort203 evaluated 354 patients with potentially difficult airways who were extubated over an AEC; 51 required reintubation. The reintubation success rate was greater than 90%. Complications during airway management, including low oxygen saturation, bradycardia, hypotension, esophageal intubation, and the need for accessory airway adjuncts, were less common when an AEC was used to assist reintubation than without. Successful outcomes have been reported in other similar studies.201,205 Visualization of the larynx, either by direct or video laryngoscopy, during AEC use can also increase the success of reintubation and reduce the incidence of complications.206

Morbidity associated with AEC use is predominantly a result of inappropriate positioning and failure of oxygenation. The distal tip of the AEC is ideally positioned in the mid-trachea; oxygen insufflation and jet ventilation through an AEC should only be undertaken with extreme caution; barotrauma and death have been reported.202,207,208

**KEY POINTS**

- Morbidity and mortality associated with airway management are key concerns for obstetric anesthesia providers.
- Difficulties with airway management occur with both intubation and extubation of the trachea.
- Physiologic and anatomic changes of pregnancy, such as airway edema, respiratory and metabolic changes, weight gain, breast enlargement, and the risk for gastroesophageal reflux, contribute to difficult airway management.
- All parturients receiving either general or neuraxial anesthesia must undergo airway assessment; plans should be devised for airway management.
- Airway difficulty is best predicted using a combination of assessments, including Mallampati class, thyromental distance, atlanto-occipital extension, and protrusion of the mandible.
- Early administration of neuraxial labor analgesia is recommended in those with an anticipated difficult airway.
- Antacid prophylaxis should be given to all parturients who require general or neuraxial anesthesia.
- Correct positioning of the parturient on the operating table is necessary to maximize the chance of successful tracheal intubation, especially in the obese parturient.
- Securing the airway before inducing general anesthesia may be the safest option in patients in whom airway management is expected to be difficult.
- Maintenance of maternal and fetal oxygenation is the primary objective in the management of an unanticipated difficult airway.
- If conventional mask ventilation is difficult or impossible, a supraglottic airway (e.g., laryngeal mask airway) is the rescue device of choice.
- Needle cricothyrotomy with transtracheal jet ventilation can be life sustaining when other means to achieve adequate oxygenation have failed.
- In parturients known to be difficult to intubate or with risk factors for a difficult airway, caution must be employed with both intubation and extubation of the trachea.
- Potential or actual airway difficulties should be discussed with obstetricians, and management decisions should incorporate multidisciplinary communication and cooperation.

**REFERENCES**

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106. Paech MJ. "Pregnant women having caesarean delivery under general anaesthesia should have a rapid sequence induction with cricoid pressure and be intubated”. Can this ‘holy cow’ be sent packing? *Anaesth Intensive Care.* 2010;38:989–991.


Postpartum headache is the complaint of cephalic, neck, or shoulder pain occurring during the first 6 weeks after delivery. The incidence of postpartum headache throughout the 6-week postpartum period has not been followed in a prospective manner. However, information is available from several sources, including an evaluation of women during the first week postpartum, from a database that recorded symptoms during pregnancy and in the first week after delivery, from a secondary analysis of parturients followed for postpartum pain, and from a survey of women at 5 months and 1 year postpartum.

Goldszmidt et al. evaluated 985 women during the first week postpartum and found a 38.7% incidence of headache. The median time to onset of symptoms was 2 days, and the median duration of headache was 4 hours. Benhamou et al. examined information collected on pregnant women who delivered at their institution during a 2-year period; exclusion criteria included recognized dural punctures, preterm deliveries, multiple gestation, and/or elective cesarean delivery. Headache was reported by 12% of 1058 patients who had epidural analgesia without recognized dural puncture and by 15% of 140 patients who delivered without epidural analgesia. Turner et al. evaluated patients at four university hospitals in the United States and Europe and found that 10% reported headache during pregnancy, 3.7% within 72 hours after delivery, and 3.6% at 8 weeks postpartum. A history of headache before pregnancy was predictive of headache during pregnancy and at 8 weeks postpartum but not at 72 hours. A history of intrapartum headaches was independently associated with headaches at 72 hours. Saurel-Cubizolles et al. surveyed 1286 women on their general health following their first or second delivery and found the incidence of headache was 22% and 42% at 5 and 12 months, respectively.

Post–dural puncture headache (PDPH) is one of the most common postpartum complications of neuraxial anesthesia. However, physicians and nurses should be aware that a dural puncture is only one of many causes of postpartum headache (Table 30.1). Most headaches are benign or do not require immediate attention; however, the timely diagnosis of some headaches (e.g., cortical vein thrombosis, subdural hematoma) is critical to good outcomes. Knowledge of both benign and nonbenign headaches is important for the anesthesiologist who is frequently the first physician to evaluate the patient with postpartum headache. Difficult diagnostic problems may require a consultation with a neurologist or imaging studies. The purpose of this chapter is to discuss the differential diagnosis of postpartum headache and PDPH in particular.
### TABLE 30.1 Differential Diagnosis of Postpartum Headache

<table>
<thead>
<tr>
<th>Headache Etiology</th>
<th>Primary Symptoms/Signs</th>
<th>Diagnostic Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension headache</td>
<td>Mild to moderate headache, lasting 30 minutes to 7 days</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often bilateral, nonpulsating, and not aggravated by physical activity</td>
<td></td>
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<tr>
<td>Migraine</td>
<td>Recurrent moderate to severe headache, lasting 4 to 72 hours</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often unilateral, pulsating, and aggravated by physical activity</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Mild to moderate headache accompanied by neck and/or shoulder pain</td>
<td>History and physical examination</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>Hypertension and/or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Headache often bilateral, pulsating, and aggravated by physical activity</td>
<td>Laboratory evaluation (alanine aminotransferase [ALT], aspartate transaminase [AST], uric acid, platelet count, urine protein)</td>
</tr>
<tr>
<td>Posterior reversible (leuko) encephalopathy syndrome (PRES)</td>
<td>Severe and diffuse headache with an acute or gradual onset</td>
<td>History and physical examination</td>
</tr>
<tr>
<td>Stroke</td>
<td>Possible focal neurologic deficits and seizures ischemic or hemorrhagic</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Cerebral infarction/ischemia: new headache that is overshadowed by focal signs and/or disorders of consciousness.</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid hemorrhage: abrupt onset of an intense and incapacitating headache.</td>
<td>CT without contrast or MRI (FLAIR sequence)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>Headache usually without typical features</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often overshadowed by focal neurologic signs and/or altered consciousness</td>
<td>CT or MRI</td>
</tr>
<tr>
<td>Carotid artery dissection</td>
<td>Late developing headache that is constant in nature</td>
<td>History and physical examination.</td>
</tr>
<tr>
<td></td>
<td>Bilateral or unilateral location</td>
<td>Carotid ultrasonography or MRA</td>
</tr>
<tr>
<td>Cerebral venous and sinus thrombosis</td>
<td>Nonspecific headache that may have a postural component.</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often accompanied by focal neurologic signs and seizures</td>
<td>MRV</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Progressive and often localized headache</td>
<td>Possible angiography</td>
</tr>
<tr>
<td></td>
<td>Often worse in the morning</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Aggravated by coughing/straining</td>
<td>CT or MRI</td>
</tr>
<tr>
<td>Idiopathic intracranial hypertension (pseudotumor cerebri/benign intracranial hypertension)</td>
<td>Progressive nonpulsating headache</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Aggravated by coughing/straining</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Spontaneous intracranial hypotension</td>
<td>No history of dural trauma</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Diffuse, dull headache worsening within 15 minutes of sitting or standing</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td></td>
<td>Associated with neck stiffness, nausea, tinnitus, and photophobia</td>
<td>Radioisotope cisternography</td>
</tr>
<tr>
<td></td>
<td>CSF opening pressure &lt; 60 mm H2O in the sitting position</td>
<td>CT myelography</td>
</tr>
<tr>
<td>Pneumocephalus</td>
<td>Frontal headache</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often an abrupt onset immediately after dural puncture</td>
<td>CT or MRI</td>
</tr>
<tr>
<td></td>
<td>Symptoms can worsen with upright posture</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Headache is most frequent symptom</td>
<td>History and physical examination</td>
</tr>
<tr>
<td></td>
<td>Often diffuse</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td></td>
<td>Intensity increases with time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated with nausea, photophobia, phonophobia, general malaise, and fever</td>
<td></td>
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</tbody>
</table>
### TABLE 30.1 Differential Diagnosis of Postpartum Headache—cont’d

<table>
<thead>
<tr>
<th>Headache Etiology</th>
<th>Primary Symptoms/Signs</th>
<th>Diagnostic Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>Frontal headache with accompanying facial pain Development of headache coincides with nasal obstruction Purulent nasal discharge, anosmia, and fever</td>
<td>History and physical examination Nasal endoscopy CT or MRI</td>
</tr>
<tr>
<td>Caffeine withdrawal</td>
<td>Onset of headache within 24 hours of cessation of regular caffeine consumption&lt;sup&gt;5&lt;/sup&gt; Often bilateral and pulsating Relieved within 1 hour of ingestion of caffeine 100 mg</td>
<td>History and physical examination</td>
</tr>
<tr>
<td>Lactation headache</td>
<td>Mild to moderate headache associated temporally with onset of breast-feeding or with breast engorgement intake</td>
<td>History and physical examination</td>
</tr>
<tr>
<td>Ondansetron headache</td>
<td>Mild to moderate headache associated with ondansetron intake</td>
<td>History and physical examination</td>
</tr>
<tr>
<td>Post–dural puncture headache</td>
<td>Headache within 5 days of dural puncture Worsens within 15 minutes of sitting or standing Associated with neck stiffness, tinnitus, photophobia, and nausea</td>
<td>History and physical examination Possible MRI</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; MRV, magnetic resonance venography.

<sup>5</sup>The International Classification of Headache Disorders criterion states that caffeine-withdrawal headache occurs on cessation of ≥ 200 mg daily caffeine consumption for more than 2 weeks. However, others have suggested that caffeine-withdrawal headache may occur after as little as 3 days’ exposure to 300 mg/day or 7 days’ exposure to 100 mg/day.  

With postpartum headache at a single center, Stella et al. noted that tension-type/migraine headache was the most common cause (47%) of postpartum headache. Preeclampsia/eclampsia and PDPH comprised 24% and 16% of cases, respectively.

### Primary Headaches

The postpartum patient can present with a recurrence of her known primary disorder or with the first manifestation of a primary condition. Patients with a history of headache disorders typically are diagnosed with one of the four major types of primary headaches. The most common postpartum headaches are tension-type and migraine headaches, which account for almost two-thirds of headaches during this period.<sup>1–2,6</sup> Tension-type headaches are often circumferential and constricting, can be associated with scalp tenderness, and are usually of mild to moderate severity.

### Migraine

Migraine headaches are defined as recurring cranial pain lasting 4 to 72 hours, often with typical features such as pulsating pain in a unilateral location, nausea, and photophobia. In the United States, the estimated overall age-adjusted 3-month prevalence of migraine is 19% in females and 9% in males, and is more common between 18 and 44 years of age.<sup>7</sup> Pregnancy has an ameliorating effect on migraine frequency in the majority of sufferers. However, symptoms may recur soon after delivery, with reports of 34% within the first week postpartum and 55% within the first month.<sup>9</sup> Generally, the symptoms are similar to their typical pattern, although often milder and less often unilateral. It is rare for a migraine to manifest for the first time during the postpartum period. Pregnant women with severe migraine experience higher rates of adverse labor and delivery outcomes (e.g., preterm delivery, preeclampsia, low birth weight) but a lower rate of cesarean delivery than the general population.<sup>7</sup> The higher rates of preeclampsia may reflect an underlying predisposition to cerebral ischemic injury.
Secondary Headaches

A common secondary headache in the postpartum period is the musculoskeletal headache, exacerbated by the maternal physical exertion of labor and associated sleep deprivation. This headache has accompanying neck and shoulder pain without a history of dural puncture. Approximately 11% to 14% of postpartum headaches are diagnosed as musculoskeletal. Other causes of secondary headache are discussed in the following paragraphs.

Hypertension

Hypertensive disorders of pregnancy, including preeclampsia, are commonly associated with headaches. Eclampsia is a form of hypertensive encephalopathy that includes headache, visual disturbances, nausea, vomiting, seizures, stupor, and coma. Seizures may occur in the absence of severe hypertension. Headache is a serious premonitory sign, present in more than 50% of women in whom eclampsia develops. About one-half of the cases of postpartum eclampsia occur within 48 hours after delivery, and the remainder occur between 2 days and 4 weeks after delivery. Occipital or frontal thunderclap headache, blurred vision, scotomas, photophobia, and altered mental status are some of the potential presenting symptoms. Other hypertensive disorders, with or without superimposed preeclampsia, are also associated with headaches both antepartum and postpartum and may lead to encephalopathy.

Posterior Reversible Leukoencephalopathy Syndrome

Posterior reversible (leuko)encephalopathy syndrome (PRES) was described in 1996 after recognition of consistent symptom presentation and brain magnetic resonance imaging (MRI) findings in a diverse group of patients. Conditions associated with PRES include preeclampsia, uremia, hemolytic-uremic syndrome, infection, malignancy, and exposure to immunosuppressant drugs. Approximately 25% of cases of PRES occur during pregnancy or in the immediate postpartum period. Mayama et al. conducted a retrospective cohort study to assess the incidence of PRES in women with eclampsia and preeclampsia with neurologic symptoms. PRES occurred in 92.3% of women with eclampsia and in 19.2% of women with preeclampsia with neurologic symptoms. PRES symptoms include headache, seizures, altered mental status, visual changes, and, occasionally, focal neurologic deficits.

The pathophysiology of PRES is believed to be similar to that of hypertensive encephalopathy in that altered cerebrovascular regulation causes loss of blood-brain barrier integrity. The accompanying vasogenic edema can be reversed by prompt recognition and supportive therapy (e.g., cessation of provocative medications, aggressive treatment of hypertension, seizure prophylaxis) in 70% to 90% of cases. However, irreversible cytotoxic edema with permanent neurologic damage can occur if the initial disorder is not diagnosed early.

The neuroradiologic features of PRES typically include symmetric areas of cerebral edema, predominantly involving the white matter regions of the posterior circulation (occipital lobes, posterior parietal and temporal lobes) (Fig. 30.1). MRI is the “gold standard” for diagnosing PRES because it can provide information about cerebral involvement earlier than computed tomography (CT).

Stroke

The physiologic changes that occur during pregnancy (e.g., venous stasis, edema, hypercoagulability) render these patients susceptible to stroke, and headache is a common presenting symptom. Approximately 50% of strokes occur within the first 6 weeks postpartum. Strokes can be ischemic or hemorrhagic.

The evaluation and treatment of stroke during pregnancy should mimic that performed for nonpregnant patients. Treatment will depend on the etiology. In addition to supportive care, acute reperfusion therapy with fibrinolytic agents (recombinant tissue plasminogen activator) and intraarterial mechanical thrombectomy should be considered in pregnant women with qualifying strokes.

Ischemic strokes account for approximately 87% of all strokes. Causes of ischemic stroke include cerebral venous sinus thrombosis, preeclampsia/eclampsia, thromboembolism related to valvular heart disease, and profound and persistent hypotension (e.g., cervical arterial dissection, amniotic fluid embolism). The clinical presentation often comprises new onset headache that is overshadowed by focal neurologic signs and/or disorders of consciousness.

Hemorrhagic strokes can be subclassified into intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), with a 10% and 3% incidence, respectively. Hemorrhagic stroke in pregnancy and the postpartum period is relatively more common than in the nonpregnant state. Conditions associated with hemorrhagic stroke include preeclampsia/eclampsia, aneurysms, and arterio-venous malformations.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage usually occurs secondary to ruptured aneurysms or arterio-venous malformations. The classic presentation is sudden onset of a severe headache that is unlike any previous headache (“worst headache of my life”). Associated symptoms may include neck stiffness, nausea, vomiting, decreased level of consciousness, and focal neurologic deficits. Suspicion of SAH necessitates urgent investigation by CT imaging; nonsurgical therapies (e.g., endovascular ablation) are available, and long-term sequelae can be minimized with early therapy.

Subdural Hematoma

Although usually associated with head trauma, subdural hematomas can occur spontaneously during pregnancy or can be associated with dural puncture (see later discussion). In several case reports, identification of the subdural hematoma was preceded by symptoms of PDPH. Dural puncture results in leakage of cerebrospinal fluid (CSF) and decreased intracranial pressure (ICP). Presumably, the reduction in ICP causes stress on bridging cerebral vessels, which precipitates...
The mean interval from delivery to headache onset was 9.3 days. The headaches were constant in character and both unilateral and bilateral. Stricken women appeared older (mean age, 35 years) than the average parturient. Diagnosis was made after carotid vessel ultrasonography or magnetic resonance angiography.

**Cerebral Venous and Sinus Thrombosis**

Cerebral venous and sinus thrombosis (CVST) is a uncommon cause of stroke (less than 1% of all strokes) that results from thrombosis of the cerebral venous system, including tearing and bleeding. Spontaneous subdural hematomas have been reported in parturients with diseases associated with angiopathy, such as preeclampsia and fatty liver disease of pregnancy. Neurologic signs of subdural hematoma are variable but include evidence of increased ICP (e.g., headache, somnolence, vomiting, confusion) and focal abnormalities.

**Carotid Artery Dissection**

A rare, vascular cause of postpartum headache is spontaneous carotid artery dissection. Borelli et al. reviewed the 19 known published cases of postpartum carotid artery dissection in 2011. The mean interval from delivery to headache onset was 9.3 days. The headaches were constant in character and both unilateral and bilateral. Stricken women appeared older (mean age, 35 years) than the average parturient. Diagnosis was made after carotid vessel ultrasonography or magnetic resonance angiography.

**Fig. 30.1** Posterior reversible (leuko)encephalopathy syndrome (PRES). MR images of a 19-year-old pregnant woman at 31 weeks’ gestation who presented with a urinary tract infection. She developed eclampsia, hemolysis–elevated liver enzymes–low platelet count (HELLP) syndrome, confusion, seizures, and a blood pressure of 190/140 mm Hg. Axial T2 fluid-attenuated inversion recovery (FLAIR) images demonstrate cortical/subcortical vasogenic edema in the frontal lobes (the superior frontal sulci), parietal lobes, and occipital lobes as well as deep gray structures such as caudate nuclei and lentiform nuclei (A, B). With magnesium sulfate, blood pressure control, and cesarean delivery, the patient had complete resolution of imaging findings (C, D) and symptoms. (From Brady E, Parikh NS, Navi BB, et al. The imaging spectrum of posterior reversible encephalopathy syndrome: A pictorial review. Clin Imaging. 2018;47:80–89.)
A dural venous sinuses, and deep and superficial cerebral veins. Approximately 2% of pregnancy-associated strokes are attributable to CVST. The most frequent symptoms in women with CVST are headache (86.1%) and epileptic seizures (26.8%). Diagnosis is best confirmed by MRI in combination with magnetic resonance venography; CT imaging identifies only one-third of cases. Treatment of cortical vein thrombosis includes anticoagulation and treatment of seizures and increased ICP. Anticoagulation therapy is recommended for patients with acute CVST, even in selected patients with intracranial hemorrhage. Thrombolysis may be a therapeutic option in a select group of patients with small hemorrhagic infarct and continued neurologic deterioration. Steroid therapy is not recommended.

**Brain Tumor**

Intracranial tumors may manifest as postpartum headache. Headache that is dull rather than throbbing may be an early feature of a brain tumor. Nausea, vomiting, seizures, and/or focal neurologic signs may be present. Neurologic examination may reveal evidence of increased ICP.

**Idiopathic Intracranial Hypertension**

Parturients with idiopathic intracranial hypertension (i.e., increased ICP in the absence of a mass lesion, also known as pseudotumor cerebri or benign intracranial hypertension) have headache and visual disturbances, usually in the antepartum period (see Chapter 48). The features of postpartum pseudotumor cerebri mimic the usual chronic headache symptoms experienced by the patient (i.e., nonspecific and varying in type, location, and frequency) and associated symptoms (e.g., visual loss, diplopia, nausea, vomiting, pulsatile tinnitus). The diagnosis largely is one of exclusion. Treatment involves reduction of CSF pressure, either with glucocorticoids, carbonic anhydrase inhibitors, diuretics, or surgical interventions (e.g., optic nerve sheath fenestration, cerebrospinal fluid diversion via lumbo-peritoneal or ventriculoperitoneal shunt, or intracranial venous sinus stenting). Since CSF volume is rapidly replaced, serial lumbar punctures are of limited value and should be reserved for patients who refuse or cannot undergo conventional medical or surgical therapy. Case reports describe the use of an intrathecal catheter for labor analgesia and administration of epidural blood patch for PDPH in patients with idiopathic intracranial hypertension.

**Spontaneous Intracranial Hypotension**

Spontaneous intracranial hypotension is an uncommon cause of headache that develops following CSF leakage secondary to dural tears. The tears usually occur at the thoracic spinal level and are not associated with prior spinal intervention. MRI of the brain with contrast will confirm the diagnosis of intracranial hypotension. MRI of the spine, CT cisternography, or CT myelography with contrast or radioisotope can help identify the exact location of CSF leak. Presentation of this disorder is identical to that of PDPH, because the pathophysiology is the same. The only difference is the lack of a prior neuraxial procedure. Spontaneous intracranial hypotension has been reported during pregnancy and in the postpartum period.

**Pneumocephalus**

The subdural or subarachnoid injection of air used for identification of the epidural space may be associated with the sudden onset of severe frontotemporal headache, sometimes accompanied by neck pain, back pain, or changes in mental status. Headache is caused by meningeal irritation by air, and symptoms can mimic those of PDPH in that they are worse in the sitting position and may be relieved by lying down. Roderick et al. noted that 2 mL of air injected into the subarachnoid space was sufficient to provoke a symptomatic pneumocephalus. CT is more sensitive than MRI to confirm the presence of air density areas within the cranial cavity. The headache typically occurs soon after air entrance into the intrathecal space and resolves within 3 to 5 days with reabsorption of the air. Treatment is symptomatic. Administration of oxygen by nasal cannula or face mask may hasten reabsorption of the air and speed recovery, although this therapy has yet to be proven for pneumocephalus after neuraxial anesthesia.

**Meningitis**

Meningitis is a complication of neuraxial procedures, and the associated severe headache typically manifests within 12 hours to several days following the procedure (see Chapter 31). Headache is accompanied by fever, nuchal rigidity, and the presence of Kernig and Brudzinski signs. Lethargy, confusion, vomiting, seizures, and a rash may also occur. Various strains of Streptococcus, organisms typically found in the upper airway and vagina, have been linked to bacterial meningitis after neuraxial procedures. In several cluster cases, the involved organisms in the patients’ CSF were matched with the proceduralists’ nasopharyngeal swabs, confirming that these cases of post–dural puncture bacterial meningitis were the result of droplet contamination. Aseptic technique during the neuraxial procedure, including donning of a face mask by the proceduralist, is of paramount importance. The diagnosis of meningitis is confirmed by examination and CSF culture, and warrants immediate treatment.

**Sinusitis**

Headache caused by inflamed paranasal sinuses is associated with purulent nasal discharge and, occasionally, fever. Pain may be unilateral or bilateral, depending on the extent of the disease, and the skin over the affected sinus may be tender. The sinuses fill overnight, and pain typically is worse on awakening. Pain improves in the upright position, which assists drainage.

**Caffeine Withdrawal**

The withdrawal of caffeine may lead to headache, increased fatigue, and anxiety. Caffeine withdrawal headaches may occur after just 3 days’ exposure to 300 mg/day or 7 days’ exposure to 100 mg/day of caffeine. Normal-sized caffeinated drinks usually contain 50 to 100 mg of caffeine per
serving. Although caffeine-withdrawal headache has not been documented as a cause of postpartum headache, the diagnosis should be considered if the parturient has been drinking caffeinated beverages during the pregnancy.

### Lactation Headache

Askmark and Lundberg\(^{39}\) reported episodes of intense headache during periods of breast-feeding in a woman known to suffer from migraine. Onset of headaches occurred within the first few minutes of breast-feeding, and the headaches resolved after cessation of nursing. The headaches were associated with an increase in plasma vasopressin concentration. Headaches have also been described in women with breast engorgement who either have elected not to breast-feed or have reduced the frequency of breast-feeding.\(^{40}\)

### Ondansetron

Sharma and Panda\(^{41}\) reported a case in which a woman received ondansetron for nausea and vomiting after uneventful spinal anesthesia for cesarean delivery. Several hours later, she developed a severe frontal headache that was worse in the upright position and in the morning and evening hours. The symptoms abruptly stopped after the discontinuation of ondansetron. Headache is a common side effect of ondansetron (incidence, 3% to 17%), owing to its antagonism of serotonin 5-HT\(_3\) receptors, and should be considered in the differential diagnosis of postpartum headache.

### POST–DURAL PUNCTURE HEADACHE

#### Incidence

PDPH may occur after intentional dural puncture with a spinal needle or unintentional dural puncture with an epidural or other needle. A meta-analysis of studies of PDPH in obstetric patients (\(n = 328,769\)) calculated a pooled risk for unintentional dural puncture with any epidural needle of 1.5% (95% confidence interval [CI], 1.5% to 1.5%).\(^{42}\) After a dural puncture with an epidural needle, the risk for PDPH was 52.1% (95% CI, 51.4% to 52.8%) (Fig. 30.2). The rate of PDPH after dural puncture with spinal needles ranged between 1.5% and 11.2%, depending on the needle size and type of needle (see later discussion) (Table 30.2).\(^{42–46}\) Although PDPH is often considered a “minor” complication of dural puncture, it was the cause of 12% of obstetric claims in the American Society of Anesthesiologists (ASA) Closed-Claims Project database.\(^ {47}\)

#### Symptoms

The ICHD-3 beta classification defines PDPH as a headache occurring within 5 days of a lumbar puncture, caused by
cerebrospinal fluid (CSF) leakage through the dural puncture. It is usually accompanied by neck stiffness and/or subjective hearing symptoms. PDPH usually remits spontaneously within 2 weeks, or after sealing of the leak with an autologous epidural blood patch. The headache is invariably orthostatic, but this is not a diagnostic criterion. Usually headache symptoms occur immediately or within seconds of assuming an upright position and resolve quickly (within 1 minute) after lying horizontally. Alternatively, the symptoms may exhibit delayed response to postural change, worsening after minutes or hours of being upright and improving, but not necessarily resolving, after minutes or hours of being horizontal.5

Van de Velde et al.48 published a 10-year retrospective review of unintentional dural puncture and PDPH in obstetric patients. Of 65 patients diagnosed with PDPH, 55% reported associated symptoms such as nausea, photophobia, tinnitus, and vertigo. Headache was frontal in 34 patients, occipital in 9 patients, and combined frontal and occipital in 15 patients. In 7 patients, headache was not localized to a specific area. In a retrospective review of 75 patients with PDPH after spinal anesthesia, symptoms associated with headache included nausea, vomiting, neck stiffness, and ocular and auditory symptoms (Table 30.3).49

Cranial nerve palsy, thought to be secondary to nerve traction caused by low CSF volume, is associated with PDPH. The sixth cranial nerve (abducens) is most susceptible to traction during its long and tortuous intracranial course. Injuries to this nerve constitute 92% to 95% of cranial nerve injuries associated with intracranial hypotension.50 The traction results in failure of the involved eye to abduct, and patients may have diplopia or extraocular muscle paralysis. In a literature review, Hofer and Scavone50 concluded that early administration of an epidural blood patch may decrease morbidity or prevent progression of ocular symptoms if PDPH is present with symptoms of nerve palsy. Corrective surgery may be necessary in persistent or permanent cases.

Hearing loss is also associated with PDPH. The deficit is usually in the low-frequency range and may be secondary to endolymph and perilymph imbalance and alteration of hair cell position in the inner ear.51 Therapeutic epidural blood patch improves hearing within 1 hour in most patients with severe PDPH.52 Other rare symptoms associated with PDPH include seizures,53 vertigo,54 bilateral forearm pain,55 abdominal pain, and diarrhea.56 In these rare case reports, the headache and associated symptoms resolved after therapy with an epidural blood patch.

Onset and Duration

In a prospective study of 75 nonobstetric patients with PDPH, 65% developed symptoms within 24 hours of the lumbar puncture and 92% developed symptoms within 48 hours.19 By ICHD-3 beta criteria, headache must appear within 5 days of dural puncture.1 However, a systematic review of PDPH in obstetric patients reported that onset of headache can occur up to 7 days after dural puncture,42 and one case report described a woman who developed a PDPH 12 days after labor neuraxial analgesia.57 Headaches caused by dural puncture with a spinal needle ranged in duration from 1 to 7 days.42 The duration of headache after dural puncture with an epidural needle has not been well studied, but is likely longer than that for a spinal needle.42,58 Webb et al.34 found that 18% of women who sustained a dural puncture with a 17-gauge Tuohy needle suffered from chronic headaches compared with 5% of women in a matched cohort who did not sustain dural puncture with an epidural needle.

Imaging

Imaging investigations are not routinely recommended for the postpartum patient with a PDPH unless the symptoms suggest other diagnoses or the diagnosis of PDPH is in doubt. Contrast-enhanced MRI is the method of choice to
study the meninges and has revealed characteristic findings of PDPH.65,66 These findings include (1) marked, diffuse pachymeningeal thickening and enhancement; (2) compression of the ventricles; (3) caudal displacement of the brain, brainstem, and optic chiasm; (4) cerebellar ectopia; (5) pituitary enlargement and enhancement; and (6) expansion of the superior sagittal sinus. The enlarged venous sinus may represent compensatory venous expansion in response to low CSF pressure. At times, imaging is needed to differentiate a PDPH from other causes of headache.

Pathophysiology

Debate continues regarding the precise etiology of PDPH symptoms. The original theory was that pain-sensitive nerve fibers were stimulated by a downward shift of the brain secondary to a loss of CSF volume. German surgeon August Bier62 is credited with the first description of successful spinal anesthesia and PDPH after his pioneering work on spinal anesthesia with cocaine. Bier and his assistant, Hildebrandt, performed spinal anesthesia on each other; using blows to the shin with an iron hammer and application of a burning cigar performed anesthesia with cocaine. Bier and his assistant, Hildebrandt, performed spinal anesthesia on each other; using blows to the shin with an iron hammer and application of a burning cigar to the skin, they demonstrated dense sensory blockade.62 Both experienced severe PDPH. The assistant forced himself to work the next day, but Bier stayed home for 9 days. Bier suggested the PDPH might be caused by CSF loss. Today there is no doubt that leakage of CSF initiates the syndrome. Kunkle et al.63 consistently produced PDPH by draining 20 mL of CSF from volunteers. Symptoms were immediately relieved by subarachnoid injection of saline to restore initial CSF pressure.

Total CSF volume is approximately 150 mL, and the production rate is approximately 0.35 mL/min or a daily rate of 500 mL. The rate of CSF leakage through a dural hole may exceed the rate of CSF production. If this occurs, low CSF pressure results in a loss of the cushioning effect provided by intracranial fluid.

CSF pressure during labor is normal between contractions but increases significantly during painful contractions and expulsive efforts. Effective epidural analgesia attenuates this increase in CSF pressure.64 In a study of five women with unintentional dural puncture, epidural pressures were normal preceding the development of headache.65 However, with development of headache symptoms, the mean epidural pressure measurements were found to decrease significantly.

Not all patients with PDPH symptoms have decreased CSF pressure, and not all patients with a significant CSF leak experience symptoms. The pain of PDPH may be caused, in part, by an increase in cerebral blood flow (and cerebral vasodilation) as a consequence of low CSF pressure or volume. This phenomenon has been observed in animals.66,67 The inverse relationship between intracranial blood volume and CSF volume reflects the body’s effort to maintain a constant intracranial volume.68 The lumbar CSF compartment is a dynamic structure and acts as a reservoir for intracranial CSF volume adjustment.69 In a descriptive study of cerebral blood flow measured by middle cerebral artery transcranial Doppler in 15 postpartum women with unintentional dural punctures following labor epidural analgesia, the authors demonstrated that women with PDPH symptoms had lower pulsatility indices compared with women without headaches.70 Pulsatility index is inversely related to cerebral blood flow. The occurrence of cerebral vasodilation may explain the relief of headache symptoms with treatment with vasoconstrictors such as caffeine, theophylline, and sumatriptan.

Risk Factors

In a classic study of 10,098 spinal anesthetics published in 1956, Vandam and Dripps71 noted that three patient factors influenced the incidence of PDPH: age, gender, and pregnancy. The analysis did not allow determination of whether these factors were independent risk factors. Subsequently, other risk factors for development of PDPH have been identified.

Age

Extensive evidence supports the observation that PDPH is uncommon in patients older than 60 years of age and is most common in patients younger than 40 years of age.72 In the elderly, the dura may be inelastic and less likely to gape after puncture. CSF leakage may be impeded by adhesions and calcification. The cerebrovascular system also may be less reactive in older patients. Further, this group is less active physically, and older patients may be less likely to complain.

Gender

Amorim et al.72 observed a gender difference with respect to the incidence of PDPH after spinal anesthesia (11.1% female versus 3.6% male). This difference may be related to differences in cerebrovascular reactivity; it is well known that migraine headaches occur predominantly in females and are influenced by hormonal changes. Women may have enhanced vascular reactivity, or perhaps changes in cerebral blood flow are more likely to produce pain in women than in men. A meta-analysis of randomized clinical trials identified a twofold higher risk for PDPH in nonpregnant females than in males.73

Vaginal Delivery

In a retrospective review of 235 parturients who suffered an unintentional dural puncture during epidural catheter placement, the rate of PDPH was lower in women who delivered via cesarean compared with those that delivered vaginally (53% versus 74%).74 This difference may be a result of the mechanical consequences of expulsive efforts during the second stage of labor and/or postpartum hormonal changes in cerebrovascular reactivity. Expulsive efforts in the second stage may increase CSF leakage. This possibility has prompted some physicians to restrict maternal pushing after dural puncture and to use forceps to shorten the second stage of labor. The evidence supporting this practice, however, is conflicting.75,76

Morbid Obesity

The results of studies assessing the relationship between body mass index (BMI) and risk for PDPH after dural puncture are
inconsistent. No association between BMI and PDPH was found in two retrospective studies.\textsuperscript{77,78} However, in the largest retrospective study of women with unintentional dural puncture ($n = 518$), Peralta et al.\textsuperscript{79} demonstrated that higher BMI was associated with a lower rate of PDPH. Using a threshold BMI of 31.5 kg/m$^2$, the incidence of PDPH was 39% and 56% in those with BMI greater than and less than the threshold, respectively. However, pain intensity at headache presentation and the highest reported pain score were similar between high and low BMI groups. Possible but unproven explanations of a lower incidence of PDPH in obese patients include increased abdominal pressure (which may reduce the extent of CSF leakage) and/or reduced physical activity in these patients. Other confounding factors, such as differences in the mode of delivery (higher rate of cesarean delivery) and neuraxial opioid administration, may also play a role.

**History of Previous Post–Dural Puncture Headache**

A history of PDPH after previous spinal anesthesia is associated with the development of PDPH with subsequent spinal anesthesia. In a cross-sectional study of nonobstetric patients who underwent spinal anesthesia for elective surgery, those with a previous history of PDPH were 4.3 times more likely (95% CI, 1.99 to 9.31) to have a second PDPH than patients without a history of PDPH (26.4% versus 6.2%, respectively).\textsuperscript{72} This finding suggests that certain individuals are predisposed to the development of PDPH.

**Multiple Dural Punctures**

Seeberger et al.\textsuperscript{79} found that multiple dural punctures significantly increased the risk for PDPH. Surgical patients who received a second spinal injection owing to failure of the initial spinal puncture had a 4.2% incidence of PDPH compared with a 1.6% incidence among patients who had a single dural puncture.

**Neuraxial Anesthetic Technique**

Technical factors related to the neuraxial technique influence the incidence of PDPH.

**Spinal needle design.** Historically, the beveled Quincke needle, a needle with a cutting bevel (Fig. 30.3) was widely used for dural puncture for both diagnostic and anesthetic purposes (see Chapter 12). In 1951, Hart and Whitacre\textsuperscript{80} introduced a solid-tipped, pencil-point spinal needle with a lateral injection port, which is now known as the Whitacre design. They believed that the new needle tip would stretch and separate rather than cut the dural fibers and result in a lower incidence of PDPH. Studies have confirmed the anticipated lower incidence of PDPH with the pencil-point tip (see Table 30.2).\textsuperscript{12,81} In vitro data suggest that fluid leak through the dural puncture site is slower with a pencil-point needle compared with a beveled needle.\textsuperscript{82} With the recognition that pencil-point spinal needle tips reduce the incidence of PDPH, other tip designs have appeared. In 1987, Sprotte et al.\textsuperscript{83} reported experience with the use of a new needle that has a solid oval tip and a longer orifice than the Whitacre needle. The incidence of PDPH was 0.02% with its use in a heterogeneous patient population of almost 35,000 patients.\textsuperscript{84} Subsequent studies have shown the incidence of PDPH with the Sprotte needle is lower than that with Quincke needles of smaller gauge.\textsuperscript{85} A 2017 meta-analysis of 8 randomized clinical trials including 1324 women undergoing cesarean delivery confirmed that spinal needles with cutting bevels were more likely to cause PDPH than pencil-point needles (relative risk (RR) 3.12; 95% CI, 1.60 to 6.10).\textsuperscript{84}

A modification of the Quincke needle, the Atraucan needle, has a cutting tip and a double bevel, which is intended to cut a small dural hole and then dilate it.\textsuperscript{86} Studies suggest that the use of this needle is associated with a higher risk for PDPH than the use of a noncutting, pencil-point needle.\textsuperscript{86}

**Spinal needle size.** With the Quincke needle, the incidence and severity of PDPH are directly related to the size of the needle. The incidence of PDPH is lower with a 27-gauge needle than with 25- and 26-gauge needles (see Table 30.2). A similar relationship may exist with pencil-point needles. The current popularity of spinal anesthesia in obstetric patients is largely a result of an improvement in needle technology, which has led to a reduction in the incidence of PDPH. Because of the morbidity associated with PDPH, every effort should be made to use a needle associated with a low incidence of PDPH (e.g., a small-gauge, noncutting needle).

**Direction of bevel of the Quincke needle.** Studies have confirmed that puncturing the dura mater with a Quincke needle bevel parallel to the long axis of the spine reduces the incidence of PDPH by 70% compared with a perpendicular orientation.\textsuperscript{87} It was originally thought that the dural fibers ran in a longitudinal direction and therefore inserting the needle parallel to the long axis of the spine caused less trauma to the dura. However, electron microscopy has revealed that the dura consists of multidirectional interlacing collagen fibers with both transverse and longitudinal elastic fibers.\textsuperscript{88}

Some authors have suggested that the insertion of the needle with the bevel parallel to the long axis of the spine most likely results in less tension on the dural hole and, therefore, a smaller aperture with less CSF leak. In vitro studies of bevel orientation and fluid leak have provided conflicting
results.87–89 However, despite confusing anatomic evidence, clinical experience strongly supports insertion of the Quincke needle with the bevel parallel to the long axis of the spine.87

**Epidural needle size/design.** The high rate of PDPH after unintentional dural puncture with an epidural needle has led investigators to alter the epidural needle design and size in an attempt to reduce headache incidence and severity. Data on the success of this endeavor are conflicting. In an *in vitro* study using cadaver dura, no differences were found in fluid leak rate among punctures made with Hustead, Tuohy, Crawford, and Sprotte epidural needles.86 In contrast, in an *in vivo* study, Morley-Forster et al.87 observed a risk difference of −0.44 (95% CI, −0.67 to −0.21) in the incidence of PDPH with the use of an 18-gauge Sprotte needle compared with the standard 17-gauge Tuohy needle despite no difference in the unintentional dural puncture rate. However, the Sprotte epidural needle, with its lateral orifice, is not commonly used as an introducer of epidural catheters.

The incidence of PDPH is greater when unintentional dural puncture occurs with a 16-gauge compared with an 18-gauge epidural needle (RR 2.21; 95% CI, 1.4 to 2.6).92

**Direction of the bevel of the Tuohy needle.** Norris et al.93 examined two groups of women who received epidural anesthesia with a Tuohy needle. In one group, the bevel was advanced with the orifice perpendicular to the long axis of the spine. In the other group, the needle entered the epidural space with the bevel parallel to the long axis and the needle was then rotated 90 degrees before insertion of the catheter. The authors observed a decreased incidence of PDPH in the latter group. However, some anesthesiologists argue that rotation of the needle within the epidural space may increase the risk for unintentional dural puncture. Richardson and Wissler94 randomized laboring women to a cephalad or lateral orientation of the Tuohy bevel during epidural needle insertion. The needle was not rotated before insertion of the epidural catheter. There was no difference in dural puncture or PDPH rates, but catheter insertion was easier with a cephalad orientation of the bevel.

**Midline or paramedian approach.** There is conflicting evidence as to whether the spinal needle approach affects the incidence of PDPH. Hatfalvi85 reported no cases of PDPH in a retrospective survey of 4465 spinal anesthesia procedures. This investigator used a paramedian approach with a 20-gauge Quincke needle, and the skin was punctured 3 cm from the midline. He suggested that tangential dural puncture creates a dural flap and prevents PDPH. In contrast, Viitanen et al.,96 prospectively monitoring obstetric patients after administration of single-shot spinal analgesia for labor (27-gauge Quincke needle), observed PDPH in 3 of 85 (3.5%) patients in whom the midline approach was used, compared with 15 of 127 (11.8%) patients in whom the paramedian approach was used. Using a rigid paper cylinder model of the dura, Kempen and Mocek97 studied median and paramedian punctures with a 22-gauge Quincke needle in different orientations. With midline punctures, all entry and exit holes were of uniform size regardless of bevel orientation, and no “dural” flaps were seen. After paramedian punctures, flaps formed when the needle bevel faced the cylinder surface with a near-tangential angle of perforation, suggesting it may be beneficial to insert the needle via the paramedian approach to reduce the incidence of PDPH. Currently, data are insufficient to recommend either the median or paramedian approach.

**Air versus saline method of locating the epidural space.** The medium (air or saline) used for the loss-of-resistance technique to identify the epidural space has not clearly been shown to influence the incidence of PDPH. Many anesthesia providers have adopted the loss-of-resistance-to-saline technique in the belief that it is associated with a lower incidence of unintentional dural puncture and PDPH than the use of air.98 However, the data are inconsistent, and not all studies have found a difference.99

Segal and Arendt100 suggested that a randomized study of air versus saline to identify the epidural space may lead to overestimation of the difference between air and saline, should one exist, because it is impossible to blind the anesthesia provider to technique, and the study design forces the provider to use a less preferred technique. In a retrospective study, they found that the rate of unintentional dural puncture was not different between the saline versus air technique.100 However, among anesthesia providers who had a preference for one technique, use of their preferred technique was associated with fewer unintentional dural punctures than use of the nonpreferred technique. Thus, current data do not support a difference in the incidence of PDPH between the loss-of-resistance-to-air versus the loss-of-resistance-to-saline technique to identify the epidural space, and providers who currently use air to identify the epidural space should not change techniques hoping it may decrease the rate of PDPH.

**Choice of local anesthetic drug for spinal anesthesia.** Naulty et al.,101 reported that the use of bupivacaine-glucose or lidocaine-glucose for spinal anesthesia was associated with a higher incidence of PDPH than the use of tetracaine-procaine. They postulated that osmotic, cerebral irritant, and/or cerebrovascular effects of the glucose could be responsible for these findings. Whether this finding is applicable to other non–glucose-containing local anesthetic preparations, such as plain bupivacaine, is unknown.

**Continuous spinal anesthesia.** A multicenter randomized clinical trial compared analgesia and safety of 28-gauge spinal microcatheters to epidural catheters for labor analgesia.102 There was no difference in the incidence of PDPH (9% versus 4%, respectively) or epidural blood patch (5% versus 2%, respectively) between women randomly assigned to receive an intrathecal catheter and those who received an epidural catheter; however, the study was insufficiently powered to assess these outcomes. Spinal microcatheters are not currently available in North America.

Three case series have evaluated a 23-gauge spinal catheter for labor analgesia or cesarean delivery.103–105 The PDPH rate ranged from 3% to 29% in these series. This range is greater than that reported in other studies using traditional epidural or combined spinal-epidural techniques.

**Combined spinal-epidural anesthesia.** The combined spinal-epidural (CSE) technique is widely used for both labor
analgesia and cesarean delivery. Intuitively, it seems that the incidence of PDPH should be identical to, or greater than, that observed after single-shot spinal anesthesia with the same size and type of needle. However, the available evidence, primarily from observational studies, suggests that the risk for PDPH is not increased with the CSE technique.\textsuperscript{106–108} PDPH rates with the CSE technique in these three studies were 1.7\%, 0.43\%, and 1.4\%, respectively, compared with 1.6\%, 0.45\%, and 0.8\%, respectively, for the epidural technique. Initial placement of the epidural needle facilitates precise dural puncture, and the subsequent increase in epidural space pressure after the epidural injection of local anesthetic may reduce CSF leakage. If the anesthesia provider is in doubt about correct epidural needle placement, a needle-through-needle dural puncture might resolve the issue and prevent unintentional dural puncture with a large-gauge epidural needle.

**Complications**

The immediate problems associated with post–dural puncture headaches include (1) the inability to perform activities of daily living, such as providing care for the newborn; (2) an extended duration of hospitalization; and (3) a higher number of emergency department visits. The National Obstetric Anaesthesia Database project of the Obstetric Anaesthetists’ Association reported that 75\% of 975 women with PDPH had difficulty performing activities of daily living.\textsuperscript{109} In a retrospective study, Angle et al.\textsuperscript{110} reported that hospital length of stay increased by a mean + SD of 17 ± 24 hours. Rare but serious complications may occur following dural puncture and PDPH, including subdural hematoma, cerebral venous sinus thrombosis, chronic headache, diplopia, and hearing loss.

Zeidan et al.\textsuperscript{111} reviewed the published reports of subdural hematoma after dural puncture. They found that subdural hematoma was associated with new neurologic symptoms in addition to changing headache characteristics. The proposed mechanism of subdural hematoma development is ongoing intracranial hypotension leading to caudal movement of the brain and rupture of fragile, bridging subdural veins (see earlier discussion). Lim et al.\textsuperscript{112} reported a case series of 11 obstetric patients who developed a subdural hematoma after neuraxial labor analgesia at a tertiary care hospital. The observed rate of subdural hematoma was 0.026\% (11 in 42,969, approximately 1:3900), and the rate of subdural hematoma following a recognized dural puncture with an epidural needle was 1.1\% (5 in 437, approximately 1:87). Ten of 11 patients with subdural hematoma had signs consistent with PDPH before the diagnosis of subdural hematoma; five had a recognized unintentional dural puncture. Subdural hematoma was diagnosed within 7 days of the neuraxial procedure (mean 4.1 days) in 10 patients; in one case the diagnosis was made 25 days later. Ten patients required a second hospital stay, and one patient required a decompressive hemicraniectomy.

Cerebral venous and sinus thrombosis has been documented after unintentional dural puncture and treatment of PDPH with an epidural blood patch.\textsuperscript{113} Contributing factors may include cerebral venous dilation (associated with decreased ICP) and the hypercoagulability of pregnancy. Anticoagulation therapy is recommended for patients with acute CVST, even in selected patients with intracranial hemorrhage (see earlier discussion).\textsuperscript{25}

**Diplopia** or hearing loss after dural puncture, secondary to cranial nerve dysfunction, may be permanent, even after successful treatment of the PDPH with an epidural blood patch.\textsuperscript{114} A review of 95 cases of neurapraxia or axonotmesis of the ocular cranial nerves (oculomotor, trochlear, and abducens nerves) concluded that symptoms may last from 2 weeks to 8 months but that almost 90\% of patients recover.\textsuperscript{114}

Several studies have described the persistence of headache, backache, or cranial nerve symptoms after PDPH.\textsuperscript{39,115,116} Ranganathan et al.\textsuperscript{115} conducted a retrospective case-control study over a 5-year period in which parturients with an unintentional dural puncture were contacted by telephone to assess acute and long-term residual symptoms. Compared with a control group, patients with an unintentional dural puncture were more prone to acute headache (87\% versus 8.7\%) and chronic headache (34.9\% versus 2.2\%) as well as backache and neck ache. These findings reinforce the concept that long-term sequelae from dural puncture can occur.

**Prevention**

Many practices and maneuvers have been used in an attempt to reduce the incidence of PDPH after unintentional dural puncture, most with limited success. A 2005 survey of British obstetric anesthesiologists quantified the frequency of such practices.\textsuperscript{117} These included encouraging postpartum fluid intake (91\%), regular analgesia (83\%), caffeine administration (30\%), and using an intrathecal catheter (15\%) at the time of unintentional dural puncture. Older practices, such as avoiding pushing during the second stage, restricting postpartum mobility, abdominal binders, and prophylactic epidural administration of saline or autologous blood, appear to be declining in use. A 2010 systematic review of prevention strategies summarized the evidence from comparative studies and concluded that studies were heterogeneous and that “no clinical recommendation can be made until the superiority of one preventative intervention over another has been unequivocally proven in a definitive multicenter RCT” [randomized controlled trial].\textsuperscript{118}

**Bed Rest**

In a 2016 systematic review, Arevalo-Rodriguez et al.\textsuperscript{119} reviewed the evidence for prolonged bed rest combined with different body and head positions, as well as supplementary fluid administration, for the prevention of PDPH after dural puncture. The review included 24 trials with 2996 patients; 26\% of study participants randomized to bed rest experienced PDPH compared with 21\% in women who were allowed to mobilize immediately after dural puncture. Given these data, and the knowledge that pregnant women are hypercoagulable and at increased risk for deep vein thrombosis and pulmonary embolism, immobility should not be used as a maneuver to prevent PDPH (see Chapter 38).
Hydration

Despite the widespread practice of encouraging women to increase oral fluid intake after unintentional dural puncture, there is little evidence that greater hydration prevents PDPH. A 2016 systematic review identified only one randomized trial in 100 nonobstetric patients. There was no difference in the incidence of PDPH in patients randomized to receive 3 L or 1.5 L of fluid per day.\textsuperscript{119}

Caffeine

Two clinical trials in nonobstetric patients have evaluated the efficacy of oral or intravascular caffeine to prevent PDPH, but neither study showed a reduction in the incidence of headache.\textsuperscript{120,121} Based on these results, prophylactic caffeine is not advocated for prevention of PDPH.

Cosyntropin

Hakim\textsuperscript{122} evaluated whether cosyntropin, an adrenocorticotropic hormone (ACTH) analogue, was effective in reducing the incidence of PDPH after unintentional dural puncture in parturients. Patients were randomized to receive intravenous cosyntropin 1 mg or placebo 30 minutes after delivery. The incidence of PDPH was significantly lower in the cosyntropin group (33\% versus 69\%). The mechanism is unknown but may be related to an aldosterone-stimulating effect on volume expansion, modulation of pain perception via central endorphin-like action, or increased CSF production by enhanced sodium ion transport. The study has not been replicated, and adequate dose-response and safety studies have yet to be performed.

Neuraxial Opioids

Early studies suggested that prophylactic neuraxial administration of a hydrophilic or lipophilic opioid does not reduce the incidence of PDPH after spinal anesthesia or unintentional dural puncture.\textsuperscript{123,124} However, in a randomized, blinded trial published in 2008, 50 parturients with unintentional dural puncture and subsequent epidural analgesia were randomized to receive epidural morphine 3 mg or saline-placebo after delivery. The incidence of PDPH was significantly lower in the morphine group (33\% versus 69\%).\textsuperscript{125} The incidence of PDPH was 48\% in the saline-placebo group and 12\% in the morphine group. Although no complications were reported, we would caution against routine administration of epidural morphine in these circumstances until this finding is confirmed and further safety studies are undertaken. The movement of morphine across the dura is increased by the presence of a large-gauge needle puncture, possibly increasing the risk for respiratory depression.\textsuperscript{126}

Intrathecal Catheters

Placing a 19- or 20-gauge epidural catheter into the intrathecal space after an unintentional dural puncture with an epidural needle has become an increasingly popular technique.\textsuperscript{127–129} The immediate benefits of an intrathecal catheter are continuous labor analgesia using low doses of local anesthetic and opioid, and rapid-onset surgical anesthesia should it be required. Some experts have speculated that the intrathecal catheter might reduce the immediate CSF leak into the epidural space by mechanical obstruction as well as inducing an inflammatory fibrous reaction in the dura rent, thus facilitating closure of the puncture after removal of the catheter. Most studies are retrospective and observational and lack rigorous outcome definitions and follow-up. Data from these studies are conflicting but suggest that intrathecal catheters do not significantly reduce the incidence of PDPH unless they are left in place for at least 24 hours after delivery (Table 30.4).\textsuperscript{74,92,127–134} Russell\textsuperscript{92} conducted a prospective, nonblinded, quasi-randomized multicenter study in parturients who had an unintentional dural puncture during epidural needle placement. Participating institutions were randomized in 6-month blocks to either repeating the epidural procedure with placement of an epidural catheter, or placement of a spinal catheter through the dural puncture if unintentional dural puncture occurred during initiation of epidural labor analgesia. Spinal catheters were left in situ for 24 to 36 hours. The incidence of PDPH was not significantly different between women in the epidural (62\%) and spinal (72\%) catheter groups.

Some studies have evaluated the effect of intrathecal catheter placement on the severity of PDPH. Heesen et al.\textsuperscript{135} conducted a meta-analysis that included nine studies of various quality. The authors concluded that placement of an intrathecal catheter did not significantly reduce the incidence of PDPH compared with placement of an epidural catheter.\textsuperscript{135} However, they did observe a significant reduction in the need for epidural blood patch (RR, 0.64; 95\% CI, 0.49 to 0.84) after intrathecal catheter placement. Similar results were reported in a more recently published retrospective study that compared laboring patients with unintentional dural puncture who had the epidural resited or had an intrathecal catheter placed.\textsuperscript{134} There was no difference in the incidence of PDPH between groups, but there was a significant increase in the number of women who received an epidural blood patch in the epidural compared with the intrathecal catheter group (52\% versus 20.3\%, respectively).\textsuperscript{134}

The current evidence suggests that advancing a traditional epidural catheter into the intrathecal space after unintentional dural puncture does not appear to reduce the incidence of PDPH but may reduce its severity or the need for an epidural blood patch. Although one retrospective study suggested that leaving the spinal catheter in place for 24 hours resulted in a lower incident of PDPH than removing the catheter shortly after delivery,\textsuperscript{127} the effect of spinal catheter dwell time has not been rigorously studied. Leaving the spinal catheter in situ after the patient leaves the birthing unit may increase the risk for drug error or infection. Further studies are required before a definitive conclusion can be reached about the benefits and safety of this technique.

Prophylactic Epidural/Intrathecal Saline

Trivedi et al.\textsuperscript{136} randomly assigned patients with unintentional dural puncture to receive either a prophylactic epidural saline bolus (40 to 60 mL) or blood patch (15 mL) just before epidural catheter removal, or conservative therapy without a
Postpartum Headache

reported a double-blind trial in which 64 parturients with unintentional dural puncture were randomly assigned to receive 20 mL of autologous blood (prophylactic epidural blood patch) or a sham procedure. Both groups had a 56% incidence of PDPH; however, the duration of headache was shorter in the prophylactic blood patch group. The systematic review highlighted the difficulty in estimating the risks and benefits of prophylactic epidural blood patch. Because of the low incidence of unintentional dural puncture, studies are small; therefore, reliable conclusions about the technique cannot be made based on current evidence.139

Because unintentional dural puncture with a 16- or 18-gauge epidural needle results in a high incidence of PDPH, some anesthesiologists believe that prophylactic blood patch is always justified. Others argue that with such an approach, a significant number of patients will receive unnecessary treatment and that a blood patch is not devoid of complications. These latter anesthesiologists call attention to the potential for epidural catheters to become contaminated after prolonged use. The injection of blood through a contaminated epidural catheter may be associated with a higher risk for infection than injection through an epidural needle placed de novo for a therapeutic blood patch. A case report of a parturient who received a prophylactic epidural blood patch and was subsequently diagnosed with streptococcal septicemia highlights the potential risk for maternal infection using this technique.141

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TABLE 30.4  Rate of Post–Dural Puncture Headache after Unintentional Dural Puncture and Prophylactic Intrathecal Catheter Placement

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Intrathecal Catheter, n/N (%)</th>
<th>No Intrathecal Catheter, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagannathan74</td>
<td>Retrospective cohort</td>
<td>117/173 (68)</td>
<td>49/63 (78)</td>
</tr>
<tr>
<td>Norris and Leighton130</td>
<td>Retrospective cohort; catheter left in place for 2 h</td>
<td>19/35 (54)</td>
<td>11/21 (52)</td>
</tr>
<tr>
<td>Cohen et al.131</td>
<td>Retrospective cohort; catheter left in place for 24 h</td>
<td>8/17 (47)</td>
<td>0/13 (0)b</td>
</tr>
<tr>
<td>Dennehy and Rosaeg132</td>
<td>Case series; catheter left in place for 13–19 h</td>
<td>0/3 (0)</td>
<td>60/76 (79)</td>
</tr>
<tr>
<td>Paech et al.129</td>
<td>Prospective cohort; catheter discontinued immediately after delivery</td>
<td>21/24 (87)</td>
<td>30/37 (81)</td>
</tr>
<tr>
<td>Rutter et al.128</td>
<td>Retrospective cohort; catheter left in place for unknown duration</td>
<td>24/34 (71)</td>
<td>34/37 (92)</td>
</tr>
<tr>
<td>Ayad et al.127</td>
<td>Retrospective cohort; catheter left in place for 24 h</td>
<td>18/35 (51)p</td>
<td>0/21 (0)b</td>
</tr>
<tr>
<td>Russell IF92</td>
<td>Prospective, randomized in 6-month blocks, nonblinded intrathecal catheter for 24–36 h</td>
<td>36/50 (72)</td>
<td>29/47 (62)</td>
</tr>
<tr>
<td>Verstraete et al.133</td>
<td>Retrospective cohort, catheter left in place for at least 24 h</td>
<td>37/89 (42)</td>
<td>24/39 (62)</td>
</tr>
<tr>
<td>Bolden and Gebre134</td>
<td>Retrospective cohort, catheters were either removed immediately after delivery or removed at variable periods up to 30 h after delivery. A subset of those with an intrathecal catheter also received an injection of preservative-free normal saline through the intrathecal catheter</td>
<td>66/118 (56)</td>
<td>68/100 (68)</td>
</tr>
</tbody>
</table>

*Superscript numbers indicate reference citations at the end of the chapter.
* Different from no catheter, P < .05.

The incidence of PDPH was not different between the saline and control groups (88% versus 67%, respectively). Shah65 studied 17 patients who received an epidural saline infusion (at a rate of approximately 40 mL/h) for 24 to 36 hours after unintentional dural puncture. Four patients complained of severe intrascapular pain, which resolved when the infusion rate was reduced. Severe PDPH developed in 47% of patients after the infusion was stopped. In contrast, in a nonrandomized, nonblinded study of patients with unintentional dural puncture, Charsley and Abram137 reported that intrathecal injection of 10 mL of saline immediately before needle or catheter withdrawal resulted in a lower incidence of PDPH (32%) than in a control group who did not receive the saline (62%), as well as a less frequent need for an epidural blood patch. The intrathecal injection of saline after unintentional dural puncture deserves further study. Intrathecal saline should not be administered until residual local anesthetic effects have resolved.

**Prophylactic Blood Patch**

Interest in the use of prophylactic epidural blood patch before the removal of a labor epidural catheter arose after early observational studies suggested that the incidence of PDPH was lower with such treatment.138 A 2010 systematic review139 identified five studies in 221 obstetric patients; four studies found a reduction in the headache rate, and one did not.140 Scavone et al.,141 in the largest study included in the review,
If performed, a prophylactic blood patch should be delayed until resolution of residual neuroblockade. The occurrence of pain during injection is a signal for the anesthesia provider to stop the injection of blood. Additionally, evidence suggests that lidocaine may inhibit coagulation. Finally, Leivers reported a case of total spinal anesthesia after the epidural injection of 15 mL of blood before epidural anesthesia had regressed. The investigator speculated that residual lidocaine in the lumbar CSF was transferred to the brain as a consequence of an increase in lumbar CSF pressure and reduced CSF volume produced by the patch. (Editors’ note: One of us [DHC] has observed one case of transient, total blindness after the rapid, bolus injection of 30 mL of epidural saline after vaginal delivery in a patient who had experienced unintentional dural puncture during labor. The blindness resolved after 15 to 20 minutes, and subsequent ophthalmologic and neurologic examinations were normal. The etiology of the transient blindness was unclear. Nonetheless, it seems prudent to delay administration of prophylactic epidural saline or blood until the block has regressed and to avoid rapid epidural administration of blood or saline at any time.)

It is important to avoid the direct intrathecal injection of blood. Aldrete and Brown reported a case of intrathecal hematoma and arachnoiditis with prolonged neurologic sequelae after prophylactic blood patch. Nineteen milliliters of blood were injected through an epidural catheter that, in retrospect, was positioned in the subarachnoid space. There was considerable resistance to injection of the blood, and severe lower back pain with tinnitus accompanied the procedure.

Prophylactic Dextran Patch
Salvador et al. reported the prophylactic epidural injection of 20 mL of dextran-40 in 17 patients who had experienced unintentional dural puncture with a 17- or 18-gauge needle. Three of the patients were parturients, and none of the 17 patients experienced PDPH. This injection was performed before regression of the local anesthetic effect. No additional studies of this technique have been reported; its safety and efficacy remain unclear.

Treatment
Early treatment of PDPH is indicated. Not only does this avert the vicious cycle of immobility, weakness, and depression, but it also may help prevent the rare case of subdural hematoma, chronic headache, or cranial nerve palsy in the patient with persistent PDPH.

Psychological Support
The patient is aware that PDPH is an iatrogenic problem, and she may be angry and resentful as well as depressed and tearful. It is imperative to include disclosure of the risk during the preoperative interview. Headache makes it more difficult to care for the newborn and to interact with other family members. Severe PDPH may delay discharge from the hospital and have economic consequences. Unless patients who have PDPH after nonobstetric surgery, these patients typically are healthy and do not expect to feel ill. Two patients have eloquently described their own miserable experiences with postpartum PDPH. Not surprisingly, a retrospective study of 43 obstetric patients with PDPH showed that this complication leads to a negative attitude toward epidural anesthesia.

It is essential that anesthesia providers visit the patient at least once daily to explain symptoms and prognosis, give support, and offer therapeutic options. If feasible, the patient’s partner should attend these discussions. Nurses can help the patient by ensuring adequate analgesics are given on a regular schedule and by teaching alternative breast-feeding techniques, such as the lateral horizontal position.

The anesthesia provider and nurses should write detailed notes in the patient’s record. After discharge, follow-up telephone conversations should be documented. Headache associated with neuraxial anesthesia was the third most common reason for litigation among obstetric cases in the ASA Closed-Claims Project database, after maternal death and neonatal brain damage. This fact should dispel any notion that postpartum PDPH is a trivial complaint.

Posture
In most cases, PDPH presents with a postural component. Significant relief should occur when the patient assumes the horizontal position. However, there is no evidence that remaining supine for a prolonged period treats or shortens the duration of the headache. The prone position relieves PDPH in some patients, presumably because increased intra-abdominal pressure results in an increase in CSF pressure. Unfortunately, this position is not comfortable for many patients, especially those who had a cesarean delivery.

Hydration
Enhanced oral hydration remains a popular therapy initiated by most anesthesiologists for parturients with PDPH, but there is no evidence that vigorous hydration has any therapeutic benefit in a patient with normal fluid intake. However, no patient with PDPH should be allowed to become dehydrated, because of the increased fluid demands of breast milk formation and CSF production.

Pharmacologic Treatment
A safe and effective drug therapy for PDPH would be very useful, even if relief is transient. The current gold standard therapy, an epidural blood patch, is not appropriate or effective in all patients. A 2015 systematic review of pharmacologic therapies for treatment of PDPH evaluated studies using caffeine, gabapentin, hydrocortisone, theophylline, sumatriptan, adrenocorticotropic hormone, pregabalin, and cosyntropin. Participants in the studies were not limited to obstetric patients. Of the drugs included in this study, caffeine and theophylline seemed most beneficial for the treatment of PDPH. The evidence was inconclusive for sumatriptan, adrenocorticotropic hormone, pregabalin, and cosyntropin. The authors noted that the results of the analysis should be interpreted with caution because of the inability to assess risk for...
bias and the small sample sizes of the studies included in their study. 149

Caffeine
Caffeine has been used to treat PDPH for many years. In the systematic review,149 two randomized trials comparing caffeine with placebo with different routes of administration but at equipotent doses were identified. Caffeine transiently reduced the number of participants with PDPH at 4 hours compared with placebo but not beyond, and also decreased the need for a conservative supplementary therapeutic medication.

Caffeine is a cerebral vasoconstrictor, and one study demonstrated a reduction of cerebral blood flow after intravenous administration of caffeine sodium benzoate for the treatment of PDPH.150 Caffeine also increases CSF production by stimulating sodium-potassium pumps.151 However, caffeine is also a potent central nervous system stimulant. Published case reports have described seizures after intravenous152 and oral administration153 of caffeine for the treatment of PDPH in postpartum patients.

Caffeine appears in breast milk in very small amounts.154 To our knowledge, there are no reports of adverse effects on the infant after maternal administration of one or two doses of caffeine for the treatment of PDPH. The risk-to-benefit ratio to mother and newborn of multiple doses of caffeine has not been addressed. Until such studies are available, it seems wise to restrict the prescription of oral caffeine to 600 mg in 24 hours. Long-term caffeine therapy cannot be recommended.

Theophylline
Theophylline, a methylxanthine, has also been used for the management of PDPH. Although several studies have demonstrated a reduction in lower pain scores than either placebo or acetaminophen, none have included obstetric patients.149 Additionally, theophylline is not commonly used for the management of PDPH because of its narrow safety profile.

Sumatriptan
Sumatriptan is a serotonin receptor agonist with cerebral vasoconstrictor properties that is administered subcutaneously for the treatment of migraine headaches. Side effects include pain at the injection site and, uncommonly, chest tightness and coronary artery vasospasm. Carp et al.155 reported that the administration of sumatriptan 6 mg resulted in complete resolution of PDPH in four of six patients. Connelly et al.156 randomized 10 patients with severe PDPH scheduled for epidural blood patch to receive sumatriptan 6 mg or placebo. After 1 hour, only one patient in each group had significant relief; the authors concluded that sumatriptan was of no value.

Adrenocorticotropic Hormone and Analogs
The use of ACTH for the treatment of PDPH was first reported in a 1994 letter.157 Subsequently, anecdotal reports have described different regimens of either intramuscular or intravenously administered ACTH or the synthetic drugs cosyntropin or tetracosactrin acetate. Mood elevation, anti-inflammatory effects, increased endorphin levels, and augmented intravascular volume are postulated as possible mechanisms of action in the relief of headache following ACTH administration. To date, the only randomized clinical trial of ACTH treatment in parturients involved 18 postpartum women who had PDPH after spinal anesthesia or unintentional dural puncture.158 There was no difference in the severity of headache or the requirement for epidural blood patch between women receiving tetracosactrin acetate 1 mg intramuscularly and those who received saline-placebo.

In a small, prospective, nonblinded, randomized trial of 28 nonpregnant patients with severe PDPH, Hanling et al.159 evaluated the efficacy of intravenous cosyntropin as an alternative to epidural blood patch for the treatment of refractory or severe PDPH. Epidural blood patch showed a significant reduction of pain and improved function compared with cosyntropin on day 1; however, cosyntropin demonstrated similar efficacy to epidural blood patch immediately after treatment, and at days 3 and 7 after treatment. The number of patients who returned to the emergency department for further treatment was greater in the cosyntropin group compared with the epidural blood patch group (60% versus 8%, respectively).159 Additional study is needed to assess the safety and efficacy of cosyntropin for the prevention and treatment of PDPH. With current evidence, we do not recommend ACTH therapy as the first-line treatment of PDPH, but it may be considered for cases that are not amenable to epidural blood patch therapy.

Miscellaneous Medications
Other agents evaluated for their effectiveness in reducing PDPH symptoms include pregabalin, methylergonovine, hydrocortisone, and gabapentin. Randomized clinical trials have been conducted with intravenous hydrocortisone160 and oral pregabalin.161 In a nonblinded study, Noyan et al.160 evaluated 60 parturients who developed PDPH after spinal anesthesia and were randomly assigned to receive intravenous hydrocortisone (200 mg loading dose followed by 100 mg three times daily for 2 days) or conventional therapy (bed rest, hydration, and scheduled acetaminophen with meperidine). Patients who received hydrocortisone had a 50% reduction in headache severity as assessed by visual analog scale (VAS) pain scores at 6 to 48 hours. Huseyinoglu et al.161 randomized 40 patients with PDPH after lumbar puncture to receive pregabalin (150 mg daily for 2 days followed by 300 mg for 3 days) or placebo; pain scores and oral analgesic requirements were lower in the treatment group.

Use of gabapentin or methylergonovine has been reported only in case series.162 Efficacy and side effects (maternal and neonatal) are unclear. All four drugs require further study before they can be recommended for therapy for PDPH.

Epidural Morphine
Eldor et al.162 reported six nonobstetric patients whose PDPH headaches were successfully treated with epidural morphine
3.5 to 4.5 mg. Further study is required before conclusions can be reached. However, this therapy should be used with caution because epidural morphine injected in the presence of a large dural puncture site may pass readily into the CSF and predispose to respiratory depression. Additionally, treatment requires that patients remain in the hospital for 24 hours to assess for respiratory depression.

**Epidural/Intrathecal Saline**

The use of epidural or intrathecal fluids to treat PDPH preceded the use of epidural blood patches. Intrathecal injection of fluid was first described by Jacobaeus et al. in 1923, and epidural injection of saline was reported by Rice and Dabbs in 1950. These first reports were in conjunction with research attempting to understand the pathophysiology of PDPH, and they demonstrated transient elevations of CSF pressure after fluid injection. Subsequently there has been sporadic interest in using injection of fluids (other than blood) into the neural axial space to treat PDPH.

Usubiaga et al. injected 10 to 30 mL of saline through a lumbar epidural catheter in 11 nonobstetric patients with a PDPH after spinal anesthesia in whom 48 hours of conservative therapy had failed. Immediate relief of headache was observed in 10 patients, and the relief was permanent in 8 patients. However, the investigators did not comment whether other therapies (e.g., supine posture, abdominal binder, analgesics) were continued. In a quasi-randomized trial, 43 parturients with PDPH after unintentional dural puncture during an epidural procedure or after spinal anesthesia with a 25-gauge needle were assigned to receive a 30-mL lumbar epidural saline bolus or a 10-mL lumbar epidural blood patch. Forty-two patients had dramatic relief of their symptoms in the first hour after the intervention; however, 12 of the 21 (57%) patients who had received saline had return of the PDPH in the next 24 hours.

Prolonged epidural saline infusion may provide better therapy for PDPH symptoms than therapy with a single bolus. In a retrospective study that included both obstetric and nonobstetric patients, patients who received a continuous epidural saline infusion for 4 days had a lower incidence of PDPH, and the headache was less severe, than patients who received conservative therapy. This therapy, however, may not be practical in hospital settings in which women are discharged 1 or 2 days after delivery. Two case reports described the use of epidural saline infusion for parturients with an unintentional dural puncture whose PDPH symptoms returned after epidural blood patch therapy. The rate of infusion (15 to 25 mL/h) was limited by the onset of pain in the back, legs, and eyes. Although both saline techniques offer only temporary relief, these options might be considered for patients who have a contraindication to epidural blood patch therapy.

**Epidural Blood Patch**

**Efficacy.** The epidural blood patch is regarded by many as the gold standard therapy for PDPH. Although reported in third person, Gormley, in 1960, is credited with performing the first successful epidural blood patch. He described relief of PDPH symptoms in seven patients after epidural administration of only 2 to 3 mL of blood. However, this report was largely ignored until 1970, when DiGiovanni and Dunbar described the immediate and permanent cure of PDPH in 41 of 45 patients in whom 10 mL of autologous blood was injected into the epidural space. Their success led to the widespread adoption of this technique for the relief of PDPH.

In early case series, the reported success rate of epidural blood patch therapy for PDPH was between 89% and 91%. Safa-Tisseront et al. reviewed their experience with epidural blood patch therapy over a 12-year period (n = 504 patients, including 78 obstetric patients). Complete relief of PDPH was obtained in 75%, partial relief occurred in 18%, and treatment failed in 7% of patients. The investigators noted a significantly higher failure rate of epidural blood patch after large-gauge needle puncture of the dura. The difference in early reports and more modern audits of PDPH and epidural blood patch success may be related to differences in the studied population, timing of epidural blood patch, blood volume injected, or the duration of follow-up after blood patch therapy.

In studies limited to obstetric patients, the published success rates of epidural blood patch have been even less encouraging. Stride and Cooper noted complete and permanent relief of PDPH in 64% of patients after one blood patch procedure. Williams et al. reported only 33% of their patients obtained complete and permanent relief from the first blood patch. Banks et al. prospectively monitored 100 patients with unintentional dural puncture. Fifty-eight received a therapeutic blood patch; the treatment completely failed in 3 patients, and 17 patients had recurrence of moderate or severe headache requiring further therapy. Finally, in a prospective trial in postpartum patients with unintentional dural puncture with an epidural needle, the proportion of patients with complete headache relief was 32% after an epidural blood patch with 20 mL autologous blood.

A 2010 systematic review identified three randomized trials comparing epidural blood patch to either a sham procedure or conservative treatment. All three studies found a reduction in headache rate in the treatment group. Seebacher et al. randomized 12 heterogeneous patients with PDPH to receive an epidural blood patch with 10 to 20 mL of blood or a sham patch procedure. Five of six patients receiving a blood patch had complete relief of headache symptoms at 24 hours, and none of the sham procedure patients did. Sandesc et al. described a randomized trial of 32 obstetric and nonobstetric patients with PDPH symptoms for a minimum of 24 hours; subjects were randomly assigned to receive conservative therapy or an epidural blood patch. The primary outcome was headache VAS pain scores at 2 and 24 hours. At 2 hours, the mean ± SD VAS score for the conservative therapy group was 8.2 ± 1.4 cm compared with 1.0 ± 0.2 cm for the group receiving a blood patch. This difference remained at 24 hours. In the largest trial to date, van Kooten et al. randomized 40 subjects with PDPH for 1 to 7 days to receive either conservative therapy or an epidural blood patch using 15 to 20 mL...
of autologous blood. The primary outcome was headache 24 hours after intervention, but patients were observed for 1 week after therapy. The incidence of headache at 24 hours was 58% in the blood patch group compared with 90% in the conservative therapy group. At 1 week the difference widened, with a 16% incidence of headache in the blood patch group compared with 86% in the conservative group. In summary, administration of an autologous epidural blood patch, although not perfect, often dramatically relieves this debilitating condition and, at present, it is the therapy with the greatest likelihood of success.

**Volume.** The optimal volume of injected blood remains controversial. Szeinfeld et al.\(^{181}\) used a gamma camera to observe the epidural spread of technetium-labeled red blood cells during and after epidural blood patch. They injected blood until pain occurred in the back, buttocks, or legs. The mean ± SD volume injected was 14.8 ± 1.7 mL of blood, and the mean ± SD spread was 9.0 ± 2.0 spinal segments. Blood spread more readily in the cephalad than in the caudal direction. The blood patch relieved the headache in all 10 patients. The investigators concluded that 12 to 15 mL of blood should be a sufficient patch volume for most patients.

The best evidence to date is an international, multicenter study by Paech et al.,\(^{177}\) who randomized 121 women after unintentional dural puncture with a Tuohy needle (16- or 18-gauge) to receive an epidural blood patch with 15, 20, or 30 mL of blood. Partial or complete relief of headache (the primary outcome) occurred in 61%, 73%, and 67% of those who received 15, 20, or 30 mL of blood, respectively. However, complete relief of headache was achieved by only 10%, 32%, and 26% of women in these same groups. The rate of complete headache relief was greater in the 20-mL than in the 15-mL group; there was no difference between the 20-mL and 30-mL groups. Thus, the investigators concluded that 20 mL of autologous blood is the optimal volume for an epidural blood patch. This suggestion is supported by a single-institution review of 466 epidural patches performed over 15 years in obstetric patients in which the mean ± SD blood patch volume was 20.5 ± 5.4 mL.\(^{182}\) A 2011 survey demonstrated that most North American anesthesiologists inject 20 mL of blood.\(^{183}\)

Beards et al.\(^{184}\) performed MRI studies after the performance of an epidural blood patch (18 to 20 mL) in five patients. Similar to Szeinfeld et al.,\(^{181}\) they noted that the injected blood spread over three to five segments in a predominantly cephalad direction. All patients had an extensive hematoma in subcutaneous fat, and some also had displacement of nerve roots and/or evidence of intrathecal blood. A thick layer of mature clot had formed by 7 hours, but the clot had broken up into smaller clots by 18 hours. These findings may help explain the back pain and occasional nerve root pain that occur after blood patch therapy.

In another MRI study, Vakharia et al.\(^{185}\) noted compression of the thecal sac and a mean spread over 4.6 segments after a lumbar epidural injection of 20 mL of blood. Djurhuus et al.\(^{186}\) employed CT epidurography in four patients immediately and 24 hours after an 18-mL blood patch. Initial images showed adherence of clot to the dura in three patients as well as dural compression in two patients, but there was no evidence of compression at 24 hours.

Using a goat model, DiGiovanni et al.\(^{187}\) examined the microscopic appearance of the dura as late as 6 months after dural puncture. Some study animals received a 2-mL blood patch in addition to dural puncture. The investigators concluded that the blood patch acted as a gelatinous tampon that produced no harmful tissue reaction.

**Mechanism of action.** The mechanism of epidural blood patch for relief of PDPH is unclear. Pain relief is often rapid, but CSF volume is not restored immediately. Thus, there must be another explanation for the immediate relief of headache besides “patching” of the dural puncture. Carrie\(^{188}\) hypothesized that epidural injection of blood increases lumbar CSF pressure, an action that restores intracranial CSF pressure and decreases symptoms. Increased CSF pressure also may result in reflex cerebral vasconstriction. Coombs and Hooper\(^{189}\) demonstrated that epidural blood patch resulted in a threefold increase in lumbar CSF pressure. Further, they noted that 15 minutes later, lumbar CSF pressure was sustained at greater than 70% of the peak pressure observed after the injection of blood. Ultrasonographic examination of the optic nerve sheath diameter (a noninvasive measurement that correlates with intracranial pressure) in 10 patients with PDPH demonstrated increased measurements after epidural blood patch.\(^{190}\) The sheath diameter increased 10 minutes after an epidural blood patch with 17 to 26 mL of blood and was sustained over the 20-hour study period. The only patient whose blood patch failed to successfully relieve the PDPH did not have the same increase in optic nerve sheath diameter.

MRI and CT studies have shown that the epidural blood is largely resorbed or broken up 18 to 24 hours after the procedure.\(^{182}\) It is unlikely that the increase in CSF pressure is sustained or that the blood acts as a mechanical plug to block CSF leak for a prolonged duration. The blood applied to the hole in the dura may initiate an inflammatory reaction that facilitates puncture site repair and closure. It is possible, and even likely, that an epidural blood patch ameliorates PDPH by several mechanisms.

**Timing.** The optimal timing for administration of a blood patch has not been adequately studied. Observational studies suggest that failure is more likely if the blood patch is performed within 24\(^{174}\) or 48 hours\(^{177}\) of the dural puncture. Booth et al.\(^{182}\) demonstrated a strong positive correlation between success of the epidural blood patch and the interval from the dural puncture or onset of PDPH to performance of the blood patch. It is unclear, however, whether this finding is a result of selection bias. Early-onset PDPH (often resulting from dural puncture with a large-gauge needle) is likely to be more severe and more difficult to treat. Alternatively, a large CSF leak may displace the clot. Partial healing of the dura may have already occurred if a blood patch is delayed, a possibility that may explain the better outcome of a delayed patch procedure.
**Technique.** The anesthesia provider should thoroughly explain the risks and benefits of the blood patch procedure to the patient, and the patient should give consent for the procedure. An epidural blood patch can be accomplished on an outpatient basis. Ideally, the environment for the procedure is one conducive to postpartum patients who may have accompanying family and a newborn. Contraindications to the administration of an epidural blood patch are related to complications of placing a needle in the central neuraxis or the injection of blood into the epidural space; they include (1) known coagulopathy (e.g., concurrent pharmacologic anticoagulation), (2) local cutaneous infection or untreated systemic infection, (3) increased ICP caused by a space-occupying lesion, and (4) patient refusal. Transient bradycardia has been observed after administration of an epidural blood patch, and some anesthesia providers may choose to establish intravenous access and monitor the electrocardiogram in selected patients.

The blood patch procedure should employ sterile measures equivalent to those used for the administration of any neuraxial procedure. The lateral position is usually more comfortable than the sitting position for patients with severe PDPH. If the anesthesia provider is uncertain about the location of the dural puncture, the more caudad interspace should be chosen. The epidural space is identified in the usual manner. Using meticulous sterile technique (including skin preparation and draping, and donning of a face mask and sterile gloves), an assistant withdraws the desired volume of blood (usually 10 to 25 mL) into a syringe. This autologous blood is injected slowly into the epidural space through the Tuohy needle; the injection is terminated if severe back, leg, or neck pain or pressure occurs. Sometimes slowing the injection rate leads to resolution of the back pain. Jehovah’s Witness patients may accept a blood patch procedure if a technique is used that keeps blood in continuity with the circulation.

Occasionally a few drops of CSF are encountered on entering the epidural space, leading to doubt about correct needle placement. One can either repeat the epidural needle placement, or a small test dose of a local anesthetic agent can be administered, sufficient to cause a rapid onset of spinal anesthesia. If no block results, the blood patch can be performed. Real-time ultrasound-guided and fluoroscopically guided epidural blood patch has been described and should be considered when difficulty with epidural needle placement is anticipated.

After the procedure, the patient should rest quietly in the supine position for 1 to 2 hours. Subsequently, the patient may resume ambulation, but she should avoid vigorous physical activity for several days. It would be wise for the patient to avoid the Valsalva maneuver and heavy lifting. A stool softener should be considered. Most patients report almost instantaneous relief of headache symptoms, although relief is delayed for 6 to 8 hours in some patients. The patient may continue to have neck and back fullness over the next 24 hours. The back pain can continue up to 5 days after the procedure. Patients should be counseled to immediately report fever, severe back pain, or radiating lower extremity pain. The anesthesia provider should contact the patient after the blood patch procedure.

The blood patch may be repeated if the initial patch fails to relieve pain. Often the second patch is successful. Although not adequately studied, it seems reasonable to wait 24 hours before repeating an epidural blood patch procedure to allow the first procedure adequate time to work. The diagnosis should be reconsidered if headache persists after two failed blood patch procedures. Consultation by a neurologist may be appropriate when a PDPH fails to respond to two blood patches and should definitely be requested if there is any doubt about the diagnosis. Imaging of the head should be considered to exclude other causes of headache.

**Complications.** Ong et al. reported that the success of neuraxial anesthesia/analgesia was impaired in women with a prior history of unintentional dural puncture with or without epidural blood patch therapy. However, this conclusion has been refuted by follow-up studies in both obstetric patients and nonobstetric patients.

Although epidural blood patch therapy is the most reliable method of relieving PDPH symptoms, adverse outcomes are associated with the procedure. These adverse events can be categorized into two broad groups: infectious/hematologic and neurologic.

**Infectious/hematologic complications.** Conventional wisdom holds that the patient should be afebrile at the time of the blood patch procedure. Many anesthesia providers believe that it is wise to avoid the epidural injection of blood in the presence of systemic infection. Meningitis has been reported after a blood patch procedure. After conservative measures have failed, the optimal treatment of a febrile patient with severe, persistent PDPH is controversial. Epidural infusion of saline involves the use of an indwelling epidural catheter for many hours, which also may be undesirable in a febrile patient. A patch using dextran-40 may be an alternative in febrile patients, but further experience is needed in healthy patients before this technique can be recommended.

The presence of high fever and/or other evidence of sepsis contraindicate the performance of a blood patch procedure. However, we do not believe that a low-grade fever of known etiology is an absolute contraindication to epidural blood patch, provided the patient is receiving appropriate antibiotic therapy. Management should be individualized, and the known benefits of blood patch should be weighed against the unknown risk for infection.

The risks associated with epidural blood patch therapy in the presence of human immunodeficiency virus (HIV) infection have been debated (see Chapter 36). However, the central nervous system is infected with HIV at the time of primary infection; therefore, it seems unlikely that the injection of autologous blood into the epidural space would alter progression of the disease. Successful use of blood patch therapy, without sequelae, has been reported in patients with acquired immunodeficiency syndrome (AIDS) or who are HIV positive.
The incidence of cancer during pregnancy is increasing, likely secondary to advancing maternal age. The development of PDPH in this population has raised a theoretical concern about seeding the neuraxial space with neoplastic cells if a blood patch procedure is performed. This concern should be discussed with the patient and her oncologist before the procedure. Bucklin et al.\textsuperscript{201} reported the conservative management of a woman with acute leukemia and PDPH; the investigators discussed the therapeutic options for this immunocompromised patient. The use of epidural fibrin glue was reported in a nonobstetric patient with metastatic breast cancer and PDPH,\textsuperscript{202} whereas a blood patch was performed for PDPH in a young woman with rhabdomyosarcoma.\textsuperscript{203}

**Neurologic complications.** Serious or permanent problems after epidural blood patch therapy are rare. Diaz and Weed\textsuperscript{204} wrote a review of case reports of adverse neurologic complications after epidural blood patch procedures. These authors identified 26 reports published between 1966 and 2004 and stratified the complications into neurologic, neurovascular, or inflammatory events. The events occurring in obstetric patients included lumbovertebral syndrome (defined as low back pain with neurologic impairment of the lower extremities), subdural hematoma, arachnoiditis, radicular back pain, pneumocephalus, seizures, and acute meningeal irritation. Compressive complications (e.g., lumbovertebral syndrome, subdural hematoma, cauda equina syndrome) were associated with larger blood patch volume (mean of 35 mL) than noncompressive complications (17 mL). Cranial nerve palsy symptoms that were present before blood patch administration did not uniformly resolve. The delay in performing the blood patch may have been a significant factor. Two patients who were treated within 4 days of the onset of PDPH symptoms recovered within 6 weeks, whereas three patients treated on days 9 to 11 had palsy that persisted for 3 to 4 months. Two obstetric patients experienced new facial nerve palsies, which manifested as facial weakness after administration of an epidural blood patch.\textsuperscript{204}

Abouleish et al.\textsuperscript{173} reported the results of the long-term evaluation of 118 patients who had received an epidural blood patch. Back pain was the most common complication; it occurred during the first 48 hours in 35% of patients and persisted in 16% of patients, with a mean duration of 27 days. These investigators also noted cases of neck pain, lower extremity radicular pain, and transient temperature elevation.

Epidural space scarring is also a possibility after placement of a blood patch. Although subsequent epidural analgesia is generally successful (see earlier discussion),\textsuperscript{189} Collier\textsuperscript{205} reported two cases of unsuccessful epidural analgesia related to suspected scarring of the epidural space. In both women, the initial epidural catheter placement was complicated by unintentional dural puncture and PDPH treated with epidural blood patch. During a subsequent pregnancy, epidural catheter placement was complicated by inadequate analgesia, and an epidurogram revealed limited spread of the contrast media, suggesting epidural space scarring.

The development of an inflammatory reaction to epidural blood can cause acute arachnoiditis, an entity that can present several days after epidural blood patch.\textsuperscript{206} This phenomenon is believed to be caused by free radical damage to spinal root nerves in the intrathecal space after hemoglobin degradation. Obstetric patients with this entity who required analgesic therapy for prolonged periods have been reported.\textsuperscript{207} The diagnosis is made with a presenting history of severe back pain, often with radicular pain, and characteristic MRI findings such as nerve root clumping in the intrathecal space and adhesions between nerve roots.

The occurrence of new neurologic symptoms appearing after an epidural blood patch should prompt consideration of the presence of other intracranial pathology. Such symptoms may include (1) mental deterioration caused by increased ICP from an intracranial tumor,\textsuperscript{208} and (2) seizures caused by late-onset eclampsia or PRES.\textsuperscript{209}

Diaz\textsuperscript{210} described a woman in whom permanent paraparesis and cauda equina syndrome developed after an epidural blood patch with 30 mL of blood injected slowly and without symptoms. Low back pain and leg pain developed after the blood patch procedure, and later the patient also experienced incontinence. Twelve days after the procedure, a subdural hematoma at L2–L4 was diagnosed and surgically treated. Six months later, the patient still had marked symptoms. Although a larger volume of blood than usual was injected, the technique appears to have been within normal practice standards. Other long-term sequelae reported in obstetric patients include a cerebral ischemic event after two blood patches that resulted in permanent hemianopsia\textsuperscript{211} and a calcified epidural blood patch leading to chronic back pain.\textsuperscript{212}

**Alternatives to Epidural Blood Patch**

Alternatives to an epidural blood patch may be considered if a blood patch is contraindicated or fails. The sphenopalatine ganglion block, in particular, has received increased consideration in patients suffering from PDPH. In extreme cases, surgery may be needed to close the dural tear.

**Sphenopalatine ganglion block.** The sphenopalatine ganglion (SPG) block has become a useful adjunct in the treatment of cluster and migraine headaches. This parasympathetic ganglion is located in the pterygopalatine fossa, immediately adjacent to the posterior component of the middle turbinate of the nose (Fig. 30.4).\textsuperscript{213} Blocking the ganglion inhibits parasympathetic outflow to cerebral vasculature and prevents vasodilation. A simple technique, the operator places a cotton pledget soaked with local anesthetic in the nose and allows diffusion across nasal mucosa. Cohen et al.\textsuperscript{214} offered SPG block to 32 obstetric patients suffering with PDPH after dural puncture with a 17-gauge epidural needle before planned epidural blood patch; 69% did not require the blood patch. Pledgets saturated with 5% water-soluble lidocaine ointment were applied to each nostril for 10 minutes. Although prospective study is required to evaluate its role in the treatment of PDPH, SPG block may be useful in providing symptom relief for those with severe, early symptoms following dural puncture.

**Dextran/gelatin patch.** Dextran-40 and gelatin-based solutions, including Gelfoam and Plasmion, have been
substituted for blood in epidural patches.\textsuperscript{145,215} These solutions were chosen as alternatives to blood owing to relative contraindications to injection of blood. The use of these agents appears to be more common in countries outside North America. In an observational study of 56 patients, Barrios-Alarcon et al.\textsuperscript{216} reported that epidural administration of 20 to 30 mL of dextran-40 was safe and effective for the relief of PDPH; all headaches were relieved permanently. The only side effect was a transient discomfort or burning sensation at the time of injection in 6 patients. Some physicians have treated intractable PDPH successfully by performing a dextran-40 patch followed by epidural infusion of dextran at 3 mL/h for 5 to 12 hours.\textsuperscript{217,218}

Information on neurotoxicity of these materials is scant; Chanimov et al.\textsuperscript{219} did not observe neurotoxicity after infusion of dextran-40 or polygeline, a gelatin powder, into the rat intrathecal space. However, further information is needed before these materials can be widely adopted for epidural administration in humans. From MRI studies in patients with an epidural blood patch, we can anticipate that some dextran will enter the subarachnoid space. The small but definite risk for anaphylaxis after the injection of dextran also must be considered, although the risk appears minimal with dextran-40.

\textbf{Fibrin sealant patch.} Fibrin sealant is composed of fibrinogen and thrombin. Several commercial products are prepared from human pooled plasma. Products may also contain antifibrinolytics, such as animal aprotinin.\textsuperscript{220} When injected, these products form a firm, nonretractable fibrin clot. Epidural injection of fibrin glue in rats produces a sustained rise in CSF pressure comparable to the increase that occurs after injection of blood.\textsuperscript{221} Fibrin sealant has been evaluated for its effectiveness in preventing dural leaks after spinal surgery.\textsuperscript{222} An epidural fibrin glue patch has been used successfully to treat recurrent PDPH,\textsuperscript{223} spontaneous intracranial hypotension,\textsuperscript{224} and CSF leak after long-term intrathecal catheterization.\textsuperscript{225} In the future, fibrin glue may have a role in patients with intractable PDPH, but further study is required before it can be recommended for routine use.

\textbf{Surgery.} There are rare reports of curative surgical closure of a dural rent for intractable PDPH. In one case, the interval between dural puncture and surgery was 5 years.\textsuperscript{226}

\textbf{Summary of Treatment}\n
The parturient with PDPH should be actively managed with scheduled analgesics and should receive psychological support as she cares for her newborn and manages her symptoms. If the headache is severe, the physician can consider additional agents, such as caffeine or SPG block, or proceed directly to an epidural blood patch. Epidural administration of fluids other than blood, such as saline or dextran, typically is not first-line therapy but may be considered if there are contraindications to the epidural injection of autologous blood or if an epidural blood patch procedure fails. The accuracy of PDPH diagnosis
must always be considered when atypical symptoms present or when therapy fails. The Obstetric Anaesthetists’ Association and the Association of Anaesthetists of Great Britain and Ireland\textsuperscript{27} have recommended that each facility providing obstetric anesthesia services should have an institution-specific protocol for the management of PDPH to facilitate the identification of parturients with this complication and to provide consistent care.

**UNANSWERED QUESTIONS**

Important information about PDPH is still lacking. A large, detailed prospective study of PDPH and epidural blood patch, with a long follow-up period (e.g., 1 year), is needed in obstetric patients. What are the long-term effects of both PDPH and blood patch therapy? How common are residual back pain, neurologic symptoms, and auditory/visual symptoms, and do they interfere with the activities of daily living? New therapies, including intravenous cosyntropin, epidural morphine, and SPG block have been described, but have not been rigorously studied. Answers to these questions are needed to give our patients reliable information, a sound basis for informed consent, and the best possible care.

**KEY POINTS**

- Dural puncture is only one of many causes of postpartum headache, although many are quick to blame postpartum headaches on dural puncture. A detailed history and physical examination as well as indicated neuroimaging should ensure diagnostic accuracy.
- A patient with post–dural puncture headache experiences an exacerbation of symptoms when she moves from the horizontal to the upright position, possibly owing to decreased intracranial pressure and secondary cerebral vasodilation, which affect pain-sensitive intracranial structures.
- Anesthesia providers should use a small-gauge (24-gauge or smaller), noncutting (pencil-point) spinal needle whenever possible to decrease the risk for post–dural puncture headache.
- No therapies reliably prevent the development of post–dural puncture headache after unintentional dural puncture with an epidural needle.
- The initial therapy for post–dural puncture headache consists of psychological support and scheduled oral analgesics. Although dehydration should be avoided, no evidence supports a role for vigorous hydration for prophylaxis or therapy for post–dural puncture headache.
- The gold standard therapy for post–dural puncture headache is an autologous epidural blood patch. A second blood patch may be performed—and typically is successful—if the first one fails. If the second procedure fails, alternative diagnoses should be excluded. Other therapies have not proved as safe or as effective as the epidural blood patch for treatment of post–dural puncture headache.

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Neurologic complications of childbirth may be associated with neuraxial analgesia and anesthesia or may result from childbirth itself. Complications of neuraxial anesthesia may be immediate, such as an unexpectedly high block or seizures after unintentional intravenous injection of local anesthetic, or they may be delayed. Immediate complications of neuraxial anesthesia are described in Chapter 23; here the discussion is focused on neurologic sequelae.

Although neurologic disorders after childbirth are more likely to have obstetric than anesthetic causes, neuraxial anesthesia is frequently suspected and often blamed. For example, Tubridy and Redmond described seven women referred with neurologic symptoms after childbirth, all of which had been attributed to epidural analgesia. The women suffered from brachial neuritis, peroneal neuropathy, femoral neuropathy, neck strain, and leg symptoms for which there was no obvious physical cause. In such circumstances, a careful history and neurologic examination, together with diagnostic aids such as electromyography, nerve conduction studies, and imaging techniques, can localize the lesion and differentiate obstetric from anesthetic causes. For example, it should be possible to distinguish by simple clinical means between a mononeuropathy, which is likely to have an obstetric cause, and a radiculopathy, which might result from neuraxial blockade. Accurate and prompt diagnosis is essential to increase the likelihood of the best possible outcome.

THE INCIDENCE OF NEUROLOGIC SEQUELAE

Patients frequently ask obstetricians and anesthesia providers about the incidence of complications of neuraxial anesthesia. However, even if accurate data were available, the question has no true answer. The incidence of neurologic complications varies widely according to local practice and the skill and training of the practitioners. Some older surveys are based on accurate local records, but the data relate to a time when obstetric and anesthetic practices, equipment, and drugs were radically different. The incidence of serious complications is now too low to be estimated accurately on a local basis. Nonetheless, anesthesia providers have a duty to inform patients of the complications associated with a proposed procedure and are expected to give some estimate of the level of risk.

Obstetric Surveys

The reported incidence of neurologic deficits in obstetric patients varies widely depending on the source and the complications that are being measured. Many surveys have attempted to assess the incidence of neurologic complications of neuraxial anesthesia, but these surveys share common limitations, including low response rates, lack of control groups who did not receive neuraxial anesthesia, and inaccurate diagnosis (Box 31.1). Moreover, bias is...
 Twenty-one women presenting with symptoms involved 3991 women who delivered in one center in a 1-year period. Twenty-one women who had not undergone an anesthetic intervention are likely to complain or bepostpartum quite frequently if sought, but only those who demonstrated that minor neurologic deficits are to be found among the 21 asymptomatic control women who had not undergone an anesthetic intervention. These results created when more attention is paid to patients who received neuraxial blockade than to those who did not. Some of the more relevant surveys are listed in Table 31.1. Although each survey is distinct in its population, measurements, and reporting, some generalizations can be made. Most of the neurologic complications in these reports were transient, most occurred in patients who labored, and only a very small minority were attributable to neuraxial anesthesia. Peripheral nerve damage was more common than central cord or plexus damage.

One of these reports from Leeds in the United Kingdom involved 3991 women who delivered in one center in a 1-year period. Twenty-one women presenting with symptoms after neuraxial blockade were matched with 21 asymptomatic control patients who had also received neuraxial blockade and 21 additional women who had not. Only one woman who had not had a neuraxial block had symptoms, and she was found to have foot drop after a vacuum extraction. Typical peripheral neuropathies occurred among those who delivered vaginally; sacral numbness was most commonly detected after cesarean delivery. All changes were transient, and none could be attributed to neuraxial anesthesia. Similar neurologic deficits were detected among the randomly selected, asymptomatic 21 control patients who had not undergone an anesthetic intervention. In contrast, negligible deficits could be detected among the 21 asymptomatic control women who had undergone an anesthetic intervention. These results demonstrate that minor neurologic deficits are to be found postpartum quite frequently if sought, but only those who have had anesthetic intervention are likely to complain or be questioned.

A prospective survey among 6057 women who delivered in one year in Chicago corroborates the findings of the Leeds study. The incidence of lower limb nerve injuries was approximately 1% (24 lateral femoral cutaneous nerve, 22 femoral nerve, 3 peroneal nerve, 3 lumbosacral plexus, 2 sciatic nerve, 3 obturator nerve, and 5 radicular injuries). Significant risk factors identified by logistic regression analysis included nulliparity and a prolonged second stage of labor but not neuraxial anesthesia.

A UK national audit of neuraxial blocks, without controls, published in 2009, found that the risk for major complications was 6- to 14-fold higher for perioperative than for obstetric procedures. Among the obstetric patients, the risk was highest for combined spinal-epidural (CSE), intermediate for spinal, and lowest for epidural procedures. Finally, the Serious Complication Repository (SCORE) project sponsored by the Society for Obstetric Anesthesia and Perinatology collected data from 30 institutions and more than 250,000 neuraxial blocks in the United States over a 5-year period (2004 to 2009); the incidence of anesthesia-related nerve injury for obstetric patients was approximately 1 in 35,000 deliveries. Four cases of epidural abscess/meningitis and a single case of epidural hematoma were reported.

Several conclusions can be drawn from these surveys. Despite an increased cesarean delivery rate in the past several decades, obstetric palsies still occur, and the reported frequency of neurologic sequelae depends on how hard one seeks them. The risk for transient mild deficits after childbirth may be quite high. A true figure for anesthetic complications cannot be calculated, even from thorough surveys, because (1) the diagnosis is rarely accurate and (2) definitions, severity, and duration are often ill defined. Table 31.1 demonstrates a variation in the incidence of neurologic sequelae from 1 in 3 for mild symptoms with no neuraxial block to 1 in 200,000 for spinal hematoma.

**Other Surveys**

Modern surveys of neurologic complications of spinal and epidural anesthesia among nonobstetric populations may yield more reliable results but still lack sensitivity to detect all potential problems and are commonly conducted in relatively elderly and sick populations. Auroy et al., Moen et al., Cook et al., and Pitkanen et al. surveyed mixed populations and found a lower incidence of serious sequelae in obstetric than in nonobstetric patients. It is therefore invalid to extrapolate findings from one population to the other. The reported risk for neurologic problems varies greatly with the patient population, local practice and skill, completeness of detection, and inclusion criteria. Hence, it is difficult to put any firm figure on the risk for neurologic complications after neuraxial anesthesia in obstetric patients.

**PERIPHERAL NERVE PALSY**

Postpartum nerve injury is often assumed to be caused by neuraxial anesthesia, but peripheral nerve palsies, which generally have obstetric causes, are much more common than anesthesia-related injury, with a reported incidence between 0.6 and 92 per 10,000. They may arise from compression in the pelvis by the fetal head, or from more distal compression, the signs of which may be overlooked in the presence of neuraxial anesthesia. Proposed risk factors for postpartum neuropathies include a prolonged second stage of labor, ...
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Population</th>
<th>Number of Neurologic Deficits (Risk Ratio)</th>
</tr>
</thead>
</table>
| Ong et al., 1987⁰              | Medical record review of all patients, interview of those receiving anesthesia in one center (1975–1983) | 23,827 deliveries, 12,964 inhalational or no analgesia, 9403 epidural procedures, 1460 general anesthetics and other | 45, all transient (1/530)
|                               |                                                                              |                                                     | 5 (1/2593)                                                                      |
|                               |                                                                              |                                                     | 34 (1/277)                                                                      |
|                               |                                                                              |                                                     | 6 (1/243)                                                                       |
| Scott and Hibbard, 1990⁰       | Retrospective multicenter review (1982–1986), no control group               | 11,701 women (39%) who responded, 4766 epidural procedures, 6935 no epidural procedures | 47 (1/10,745)
|                               |                                                                              |                                                     | 1 anterior spinal artery syndrome, 1 epidural abscess, 1 epidural hematoma (unconfirmed) |
|                               |                                                                              |                                                     | 38 mononeuropathies, 5 cranial nerve palsies                                               |
|                               |                                                                              |                                                     | 1 subdural hematoma                                                                |
| MacArthur et al., 1992⁴        | Questionnaire sent in 1987 to mothers delivering in one center (1978–1985)   | 11,701 women (39%) who responded, 4766 epidural procedures, 6935 no epidural procedures | Tingling/paresthesias                                                              |
|                               |                                                                              |                                                     | 143 upper limb, 23 lower limb                                                        |
|                               |                                                                              |                                                     | 150 upper limb, 3 lower limb                                                         |
| Palot et al., 1994⁵            | Questionnaire listing possible complications sent to hospitals with obstetric beds (1988–1993), no control group | 288,351 epidural procedures                       | 92 (1/3134)
|                               |                                                                              |                                                     | 1 cranial subdural hematoma                                                          |
|                               |                                                                              |                                                     | 88 temporary radiculopathy (1/3277)                                                  |
|                               |                                                                              |                                                     | 3 meningitis (1/96,117) (also reported negligence cases: 1 sciatic nerve palsy, 1 intracranial hematoma) |
| Scott and Tunstall, 1995⁶      | Prospective multicenter review (1990–1991), no control group                 | 467,491 deliveries, 108,133 epidural procedures, 14,856 spinal procedures             | 46 neuropathies (details for procedures not given)                                 |
|                               |                                                                              |                                                     | 38 (1/2846)                                                                      |
|                               |                                                                              |                                                     | 8 (1/1857)                                                                       |
| Holdcroft et al., 1995⁷        | Regional community and hospital-based trawl (1991–1992)                       | 48,066 deliveries, 34,430 no neuraxial block, 13,007 epidural procedures             | 10 new neurologic complications (1/4807)                                           |
|                               |                                                                              |                                                     | 1 foot drop, 1 cervical nerve lesion (1/17,215)                                      |
|                               |                                                                              |                                                     | 1 paresthesia of nerve root distribution (1/13,007) (Disorders unrelated to anesthesia: 2 cranial nerve palsies, 1 hypotensive cord damage; 5 peripheral nerve lesions) |
| Paech et al., 1999⁹            | Prospective local audit (1989–1994), no control group                         | 629 spinal procedures, 10,995 epidural procedures | 0                                                                                |
|                               |                                                                              |                                                     | 1 traumatic “mononeuropathy” (1/10,995)                                             |
| Holloway et al., 2000⁰         | Retrospective multicenter trawl, elastic time frame, no control group         | 29,698 spinal procedures                           | 4 unrelated to anesthesia (3 meralgia paresthetica, 1 peroneal neuropathy, 10 ?root damage, 1 conus damage, 22 uncertain (overall incidence 71/986) |
|                               |                                                                              |                                                     | 5 unrelated to anesthesia (1 femoral neuropathy, 2 foot drop, 2 paresthesia, 6 root damage, 1 meningitis, 1 conus damage, 6 uncertain (overall incidence ?1/901) |
| Dar et al., 2002¹⁰             | Prospective local audit of immediate symptoms (1998–1999)                    | 1376 vaginal deliveries without anesthesia (random sample of 21 examined + 1 complaint), 2615 regional blocks (all followed up), 1782 vaginal deliveries, 833 cesarean deliveries | 4 peripheral neuropathy, 1 foot drop, 2 vague (1/3)                               |
|                               |                                                                              |                                                     | 21 had neurologic symptoms                                                          |
|                               |                                                                              |                                                     | 7 peripheral neuropathies, 1 foot drop, 3 vague (1/162)                            |
|                               |                                                                              |                                                     | 8 numb areas, 2 vague (1/83)                                                        |
TABLE 31.1  Surveys of Neurologic Complications of Childbirth and of Neuraxial Blocks in Obstetrics—cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Population</th>
<th>Number of Neurologic Deficits (Risk Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auroy et al., 2002¹¹</td>
<td>Prospective multicenter survey, no control group</td>
<td>29,732 epidural procedures</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>5640 spinal procedures</td>
<td>2 “peripheral neuropathy”</td>
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<tr>
<td></td>
<td></td>
<td>205,000 epidural procedures</td>
<td>1 epidural hematoma (HELLP), 1 epidural abscess, 2 cord damage, 2 intracranial subdural hematoma, 1 abducent nerve palsy (1/29,286)</td>
</tr>
<tr>
<td>Moen et al., 2004¹³</td>
<td>National postal survey and search of administrative files (1990–1999), no control group</td>
<td>50,000 spinal procedures</td>
<td>1 spinal hematoma (HELLP), 1 cord damage (1/25,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 epidural hematoma, 1 epidural abscess, 2 cord damage (1/29,286)</td>
</tr>
<tr>
<td>Wong et al., 2003¹²</td>
<td>Prospective 1-year survey (1997–1998) at a single institution</td>
<td>5603 laboring patients (72% with neuraxial blocks) and 454 nonlaboring patients</td>
<td>66 nerve injuries (63 in laboring, 3 in nonlaboring). Lateral femoral cutaneous nerve (24) and femoral nerve (22) injuries most common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>329,425 obstetric procedures</td>
<td>1 epidural abscess, 2 nerve injury, 1 unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>161,550 epidural procedures</td>
<td>Possible harm per 100,000 (95% CI), 0.6 (0–3.4)</td>
</tr>
<tr>
<td>Cook et al., 2009¹⁴</td>
<td>National audit of major complications of neuraxial blockade over 1 year (unstated), obstetric and nonobstetric, no control group</td>
<td>133,525 spinal procedures</td>
<td>Possible harm per 100,000 (95% CI), 1.5 (1–5.4)</td>
</tr>
<tr>
<td></td>
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<td>25,350 CSE procedures</td>
<td>Possible harm per 100,000 (95% CI), 3.9 (1–22)</td>
</tr>
<tr>
<td>D’Angelo et al., 2014¹⁵</td>
<td>Prospective multicenter survey (2004–2009)</td>
<td>307,495 deliveries</td>
<td>27 cases of serious neurologic injury (1/11,389); 7 related to anesthesia (1/35,923), 1 epidural hematoma, 4 epidural abscess/ meningeitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131,460 epidural procedures</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>35,369 spinal procedures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>84,634 CSE procedures</td>
<td></td>
</tr>
</tbody>
</table>

CI, Confidence interval; CSE, combined spinal-epidural; HELLP, hemolysis, elevated liver enzymes, and low platelet count.

difficult instrumental delivery, nulliparity, and prolonged use of the lithotomy position.¹⁸

Reference to the distribution of spinal dermatomes and peripheral nerve sensory innervation demonstrates the distinction between peripheral and central lesions (Fig. 31.1). Central lesions are most often bilateral, create weakness or paralysis from the site of the lesion distally, and are often associated with autonomic dysfunction, and may be associated with upper motor neuron signs such as spasticity, brisk reflexes, and bowel and bladder dysfunction. In contrast, peripheral nerve lesions are typically unilateral, with weakness or paralysis limited to a single muscle or muscle group that the peripheral nerve innervates. Peripheral injuries create sensory deficits in the distribution of the specific nerve, while central lesions typically involve multiple dermatomes with a defined sensory level. Spinal nerve root lesions are also manifested by weakness that involves several lower extremity joints and movements (Fig. 31.2). Obstetric peripheral nerve injuries include compression of the lumbosacral trunk and palsies of the obturator, femoral, lateral femoral cutaneous, sciatic, and peroneal nerves.

**Compression of the Lumbosacral Trunk**

Compression of the lumbosacral trunk by the fetal head at the pelvic brim (Fig. 31.3) preferentially affects the more medial fibers that make up the peroneal rather than the tibial nerve.¹⁸ In addition to weakness that predominantly affects ankle dorsiflexion (foot drop), compression of the lumbosacral trunk produces sensory disturbance mainly involving the L5 dermatome (see Fig. 31.1). This palsy most often results from cephalopelvic disproportion and is therefore typically seen after prolonged labor and difficult vaginal delivery.⁸–¹⁰,¹²

**Obturator Nerve Palsy**

The obturator nerve is susceptible to compressive injury as it crosses the brim of the pelvis and within the obturator canal (see Fig. 31.3). The mother may complain of pain when the damage occurs, followed by weakness of hip adduction and internal rotation, with sensory disturbance over the medial thigh (see Fig. 31.1). She may have an abnormal gait secondary to weakness of thigh adduction. Cases are reported after both labor and cesarean delivery¹⁹,²⁰; three of 66 new nerve injuries detected in a prospective study by Wong et al.¹² were obturator nerve injuries. The most likely cause of obturator nerve palsy is compression of the nerve between the pelvis and fetal head or forceps applied to the fetal head.

**Femoral Nerve Palsy**

The femoral nerve does not enter the true pelvis and is therefore not vulnerable to compression by the fetal head but rather is vulnerable to stretch injury as it passes beneath the inguinal ligament. The femoral nerve may be injured
proximal to or at the inguinal ligament. Proximal injuries are associated with weakness of hip flexion, whereas more distal injuries spare the motor supply to the iliopsoas muscle. The patient with a femoral neuropathy may walk satisfactorily on a level surface but may be unable to climb stairs; the patellar reflex is diminished or absent. Although the incidence of femoral nerve palsy has decreased as a result of changes in obstetric management (e.g., fewer deliveries with prolonged second stage), it is still one of the most common obstetric nerve injuries. Approximately one-third of the postpartum palsies detected by Wong et al.12 were femoral nerve palsies. Dar et al.10 detected five cases in their small population, although the symptoms were transient. Damage may result from prolonged flexion, abduction, and external rotation of the hips during the second stage of labor and also during procedures conducted in an excessive lithotomy position.21 The hips should therefore never remain continuously flexed during the second stage of labor.

**Meralgia Paresthetica**

Meralgia paresthetica is a neuropathy of the lateral femoral cutaneous nerve, a purely sensory nerve also known as the lateral cutaneous nerve of the thigh. First described more than 100 years ago, meralgia paresthetica is commonly encountered in pregnancy and childbirth.12 The palsy may arise both during pregnancy, typically at about 30 weeks’ gestation, and intrapartum, in association with increasing intra-abdominal pressure.12,22 The distribution is unlike that of a nerve root lesion (see Fig. 31.1), yet the disturbance is commonly misattributed to neuraxial blockade. Meralgia paresthetica manifests as numbness, tingling, burning, or other paresthesias affecting the anterolateral aspect of the thigh. The most likely cause is entrapment of the nerve as it passes proximal to the inguinal ligament.
the inguinal ligament, where its vulnerability is increased by a gravid uterus or by retractors used during pelvic surgery. The compressive effect of edema may also contribute. The condition can be expected to resolve after childbirth.

**Sciatic Nerve Palsy**

Sciatic nerve palsy arises from compression of the nerve, usually in the buttock. It is not commonly mentioned in surveys or generally recognized as a complication of childbirth, possibly because it is mistaken for a lesion of the lumbosacral trunk. It gives rise to loss of sensation below the knee with sparing of the medial leg, and loss of movement below the knee. Posterior cutaneous nerve and gluteal function are preserved, implying damage distal to the lumbosacral plexus, where the gluteal nerves branch off the sciatic nerve (Fig. 31.4). Three cases out of 66 new nerve injuries were detected by Wong et al.\(^\text{12}\) It has occurred during childbirth with neuraxial blockade, either from sitting in one position too long\(^\text{23}\) or from a hip wedge misplaced during cesarean delivery.\(^\text{23–25}\) It has also been reported after iliac artery balloon placement for cesarean delivery in a woman with placenta percreta.\(^\text{26}\)

**Peroneal Nerve Palsy**

The common peroneal nerve is vulnerable to compression as it passes around the head of the fibula below the knee. It is also susceptible to damage while it still forms part of the sciatic nerve as it leaves the pelvis. When the peroneal nerve is damaged at the knee, there is sensory impairment on the anterolateral calf and the dorsum of the foot. Foot drop may be profound, with steppage gait and weak ankle eversion, but plantar flexion and inversion at the ankle are preserved. Peroneal nerve palsy may be caused by prolonged squatting,\(^\text{27}\) sometimes popular in “natural childbirth,” by excessive knee flexion for any reason, by compression of the lateral side of the knee against any hard object, even the patient’s hand,\(^\text{28}\) and by prolonged use of the lithotomy position. The incidence of peroneal nerve palsy is lower than that of lateral femoral cutaneous and femoral nerve palsy.\(^\text{12}\)

**Compression as a Risk Factor for Peripheral Neuropathy**

During pregnancy, nerve compression caused by edema may be a factor in the genesis of several peripheral neuropathies, such as carpal tunnel syndrome, Bell’s palsy, and meralgia paresthetica.\(^\text{22,29,30}\) Neuraxial blockade may indirectly contribute to compression injuries because it may decrease the ability of a woman to perceive that her legs are in a position that contributes to compression-induced neuropathy. Practices that providers should observe to lessen the risk for compression-induced neuropathy are listed in Box 31.2.

**POSTPARTUM BLADDER DYSFUNCTION**

There are several mechanisms by which bladder function may be disturbed postpartum (Fig. 31.5). In theory, neuraxial blockade (1) may provoke the need for bladder catheterization with increased risk for infection, (2) may allow bladder distention to go undetected, and (3) on very rare occasions, may be associated with cauda equina syndrome (see later discussion). However, several postpartum studies of bladder function have found no association with neuraxial analgesia\(^\text{31,32}\) or only a weak correlation between epidural analgesia and an increased residual volume immediately postpartum.\(^\text{33}\) In contrast, a prolonged second stage of labor, instrumental delivery, and perineal damage have been identified as significant factors for postpartum bladder dysfunction.\(^\text{31,33}\) No association has been found between epidural analgesia and stress incontinence or urinary frequency.\(^\text{6,34}\)

**BOX 31.2 Safeguards to Minimize Peripheral Nerve Compression**

- Be mindful of patient positioning that could contribute to nerve compression, particularly with neuraxial blockade.
- Avoid prolonged use of the lithotomy position; regularly reduce hip flexion and abduction.
- Avoid prolonged positioning that may cause compression of the sciatic or peroneal nerve.
- Place the hip wedge under the bony pelvis rather than the buttock.
- Use low-dose local anesthetic/opioid combinations during labor to allow maximum mobility.
- Encourage the parturient to change position regularly.
- Ensure that those caring for women receiving low-dose local anesthetic/opioid combinations understand that numbness or weakness may be signs of nerve compression; such symptoms should prompt an immediate change of position.
CENTRAL NERVOUS SYSTEM LESIONS

Lesions of the central nervous system (CNS) after childbirth have complex causes (Fig. 31.6), and may be classified as traumatic (to nervous tissue, meninges, or blood vessels), infectious, ischemic, or chemical (to nervous tissue or meninges). Anesthesia providers should bear in mind that even central lesions may have causes other than neuraxial block, for example a prolapsed intervertebral disc. Apart from sequelae of dural puncture, serious iatrogenic complications related to neuraxial analgesia and anesthesia are remarkably rare.

Neurologic Sequelae of Dural Puncture

The subject of post–dural puncture headache is discussed in detail in Chapter 30. Other neurologic sequelae of dural puncture include meningitis (see later discussion), cranial nerve palsies, and subdural hematoma. These often present as headache but are distinct from disorders that should be included in the differential diagnosis for postpartum headache, including tension/stress and migraine headaches, cortical vein and venous sinus thrombosis, preeclampsia, and posterior reversible encephalopathy syndrome. It can be difficult to distinguish post–dural puncture headache from other serious causes of headache because signs and symptoms overlap.

Cranial Nerve Palsy

Major loss of cerebrospinal fluid (CSF), usually following unintentional dural puncture with a large-bore needle, may cause a number of cranial nerve palsies; those affecting cranial nerves VI, VII, and VIII are the most frequently reported.35–41 Because of its long course within the cranium, the abducens nerve (VI) is the most vulnerable. All cranial nerve palsies require prompt PDPH treatment (e.g., epidural blood patch), but even after the blood patch recovery may be delayed. In the case of cranial nerve VIII dysfunction, tinnitus may not resolve.40,41 Trigeminal nerve dysfunction is usually a transient effect of high neuraxial blockade, but trigeminal and facial nerve palsies have also been reported in relation to post–dural puncture headache and subdural hematoma.42

Cranial Subdural Hematoma

More seriously, reduced CSF pressure may cause rupture of bridging meningeal veins and result in cranial subdural hematoma, a rare but potentially fatal condition.43 Palot et al.5 identified one case in 288,351 obstetric epidural procedures. In 2000, Loo et al.17 identified eight cases in their systematic review of published cases of neurologic complications in obstetric regional anesthesia. Although commonly believed to result only from dural puncture with a large-bore needle or a cutting spinal needle, subdural hematoma requiring craniotomy has been reported after puncture with a small-gauge, pencil-point spinal needle44 and after an unintentional dural puncture that had been appropriately treated with an epidural blood patch.45 A thorough review of 56 cases of subdural hematoma in obstetric patients who received neuraxial blocks (34 epidural, 20 spinal, 2 CSE) published in 2016 showed that predisposing risk factors such as coagulation disorders, aneurysms or arteriovenous malformations, or head trauma were present in only a minority of patients.46 Persistent headache was present in more than 80% of cases, and focal neurologic signs were present in nearly 70%. Whenever headache persists after treatment with an epidural blood patch (particularly if the headache is accompanied by altered consciousness, seizures, or other focal neurologic findings), magnetic resonance imaging (MRI) is warranted to exclude subdural hematoma, which may be fatal without urgent surgery.

Trauma to Nerve Roots and the Spinal Cord

Insertion of a spinal needle or epidural catheter may be accompanied by paresthesia that is sometimes painful. However, such a paresthesia is neither sensitive nor specific
for nerve injury. If a paresthesia is encountered, advancement of the needle or catheter should be halted. It is generally deemed appropriate to then continue spinal or epidural catheter placement after the paresthesia subsides. Continued paresthesias should prompt removal and redirection of the needle. Although a flexible catheter is unlikely to do lasting damage to a nerve root in the epidural space, nerve roots in the subarachnoid space are more vulnerable.

**Trauma Associated with Attempted Epidural Catheter Insertion**

An epidural catheter may injure nerve roots either because it is inappropriately rigid or because an undue length is advanced and ensnares a root. A catheter seemingly advanced into the epidural space may lodge in an intervertebral foramen or even pass into the paravertebral space. In rare instances, the epidural catheter and the artery of Adamkiewicz share the same foramen. If the epidural catheter is stiff enough to compress the artery within the unyielding foramen, the blood supply to the spinal cord may be impaired. This is a possible cause of anterior spinal artery syndrome. Clinical reports indicate that the condition resolves rapidly and completely if the catheter is withdrawn before permanent damage has occurred.

Injury to the spinal cord may result from attempted identification of the epidural space in the presence of a tethered spinal cord or as a result of unintentional dural puncture at a higher-than-anticipated interspace (see later discussion). Patients with spina bifida occulta may safely undergo both epidural and spinal anesthesia as the spinal cord is rarely tethered in true spina bifida occulta (see Chapter 47). However, if there is concern for occult spinal dysmorphism, which is more frequently associated with a tethered cord, it is prudent to obtain a lumbar MRI before initiating a neuraxial procedure. Insertion of an epidural catheter in an anesthetized patient increases the risk for spinal cord damage, and catastrophic injury may occur with injection of fluid into the substance of the spinal cord.
CSE anesthesia using a pencil-point needle.\textsuperscript{9,13,55,56} Typically, the patient complains of pain on needle insertion before any fluid is injected, often followed by the normal appearance of CSF from the needle hub, easy injection of the local anesthetic agent, and a normal onset of neural blockade. On recovery, there is unilateral numbness, which is succeeded by pain and paresthesia in the L5 to S1 distribution and foot drop, and in some cases urinary symptoms; sensory symptoms may last for months or years. The MRI appearance is one of a small syrinx or hematoma within the conus on the same side as the pain on insertion and subsequent leg symptoms (Fig. 31.7).\textsuperscript{56}

In the majority of cases, the anesthesia provider believed the interspace selected was L2–L3. In one patient who subsequently died of other causes, hematomyelia was confirmed at autopsy.\textsuperscript{57} After a rash of cases of conus damage in the 1990s, the practice of spinal needle insertion may have been modified by aware providers, but an abnormally long cord may still be damaged with the best of techniques.\textsuperscript{58}

These injuries may have occurred for the following reasons:

• Identification of lumbar interspaces was far from accurate. Studies showed that it was common to select a space that is higher than assumed by one, two, or even more segments (Fig. 31.8).\textsuperscript{59,60}

• Although the spinal cord typically ends level with the lower body of L1 or the L1–L2 interspace, the length varies (Fig. 31.9).\textsuperscript{61} From the L1–L2 interspace, the needle tip can easily reach the conus in 27\% of men and 43\% of women.\textsuperscript{61,62}

• The standard method of identifying lumbar interspaces involves the use of Tuffier’s line, the imaginary line joining the two iliac crests. This method can be inaccurate, however, particularly in obese or pregnant women (Fig. 31.10). Moreover, even when accurately assessed, Tuffier’s line is an inconstant landmark.\textsuperscript{63} Although typically at the level of the L4 spinous process, it may lie anywhere between the L3–L4 and L5–S1 interspaces.

• Pencil-point spinal needles must be advanced further than cutting needles before the orifice is within the subarachnoid space, at which point the tip may impinge on the spinal cord.

Given the inaccuracy of identification of lumbar interspaces and the variability of the position of the conus, it is

**Fig. 31.7** (A and B) Magnetic resonance images of a conus medullaris lesion (arrows). (From Reynolds F. Damage to the conus medullaris following spinal anaesthesia. Anaesthesia. 2001;56:238–247.)

**Fig. 31.8** Identification of lumbar interspaces by Oxford anesthetists. The horizontal axis shows the position of the actual interspace identified on magnetic resonance imaging, relative to the assumed space, in 200 observations. (Data from Broadbent CR, Maxwell WB, Ferrie R, et al. Ability of anaesthetists to identify a marked lumbar interspace. Anaesthesia. 2000;55:1122–1126.)
intraspinal tumors, any of which, within the rigid confines of the bony spinal canal, can cause dangerous compression of nervous tissue and its blood supply. Urgent laminectomy is required to avoid permanent neurologic damage. Delayed recognition and treatment (more than 6 to 12 hours after onset of symptoms) may have a catastrophic outcome.

Epidural analgesia in labor does not normally behave like a space-occupying lesion and produces no lasting deformation of the thecal sac on MRI. Nevertheless, in the presence of vertebral stenosis or lumbar disc protrusion, a large volume injected into the epidural space may tip the balance and produce signs of nervous tissue compression that normally resolve in a few hours.

The neurologic deficit that may arise from a compressive lesion depends on the vertebral level; lower thoracic lesions are associated with leg weakness or paraplegia, and lumbar lesions with cauda equina syndrome, including urinary retention and incontinence. Back pain (often radiating to the legs) is a common feature.

Neuraxial Hematoma

Neuraxial hematoma is fortunately very rare, and even rarer in pregnant patients than in the general population. During pregnancy and the peripartum period, spontaneous neuraxial hematoma is reported more frequently than hematoma associated with neuraxial blockade. Loo et al. reported three cases in 2000, which may have been included in another review, and more have been reported in the past two decades. Epidural hematoma in pregnancy associated with coagulopathy but not neuraxial anesthesia has also been reported.

Epidual Hematoma after Neuraxial Blockade

Incidence. Epidural hematoma after neuraxial blockade typically causes neurologic deficit in elderly patients with arterial disease; it is very rare in obstetric patients, despite the engorgement and possible fragility of epidural veins. Ten surveys, covering 1,462,631 obstetric epidural procedures, identified three cases (see Table 31.1), two without

both logical and prudent to insert a spinal needle into a lower lumbar interspace. Box 31.3 summarizes the problems and precautions in identifying lumbar interspaces and avoiding damage to the conus medullaris. In cases in which there is doubt about the level of lumbar interspace for injection, ultrason sound guidance may be useful in accurately identifying the correct interspace.

Catheters advanced into the intrathecal space theoretically would seem to place patients at risk for traumatic nerve injury. However, a retrospective study of 761 short-term intrathecal catheters placed over a 12-year period found no neurologic or serious complications. Transient paresthesias with catheter placement into the intrathecal space have been reported; whether long-term consequences occur is not known.

**Space-Occupying Lesions of the Vertebral Canal**

Space-Occupying Lesions of the Vertebral Canal include intraspinal hematoma (epidural or subdural), epidural abscess, and

**Fig. 31.9** Variation in the level of the tip of the conus medullaris assessed by magnetic resonance imaging of the lumbar spine among 504 consecutive adults. L, lower third of vertebral body listed; M, middle third of vertebral body listed; T12/L1, interspace between T12 and L1; U, upper third of vertebral body listed. (Data derived from Saifuddin A, Burnett SJ, White J. The variation of position of the conus medullaris in an adult population: a magnetic resonance imaging study. *Spine*. 1998;23:1452–1456.)

**Fig. 31.10** Error that may arise if Tuffier’s line is judged in a pregnant patient in the lateral position, when a line is drawn perpendicular from the upper iliac crest rather than through both iliac crests. In pregnant patients at term, the hips may have a greater width than the shoulders. The resulting cephalad pelvic tilt may lead to an error in the cephalad direction.

**Box 31.3 Points to Remember to Reduce Risk for Damage to the Conus Medullaris during Spinal Anesthesia**

- The conus medullaris reaches L2 in 27% of men but in 43% of women.
- Tuffier’s line is not in a constant position relative to the spine.
- The interspace chosen is usually higher than supposed.
- The spinal needle should be inserted into a lower lumbar level.
- Advancement of the spinal needle should be halted immediately, and the stylet removed to check for CSF, if entry of the needle tip into the subarachnoid space is suspected.
- The procedure should be abandoned if the patient is unable to cooperate.

**Neuraxial Hematoma**

Neuraxial hematoma is fortunately very rare, and even rarer in pregnant patients than in the general population. During pregnancy and the peripartum period, spontaneous neuraxial hematoma is reported more frequently than hematoma associated with neuraxial blockade. Loo et al. reported three cases in 2000, which may have been included in another review, and more have been reported in the past two decades. Epidural hematoma in pregnancy associated with coagulopathy but not neuraxial anesthesia has also been reported.

**Epidual Hematoma after Neuraxial Blockade**

**Incidence.** Epidural hematoma after neuraxial blockade typically causes neurologic deficit in elderly patients with arterial disease; it is very rare in obstetric patients, despite the engorgement and possible fragility of epidural veins. Ten surveys, covering 1,462,631 obstetric epidural procedures, identified three cases (see Table 31.1), two without...
confirmatory details and the other in a patient with HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. This gives an incidence of 0.205 per 100,000 epidural procedures.

**Causation.** Risk factors identified from comprehensive reviews of case reports include (1) difficult or traumatic epidural needle/catheter placement, (2) coagulopathy or therapeutic anticoagulation, (3) spinal deformity, and (4) spinal tumor. Antiplatelet therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) does not appear to be associated with an increased risk for hematoma after neuraxial anesthesia.

Of the five cases of epidural hematoma in obstetric patients identified by Loo et al., four were without details and the other was associated with coagulopathy. In the most recent analysis from the American Society of Anesthesiologists' (ASA) Closed-Claims Project database, there were four cases of epidural hematoma, of which only one had coagulopathy; again, other details were not provided. The SCORE project reported a single case of epidural hematoma in more than 215,000 epidural and CSE procedures; again, details were not provided. Two further case reports are of interest. An eclamptic patient with thrombocytopenia suffered a persistent lower limb deficit after a traumatic epidural catheter insertion using the loss-of-resistance-to-air technique. Laminectomy revealed multiple bubbles and a 4-mL blood clot, the exact site of which was not stated. Such a small volume could have caused neurologic deficit only if it was subdural rather than epidural. In another case, an epidural hematoma was reported presenting 9 days after removal of an epidural catheter that had been sited and used uneventfully for labor analgesia. Apparently the only risk factor was a traumatic insertion. The coagulation assessment was normal, but the hematoma was extensive and required decompressive surgery. It is possible that this was a spontaneous hematoma and neuraxial analgesia was coincidental.

Both vessel damage and coagulopathy (whether inherited, acquired, or caused by anticoagulation) are usually necessary to produce a hematoma large enough to cause a neurologic deficit in the parturient. Safe epidural catheter insertion in coagulopathic parturients has often been recorded, but the frequency of vessel trauma is rarely mentioned. Although vessel trauma can occur during removal of the epidural catheter, intuitively there is likely to be a higher chance for vessel trauma with needle placement and catheter insertion. In a series of 4365 nonobstetric patients receiving warfarin anticoagulation, epidural catheters were removed with a mean INR (international normalized ratio) of 1.9 (range of 1.5 to 7.1) without any observed epidural hematomas. The increasing number of women receiving pharmacologic thromboprophylaxis in the peripartum period has important implications for anesthesiologists. Although there is obvious concern that these patients may be at increased risk for bleeding complications, a systematic review published in 2017 revealed no cases of spinal-epidural hematoma associated with neuraxial anesthesia and thromboprophylaxis with unfractionated or low-molecular-weight heparin in obstetric patients. Caring for obstetric patients receiving anticoagulation requires a thoughtful weighing of risks and benefits before deciding to proceed with a neuraxial anesthetic technique.

**Protective factors.** Some epidural hematomas may occur that are too small to cause neurologic deficit. One factor may be the hypercoagulable status of parturients. Another is the ease with which a large volume of anticoagulated blood may flow out of the unrestricting intervertebral foramina in young patients. Injected blood is known to disappear from the epidural space rapidly in the parturient. During performance of an epidural blood patch, 20 mL of blood is commonly injected with impunity. Although compressive symptoms may be experienced with a volume larger than 20 mL, they do not normally presage any neurologic deficit in obstetric patients.

**Subdural and subarachnoid hematoma.** Spinal subdural hematoma has been reported in obstetric patients, one in association with an ependymoma, one after spinal anesthesia and an epidural blood patch, and another in a woman with preeclampsia, known vessel puncture during epidural catheter insertion, and mild coagulopathy. A subarachnoid hematoma after spinal anesthesia was reported in a patient with HELLP syndrome. A fourth report described a healthy woman who suffered major subarachnoid hematoma after apparently straightforward CSE anesthesia. All four patients developed cauda equina syndrome, and laminectomy was required in three.

Dural puncture (with or without arachnoid puncture) is a prerequisite for subdural and subarachnoid hematoma. However, coagulopathy may not be a prerequisite, because the extravasated blood is confined in a small space in which even a small volume may compress adjacent nerve roots.

**Prevention, diagnosis, and management.** It is clearly important to assess the coagulation status in an at-risk parturient before initiating a neuraxial procedure, and possibly when removing the epidural catheter as well. If neuraxial blockade is found to have been conducted in the presence of risk factors for spinal hematoma, it is a responsibility of the anesthesia provider to examine the lower extremities after delivery, to confirm and document the return of normal motor and sensory function, and to request subsequent regular checks by the nursing staff, typically for 24 hours. Severe back pain and a significant delay in normal recovery or deterioration of lower extremity or bladder function signal the need for emergency imaging of the spine. If intraspinal compression is confirmed by MRI, a neurosurgical opinion must be urgently sought.

Neuraxial anesthesia in the presence of coagulopathy and anticoagulant treatment are discussed in Chapters 38 and 44.

**Infection**

Neuraxial infection (epidural abscess and meningitis) was identified as the most common cause of neuraxial injury in obstetric cases in the ASA Closed-Claims Project database between 1980 and 1999. Infections that have been reported include epidural abscess, paraspinial and other epidural-related infection, and meningitis.
Epidural Abscess

**Frequency.** Epidural abscess may occur spontaneously in pregnancy and the puerperium as at other times. An analysis of 915 reports of spinal-epidural abscess published between 1954 and 1997 found that epidural blockade had been performed in only 5.5% of cases. After neuraxial blockade, epidural abscess, like neuraxial hematoma, appears to be rare in obstetric patients. Seven cases were found among 1,462,631 epidural procedures listed in ten surveys summarized in Table 31.1, a frequency of 0.479 per 100,000. The incidence among general surgical patients has been reported as 10-fold to 100-fold higher, with most cases arising in elderly and immunocompromised patients. A 4-year Australian study of 9482 obstetric patients who underwent childbirth in a center where correct sterile procedures were used found 49 epidural catheter–related infections (0.52%): 45 superficial, 2 epidural, and 2 paraspinal, giving an epidural infection rate of 21 per 100,000, which was 100-fold higher than the calculated frequency from larger, but potentially less sensitive, surveys.

Multiple case reports of epidural abscess after epidural analgesia in obstetric patients illustrate that even when the principal risk factors of prolonged catheterization, suboptimal aseptic technique, and traumatic insertion are avoided, epidural abscess still may occur. A comprehensive review of epidural abscess cases after neuraxial anesthesia details that all cases occurred after epidural catheterization, with three following CSE anesthesia; none followed spinal anesthesia alone.

Possible risk factors identified from these cases are summarized in Table 31.2. An epidural abscess typically follows prolonged epidural catheterization, usually between 1 and 4 days in obstetric cases. Other possible etiologic factors are traumatic or difficult insertion of the catheter, and diabetes or immunosuppression from any cause. Inflammation at the epidural catheter entry point may presage epidural space infection. In light of these reports, it may be prudent to avoid prolonged epidural catheterization in the patient with other risk factors for infection.

**Table 31.2 Possible Etiologic Factors for Epidural Abscess and Meningitis**

<table>
<thead>
<tr>
<th>Entry point</th>
<th>Through the epidural catheter or along its track</th>
<th>Via dural puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual causative organism</td>
<td><em>Staphylococcus aureus</em></td>
<td><em>Streptococcus salivarius</em></td>
</tr>
<tr>
<td>Possible source of infection</td>
<td>Patient’s skin, tracking along the catheter entry point</td>
<td>Operator’s mouth</td>
</tr>
<tr>
<td></td>
<td>Epidural equipment contaminated by operator’s skin</td>
<td>Talking without a mask</td>
</tr>
<tr>
<td></td>
<td>Body fluids in the bed</td>
<td>Blood borne</td>
</tr>
<tr>
<td></td>
<td>Injectate without racemic local anesthetic</td>
<td>Vagina</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Prolonged catheterization</td>
<td>Dural puncture</td>
</tr>
<tr>
<td></td>
<td>Poor aseptic technique</td>
<td>Labor</td>
</tr>
<tr>
<td></td>
<td>Multiple attempts at insertion, traumatic insertion</td>
<td>No face mask</td>
</tr>
<tr>
<td></td>
<td>No bacterial filter</td>
<td>Manual removal of the placenta</td>
</tr>
<tr>
<td></td>
<td>Lying in a wet, contaminated bed</td>
<td>Vaginal infection</td>
</tr>
<tr>
<td></td>
<td>Polyurethane occlusive dressing</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Immunocompromise: corticosteroids, diabetes, acquired immunodeficiency syndrome</td>
<td>Immunocompromise</td>
</tr>
</tbody>
</table>

**Clinical presentation.** In contrast to epidural hematoma, symptoms of epidural abscess are more insidious. Severe backache (with local tenderness) and fever, with or without radiating or root pain, are the presenting features. The catheter entry point may be inflamed with some fluid leak, and a hematology screen typically reveals leukocytosis and increased C-reactive protein. Fever, neck stiffness, headache, and signs of inflammation serve to differentiate epidural abscess from hematoma. These signs and symptoms should prompt MRI, which may allow early diagnosis before the onset of neurologic changes (Fig. 31.11). If untreated, symptoms may progress to leg weakness, paresthesias, bladder dysfunction, and other evidence of cauda equina syndrome. Blood culture may identify the organism before or without surgical drainage.

**Etiology.** *Staphylococcus aureus* is the most common causative organism in cases of epidural abscess, with the occasional infection with *Streptococcus* and *Pseudomonas* species. The skin appears to be the most likely source of infection.

The skin is commonly colonized by *Staphylococcus epidermidis* and other weakly pathogenic bacteria and occasionally by *Staphylococcus aureus*. The highest concentration of colonies is found in the hair follicles, where organisms may be protected from poorly applied disinfectants. Infectious organisms from the skin can reach deeper tissue planes via the needle track or an implanted epidural catheter to create a localized abscess in the paraspinal or epidural space. Despite all aseptic precautions, some level of detectable bacterial colonization of the epidural catheter is very common, but robust host defenses normally prevent infection. When defenses are weak and infection containment breaks down, epidural abscess formation begins.

**Management.** As with spinal hematoma, once neurologic signs are present, early diagnosis with prompt laminectomy is essential to recovery. In the presence of mild symptoms without neurologic changes, successful conservative treatment with antibiotics and successful percutaneous needle drainage of epidural abscesses have also been reported, although only laminectomy can ensure that all loculations are
drained under direct vision. Prompt identification of the infectious organism(s) and directed antibiotic therapy are mandatory. The duration of antibiotic therapy should be determined on a case-by-case basis, but is usually 4 to 6 weeks if there are no complications.

Other Epidural-Related Infections

Paraspinal abscess and osteomyelitis after epidural analgesia\(^{112,113}\) and discitis after spinal blockade\(^{114}\) have been reported in obstetric patients. Catheter-site inflammation is relatively common with prolonged postoperative epidural analgesia.\(^{98,115}\) One report described both a subdural abscess after CSE anesthesia and infection in the subcutaneous tissues after an apparently misplaced epidural blood patch.\(^{116}\)

A variety of organisms have been associated with epidural-related infections.\(^{107}\) All such conditions are associated with back pain and signs of inflammation and pose a threat of spread to the epidural space. Moreover, paraspinal abscess may itself cause neurologic deficit.\(^{117}\)

Meningitis

Although not consistently included in surveys, post–spinal meningitis has become a cause for concern\(^{118}\) and is a serious neurologic complication of neuraxial labor analgesia. It was suspected in two cases in the prospective survey of 108,133 epidural procedures and 14,865 spinal anesthetic procedures by Scott and Tunstall,\(^{9}\) although the specific type of anesthesia was not stated. Palot et al.\(^{5}\) reported three cases of meningitis among 288,351 obstetric epidural procedures but did not state whether they followed dural puncture. One case was identified in a survey of spinal and CSE anesthesia (1/42,000 procedures).\(^{9}\) A 2008 review found an incidence derived from surveys of spinal and CSE anesthesia in obstetrics of 1 in 39,000.\(^{107}\) Table 31.3 summarizes 54 published reports of post–spinal meningitis in obstetric patients.\(^{118–145}\)

**Causative organisms.** Community-acquired meningitis may occur in pregnancy as at other times. It is commonly caused by *Neisseria meningitidis, Streptococcus pneumoniae,* or *Haemophilus influenzae,* while occasional cases caused by tuberculosis, several \(\beta\)-hemolytic streptococci, and viruses are also reported in pregnancy. Post–spinal meningitis, by contrast, is most commonly caused by streptococci of the viridans type (\(\alpha\)-hemolytic streptococci such as *S. salivarius, S. sanguis,* and *S. uberis*) (see Table 31.3). These organisms are found in the upper airway and the vagina. *Pseudomonas* meningitis has also been reported.\(^{122}\) Neither *Pseudomonas* nor \(\alpha\)-hemolytic streptococci are normally virulent; they do not, for example, cause wound infection, but they thrive in a watery medium and flourish if introduced into CSF. In several early cases (before the use of the polymerase chain reaction), no organisms were grown on culture and chemical meningitis was diagnosed. In most cases, however, there were features of bacterial meningitis, including low CSF glucose concentration. Of note, streptococci of the viridans type do not grow readily in conventional culture media and may well have been present but not detected.

**Risk factors.** Dural puncture is probably a prerequisite for iatrogenic meningitis. A retrospective review of surgical patients in one hospital in Brazil found three cases among 38,128 patients receiving spinal anesthesia (1/12,709) and none among 12,822 patients receiving other types of anesthesia.\(^{146}\) Among 73 women with \(\beta\)-hemolytic streptococcal infections in the puerperium identified in a survey from Iowa,\(^{147}\) the only woman who suffered meningitis had received spinal anesthesia. In normal circumstances, the blood-brain barrier (the endothelial lining of the capillaries, which are continuous with tight junctions and no pinocytotic vesicles) protects the CNS against weakly pathogenic bacteria. The dura mater should not be confused with the blood-brain barrier, but dural puncture is commonly associated with vascular trauma,\(^{148}\) which allows blood to enter the CSF.

Of the 54 published cases of puerperal post–spinal meningitis for which details are available (see Table 31.3), 48 occurred after known dural puncture. Among the six cases that followed apparently uncomplicated epidural analgesia, one was viral and may have been a chance event,\(^{141}\) one was probably an epidural abscess,\(^{142}\) and two were blood borne from vaginal infection caused by group B streptococcus.\(^{143,144}\) Uncomplicated epidural catheterization itself is unlikely to

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**Fig. 31.11** Epidural abscess. Mid-sagittal T1-weighted magnetic resonance image of the lumbar and lower thoracic region, after intravenous gadolinium DTPA. Note the dorsal epidural mass located at T12–L1 (arrows), convex anteriorly but not compressing the conus. Normal epidural fat is flat anteriorly. (From Roayakers AA, Willigers H, van der Ven AJ, et al. Catheter-related epidural abscesses—don’t wait for neurological deficits. *Acta Anaesthesiol Scand* 2002;46:611–615.)
increase the risk for puerperal meningitis. Although spinal analgesia is used less commonly than epidural analgesia during labor, case reports of meningitis after spinal analgesia far outnumber those after epidural analgesia. A causative relationship between epidural catheterization and meningitis after vaginal delivery may be attributed to unrecognized dural puncture, which may occur during multiple attempts at epidural catheter insertion or even with apparently uncomplicated catheter insertion.

Labor may also be a risk factor for meningitis. The great majority of parturients with nosocomial meningitis had labored (see Table 31.3). Meningitis appears surprisingly rare

<table>
<thead>
<tr>
<th>References</th>
<th>Number of Cases</th>
<th>Organism; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbons, 1969</td>
<td>3</td>
<td>Case cluster, no growth, “chemical meningitis,” CSF findings suggested bacterial etiology</td>
</tr>
<tr>
<td>Phillips, 1970</td>
<td>1</td>
<td>No growth, CSF findings suggested bacterial etiology</td>
</tr>
<tr>
<td>Corbett and Rosenstein, 1971</td>
<td>3</td>
<td>Case cluster, single anesthesiologist, unsterile technique, Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Newton et al., 1994</td>
<td>1</td>
<td>Streptococcus salivarius</td>
</tr>
<tr>
<td>Lurie et al., 1999</td>
<td>1</td>
<td>Streptococcus viridans</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention, 2010</td>
<td>2</td>
<td>Case cluster, single anesthesiologist, Streptococcus salivarius, one death</td>
</tr>
<tr>
<td>Bugedo et al., 1991</td>
<td>1</td>
<td>Signs of bacterial meningitis, labor unknown</td>
</tr>
<tr>
<td>Lee and Parry, 1991</td>
<td>1</td>
<td>No growth, CSF findings suggested bacterial etiology, in labor, three attempts at epidural analgesia</td>
</tr>
<tr>
<td>Stallard and Barry, 1996</td>
<td>1</td>
<td>No growth, CSF findings suggested bacterial etiology, in labor, three attempts at epidural analgesia, spinal anesthesia at same interspace</td>
</tr>
<tr>
<td>Donnelly et al., 1998</td>
<td>1</td>
<td>No growth, CSF findings suggested bacterial etiology, membranes ruptured</td>
</tr>
<tr>
<td>Thomas and Cooper, 2001</td>
<td>1</td>
<td>Preeclampsia, labor unknown, patient died</td>
</tr>
<tr>
<td>Rodrigo et al., 2007</td>
<td>6</td>
<td>Aspergillus, five elective cesarean deliveries, one in labor, three patients died</td>
</tr>
<tr>
<td>Celik et al., 2014</td>
<td>1</td>
<td>No growth, CSF findings suggested aseptic meningitis</td>
</tr>
<tr>
<td>Ersoz et al., 2014</td>
<td>12</td>
<td>Serratia marcescens, elective cesarean deliveries, extrinsic vial contamination</td>
</tr>
<tr>
<td>Roberts and Petts, 1990</td>
<td>1</td>
<td>Two attempts at spinal anesthesia, no growth, CSF findings suggested bacterial etiology</td>
</tr>
<tr>
<td>Harding et al., 1994</td>
<td>2</td>
<td>No growth, CSF findings suggested bacterial etiology</td>
</tr>
<tr>
<td>Cascio and Heath, 1996</td>
<td>1</td>
<td>Streptococcus salivarius (dismissed as contaminant)</td>
</tr>
<tr>
<td>Bouhemad et al., 1998</td>
<td>1</td>
<td>Streptococcus salivarius</td>
</tr>
<tr>
<td>Duflo et al., 1998</td>
<td>1</td>
<td>Streptococcus viridans</td>
</tr>
<tr>
<td>Vernis et al., 2004</td>
<td>1</td>
<td>One case in the course of a randomized trial</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention, 2010</td>
<td>3</td>
<td>Cluster, single anesthesiologist, Streptococcus salivarius</td>
</tr>
<tr>
<td>Berga and Trierweiler, 1989</td>
<td>1</td>
<td>Streptococcus sanguis</td>
</tr>
<tr>
<td>Sansome et al., 1991</td>
<td>1</td>
<td>No growth, CSF findings ambivalent</td>
</tr>
<tr>
<td>Baer, 2006</td>
<td>1</td>
<td>Staphylococcus simulans and Streptococcus salivarius; patient died</td>
</tr>
<tr>
<td>Neumark et al., 1980</td>
<td>1</td>
<td>Coxsackievirus B</td>
</tr>
<tr>
<td>Ready and Helfer, 1989</td>
<td>2</td>
<td>1 Streptococcus uberis</td>
</tr>
<tr>
<td>Davis et al., 1993</td>
<td>1</td>
<td>1 Streptococcus faecalis (epidural inflammation)</td>
</tr>
<tr>
<td>Goldstein et al., 1996</td>
<td>1</td>
<td>Group B streptococcus</td>
</tr>
<tr>
<td>Choy, 2000</td>
<td>1</td>
<td>Group B streptococcus</td>
</tr>
<tr>
<td>Total (54 cases)</td>
<td>48 known dural punctures</td>
<td>17 elective cesarean deliveries, all with extrinsic contamination of medication or equipment</td>
</tr>
</tbody>
</table>

CSE, Combined spinal-epidural anesthesia; CSF, cerebrospinal fluid.
after elective cesarean delivery, despite the extensive use of spinal anesthesia in this context.

The possible reasons why meningitis is reported more commonly in laboring women than among those undergoing elective cesarean delivery are as follows:

1. The vagina may be colonized by streptococci, and vaginal delivery is commonly followed by mild bacteremia. Thus labor, with its potential for vaginal trauma, is clearly an important risk factor. Unlike vaginal delivery, elective cesarean delivery is not normally associated with streptococcal bacteremia.

2. For elective cesarean delivery, spinal anesthesia is administered in the operating room, which is a cleaner environment than the labor and delivery room.

3. The anesthesia provider is more likely to wear a face mask in the operating room.

4. The nonlaboring patient is not thrashing about in a (possibly) contaminated bed.

5. An antibiotic is usually administered immediately before or after cesarean delivery.

Infection at a remote site may also be a risk factor for meningitis. Bacteremia has been detected in approximately 8% of women with chorioamnionitis, although two small studies found no evidence of spinal infection among 12 women with bacteremia who received epidural blockade without antibiotic treatment. Although such negative findings are reassuring, they are not conclusive and do not apply to spinal anesthesia. Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) should not be regarded as contraindications to neuraxial anesthesia. Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) should not be regarded as contraindications to neuraxial analgesia, in view of the early presence of the virus within the CNS. Performing an epidural blood patch in the presence of bacteremia is also a theoretical risk for both meningitis and abscess, but neither has been reported in this context. Neuraxial analgesia in the presence of maternal fever is discussed in detail in Chapter 36.

Other risk factors for meningitis include faulty technique, in particular failure to wear a mask (see later discussion). Manual removal of the placenta is a postulated risk factor for meningitis, and one such case has been reported, although given the popularity of spinal anesthesia for this indication, one would perhaps expect a higher frequency. It may be postulated that use of the CSE technique, with the presence of a foreign body next to a dural hole, may increase the risk for meningitis.

Clinical presentation and management. Fever, headache, photophobia, nausea, vomiting, and neck stiffness are typical symptoms of meningitis; when they are accompanied by confusion, drowsiness, and Kernig’s sign (inability to straighten the knee when the hip is flexed), meningitis should be strongly suspected. The onset of nosocomial meningitis may be 12 hours to a few days after delivery. Diagnostic lumbar puncture (best avoided in the presence of raised intracranial pressure or suspicion of epidural abscess) shows increased CSF pressure, increases in CSF protein level and white blood cell count (mainly polymorphonuclear leukocytes in patients with bacterial meningitis), and a CSF glucose concentration that is lower than that in the blood. Because of the nature of the S. viridans group, culture on plates rather than in broth may have negative results, particularly if antibiotics have been given. Treatment with an appropriate antibiotic should not await the microbiology results and should result in full recovery. Vancomycin and third-generation cephalosporins have been recommended as first-line treatment. The treatment regimen should be adjusted according to results of culture and sensitivity testing.

Prevention of Intraspinal Infection after Neuraxial Anesthesia

Measures to prevent intraspinal infection are summarized in Box 31.4. Means of preventing meningitis and epidural abscess are not identical, because abscess usually follows epidural catheterization and is commonly caused by S. aureus, which enters via the skin, whereas meningitis classically follows dural puncture, is caused by vaginal or nasal organisms, may be blood borne, and is usually caused by streptococcus and never by S. aureus.

Because adverse outcomes are rare, the use of sterile precautions can rarely be supported by evidence from randomized trials. The components of good sterile technique should be guided by common sense and the best available indirect evidence. It is notable that in many case reports of neuraxial infection, sterile precautions used in initiating neuraxial blockade receive no mention.


Mask. Several surveys indicate widespread disregard of surgical masks for infection control during neuraxial block administration. Among case reports of nosocomial

<table>
<thead>
<tr>
<th>BOX 31.4 Procedures to Decrease the Risk for Infection after Neuraxial Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wear an effective mask; wear a new mask for each patient.</td>
</tr>
<tr>
<td>• Remove hand jewelry and watches, and wash hands with an alcohol-based scrub solution.</td>
</tr>
<tr>
<td>• Consider wearing a sterile gown.</td>
</tr>
<tr>
<td>• Use sterile gloves in correct manner.</td>
</tr>
<tr>
<td>• Apply chlorhexidine-in-alcohol solution to the patient’s skin, following the package instructions, and allow the skin to dry after application.</td>
</tr>
<tr>
<td>• Make sure the back is securely draped.</td>
</tr>
<tr>
<td>• Avoid contaminating any equipment that is used in the procedure, and minimize touching parts of the equipment that will enter the patient.</td>
</tr>
<tr>
<td>• After the procedure, apply a suitable dressing to the catheter entry point.</td>
</tr>
<tr>
<td>• Bacterial filters may be considered during extended continuous epidural infusion.</td>
</tr>
<tr>
<td>• Remove the epidural catheter shortly after delivery unless there are specific indications for not doing so.</td>
</tr>
</tbody>
</table>
meningitis, a mask was not mentioned or was not worn ("as it is of doubtful value" or because it "contributes little to prevent infection during spinal or epidural anesthesia" or is not considered part of "full aseptic technique").

Confusion has arisen because randomized trials have demonstrated that omission of masks in the operating room does not increase the occurrence of wound infection. This is not surprising, however, because organisms from the upper airway do not cause wound infection, but they certainly do cause nosocomial meningitis. The effect of wearing a mask in the prevention of such rare complications cannot readily be ascertained by a randomized controlled trial. Nevertheless, the obvious value of masks in reducing the dispersion of bacteria from the mouth and nose has been well demonstrated.

A mask is an essential part of aseptic precautions that should be taken for neuraxial needle and catheter insertion. Although undeniably part of "full aseptic precautions" employed by surgeons, a sterile gown is rarely worn for spinal needle placement. For insertion of an epidural catheter, a gown is commonly worn in the United Kingdom, although rarely in the United States. The value of wearing a gown is not supported by evidence, but some postulate that wearing one may be safer than not doing so.

Sterile gown. Although undeniably part of "full aseptic precautions" employed by surgeons, a sterile gown is rarely worn for spinal needle placement. For insertion of an epidural catheter, a gown is commonly worn in the United Kingdom, although rarely in the United States. The value of wearing a gown is not supported by evidence, but some postulate that wearing one may be safer than not doing so.

Sterilizing the skin. Evidence from laboratory and clinical studies show that chlorhexidine in 70% alcohol consistently outperforms povidone-iodine for skin disinfection. The concentration of chlorhexidine used varies from 0.5% to 2%. It is superior in speed of onset and duration of action and is less likely to provoke a skin reaction. Unlike povidone-iodine, it is effective in the presence of blood or pus, it stays sterile in the container, and bacterial resistance to it is unlikely. Alcohol provides the rapid onset, and chlorhexidine provides the longer duration of action.

Concerns have been raised about its neurotoxicity. Both chlorhexidine and iodine have been shown to damage neuronal cells during in vitro experiments. Neither chlorhexidine nor iodine is licensed for skin sterilization before neuraxial block administration. Although there are a few case reports of adhesive arachnoiditis in which chlorhexidine was suspected as a possible cause, the only clinical study performed supports its safety for use before spinal anesthesia. Additionally, the risk for infection usually outweighs that for neurotoxicity, and the superiority of chlorhexidine as an antiseptic should be paramount. It is appropriate, nevertheless, to take precautions, such as using the lowest effective concentration available and not allowing the solution to come into contact with solutions or equipment that will enter the patient’s neuraxis. Use of a single application “swab stick” overcomes this concern; if such an applicator is not used, the aqueous chlorhexidine container must be removed from the immediate area before equipment for neuraxial insertion is deployed. Adequate drying time should be allowed after application of the antiseptic solution to the skin.

Maintaining sterility of the epidural catheter, its contents, and the entry point. The entry point of the epidural catheter clearly needs to be protected from contamination by a suitable dressing. For prolonged analgesia, racemic bupivacaine may be safer than an opioid alone or the pure L-isomers of local anesthetics, which are more likely to permit bacterial growth in the solution. Although it would seem logical, there is no evidence to support or discourage the use of a bacterial filter during a short-term (1 to 2 days) epidural infusion. Prolonged catheterization is best avoided after dural puncture, whether unintentional or deliberate, and when sepsis or immunocompromise is present or suspected.

Vascular Disorders
Ischemic Injury to the Spinal Cord
Ischemic injury to the spinal cord is typically seen in elderly patients after epidural or spinal anesthesia, or after general anesthesia with accompanying hypotension. It is rare in the obstetric population, in whom arterial disease is unusual and hypotension is treated aggressively.

The blood supply to the spinal cord depends on a single anterior spinal artery and bilateral posterior spinal arteries. The arteries arise from the circle of Willis and receive reinforcements during their descent in the spinal canal. The posterior spinal arteries receive regular contributions from radicular arteries, but the single anterior spinal artery, which supplies the anterior two-thirds of the spinal cord, receives only sporadic reinforcement. Anterior spinal artery syndrome, which may result from arterial compression or hypotension, is characterized by a predominantly motor deficit, with or without loss of pain and temperature sensation, but with sparing of vibration and joint sensations, which are transmitted in the posterior columns. The condition has been reported among obstetric patients with particular risk factors (see later discussion). In one report, a parous woman received epidural analgesia with lidocaine, then bupivacaine with epinephrine, followed by 2-chloroprocaine when she required urgent cesarean delivery. Hypotension caused by blood loss from a placenta previa and a ruptured uterus was followed by typical irreversible anterior spinal artery syndrome. The use of epinephrine may have contributed to the adverse outcome in this case.

Chemical Injury
Many substances, primarily drugs, have been injected in error in the neuraxial canal. In a review covering the years 1950 to 2014, 29 case reports of drug errors during obstetric neuraxial procedures were identified. Drugs injected in error included ephedrine, magnesium sulfate, antibiotics, labetalol, ondansetron, and tranexamic acid, among others.

The Epidural Space
The epidural space is remarkably tolerant of foreign and potentially neurotoxic substances because of two protective factors. First, vascular uptake and outward flow via the intervertebral foramina remove a large proportion of solutions deposited in the epidural space. Second, nerve roots within the epidural space are protected by a cuff of dura...
and arachnoid as well as pia mater. Severe neuraxial damage occurs only when these defenses are overwhelmed either by gross overdose or if there is unintentional contamination of the subarachnoid space. There are many case reports of unintentional epidural injection of the wrong substance, including the following:

1. **Vaspressors (ephrine and metaraminol).** Epidural administration resulted in severe hypertension.\(^{166}\)

2. **Potassium chloride.** At least four well-documented cases have been reported.\(^{162,166}\) All patients had profound motor and sensory block with pain or depolarizing spasms. Only one, who received the largest epidural dose (15 mL of 11.25% KCl), remained permanently paraplegic.\(^{168}\)

3. **Other potentially noxious substances.** Administration of an unknown substance, possibly paraldehyde, given in error as an epidural bolus injection during labor, resulted in permanent painful quadriplegia and the largest monetary award for damages in the United Kingdom at that time.\(^{166}\) Additionally, the inadvertent administration of a large volume of chlorohexidine resulted in severe adhesive arachnoiditis.\(^{170}\) Unintentional misconnections of intravenous and epidural infusion systems have led to large-volume epidural infusions of potentially harmful substances, including total parenteral nutrition solutions with a high osmolality\(^{171}\) and ranitidine in a phenol-containing solution.\(^{172}\) Fortunately, in most cases of this type of drug error, neurologic sequelae have not been reported.

With these few exceptions, the epidural space appears to be tolerant of most inadvertent administrations. Nevertheless, the possibility of occult dural puncture means that unintentional administration of a potentially neurotoxic substance (e.g., traces of alcohol, antioxidant, or preservative) may migrate into the subarachnoid space. Vigilance and systems to avoid these errors are mandatory.

### The Subarachnoid Space

The subarachnoid space, with its poorly protected nerve roots and direct communication with intracranial structures, presents a greater risk than the epidural space for adverse outcome after unintentional injection of toxic substances. Intrathecal potassium can be lethal.\(^{173}\) A 2015 review of neuraxial drug administration errors\(^{165}\) identified four reports of intrathecal injection of tranexamic acid (all caused by misidentification of the drug ampule). All four cases were fatal; the patients ultimately died from refractory ventricular tachycardia and fibrillation.

Nerve roots within the subarachnoid space are highly vulnerable to chemical damage, particularly the sacral roots, which are poorly myelinated. Irritant solutions may cause neurotoxicity and arachnoiditis. Neurotoxicity may manifest as **cauda equina syndrome** or, if more extensive, as paraplegia or quadriplegia. For example, in 1937, 14 cases of severe cauda equina syndrome were reported after spinal anesthesia using a solution called “heavy duracaine,” a mixture (in 15% ethanol) of procaine, glycerin, and gladin or gum acacia, which presumably was added in an attempt to prolong the action of procaine.\(^{174}\) In the 1940s and 1950s in the United Kingdom, spinal injection of 10 mL of hypo-osmolar dibucaine was associated with paraplegia, but whether the paraplegia resulted from disturbance of the intrathecal milieu or contamination with phenol is argued.

More recently, there were numerous reports of cauda equina syndrome after intrathecal injection of lidocaine (all types of administration, both intended and unintended, most commonly hyperbaric 5%)\(^{175-177}\) and occasionally after intrathecal administration of other local anesthetics.\(^{170,178}\) None of these cases involved obstetric patients. In all cases, other causes of neurologic deficit (trauma, ischemia, infection, compression, contamination, and adverse positioning) were excluded. An upper safe dose limit for intrathecal lidocaine of 60 mg\(^{176,180}\) has been recommended. More concerning, cauda equina syndrome has also been reported after CSE anesthesia with spinal levobupivacaine for cesarean delivery.\(^{181}\) Postpartum MRI showed contrast enhancement in the cauda equina fibers concordant with arachnoiditis; the patient made a complete recovery after 8 weeks of rehabilitation therapy. A similar presentation has also been reported after CSE anesthesia with hyperbaric bupivacaine for cesarean delivery.\(^{182}\)

The various risk factors for neurotoxic damage are summarized in **Box 31.5**.

#### Conus damage and cauda equina syndrome may appear similar—back pain, leg weakness and numbness, and/or bowel and bladder dysfunction. Although conus damage may involve upper motor neuron signs, these are not always present, and both conditions may have unilateral or bilateral features.\(^{56}\) However, the causation is different. Whereas conus damage may result from ischemia or trauma, cauda equina syndrome typically results from either compression or chemical damage within the lumbar spinal canal.

### Transient Neurologic Syndrome

Transient neurologic syndrome (also called transient radicular irritation) is not associated with any detectable neurologic deficit, but the distribution of pain in the back, buttocks, and thighs mirrors the distribution of nerve damage in cauda equina syndrome sufficiently to support the theory

<table>
<thead>
<tr>
<th><strong>Risk Factors for Chemical Damage to the Cauda Equina</strong></th>
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<tbody>
<tr>
<td>Poor spread of local anesthetic</td>
</tr>
<tr>
<td>Block failure, followed by repeat injection</td>
</tr>
<tr>
<td>Fine-gauge or pencil-point needle</td>
</tr>
<tr>
<td>Microspinal catheter</td>
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<tr>
<td>Continuous infusion</td>
</tr>
<tr>
<td>Hyperbaric solution</td>
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<tr>
<td>Lithotomy position</td>
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<tr>
<td>Unintentional intrathecal injection of a large volume intended for the epidural space</td>
</tr>
<tr>
<td>Incorrect formulation, with unsuitable preservative or antioxidant</td>
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<tr>
<td>Intrathecal injection of lidocaine, particularly 5% (possibly also tetracaine or dibucaine)</td>
</tr>
</tbody>
</table>
that the nerves are indeed irritated by a noxious intrathecal injection. Like cauda equina syndrome, it follows spinal anesthesia, most commonly with lidocaine. Moreover, other risk factors for cauda equina syndrome and transient neurologic syndrome are similar (see Box 31.5), although transient neurologic syndrome may be less dependent on lidocaine dose or the presence of a vasoconstrictor.\textsuperscript{183} Transient neurologic syndrome occurs more than four times more frequently with spinal lidocaine than with other local anesthetics.\textsuperscript{184} It is, however, much more common in surgical than obstetric patients, with a median frequency, according to one review, of 22\%.\textsuperscript{185} Parturients are not exempt from transient neurologic symptoms, with reported frequencies of 0\%,\textsuperscript{185} 4.2\%,\textsuperscript{186} 5.3\%,\textsuperscript{187} and 8.9\%.\textsuperscript{188}

**Arachnoiditis**

Arachnoiditis is a disastrous condition, usually with a delayed onset of permanent quadriplegia. It is extremely rare and has not been detected in any surveys of neurologic sequelae of obstetric neuraxial blockade. Among parturients, chronic adhesive arachnoiditis of chemical origin has arisen after unintentional intrathecal injection of a large dose of 2-chloroprocaine with antioxidant and preservative intended for the epidural space,\textsuperscript{189} while seven cases have been reported after epidural analgesia for childbirth with 2\% lidocaine, probably with preservative.\textsuperscript{190} Six cases were reported among Italian surgical patients after apparently standard epidural anesthesia with bupivacaine and/or mepivacaine, usually with epinephrine.\textsuperscript{191} The local anesthetic agents, however, were obtained from multidose vials containing parabens as preservative, and the glass syringes used for loss-of-resistance identification of the epidural space had been washed in detergent. With earlier publications, it is not always possible to distinguish the cause of arachnoiditis, but it seemed to appear in clusters, suggesting that there may have been shortcomings in anesthetic technique. In a more recent case, a woman suffered severe arachnoiditis after spinal anesthesia for elective cesarean delivery.\textsuperscript{192} Her skin had been cleaned with iodine and then chlorhexidine in alcohol and allowed to dry. It was unclear whether the tray containing antiseptic solutions was removed before the rest of the procedure. Because of pain during attempted insertion of the spinal needle, the skin was infiltrated at least three times with lidocaine before intrathecal bupivacaine was given. Shortly thereafter, she became disturbed and experienced a severe headache, so she was given general anesthesia for the operation. Postpartum she developed obstructive hydrocephalus and extensive adhesive arachnoiditis. The judge determined that, on balance of probabilities, there must have been contact in some way between the chlorhexidine and the local anesthetic solution.

**Vulnerable Patients**

Various conditions may render some women more vulnerable than normal to neurologic injury precipitated by neuraxial anesthesia. The following discussion of conditions is not exhaustive.

**Vertebral Abnormality**

Skeletal abnormalities involving the spine, including congenital anomaly, trauma, and back surgery, can make epidural or spinal needle insertion difficult. Patients with spinal dysraphism are at risk for accidental dural puncture and nerve root damage unless the needle is inserted above the defect (see Chapter 47). Those with tethered cord syndrome are at risk for cord damage if the spinal or epidural needle is inserted at a vertebral level that would normally be expected to be below the conus.\textsuperscript{193} Occasionally, a low-lying conus may be present without any premonitory signs.\textsuperscript{56} Pressure from spinal stenosis or prolapsed intervertebral disc, coupled with a large-volume epidural injection, may result in spinal cord compression and neurologic deficit.\textsuperscript{59}

**Vascular Abnormalities**

Vascular disease and malformation are risk factors for spinal cord ischemia, hematoma, and compression. The major supply to the lumbar enlargement of the spinal cord is the artery of Adamkiewicz, a unilateral structure that typically arises from the lower thoracic or upper lumbar portion of the aorta between T9 and L2. Compression of this single vessel may therefore jeopardize the blood supply to the lower cord in susceptible individuals. In 15\% of individuals, a secondary blood supply to the spinal cord that ascends from the internal iliac arteries\textsuperscript{193} assumes a major role. These ascending arteries lie close to the lumbarosacral trunk and are, in theory, vulnerable to pressure from the fetal head or damage by obstetric instrumentation, thus causing conus ischemia.

A neuraxial arteriovenous malformation is an obvious cause for concern for the obstetric anesthesia provider.\textsuperscript{194} Small arterial feeders from a segmental intercostal artery supply dilated serpiginous epidural veins that may extend over many segments of the spinal canal.\textsuperscript{195} The resulting hemangioma raises the pressure on epidural veins and reduces spinal cord blood flow. Oxygen delivery to local tissues is reduced, and the risk for spinal hematoma or ischemic damage and compression is increased. Pregnancy and epidural analgesia have been known to precipitate paraplegia in previously asymptomatic patients\textsuperscript{196,197}; aortocaval compression, a large blood volume, and a large epidural injection (which may cause severe pain) all increase epidural pressure.

The preanaesthesia examination should include inspection of the back for cutaneous angiomas or macular areas of skin discoloration, which may suggest the presence of an underlying spinal angioma at the same segmental level. Because spinal cord capillary flow is compromised in the drainage area of an arteriovenous malformation, systemic arterial pressure should be kept close to normal throughout the peripartum period, regardless of anesthetic technique.

**Spinal Tumor**

Epidural blockade has been reported to precipitate neurologic symptoms in the presence of previously undiagnosed spinal tumors. Spinal tumors also predispose to spinal hematoma after neuraxial blockade,\textsuperscript{12} and epidural analgesia may precipitate extreme pain.\textsuperscript{198}
Coagulopathy or Anticoagulation
The risk associated with neuraxial procedures in patients with a preexisting coagulopathy or anticoagulation therapy is discussed earlier in this chapter and in Chapters 38 and 44.

Immunocompromise. Most cases of epidural infection that have been reported in surveys involve elderly patients with immunocompromise.13,97 It is advisable to avoid prolonged epidural catheterization in immunocompromised patients, although prophylactic antibiotic therapy is not warranted.

Preexisting neurologic disorder. Patients with hereditary neuropathy with liability to pressure palsy are particularly sensitive to compression neuropathy during the course of labor and delivery.199

It is postulated that patients with preexisting peripheral neuropathies may be more susceptible to nerve injury when exposed to a second insult, the so-called double crush phenomenon.200 To explore whether neuraxial anesthesia represented such an insult, Hebl et al.200 reviewed the medical records of 567 patients with peripheral neuropathies who had spinal or epidural blockade, including 12 obstetric patients. There were two instances of worsening neurologic status, both in elderly diabetic patients. There were no control patients, but clearly, if there is a risk that neuraxial anesthesia will exacerbate a neuropathy, it is very small. The exception may be patients with spinal stenosis. Reports of worsening neurologic status after spinal anesthesia should cause providers to think carefully before initiating neuraxial blockade in patients with known spinal stenosis.201 Fortunately, spinal stenosis is rare in the obstetric population.

Relapse rates in patients with multiple sclerosis are increased in the postpartum period, and the fear is that neuraxial blockade will be blamed (see Chapter 48).202 Epidural rather than spinal anesthesia has traditionally been recommended in patients with multiple sclerosis because the concentration of local anesthetic in the white matter of the spinal cord is less after epidural than after spinal injection, and exposing demyelinated spinal cord to local anesthetics could theoretically worsen disease.203 However, although many providers are reluctant to perform spinal anesthesia in patients with multiple sclerosis, there is no good evidence that it will worsen the neurologic conditions in these patients.204 In fact, the most recent study showed no new or worsening symptoms in 35 patients with multiple sclerosis undergoing a variety of surgical procedures.205 Similarly, no association between worsening multiple sclerosis symptoms and any form of neuraxial anesthesia was found in a study cohort limited to obstetric patients.203 It is clearly important to document neurologic status and to discuss relapse rates with the mother before and after any anesthetic intervention, but patients can be reassured that no type of anesthesia has been shown to increase postpartum relapse risk or negatively influence long-term disease progression.

Diabetes. Diabetic patients are vulnerable to neurologic injury for three reasons. They are susceptible to infection, they may have vascular disease, and they may have a peripheral neuropathy. Diabetic spinal artery syndrome has also been described in diabetic parturients,163 and worsening neuropathy has been observed in diabetic surgical patients.200 Patients with gestational diabetes alone are unlikely to have developed chronic vascular or neurologic sequelae that would place them at high risk for neurologic injury.

RISK MANAGEMENT AND FOLLOW-UP
High-risk women should be referred to the obstetric anesthesia clinic during pregnancy, so that an anesthesia provider can obtain a thorough history, examine the patient, organize consultations or imaging studies as needed, and discuss and plan the anesthetic strategy with the patient and her obstetric providers. The recommended points to explore during the history and physical examination are summarized in Boxes 31.6 and 31.7.

**BOX 31.6 Topics to Explore in the Preanesthesia History**
- Allergies, medications, and use of recreational drugs
- Diabetes or cardiovascular disorder
- Previous spinal or epidural anesthetics (what was the outcome?)
- Preexisting neurologic signs or symptoms (e.g., sciatica, leg weakness)
- Skeletal abnormality or back surgery
- Anticoagulant medication or easy bleeding/bruising
- Possibility of immunocompromise

**BOX 31.7 Preanesthesia Neurologic Examination**
- If there is a question of neurologic disorder, examine the lower limbs:
  - Sensation to pinprick or ice, and vibration sense using a tuning fork
  - Knee and ankle tendon reflexes and Babinski reflex
  - Motor power of hips, knees, and ankles
- Examine the back for:
  - Signs of infection (pustules to be avoided)
  - Nevus suggestive of arteriovenous malformation
  - Midline hair tuft or fat pad, suggesting dysraphism (e.g., spina bifida occulta)
  - Scoliosis
- If the spine looks technically difficult, as in severe scoliosis, is there an easily palpable sacral hiatus as an alternative to the lumbar epidural space?
- Range of motion and maneuvers that might aggravate radicular pain
- Look for signs of bleeding tendency
- Document:
  - The history and physical examination
  - Abnormalities and treatment decisions
  - Differences of opinion
  - The reasons the anesthetic is administered despite a relative contraindication
In addition to minimizing risk by adopting good and safe practices, vigilance must be extended postpartum to detect, diagnose, and treat any disorders that may arise. It is important that those caring for women in the puerperium are taught to look for signs of neurologic pathology and that the women themselves, once home, are taught to recognize symptoms that might be attributable to anesthetic complications, and to contact an anesthesia provider if they experience them.

**Diagnosis of Possible Neurologic Injury**

Through clinical examination coupled with knowledge of basic neuroanatomy outlined in this chapter, it should be possible to distinguish peripheral from central lesions. Preanesthesia history (see Box 31.6) and physical examination (see Box 31.7) may reveal some helpful clues, and any preexisting signs or deficits documented in the record will narrow the search or even provide an immediate answer. The history and physical examination are integral to establishing associations between the complaint and the manifested physical signs and symptoms as well as helping to determine the site of injury and cause.

**KEY POINTS**

- The vast majority of maternal nerve injuries can be attributed to the process of labor and delivery. Some patients may have preexisting maternal disease that predisposes to nerve injury.
- Intrapartum symptoms of nerve compression may go unnoticed, particularly when neuraxial analgesia/ anesthesia is used. Therefore, neurologic status should be regularly assessed, and the patient should be encouraged to change positions.
- Postpartum neurologic deficit is most often transient in nature and likely to be a result of causes other than anesthesia. Nevertheless, there is a tendency to attribute neurologic deficits to neuraxial anesthesia.
- The exact incidence of neurologic complications caused by neuraxial anesthesia is difficult to determine because of wide variations in practice, accuracy of records, and overall low frequency of serious injury.
- Neuraxial anesthesia is more likely to cause central than peripheral nerve injuries, which are more likely to have obstetric causes.
- Proper sterile technique involves wearing a face mask, hand washing, donning sterile gloves, and cleansing the skin with chlorhexidine in alcohol and allowing it to dry before initiating neuraxial blockade.
- Choosing a lower lumbar interspace (L2–L3 or below) for insertion of the spinal needle minimizes the risk for trauma to the spinal cord.
- The risk for meningitis may be decreased by avoiding dural puncture during labor in a patient with systemic infection who has not received appropriate antibiotic treatment.
- The results of the history and physical examination, the rationale behind the chosen anesthetic procedure, and the details of all procedures should be thoroughly documented.
- Rapid diagnosis and treatment are essential to minimizing permanent neurologic sequelae. Compressive intraspinal lesions with neurologic changes require urgent laminectomy within 6 to 12 hours of the onset of symptoms.

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The relationship between a physician and his or her patient is rooted in common moral principles of autonomy, beneficence, nonmaleficence, and justice. Respect for a patient’s autonomy underscores the patient’s right to be involved in decisions that affect her welfare. Throughout history, the role of this relationship during times of decision-making has ranged from paternalism, wherein the physician makes decisions for the patient, to full autonomy, wherein the physician provides the medical facts and the patient makes the decision with little or minimal input from her caregiver. Now, a healthy doctor-patient encounter falls somewhere in between: neither completely autonomous nor devoid of a touch of paternalism. Current focus on consumerism and a rise in patient advocacy have caused the foundation for patient-centered care to involve the creation of a partnership between the patient and her medical team. Meaningful dialogue is at the core of this relationship.

INFORMED CONSENT AND SHARED DECISION-MAKING

Informed Consent

Though conspicuously absent from the Hippocratic Oath, the concept of informed consent is the backbone of the ethical practice of modern medicine in the United States. Its purpose is to facilitate care in a manner that honors the autonomy of the patient while acknowledging the expertise of the provider. As opposed to words signed on a form by the patient, true informed consent is a process whereby a patient and her health care provider engage in information exchange and discuss the patient’s condition and the nature of the proposed treatment, risks, benefits, and alternatives, including lack of treatment. Evidence of this process and the physician’s involvement may be found among consultation notes (paper or electronic), informational aids shared with patients, and signed consent forms acknowledging that the process has occurred.

A solid and meaningful informed consent process includes the following hallmarks:

1. A patient who has capacity and is able to understand the nature and consequences of the proposed therapy/procedure, and of alternatives, including no therapy
2. A physician who tailors his or her disclosure to the patient’s particular competency, comprehension, and need and desire for detail
3. Freedom from external influence (meaning it is given voluntarily)
4. Understanding that consent can be withdrawn at any time before the therapy/procedure has occurred.

Legal precedent establishes what risks are essential to disclose during an informed consent discussion, specifically any
risk that a “reasonable patient would consider reasonable and material to the decision of whether to consent to a procedure offered.” Dornette suggested that significant risk is one that poses a high (greater than or equal to 10%) incidence of a transient complication or a low (0.5% to 1%) incidence of permanent consequences. Broaddus and Chandrasekhar have recommended discussion of risks with high incidence, high morbidity, or adverse fetal effects.

** Shared Decision-Making**

Shared decision-making (SDM) is a process by which the physician expands upon the requirements of informed consent to establish a collaborative decision-making partnership. SDM shifts the focus in the delivery of care away from the disease process itself, and toward the patient and family navigating health care decisions. When ideally executed, SDM establishes a longitudinal partnership to address a series of decisions throughout the healthcare encounter. Recent advocacy efforts have defined patient- and family-centered care as a major component of health care quality and safety, and embraced SDM as a quality indicator.

At a minimum, SDM requires a patient and her clinician. The clinician frames the series of health care decisions that must be made, and for each, explains the integral elements of informed consent; elicits questions, values, and preferences from the patient; and guides the discussion toward a decision that is consistent with the patient’s values and preferences, and current evidence. Conversations may also involve family members, friends, and other members of the care team, according to the preferences of the patient. Clear communication is critical and requires careful attention to both verbal and nonverbal cues. Explanations must avoid language that is overly technical and clinical, but also remain specific enough to meaningfully guide the patient to an understanding of the complex clinical decisions she faces.

Decision aids may be used to facilitate SDM, and are available online, on paper, or on video. Just as cognitive aids can help guide operating room teams through the critical steps of a crisis, decision aids help patients absorb clinical evidence and communicate their preferences. The use of decision aids also helps clinicians set aside their traditional paternalistic role in order to be partners and coaches in the patient-centered process. Explicitly asking “what matters to you?” can help the team align its interventions. When SDM occurs, a properly informed patient can choose between various options (e.g., between different methods of pain management or between regional and general anesthesia) on the basis of her own values and preferences, even when the decision differs from her clinician’s preferred decision.

The process of SDM appears to increase patients’ subsequent participation, compliance, and self-monitoring. A Cochrane review of 105 trials published through 2015 demonstrated that the use of decision aids resulted in increased patient knowledge, more accurate perceptions of treatment risks, better alignment of treatments with patient values, a decreased sense of conflict for patients, and greater patient participation.

According to observations, focus groups, and questionnaires conducted as part of the Making Good Decisions in Collaboration (MAGIC) program in the United Kingdom, even when SDM conversations are imperfect or when there is a lack of complete agreement on best choices, the process of bringing perspectives together improves the likelihood that decisions are more informed and better accepted by patients, families, and staff. Using a “plan-do-study-act” rapid-cycle approach, MAGIC researchers determined that incorporating effective SDM requires a holistic bundle of interventions to drive culture change and to establish a supportive health care delivery system. Younger patients, women, and those with more education are most likely to prefer SDM, according to a study of anesthesia decision-making in Germany that measured preferences using the autonomy preference index (API) and the preference for involvement in care scale (PICS). Based on a Swiss study of 197 clinician-patient dyads, anesthesia clinicians frequently overestimate how much SDM occurs. In this study, Flierler et al. showed that 94% of surgical patients wanted to be involved in preoperative anesthetic management decisions. Patients had a stronger desire for a “balanced” decision-making process, wherein each party would have an equal contribution to decision making (desired by 65% of patients versus 32% of clinicians). Satisfaction decreased when patients perceived insufficient opportunity for involvement, and when anesthesia providers underestimated patient preference for SDM.

Beyond patient compliance and satisfaction, the impact of SDM on clinical outcomes is less clear. A 2015 systematic review of SDM identified a positive relationship between SDM and patient outcomes for 42 of 97 unique outcomes assessed, among 39 studies that met inclusion criteria. The authors noted differences in the way SDM was measured (patient-reported, observer-reported, and clinician-reported). Regardless of measurement methods, 54% of affective-cognitive outcomes were positively associated with the patient’s perception that SDM had occurred; such outcomes included improved patient satisfaction, resolved concerns and anxieties about illness, resolved decisional conflict, improved knowledge, and enhanced confidence in the decision. Thirty-seven percent of the behavioral outcomes studied were improved with the presence of SDM, including greater medication adherence. Twenty-five percent of the clinical outcomes studied were improved when there was SDM, with specific improvements in patient ratings of overall health, quality of life, depressive symptoms, and physiologic measures such as blood pressure. Evidence for improved clinical outcomes appears most robust for patients with chronic conditions that require self-management, such as hypertension. Certainly unsatisfactory communication with patients has been associated with treatment noncompliance in diabetes, asthma, and chronic disease.

**Clinical Capacity versus Legal Capacity**

For the informed consent process to be both meaningful and legal, the adult patient, or guardian for a minor patient, must have capacity to (1) understand the relevant information, (2)
appreciate the situation and its consequences, (3) reason about treatment options, and (4) communicate a choice.\textsuperscript{34} Competence is an alternative term for capacity that is used in some legal jurisdictions. Characteristics such as an individual’s level of education, intellectual ability, preferred conversational language, and cultural background may influence how the individual processes information, but should not impair legal capacity to make an informed decision. It is the provider’s responsibility to make the information accessible and understandable. Translation services are a legal requirement for health care in the United States.\textsuperscript{25}

Even when information is presented at an appropriately straightforward level, there are patients who may not have capacity to truly understand the information being disclosed by the physician. The patient’s capacity may be compromised temporarily or permanently by her condition, medications, or a combination of the two.\textsuperscript{26} By definition, incapacitated patients cannot give informed consent. In emergency situations in which there is no indication to the contrary, physicians can provide necessary care under the presumption that a reasonable person would have consented to the anticipated treatment, which is discussed further later.\textsuperscript{27} In most clinical situations, incapacitated patients require a surrogate decision-maker who can engage with the informed consent process as if he or she were the patient.\textsuperscript{27} Legally, it is necessary both to establish the need for a surrogate decision maker, and to identify the most appropriate person to serve in this role.

In cases of permanent impairment, a court may have already made a determination of legal incapacity of a particular patient,\textsuperscript{28} and invested a surrogate with authority to make medical decisions on behalf of the patient. Such legal determinations are usually made in the course of a petition for guardianship filed on behalf of the allegedly incapacitated individual, supported by evidence of clinical incapacity.\textsuperscript{29} Petitions for guardianship are sometimes made in the course of other legal proceedings, such as a motion to confirm a health care proxy (in which the health care proxy agent must prove the existence of the health care proxy document, executed at the time the patient had clinical and legal capacity to do so, as well as the fact that the patient currently lacks clinical capacity as determined by an appropriately licensed clinician).\textsuperscript{28}

A surrogate decision maker may have been established through legal guardianship, durable power of attorney for health care, a binding living will, or other advance directive. Regardless of how decision-making authority was legally established, the named surrogate generally serves as the final decision maker for all health care decisions for that patient.\textsuperscript{30}

Decision-making authority for patients who lack legal capacity can be revoked only if the patient or some other third party goes back to court and challenges the determination, either because circumstances have changed and the patient has regained clinical capacity, or because the patient or third party appeals the initial determination of the court and has it overturned.\textsuperscript{31}

If a court has not yet made a legal determination that a patient lacks legal capacity (or, is legally incompetent, as termed in some states), then the determination of a patient’s clinical capacity to give informed consent is a professional judgment made by the treating clinician. At a minimum, a judgment of clinical incapacity must be documented in the medical record by a licensed physician (or nurse practitioner in some states) before utilizing a surrogate decision maker.\textsuperscript{31} Some states may have additional requirements detailing how such a determination is recorded and published (e.g., Minnesota requires all conditions and circumstances to be documented within the medical record).\textsuperscript{32} It is often helpful to have a mental health clinician or, in the case of a patient with neurologic issues, a neurologist, weigh in on the determination,\textsuperscript{33} as it will be more authoritative if reviewed in court or challenged in any way by a third party.\textsuperscript{33}

If a surrogate decision maker has not been previously identified, then state statutes may delineate the process to identify the most appropriate surrogate. Some states designate a default list of family members and other persons (in order of priority) who may give consent.\textsuperscript{34} Other states limit surrogate decision makers to health care proxy agents previously designated by the patient (when she had capacity to do so) on a specific health care proxy form (e.g., Massachusetts),\textsuperscript{31} durable powers of attorney for health care (e.g., Ohio),\textsuperscript{35} or a guardian appointed by a court after a petition has been filed and evidence regarding the incapacity presented (e.g., Arizona).\textsuperscript{36} Even in states in which there is no line of kin prescribed by statute, there are generally provisions for how to manage consent in emergency situations (such as using available family, or presuming consent, or both).\textsuperscript{37}

All surrogate decision makers are required to make “substituted judgment” decisions on behalf of the patient (i.e., they are obligated to decide as they believe the patient would, not according to the surrogate’s own preferences).\textsuperscript{38} This may differ from the decision the surrogate decision maker might make for himself or herself. Thus it is imperative to encourage and, where possible, require that the surrogate make decisions from the point of view of the patient: “the surrogate decision maker (judge or guardian) should attempt to determine what the incapacitated person would decide regarding the proposed treatment or procedure were he or she competent.”\textsuperscript{39} When it is impossible to determine what decision the patient would have made (e.g., the patient never had capacity as a result of an intellectual disability that has existed from birth, or the surrogate decision maker did not know the patient well enough to discern what decision she might have made when she was most capacitated) and there is little or no collateral information to help guide the surrogate, it may be necessary to switch to a “best interest” standard rather than a “substituted judgment” one.\textsuperscript{35} Regardless, it is not appropriate for the surrogate to impose his or her own values on the decision-making process. If the surrogate seems to be unable to follow this obligation, it may be necessary to challenge that surrogate’s right to make decisions for the patient, either through institutional processes governed by the policies and procedures of the institution or through the courts.\textsuperscript{38}

It is also important to note that some decisions the surrogate decision maker might want to make, or some clinical
interventions, might require additional court involvement. These kinds of decisions are often referred to as “extraordinary” decisions, and can include major surgery, general anesthesia, use of antipsychotic medications, amputation, sterilization, hysterectomy, chemotherapy, institution of comfort measures only, the removal of life-sustaining treatment, or other change of code status. The necessity to return to court to request specific authority for these “extraordinary” decisions is driven by state law, and so it is important to determine the breadth of a surrogate decision maker’s authority to consent to various treatments and care plans within the laws of the state in which the treatment is being provided. The authority of a health care proxy agent or a durable power of attorney for health care may also have been limited by the patient in the language within the health care proxy or power of attorney document itself, underscoring the importance of consulting these documents as well.

Finally, in states that allow for binding living wills or other advance directives, a surrogate decision maker may be bound to follow the directives within such documents that may impact the decisions being made. Therefore, it is critical to know whether any such documents exist, and if they do, whether they are binding or merely evidentiary as collateral information; some states explicitly do not recognize the binding nature of these advance directives but do hold them to be persuasive in helping determine what the patient would have wanted done in a particular clinical circumstance.

DEcision MAKING IN OBSTETRIC ANESTHESIA

Challenges in Obstetric Anesthesia

There are unique challenges to obtaining consent and engaging in SDM in the labor and delivery setting. These can include the balancing of competing interests of mother and fetus, the interaction with distressed patients, who can be part of a complex family system, and interdisciplinary collaboration during rapidly evolving clinical situations. The anesthesia provider must work quickly to establish trust, elicit preferences for information and decision making, and tailor SDM to the patient and her chosen support team, while coordinating decisions with other members of the interdisciplinary care team. This is no easy task. Misunderstandings, unmet expectations, patient dissatisfaction, and liability are potential outcomes.

Historically, consent for anesthesia was incorporated into consent for surgery, and direct participation of the anesthesia provider in the consent conversation was not mandated. Now most states require separate consent conversations (and forms) for surgery and anesthesia procedures. This separate, focused discussion on the benefits and risks of anesthesia provides a unique opportunity to address misconceptions and discuss the facts. In a survey study of 509 English-speaking parturients (63% white, 23% Hispanic, 14% African-American) admitted to a single institution, Toledo et al. showed that 39% of participants expressed concerns regarding neuraxial anesthesia. These ranged from general misunderstandings about the anesthetic (e.g., epidurals slow down labor or cause cerebral palsy), fears about long-term complications of the procedure, and lack of trust in providers, to concerns regarding fetal effects of medications administered in the epidural space. Ideally, informed consent discussions about anesthesia services begin with an antepartum consultation or with the admission history and physical examination, and address possible delivery scenarios and corresponding anesthetic options in general terms. This conversation opens an ongoing dialogue to support SDM, which continues throughout the hospitalization for delivery.

The informed consent document may be amended as needed, with the additional conversations documented in the medical record. Alternatively, specific informed consent for each anesthetic procedure may be obtained shortly before the intervention. At many institutions, a separate written consent signed by the patient is not obtained before administration of anesthesia. A 1995 survey of obstetric anesthesia providers in the United States and the United Kingdom indicated that 52% of U.S. anesthesia providers (but only 15% of UK anesthesia providers) obtained a separate written consent for epidural analgesia during labor. In a survey performed in the United Kingdom in 2007, only 7% of obstetric units routinely obtained written informed consent for epidural analgesia during labor. In a 2004 survey from Australia and New Zealand, less than 20% of anesthesia providers obtained written consent before initiating neuraxial labor analgesia. Some health care facilities and organizations have begun using a single consent form for obstetric and anesthetic procedures that may be desired or necessary during labor and delivery. The process of reviewing and signing the consent form provides a specific opportunity for the patient to ask questions. It also provides additional documentation that consent was obtained. The combined form has the additional advantage of not requiring the patient to sign multiple medicolegal documents. Although a signed consent form is not necessary, at a minimum, it should be standard practice for anesthesia providers to document that a discussion of risks and benefits of labor analgesia took place and that verbal informed consent was obtained before administration of anesthesia.

Many patients have strong opinions about their analgesic options, based on information gathered from their obstetric provider, websites, books, magazines, classes, and friends and family. The nature of the consent process will differ depending on the level of prior knowledge, health literacy, decision-making preferences, and clinical circumstances, but a paternalistic approach, grounded on the premise that patients cannot have the same clinical knowledge of the clinicians, can no longer be justified.

Special Situations in Obstetric Anesthesia

Patient Who Is in Pain

A study of women’s preferences for labor analgesia counseling revealed that most women prefer to learn about the options for labor analgesia from their obstetric care providers. This is not surprising given the trust that exists within the bounds
of an established relationship. However, a discussion of anesthetic options for the first time frequently takes place upon arrival to the labor and delivery unit. A survey of Canadian women revealed their strong preference to be informed of all possible complications of epidural anesthesia, especially serious ones, even when the risk was quite low. This study and others have emphasized the parturients’ desire to have these discussions as early in labor as possible.

Unfortunately, the anesthesia provider often first encounters the patient when she is in severe pain. Many have questioned the ethics and truly “informed” nature of consent when it is obtained from a patient who is experiencing severe pain (e.g., during labor). Although the provider may tailor the consent process to the circumstances, the presence of maternal pain and distress does not obviate the need for a frank discussion of the risks associated with anesthesia as well as the alternatives. A 2005 study evaluated whether labor pain and neuraxial fentanyl administration affect the intellectual function of laboring women. The Mini-Mental Status Examination (MMSE) was used to evaluate orientation, registration, attention, calculation, recall, and language both before and after initiation of analgesia in 41 laboring women. There was no difference in MMSE scores before and after administration of neuraxial analgesia.

Other investigations have shown that women in labor demonstrate not only adequate understanding of options but also good recall of the discussions afterward. Gerancher et al. performed a study to evaluate the ability of laboring women to recall the details of a pre-anesthesia discussion and to determine whether verbal consent alone or a combination of verbal and written consent provided better recall. The investigators randomly assigned 113 laboring women to one of two groups, those from whom verbal consent alone was obtained and those from whom verbal consent plus written consent was obtained. The verbal-plus-written consent group had significantly higher median (range) recall scores (90 [80 to 100]) than the verbal-only group (80 [70 to 90]). Only two women (both in the verbal group) believed that they were unable (because of either inadequate information or situational stress) to give valid consent. The investigators concluded that “the high recall scores achieved by the women in both groups suggest that the majority of laboring women are at least as mentally and physically competent to give consent as preoperative cardiac patients.”

Clark et al. randomly assigned hospital inpatients to receive either a verbal anesthesia discussion alone or both a verbal anesthesia discussion and a preprinted anesthesia consent form. In contrast with the results of Gerancher et al., these investigators found that “patients remembered less of the information concerning anesthetic risks discussed during the preoperative interview if they received a preprinted, risk-specific anesthesia consent form at the beginning of the interview.” They speculated that “patients who see an anesthesia consent form for the first time during the preoperative interview may try to read and listen simultaneously, and with their attention divided, may remember less of the preoperative discussion.”

Thus, it seems reasonable for the patient to provide her signature as evidence of her consent, if her condition permits. This consent can be distinguished on a separate anesthesia consent form or as part of a consent form for all obstetric care, including anesthesia. In the event that a consent form is not available, it should be standard practice for the anesthesia provider to explain the intended procedure, risks, and alternatives, and to document this discussion in the medical record.

**Patient Who Has Received Sedatives**

Though it may be tempting to assume that a patient who has received a sedative or opioid medication is incapable of providing informed consent, this may not be the case. Judicious use of sedatives to alleviate significant anxiety or opioids to treat severe pain can enhance the patient’s ability to interact and participate in SDM. Nevertheless, it is inappropriate to use sedatives to manipulate the patient’s decision or to eliminate her decision-making capacity. Use of drugs with amnesic potential merit thoughtful consideration as the patient may not recall the informed consent process afterward. However, even when a patient cannot recall the details of the informed consent discussion, that does not necessarily mean that she did not, at the time consent was obtained, understand the risks, benefits, and alternatives presented.

Patient satisfaction has been used as a surrogate measure of the adequacy or effectiveness of the consent conversation. Pattee et al. sought to quantify the influence of factors including pain, anxiety, opioid premedication, and patient education on patient satisfaction with the consent process. In this survey study of 60 patients, queried up to 2 months after delivery, the level of patient satisfaction was high (8.1/10) and not affected by any of these complicating factors ($r = 0.013$ for pain and $r = 0.048$ for anxiety). Subsequently, a study conducted by Gerancher et al. demonstrated no difference in patient satisfaction with the consent process, whether or not the patient had received opioid premedication before obtaining consent.

**Patient with a Birth Plan**

The birth plan is a document wherein mothers-to-be state their wishes and preferences for the management of certain aspects of their labor and delivery course. The practice of using a formal, written birth plan dates back to the 1970s. Its intended purpose was to enhance communication between the expectant mother and health care provider. The premise was that patient participation in childbirth decision making would result in a positive labor and delivery experience for the mother. To investigate the association between presence of a birth plan, mode of delivery, obstetric intervention, and patient satisfaction, Afshar et al. prospectively studied a cohort of 300 women in a tertiary care center. Compared with the group that did not have a birth plan ($n = 157$), the 143 women with a birth plan experienced fewer intrapartum obstetric interventions such as oxytocin augmentation (61% versus 78%, $P < .01$) and artificial rupture of membranes (15% versus 29%, $P < .01$). There was no difference in the cesarean delivery rate between the groups.
Interestingly, parturients with a birth plan reported less satisfaction with their birth experience compared with parturients without one. A possible explanation for this finding may be that a departure from the expected plan may be met with disappointment, irrespective of the outcome.62

Although birth plan documents vary on the level of detail, a typical birth plan may include the woman's preference for pain management during labor.60 In the previously mentioned study by Afshar et al.,28 there was no difference between groups regarding use of intravenous analgesia; however, women with a birth plan were less likely to utilize epidural analgesia.

The birth plan is a written expression of the patient’s wishes, not a binding contract that prevents her from receiving epidural analgesia at a later time. As such, it provides a good starting point for a thoughtful discussion that dispels myths, addresses anxieties, and educates the patient on the evidence-based risks and benefits of analgesia and anesthesia for labor and delivery. As a birth plan is typically drafted before admission to the labor and delivery unit, it is possible that a patient may change her mind regarding her wishes. It reflects her best assessment of the balance between risks and benefits before the onset of labor. As the pain of labor escalates, the benefit of epidural analgesia becomes increasingly salient, and she may shift her rational calculus accordingly.61 Although she may have specifically stipulated, “I don’t want any kind of anesthesia offered to me during labor,” she may change her mind in the course of labor, and request and receive any anesthetic or analgesic service. This highlights an important aspect of informed consent: it must be contemporaneous with the actual situation. It is incumbent on health care providers to read this document and use it as a tool to facilitate communication during SDM. As with all decisions regarding informed consent, a surrogate decision maker can use substituted judgment, as described earlier in this chapter, to modify the birth plan for an incapacitated patient, recognizing that pain alone is not grounds to question a patient’s capacity to make her own decisions. In such a case, it would be important for the clinicians involved in the patient’s care to question a surrogate carefully regarding significant alterations, because the document may be the best evidence of the patient’s wishes.

Emergency Procedures

Generally, health care professionals should provide emergency treatment under a “presumed consent” model, meaning that, absent any collateral information to the contrary, a patient should receive care in her “best interest” in emergent situations even if such a patient cannot provide informed consent.63 However, in many jurisdictions, family or the decision-making surrogate can refuse such care on behalf of the incapacitated patient if they can genuinely state that they know the patient would refuse such care were the patient able to consent herself.53 When in doubt as to the accuracy of the family’s refusal, it may be necessary to preserve the best interest of the patient in the face of uncertainty as to the patient’s wishes. If the health care providers’ treatment was authorized under a medical emergency, the providers should carefully document their determination.62 The documentation in the patient’s medical record should contain a description of the patient’s presenting condition, its immediacy, its magnitude, and the nature of the immediate threat or harm to the patient.63 It is advisable for at least two health care providers to document this information, because the documentation would support their actions if a lack-of-informed-consent lawsuit were filed. The provider should provide only the care that is reasonable for the patient’s condition.

Vulnerable Populations

Consenting Minors

Traditionally, minors have not been allowed to provide informed consent, based on concerns that they may lack the experience or capacity to inform judgments related to health care decisions.64 Consequently, in most states, a minor child needs a parent or guardian to make legal decisions, including informed consent for treatment.64 Exceptions to this rule are based on both statutory laws (i.e., by the state legislature)65 and case law (i.e., decided by judges in court decisions, which then become binding precedent in the jurisdiction represented by the court).66 In some states, pregnant women younger than 18 years of age are considered “emancipated minors” and may consent for procedures related to their prenatal, intrapartum, and postpartum care, as well as interventions that benefit the fetus.67,68 Regulations pertaining to consent from pregnant emancipated minors vary among the individual states.67 Minor and parental rights in Massachusetts are presented in Tables 32.1 and 32.2.

The following are the most common situations.

**Mature Minor Rule.** Sometimes statutory, sometimes based on case law, the Mature Minor Rule generally requires a finding that (1) the minor in question is mature enough to weigh the risks and benefits of a proposed treatment and is able to make a true informed consent decision, and (2) there is good reason not to involve the parents or guardians.69 This rule is generally applied to adolescent minors, and when it is applied, the general rule that allows parents or guardians to control the minor’s health care decisions is suspended for that course of treatment.69 Access to information contained in the medical record by parents or guardians should be restricted for all Mature Minors, because there may be aspects of the record that contain information regarding treatment that was provided without the parents’ or guardians’ consent; the medical records department should have the opportunity to review such records and redact such information from the record before releasing it to the parents or guardians.69 It is important, therefore, that any medical record relating to treatment provided under the Mature Minor Rule be flagged or otherwise indicated as such.71 In some states, only certain health care decisions can be made by a Mature Minor, and others must include the parent or guardian.71

**Minor who is pregnant or believes herself to be pregnant.** Many states allow minors who are pregnant, or in some states believe themselves to be pregnant, to make their own health care decisions, regardless of age.71 Sometimes those
TABLE 32.1  Minors’ Rights in Massachusetts*

<table>
<thead>
<tr>
<th>If Patient Is Younger Than 18 and...</th>
<th>Who Consents to Medical Treatment (and Pays)?</th>
<th>Access to PHI?</th>
<th>Restrictions</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No special circumstances (but see Mature Minor doctrine)69</td>
<td>Parent or guardian</td>
<td>Parent or guardian</td>
<td>Parent or guardian cannot consent to sterilization; court order required</td>
<td>Abortion requires consent of one parent or guardian</td>
</tr>
<tr>
<td>Married, widowed, or divorced</td>
<td>Minor</td>
<td>Minor only</td>
<td>None</td>
<td>Minor can consent to abortion or sterilization</td>
</tr>
<tr>
<td>Emergency, parent/guardian not available</td>
<td>Treat without consent, try to reach parent as soon as possible</td>
<td>Parent or guardian</td>
<td>Only emergency treatment may be provided</td>
<td></td>
</tr>
<tr>
<td>Living apart from parent or guardian and managing own finances</td>
<td>Minor</td>
<td>Minor only</td>
<td>Cannot consent to abortion or sterilization</td>
<td></td>
</tr>
<tr>
<td>Pregnant or believes herself to be pregnant</td>
<td>Minor</td>
<td>Minor only</td>
<td>Cannot consent to abortion or sterilization</td>
<td></td>
</tr>
<tr>
<td>A member of any of the armed services</td>
<td>Minor</td>
<td>Minor only</td>
<td>Cannot consent to abortion or sterilization</td>
<td></td>
</tr>
<tr>
<td>Seeking care for any disease defined as dangerous to public health</td>
<td>Minor</td>
<td>Minor only</td>
<td>Only diagnosis or treatment of the disease may be provided</td>
<td></td>
</tr>
<tr>
<td>A parent of a child</td>
<td>Minor</td>
<td>Minor only</td>
<td>Cannot consent to abortion or sterilization</td>
<td>Minor can also consent to treatment of the child</td>
</tr>
<tr>
<td>12 years or older, seeking treatment for drug dependency</td>
<td>Minor</td>
<td>Minor only</td>
<td>Treatment of drug dependency only; two physicians must concur in diagnosis</td>
<td></td>
</tr>
<tr>
<td>Treated for a drug or alcohol overdose</td>
<td>Parent or guardian; N/A if emergent situation</td>
<td>Parent or guardian; but if seeking treatment see above</td>
<td>Parents must be notified of overdose regardless of Mature Minor doctrine/emancipation</td>
<td>See M.G.L. ch. 112, § 12E1/2</td>
</tr>
</tbody>
</table>

*Table is representative of Massachusetts laws and regulations only.

decisions are limited to decisions related to the pregnancy, and other times the statute “medically emancipates” such minors and gives them authority to consent to any and all health care on their own.72 In contrast, procedures to end pregnancy or to provide permanent sterilization receive special legal treatment in many states, and require more traditional involvement of parents, guardians, and the courts, on behalf of minor patients, in the informed consent process.76

Abortion. A number of state legislatures have established laws that effectively restrict access to termination services for minor patients. Among a panel of statutory requirements, it is common to specifically require parental or guardian authorization and informed consent for abortion in adolescents. In some states, a judicial bypass exists to allow a minor to petition a court for the authority without involving her parents/guardians.76,77 This approach may be particularly important in cases of incest and sexual abuse involving a parent, guardian, or other family member.

Some procedures, most notably a procedure the federal government refers to as “Partial Birth Abortion,” are banned outright even if the provider and the patient agree that it is the safest care under the clinical circumstances presented.79 The Supreme Court has thus far continued to maintain that the right to abortion “previability” generally cannot be
you have a reasonable basis to think it is inadvisable (i.e., domestic violence situation).

Factors that confer a protective factor for perinatal outcomes.82–84 Factors that may protect both the mother and the newborn from poor obstetric and perinatal outcomes include recent arrival, limited access to health care, limited language proficiency, and poor support network.85

Infringed by states, but the determination of when viability is reached continues to be an issue of legal debate.78

**Sterilization.** Although adult patients with capacity can generally consent to their own sterilization procedures, most jurisdictions limit minors and incapacitated patients, relying on surrogate decision makers to make such decisions on behalf of the patient.79 As with abortion, the adolescent parturient may petition a court for the ability to consent to sterilization, without the involvement of her parent or guardian.79

**Language Considerations**

In 2014, more than 900,000 births in the United States were to immigrant mothers, a threefold increase since 1970.80 This rise in cultural diversity challenges the ability of health care providers and institutions to appropriately care for the migrant obstetric patient. Although some studies have shown poorer obstetric and perinatal outcomes in migrant versus native women,81 others have found that immigrant status confers a protective factor for perinatal outcomes.82–84 Factors associated with significant risk for poor maternal outcomes include recent arrival, limited access to health care, limited language proficiency, and poor support network.85

The Institute of Medicine describes patient-centered care as care that honors the individual patient and respects his or her choices, culture, ethnicity, social context, values, and informational needs.12 Effective communication between patients and care providers is a building block of patient-centered care and a cornerstone of patient safety and optimal health care delivery. Using interviews of pregnant women of Mexican origin to explore their expectations of health care providers, Baxley and Ibitayo86 noted that patients “wanted to hear everything, hear it directly and have it presented to them as if from a friend.” For these study participants, faith was a major component of their culture and a strong influence on their perceptions of health outcomes.86 Similarly, newly arrived Somali couples expressed the importance of their beliefs and cultural values during perinatal interviews.87 In their culture, having many children is considered desirable. Thus a high value is placed on a vaginal delivery; a cesarean delivery can limit the number of children and, in their culture, cesarean delivery is also believed to be associated with death.88

The language gap between a patient and her health care provider is commonly bridged by the use of an interpreter. Use of bilingual family members, especially children, is discouraged as their unfamiliarity with medical terminology and emotional ties to the patient may hinder the accurate transfer of information from patient to doctor and vice versa.89,90 Suboptimal interpretation not only impairs information exchange, but can undermine the SDM and informed consent processes.91 However, use of professional medical interpreters is a resource-intensive tool not always available for all languages or after regular work hours.

In addition to language discordance, low levels of health literacy can impair the patient’s ability to understand the information provided by her health care provider. Unlike functional literacy, which refers to an individual’s operational capacity to function in daily life through use of basic reading, writing, and computational skills,92 functional health literacy demands the use of more complex language skills as well

<table>
<thead>
<tr>
<th>TABLE 32.2 Parental Rights in Massachusetts&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child’s Parents Are:</strong></td>
</tr>
<tr>
<td>Married&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unmarried&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Legally Separated</td>
</tr>
<tr>
<td>Divorced</td>
</tr>
</tbody>
</table>

<sup>a</sup>Table is representative of Massachusetts laws and regulations only.

<sup>b</sup>If the child’s parents are separated (without a court document recognizing separation), treat the situation as if the parents are married UNLESS you have a reasonable basis to think it is inadvisable (i.e., domestic violence situation).

<sup>c</sup>If the child is born to unmarried parents, the father has only the privileges the mother gives him. If the father is not happy with the privileges provided by the mother, he is free to go to court to obtain a clarification of his legal rights with respect to the child.
as the ability to process numerical information.93 Basically, health literacy is defined as the “degree to which individuals have capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”94 In 2004, the Institute of Medicine reported that “nearly half of all American adults—90 million people—have difficulty understanding and using health information, and there is a higher rate of hospitalization and use of emergency services among patients with limited health literacy.”95 Low health literacy also affects immigrants with limited English proficiency.95 In a prospective, matched cohort design investigation, Brice et al.96 compared the health literacy level of adult English-speaking patients to Spanish-speaking patients presenting to an emergency department in suburban North Carolina. The Test of Functional Health Literacy in Adults (TOFHLA) was administered to both groups. The results revealed that 74% of Spanish-speaking participants possess less-than-appropriate functional health literacy compared with 7% of the English-speaking cohort.97 In a recent survey of medically trained interpreters and anesthesia providers at a major teaching hospital in Boston (U.S.), 43% of interpreters felt that “less than half of their patient population was sufficiently literate to read and consent in their native language.”98 Unfortunately, published materials available for public education in anesthesia are written at a level higher than what the public can understand. In a review of educational material downloaded from 24 national anesthesia society websites, Govender et al.99 discovered all material was above an eighth-grade level, which is too complex for lay comprehension.

Educational aids such as written material (brochures, illustrations, models) and video-assisted patient education can be invaluable in the transfer of information to patients, particularly if the material is presented in the patient’s own language with minimal use of medical jargon.100–102 Additionally, use of educational videos has been shown to decrease patient anxiety and increase patient satisfaction with medical care.102 Obstetric patients frequently need to make complex health care decisions in unfamiliar surroundings when their health care providers are burdened by time constraints. By standardizing the information presented on specific topics, supplemental educational aids can help minimize misleading information, censoring of information, or devaluing of information.

Cultural Considerations
Patient autonomy is an important principle to uphold in decision-making. In many cultures and social contexts, this autonomy is preserved even when power to make medical decisions is passed on to another individual. For example, a competent patient may choose to allow a spouse or other family member to make “first-order” decisions regarding medical care. If her decision to defer to the judgment of another person is truly free and voluntary, then this “second-order” decision is authentic and autonomous.103 Although justified in principle, this can be difficult to carry out in practice. One can imagine a situation in which a nulliparous woman has decided with her spouse that she does not want epidural analgesia for labor pain management and that medical management decisions have been willingly relinquished to her partner. If the patient changes her mind once labor pains have started but the surrogate, with all good intentions, insists on the predetermined plan, the patient’s wishes are no longer being properly represented. In this setting, the will of the patient needs to be confirmed and takes priority over predetermined proxy arrangements.104 Strong-willed family members, intending to advocate for their loved ones, may seem angry and even threatening. Often, they respond to patience and empathy, nonconfrontational communication, and input from the laboring patient and other parties.

Religious or Culturally Based Objections to Care
When a provider is aware that a patient has expressed a religious or culturally-based objection to certain aspects of medical care (e.g., blood transfusion for a Jehovah's Witness), that portion of the care should not be provided even in an emergency context.105 If a blood transfusion would be required to save the life of an individual who has expressed objection to blood transfusion, absent any collateral information to the contrary, it is appropriate to withhold that aspect of care.105 Detailed lists of blood products and blood conservation therapies are available106,107 to facilitate SDM and to clarify the specific interventions individual patients will and will not accept. Certain therapies (e.g., cell salvage with a continuous circuit) may be acceptable to some individuals.108 It is also helpful to explicitly consider likely clinical scenarios in advance. Such patients can change their minds about receiving life-saving interventions, but the presumption is that an incapacitated patient with a clear objection to the provision of some or all care, should not have that right overridden just because he or she does not have capacity in an emergency situation.105

Although an adult patient can refuse some or all care on his or her own behalf, a parental refusal of care for their child is more complex. The courts generally recognize that the state’s interest in protecting the life and well-being of a child outweighs the parents’ right to make decisions for the child, when that decision could result in a significantly poor outcome.109 In some jurisdictions, the default is that the parents retain such rights and providers must go to court to overcome that presumption.110 In other jurisdictions, providers faced with a similar situation have the right to provide care to the child over the objection of the parents, and the parents or guardians must go to court to attempt to obtain an injunction to bar the provision of such care.

Gestational Carriers or Surrogates
A gestational carrier is a pregnant woman whose fetus was created from a donated ovum (rather than her own) on behalf of another family.111 In jurisdictions in which such an arrangement is legal, the gestational carrier is considered the patient at all times throughout the pregnancy, regardless of the level of involvement of the intended parents during such
time. Although gestational carriers may, and likely do, have a contract with the intended parents that specifies the gestational carrier’s obligations, such as not having an abortion, any agreement is only applicable to the gestational carrier and the intended parents. The providers are not parties to such agreements, and are not bound to any provisions contained therein. If a gestational carrier violates a provision, the intended parents may have a contractual recourse available to them against the gestational carrier, but this has nothing to do with the providers’ obligation to treat the gestational carrier as the patient and allow the gestational carrier to remain the sole decision maker. Health care providers should always remember that the gestational carrier is their patient, and it is their obligation to only provide care to which the gestational carrier consents, irrespective of the intended parents’ position.

This arrangement is distinguished from a traditional surrogate, who carries a fetus originating from her own ovum on behalf of another family. In these situations, the surrogate is a legal parent to the child even after birth, until a traditional adoption has taken place.

Conflicts Arising out of the Maternal-Fetal Relationship

Almost all pregnant women consider the welfare of their unborn child to be of utmost importance. However, there may be situations in which maternal and fetal interests appear divergent or, potentially, in conflict. One example is when a pregnant woman refuses a diagnostic procedure, a medical treatment, or a surgical procedure that is intended to enhance or preserve fetal well-being. Another may arise when the pregnant woman’s behavior is considered harmful to the fetus. Physicians who care for pregnant women may confront challenging dilemmas when their patients reject medical recommendations, use illegal drugs, or engage in other behaviors that may adversely affect fetal well-being.

Appellate court decisions typically have held that a pregnant woman’s decisions regarding medical treatment take precedence over the presumed fetal consequences of the maternal decisions. One case illustrates the evolution of this judicial approach. Angela Carder was a 26-year-old married woman with cancer since 13 years of age. At 25 weeks’ gestation, she was admitted to George Washington University Hospital, where a massive tumor was found in her lung. Her physicians determined that she would die within a short time, and she expressed her wish to be kept comfortable during her dying process to which her husband, her mother, and her physician agreed. Ultimately, the hospital sought judicial review of this course of action. The hospital asked whether a surgical delivery should be authorized to save the potentially viable fetus. The situation was presented to a judge, who authorized an emergency cesarean delivery without first ascertaining (using the principle of substituted judgment) the patient’s wishes. A cesarean delivery was performed without full consideration of the patient’s wishes, and the infant died approximately 2 hours after delivery while the mother died 2 days later. This case spawned extensive debate as to whether coercive intervention to protect the fetus is ever morally and legally justifiable. With the assistance of the American Civil Liberties Union, Angela’s parents sued the hospital, 2 administrators, and 33 physicians for claims including battery, false imprisonment, discrimination, and medical malpractice. These civil lawsuits were settled after several years of litigation, and as part of this process, the hospital adopted a written policy concerning decision-making for pregnant patients. The court later reversed its initial decision authorizing the surgical delivery and ultimately issued an opinion setting forth the legal principles that should govern the doctor-parturient relationship. The court stated: “In virtually all cases the question of what is to be done is to be decided by the patient—the pregnant woman—on behalf of herself and the fetus. If the patient is incompetent...her decision must be ascertained through substituted judgment.” In affirming that the patient’s wishes, once ascertained, must be followed in “virtually all cases” unless there are “truly extraordinary or compelling reasons to override them,” the court did not foreclose the possibility of exceptions to this rule.

Many contemporary medical ethicists agree that a pregnant woman’s informed refusal of medical intervention should prevail as long as she has capacity to make medical decisions. In the case of an incapacitated patient, a legal surrogate decision maker has the right to speak for the patient in refusing such medical intervention. Newer legislation and some high-profile legal cases (some involving criminal prosecution) have challenged this notion and have raised the question of whether there are circumstances in which a pregnant woman’s rights to informed consent and bodily integrity may be subordinated to protect her unborn child. For example, in 2004, Melissa Rowland was charged by the state of Utah with murder for the stillbirth of one twin because she initially refused cesarean delivery, even though she later accepted delivery by cesarean and her second twin survived. She pleaded guilty to child endangerment in order to avoid more serious charges.

Other cases have focused on prosecuting pregnant women with substance use disorders. In 1991, Regina McKnight, who was pregnant at the time, began using cocaine after her mother’s death. She had a stillbirth, and the state of South Carolina charged her with homicide by child abuse, claiming that her drug use caused the stillbirth. She became the first South Carolina woman to be convicted of this crime, for what both the defense and prosecution agreed was an unintentional stillbirth, and she spent nearly 8 years in jail. In 2008, the South Carolina Supreme Court unanimously reversed her conviction on the grounds that she did not receive a fair trial, primarily on the basis that her attorney failed to challenge the science that was used to convict her.

In a similar instance, Shekelia Ward delivered an infant on January 8, 2008, where both she and her newborn tested positive for cocaine during their hospital stay, and the facility reported it to authorities for possible child abuse. The following day she was arrested, imprisoned, and charged with a felony—chemical endangerment of a child. The state statute
at issue was passed by the Alabama legislature in 2006, for the purpose of prosecuting parents who exposed children to the toxins associated with methamphetamine production; the statute did not mention pregnant women or their fetuses. As a result, the Southern Poverty Law Center, along with 25 medical, public health, and health advocacy groups, filed an *amicus curiae* brief against the prosecution of pregnant women in Covington County, Alabama.

These statutes reflect the concept that a fetus can and should be treated as separable and legally, philosophically, and essentially independent from the mother. The refinement of techniques of intrauterine fetal imaging, testing, and treatment prompted the view that fetuses are independent patients who can be treated directly while *in utero*. The prominence of some ethical models with assertions that physicians have moral obligations to fetal patients separate from their obligations to pregnant women also contributed to these developments. Finally, a number of laws (primarily passed at the state level) were enacted with the aim of defining fetal rights separate from a pregnant woman’s rights. In 2011, the ACOG Committee on Health Care for Underserved Women issued a statement addressing the role of the obstetrician in reporting substance use. This document described a “disturbing trend” in legal actions and policies that criminalized drug use during pregnancy when thought to be associated with fetal harm or adverse outcomes. Noting that women seeking obstetric care should not be exposed to criminal or civil penalties and that few treatment facilities are available to effectively treat drug abuse in pregnancy, the ACOG concluded that the use of the legal system to address alcohol and substance use issues is inappropriate and urged that policy makers and legislators instead focus on strategies to address the needs of pregnant women with addictions.

The American Medical Association (AMA) has taken a similar position, stating that (1) drug addiction is a disease amenable to treatment, rather than criminal activity; and (2) there is a pressing need for maternal drug treatment and supportive child protective services. Any legislation that criminalizes maternal drug addiction or requires physicians to function as agents of law enforcement will be opposed by the AMA.

During the past two decades, practitioners have only infrequently resorted to court-ordered interventions against the wishes of the pregnant woman. In overturning the previous court’s decision in the Angela Carder case (mentioned earlier), the Washington, DC, Court of Appeals noted that if a pregnant woman makes an informed decision, “her wishes will control in virtually all cases.” The court added, “We do not foreclose the possibility that a conflicting state interest may be so compelling that the patient’s wishes must yield, but we anticipate that such cases will be extremely rare and truly exceptional.”

There has been an evolution in the approach of the ACOG and medical ethicists on the best means to address maternal-fetal conflict. A 1999 ACOG opinion offered the following three options: (1) respect the patient’s autonomy and not proceed with the recommended intervention regardless of the consequences, (2) offer the patient the option of obtaining medical care from another individual before conditions become emergent, and (3) request that the court issue an order to permit the recommended treatment. In 2004, the ACOG addressed the situation in which health care providers may consider this last option (i.e., legal intervention against a pregnant woman). Specifically, the ACOG stated that the following criteria should be satisfied: (1) “there is a high probability of serious harm to the fetus in respecting the patient’s decision”; (2) “there is a high probability that the recommended treatment will prevent or substantially reduce harm to the fetus”; (3) “there are no comparably effective, less intrusive options to prevent harm to the fetus”; and (4) “there is a high probability that the recommended treatment [will] also benefit the pregnant woman or that the risks to the pregnant woman are relatively small.” The most recent 2016 ACOG recommendations emphasize the key principles of SDM and discourage external coercion from the court system.

The ACOG opinions assume the presence of competency and informed consent. Thus, if a pregnant patient is believed to be incompetent and incapable of providing informed consent, the health care providers may not be required to respect the patient’s refusal of care. Moreover, if the patient is deemed incompetent and/or a medical emergency exists, care may be provided with consent from a legally authorized surrogate decision maker or as an “emergency exception.” Importantly, a legally authorized surrogate decision maker may refuse care on behalf of the patient if he or she believes that he or she is making the decision the patient would make for herself if she were capable to do so.

In summary, two approaches are available to the practitioner dealing with maternal-fetal conflict. One approach is to honor a competent pregnant patient’s refusal of care. The other approach (which appears least favored by many medical ethicists and the ACOG) is to seek judicial authorization of treatment, which overrides a competent pregnant woman’s refusal of care.

In honoring a competent patient’s desires to refuse treatment, the health care providers should carefully document the woman’s competency and ability to provide informed consent. Every attempt should be made to counsel her to follow the treatment recommendations. Documentation should include how, when, and what information was provided to the patient and family regarding the significant risks to both the patient and fetus if the recommended care were not provided. If time permits, the treatment options should be reevaluated with the patient at frequent intervals, with detailed documentation in the patient’s medical record. Additionally, legal counsel for the health care providers and medical facility may wish to prepare an “assumption of risk” form for the patient (and, if possible, her partner) to sign. This form represents another level of documentation (beyond the detailed notes in the patient’s medical record) demonstrating that the patient was fully informed about the risks associated with her refusal of treatment and that she...
voluntarily elected to accept those risks. However, such a release signed by the parents may not protect the physician and medical facility from a claim brought on behalf of the child who suffers an injury as a result of nonintervention. In some cases, the court has found that physicians have a duty to provide care to the unborn child.130

Patient “assumption of risk” does not release a health care provider from his or her obligations to provide other treatment within the accepted standard of care. For example, in Shorter v. Drury,131 a case that involved a patient’s refusal of blood transfusion because of religious preferences, the court upheld the validity of an “assumption of risk” (i.e., release) that relieved the physician from liability for compliance with the patient’s refusal of blood transfusion before and after surgery but nonetheless held him partially responsible for her death because of his negligent performance of the surgery.132

Before deciding whether to seek court review, health care providers should identify what issue they want the court to resolve. Is it whether the pregnant woman is competent? Is it whether there is a superior state interest in preserving the life of the viable fetus and/or the pregnant woman despite the (competent) patient’s desire to refuse recommended care? Health care providers also should consider whether a court is the proper forum for resolving these issues or whether another forum (e.g., an institutional ethics committee) may be a better choice. If a patient care dilemma is put before a judge, the health care providers give up a large amount of control over the disposition of the case. Nonetheless, in the absence of a legally authorized decision maker, if a patient’s competency is at issue and there is adequate time, court review to settle the patient’s competency may be beneficial and is supported by both the ACOG guidelines112 and the Angela Carder decision, discussed earlier.126 It is beneficial to obtain authorization for the provision of medically recommended care without waiting until the situation becomes an emergency. If the patient is deemed incompetent, the court may either appoint a surrogate decision maker or directly authorize (by court order) the provision of medically indicated care.

It is not unusual for physicians to disagree with their patients’ health care decisions, and such differences are expected. In some cases, physicians conclude that providing the requested care would present a personal moral problem—a conflict of conscience, which prompts them to refuse to provide the requested care. Conscientious refusals have become especially prevalent in the practice of reproductive medicine, an area characterized by deep societal divisions regarding the morality of contraception and pregnancy termination. The ACOG Committee on Ethics135 has acknowledged that “respect for conscience is one of many values important to the ethical practice of reproductive medicine.” The ACOG stated that when conscience implores physicians to refuse to perform abortion, sterilization, and/or provision of contraceptives, “they must provide potential patients with accurate and prior notice of their personal moral commitments.” The ACOG committee opinion also emphasized that providers have an obligation to provide medically indicated care in an emergency that threatens the patient’s health, in which referral is not possible.132

**TEAM-BASED COMMUNICATION**

**Intraprofessional Collaborative Practice**

Most clinical work on the labor and delivery unit is unscheduled. The evolving clinical needs of both parturient and fetus require the coordinated efforts of obstetricians, midwives, nurses, anesthesia providers, and pediatricians. Birnbach and Salas have highlighted how coordinated care in the perinatal setting can benefit from the same team-building and team-training strategies that are inherent in other high-reliability organizations (e.g., highly hazardous industries, such as nuclear power, the military, and aviation) that have far fewer accidents than would be expected (see Chapter 11).

There is increasing evidence that bringing clinical providers together, to practice the management of critical events or to debrief real events, helps ensure a more unified and effective therapeutic environment. For example, a recent simulation-based multidisciplinary obstetric team training exercise resulted in transiently improved management of real-life shoulder dystocia and obstetric hemorrhage.133 Ackenbom et al.134 administered a survey to labor floor providers before and after their unit’s implementation of routine debriefing after all deliveries. The investigators found that universal debriefings led to better communication among providers, and in particular, more providers chose to participate in debriefings and were more likely to speak up about patient care concerns. Intraprofessional team training on the labor floor also affects worker attitudes that can secondarily affect the patient experience. Blumenthal et al.135 used the Safety Attitudes Questionnaire (SAQ) to demonstrate that implementing collaborative training exercises led to improved perceptions of safety, error management, safety practices, job satisfaction, and working conditions.

Developing strategies that support and engage all roles, and integrate the needs and contributions of all care providers, is a key component of a strong safety culture. Institutional culture encompasses the “shared values and beliefs that interact with an organization’s structures and control systems to produce behavioral norms.”136 In safe work environments where employees are free to speak up and are encouraged to collaborate, connectedness and cross-monitoring allow for team success, even during times of rapidly evolving situations or uncertainty.137,138

Shared decision-making is a collaborative process. In addition to bringing together the values of the patient and input of the clinicians, it requires that clinicians with varying experiences and perspectives also “be on the same page.” Despite the lack of direct data regarding the impact of clinician collaboration on the SDM process or outcome, the link seems both logical and intuitive. Analysis of closed claim data has shown that communication barriers include hierarchy, intimidation, failure to function as a team, and failure to follow a chain of communication.139 Mann et al.140 described their experience with scheduled team meetings on
the labor floor to facilitate “situational monitoring,” where collective input contributed to a “shared mental model” of patients’ conditions and care plans. In particular, they discussed the importance of closed-loop communication to confirm plans and directives, the value of having standardized hand-over language, and the benefits these simple techniques can have on fostering mutual support and minimizing burnout.

Austin et al.141 recently provided a summary of initiatives from their institution aimed at overcoming these barriers and enhancing intraprofessional collaboration and communication. Regularly scheduled intraprofessional safety rounds, including nurses, physicians, and other health care professionals, provide a standardized format with which to share information. This approach has been shown to foster a sense of “team,” improve outcomes, align goals, and promote discussion, even when participants have competing priorities.142–145 Intraprofessional discussion of patient care plans should include a discussion of patient values and goals. One can imagine a situation in which, for example, a parturient with an unfavorable airway has expressed to the anesthesia provider a desire for natural childbirth, and the anesthesia provider could then share this information with the rest of the team during intraprofessional rounds. Then, if the obstetric provider was concerned about her nonreassuring situational awareness, and clear communication among team members—facilitate clinicians’ ability to timely identify signs of distress and take appropriate action.149

The most effective safety programs establish policies and procedures to learn from medical errors and unanticipated adverse outcomes, and to improve systems of care to reduce risk for future patients. Generally this requires both effective systems for reporting and honest discussion of medical error.150 “Peer review” confidentiality laws in most states protect such internal discussions from disclosure to outside interests, including plaintiffs in medical malpractice claims. Of note, the peer review protection does not generally apply in federal court, which can result in information that was considered confidential being disclosed in certain federal matters, such as a patient race discrimination complaint.

**UNANTICIPATED OUTCOMES AND MEDICAL ERRORS**

**Medical Liability**

Medical malpractice is a form of tort law that is based in negligence. As with all negligence claims, the plaintiff (either the patient or the patient’s legal surrogate) must prove four elements: duty, breach of such duty, injury, and proximate causation (meaning that the “breach” was the “cause” of the “injury”). If the plaintiff is unable to prove even one of these elements, then the claim will fail as a matter of law.

In a malpractice case, the “duty” that must be proven to have been “breached” is the duty to provide care that meets a minimum level of competence as determined by expert opinion on both sides of the case. It does not need to be the highest level of care, nor does it even need to be the level of care provided by most clinicians. However, it must not be beneath the minimum standard of care expected of a licensed provider. The standard of care is generally defined as “that care which a reasonable, similarly situated professional would have provided to the patient.”150,151 Proving that such a standard of care has been breached is the role of experts.152 Because medicine is a complex, continuous evolving discipline, it is the province of experts in the field to weigh in on whether the standard of care was met.151 In making these judgments, experts can rely on their own knowledge, developed through education and practice, and on authoritative sources such as the Physician’s Desk Reference, pharmaceutical publications and FDA-approved inserts, scientific journals, and professional organizational standards, guidelines, and practice advisories.153 Ultimately, expert testimony and other evidence presented by both parties will be evaluated by judges or juries for their persuasiveness. If either the judge or jury determines that the standard of care was not met, then the plaintiff will still need to prove that there was an “injury” that was “caused” by the “breach.”151

It is important to remember that the burden of proof lies with the plaintiff (i.e., the injured patient) to show that the standard of care was not met, and that such breach caused the injury from which the patient suffers.151 The plaintiff must prove by a “preponderance of the evidence” (meaning it is more than 50% likely) that each element of the claim has
been proven. Although this “preponderance of the evidence” standard is significantly lower than the criminal law standard of “proof beyond a reasonable doubt,” it is still a relatively high burden to meet. The evidence presented, including the expert testimony, must be significant and objectively strong.

Some of the most common standards of care that are evaluated in a medical malpractice claim include whether an appropriate diagnosis was made, whether there was a surgical error, or whether pharmaceuticals have been prescribed and/or administered appropriately. It is also important to remember that an unanticipated outcome does not mean that malpractice has occurred. In fact, most unanticipated outcomes in medical care are a result of known risks, and despite the plaintiff’s wish to establish fault through a medical malpractice claim, it is often established that the standard of care was met even though the outcome was not the desired one.

Sometimes, a physician makes a promise of a specific outcome to the patient, which could create a cause of action against the physician if such an outcome is not met. But such cases are a rarity, and require the plaintiff to make the case that a reasonable patient would have understood the words of the physician to indicate a promise of that specific outcome. It is more often the case that the process of care is being evaluated, rather than the outcome. A physician is liable for a misjudgment or mistake only when it is proved to have occurred through a failure to act in accordance with the “care and skill of a reasonably prudent practitioner.”

Many potential plaintiffs struggle to file a medical malpractice claim in a timely manner. Numerous factors may get in the way of bringing timely claims, not the least of which is the awareness that an unanticipated outcome has occurred. Even when a medical error led to iatrogenic injury, this may never be disclosed to the patient and family, and knowing the cause of any particular outcome can be difficult for the average patient (or their legal surrogates) to discern. Injured patients may serve notice of the intent to sue for malpractice as a strategy to find out what happened, and use legal procedures to require disclosure of the details of care that may otherwise be inaccessible. Statutes of limitations, legal time frames in which legal claims must be brought for such claims to be valid, vary from state to state but are generally 2 to 3 years. Most laws establish that this time frame begins when a reasonable person becomes aware of an injury that might be the result of a breach of the standard of care. If this acknowledgement occurs right after care has been provided, then the time frame has begun; if it is years later (such as when the patient tries to conceive and discovers that she suffers from sterility), then the time frame will begin at the point of discovery of the injury. If a plaintiff can show that she would have been aware of an injury if not for fraudulent concealment by the provider, then the time frame may be extended to take such fraudulent behavior into account. Additionally, if the plaintiff was a minor when the alleged breach occurred, then the statute of limitations does not usually begin until she reaches the age of majority.

Disclosure of Unanticipated Outcomes and Medical Errors

Most practitioners strive to provide the highest quality of care, but even with the growing focus on patient safety, unintended consequences—including patient injury and death—do occur. Unfortunately, most physicians remain largely unprepared to engage patients and their families in a timely, truthful, and candid manner in the aftermath of such events. Although many providers and medical malpractice insurers might want potential breaches of the standard of care to go unnoticed or unrecognized, emerging evidence suggests that timely disclosure may reduce legal risk. In cases of unanticipated adverse outcomes, patients and families most commonly seek truthfulness, empathy, and a plan to ensure similar patients will not face similar risks in the future. Transparency, as well as a culture of accountability that includes providing apologies after such events, can mitigate distrust between the patient and provider, and ameliorate the desire to find someone to blame. Many states have laws that protect providers from having disclosure and apology held against them should a malpractice claim be subsequently brought. Some states even require reporting of medical errors.

The ethical imperative to disclose is captured in the following passage from the Charter on Medical Professionalism, published by the American Board of Internal Medicine (ABIM) Foundation:

Physicians should also acknowledge that in health care, medical errors that injure patients do sometimes occur. Whenever patients are injured as a consequence of medical care, patients should be informed promptly because failure to do so seriously compromises patient and societal trust. Reporting and analyzing medical mistakes provide the basis for appropriate prevention and improvement strategies and for appropriate compensation for injured parties.

The AMA’s Code of Medical Ethics contains the following statement: “It is a fundamental ethical requirement that a physician should at all times deal honestly and openly with patients. Concern regarding legal liability, which might result following truthful disclosure, should not affect the physician’s honesty with a patient.” The Joint Commission standard RI.2.90 requires that “patients and, when appropriate, their families, are informed about the outcomes of care, treatment, and services that have been provided, including unanticipated outcomes.”

In 2006, the Harvard teaching hospitals and their associated Risk Management Foundation developed a document entitled, “When Things Go Wrong: Responding to Adverse Events.” This white paper acknowledged the presence of many barriers to disclosure, including the fear of being sued, but the authors insisted that communication with patients and their families must be timely, open, and ongoing. In addition to stressing the imperative of providing support for the patient and family involved in the unexpected...
outcome, the paper emphasized the need to provide support to the health care providers involved. This concern is reflected in a 2008 survey that indicated that as many as 75% of obstetricians felt that caring for a patient with an unanticipated stillbirth exacted a large toll on them, with almost 10% of those affected considering giving up their obstetric practice.166

Even in the absence of laws requiring prompt disclosure of patient harm, some health care entities and their insurers have adopted disclosure policies that also contain early settlement or “offer” programs.167 These types of programs encourage patients or their families to accept an early, modest payment for an unanticipated outcome that will eliminate the need for complex, expensive, and uncertain litigation that could take years to resolve.167 Such offers are often protected from legal discovery, meaning the fact of such offer cannot be used against the providers in any future litigation.167

Regardless, team debriefing can be used to establish the need for disclosure, to clarify what is known about the event, and to decide who will lead the disclosure process. Experts advise to limit disclosure to factual information that is known at the time of the discussion, and state that discovery is ongoing and information may evolve as the discovery process unfolds. A simple apology (e.g., “I am sorry this happened”) conveys empathy without laying blame or fault. It is important to maintain open dialogue with the patient and family as information is clarified, but this requires careful coordination among different members of the health care team. Conflicting information and speculation, especially speculation that places blame on other members of the health care team, can raise concerns that the entire team may be hiding the truth. The process is analogous to SDM, and effective communication established before a patient safety incident or adverse outcome will carry over into the communication that must continue after the event.

**KEY POINTS**

- Effective communication with the parturient and her family is an important component of obstetric anesthesia practice.
- Informed consent may be either verbal or both verbal and written. Written consent provides documentation that the consent process has occurred. If possible, it is best to obtain consent early in labor, before the onset of severe pain.
- Shared decision-making is a best practice for communication in which the clinician partners with the patient to address a series of decisions throughout the health care encounter. In addition to standard disclosure of risks, benefits, and alternatives, the clinician elicits questions, values, and preferences from the patient, and guides the discussion toward a decision that is consistent with both the patient’s preferences and current evidence.
- Techniques to ensure understanding and avoid coercion are particularly important for vulnerable populations, including pregnant adolescents, non–English speakers, and women from diverse cultural backgrounds.
- Honest, caring, and comprehensive discussion with the patient before the administration of anesthesia meets legal and ethical standards, improves the image of the anesthesia provider, and reduces the likelihood of dissatisfaction and possible litigation after unanticipated complications.
- Refusal of care by pregnant patients may raise unique legal and ethical concerns. In such situations, the woman’s competency or ability to make an informed medical decision may be an issue. When the patient is competent, the health care providers should attempt to resolve treatment conflicts through additional patient education and discussion. Rarely, it may be advisable to seek a court order to resolve competency or medical treatment issues.
- Effective intraprofessional team communication is essential to ensure optimal team performance, minimize the risk for medical error, and maintain consistent communication with the patient and family, all of which serves to mitigate the risk for medical liability in the event of an unanticipated adverse outcome.

**REFERENCES**

32. See Minn. Stat. Ann. § 144.651 (LexisNexis 2016) (requiring that all conditions and circumstances must be documented within the medical record).
34. See 42 C.F.R. §§ 483.10(b)(4), (b)(7) (2016); Saikewicz, 370 N.E.2d at 430.
36. See Ariz. Rev. Stat. § 14-5303 (LexisNexis 2014) But see Ariz. Rev. Stat. § 36-3221 (LexisNexis 2009), which provides that an adult individual may designate another individual to make health care decisions on that individual’s behalf by executing a written power of attorney; and Ariz. Rev. Stat. § 36-3261 (LexisNexis 1992), which provides that an individual may prepare a living will that will control the health care decisions that can be made on the individual’s behalf.


62. See Bellotti v. Baird, 443 U.S. 622, 635 (1979) (“[D]uring the formative years of childhood and adolescence, minors often lack the experience, perspective, and judgment to recognize and avoid choices that could be detrimental to them”).


69. Parker RM, Baker DW, Williams MV, Nursj JR. The test of functional health literacy in adults: a new instrument for


109. See Commonwealth v. Nixon, 761 A.2d 1151 (Pa. 2000); Jehovah’s Witnesses v. King County Hospital, 278 F. Supp. 488 (W.D. Wash. 1967), aff’d. per curiam, 390 U.S. 598 (1968); Prince v. Massachusetts, 321 U.S. 158, 170 (1944) (“Parents may be free to become martyrs themselves. But it does not follow that they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves.”) Courts generally do not recognize a fetus as a child, even if the fetus is viable. See In re A.C., 573 A.2d 1235 (D.C. 1990); in re Doe 632 N.E.2d 326 (Ill. App. Ct. 1st Dist. 1994), cert. denied, 114 S. Ct. 1198 (1994). See also Planned Parenthood v. Casey, 505 U.S. 833, 860 (1992), for a discussion regarding the viability of a fetus in the context of abortion.


140. Mann S, Marcus R, Sachs B. Lessons from the cockpit: how team training can reduce errors on L&D. *Contemporary OB/GYN.* 2006;51:34.


155. See Cox, 313 S.W.3d at 259-60.


158. Statutes of limitation for medical malpractice claims vary by state, but generally span from two to three years. See, e.g., Iowa Code § 614.1(9)(a) (2013) (“[A]ctions shall be brought within two years after the date on which the claimant knew, or through the use of reasonable diligence should have known, or received notice in writing of the existence of, the injury or death…. ”); Cal. Civ. Proc. Code § 340.5 (Deering 1975) (“[T]he time for the commencement of action shall be three years after the date of injury or one year after the plaintiff discovers, or through the use of reasonable diligence should have discovered, the injury, whichever occurs first.”); Fla. Stat. Ann. § 95.11(4)(b) (LexisNexis 2017) (“An action for medical malpractice shall be commenced within 2 years from the time the incident giving rise to the action occurred or within 2 years from the time the incident is discovered, or should have been discovered with the exercise of due diligence.”).


Preterm delivery is defined as delivery before 37 weeks’ gestation. It occurs in 5% to 9% of pregnancies in developed countries and is responsible for 75% to 80% of all neonatal deaths and significant neonatal morbidity. Preterm delivery leads to a large economic burden to society. For example, in 2005, in the United States the cost associated with preterm birth was at least $26.2 billion.

Preterm delivery in the United States increased 20% between 1990 and 2006 (from 10.6% to 12.8%), before declining to 9.9% of all births in 2016 (Figs. 33.1 and 33.2). There is notable racial/ethnic disparity in the frequency of preterm birth. In 2015, 9.0% of non-Hispanic whites, 13.8% of non-Hispanic blacks, and 9.5% of Hispanics delivered preterm. This is not explained by differential use of assisted reproductive technology. Late preterm is defined as 34 0/7 to 36 6/7 completed weeks’ gestation, and early preterm is defined as less than 34 completed weeks’ gestation. Table 33.1 lists subdivisions of early preterm births. In 2016, late preterm deliveries composed 7.1% of all births, and early preterm births composed 2.8% of all births.

The concern about preterm birth is not confined to the United States; the World Health Organization (WHO) and other nongovernmental organizations have identified the frequency of preterm birth as a critical health issue. Worldwide, on a yearly basis, 15 million infants are born preterm. More than 60% of preterm births occur in Africa and South Asia, with Malawi having the highest rate (18.1 per 100 live births). Although truly a global problem, economic disparity exists. In lower-income countries, the preterm birth rate is 12% with a mortality rate greater than 90% in those born extremely preterm (less than 28 weeks). In higher-income countries, the preterm birth rate is 9% with a neonatal mortality rate less than 10%. The global neonatal mortality rate is 19 per 1000 live births. The United States has a slightly higher neonatal mortality rate than Europe (4 versus 3 per 1000 births, respectively), which reflects the higher preterm birth rate in the United States.

In 2006, the Institute of Medicine recommended that investigators focus on (1) better defining the problem; (2) developing treatments to prevent both preterm delivery and morbidity for children born preterm; (3) identifying the causes of preterm birth, including modifiable risk factors and the reasons for disparity among different ethnic, racial, and socioeconomic groups; and (4) developing policies and public programs that can be used to reduce the rate of preterm birth.
CHAPTER 33 Preterm Labor and Delivery

DEFINITIONS

A preterm infant is defined as one who is born between 20 0/7 weeks and 36 6/7 weeks, inclusive, after the first day of the last menstrual period. The American College of Obstetricians and Gynecologists (ACOG) has defined periviable birth as birth between 20 weeks’ and 25 6/7 weeks’ gestation.9 Further classification of deliveries based on gestational age is outlined in Table 33.1. If a good basis does not exist for establishing the gestational age from either maternal history or first-trimester ultrasound, the exact gestational age is difficult to determine. A low birth weight (LBW) does not necessarily signify that a

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Fig. 33.2 Total, early, and late preterm birth rates: United States 1990 and 2007 to 2015. Preterm birth is defined as less than 37 weeks’ completed gestation. Early preterm birth is defined as less than 34 weeks’ completed gestation. Late preterm birth is defined as 34 to 36 weeks’ completed gestation. EPTB, Early preterm birth; LPTB, late preterm birth. (Data from the Centers for Disease Control and Prevention/National Center for Health Statistics: National Vital Statistics System. 2018. https://www.cdc.gov/nchs/nvss/index.htm. Accessed July 25, 2018.)
neonate has been born preterm, because some newborns have a LBW because they are small for gestational age (SGA) rather than preterm. A neonate who weighs less than 2500 g at birth is considered to have a LBW, regardless of gestational age. Likewise, an infant who weighs less than 1500 g at birth is considered to have a very low birth weight (VLBW), and an infant who weighs less than 1000 g at birth is considered to have an extremely low birth weight (ELBW).

**TABLE 33.1 Classification of Deliveries Based on Gestational Age**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely preterm</td>
<td>Less than 28 weeks</td>
</tr>
<tr>
<td>Very preterm</td>
<td>28 0/7 weeks to 31 6/7 weeks</td>
</tr>
<tr>
<td>Moderate preterm</td>
<td>32 0/7 weeks to 33 6/7 weeks</td>
</tr>
<tr>
<td>Late preterm</td>
<td>34 0/7 weeks to 36 6/7 weeks</td>
</tr>
<tr>
<td>Early term</td>
<td>37 0/7 weeks to 38 6/7 weeks</td>
</tr>
<tr>
<td>Full term</td>
<td>39 0/7 weeks to 40 6/7 weeks</td>
</tr>
<tr>
<td>Late term</td>
<td>41 0/7 weeks to 41 6/7 weeks</td>
</tr>
<tr>
<td>Postterm</td>
<td>42 0/7 weeks and beyond</td>
</tr>
</tbody>
</table>


**NEONATAL MORTALITY**

The survival rate among neonates increases as the birth weight and/or gestational age increases (Fig. 33.3; Table 33.2)." After data are controlled for gestational age and weight, male infants have a higher mortality than female infants.11 During the past three decades, there has been a significant improvement in the survival rate for preterm infants, with the greatest improvement occurring in the subgroup with a birth weight between 501 and 1250 g.12 The rate of neonatal survival now is approximately 94% for infants born at 28 weeks’ gestation.13

Infants born at the threshold of viability (22 to 24 weeks’ gestation) continue to have the greatest risk for poor

**TABLE 33.2 Neonatal Deaths by Gestational Age**

<table>
<thead>
<tr>
<th>Completed Weeks’ Gestation</th>
<th>Percentage of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>93</td>
</tr>
<tr>
<td>23</td>
<td>68</td>
</tr>
<tr>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>28</td>
<td>6</td>
</tr>
</tbody>
</table>


outcome.\textsuperscript{9} A retrospective cohort study assessed survival rates for infants delivered between 22 and 28 weeks’ gestation.\textsuperscript{10} Neonatal survival was 9% at 22 weeks, 33% at 23 weeks, and then 65%, 81%, and 87% at 24, 25, and 26 weeks’ gestation, respectively.\textsuperscript{10} The majority of women received antenatal corticosteroids, and the majority of neonates received exogenous surfactant. A delay in delivery of even 1 week at this time in gestation leads to significantly better outcome and reduced cost.

Younge et al.\textsuperscript{14} examined outcomes for infants born between 22 and 24 weeks’ gestation between 2000 and 2011 (Table 33.3).\textsuperscript{14} The mortality rate decreased over time overall (72% from 2000 to 2003 to 66% from 2008 to 2011). However, the mortality rate did not change for 22-week infants. As expected, the greatest decrease in mortality was seen in the 24-week group (55% from 2000 to 2003 to 18% from 2008 to 2011).\textsuperscript{14} Those born later in the study period were more likely to have been exposed to antenatal maternal corticosteroids, be delivered by cesarean, and be resuscitated at birth, regardless of gestational age. Excess mortality risk for infants born preterm is concentrated in the first year.\textsuperscript{13}

### NEONATAL MORBIDITY

Approximately 84% of preterm births occur between 32 0/7 and 36 6/7 weeks’ gestation.\textsuperscript{6} Compared with earlier gestational ages, mortality is less common, but morbidity is a relatively greater concern in this gestational age range. Researchers have examined the association between late preterm birth and neurocognitive performance in late adulthood; 919 Finnish men and women were evaluated at a mean age of 68.2 years.\textsuperscript{15} When controlling for confounders, those who were born between 34 and 37 weeks’ gestation had lower scores on tests evaluating neurocognitive performance than those born after 37 weeks’ gestation.\textsuperscript{15}

As with mortality, most morbidity decreases in frequency as gestational age increases. For example, the incidence of high-grade (III or IV) intraventricular hemorrhage diminishes rapidly after 27 weeks’ gestation, and grade III or IV intraventricular hemorrhages are very rare after 32 weeks’ gestation. Likewise, neonatal morbidity from patent ductus arteriosus and necrotizing enterocolitis diminishes significantly after 32 weeks’ gestation.\textsuperscript{16} Data from the National Institute of Child Health and Development (NICHD) Neonatal Research Network sites from 1997 to 2002 indicate that survival without complications (e.g., bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis, or a combination of these disorders) ranged from 20% for infants with a birth weight between 501 and 750 g to 89% for those with a birth weight between 1251 and 1500 g.\textsuperscript{2}

Piecuch et al.\textsuperscript{17} reported data for a cohort of 138 nonanomalous infants delivered between 24 and 26 weeks’ gestation between 1990 and 1994. The incidence of cerebral palsy did not differ significantly among the three groups born at 24, 25, and 26 weeks’ gestation (11%, 20%, and 11%, respectively). However, the incidence of normal cognitive outcome rose with increasing gestational age at birth (28%, 47%, and 71% at 24, 25, and 26 weeks’ gestation, respectively).

The EPICure study group assessed the association between extreme preterm delivery and long-term physical and mental disability in a cohort of infants delivered between 22 and 25 weeks’ gestation during a 10-month period in 1995.\textsuperscript{18} These investigators noted rates of severe disability of 54%, 52%, and 45% among infants delivered at 24, 25, and 26 weeks’ gestation, respectively. In a later cohort of infants, born between 1997 and 2002, the rates of severe disability were 33%, 21%, and 12% for infants delivered at 23, 24, and 25 weeks’ gestation, respectively.\textsuperscript{19} A 6-year follow-up to the EPICure study cohort reported persistent severe disability in 25%, 29%, and 18% of infants born at 23, 24, and 26 weeks’ gestation, respectively.\textsuperscript{20}

Hack et al.\textsuperscript{21} monitored a cohort of ELBW infants born between 1992 and 1995 until they were 8 years of age. The mean birth weight was 810 g, and the mean gestational age at delivery was 26 weeks. Compared with a cohort of age-matched children of normal birth weight, the ELBW group had a higher incidence of significant neurosensory impairment (16% versus 0%, respectively) and asthma (21% versus 9%). The ELBW children differed significantly from the cohort with normal birth weight in rates of suboptimal intelligence, academic achievement, motor skills, and adaptive functioning. These data underscore the long-term medical, educational, and social services required by these children.

### TABLE 33.3 Selected Outcomes for Extremely Preterm Infants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of antenatal therapy:</td>
<td></td>
</tr>
<tr>
<td>Maternal corticosteroid administration</td>
<td>64</td>
</tr>
<tr>
<td>Maternal antibiotic administration</td>
<td>66</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>38</td>
</tr>
<tr>
<td>Male gender</td>
<td>52</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>27</td>
</tr>
<tr>
<td>Surfactant therapy after birth</td>
<td>66</td>
</tr>
<tr>
<td>Death before discharge</td>
<td>64</td>
</tr>
<tr>
<td>Survival without neurodevelopment impairment</td>
<td>20</td>
</tr>
<tr>
<td>Survival without neurosensory impairment</td>
<td>29</td>
</tr>
</tbody>
</table>

Total N = 1348.

Gestational age between 22 and 24 weeks’ gestation, born between 2008 and 2011.

Neurodevelopmental impairment defined as at least one of the following conditions: moderate or severe cerebral palsy, Gross Motor Function Classification System level 2 or greater, profound hearing loss requiring amplification in both ears, profound visual impairment with visual acuity of less than 20/200 in both eyes, or cognitive impairment.

Neurosensory impairment defined as moderate or severe cerebral palsy, Gross Motor Function Classification System level 2 or greater, profound hearing loss, or profound visual impairment.

The economic costs for the care of surviving preterm infants (especially VLBW infants) can be enormous. A conservative estimate is that 7.7% of insured infants born preterm accounted for 37% of $2.0 billion spent by participating plans on the care of infants born during 2013. With a mean difference in plan expenditures between preterm and term infants of approximately $47,100 per infant, preterm births cost the included plans an extra $600 million during the first year of life. These figures likely will continue to rise with the escalating cost of health care.

**PRETERM LABOR**

**Risk Factors**

Box 33.1 lists factors associated with preterm labor. These associations do not necessarily indicate cause-and-effect relationships. Significant risk factors include a history of preterm delivery, non-Hispanic black race (irrespective of socioeconomic status), and multiple gestation.

The process of normal parturition involves anatomic, physiologic, and biochemical changes that lead to (1) greater uterine contractility, (2) cervical ripening, and (3) membrane/decidual activation. The fetus also appears to play a role in parturition. It is hypothesized that the mature fetal hypothalamus secretes more corticotropin-releasing hormone (CRH), which in turn stimulates fetal adrenal production of adrenocorticotropic hormone (ACTH) and cortisol. Preterm labor results from the pathologic activation of one or more of these components (Fig. 33.4). Preterm delivery

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**BOX 33.1  Factors Associated with Spontaneous Preterm Labor**

**Demographic and Medical Characteristics**

- Non-Caucasian race
- Extremes of age (less than 17 or greater than 35 years)
- Low socioeconomic status
- Low prepregnancy body mass index
- History of preterm delivery
- Interpregnancy interval less than 6 months
- Periodontal disease
- Abnormal uterine anatomy (e.g., myomas)
- Trauma
- Abdominal surgery during pregnancy

**Behavioral Factors**

- Tobacco use
- Substance abuse

**Obstetric Factors**

- Previous preterm birth
- Vaginal bleeding
- Infection (systemic, genital tract, periodontal)
- Short cervical length
- Multiple gestation
- Assisted reproductive technologies
- Preterm premature rupture of membranes
- Polyhydramnios

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![Fig. 33.4](image-url) Major etiologic factors in preterm birth, including activation of the maternal or fetal hypothalamic-pituitary axis (stress), inflammation, decidual hemorrhage, and pathologic distention of the myometrium. The pathways are not mutually exclusive and may overlap, and they share a common biochemical pathway. PPROM, Preterm premature rupture of membranes. (From Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiological and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand. 2008;87:590–600.)
results from (1) preterm premature rupture of membranes (preterm PROM) in approximately 25% of cases; (2) spontaneous preterm labor in approximately 45% of cases; and (3) maternal or fetal indications for early delivery in approximately 30% of cases. However, the “spontaneous” causes do not have a uniform underlying pathophysiology, and it appears that preterm labor is a syndrome with multiple causes influenced by a number of genetic, biologic, biophysical, psychosocial, and environmental factors.

Two factors of interest are the influences of infection and uterine distention on initiation of myometrial contractility. Infection is thought to be present in up to 40% of preterm deliveries. Commonly identified organisms include Ureaplasma urealyticum, Bacteroides species, Neisseria gonorrhoeae, Chlamydia trachomatis, group B streptococci, Staphylococcus aureus, Treponema pallidum, and enteropharyngeal bacteria. Although approximately 50% of preterm deliveries occur in women with no apparent risk factors, subclinical infection may precipitate preterm labor in some of these cases. In addition, infection compounds the effects of preterm birth with increased rates of neurologic injury.

Multiple gestation accounts for 21.6% of all preterm births. In the past three decades, there was a significant rise in the incidence of multiple gestation (see Chapter 34), attributed to a shift toward older maternal age at conception, and to increased use of assisted reproductive technology (ART). The twinning rate (births in twin deliveries per 1000 total births) rose 76% from 1980 to 2009 (from 18.9 to 33.2 per 1000). Recently, rates of multifetal pregnancies have started to decline. The twin birth rate peaked at 33.9 twins per 1000 births in 2014, and has since decreased to 33.4 in 2016. Likewise, the triplet and higher-order multiple birth rate has fallen 48% since the 1998 peak (193.5) to a rate of 101.4 multiples per 100,000 births in 2016.

Modifications in ART may be contributing to changes in the preterm birth rate and recent declines in multiple gestation. In 2015, ART contributed to 1.7% of all births in the United States and 17.0% of all multiple-birth infants, including 16.8% of all twin infants and 22.2% of all triplets and higher-order infants. Risk for preterm birth is elevated even for singleton pregnancies conceived by ART. A 2004 meta-analysis of 15 studies that compared outcomes for 12,283 ART singleton pregnancies with outcomes for 1.9 million spontaneously conceived singleton pregnancies demonstrated a higher risk for preterm and SGA deliveries in the ART group.

The ability to prevent spontaneous preterm birth would be facilitated if it were possible to intervene prophylactically to prevent preterm labor or to effectively treat preterm labor once it occurs. Both prophylaxis and treatment would require the ability to accurately predict which asymptomatic or symptomatic patients will go on to have spontaneous preterm delivery. Several methods of predicting preterm delivery have been proposed, including home uterine activity monitoring and fetal fibronectin screening. However, available interventional studies based on the use of these tests for screening asymptomatic women have not demonstrated improved perinatal outcomes. Thus, these methods are not recommended as screening strategies.

Novel biomarkers are being investigated for their ability to predict preterm birth. A recent study found that two serum proteins (insulin-like growth factor–binding protein 4 [IGFBP4] and sex hormone–binding globulin [SHBG]) identified asymptomatic pregnant women at risk for spontaneous preterm delivery. Although promising, these markers have yet to be used in clinical practice.

Short cervical length, as assessed by transvaginal ultrasonography, is associated with a greater risk for preterm delivery. In a 2006 systematic analysis, Kagan et al. concluded that cervical length is associated with preterm delivery (i.e., the shorter the cervix the greater the risk for preterm delivery) in symptomatic women. Further, multiple studies have shown an increased risk for preterm delivery in asymptomatic women with a shortened cervix. A Maternal-Fetal Medicine Units Network study of nearly 3000 women found that the risk for spontaneous preterm delivery is increased in women with evidence of a short cervix detected by transvaginal ultrasonography between 24 and 28 weeks’ gestation. A cervical length below the 10th percentile had a sensitivity of 37% and a specificity of 92% in predicting preterm birth before 35 weeks’ gestation, with a corresponding positive predictive value of 18% and a negative predictive value of 97%. The cervix appears to shorten at a similar rate before preterm birth whether the presentation is preterm labor (–0.96 mm/week) or rupture of membranes (–0.82 mm/week).

A history of cervical surgery, including conization and loop electrosurgical excision procedure, traditionally has been thought to be a risk factor for preterm birth because of associated cervical injury. However, this relationship may be related to environmental factors and/or behavioral factors that underlie the progression of cervical dysplasia. Uterine instrumentation, such as dilation and curettage, also has been associated with an increased risk for preterm birth in some, but not all, studies; the mechanism is unclear, but it may be a result of intrauterine microbial colonization, injury to the endometrium, or both, together with host and environmental factors.

Prevention of Preterm Labor

Screening for any disease is of greatest benefit when there are interventions available to decrease the incidence of said disease. Unfortunately, few if any interventions have been shown to definitively reduce the incidence of preterm labor and delivery. Interventions that have been studied include detection and suppression of uterine contractions, antimicrobial therapy, prophylactic cervical cerclage, maternal nutritional supplements, and reduction of maternal stress. It is not surprising that most of these simple interventions have
not been shown to alter outcome, given that preterm labor is increasingly understood to be a complex syndrome with multiple, overlapping causes.

Prophylactic cervical cerclage in the early second trimester has been performed to prevent preterm birth, typically in women with a history of mid-trimester pregnancy loss. Evidence supporting the efficacy of this practice is weak.36 There remains controversy with regard to whether cerclage should be placed in response to transvaginal ultrasonographic evidence of a short cervix in the second half of the mid-trimester. Data do not support such a practice in the general population, but there is some evidence that the practice may be beneficial among high-risk women, such as those with a prior preterm birth.37

Evidence does not support the administration of prophylactic antibiotics in asymptomatic women at risk for preterm labor.38 Likewise, evidence does not support the prophylactic use of beta-adrenergic receptor agonists to prevent preterm labor in high-risk women.39,40

By contrast, evidence suggests that progesterone therapy may be effective in reducing the rate of preterm birth in some patient populations. The Maternal-Fetal Medicine Units Network performed a randomized controlled trial that compared prophylactic intramuscular 17α-hydroxyprogesterone caproate (17P) (250 mg weekly beginning at 16 to 20 weeks’ gestation, and continued until delivery or 36 weeks’ gestation) with placebo in women with a history of spontaneous preterm delivery.41 The risk for delivery before 37 weeks’ gestation was reduced in the 17P group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.54 to 0.81). A systematic review of 11 randomized controlled trials (n = 2425) also concluded that progesterone administration was associated with a significant reduction in recurrent preterm birth in women with a history of spontaneous preterm delivery.42

Progesterone therapy also has been shown to be beneficial in reducing the incidence of preterm delivery in the subset of women with a sonographically identified short cervix. In two double-blind, placebo-controlled trials, women with a mid-trimester diagnosis of a short cervix (less than 15 mm in one trial43 and 10 to 20 mm in the other44) were randomized to receive either vaginal progesterone or placebo. Women who received vaginal progesterone experienced a significant reduction in the frequency of preterm delivery before 33 weeks’ gestation.43,44 By contrast, in a trial that enrolled nulliparous women with a cervical length less than 30 mm, women randomized to receive 17P did not experience a reduction in preterm delivery compared with women who received placebo.45

A number of studies have examined whether progesterone is efficacious in reducing preterm birth among women with multiple gestation. A recent meta-analysis comparing progesterone (both intramuscular and vaginal preparations), pessary, and cerclage found that vaginal progesterone may be beneficial in twin pregnancy.46

Even among women for whom progesterone is thought to be indicated, the optimal type, timing, and dosing of progesterone is unclear. Based on existing evidence, the ACOG31 has concluded that vaginal progesterone should be offered to asymptomatic women with a singleton gestation without a previous preterm delivery, who have a very short cervical length (i.e., less than or equal to 20 mm at or before 24 weeks’ gestation).

Diagnosis

Determining whether a woman is in early preterm labor or in false labor is often difficult. Criteria for the diagnosis of preterm labor include gestational age between 20 0/7 and 36 6/7 weeks’ gestation and regular uterine contractions accompanied by a change in cervical dilation, effacement, or both (or initial presentation with regular contractions and cervical dilation of 2 cm or more). Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation.

Assessment and Therapy

Initial assessment of the patient with possible preterm labor includes physical examination and external monitoring of contractions with a tocdynamometer (and fetal heart rate if indicated by gestational age). Acute conditions associated with preterm labor should be considered, including infection and placental abruption. Maternal physical examination may include a sterile speculum examination to exclude preterm PROM if symptoms or signs indicate this possibility. In many women who have preterm uterine contractions, these contractions will cease spontaneously. In the past, clinicians assumed that intravenous hydration was a useful component of therapy. However, there is no evidence that intravenous hydration reduces the chance of preterm delivery.47

Once the diagnosis of preterm labor is established, the obstetric care provider must decide whether intervention is warranted. The administration of antenatal corticosteroids for fetal lung maturation48 and magnesium sulfate for fetal neuroprotection49 are associated with improved neonatal outcomes. Although widely used before 34 weeks’ gestation, acute tocolytic therapy remains a source of controversy. Tocolysis is currently recommended between 24 and 34 weeks’ gestation. However, certain clinical scenarios may be favorable for administration of this intervention between 23 and 24 weeks’ gestation as well.9 There is no consistent evidence that the use of acute tocolysis reduces the chance of preterm birth or improves neonatal outcome. However, because acute tocolysis has been associated with a short (approximately 48-hour) prolongation of pregnancy, it may be used to facilitate transfer of the patient from a community hospital to a tertiary care facility that can provide optimal care for the preterm neonate. Moreover, a short course of tocolytic therapy may delay delivery for 24 to 48 hours, allowing maternal administration of (1) a corticosteroid to accelerate fetal lung maturity and (2) antibiotic therapy to prevent neonatal group B streptococcal infection. Thus, the ACOG48 supports the use of acute tocolysis to allow administration of a complete course of antenatal corticosteroids, but discourages the continued use of tocolysis after corticosteroid administration is complete.
Criteria for the use of tocolytic therapy include (1) gestational age after viability (23 weeks) and before 34 weeks’ gestation, (2) reassuring fetal status, and (3) no overt clinical signs of infection. The potential benefits of delaying delivery of the preterm infant (i.e., decreased neonatal morbidity and mortality) must be weighed against the maternal and fetal risks (e.g., maternal side effects of tocolytic drugs, deterioration of a compromised fetus). Box 33.2 lists contraindications to inhibiting labor.

In the setting of preterm PROM, obstetricians have worried that tocolytic therapy might increase the risk for maternal and/or fetal infection. It also seems logical that tocolytic therapy is less effective in patients with preterm PROM. Prospective, randomized studies have shown that tocolytic therapy per se does not improve neonatal outcome compared with conservative expectant management in patients with preterm PROM, but may afford time to optimize conditions before delivery (see later discussion).

**Antenatal Administration of Corticosteroids**

The neonatal benefits of corticosteroid administration (Table 33.4) before preterm delivery have been clearly demonstrated in large clinical trials. The NICHD Neonatal Research Network evaluated outcomes for 11,718 preterm infants delivered after antenatal maternal corticosteroid administration between 1988 and 1992. Antenatal corticosteroid treatment significantly reduced the incidence of neonatal respiratory distress syndrome, intraventricular hemorrhage, and neonatal death in all subgroups of the population studied (including male and female infants, African and Caucasian race infants, and infants delivered before 30 weeks’ gestation). The reduction in neonatal morbidity and mortality from antenatal corticosteroid administration is additive to the reduction observed with the use of neonatal surfactant alone. A randomized trial has demonstrated that these benefits may not be limited to those born before 34 weeks. A single course of corticosteroids administered to women at risk for preterm birth after 34 weeks’ but before 37 weeks’ gestation resulted in a significantly lower incidence of severe neonatal respiratory morbidity.

Although there is little controversy about the efficacy of a single course of antenatal corticosteroids, there remains debate over the use of multiple courses of corticosteroids for women who remain undelivered 7 days after the initial dose of corticosteroids. A large study performed by the Maternal-Fetal-Medicine Units Network randomly assigned women at risk for preterm delivery between 23 and 32 weeks’ gestation to receive either a single course or repeated (weekly) courses of antenatal corticosteroids. Weekly corticosteroid administration did not significantly reduce the composite primary morbidity outcome, but it significantly reduced the need for neonatal surfactant, mechanical ventilation, and continuous positive airway pressure (CPAP), as well as the incidence of pneumothorax. However, weekly corticosteroid administration was associated with an increase in the delivery of SGA infants, and there was a significant reduction in the birth weight of the infants whose mothers received four or more courses of corticosteroids.

To balance the potential beneficial effects and risks of additional courses of corticosteroids, some have advocated a single “rescue” course (i.e., a second course of corticosteroids), which is administered at the time of a second episode of preterm labor with a high probability of preterm delivery. A large randomized placebo-controlled trial found neonatal benefit in administering an additional course of corticosteroids. Criteria for administration included absence of rupture of membranes, prior corticosteroid administration at least 2 weeks previously and who are at acute risk for preterm delivery before 34 weeks’ gestation, and a change in clinical scenario such that it was believed that preterm birth was likely to occur within 1 week. A meta-analysis concluded that a single “rescue” course of antenatal corticosteroids should be considered in women whose prior course of antenatal corticosteroids was administered at least 7 days previously and who are at acute risk for preterm delivery before 34 weeks’ gestation. The ACOG has stated that one rescue course of corticosteroids may be considered in these specific populations. However, regularly scheduled repeat courses or multiple courses (more than two) of corticosteroids are not currently recommended.

**Antibiotic Therapy**

The results of a large, multicenter, randomized controlled trial and a meta-analysis do not support the use of prophylactic antibiotic therapy in the management of preterm labor in patients with intact membranes as a method to reduce the likelihood of preterm birth. In fact, there was an increase in cerebral palsy in children born to mothers in preterm labor with intact membranes who received any prophylactic antibiotics versus no antibiotics (RR 1.82, 95% CI 0.99 to 3.34; 3173 children). Accordingly, the ACOG does not recommend empirical antibiotic therapy in this population. It should be
noted, however, that prophylactic antibiotic administration remains appropriate in women who are positive for group B streptococcus (GBS) who are thought to be in preterm labor.60

In contrast, in patients with preterm PROM, randomized controlled trials and a meta-analysis have concluded that antimicrobial therapy prolongs pregnancy and reduces both maternal and neonatal morbidity.51,62 Thus, when preterm PROM is diagnosed, the ACOG43 recommends a 7-day course of antimicrobial therapy. The best antibiotic regimen is not known with certainty, although intravenous ampicillin and erythromycin (48 hours), followed by oral amoxicillin and erythromycin (5 days), is a commonly used regimen for women with preterm PROM who are receiving expectant management.63 Regardless, prolonged expectant management for preterm PROM is a known risk for chorioamnionitis and maternal sepsis (see Chapter 36).

Neuroprotection
Several clinical trials have provided evidence that maternal administration of magnesium sulfate provides fetal neuroprotection when given to women at risk for preterm delivery. In 2003, Crowther et al.64 reported the results of a multicenter randomized, placebo-controlled study of 1062 women (1255 infants) at less than 30 weeks’ gestation, in whom delivery was planned or expected within 24 hours. The investigators observed no significant difference between groups in the primary outcomes, which included total pediatric mortality, cerebral palsy, or both, at a corrected age of 2 years. However, they observed a significantly reduced rate of substantial gross-motor dysfunction, as well as a reduced combined rate of death or substantial gross-motor dysfunction, in the children exposed to magnesium sulfate in utero.64 Similarly, a randomized controlled trial of magnesium sulfate administration to 573 pregnant women at less than 33 weeks’ gestation, and in whom delivery was planned or expected within 24 hours, found that infants exposed to magnesium sulfate had a reduced rate of total neonatal mortality, severe cerebral white matter injury (which is associated with cerebral palsy), and the combination of severe white matter injury and/or death, but the differences were not statistically significant.65 In the largest randomized trial,66 2241 women at imminent risk for delivery before 32 weeks’ gestation were randomized to receive magnesium sulfate or placebo. The offspring who had been exposed to magnesium sulfate in utero were significantly less likely to develop moderate/severe cerebral palsy (1.9% versus 3.5%; RR, 0.55; 95% CI, 0.32 to 0.95).66

Meta-analysis of clinical trials suggests that prenatal administration of magnesium sulfate reduces the occurrence of cerebral palsy (RR, 0.68; 95% CI, 0.54 to 0.87).67 The ACOG has stated that, based on available evidence, magnesium sulfate—given before anticipated early preterm birth—reduces the risk for cerebral palsy in surviving infants.68 Because the best regimen of magnesium sulfate administration remains unclear, physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring based on the protocols of the larger published trials.68

Rescue Cerclage
Prophylactic cervical cerclage (see earlier discussion) is typically performed when the cervix is closed (see Chapter 16). A rescue cerclage (also known as emergency or physical exam-indicated cerclage) is typically a procedure to prolong gestation in women with cervical dilation and/or prolapsed membranes. The efficacy and safety of this procedure remain controversial. A 2014 article reviewed the contemporary evidence of this procedure.69 Contraindications include established preterm labor with impending preterm birth, chorioamnionitis, heavy vaginal bleeding, preterm PROM, fetal compromise, major fetal anomalies, and fetal death. Data are mixed regarding mandating a waiting period before placement. Some experts advocate for immediate placement, and others recommend delaying for up to 24 hours; there is no single evidence-based standard to define best practice with regard to timing of rescue cerclage placement.

When placing the cerclage, prolapsing membranes need to be replaced in the uterine cavity to reduce the risk for iatrogenic preterm PROM. The surgical technique typically involves the lithotomy position with steep Trendelenburg tilt, overfilling the bladder and/or placing ring forceps or stay sutures around the circumference of the external os, and placing traction on these structures to ease the membranes back into the uterus. Invasive methods may also be used, including using a Foley catheter balloon to directly push the membranes back into the uterus. However, this practice may be associated with increased risk for iatrogenic preterm PROM. Amniocentesis/amnioreduction can also be performed to reduce the volume and pressure of the amniotic fluid on the prolapsed sac. For the actual cerclage, the McDonald technique is typically preferred; purse-string sutures are placed around the circumference of the cervix. Other techniques have been described (Shirodkar and Wurm); the ultimate decision on technique is based on surgeon preference. Some evidence suggests a course of perioperative antibiotic and tocolytic administration is beneficial in these patients.70

Only one small randomized controlled trial has compared rescue cerclage with bed rest compared with bed rest alone; the study population was heterogeneous and included twin gestation.71 Improved outcomes were reported in the cerclage group, including prolongation of gestation by 4 weeks, and reductions in the rates of neonatal intensive care unit admission and neonatal death. Similarly, a small (n = 29) nonrandomized prospective trial found prolongation of gestation by over 8 weeks compared with bed rest alone.72

**Cerclage removal.** Cerclage removal does not routinely precipitate the labor process. When vaginal delivery is planned, it is recommended to proceed with removal at 36 to 37 weeks’ gestation. By contrast, in cases of planned cesarean delivery, it is permissible to defer cerclage removal until delivery. However, labor may occur before the planned delivery date, and removal may need to be performed urgently.
There is a paucity of data to guide management of women with a cerclage who subsequently experience preterm PROM and/or preterm labor. In the case of isolated preterm labor, the decision to remove the cerclage can be a difficult one. Management of preterm labor should not be influenced by the presence of a cerclage; if the patient demonstrates cervical change, painful contractions, or vaginal bleeding, the cerclage should be removed.37

In some studies, cerclage retention following preterm PROM has been associated with increased incidence of infectious morbidities, both maternal and neonatal, as well as neonatal respiratory distress syndrome. However, other studies have not identified these associations. Given current evidence, it is reasonable to either remove or retain the cerclage after diagnosis of preterm PROM. However, if cerclage is retained, women should receive 7 days of antibiotic prophylaxis.63

Cerclage removal is usually a straightforward procedure. With the patient in the dorsal lithotomy position, a speculum is inserted. The suture is grasped with rings and the suture beneath the knot is transected with scissors. In most cases, elective removal of a cerclage in an office setting is appropriate.37 Occasionally the entire stitch becomes embedded within the cervical mucosa (i.e., “buried”), and neuraxial anesthesia (see later discussion) may be required to facilitate cervical dissection and cerclage removal.

**Tocolysis**

Once the obstetrician has decided to begin tocolytic therapy, an appropriate agent must be selected (Table 33.5). (Each specific class of tocolytic agent is discussed in detail later in this chapter.) A 2003 analysis of studies that compared the four classes of tocolytic agents currently in use (i.e., beta-adrenergic receptor agonists, calcium entry–blocking agents, magnesium sulfate, and nonsteroidal antiinflammatory drugs [NSAIDs]) concluded that all are more effective than placebo in prolonging pregnancy, but the investigators found no evidence of a beneficial effect on neonatal morbidity or mortality.73 A 2014 analysis suggested that magnesium sulfate is not efficacious and should not be used for tocolysis.74

**Physiology of Uterine Contractions**

Myometrial smooth muscle consists of thick (myosin) and thin (actin) filaments that slide past one another and thereby lead to the contractile force of uterine contractions. The myometrium also has pacemaker cells; electrical activity is spread by gap junctions between myometrial cells. A rise in intracellular calcium concentration from influx across the sarcolemma and/or release from internal calcium stores leads to contractions. Hormones and neurotransmitters also may regulate uterine activity through agonist-induced entry of calcium or other ions by means of receptor-controlled channels and the release of internally stored calcium.75

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**TABLE 33.5  Tocolytic Drugs for Preterm Labor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraindications</th>
<th>Maternal Side Effects</th>
<th>Fetal/Neonatal Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium entry–blocking agents</td>
<td>Cardiac disease, Renal disease (use with caution)</td>
<td>Transient hypotension, flushing, headache, dizziness, nausea</td>
<td>None identified</td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors (NSAIDs)</td>
<td>Cardiac dysrhythmias, Poorly controlled thyroid disease</td>
<td>Cardiopulmonary: dysrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia</td>
<td>Constriction of the ductus arteriosus, pulmonary hypertension, reversible renal dysfunction (leading to oligohydramnios), IVH, hyperbilirubinemia, necrotizing enterocolitis</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Myasthenia gravis, Myotonic dystrophy</td>
<td>Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest</td>
<td>Lethargy, hypotonia, respiratory depression, demineralization (prolonged use)</td>
</tr>
</tbody>
</table>

IVH, Intraventricular hemorrhage; NSAIDs, nonsteroidal anti-inflammatory drugs.
Calcium binds to calmodulin, which then activates myosin light-chain kinase (MLCK), leading to phosphorylation of the light-chain subunit of myosin. This phosphorylation allows actin to bind to myosin, with the subsequent activation of myosin adenosine triphosphatase. Adenosine triphosphate (ATP) is then hydrolyzed, and muscle shortening or contraction results. Increases in intracellular cyclic adenosine monophosphate (cAMP) cause muscle relaxation by (1) activation of a cAMP-dependent protein kinase, which decreases the activity of MLCK and (2) a reduction of the intracellular calcium concentration.

The actual signals for the onset of contractions and labor, however, are complex and incompletely understood. Before labor, the uterus is in a state of functional quiescence as a result of various inhibitors, including progesterone, prostacyclin, relaxin, nitric oxide, parathyroid hormone–related peptide, corticotropin-releasing hormone, human placental lactogen, calcitonin gene–related peptide, adrenomedullin, and vasoactive intestinal peptide (Fig. 33.5). Before term, the uterus goes through an activation phase characterized by (1) greater expression of a series of contraction-associated proteins (including myometrial receptors for prostaglandins and oxytocin), (2) activation of certain ion channels, and (3) an increase in connexin-43 concentration. Expression of the oxytocin receptor in the human myometrium is tightly regulated during pregnancy. Its levels increase during gestation, with a relative paucity of receptors in mid-gestation, accumulation in the third trimester, and peak at labor onset. The receptors fall sharply in advanced labor and the postpartum period, when the uterus becomes refractive to oxytocin.

There is evidence, albeit from animal models, that the fetus may contribute to changes in uterine activity through (1) its influence on the production of placental steroid hormones, (2) mechanical distention of the uterus, and (3) secretion of neurohypophyseal hormones and other stimulators of prostaglandin synthesis. The final common pathway for labor is thought to be activation of the fetal hypothalamic-pituitary-adrenal axis. Of interest, however, is the observation that spontaneous labor occurs in women even if a fetus is anencephalic (without a functioning pituitary gland), suggesting that intact neurohypophyseal function is not a prerequisite for the onset of human labor.

In recent years, the hormonal control of human parturition has been linked to progesterone signaling, and it appears that human parturition may be triggered by a functional progesterone withdrawal, mediated at least in part by changes in progesterone receptor transcriptional activity. It is also thought that parturition may be related to changes in inflammation, which itself is linked to functional progesterone withdrawal.

### Efficacy of Tocolytic Therapy

There is general consensus that acute tocolytic therapy (of any type) for the treatment of preterm labor offers only limited benefit and does not reduce the rate of preterm birth. According to a network meta-analysis, compared with placebo, the probability of delivery being delayed by 48 hours was highest with prostaglandin synthesis inhibitors (odds ratio [OR], 5.39; 95% CI, 2.14 to 12.34) followed by magnesium sulfate (OR, 2.76; 95% CI, 1.58 to 4.94), calcium entry-blocking agents (OR, 2.71; 95% CI 1.17 to 5.91), beta-adrenergic receptor agonists (OR, 2.41; 95% CI, 1.27 to 4.55), and the oxytocin receptor blocker, atosiban (OR, 2.02; 95% CI, 1.10 to 3.80). No class of tocolytic was significantly superior to placebo in reducing neonatal respiratory distress syndrome. Meta-analysis has also suggested that calcium entry–blocking agents (e.g., nifedipine), which block calcium inflow into cells through voltage-dependent calcium channels, have benefits over beta-adrenergic receptor agonists with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects.

Although beta-adrenergic receptor agonists (e.g., ritodrine, terbutaline), which relax smooth muscle via

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**Fig. 33.5** The regulation of uterine activity during pregnancy and labor can be divided into four distinct physiologic phases—quiescence, activation, stimulation, and involution—that are, or may be, influenced by a number of stimulatory and inhibitory factors. (From Liao JB, Buhimschi CS, Norwitz ER. Normal labor: mechanism and duration. Obstet Gynecol Clin North Am. 2005;32:145–164; modified from Challis JRG, Gibb W. Control of parturition. Prenat Neonat Med. 1996;1:283.)
beta₂-adrenergic receptor stimulation, were used as tocolytic agents for many years, in current practice they are utilized less than other tocolytic agents (e.g., nifedipine, oxytocin antagonists) that are equally efficacious with fewer side effects.⁷⁹,⁸⁰ A 2014 meta-analysis that compared beta-adrenergic receptor agonists with placebo concluded that use of beta-adrenergic receptor agonists reduced the number of women who delivered within 48 hours and decreased the number of births within 7 days.⁸¹ However, there was no reduction in preterm birth rate or in perinatal/neonatal death or neonatal morbidity. Tocolysis was significantly associated with adverse maternal side effects (see Table 33.5). Intravenous ritodrine is no longer marketed in the United States. In 2011, the United States Food and Drug Administration (FDA) issued a warning regarding terbutaline use.⁸² Specifically, it stated that injectable terbutaline should not be used in pregnant women for prolonged treatment (beyond 48 to 72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for maternal cardiac problems and death. It also noted that oral terbutaline should not be used for prevention or treatment of preterm labor because it had not been shown to be effective and was associated with similar safety concerns.⁸²

Prostaglandins are mediators in the final pathways of uterine contraction. They increase intracellular calcium concentrations, increase activation of MLCK, and promote gap junction formation. The nonselective cyclooxygenase inhibitor indomethacin is the agent in this class most often studied as a tocolytic agent. Serious maternal side effects are uncommon. Fetal concerns, in particular in the setting of prolonged use (greater than 48 hours), include a risk for constriction of the ductus arteriosus and oligohydramnios (caused by fetal renal dysfunction). A recent systematic review concluded no clear benefit for cyclooxygenase inhibitors was shown compared with placebo or any other tocolytic agents.⁸³ The oxytocin receptor antagonist atosiban has also been used as a tocolytic agent. Although available in Europe, the drug was not approved by the FDA because of the finding from a randomized trial that women in the atosiban group had a higher rate of fetal death.⁸⁴ A 2014 meta-analysis did not demonstrate superiority of oxytocin receptor antagonists (largely atosiban) compared with placebo, beta-adrenergic receptor agonists, or calcium entry–blocking agents (largely nifedipine) for pregnancy prolongation or neonatal outcomes, although treatment with oxytocin receptor antagonists was associated with fewer adverse maternal effects than treatment with the other two drug classes.⁸⁶ A subsequent large randomized controlled trial comparing atosiban with nifedipine found that 48 hours of tocolysis with nifedipine or atosiban results in similar perinatal outcomes.⁸⁵

Magnesium sulfate also has been used as a tocolytic agent. A 2014 meta-analysis of 37 heterogeneous trials that compared magnesium with placebo, no treatment, or other tocolytic drugs⁸⁴ concluded that magnesium is ineffective in delaying or preventing preterm birth and has no apparent advantages for a range of neonatal and maternal outcomes as a tocolytic agent, and its use for this indication may be associated with an increased risk for total fetal, neonatal, or infant mortality.

The nitric oxide donor nitroglycerin has also been evaluated for its efficacy as a tocolytic. However, findings from meta-analyses indicate that nitroglycerin does not result in significantly later gestational age at delivery or better neonatal outcome compared with placebo or other tocolytic drugs.⁸⁶ The ACOG⁸⁸ has stated that evidence supports the use of tocolytic treatment with beta-adrenergic receptor agonist therapy, calcium entry–blocking agents, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for antenatal maternal corticosteroid administration. Multiple clinical trials have demonstrated that prolonged use of tocolytic agents (as prophylactic therapy or after completion of acute treatment) does not alter outcome. No matter which tocolytic agent is chosen, the risk for side effects appears to increase when more than one tocolytic agent is administered simultaneously.⁸⁷ It is unclear whether a combination of tocolytic drugs for preterm labor is more effective for women and/or newborns because there is a lack of large, well-designed trials that include the outcomes of interest.⁸⁷

THE PRETERM INFANT

Physiology

Several, but not all, studies have suggested that the incidence of intrapartum acidosis is greater in the preterm fetus than in the term fetus.⁸⁸ The preterm fetus has lower hemoglobin concentration and oxygen-carrying capacity than a term fetus. Nonetheless, these characteristics do not translate into a higher risk for intrapartum fetal neurologic injury.

Preterm infants are at risk for a number of complications, including respiratory distress syndrome, hyperbilirubinemia, necrotizing enterocolitis, intraventricular hemorrhage, perinatal infection, retinopathy of prematurity, patent ductus arteriosus, pulmonary hypertension, water and electrolyte imbalances, acid-base disturbances, anemia, and hypoglycemia. In the long term, preterm infants also are more likely to experience adverse outcomes such as bronchopulmonary dysplasia, reactive airway disease, failure to thrive, cerebral palsy, neurodevelopmental delay, hearing loss, blindness, pulmonary hypertension, adult hypertension, and impaired glucose regulation.²

Method of Delivery

For very preterm infants, especially less than 26 weeks’ gestation, there is controversy regarding best mode of delivery. Although some studies have suggested survival advantage for those delivered by cesarean, these data are not consistent, and the potential for confounding (and particularly confounding by indication) is such that preterm birth at any gestational age is not considered a contraindication for trial of labor.⁸⁹ A systematic review of six randomized controlled trials comparing elective with selective cesarean delivery for preterm infants (n = 122) found no difference in outcomes between groups, although the confidence intervals were wide.
because of the small number of patients included in the analysis. A retrospective analysis of 2466 VLBW preterm infants delivered in the state of Washington between 1994 and 2003 did not demonstrate any benefit of cesarean delivery for improving survival. In a study published in 2012, Reddy et al. examined neonatal outcomes by attempted route of delivery for singleton births that occurred between 24 0/7 and 31 6/7 weeks’ gestation. Among women who delivered between 24 0/7 and 27 6/7 weeks’ gestation with a vertex presentation, 77.2% attempted vaginal delivery (85% success rate) with the remainder undergoing scheduled cesarean delivery. No difference was observed in neonatal mortality or other adverse neonatal outcomes between the two groups. Similarly, when examining outcomes in women with a vertex presentation between 28 0/7 and 31 6/7 weeks’ gestation, no difference in neonatal mortality was found in women who attempted vaginal delivery compared with those who underwent planned cesarean delivery.

Aside from operative risks in the index pregnancy, preterm cesarean delivery may increase maternal risk in subsequent pregnancies. In an observational study that involved 26,454 women with previous cesarean delivery, the Maternal-Fetal Medicine Units Network noted that women with a prior preterm cesarean delivery were at higher risk for uterine rupture than women with a prior term cesarean delivery (OR, 1.6; 95% CI, 1.01 to 2.50).

Most obstetricians perform cesarean delivery for the delivery of a VLBW singleton fetus in a breech presentation. A systematic review of seven studies involving more than 3500 women concluded that cesarean delivery reduces neonatal morbidity when compared with vaginal delivery for breech presentation. Head entrapment behind an incompletely dilated cervix is more common in preterm singleton fetuses with a breech presentation than in term infants because the head is larger than the wedge formed by the buttocks and thighs. Similarly, cesarean delivery has been recommended for preterm twins in whom the presenting fetus has a nonvertex presentation, although there are no prospective, controlled studies to support this practice. The management of preterm twins when twin A is vertex and twin B is nonvertex is more controversial; there are no good data from clinical trials, and the results from observational studies suffer from potential selection and confounding bias. Thus, a definitive recommendation regarding whether a breech second twin should be delivered by cesarean remains elusive; it seems reasonable that practitioners with experience can individualize care, taking into account the clinical circumstances, and offer certain patients the option of delivering preterm twins vaginally if the first twin has a vertex presentation.

The survival rate remains low for infants with a birth weight between 500 and 750 g. In these cases, obstetricians must decide whether to recommend cesarean delivery for fetal indications, such as in cases of nonreassuring fetal status or breech presentation. The neonatologist is frequently asked to speak with the patient about the risk for neonatal morbidity and mortality so that the patient can make an informed decision about the method of delivery. Regardless of the mode of delivery, if resuscitation is planned, additional support personnel (ideally a neonatologist and a neonatal resuscitation team) should be prepared and present for the delivery.

Ethical Issues

The antenatal maternal administration of corticosteroids, the application of advanced neonatal ventilation techniques, the use of neonatal surfactant therapy, and the use of extracorporeal membrane oxygenation (ECMO) have reduced mortality and morbidity for preterm neonates. However, below a certain gestational age (i.e., less than 22 0/7 to 23 0/7 weeks), survival is not typically possible and the relationship between new treatments and reduced mortality is not relevant. Around the time when survival becomes at least possible, the chance of survival, and particularly survival without long-term major adverse outcomes, remains low and difficult to predict for any individual neonate. These uncertainties often lead to controversy about the decision to resuscitate (or not resuscitate) a preterm infant. Parents, obstetricians, and neonatologists should all be involved in the decision-making process.

Anesthesia providers may find themselves in the middle of these ethical dilemmas if they are practicing at a location in which the anesthesia provider is responsible for neonatal resuscitation. Although no firm rules exist, some basic principles can be applied. First, the parents should have a critical role in the decision-making process. Second, as much data as possible should be obtained to provide a prognostic assessment. Third, discussion of these issues ideally should be held before delivery, not in the moment of crisis. The ACOG has published general recommendations about the care of infants on the threshold of viability but has not made specific recommendations for neonatal resuscitation on the basis of gestational age.

Withholding and/or discontinuation of life-sustaining treatment during or following resuscitation are considered by many to be ethically equivalent, and it is considered reasonable to withdraw support when the possibility of functional survival is highly unlikely. In cases of very early gestation (gestational age less than 22 to 23 weeks), extremely low birth weight (less than 400 g), and life-limiting anomalies, resuscitation is generally not indicated. Resuscitation is nearly always indicated in conditions associated with a high survival rate and acceptable morbidity. This will generally include infants with a gestational age of 25 weeks or above. In conditions associated with uncertain prognosis, parental desires regarding resuscitation should be supported.

Fetal Heart Rate Monitoring

Most obstetricians use continuous electronic fetal heart rate (FHR) monitoring once preterm labor becomes established and the gestational age and circumstances are consistent with the possibility of neonatal survival. Preterm gestation may complicate the interpretation of FHR patterns, given that the FHR pattern of preterm fetuses may have relatively decreased
variability and magnitude of accelerations compared with the FHR pattern of term fetuses.39

The value of continuous electronic FHR monitoring over intermittent auscultation of the FHR remains controversial. Luthy et al.100 performed a randomized trial comparing continuous electronic FHR monitoring (with selective fetal blood gas assessment) with periodic auscultation of the FHR during preterm labor in women with fetuses weighing between 700 and 1750 g. There was no significant difference between groups in the incidence of cesarean delivery, low 5-minute Apgar scores, intrapartum acidosis, intracranial hemorrhage, or perinatal death. A meta-analysis, which added a second trial, also showed no benefit in preventing cerebral palsy (RR, 1.75; 95% CI, 0.84 to 3.63).59 In a follow-up study at 18 months of age in the infants included in the study by Luthy et al.,106 the incidence of cerebral palsy was significantly higher in the electronic FHR group than in the intermittent auscultation group (20% versus 8%, respectively).101

ANESTHETIC MANAGEMENT

Anesthesia providers often participate in the care of women with preterm delivery. Many women who deliver preterm request neuraxial analgesia for labor and vaginal delivery. These patients may also require cesarean delivery, for example, in situations of nonreassuring fetal status, and may require urgent administration of anesthesia.

Conventional wisdom holds that the preterm fetus is more vulnerable than the term fetus to the depressant effects of analgesic and anesthetic drugs, for the following reasons: (1) less protein available for drug binding, leading to a reduction in protein-drug affinity; (2) higher levels of bilirubin, which may compete with the drug for protein binding; (3) greater drug access to the central nervous system (CNS) because of the presence of an incomplete blood-brain barrier; (4) decreased ability to metabolize and excrete drugs; and (5) a higher incidence of acidosis during labor and delivery.88,102 However, few controlled studies have documented the maternal and fetal pharmacokinetics and pharmacodynamics of anesthetic agents throughout gestation. The preterm fetus may be less vulnerable to the depressant effects of local anesthetics than originally thought. The human fetal liver cytochrome P450 system is present as early as 14 weeks’ gestation and has the capability to oxidize several drugs.103,104

Perinatal Effects of Maternal Local Anesthetics

Teramo et al.105 noted that the amount of lidocaine necessary to produce seizure activity in preterm fetal lambs was greater than that required in older fetal lambs. These investigators also observed that the cardiovascular response to lidocaine (i.e., increases in blood pressure and heart rate) was less severe in fetuses with a younger gestational age. Pedersen et al.106 evaluated the effects of gestational age on the pharmacokinetics and pharmacodynamics of lidocaine in gravid ewes and fetal lambs. They studied two groups of animals, preterm (119 ± 1 days’ gestation or 0.8 of term pregnancy) and near-term (138 ± 1 days’ gestation or 0.95 of term pregnancy). They administered an intravenous infusion of lidocaine to obtain a maternal steady-state plasma concentration of 2 µg/mL. Transplacental transfer of lidocaine did not adversely affect fetal cardiac output, organ blood flow, or blood gas and acid-base measurements in either group. Tissue uptake of lidocaine was similar in the two groups of fetal lambs, except that it was greater in the lungs and liver of the term fetuses. The investigators concluded that there was no significant difference in the pharmacokinetics and pharmacodynamics of lidocaine between the two gestational ages studied.106

Smedstad et al.107 also concluded that there was no difference in fetal blood pressure, heart rate, or blood gas measurements in response to maternal intravenous infusion of lidocaine or bupivacaine between early preterm (119 days’ gestation) and late preterm (132 days’ gestation) fetal lambs. In addition, the plasma concentrations of bupivacaine and lidocaine and the fetal-to-maternal ratios of both drugs were similar in the two groups of fetuses.

None of these studies evaluated the effects of anesthetic agents on the acidic preterm fetus. Asphyxia may increase the risk for adverse effects by causing the following changes in the fetal environment: (1) reduced plasma protein-binding capacity (which increases the proportion of free drug available)108; (2) greater maternal-fetal hydrogen ion difference, which causes “ion trapping” of weak bases (e.g., amide local anesthetics, opioids) on the fetal side of the circulation;109; (3) greater blood-brain barrier permeability110; and (4) enhanced susceptibility to the myocardial depressant effects of local anesthetics.111,112

Morishima et al.111 subjected a group of preterm fetal lambs (0.8 of term gestation) to asphyxia by causing partial occlusion of the umbilical cord. They subsequently administered either lidocaine or saline-control intravenously to the gravid ewes for 180 minutes. The mean (± SD) maternal and fetal steady-state plasma lidocaine concentrations were 2.32 ± 0.12 and 1.23 ± 0.17 µg/mL, respectively. (These concentrations are similar to those that occur during administration of epidural anesthesia in humans.) Umbilical cord occlusion resulted in the typical fetal compensatory response to hypoxia (i.e., decreased FHR and increased blood flow to the fetal brain, heart, and adrenal glands). Maternal administration of saline-control did not result in additional deterioration of the fetus. However, maternal administration of lidocaine resulted in a significant increase in PaCO2, and decreases in pH, mean arterial pressure (MAP), and blood flow to the brain, myocardium, and adrenal glands. Thus, lidocaine attenuated the normal fetal compensatory response to asphyxia.

In an earlier study, the same investigators observed that lidocaine did not affect the fetal compensatory response to asphyxia in term fetuses.112 They concluded that “the immature fetus loses its cardiovascular adaptation to asphyxia when exposed to clinically acceptable plasma concentrations of lidocaine obtained transplacentally from the mother.”93,111 Limitations of this study include (1) a failure to compare the fetal response to lidocaine with the response to other...
anesthetic, analgesic, or sedative drugs and (2) consideration of only the effects of a steady-state concentration of lidocaine in the presence of asphyxia. That is, the investigators did not evaluate the potential benefits derived from epidural anesthesia, such as reduced maternal concentrations of catecholamines and the ability of epidural anesthesia to facilitate a controlled, atraumatic delivery of the preterm infant.

Bupivacaine has a low fetal-to-maternal plasma concentration ratio because of its high (96%) maternal protein binding; therefore, the potential for fetal toxicity seems minimal. Studies of the effects of bupivacaine on the compensatory response to asphyxia in preterm fetal lambs have demonstrated results similar to those seen with lidocaine. Santos et al. observed that bupivacaine abolished the compensatory increase in blood flow to vital organs in asphyxiated preterm fetal lambs. However, bupivacaine did not affect fetal heart rate, blood pressure, or acid-base measurements. The investigators suggested that these changes were less severe than those seen with lidocaine in their earlier study.

Ropivacaine and bupivacaine have almost identical dissociation constants (pKₐ of 8.0 and 8.2, respectively), but ropivacaine's protein binding is slightly less than that for bupivacaine (92% versus 96%, respectively), and it is substantially less lipid soluble than bupivacaine (see Chapter 13). These differences may affect maternal and fetal free plasma concentrations of drug. Investigators have documented higher maternal and fetal plasma concentrations with ropivacaine than with bupivacaine. Studies suggest that ropivacaine is less cardiotoxic than bupivacaine. However, no study has evaluated the effect of ropivacaine on the fetal compensatory response to hypoxia.

2-Chloroprocaine also is a good choice of local anesthetic to use for the mother of a preterm fetus because it is rapidly metabolized in both the maternal plasma and fetal plasma. Further, placental transfer of 2-chloroprocaine is not increased by fetal acidosis.

Vaginal Delivery

Neuraxial labor analgesia decreases maternal concentrations of catecholamines, ameliorates cycles of maternal hyperventilation and hyperventilation, and may thereby improve uteroplacental perfusion as long as hypotension is avoided. No prospective, controlled studies have evaluated the effect of neuraxial analgesia on preterm infant outcome. The timing of the intrapartum administration of neuraxial analgesia in preterm parturients may be problematic for several reasons. First, there may be uncertainty as to whether women who have contractions are in labor. Second, even women with a clear diagnosis of preterm labor often have a prolonged latent phase of labor, with or without the use of tocolytic agents. Third, once active labor begins, patients often progress though labor very quickly. Thus, in some cases, it may be appropriate to establish neuraxial analgesia even before it is clear that a preterm delivery will soon occur. An advantage of early initiation of neuraxial analgesia is the ability to rapidly convert labor analgesia to surgical anesthesia if emergency cesarean delivery should be necessary.

Cesarean Delivery

Administration of general anesthesia for preterm cesarean delivery is similar to that for parturients at term (see Chapter 26). Most anesthetic agents that are used for induction and maintenance of general anesthesia cross the placenta. If cesarean delivery is necessary, conventional wisdom holds that it is preferable to administer either epidural or spinal anesthesia to avoid the depressant effects of agents given for general anesthesia. Roblin et al. observed that preterm infants exposed to epidural anesthesia for cesarean delivery had higher 1- and 5-minute Apgar scores than similar infants exposed to general anesthesia. Laudenbach et al. performed a secondary analysis of prospectively gathered data from a population-based cohort study of all deliveries before 33 weeks’ gestation in nine regions in France in 1997 (n = 1338). Of concern, after controlling for known confounders, infants born by cesarean delivery to mothers who received spinal anesthesia had a higher mortality rate than those born to mothers who received general or epidural anesthesia (adjusted OR, 1.7; 95% CI, 1.1 to 2.6). However, the authors noted that the secondary analysis of a preexisting database did not allow them to adjust for confounders known to affect anesthetic outcome (e.g., intraoperative hypotension, choice of vasopressor, fluid management). Nonetheless, for these high-risk births, it seems reasonable that anesthesia providers should pay meticulous attention to maternal hemodynamic variables regardless of the type of anesthesia that is administered.

Data from animal studies suggest that exposure of the immature brain to anesthetic agents such as propofol, thiopental, ketamine, and inhalation agents can trigger significant brain cell apoptosis in the developing fetal/neonatal brain and cause functional learning deficits in later life. However, in these animal studies, the duration of exposure to anesthetic agents was much longer than is typical for cesarean delivery in humans. Whether clinical exposure to anesthetic agents during general anesthesia for cesarean delivery results in clinically significant brain cell apoptosis in humans remains to be determined (see Chapter 10).

The term pregnant patient requires significantly less local anesthetic to achieve adequate surgical anesthesia than nonpregnant women (see Chapter 2). There are limited data about spinal dose requirements for cesarean delivery in preterm parturients. A retrospective study of over 5000 patients investigated the association between gestational age and the risk for inadequate spinal anesthesia for cesarean delivery. The incidence of neuraxial block failure correlated inversely with gestational age, decreasing from 10.8% for women who were less than 28 weeks’ gestation, to 7.7% for those between 28 and 32 weeks, and 5.3% or less for those beyond 32 weeks. In multivariable analysis, the association of gestational age with block failure was not significant; however, birth weight less than 2500 g was associated with a 2.5-fold increased odds of failed neuraxial anesthesia.

In summary, at the current time there is minimal evidence to support altering the anesthetic technique for cesarean
delivery merely because the infant is preterm. Further study is necessary to determine whether one technique or medication has specific risks or benefits relative to the preterm infant.

**Anesthesia for Rescue Cerclage Placement and Cerclage Removal**

Cerclage placement requires a T10 level of surgical anesthesia (see Chapter 16). Frequently, rescue cerclage placement is a brief surgical procedure lasting less than 30 minutes. Occasionally, surgical complexity can extend the procedure to as long as 2 hours. Advanced cervical dilation and prolapsed membranes increase complexity. In addition, patient characteristics (e.g., morbid obesity) may extend the duration required for positioning and increase the risks associated with unplanned induction of general anesthesia. The optimal anesthetic technique depends on the obstetric plan, specifically whether the patient will be admitted for prolonged observation or will be discharged home. Shorter-acting spinal anesthetics may accelerate recovery and discharge for those going home. For those who will be admitted for postprocedure monitoring, a longer-duration spinal anesthetic or a catheter-based neuraxial technique may be appropriate.

Usually, cerclage removal does not require anesthesia, but surgical anesthesia may be necessary if the stitch is embedded under the cervical mucosa (i.e., “buried”). Spinal anesthesia for cerclage removal requires a T10 sensory level, and depending on gestational age and fetal weight, may result in excessive blockade if doses typically used for early second-trimester cerclage placement are used. The decision to utilize a catheter-based technique or single-shot spinal anesthesia depends on the obstetric plan, specifically, whether the patient will remain in hospital for delivery or will be discharged home to await spontaneous labor.

**Venous Thromboembolism Prophylaxis**

Obstetric venous thromboembolism (VTE) is a leading cause of maternal morbidity and mortality (see Chapter 38). Antepartum hospitalization and prolonged immobility increase the risk for VTE, particularly among obese women. Several professional societies recommend pharmacologic VTE prophylaxis for prolonged antepartum admissions, although the suggested dosing regimens are not uniform. For example, the National Partnership for Maternal Safety recommends daily thromboprophylaxis with low-molecular-weight heparin, or twice-daily thromboprophylaxis with unfractionated heparin, for all antepartum patients hospitalized for more than 72 hours. With wider adoption of these VTE guidelines, an increasing number of pregnant women will present for neuraxial analgesia or anesthesia in the context of pharmacologic anticoagulation. Strategies to ensure safe neuraxial blockade for women receiving anticoagulant drugs are discussed in Chapter 38 and are addressed by consensus documents from the Society for Obstetric Anesthesia and Perinatology and the American Society of Regional Anesthesia. Regular, ongoing communication between obstetricians and anesthesia providers to discuss women admitted to the hospital for antepartum care is required to ensure that evolving plans for delivery or surgical intervention appropriately inform optimal anticoagulation and anesthetic management.

**INTERACTIONS BETWEEN TOCOLYTIC THERAPY AND ANESTHESIA**

**Indications for Anesthesia during and after Tocolytic Therapy**

There are several situations in which obstetric patients require analgesia or anesthesia during or after tocolytic therapy. First, preterm labor may progress and delivery may occur despite tocolysis. In this case, the patient may desire pain relief during labor and vaginal delivery or may require anesthesia for cesarean delivery. Second, some obstetricians give a tocolytic agent before and during the performance of therapeutic cervical cerclage. Third, some obstetricians advocate the bolus injection of a tocolytic agent when there is a tetanic uterine contraction or tachysystole in the setting of FHR abnormality. Fourth, many obstetricians administer tocolysis when attempting external cephalic version, a procedure that may also involve neuraxial analgesia.

**Calcium Entry–Blocking Agents**

Nifedipine is the specific drug within this class that has undergone the most extensive evaluation as a tocolytic agent; it has been proposed by some as a first-line therapy for treatment of preterm labor. Typical nifedipine dose regimens for preterm labor are listed in Table 33.6.

**TABLE 33.6 Tocolytic Dose Regimens for Preterm Labor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initiation Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>20–30 mg PO</td>
<td>10–20 mg every 4–6 h</td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors (NSAIDs)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>50–100 mg PO or PR</td>
<td>25–50 mg every 4–6 h</td>
</tr>
<tr>
<td>Ketrocolac</td>
<td>60 mg IM</td>
<td>30 mg every 6 h</td>
</tr>
<tr>
<td>Sulindac</td>
<td>200 mg PO</td>
<td>200 mg every 12 h</td>
</tr>
<tr>
<td>Terbutaline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.25 mg SQ</td>
<td>0.25 mg every 20 min to 3 h</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>4–6 g IV bolus over 20 min</td>
<td>2–4 g/h continuous IV infusion</td>
</tr>
</tbody>
</table>

IM, Intramuscularly; IV, intravenously; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, per os (orally); PR, per rectum; SQ, subcutaneously.

<sup>a</sup>NSAI administration should be limited to 48 to 72 hours and restricted to gestations less than 32 weeks.

<sup>b</sup>Treatment with terbutaline administered by injection or by continuous infusion pump should not be used beyond 48 to 72 hours. In particular, injectable terbutaline should not be used in the outpatient or home setting.
Mechanism of Action

Calcium-entry blocking agents block the aqueous voltage-dependent cell membrane channels that are selective for calcium and prevent calcium release from the sarcoplasmic reticulum. The net result is a decrease in available intracellular calcium, which inhibits MLCK activity. This inhibition leads to decreased actin-myosin interaction, which results in relaxation of smooth muscle (including myometrial smooth muscle).128

Side Effects

Nifedipine has fewer side effects than beta-adrenergic receptor agonists. Common side effects include headache, flushing, dizziness, palpitations, and nausea.129 Most effects are mild, but pulmonary edema has been reported. Nifedipine induces significant afterload reduction. This triggers a compensatory increase in cardiac output, which is usually well tolerated, but may increase the risk for demand myocardial ischemia or heart failure in women with underlying cardiac disease.

Although some initial animal studies raised concern that nifedipine and nicardipine could decrease uterine blood flow and increase fetal hypoxemia and acidosis, clinical studies have not demonstrated these outcomes.131-135

Anesthetic Management

Although nifedipine has fewer effects on cardiac conduction than some of the other calcium entry–blocking agents, it has the potential to cause vasodilation, hypotension, myocardial depression, and conduction defects when used in combination with volatile halogenated anesthetic agents.136 One report noted that administration of both nifedipine and magnesium sulfate was associated with neuromuscular blockade in a preeclamptic patient at 28 weeks’ gestation.137

Cyclooxygenase Inhibitors

Indomethacin is the cyclooxygenase inhibitor most typically used for tocolysis, although other agents such as sulindac and ketorolac have been evaluated. Typical doses of this class of medication used for tocolysis are listed in Table 33.6.

Mechanism of Action

Cyclooxygenase inhibitors inhibit the enzyme cyclooxygenase, and thereby prevent the conversion of arachidonic acid to prostaglandins, which stimulate uterine contractions.

Side Effects

Maternal side effects from indomethacin are minimal when it is used for tocolytic therapy; nausea and heartburn are the most common complaints.138 Indomethacin is often used to promote closure of the ductus arteriosus in the preterm neonate; thus, there has been concern that maternal administration may result in premature ductus closure in the fetus.139 Moise et al.139 used fetal echocardiography to evaluate the fetal response to short-term (less than 72 hours) indomethacin therapy. They observed evidence of transient ductal constriction in 7 of 14 fetuses between 26 and 31 weeks’ gestation. Tricuspid regurgitation was also noted in three fetuses. These changes, however, were reversed within 24 hours of discontinuation of indomethacin, and are less likely at earlier gestational ages.138,140-142 Additionally, studies suggest that clinically significant adverse neonatal effects are unlikely if indomethacin is used in short courses (e.g., 24 to 48 hours).138,141,142

Indomethacin administration also may result in fetal oligohydramnios secondary to decreased fetal urine output.143-145 However, even when it occurs, amniotic fluid usually increases to normal levels within 1 week after its discontinuation. One proposed mechanism for the decrease in fetal urine output is an enhanced antidiuretic hormone effect.146 Wurtzel147 showed that maternal administration of indomethacin did not significantly alter neonatal renal function. There is no consistent evidence that transient prenatal administration of indomethacin results in poorer neonatal outcomes.148

Anesthetic Management

The effects of indomethacin on platelet function are transient. Several large studies have demonstrated the safety of epidural and spinal anesthesia in patients receiving low-dose aspirin or one of a variety of cyclooxygenase inhibitors.126 Consensus statements from professional anesthesiology societies have concluded that such therapy is not a contraindication to administration of neuraxial anesthesia, but that additional caution is recommended for patients receiving NSAIDs in combination with other pharmacologic anticoagulation (see Chapter 38).126

NSAIDs and acetaminophen are key components of effective postcesarean delivery pain management. Administration of ketorolac or other NSAIDs for postoperative analgesia should consider the timing and dose of any previously administered indomethacin.

Beta-Adrenergic Receptor Agonists

The use of the beta-adrenergic receptor agonists, ritodrine and terbutaline, for tocolysis has declined substantially because of maternal side effects.141

Mechanism of Action

Beta2-adrenergic receptors are found in smooth muscle (uterus, blood vessels, bronchi, intestine, detrusor, and spleen capsule) as well as a variety of other tissues. Ritodrine and terbutaline are relatively selective for beta2-adrenergic receptors; stimulation of these receptors in the myometrium results in relaxation of uterine smooth muscle. Unfortunately, other undesired beta2-adrenergic agonist effects (e.g., vasodilation) and beta1-adrenergic agonist effects (e.g., increased maternal heart rate and cardiac output) still occur.149

Beta-adrenergic agonists interact with beta2-adrenergic receptors on the outer membrane of uterine myometrial cells, activating the enzyme adenylyl cyclase, which catalyzes the conversion of ATP to cAMP and causes a decrease in intracellular calcium.143
Treatment Regimen
Before initiation of treatment, the provider should obtain baseline maternal vital signs and weight, and exclude significant cardiovascular or pulmonary disease. There is no evidence that a continuous long-term infusion of terbutaline alters pregnancy outcome. In 2011, the FDA warned against both outpatient treatment with terbutaline and inpatient treatment beyond 48 to 72 hours.82

Side Effects
The administration of beta-adrenergic tocolytic therapy has resulted in the following maternal side effects: (1) hypotension; (2) tachycardia, with or without cardiac arrhythmias and myocardial ischemia; (3) pulmonary edema; (4) hyperglycemia; and (5) hypokalemia.143 The reported frequency of these side effects varies from 0.5% to 9%.150–152 Other uncommon maternal side effects reported with the use of beta-adrenergic receptor agonists are elevations in serum transaminase levels,153 paralytic ileus,154 cerebral vasospasm in patients with a previous history of migraine,154 and respiratory arrest caused by increased muscle weakness in a patient with myasthenia gravis.156

Anesthetic Management
Ideally, the initiation of anesthesia would be delayed until beta-adrenergic receptor agonist–induced maternal tachycardia subsides. A delay of 15 minutes often results in slowing of the maternal heart rate. However, advanced labor, an abnormal presentation, and/or nonreassuring fetal status often require emergency administration of anesthesia. Published reports of anesthetic management after administration of a beta-adrenergic receptor agonist are scarce.157–161 Ravindran et al.159 reported one case each of intraoperative pulmonary edema, sinus tachycardia, and ventricular arrhythmia during general anesthesia in patients who had received terbutaline therapy immediately before or 15 minutes after the induction of anesthesia.

Theoretically, induction of epidural analgesia or anesthesia after beta-adrenergic receptor agonist therapy may cause less hemodynamic compromise than spinal anesthesia because of the slower onset of sympathetic blockade. However, this theory remains unproven. Patients receiving beta-adrenergic receptor agonist therapy are at risk for development of pulmonary edema. Therefore, aggressive hydration should be avoided before and during the induction of anesthesia in these patients.

If general anesthesia is required in a patient who has recently received tocolysis with a beta-adrenergic receptor agonist, agents that might exacerbate maternal tachycardia (e.g., atropine, glycopyrrolate, ephedrine, norepinephrine) should be avoided. Residual maternal tachycardia may make it more difficult to assess volume status and depth of anesthesia. Hyperventilation should be avoided, because it may exacerbate hypokalemia and potentiate the hyperpolarization of the cell membrane. In nonpregnant patients, Slater et al.162 found that terbutaline pretreatment shortened the onset time and recovery of succinylcholine-induced neuromuscular blockade. It seems prudent to monitor neuromuscular function with a peripheral nerve stimulator during general anesthesia.

Oxytocin Receptor Antagonists
Atosiban (1-deamino-2-3-Tyr-1[OEt]-4-Thr-8-Orn-vasotocin/ oxytocin) is an oxytocin receptor antagonist. It is a competitive inhibitor of oxytocin that binds to both myometrial and decidual receptors. It does not alter the subsequent sensitivity of the myometrium to oxytocin.189 Clinically, this feature represents a major advantage; it should reduce the risk for postpartum uterine atony and hemorrhage.

Studies have suggested that atosiban has efficacy similar to that of beta-adrenergic receptor agonists and nifedipine in obtaining and maintaining uterine quiescence. However, a meta-analysis of studies comparing atosiban with either placebo or beta-adrenergic receptor agonists did not demonstrate that atosiban resulted in a reduction in preterm birth or improved neonatal outcome, although side effects were fewer with atosiban.164 Phase II and III studies have shown that atosiban has few maternal side effects, undergoes minimal placental transfer, and does not increase maternal blood loss at delivery.84,85,165 The FDA has not approved atosiban for use in the United States because of a higher rate of perinatal deaths in the atosiban arm of the study that it reviewed.19

There are no data on the interaction between atosiban and anesthetic agents. However, given the hemodynamic profile of this agent, one would not expect significant interactions. Atosiban is widely used in Europe.

Magnesium Sulfate
Mechanism of Action
Extracellular magnesium functions as a competitive antagonist of calcium, thus reducing calcium influx into the uterine myocyte.143

Side Effects
Magnesium sulfate results in less frequent and less severe cardiovascular side effects than beta-adrenergic tocolytic agents.166–168 Nonetheless, magnesium sulfate may lead to chest pain and tightness, palpitations, nausea, transient hypotension, blurred vision, sedation, and pulmonary edema.167,168 Hypermagnesemia may attenuate the normal compensatory responses to hemorrhage in the mother and fetus.169,170

Magnesium is eliminated almost entirely by renal excretion. Therefore, patients with abnormal renal function should be monitored carefully if they receive magnesium sulfate, and consideration should be given to administering a lower maintenance dose (i.e., infusion rate) in women with renal dysfunction.

Anesthetic Management
It has been suggested that magnesium sulfate should be discontinued before the administration of neuraxial analgesia or anesthesia because magnesium may increase the likelihood of hypotension through its generalized vasodilating properties. Vincent et al.171 observed that magnesium sulfate reduced
maternal mean arterial pressure but not uterine blood flow or fetal oxygenation during epidural lidocaine anesthesia in gravid ewes. This study suggests that hypermagnesemia may increase the likelihood of modest hypotension during neuraxial anesthesia in normotensive parturients. Clinical relevance in humans is debatable; any effect on hemodynamic parameters may be managed with appropriate fluid and vasopressor therapy, and thus it is not recommended to routinely discontinue magnesium at the time of analgesia or anesthesia is administered.

In contrast, magnesium overdose can have serious consequences for both the mother and fetus. Magnesium sulfate administered for the purpose of fetal neuroprotection may be discontinued at the time of delivery. In the case of emergency cesarean delivery, it may be safest to discontinue the magnesium infusion before transfer to the operating room, given the risk for inadvertent magnesium bolus administration.172

Magnesium potentiates the action of both depolarizing and nondepolarizing muscle relaxants.173 A defasciculating dose of a nondepolarizing muscle relaxant should not be given before administration of succinylcholine in women with hypermagnesemia. A standard intubating dose of muscle relaxant (e.g., succinylcholine 1 mg/kg) should be used because the extent of potentiation by magnesium sulfate is variable.174 Subsequent nondepolarizing neuromuscular muscle relaxants should be administered only if necessary, at the lowest required dose to facilitate surgery.

Parturients receiving magnesium sulfate often appear sedated. Thompson et al.175 evaluated the anesthetic effects of magnesium sulfate and ritodrine on the minimum alveolar concentration of halothane in pregnant and nonpregnant rats and reported a 20% decrease with serum magnesium levels of 7 to 11 mg/dL. A more detailed discussion of magnesium sulfate, its interactions with anesthetic agents, and management of overdose is found in Chapter 35.

**KEY POINTS**

- Despite improved antenatal care, the incidence of preterm delivery in the United States remains approximately 10%.
- Preterm birth is a leading cause of neonatal mortality. Survivors have an increased chance of disability.
- Spontaneous preterm labor or preterm premature rupture of membranes account for the majority of preterm births.
- Treatment with tocolytic therapy may prolong labor by up to 48 hours, and thereby facilitate transfer of the patient from a small community hospital to a tertiary care facility, maternal administration of a corticosteroid to accelerate fetal lung maturity, and maternal administration of magnesium for fetal neuroprotection. Long-term tocolytic therapy does not improve neonatal outcome.
- Nifedipine and indomethacin are used commonly to treat preterm labor in the United States; oxytocin receptor antagonists are used in Europe. Magnesium sulfate is not an effective tocolytic but is considered beneficial when used specifically for neuroprotection in reducing rates of cerebral palsy in preterm infants.
- Terbutaline is associated with a high incidence of maternal and fetal side effects, including hypotension, tachycardia (with or without cardiac arrhythmias and myocardial ischemia), pulmonary edema, hyperglycemia, and hypokalemia. Pulmonary edema is the most serious complication, and it may be life threatening.
- Cyclooxygenase inhibitors reversibly inhibit cyclooxygenase, resulting in a transient effect on platelet function. However, their use does not necessitate the assessment of platelet or coagulation function before administration of neuraxial analgesia/anesthesia in a patient whose only risk factor for bleeding is recent ingestion of a cyclooxygenase inhibitor.
- Prior administration of a tocolytic agent, regardless of drug class, does not contraindicate the administration of neuraxial anesthesia.

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Abnormal Presentation and Multiple Gestation

Joy L. Hawkins, MD

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The labor and delivery of a parturient with a multiple gestation and/or fetal breech presentation represents a major challenge for the obstetrician and the anesthesia provider. Anesthetic requirements may change from moment to moment, and an obstetric emergency may necessitate immediate intervention. All members of the perinatal care team must communicate directly and clearly with each other as well as with the parturient and her family to ensure the best possible outcome for both the mother and the neonate(s).

The presentation denotes that portion of the fetus that overlies the pelvic inlet. In most cases, the fetal presenting part can be palpated through the cervix during a vaginal examination. The presentation may be cephalic, breech, or shoulder. Breech and shoulder presentations occur with increased frequency in patients with multiple gestation. Cephalic presentations are further subdivided into vertex, brow, and face presentations according to the degree of flexion of the neck. With an asynclitic presentation, the fetal head is tilted toward one shoulder and the opposite parietal eminence enters the pelvic inlet first.

The lie refers to the alignment of the fetal spine with the maternal spine. The fetal lie can be either longitudinal or transverse. A fetus with a vertex or breech presentation has a longitudinal lie. A persistent oblique or transverse lie typically requires cesarean delivery.

The position of the fetus denotes the relationship of a specific fetal bony point to the maternal pelvis. The position of the occiput defines the position for vertex presentations (Fig. 34.1). Other markers for position are the sacrum for breech presentations, the mentum for face presentations, and the acromion for shoulder presentations. The attitude of the fetus describes the relationship of the fetal parts with one another; the term is typically used to refer to the position of the head with regard to the trunk, as in flexed, military, or hyperextended.

ABNORMAL POSITION

During normal labor, the fetal occiput rotates to a direct occiput anterior position (see Fig. 34.1). In a minority of patients with a right or left occiput posterior position, the occiput rotates directly posteriorly and results in a persistent occiput posterior position. The occiput posterior position may lead to a prolonged labor that is associated with increased maternal discomfort. Less often, the vertex remains in the occiput transverse position; this condition is known as deep transverse arrest. Obstetricians diagnose fetal head position with ultrasonography or palpation of the sagittal suture during vaginal examination.

Obstetricians may perform manual or forceps rotation to hasten delivery and lessen perineal trauma in women with an abnormal position of the vertex. Today, many obstetricians are reluctant to perform rotational forceps delivery for fear of causing excessive maternal and/or fetal trauma; however, manual rotation of the vertex is often attempted as obstetricians work to facilitate vaginal birth. Some cases of persistent occiput posterior position, and many cases of deep transverse arrest, require cesarean delivery because of dystocia.

During administration of epidural analgesia to a patient with an abnormal position, the addition of a lipid-soluble opioid to a dilute solution of local anesthetic is particularly useful. This combination provides analgesia while preserving
Abnormal Presentation and Multiple Gestation

CHAPTER 34

Abnormal Presentation and Multiple Gestation

presentation may influence the obstetrician’s decision regarding the mode of delivery. The fetus with a frank breech presentation tends to remain in that presentation throughout labor. In contrast, a complete breech presentation may change to an incomplete breech presentation at any time before or during labor.

Epidemiology

The breech presentation is the most common of the abnormal presentations. Both the incidence and the type of breech presentation vary with gestational age (Table 34.1). Before 28 weeks’ gestation, approximately 25% of fetuses are in a breech presentation. In contrast, profound pelvic floor relaxation is needed to facilitate instrumental vaginal delivery with forceps.

BREECH PRESENTATION

Breech presentation describes a longitudinal lie in which the fetal buttocks and/or lower extremities overlie the pelvic inlet. Fig. 34.2 shows the three varieties of breech presentation:

- **Frank breech**—lower extremities flexed at the hips and extended at the knees
- **Complete breech**—lower extremities flexed at both the hips and the knees
- **Incomplete breech**—one or both of the lower extremities extended at the hips

Ultrasonographic or radiographic examination typically allows the obstetrician to confirm the type of breech presentation and to exclude the presence of associated severe congenital anomalies (e.g., anencephaly). The type of breech presentation may influence the obstetrician’s decision regarding the mode of delivery. The fetus with a frank breech presentation tends to remain in that presentation throughout labor. In contrast, a complete breech presentation may change to an incomplete breech presentation at any time before or during labor.

Epidemiology

The breech presentation is the most common of the abnormal presentations. Both the incidence and the type of breech presentation vary with gestational age (Table 34.1). Before 28 weeks’ gestation, approximately 25% of fetuses are in a breech presentation. Most change to a vertex presentation by 34 weeks’ gestation, but 3% to 4% of fetuses remain in a breech presentation at term.

Many factors predispose to breech presentation (Box 34.1). Abnormalities of the fetus or the maternal pelvis or uterus may play a role. Among patients with pelvic or uterine abnormalities, a breech presentation may allow more room for fetal growth and movement. Likewise, hydrocephalic fetuses...
Obstetric Complications

Obstetric complications are more likely with a breech presentation (Table 34.2). Cesarean delivery decreases the risk for some of these complications. Vaginal breech delivery entails a higher risk for neonatal trauma than delivery of an infant with a vertex presentation, but cesarean delivery does not eliminate the risk for trauma to the infant. Rather, cesarean delivery of a breech presentation can be difficult and traumatic, especially if the skin and uterine incisions are insufficient or maternal muscle relaxation is inadequate.

The risk for umbilical cord prolapse varies with the type of breech presentation (Table 34.3). In the parturient with an incomplete breech presentation, the presenting part does not fill the cervix as well as the vertex or buttocks, allowing the umbilical cord to prolapse into the vagina before delivery. Umbilical cord prolapse typically necessitates emergency cesarean delivery.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrapartum fetal death</td>
<td>Increased 16-fold&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>Increased 3.8-fold&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Umbilical cord prolapse</td>
<td>Increased 5- to 20-fold&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>Increased 13-fold&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Arrest of aftercoming head</td>
<td>4.6%–8.8%</td>
</tr>
<tr>
<td>Spinal cord injuries with deflexion</td>
<td>21%</td>
</tr>
<tr>
<td>Major congenital anomalies</td>
<td>6%–18%</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>16%–33%</td>
</tr>
<tr>
<td>Hyperextension of head</td>
<td>5%</td>
</tr>
<tr>
<td>Fetal heart rate abnormalities</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Compared with cephalic presentation.

Relative perinatal mortality rates (calculated from data for linked siblings from the Medical Birth Registry of Norway) confirm that breech presentation is a marker of perinatal risk, regardless of the mode of delivery. Even after successful external cephalic version (ECV), women are at increased risk for cesarean delivery due to dystocia or an abnormal fetal heart rate (FHR) tracing, as compared with women presenting with a cephalic presentation.

Vaginal breech delivery entails a higher risk for maternal morbidity (e.g., infection, perineal trauma, hemorrhage) than vertex delivery. However, among women with a fetal breech presentation, maternal outcomes are similar between women who had a planned cesarean delivery and those who had a trial of labor. At 2 years postpartum, maternal morbidity assessed by questionnaire (917 responses for a 79% return) was not different for urinary incontinence, breast-feeding, pain, depression, menstrual problems, fatigue, and distressing memories of the birth experience. In a single-center study of 846 singleton breech deliveries, Schiff et al. also did not find a higher risk for maternal morbidity in women who underwent cesarean delivery during labor than in women who underwent planned cesarean delivery.

**Obstetric Management**

**External Cephalic Version**

The process of ECV converts a breech or shoulder presentation to a vertex presentation. The average success rate for this procedure is 58%, with a wide range reported in published studies. ECV is most likely to be successful if (1) the presenting part has not entered the pelvis, (2) amniotic fluid volume is normal, (3) the fetal back is not positioned posteriorly, (4) the patient is not obese, (5) the patient is parous, and (6) the presentation is either frank breech or transverse. Early labor does not preclude successful ECV, but ECV is rarely successful when the cervix is fully dilated or when the membranes have ruptured. No scoring system has been developed that reliably predicts which candidates will have a successful version attempt, although the variables just listed can be used when obtaining informed consent.

The optimal timing of ECV is after 36 or 37 weeks’ gestation, for the following reasons. First, if spontaneous version to a vertex presentation is going to occur, it will likely happen by 36 or 37 weeks’ gestation, and successful performance of ECV after 37 weeks’ gestation decreases the likelihood of reversion from a vertex to a breech presentation. Second, if complications occur during ECV performed after 37 weeks’ gestation, emergency delivery will not result in delivery of a preterm infant.

Successful ECV helps reduce the risk for perinatal morbidity and mortality associated with breech delivery. The American College of Obstetricians and Gynecologists (ACOG) has suggested that “because the risk for an adverse event occurring as a result of external cephalic version is small and the cesarean delivery rate is significantly lower among women who have undergone successful version, all women near term with breech presentations should be offered an ECV attempt if there are no contraindications.” There is no general consensus on eligibility for ECV, and contraindications vary between published guidelines. Oligohydramnios may be the most common contraindication cited. Labor and vaginal delivery occur in the majority of patients who have undergone successful ECV, but anesthesia providers should remain vigilant because of the increased risk for intrapartum cesarean delivery necessitated by dystocia or a nonreassuring FHR tracing. ECV is associated with a low rate of morbidity in contemporary obstetric practice, although placental abruption and preterm labor have been reported. Safe ECV requires FHR monitoring and access to cesarean delivery services. In a systematic review of 84 studies that involved 12,955 women, complications included transient (6.1%) and persistent (0.22%) FHR abnormalities, vaginal bleeding (0.30%), placental abruption (0.08%), emergency cesarean delivery (0.35%), and stillbirth (0.19%). Fetal-maternal hemorrhage is another potential complication of ECV. In one study, 16 of 89 (18%) patients undergoing ECV had Kleihauer-Betke stains that signaled the occurrence of fetal-maternal hemorrhage.

Obstetricians usually administer a tocolytic agent (e.g., terbutaline or nitroglycerin) before performing ECV. A randomized placebo-controlled trial found that the success rate of version was doubled when terbutaline was given rather than placebo. A randomized controlled trial of intravenous nitroglycerin for tocolysis (100- to 300-µg bolus doses, up to a maximum total dose of 1000 µg) found that the success rate was 24% in nulliparous women who received nitroglycerin versus 8% in the placebo group. The success rate was higher in parous women (43%), but it did not differ between the nitroglycerin and placebo groups. Interestingly, the rates of hypotension were similar between groups. A Cochrane Review found that tocolytic therapy with a beta-adrenergic agonist drug for ECV increases the number of women with a cephalic presentation at the onset of labor (relative risk [RR], 1.68; 95% confidence interval [CI], 1.14 to 2.48) and reduces the number of cesarean deliveries (RR, 0.77; 95% CI, 0.67 to 0.88).

Another method to improve the success rate of ECV may be use of neuraxial analgesia or anesthesia. Several studies have described the use of epidural or spinal analgesia or anesthesia for ECV. For example, Weiniger et al. randomly assigned 70 nulliparous women to receive either spinal anesthesia with bupivacaine 7.5 mg or no anesthesia for ECV. The success rate was 67% in those receiving spinal anesthesia,
32% in those without analgesia, and 42% in those who did not consent to enroll in the study. A randomized controlled trial in parous women using similar methodology also found an increased success rate with spinal anesthesia (87% versus 58%).20 A meta-analysis of 9 trials and 934 women found that compared with control, neuraxial anesthesia increased ECV success rates, increased the occurrence of cephalic presentation in labor, increased vaginal delivery rates, decreased cesarean delivery rates, and decreased maternal discomfort.21 There was no difference in the incidence of emergency cesarean delivery, transient fetal bradycardia, nonreassuring fetal testing, or placental abruption.

Maternal discomfort may be significant during ECV; greater pain during the procedure is associated with a lower chance of success.22 Some obstetricians argue that the absence of anesthesia limits the force that the obstetrician can apply during the procedure. They contend that administration of anesthesia may encourage the obstetrician to use excessive force, possibly increasing the risk for perinatal morbidity and mortality, but that concern is not supported by published evidence. In fact, spinal anesthesia reduces the force required for successful version.23

Several investigators have reported successful outcomes with neuraxial analgesia or anesthesia in women in whom the first attempt at ECV without neuraxial analgesia had been unsuccessful.19,24 These patients elected to undergo another version attempt with neuraxial analgesia. Weiniger et al.19 found that failure of ECV was attributed to pain in 15 women in their control group. Eleven of those 15 (73%) women subsequently had successful ECV with spinal analgesia.

The optimal dose of spinal local anesthetic is controversial. A meta-analysis of seven studies using neuraxial blockade to facilitate ECV concluded that administration of an anesthetic dose of local anesthetic doubles the success rate of ECV (RR, 1.95; 95% CI, 1.46 to 2.60), whereas an analgesic dose does not have any effect (RR, 1.18; 95% CI, 0.94 to 1.49).25 A subsequent prospective, randomized, blinded trial addressed the question of optimal intrathecal bupivacaine dose to facilitate ECV success.20 Patients were randomized to receive intrathecal bupivacaine doses of 2.5, 5.0, 7.5 or 10.0 mg combined with fentanyl 15 µg as part of a combined spinal-epidural technique. Overall success rate of ECV was 51.5% with no difference in success rates or cesarean delivery rates between the groups, demonstrating that intrathecal bupivacaine doses greater than 2.5 mg are not necessary and may only increase the incidence of hypotension. Obstetricians did not perceive a difference in abdominal wall relaxation between the groups, even though pain scores were higher in the 2.5 mg bupivacaine group (12 versus 4 to 5 on a 0 to 100 scale). Patient satisfaction was high and not different between groups.26 In an accompanying editorial, Carvalho and Bateman27 suggested that the optimal dose varies according to the clinical situation. If the goal is timely discharge whether or not the version is successful, then a lower-dose spinal anesthetic will allow earlier discharge as a result of faster resolution of the block. If the patient will be admitted for delivery regardless of whether the version is successful, then a higher dose will not affect the patient’s length of admission and could facilitate emergent cesarean delivery should that become necessary.27

In contrast to neuraxial analgesia or anesthesia, intravenous analgesia does not appear to facilitate successful ECV. Khaw et al.24 randomized parturients to receive either spinal anesthesia with intrathecal hyperbaric bupivacaine 9 mg plus fentanyl 15 µg, intravenous analgesia using a remifentanil infusion at 0.1 µg/kg/min, or control (no anesthetic or analgesic intervention) before attempted ECV. On the first attempt, success rates were 83% in the spinal group versus 64% in the remifentanil group and 64% in the control group. Among those that failed, a second attempt was successful in 78% of the patients with spinal anesthesia versus 0% receiving remifentanil. There was no significant difference in fetal bradycardia requiring cesarean delivery.24

In our practice, we provide spinal or combined spinal-epidural anesthesia during ECV at patient or obstetrician request. Evidence suggests that neuraxial anesthesia may help facilitate successful version and vaginal delivery, and therefore it should be used routinely. If a neuraxial technique is used, intrathecal administration of 2.5 mg bupivacaine combined with fentanyl may provide optimal conditions. Higher local anesthetic doses may be appropriate if delivery is planned for the admission, but may increase the incidence of hypotension.26,27

Mode of Delivery
A substantial number of obstetricians recommend the routine performance of cesarean delivery in patients with a breech presentation. The publication of the Term Breech Trial in 2000 changed clinical practice around the world.2 In contemporary obstetric practice in the United States, most parturients with a breech presentation are delivered by cesarean.

The Term Breech Trial Collaborative Group3 enrolled 2088 women from 26 countries with a singleton fetus in a frank or complete breech presentation. These women were randomly assigned to undergo planned cesarean delivery or planned vaginal delivery. Using an intent-to-treat analysis, the investigators noted that perinatal and neonatal mortality rates, and serious neonatal morbidity, were significantly lower in the planned cesarean delivery group (1.6% versus 5%). This difference was greatest in those countries with a low perinatal mortality rate (e.g., Canada, United Kingdom, United States). Secondary analysis of perinatal outcomes demonstrated that the lowest risk for adverse outcome occurred when a prelabor cesarean delivery was performed at term gestation.28 The risk for adverse perinatal outcome progressively increased with cesarean delivery performed during early labor and active labor and was highest with a vaginal birth. Labor augmentation and a longer time between the start of pushing and delivery were associated with an increased risk for adverse perinatal outcome, whereas the presence of an experienced clinician at delivery was associated with a reduced risk for adverse perinatal outcome.28

In the Term Breech Trial, maternal morbidity and mortality did not differ between the two groups for the first 6 postpartum weeks. Women who underwent planned cesarean
delivery were less likely to report urinary incontinence at 3 months; however, there was no difference at 2 years. As assessed by questionnaire, maternal outcomes at 2 years after delivery were similar after planned abdominal delivery and after planned vaginal delivery for singleton breech infants born at term.

Despite the results of the Term Breech Trial, Canadian multicenter data from 2003 to 2011 illustrate that vaginal delivery was increasingly popular for Canadian women with breech presentation of nonanomalous singleton infants at term. The vaginal delivery rate increased from 2.7% to 3.9% over that time, and the rate of cesarean deliveries in labor increased from 8.75% to 9.8%. Delivery by planned cesarean had the lowest morbidity. Composite neonatal morbidity and mortality rates were significantly higher after vaginal delivery than planned cesarean with an adjusted rate ratio of 3.6 (95% CI, 2.50 to 5.15). Cesarean delivery during labor also resulted in higher neonatal morbidity and mortality. The Canadian data support the results of the Term Breech Trial.

In many other regions of the world, the number of planned vaginal breech deliveries has decreased as a result of the Term Breech Trial. For example, in Denmark, the proportion of singleton term breech infants delivered vaginally decreased abruptly from 20% before 1999 to 6% after 2001. At the same time, intrapartum or early neonatal mortality among all term breech infants decreased from 0.13% to 0.05% (RR, 0.38; 95% CI, 0.15 to 0.98). The downward trend in rates of vaginal breech delivery is likely to continue. As the number of practitioners with experience in performing vaginal breech delivery has decreased, the number of vaginal breech deliveries available to teach obstetric residents may no longer be adequate. Unintended results of this practice change include a generation of obstetricians who have lost the skills to practice vaginal breech deliveries and medicolegal concerns that now discourage the practice of vaginal breech delivery.

Nevertheless, obstetricians in some regions of the world retain a strong tradition of offering vaginal breech delivery for selected patients. Published in 2006, the PREsentation et MODe d’Accouchement (PREMODA; presentation and mode of delivery) study described birth outcomes for all term breech deliveries in 2001 through 2002 in 174 centers in France and Belgium. The study included 5579 women who planned cesarean breech delivery and 2526 women who planned vaginal breech delivery, of whom 1796 actually delivered vaginally. The primary outcome captured a composite of fetal and neonatal mortality and serious morbidity and was not different between women who planned to undergo vaginal delivery (1.60%; 95% CI, 1.14 to 2.17) and women who planned to undergo cesarean delivery (1.45%; 95% CI, 1.16 to 1.81), with an overall odds ratio (OR) of 1.10 (95% CI, 0.75 to 1.61). The authors suggested that rigorous adherence to protocols for patient selection, intrapartum fetal surveillance, and second-stage management contributed to improved outcomes for women attempting vaginal breech delivery.

In 2006, in recognition of results from the PREMODA study and other single-center descriptions of excellent outcomes for vaginal breech delivery, the ACOG made the following recommendations about mode of singleton breech delivery at term:

- “The decision regarding the mode of delivery should depend on the experience of the health care provider. Cesarean delivery will be the preferred mode of delivery for most physicians because of the diminishing expertise in vaginal breech delivery.”
- “Obstetricians should offer and perform external cephalic version whenever possible.”
- “Planned vaginal delivery of a term singleton breech fetus may be reasonable under hospital-specific protocol guidelines for both eligibility and labor management.”
- “In those instances in which breech vaginal deliveries are pursued, great caution should be exercised, and detailed patient informed consent should be documented.”
- “Before embarking on a plan for a vaginal breech delivery, women should be informed that the risk of perinatal or neonatal mortality or short-term serious neonatal morbidity may be higher than if a cesarean delivery is planned.”

Although a planned trial of labor and vaginal breech delivery occurs uncommonly in most hospitals in North America and the United Kingdom because of concerns for higher rates of adverse perinatal outcomes, vaginal breech delivery still occurs because some patients present in advanced labor. Selection criteria such as those listed in Box 34.2 are used by advocates of a trial of labor and vaginal delivery. The availability of personnel experienced in obstetric anesthesia and neonatal resuscitation are prerequisites for a trial of labor. Hyperextension of the fetal head remains an absolute contraindication to a trial of labor in the patient with a breech presentation.

### Vaginal Breech Delivery

Several aspects of the conduct of breech labor differ from those for a vertex presentation. The cervix must be fully

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**BOX 34.2 Criteria for a Trial of Labor and Vaginal Delivery for Patients With Fetal Breech Presentation**

- Frank breech presentation
- Adequate pelvis by imaging pelvimetry
- Estimated fetal weight between 2000 and 3500 g by ultrasonography or by two experienced examiners
- Flexion of the fetal head (the neutral position—the so-called military position—is also acceptable)
- Continuous electronic fetal heart rate monitoring
- Spontaneous progression of labor, with timely effacement and dilation of the cervix and timely descent of the breech
- Availability of an individual skilled in vaginal breech delivery and an assistant
- Availability of an individual skilled in the administration of obstetric anesthesia
- Spontaneous delivery to the level of the umbilicus
- Ability to perform an abdominal delivery promptly
- Availability of an individual with skills in neonatal resuscitation
dilated before the patient begins to push. Indeed, some obstetricians delay maternal expulsive efforts until 30 minutes after the diagnosis of full cervical dilation. Others delay expulsive efforts until the breech is at the perineum.

There are three varieties of vaginal breech delivery. **Spontaneous breech delivery** is delivery without any traction or manipulation other than support of the infant’s body. With **assisted breech delivery** (also known as partial breech extraction), the infant is delivered spontaneously as far as the umbilicus; at that time, the obstetrician assists delivery of the chest and the aftercoming head. With **total breech extraction**, the obstetrician applies traction on the feet and ankles to deliver the entire body of the infant. Except for vaginal delivery of a second twin, obstetricians almost never perform total breech extraction. Total breech extraction increases the likelihood of difficult, traumatic delivery, including entrapment of the fetal head.

During assisted breech delivery or total breech extraction, the obstetrician attempts to maintain flexion of the cervical spine during delivery of the aftercoming head. This may be accomplished manually or by the application of Piper forceps (Figs. 34.3 to 34.5). In most cases, the obstetrician performs a generous episiotomy to prevent perineal obstruction of the aftercoming head.

**Cesarean Delivery**

Cesarean delivery does not guarantee an atraumatic delivery. Generous skin and uterine incisions should be made based on estimated fetal size. In preterm deliveries, a vertical uterine incision may need to be performed if the lower uterine segment is poorly developed. In such cases, the obstetrician should perform a low vertical uterine incision, which can be extended to facilitate an atraumatic delivery. Unfortunately, such incisions often extend to the body of the uterus, which does not heal as well as the lower uterine segment. It is unclear whether a low vertical uterine incision increases the risk for uterine rupture during a trial of labor in a subsequent pregnancy, but a classic uterine incision is associated with a 1% to...
12% risk for uterine rupture in subsequent pregnancies (see Chapter 19).

**Anesthetic Management**

Benefits of neuraxial analgesia during labor include (1) pain relief, (2) inhibition of early pushing by blocking the perineal reflex, (3) ability of the parturient to push during the second stage and spontaneously deliver the infant to the level of the umbilicus, (4) a relaxed pelvic floor and perineum at delivery, and (5) the option to extend analgesia to surgical anesthesia for emergency cesarean delivery if needed.

**Analgesia for Labor**

Emergency cesarean delivery may be required at any time during a trial of labor. Epidural analgesia and CSE analgesia are excellent choices during a trial of labor in patients with a breech presentation. The anesthesia provider should tailor the analgesic technique to the needs of the individual patient. Patients with a breech presentation often have earlier complaints of rectal pressure than patients with a vertex presentation. It is important to provide sufficient sacral analgesia to inhibit pushing during the first stage of labor. The patient must not push before the cervix is fully dilated; otherwise, the patient might push a fetal lower extremity through her partially dilated cervix, which may result in umbilical cord prolapse or fetal head entrapment. A bolus dose of local anesthetic solution that includes a lipid-soluble opioid (e.g., fentanyl, sufentanil) may be required to block the sacral segments and the reflex urge to push during the late first stage of labor. Use of a local anesthetic alone to eliminate low back and perineal discomfort results in extensive motor blockade, which may decrease the effectiveness of maternal expulsive efforts during the second stage.

**Anesthesia for vaginal breech delivery.** The patient with a breech presentation should deliver in an operating room where an emergency abdominal delivery can be performed immediately. The anesthesia provider should consider administration of a nonparticulate antacid at the time of transfer to the operating room. The anesthesia provider should be prepared for emergency administration of general anesthesia at any time. Umbilical cord compression is common during the second stage of labor in a patient with a breech presentation.

Provision of effective analgesia/anesthesia for vaginal breech delivery represents a true challenge for the anesthesia provider. During the second stage of labor, the anesthesia provider is asked to provide adequate analgesia (which should include blockade of the sacral segments) while maintaining adequate maternal expulsive efforts. If a patient is unable to achieve spontaneous delivery of a vertex presentation, the obstetrician may perform instrumental vaginal delivery. In contrast, total breech extraction of a singleton fetus is unacceptable in modern obstetric practice. Most obstetricians insist on spontaneous delivery of the infant to the level of the umbilicus.

At any time, the anesthesia provider may be asked to quickly provide dense anesthesia for vaginal or cesarean delivery. Many obstetricians routinely apply Piper forces to the aftercoming head. This maneuver requires adequate anesthesia and perineal muscle relaxation. Because a dilute solution of local anesthetic has been administered during the first stage of labor, it is often necessary to administer a more concentrated solution of local anesthetic at the time of delivery. Either 3% 2-chloroprocaine or 2% lidocaine with epinephrine and bicarbonate may be used to rapidly extend the epidural analgesia to anesthesia for operative delivery. To ensure adequate anesthesia for operative delivery, we begin to inject a more concentrated solution of local anesthetic at the first evidence of difficulty.

Perhaps the obstetrician’s greatest fear is the risk for **fetal head entrapment.** Most cases of this complication involve entrapment of the fetal head behind a partially dilated cervix. The head may also be entrapped by the perineum. Fetal head entrapment is more likely to occur in patients at less than 32 weeks’ gestation. Before 32 weeks’ gestation, the fetal head is larger than the wedge formed by the fetal buttocks and thighs. The lower extremities, buttocks, and abdomen may deliver before the cervix is fully dilated, and the cervix may then entrap the head. If this complication occurs, the obstetrician may choose one of the following three options: (1) performance of Dührssen incisions in the cervix, (2) relaxation of skeletal and cervical smooth muscle, or (3) cesarean delivery.

The performance of **Dührssen incisions** involves two or three radial incisions in the cervix at the 2-, 6-, and 10-o’clock positions. This procedure is associated with a high risk for maternal morbidity (e.g., genitourinary trauma, hemorrhage). The blood loss may be substantial and concealed. Bleeding within the peritoneal cavity may not be visible externally.

More often, the obstetrician requests that the anesthesia provider establish **relaxation of skeletal and cervical smooth muscle.** Smooth muscle represents less than 15% of total cervical tissue, and some physicians argue that it is not possible to provide profound relaxation of the cervix through smooth muscle relaxation. Nonetheless, the provision of both skeletal and smooth muscle relaxation often facilitates vaginal delivery of the aftercoming head. In the past, the technique of choice was rapid-sequence induction of general anesthesia, followed by administration of a high concentration (2 to 3 minimum alveolar concentration [MAC]) of a volatile halogenated agent. This technique results in uterine and cervical relaxation in 2 to 3 minutes. If fetal head entrapment results from perineal obstruction by skeletal musculature, delivery may soon follow the administration of succinylcholine.

Immediately after delivery, the anesthesia provider should discontinue administration of the volatile halogenated agent and substitute nitrous oxide, with or without an opioid. Administration of a high concentration of a volatile halogenated agent increases the risk for uterine atony and hemorrhage after delivery. Prompt discontinuation of the volatile halogenated agent, along with intravenous infusion of oxytocin, should facilitate adequate uterine tone in most patients. Anesthesia should be maintained until the placenta is delivered, the episiotomy and lacerations are repaired, and hemostasis is secured.
In modern practice, intravenous or sublingual administration of nitroglycerin has nearly replaced the use of volatile halogenated agents as agents for uterine relaxation. Administration of nitroglycerin results in the release of nitric oxide, which helps mediate the relaxation of smooth muscle. Transient hypotension is common. Use of nitroglycerin for this purpose is based on case reports and small series of cases. Well-designed clinical trials of the use of nitroglycerin to provide uterine relaxation in obstetric emergencies are lacking, although the administration of nitroglycerin for this purpose appears safe for both the mother and the infant.

Published case reports have described clinically apparent uterine relaxation achieved with cumulative intravenous nitroglycerin doses ranging from 50 to 1500 μg. The actual dose required for specific clinical situations is unknown. Sublingual tablets or sprays of metered-dose nitroglycerin (400 μg) may provide a more convenient means of administration, whereas intravenous administration may allow for more rigorous titration. Either sublingual or intravenous routes of administration appear to provide a rapid onset of uterine relaxation, and the effect typically is very brief. The patient should be warned about the acute onset of headache, and she should be treated with a vasopressor such as phenylephrine if hypotension occurs. The anesthesia provider should simultaneously prepare for the induction of general anesthesia should nitroglycerin not provide enough relaxation.

The use of epidural analgesia has likely lowered the incidence of fetal head entrapment during vaginal breech delivery for at least two reasons. First, epidural analgesia inhibits early pushing during the first stage of labor. Second, although epidural analgesia does not relax the cervix at delivery, it provides effective pain relief and skeletal muscle relaxation. A relaxed pelvic floor and perineum facilitates placement of Piper forceps and delivery of the aftercoming head. Moreover, effective analgesia and skeletal muscle relaxation allow an assistant to provide maternal suprapubic pressure, which helps maintain flexion of the fetal cervical spine during delivery.

**Anesthesia for Cesarean Delivery**

Spinal, epidural, or general anesthesia can be administered for cesarean delivery. At cesarean delivery, the obstetrician should perform a uterine incision that allows an atraumatic delivery of the infant. Rarely, the obstetrician may request provision of uterine relaxation even when a vertical uterine incision has been performed. Uterine relaxation may be necessary in cases of fetal malformations (e.g., sacral teratoma, hydrocephalus). When general anesthesia is used, the anesthesiologist may increase the concentration of the volatile halogenated agent. When neuraxial anesthesia is used, intravenous or sublingual administration of nitroglycerin, or intravenous administration of a beta-adrenergic tocolytic agent such as terbutaline, typically provides adequate relaxation. Rarely, it is necessary to perform intraoperative induction of general anesthesia followed by administration of a high concentration of a volatile halogenated agent.

Regardless of the route of delivery, all members of the obstetric care team should remember that newborn infants with a breech presentation tend to be more depressed than infants with a vertex presentation. An individual skilled in neonatal resuscitation should be immediately available.

**OTHER ABNORMAL PRESENTATIONS**

**Face Presentation**

Face presentation, in which the neck is deflexed (extended backward) occurs in 1 in 600 to 800 live births. Vaginal delivery can be achieved in 70% to 80% of infants with a face presentation if the mentum rotates to an anterior position, but FHR abnormalities are common. Manual efforts to flex the fetal cervical spine or convert an unfavorable mentum posterior position to a more favorable mentum anterior position are rarely successful and may result in significant maternal complications including uterine rupture, as well as adverse neonatal complications including spinal cord injury and difficult ventilation due to tracheal and laryngeal edema.

**Brow Presentation**

In patients with a brow presentation, the cervical spine position is intermediate between the full flexion of a normal vertex presentation and the full extension of a face presentation. On vaginal examination, the obstetrician can palpate the brow, orbits, and saddle of the nose, but not the mouth or chin. Brow presentation occurs in approximately 1 in 500 to 4000 deliveries. Persistent brow presentation typically requires cesarean delivery due to dystocia. Spontaneous flexion or extension of the neck may occur during labor, which may allow vaginal delivery.

**Compound Presentation**

Compound presentation (an extremity is prolapsed alongside the main presenting fetal part) occurs in 1 in 300 to 1000 deliveries. Most often, an upper extremity presents with the vertex. Umbilical cord prolapse is more common (10% to 20%) in deliveries with a compound presentation, as is neurologic or musculoskeletal damage to the involved extremity. Labor and delivery may occur safely, but abdominal delivery is needed in patients with cord prolapse or arrest of labor. Expectant management rather than manipulation of the prolapsed extremity is the most common practice.

**Shoulder Presentation**

A shoulder presentation (also known as a transverse lie) mandates performance of cesarean delivery except in two circumstances. First, successful ECV will allow vaginal delivery. Second, the obstetrician may perform internal podalic version and total breech extraction of a second twin with a shoulder presentation.

Transverse lie can present back down or back up. Cesarean delivery of a fetus with a back-down transverse lie can be especially difficult with no presenting part to grasp. If intra-abdominal version cannot be accomplished before
hysterotomy, this presentation represents an indication for a classic or low vertical uterine incision.

**MUTLIPLE GESTATION**

**Epidemiology**

Monozygotic twins (which occur when a single fertilized ovum divides into two distinct individuals after a variable number of divisions) exhibit a constant incidence of approximately 4 per 1000 births. The incidence of dizygotic twins (which occur when two separate ova are fertilized) varies among races and by maternal age. In the United States, dizygotic twins occur most frequently among non-Hispanic black and white Americans, with an intermediate frequency among Asian Americans and Puerto Ricans, and least frequently among other Hispanic groups and Native Americans. The incidence increases with parity, independent of maternal age. In the United States, the twin birth rate rose 76% between 1980 and 2009, from 19 to 33 per 1000 live births. Twin birth rates rose by nearly 100% among women 35 to 39 years of age and more than 200% among women 40 years of age and older. Delayed childbearing and spontaneous twinning among women older than 30 years of age appears to explain one-third of the increase in the rate of multiple gestation between 1980 and 2010, with the remainder attributed to greater use of assisted reproductive technologies.

**Placenta**

Placentas in multiple gestation may be (1) monochorionic monoamnionic; (2) monochorionic diamniotic; or (3) dichorionic diamniotic (Fig. 34.6). In all occurrences of dizygotic twins, the placenta is dichorionic diamniotic. A dichorionic diamniotic placenta is also present if monozygotic twinning occurs during the first 2 to 3 days after fertilization. Twinning between 3 and 8 days commonly results in a monochorionic diamniotic placenta. Monochorionic monoamniotic placentas are found when twinning occurs at 8 to 13 days. Embryonic cleavage between 13 and 15 days results in conjoined twins with a monochorionic monoamniotic placenta. Chorionicity is best determined by ultrasonography in the first or early second trimester. It is important to know the type of placentation because it determines the likelihood of vascular communications. Vascular communications occur in nearly all monochorionic placentas and are rare in dichorionic placentas. Vascular communications may result in twin-to-twin transfusion syndrome and intrauterine fetal death. Monochorionic placentation also increases the risk for intrauterine fetal death from other causes (e.g., cord accident).

**Physiologic Changes**

Multiple gestation accelerates and may exaggerate the physiologic and anatomic changes of pregnancy. Of interest to the anesthesia provider, multiple gestation intensifies the cardiovascular and pulmonary changes of pregnancy. In contrast, the renal, hepatic, and central nervous system changes resemble those that occur in women with a singleton fetus. Increased uterine size, especially near term, may result in a reduction in both total lung capacity and functional residual capacity. During periods of hypoventilation or apnea, hypoxemia develops more rapidly because of the decreased functional residual capacity and an increased maternal metabolic rate. However, one cross-sectional study demonstrated no significant difference in pulmonary function tests between 68 women with a twin pregnancy and 140 women with a singleton pregnancy.43 Maternal weight increases at a greater rate after 30 weeks’ gestation in women with multiple gestation.44 Greater uterine size displaces the stomach cephalad, decreasing the competence of the lower esophageal sphincter and increasing the risk for passive regurgitation and potential pulmonary aspiration of gastric contents. All these physiologic and anatomic factors, plus increased breast size, combine to potentially increase the risk for difficult tracheal intubation and ventilation.

Normal plasma volume increases by an additional 750 mL with twin gestation. Relative or actual anemia often occurs. Likewise, multiple gestation results in a 20% greater increase in cardiac output than occurs in women with a singleton fetus, owing to a greater stroke volume (15%) and a higher heart rate (3.5%). In a longitudinal study comparing uncomplicated twin pregnancies to singleton pregnancies, at all points cardiac output was higher with twins while total vascular resistance was lower. The greater fetal weight and larger volume of amniotic fluid predispose the mother with...
multiple gestation to aortocaval compression and the supine hypotension syndrome.

Obstetric Complications

Fetal Complications

Fetal complications include those related solely to multiple gestation (e.g., twin-to-twin transfusion syndrome) and those related to abnormal presentation (e.g., prolapsed umbilical cord) (Box 34.3).

Twin-to-twin transfusion. Nearly all monochorionic twin placentas have vascular anastomoses. Deep arteriovenous anastomoses create a common villous compartment in about one-half of monochorionic twin placentas. Most of these anastomoses have little fetal consequence. Those with deep arteriovenous vascular communications may result in twin-to-twin transfusion, in which one twin becomes the donor and the other twin becomes the recipient. The donor twin is smaller and is at risk for fetal growth restriction (also known as intrauterine growth restriction) and anemia. The recipient twin is plethoric and is at risk for volume overload and cardiac failure. Alternative explanations for the syndrome include unequal blood volumes secondary to compression of a velamentous umbilical cord insertion and higher arterial blood pressure in the donor than in the recipient. Twin-to-twin transfusion increases both the perinatal mortality rate and the risk for adverse neurodevelopmental outcome in survivors.

The therapeutic options most often considered are decompression amniocentesis, amniotic septostomy, interruption of the placental vessel communications, and selective feticide. Decompression amniocentesis or serial amnio redirection to treat polyhydramnios in the recipient twin may improve circulation to a “stuck” donor twin (the term refers to such severe oligohydramnios in the donor twin that the fetus is wedged in the corner of the uterus and appears “stuck”). Amnio redirection restores normal amniotic fluid volume and improves fetal growth in the donor twin. Compared with serial amnio redirection, septostomy has the advantage of requiring only a single procedure. Selective fetoscopic laser photocoagulation may be used to reduce the vascular anastomoses, and may improve perinatal outcomes. Anesthetic management of these procedures focuses on maintaining uteroplacental circulation, achieving profound uterine relaxation, optimizing surgical conditions, monitoring fetal hemodynamics, and minimizing maternal and fetal risk.

Fetal growth restriction. Twin-to-twin transfusion represents only one of the potential causes of fetal growth restriction in multiple gestation. The polyhydramnios within one fetal sac may limit the growth of the other fetus. In patients with three or more fetuses, limited intrauterine size may restrict fetal growth. Of course, factors that cause fetal growth restriction in singleton pregnancies also may cause fetal growth restriction in multiple gestation (e.g., uteroplacental insufficiency, chromosomal abnormalities).

Preterm labor. Patients with multiple gestation are at high risk for preterm labor and delivery. Preterm labor occurs in 52% of women with twins resulting from in vitro fertilization compared with 22% of women with spontaneous twins. Sixty percent of women with twins deliver before 37 weeks’ gestation, and only 6.4% of triplet pregnancies reach term. Routine use of bed rest, prophylactic cerclage, vaginal progesterone, and/or tocolytic therapy has not been shown to improve perinatal outcome in multiple gestation pregnancies. When preterm labor occurs, the patient may receive parenteral tocolytic therapy to facilitate administration of betamethasone to accelerate fetal lung maturation, or magnesium sulfate for fetal neuroprotection, or both. The side effects of magnesium and other tocolytic agents may affect the response to anesthesia (see Chapter 33) and may increase the risk for postpartum hemorrhage. Multiple gestation most likely increases the risk for pulmonary edema associated with tocolytic therapy.

Abnormal presentation. Multiple gestation is associated with a higher incidence of abnormal presentation, which results in part from the need to accommodate two or more fetuses within the uterine cavity. Malpresentation increases the risk for umbilical cord prolapse, which may occur either before or after delivery of the first infant.

Morbidity and mortality. In 2013, 8.6% of fetal deaths occurred in multiple gestations. The perinatal mortality rate in twin pregnancies is 2.5 times greater than that associated with singleton pregnancies (14.1 deaths per 1000 births versus 5.7 per 1000 births, respectively) and is 5-fold higher in triplet or higher-order gestations (30.5 per 1000 births). Preterm delivery accounts for most of this increase, although twins and triplets also have a higher weight-specific mortality, which may be related to twin-to-twin transfusion, congenital malformations, preeclampsia, malpresentation, and/or prolapsed umbilical cord. Some maternal-fetal medicine specialists advocate selective multifetal reduction to reduce the risk for maternal morbidity and the perinatal morbidity and mortality associated with three or more fetuses; this issue is a moral and ethical dilemma for some patients and physicians. The ACOG has stated:

Women who underwent pregnancy reduction from triplets to twins, as compared with those who continued with triplets, were observed to have lower frequencies of pregnancy loss, antenatal complications, preterm birth, low-birth-weight infants, cesarean delivery, and neonatal deaths, with rates similar to those observed in women with spontaneously conceived twin gestations.
Intensive inpatient monitoring improves perinatal survival of monoamniotic twins. A literature review of studies comparing inpatient and outpatient monitoring of monochorionic twins suggested a 10-fold reduction in fetal death with inpatient monitoring after 28 weeks’ gestation. In addition to the risks faced by all twins, monoamniotic twins face the unique risk for cord entanglement. Three-times daily fetal monitoring and nonstress tests are used to check for multiple deep variable decelerations that could be related to cord entanglement. Intensive surveillance may also benefit monochorionic diamniotic pregnancies. The long-term outcome of the complications of monochorionicity remains unclear.

Death of one fetus may occur well before term. Johnson and Zhang evaluated outcome for 150,386 sets of twins and 5240 sets of triplets born between 1995 and 1997; fetal death at 20 weeks’ gestation or later occurred in 2.6% of twin gestations and 4.3% of triplet gestations. The investigators noted that “survival of the remaining fetuses was inversely related to the time of the first fetal demise.” Opposite-gender twins were more likely to survive, possibly reflecting the absence of monochorionic placenta. In monochorionic twin gestations complicated by twin-to-twin transfusion and fetal death, approximately 40% of the surviving twins experience mortality or serious neurodevelopmental morbidity. Obstetric management decisions are based on the cause of death and the status of both the surviving fetus and the mother. If the cause of death was an abnormality of the fetus rather than maternal or uteroplacental pathology, expectant management of the pregnancy may be warranted. Development of maternal pulmonary edema from mirror syndrome or disseminated intravascular coagulation from dead fetal tissue are theoretical complications that occur rarely.

Multiple gestation is also associated with an increased risk for neonatal morbidity and mortality. Triplet and quadruplet pregnancies have significantly higher risks than twin pregnancies for neonatal complications.

**Order of Delivery**

Compared with first-born twins, the second-born has a higher incidence of adverse outcome due to lower birth weight, higher frequency of malpresentation, umbilical cord prolapse, and placental abruption. Abruptio can occur when rapid decompression of the uterus with delivery of the first twin leads to shearing forces through the basal plate of the placenta. Delivery of the second twin may require internal podalic version due to nonvertex presentation.

Administration of neuraxial anesthesia may improve the outcome for the second twin. In 1987, Crawford observed that among women who received epidural analgesia, the two twins had similar umbilical cord blood pH measurements. In contrast, among women who received general anesthesia, the second twin tended to be more acidic than the first. Likewise, Jarvis and Whitfield reported no difference in outcome for first and second twins when the mother received epidural analgesia. Administration of general anesthesia is increasingly rare for cesarean delivery in women with multiple gestation.

**Maternal Complications**

Multiple gestation increases the incidence of maternal morbidity and mortality (Box 34.4), even with adjustment of data for confounding factors. A population-based cohort study in the Netherlands found the overall incidence of severe acute maternal morbidity was 7.0 per 1000 deliveries, but was 6.5 and 28.0 per 1000 for singletons and multiple pregnancies, respectively. The relative risk for severe acute maternal morbidity in twins compared with singleton pregnancies was 4.3 (95% CI, 3.7 to 5.0) and increased to 6.2 (95% CI, 2.5 to 15.3) in triplet pregnancies. Risk factors for morbidity included age greater than 40 years, nulliparity, use of assisted reproductive technology, and nonspontaneous onset of labor. The increased incidence of cesarean delivery contributes to the higher risk for maternal morbidity and mortality associated with multiple gestation. Multiple gestation and the associated use of assisted reproductive technologies also increase both the incidence and severity of preeclampsia. The ACOG has stated: “Women with multiple gestations are nearly 6 times more likely to be hospitalized with complications, including preeclampsia, preterm labor, preterm premature rupture of membranes, placental abruption, pyelonephritis, and postpartum hemorrhage.”

The incidence of maternal complications increases in proportion to the number of fetuses. Compared with mothers of twins, mothers of triplets and quadruplets are more likely to have preterm premature rupture of membranes, hypertension, and/or excessive bleeding; require tocolysis; require cesarean delivery at less than 29 weeks’ gestation; and have one or more infants die. Abdominal distention and diaphragmatic elevation can cause respiratory distress and may necessitate early delivery in some patients with three or more fetuses.

Blood loss with delivery is approximately 500 mL greater in multiple gestation pregnancies than in singleton pregnancies. Uterine distention increases the risk for uterine atony and postpartum hemorrhage. Most cases of atony respond to standard pharmacologic therapy (e.g., oxytocin, methylergonovine, 15-methyl prostaglandin F2α [carboprost]). Persistent uterine atony may require the performance of interventions such as a uterine brace or B-Lynch suture or emergency hysterectomy.

**BOX 34.4 Maternal Complications Associated With Multiple Gestation**

- Preterm premature rupture of membranes
- Preterm labor
- Prolonged labor
- Preeclampsia/eclampsia
- Placental abruption
- Disseminated intravascular coagulation
- Operative delivery (forceps and cesarean)
- Uterine atony
- Obstetric trauma
- Antepartum and/or postpartum hemorrhage
Obstetric Management

Delivery at 38 weeks’ gestation for twins and 35 weeks’ gestation for triplets may be associated with the lowest risk for perinatal mortality, although timing of delivery also depends on chorionicity and presence of fetal growth restriction.41 Twin gestation itself does not contraindicate labor and vaginal delivery. However, multiple gestation is associated with a higher incidence of cesarean delivery. Most obstetricians favor cesarean delivery for all patients with three or more fetuses.42

Several studies have investigated outcomes for twin delivery by planned cesarean or trial of labor.73 Barrett et al.74 randomized a total of 1398 women (2795 fetuses) to planned cesarean delivery and 1406 women (2812 fetuses) to planned vaginal delivery. The rate of cesarean delivery was 90.7% in the planned cesarean-delivery group and 43.8% in the planned-vaginal-delivery group. The authors found that planned cesarean delivery did not significantly decrease or increase the risk for fetal or neonatal death or serious neonatal morbidity, as compared with planned vaginal delivery.74

A 2-year neurodevelopmental follow-up of these children found no significant difference in the outcome of death or neurodevelopmental delay: 5.99% in the planned cesarean versus 5.83% in the planned vaginal delivery group (OR, 1.04; 95% CI, 0.77 to 1.41; P = .79).75

Observational data suggest that perinatal outcomes may be improved with a trial of labor when the presenting twin is in a vertex position. A large cohort study of 5915 twin deliveries in France compared planned cesarean delivery with planned vaginal delivery.76 Of those with a cephalic presentation of the first twin at or beyond 32 weeks’ gestation, 75.4% had planned vaginal deliveries, of whom 80.3% delivered both twins vaginally. They found that planned cesarean compared with planned vaginal delivery before 37 weeks’ gestation was associated with increased composite neonatal mortality and morbidity, and they recommended planned vaginal rather than cesarean delivery between 32 and 37 weeks’ gestation.75

A second cohort study of 2597 twin deliveries at or after 34 weeks’ gestation, with the first twin in a cephalic presentation, found that intrapartum and postpartum neonatal complications occurred in 26.5% of intended vaginal deliveries and 31.7% of scheduled cesarean deliveries (P = 0.005).77 The authors concluded that their findings do not support a policy of planned cesarean delivery for twin pregnancies at or after 34 weeks’ gestation.77 A meta-analysis of 39,571 twin pregnancies found that neonatal morbidity was lower after vaginal delivery than after cesarean delivery for twin A, but there was no significant difference in neonatal morbidity between the two modes of delivery for twin B.78 When outcomes were stratified for both presentation and mode of delivery, the mortality rate was lower after vaginal delivery than after cesarean delivery for both vertex and nonvertex twin B.78 If twin A is in a vertex presentation, the evidence supports a planned vaginal delivery after 32 weeks’ gestation. Retrospective data support a similar policy for twin delivery before 32 weeks’ gestation.79 A policy of planned vaginal delivery of very preterm twins from 26 to 32 weeks’ gestation with the first twin in cephalic presentation did not increase either severe neonatal morbidity or mortality.79

Maternal morbidity depends on the likelihood of achieving vaginal birth for both twins. A 7-year retrospective cohort study of women delivering twins after 32 weeks’ gestation compared maternal morbidity after trial of labor or elective cesarean delivery.80 Vaginal delivery of both twins was successful in 74% of those having a trial of labor, but they found that postpartum hemorrhage was more common among women who attempted vaginal delivery compared with those electing cesarean delivery, with rates of 9.1% compared with 4.9%, respectively (P < .01, adjusted OR 2.2, 95% CI, 1.4 to 3.6). Hemorrhage was responsible for the difference in the composite morbidity rate between groups.80 The authors noted that the tradeoff for a 74% chance of vaginal delivery is a 4% absolute increase in the rate of serious postpartum hemorrhage, a discussion that should occur between the patient and her obstetrician during delivery planning. The ACOG recommends a trial of labor for women with twin delivery when the first twin is in cephalic presentation as one method of safe reduction of the rate of primary cesarean deliveries.81

Both fetuses have a vertex presentation in 30% to 50% of cases of twin gestation, and in 25% to 40% of cases the presentation is a vertex/breech combination. The remaining patients have various combinations of vertex, breech, and transverse lie. Most obstetricians allow a trial of labor if both twins have a vertex presentation. Similarly, a majority of obstetricians opt for cesarean delivery if the first twin has a breech or shoulder presentation. Notwithstanding the results of recent studies,73–79 there may still be variations in management when twin A has a vertex presentation and twin B has a nonvertex presentation.41 As in decisions about mode of delivery after prior cesarean delivery, these choices reflect shared decision-making between the patient and the obstetrician, informed by the likelihood of achieving intended vaginal birth, her desire for future pregnancies, and a tailored risk assessment for each mode of delivery.

Twin A

Decisions regarding the method of delivery typically begin with the gestational age and presentation of twin A. An obstetrician who is unwilling to allow a trial of labor in a patient with a singleton breech presentation is unlikely to allow a trial of labor in a patient with a breech presentation for twin A. Moreover, if twin A has a breech presentation and twin B has a vertex presentation, the chins may become interlocked during labor and delivery. This complication occurs infrequently, but the consequences can be devastating.42 The unanticipated case of head entrapment, deflexed head, or locked twins may necessitate emergency abdominal delivery of both twins. The obstetrician proceeds with cesarean delivery while an assistant supports the exteriorized body of twin A. The obstetrician applies gentle traction on the head while the infant’s body is guided back into the uterus.42

When twin A has a cephalic presentation, decisions about mode of delivery must account for the relative size,
presentation, and position of twin B. Antepartum ultrasonographic examination allows the obstetrician to assess the presentation, position, head size, and weight of both fetuses. Indications for planned cesarean delivery of twins include (1) evidence of discordant growth (especially if twin B is larger than twin A); (2) twin-to-twin transfusion syndrome; (3) selected congenital anomalies; and (4) evidence of uteroplacental insufficiency.82

A trial of labor mandates continuous FHR monitoring of both fetuses. After amniotomy, an electrocardiography lead may be placed on the scalp of twin A and Doppler ultrasonography may be used to monitor twin B.

**Twin B**

If twin A is delivered vaginally, the obstetrician must make a decision about the method of delivery of twin B. Presentation and position should be verified, because these can change after delivery of twin A. If twin B has a vertex presentation and the head is well applied to the cervix, or if the amniotic membranes are still intact in a diamniotic pregnancy, the obstetrician may allow the patient to resume labor and await spontaneous vaginal delivery.

For the twin B with nonvertex presentation, options include (1) ECV followed by a resumption of labor, (2) internal podalic version and total breech extraction, and (3) performance of cesarean delivery. Real-time ultrasonography facilitates the performance of ECV. Mothers who received epidural anesthesia will be more relaxed and should tolerate the procedure better than those without neuraxial anesthesia.41 Internal podalic version and total breech extraction may increase the likelihood of vaginal birth when compared with attempted ECV. Total breech extraction is considered appropriate if twin A is the same size or larger than twin B to ensure that the pelvis and cervical dilation are adequate for vaginal delivery of twin B, and if delivery is attempted early after delivery of twin A to ensure that the cervix has not begun to contract.42 In a retrospective cohort study of women who labored with twin pregnancies, patients with nonvertex second twins had comparable, if not higher, rates of vaginal delivery than their vertex-presenting counterparts.82 Vaginal birth of both twins was associated with labor induction and the physician’s years in practice, leading the authors to suggest a role for provider selection and delivery planning.82 Indications for emergency cesarean delivery of twin B include malpresentation not amenable to obstetric maneuvers, non-reassuring FHR tracing, and umbilical cord prolapse.

In the past, obstetricians favored the delivery of twin B within 15 to 30 minutes of delivery of twin A. However, most data supporting this practice were obtained before the use of intrapartum FHR monitoring. In a review of 118 twin deliveries, Leung et al.83 demonstrated an association between the twin-twin delivery interval and the umbilical cord blood gas and pH measurements for twin B. Some 73% of the second twins not delivered by 30 minutes required operative delivery because of a nonreassuring FHR tracing. A German retrospective analysis of 4110 twin pregnancies suggested that an increasing interval between delivery of twins is an independent risk factor for adverse short-term outcomes for twin B.84 Continuous FHR monitoring of twin B is essential.

**Anesthetic Management**

**Labor and Vaginal Delivery**

Epidural analgesia provides optimal analgesia and flexibility for subsequent anesthetic needs. The anesthesia provider must be vigilant, because obstetric conditions are dynamic and anesthetic requirements may change rapidly. Given the greater risk for cesarean delivery in patients with multiple gestation, the anesthesia provider should aim for optimal epidural analgesia. If there is any question regarding the location of the catheter or the efficacy of the block, the catheter should be removed and replaced.

Patients with multiple gestation may be at higher risk than singleton pregnancies for aortocaval compression and hypotension during the administration of neuraxial analgesia and anesthesia. Use of the full left or right lateral position after induction of epidural analgesia reduces the risk for aortocaval compression. Because these patients are at increased risk for uterine atony and postpartum hemorrhage, establishment of large-bore intravenous access is recommended before delivery.

Patients with multiple gestation should deliver in a room where an emergency abdominal delivery can be performed immediately. As the time for delivery of twin A nears, the epidural analgesia is evaluated once more and augmented if necessary, although motor block is avoided so that the patient can continue to push effectively. Effective anesthesia facilitates the performance of internal podalic version and total breech extraction of twin B if necessary, and it also enables the extension of anesthesia for cesarean delivery if necessary. We prepare a syringe of 3% 2-chloroprocaine to be used if emergency extension of epidural analgesia is required, and we also have nitroglycerin immediately available in case uterine relaxation is needed acutely for delivery of twin B. At least one member of the anesthesia team stays with the patient until twin A is delivered and twin B is either delivered or the vertex is well applied in the pelvis.

We prefer to administer CSE anesthesia for vaginal delivery in patients with multiple gestation who do not have pre-existing epidural analgesia. An analgesic spinal dose can be administered for the second stage of labor and vaginal delivery, while the epidural catheter can be used to extend the block if cesarean delivery is required. We do not administer single-shot spinal anesthesia for vaginal delivery in these patients because of its lack of flexibility in cases of rapidly changing conditions. If a single-shot analgesic spinal dose is administered, it will not be adequate when cesarean delivery is required, and if an anesthetic dose is administered it will cause too much motor block for effective pushing and vaginal delivery.

**Vaginal Delivery of Twin A/Operative Delivery of Twin B**

The flexibility associated with epidural analgesia is especially advantageous if the obstetrician delivers twin A vaginally but twin B requires operative delivery. We administer a
nonparticulate antacid at the first sign of obstetrician concern, or even before proceeding to the operating room. Once the obstetrician determines that cesarean delivery will be necessary, we inject additional local anesthetic to extend the surgical sensory level to approximately T4 using 3% lidocaine for fastest onset. In cases of prolonged fetal bradycardia or umbilical cord prolapse, it may be necessary to administer general anesthesia if adequate neuraxial anesthesia cannot be achieved rapidly. This problem can usually be avoided if (1) both the level and density of analgesia are optimized at the time of delivery of twin A and (2) the anesthetic provider is present in the room and gives attention to both the FHR tracing and the obstetrician.

If the obstetrician opts for internal podalic version and total breech extraction of twin B, it is better to perform the procedure shortly after delivery of twin A, before the uterus and the cervix begin to contract. Pain relief and skeletal muscle relaxation (both provided by epidural anesthesia) facilitate internal version and total breech extraction of twin B. In some cases, pharmacologic uterine relaxation may be required to facilitate internal version and breech extraction of twin B. Sublingual (400 µg) or intravenous (150 to 250 µg) administration of nitroglycerin should provide adequate relaxation for internal podalic version. Intravenous or subcutaneous terbutaline 250 µg may also be used for uterine relaxation. If this maneuver is unsuccessful, rapid-sequence induction of general anesthesia, followed by administration of a high concentration of a volatile halogenated agent may be needed.

**Cesarean Delivery**

Epidural, spinal, or general anesthesia can be safely administered for elective abdominal delivery. Spinal anesthesia is increasingly preferred by many anesthesia providers. A historical preference for epidural anesthesia was based on the gradual onset of sympathetic blockade, which was thought to reduce the incidence of severe hypotension. It has been long believed that women with multiple gestation are at higher risk for hemodynamic instability during administration of neuraxial anesthesia than women with a singleton gestation. Ngan Kee et al.97 compared the incidence of hypotension and vasopressor requirements in women with multiple and singleton gestations undergoing cesarean delivery with spinal anesthesia. There were no differences between groups in maternal and neonatal outcomes.

Comparison of brachial artery (arm) and popliteal artery (leg) blood pressures could allow the detection of occult supine hypotension, which results in reduced uteroplacental perfusion in the presence of a normal brachial artery pressure. If either hypotension or occult supine hypotension is detected or suspected, additional left uterine displacement or displacement to the other side may resolve the problem. A nonreassuring FHR tracing for either infant should also prompt the administration of additional efforts to optimize uteroplacental perfusion.

Jawan et al.86 found that women with multiple gestation had a greater cephalad spread of neuroblockade with spinal anesthesia than women with a singleton gestation, whereas Ngan Kee et al.97 did not. Similarly, Behforouz et al.89 found no difference in the extent of sensory blockade after administration of epidural anesthesia between women with higher-order multiple gestation pregnancies and women with a singleton gestation. Any difference that may exist is likely to be of little clinical significance. A combined spinal-epidural anesthetic allows the anesthesiologist to use a lower dose of spinal anesthetic if desired, while retaining the capability of raising the anesthetic level using epidural local anesthetic if needed.

Vallejo and Ramanathan90 demonstrated that mean umbilical venous and umbilical arterial lidocaine concentrations were 35% to 53% higher in twin newborns than in singleton newborns exposed to epidural anesthesia for cesarean delivery. Mean fetal-to-maternal lidocaine ratios were at least 18% higher in the twin newborns than in the singleton newborns. The investigators speculated that this difference may be a result of greater maternal cardiac output and plasma volume associated with twin gestation as well as the decreased total plasma protein concentration, which leads to an increase in the free lidocaine concentration.90 The clinical relevance of these findings is unclear.

When general anesthesia is used, greater oxygen consumption and decreased functional residual capacity associated with multiple gestation increases the risk for maternal hypoxemia during periods of apnea. Adequate denitrogenation and preoxygenation is essential.

The presence of two or more fetuses results in a prolonged uterine incision-to-delivery interval because of the longer time required to deliver multiple infants. A prolonged interval increases the risk for umbilical cord blood acidemia and neonatal depression. Neonatal depression, especially of twin B, is less likely with neuraxial anesthesia than with general anesthesia. In any case, an individual skilled in neonatal resuscitation should be immediately available.

### **KEY POINTS**

- A higher incidence of breech presentation occurs among patients with preterm labor.
- External cephalic version has a low rate of morbidity in contemporary obstetric practice and is recommended by the ACOG for most women with a singleton breech presentation near term. Successful external cephalic version helps reduce the risk for perinatal morbidity and mortality associated with breech delivery and lowers the cesarean delivery rate. Neuraxial anesthesia may improve the success rate of external cephalic version, including after an initial failed attempt.
• Both breech presentation and multiple gestation are associated with an increased incidence of perinatal morbidity and mortality, regardless of the method of delivery.

• Epidural analgesia offers several advantages during a trial of labor in the patient with a breech presentation. Specifically, it (1) provides effective pain relief; (2) inhibits early pushing; (3) relaxes the pelvic floor and perineum, facilitating atraumatic delivery of the aftercoming head; and (4) enables provision of anesthesia for emergency cesarean delivery.

• Multiple gestation exaggerates the physiologic and anatomic changes of pregnancy.

• Epidural analgesia is the analgesic technique of choice during labor in the patient with multiple gestation.

Provision of pain relief and skeletal muscle relaxation facilitates the vaginal delivery of twin B. Provision of epidural analgesia also facilitates the administration of anesthesia for emergency cesarean delivery if it is needed.

• The obstetrician may request pharmacologic provision of uterine and/or cervical relaxation to facilitate vaginal delivery of twin B or, in cases of breech presentation, to facilitate the delivery of the aftercoming fetal head. Intravenous or sublingual nitroglycerin provides rapid uterine relaxation of short duration. Alternatively, rapid-sequence induction of general anesthesia followed by administration of a high concentration of a volatile halogenated agent is another reliable method of providing uterine and cervical relaxation.

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Hypertensive Disorders

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Hypertension is the most common medical disorder of pregnancy, affecting 6% to 10% of pregnancies. It is a leading cause of maternal mortality; together with hemorrhage it accounts for about one-half of all maternal deaths worldwide. Hypertensive disorders are an important risk factor for fetal complications, including preterm birth, fetal growth restriction, and fetal/neonatal death. They also pose very significant anesthesia risks.

Anesthesia providers play a critical role in the management of women with preeclampsia; they are well positioned to understand the pathophysiology, assist with assessment of the severity of preeclampsia, and assess the impact of the disease on the administration of anesthesia, cardiovascular monitoring, and critical care. Working as part of a multidisciplinary team that includes obstetricians, cardiologists, neonatologists, midwives, and critical care specialists, anesthesia providers play a critical role in ensuring optimal outcomes for women with preeclampsia.

CLASSIFICATION OF HYPERTENSIVE DISORDERS

Hypertensive disorders of pregnancy encompass a range of conditions—chronic hypertension, gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and eclampsia—that can be difficult to differentiate because the clinical presentation is often similar despite complex differences in their underlying pathophysiology and prognoses. In 2000, the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy published a classification scheme (Box 35.1). This classification was updated in 2013 when the American College of Obstetricians and Gynecologists (ACOG) Taskforce on Hypertension in Pregnancy reviewed available literature and published a summary of current knowledge and recommendations for the care of women with preeclampsia.

Gestational hypertension is the most frequent cause of hypertension during pregnancy, affecting approximately 5% of parturients. Gestational hypertension presents as elevated blood pressure after 20 weeks’ gestation without proteinuria (in the absence of chronic hypertension or systemic manifestations of preeclampsia) that resolves by 12 weeks postpartum. Most cases of gestational hypertension develop after 37 weeks’ gestation. Approximately one-fourth of patients diagnosed with gestational hypertension will develop preeclampsia. A definitive diagnosis of gestational hypertension can be made only in retrospect after delivery when the diagnosis of chronic hypertension can be excluded based on return to a normotensive state.

Preeclampsia is defined as the new onset of hypertension and proteinuria after 20 weeks’ gestation (Box 35.2). The diagnosis of preeclampsia should also be considered in the absence of proteinuria when any of the following signs or symptoms of end-organ involvement are present: (1) persistent epigastric or right upper quadrant pain, (2) persistent
cerebral symptoms, (3) fetal growth restriction, (4) thrombocytopenia, or (5) elevated serum liver enzymes. The term eclampsia is used when central nervous system (CNS) involvement results in the new onset of seizures in a woman with preeclampsia. HELLP syndrome refers to the development of hemolysis, elevated liver enzymes, and low platelet count in a woman with preeclampsia. This condition may be a variant of severe preeclampsia, but this classification is controversial because the disease may represent a pathophysiologically distinct entity.

Chronic hypertension involves either (1) systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher presenting before pregnancy or before 20 weeks’ gestation or (2) elevated blood pressure that fails to resolve after delivery. Chronic hypertension develops into preeclampsia in approximately one-fifth to one-fourth of affected patients. However, even in the absence of preeclampsia, chronic hypertension is an important risk factor for unfavorable maternal and fetal pregnancy outcomes.

Chronic hypertension with superimposed preeclampsia occurs when preeclampsia develops in a woman with chronic hypertension before pregnancy. The diagnosis is made in the presence of new onset of proteinuria or a sudden increase in proteinuria or hypertension, or both, or when other manifestations of severe preeclampsia appear. Morbidity is increased for both the mother and fetus compared with preeclampsia alone.

The clinical findings in chronic hypertension, gestational hypertension, and preeclampsia are compared in Table 35.1.

### PREECLAMPSIA

Preeclampsia is a multisystem disease unique to human pregnancy. It is characterized by diffuse endothelial dysfunction with maternal complications, including placental abruption, pulmonary edema, acute renal failure, liver failure, stroke, and neonatal complications, including indicated preterm delivery.
Epidemiology

Preeclampsia occurs in 3% to 4% of pregnancies in the United States. Delivery of the infant and placenta is the only definitive treatment; thus, preeclampsia is a leading cause of indicated preterm delivery in developed countries. Low-birth-weight and preterm infants born to women with preeclampsia present major medical, social, and economic burdens to families and societies. Preterm delivery is the most common indication for admission to the neonatal intensive care unit. Preeclampsia is also a leading indication for maternal peripartum admission to an intensive care unit.

The clinical findings of preeclampsia can manifest as a maternal syndrome (e.g., hypertension and proteinuria with or without other systemic abnormalities) or with or without an accompanying fetal syndrome (e.g., fetal growth restriction, oligohydramnios, abnormal oxygen exchange). In approximately 75% of cases, preeclampsia occurs without severe features near term or during the intrapartum period. In contrast, disease onset before 34 weeks’ gestation correlates with increased disease severity and poorer outcomes for both the mother and fetus.

A significant increase in the incidence of hypertensive disorders of pregnancy has occurred, with a near doubling in the rate in the United States in the past quarter century. The increase is at least partially explained by major shifts in the demographics and clinical conditions of pregnant women in the United States and other developed countries. Average maternal age is increasing; advanced maternal age is a recognized risk factor for preeclampsia. Both the growing epidemic of obesity and the increased prevalence of diabetes and chronic hypertension in the developed world may also contribute to this trend. An increase in the use of assisted reproductive techniques and the use of donated gametes is contributory; these techniques increase the risk for the disease, potentially by altering the maternal-fetal immune reaction and by increasing the incidence of multiple gestation. Last, improvements in record keeping and the use of

<table>
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<th>TABLE 35.2 Differences between Early- and Late-Onset Preeclampsia</th>
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<td><strong>Early Onset</strong></td>
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<tr>
<td>Onset of clinical symptoms</td>
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<td>Association with fetal growth restriction</td>
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<td>Risk factor (relative risk)</td>
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*Defined as recurrence across generations and occurrence within families.


*Reduced extravillous trophoblast invasion.

*Predisposed maternal constitution reflecting microvascular disease or predisposed genetic constitution with cis- or trans-acting genomic variations subject to interaction.

consistent disease definitions since 2000 may have contributed to the increased number of reported cases.\(^1\)

Numerous preconception and pregnancy-related risk factors associated with the development of preeclampsia have been identified (Box 35.3). Risk factors for preeclampsia can be divided into maternal demographic factors, genetic factors, medical conditions, obstetric conditions, behavioral factors, and partner-related factors.

**Risk Factors**

**Demographic factors.** Advanced maternal age has consistently been shown to be a risk factor for preeclampsia, with women who are 40 years of age or older having an approximately twofold increase in risk compared with women between 20 and 29 years of age.\(^27,28\) This risk may be independent of the increased prevalence of medical conditions and obesity that accompany advancing age.\(^27\) Teenage pregnancy may also be a risk factor for preeclampsia,\(^29-31\) but data are inconsistent.\(^32\)

Black women constitute a high-risk group, with increased rates of chronic hypertension,\(^33,34\) obesity,\(^34,35\) and preeclampsia.\(^36-39\) Black women with severe preeclampsia demonstrate more extreme hypertension, require more antihypertensive therapy,\(^40\) are more likely to develop eclampsia,\(^41\) and are more likely to die of the condition compared with women of other racial backgrounds.\(^42\) Hispanic ethnicity may also confer increased risk for developing preeclampsia and eclampsia.\(^42,43,44\)

**Genetic factors.** Maternal genetic factors are known to be important risk factors for the development of preeclampsia. Pregnant women with a family history of preeclampsia are approximately twice as likely to develop the disorder.\(^45,46\) It is estimated that approximately one-third of the variance in liability to preeclampsia is caused by maternal genetic factors.\(^47\)

In a study of 1.7 million births in the Medical Birth Registry of Norway, men who fathered one preeclamptic pregnancy were found to be nearly twice as likely to father a preeclamptic pregnancy with a different woman, irrespective of her previous obstetric history.\(^48\) Therefore, paternal genes (in the fetus) contribute significantly to a pregnant woman’s risk for preeclampsia. It is estimated that approximately one-fifth of the variance in liability for preeclampsia is conferred through the fetal genes.\(^47\)

Women with a history of preeclampsia in a previous pregnancy are at increased risk for preeclampsia in a subsequent pregnancy,\(^38,49\) particularly if the preeclampsia was of early-onset.\(^40\) Risk for recurrence increases with multiple affected pregnancies.\(^50\) In addition, women with a history of previous placental abruption and fetal growth restriction are at increased risk for preeclampsia in a subsequent pregnancy,\(^51\) and women with a history of preeclampsia are
at risk for these outcomes even in the absence of recurrent preeclampsia.\textsuperscript{52} These associations suggest that some women harbor a susceptibility (potentially genetically mediated) to obstetric conditions caused by placental dysfunction, which manifests differently in different pregnancies.

**Medical and obstetric conditions.** Obesity is an important risk factor for preeclampsia, and risk escalates with increasing body mass index (BMI).\textsuperscript{53,54} A systematic review found that an increase in BMI of 5 to 7 kg/m\textsuperscript{2} was associated with a twofold increased risk for preeclampsia.\textsuperscript{55} Obesity is strongly associated with insulin resistance, another risk factor for preeclampsia.

Women with chronic hypertension are also at increased risk for preeclampsia. Primary hypertension increases the odds of developing preeclampsia 10-fold, and secondary hypertension increases the odds nearly 12-fold.\textsuperscript{5} Chronic hypertension in association with other risk factors, including diabetes, renal disease, and collagen vascular disease, confers particularly elevated risk.\textsuperscript{5}

Diabetes mellitus is associated with an approximately twofold increase in the risk for development of preeclampsia.\textsuperscript{3,28} The prevalence of preeclampsia also increased with the severity of diabetes as determined by the White classification.\textsuperscript{55}

The metabolic syndrome, which occurs in about one-fifth of women of childbearing age in the United States, is characterized by the presence of obesity, hyperglycemia, insulin resistance, and hypertension.\textsuperscript{56} The metabolic syndrome increases the risk for preeclampsia.\textsuperscript{57} The insulin resistance and microvascular dysfunction observed in this condition have been implicated as a common factor in both preeclampsia and cardiovascular disease; these conditions may partially mediate the association of preeclampsia and increased risk for cardiovascular disease later in life.\textsuperscript{58-60}

Additional maternal medical conditions that are well-recognized risk factors for preeclampsia include chronic renal disease,\textsuperscript{61,62} antiphospholipid antibody syndrome,\textsuperscript{28} and systemic lupus erythematosus.\textsuperscript{5,63} Pregnancy-related conditions that increase placental mass, including multifetal gestation\textsuperscript{28,64} and hydatidiform mole,\textsuperscript{65} are associated with higher rates of preeclampsia as well.

**Behavioral factors.** Paradoxically, cigarette smoking during pregnancy has been associated with a decreased risk for preeclampsia,\textsuperscript{66,67} an effect consistently observed across studies in various countries. Women who smoke during pregnancy have a 30\% to 40\% lower risk for developing preeclampsia compared with women who do not smoke. The mechanism may include nicotine inhibition of thromboxane A\textsubscript{2} synthesis,\textsuperscript{68} simulation of nitric oxide release,\textsuperscript{69} or a combination of these factors.

**Recreational physical activity.** Recreational physical activity during pregnancy has been associated with a decrease in the risk for gestational hypertensive disorder,\textsuperscript{70} particularly in nonobese women.\textsuperscript{71} Mechanistically, this may occur through exercise promoting placental growth, decreasing oxidative stress, enhancing endothelial function, and modulating the immune and inflammatory response.\textsuperscript{72}

**Partner-related risk factors.** The unifying theme among partner-related risk factors is limited maternal exposure to paternal sperm antigens before conception, which suggests an immunologic role in the pathophysiology of preeclampsia. A leading risk factor for preeclampsia is nulliparity; the incidence is approximately threefold higher compared with parous women.\textsuperscript{28} Preeclampsia is also more common in (1) parous women who have conceived with a new partner, (2) women who have used barrier methods of contraception before conception, and (3) women who have conceived with donated sperm.\textsuperscript{73,74} Long-term sperm exposure with the same partner appears to be protective; this protective effect is lost in a pregnancy conceived with a new partner.

**Pathogenesis**

The exact pathogenic mechanisms responsible for the initiation and progression of preeclampsia are not known. The placenta is the focus of hypotheses regarding disease pathogenesis; delivery of the placenta results in resolution of the disease, and the disease can occur in the absence of a fetus (e.g., a molar pregnancy).\textsuperscript{75}

**Preeclampsia as a Two-Stage Disorder**

Contemporary hypotheses generally conceptualize preeclampsia as a two-stage disorder.\textsuperscript{76} The asymptomatic first stage occurs early in pregnancy with impaired remodeling of
the spiral arteries (the end branches of the uterine artery that supply the placenta). In normal pregnancy, embryo-derived cytotrophoblasts invade the decidual and myometrial segments of the spiral arteries, replacing endothelium and causing remodeling of vascular smooth muscle and the inner elastic lamina (Fig. 35.2). The luminal diameter of the spiral arteries increases fourfold, resulting in the creation of flaccid tubes that provide a low-resistance vascular pathway to the intervillous space. Furthermore, the remodeled arteries are unresponsive to vasoactive stimuli. These alterations in maternal vasculature ensure adequate blood flow to nourish the growing fetus and placenta.

In contrast, in preeclamptic pregnancies, cytotrophoblast invasion is incomplete and only the decidual segments undergo change; the myometrial spiral arteries are not invaded and remodeled and thus remain small, constricted, and hyperresponsive to vasomotor stimuli. This failure of normal angiogenesis results in superficial placentation. Abnormal placentation results in decreased placental perfusion and placental infarcts, predisposing the fetus to growth restriction (Fig. 35.3). Placental ischemia worsens throughout pregnancy as narrowed vessels are increasingly unable to meet the needs of the growing fetoplacental unit.

In some women, the reduced perfusion of the intervillous space in the first stage leads to the **symptomatic second stage**, which is characterized by the release of antiangiogenic factors from the intervillous space into the maternal circulation; these factors cause widespread maternal endothelial dysfunction and an accentuated systemic inflammatory response. In the absence of preeclampsia, healthy endothelium prevents platelet activation, activates circulating anticoagulants, buffers the response to vasopressors, and maintains fluid in the intravascular compartment. These normal functions are disrupted in preeclampsia. As a result, the pregnant woman develops hypertension and proteinuria, and is at risk for other manifestations of severe systemic disease (e.g., HELLP syndrome, eclampsia, other end-organ damage). By definition, these clinical manifestations manifest after 20 weeks’ gestation.

**Abnormal Placentation**

The basis for abnormal uteroplacental development has not been fully elucidated and is likely due to a complex interaction of immunologic, vascular, environmental, and genetic factors. The hypothesis that immune maladaptation may play a central role in predisposing to abnormal placentation and subsequent preeclampsia is supported by evidence showing that long-term exposure to paternal antigens in sperm is protective. Furthermore, the importance of an intact immune system in the development of preeclampsia is demonstrated by the lower incidence of preeclampsia in women with untreated human immunodeficiency virus; the incidence returns to baseline after treatment with antiretroviral therapy.

The immune cells present in the decidua—the endometrium in the nonpregnant state becomes the decidua in pregnancy—include macrophages, dendritic cells, and natural killer (NK) cells. Macrophages and dendritic cells are found in greater density in preeclamptic placentas than in control placentas. Similarly, levels of chemokines that attract these immune cells are also elevated. Excess macrophages in the decidua are associated with impaired trophoblast invasion, suggesting that excess inflammation may be one of the causal components of impaired placentation. NK cells may also be
important in regulating vascular development during placentation. NK cells interact with fetal trophoblast cell markers via killer immunoglobulin receptors (KIR) to influence trophoblastic invasion. Specific genotypic combinations of maternal KIR and trophoblastic human leukocyte antigen C (HLA-C) may mediate the risk for preeclampsia.\(^\text{82,83}\)

Aberrant hemostatic activation during placental development has also been proposed to contribute to the abnormal placental that is a hallmark of pregnancies destined to develop preeclampsia.\(^\text{84}\) Increased tissue factor expression may cause inappropriate activation of clotting pathways, which in turn may impair trophoblast invasion of the decidua. Abnormal protease-activated receptor 1 (PAR 1) may also play a role in failure of trophoblasts to convert to an endothelial phenotype.

Agnostic autoantibodies to the angiotensin type 1 receptor (AT\(_1\)) are present in many women with preeclampsia in association with defective remodeling of the uteroplacental vasculature.\(^\text{85,86}\) These autoantibodies activate AT\(_1\) receptors on trophoblast cells, endothelial cells, and vascular smooth muscle cells.\(^\text{87-89}\) They appear to block trophoblastic invasion\(^\text{88}\) and may induce the production of reactive oxygen species\(^\text{89}\) and thus play a significant role in the pathophysiology of preeclampsia (Fig. 35.4). Furthermore, introduction of these autoantibodies into pregnant mice increases production of soluble fms-like tyrosine kinase-1 (sFlt-1) and results in hypertension and proteinuria.\(^\text{90}\) Thus, these autoantibodies may play an important role in the pathogenesis of preeclampsia at several different stages.

Oxidative stress is another mechanism that has been postulated as an important component of impaired placentaion.\(^\text{80}\) Oxidative stress and the resultant oxygen free radicals are known to contribute to atherosclerosis and thus may contribute to placental atherosis.\(^\text{90}\) Volatile organic compounds measured in a breath test, a marker for oxidative stress, are found in greater quantity in women with preeclampsia compared with healthy pregnant controls.\(^\text{91}\) Enthusiasm for this theory is tempered by the failure of antioxidant supplementation to decrease the risk for preeclampsia in clinical trials.\(^\text{80}\)

**Maternal Systemic Disease**

The symptomatic second stage of preeclampsia is marked by signs and symptoms attributable to the manifestations of widespread endothelial dysfunction specific to each

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**Fig. 35.4** Angiotensin receptor autoantibodies (AT\(_1\)-AAs) in preeclampsia. AT\(_1\)-AAs and other factors (e.g., oxidative stress and genetic factors) may cause placental dysfunction, which, in turn, leads to the release of antiangiogenic factors (e.g., soluble fms-like tyrosine kinase-1 [sFlt-1] and soluble endoglin [sEng]) and other inflammatory mediators to induce preeclampsia. AT\(_1\)-AAs may also act directly on the maternal vasculature to enhance angiotensin II sensitivity and hypertension. NK, Natural killer. (From Parikh SM, Karumanchi SA. Putting pressure on preeclampsia. *Nat Med.* 2008;14:810–812.)
organ system. This notion is supported by studies showing increased levels of biomarkers indicating endothelial activation or injury, or both, including endostatin-1, fibronectin, von Willebrand factor, and thrombomodulin. The central role of endothelial dysfunction is further evidenced by the fact that chronic conditions that cause pre-pregnancy endothelial injury, including chronic hypertension, pre-existing diabetes, and renal disease, are risk factors for preeclampsia. A predilection for endothelial dysfunction may similarly explain the association of preeclampsia and future cardiovascular disease.

The mechanistic link between abnormal placentation and subsequent widespread endothelial dysfunction is an area of great interest and ongoing investigation. The prevailing hypothesis is that the placenta becomes relatively hypoxic as the pregnancy progresses, and this change results in an overexpression and release into the maternal circulation of placentally derived antiangiogenic factors, including sFlt-1 and soluble endoglin (sEng).

The vascular endothelium requires proangiogenic factors for normal function. sFlt-1 antagonizes the angiogenic growth factors, vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). Evidence for a central role of sFlt-1 in the pathogenesis of preeclampsia comes from both animal and human studies. Maynard et al. demonstrated that sFlt-1 levels increase during gestation and fall after delivery and that increased circulating sFlt-1 levels reduce circulating levels of free VEGF and PIGF, causing endothelial dysfunction that can be rescued by exogenous VEGF and PIGF. Furthermore, these investigators found that the administration of sFlt-1 to pregnant rats induced hypertension, proteinuria, and glomerular endotheliosis, which is the classic renal lesion of preeclampsia. When administered in vitro, VEGF and PIGF cause rat renal arteriolar relaxation, which is blocked by sFlt-1. In response to increased circulating levels of sFlt-1, VEGF and PIGF levels are reduced, resulting in endothelial dysfunction in maternal vessels (Fig. 35.5). In a study in humans, elevated sFlt-1 levels and reduced levels of PIGF predicted the subsequent development of preeclampsia before the development of any maternal symptoms. In women presenting at less than 35 weeks’ gestation with a possible diagnosis of preeclampsia, a low PIGF level has a high sensitivity and negative predictive value for the development of preeclampsia within 14 days. Studies have also confirmed

![Fig. 35.5 Hypothesis on the role of soluble fms-like tyrosine kinase (sFlt-1) in preeclampsia. (A) During normal pregnancy, the uterine spiral arteries are infiltrated and remodeled by endovascular invasive trophoblasts, thereby increasing blood flow significantly to meet the oxygen and nutrient demands of the fetus. (B) In the placenta of preeclamptic women, trophoblast invasion does not occur and blood flow is reduced, resulting in placental hypoxia. In addition, increased amounts of soluble sFlt-1 are produced by the placenta and scavenge vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), thereby lowering circulating levels of unbound VEGF and PIGF. This altered balance causes generalized endothelial dysfunction, resulting in multiorgan disease. (From Luttun A, Carmeliet P: Soluble VEGF receptor Flt1: the elusive preeclampsia factor discovered? J Clin Invest. 2003;111:600–602.)](image-url)
the importance of the sFlt-1–to–PIGF ratio as a marker of preeclampsia.  

sEng is another placentally derived antiangiogenic protein that appears to be important in the pathogenesis of preeclampsia. Circulating levels of sEng are markedly increased in women who subsequently develop preeclampsia. Furthermore, if women have both elevated sEng and increased sFlt-1/PIGF ratios, their risk for preeclampsia is elevated approximately 30-fold compared with women who have normal levels of both factors/ratios.

The study of antiangiogenic proteins is an active area of current research, and rapid progress is being made in understanding the role of these proteins in the pathogenesis of preeclampsia. However, the importance of recent findings is tempered by the knowledge that preeclampsia does not develop in all women with high sFlt-1 and low PIGF levels, and the syndrome occurs in some women with low sFlt-1 and high PIGF levels. These observations are consistent with those from a large, longitudinal study involving 2246 singleton pregnancies that found that PIGF and sFlt-1 levels had limited sensitivity, specificity, and positive predictive value for predicting the development of preeclampsia.

Kanasaki et al. hypothesized that a molecular defect upstream from the soluble factors contributes to preeclampsia. The investigators demonstrated that pregnant mice deficient in catechol-O-methyltransferase (COMT) demonstrate a preeclampsia-like phenotype in response to the absence of 2-methoxyestradiol (2-ME), a natural metabolite of estradiol that is elevated during the third trimester of normal pregnancy. Administration of 2-ME to COMT-deficient mice suppresses placental hypoxia and sFlt-1 elevation. In addition, women with severe preeclampsia have significantly lower levels of COMT and 2-ME than women with healthy pregnancies. However, a subsequent study in humans failed to find a significant difference in placental COMT expression in women with early-onset, severe preeclampsia compared with normotensive women; therefore, further research is needed to determine what role, if any, COMT plays in the pathogenesis of preeclampsia.

Genetic Factors
There is a strong genetic basis underlying the risk for preeclampsia that is attributable to both maternal and fetal genetic factors. It is estimated that approximately one-fifth of the variance in disease risk is attributable to fetal genetic effects, and one-third is attributable to maternal genetic factors. A recent genome-wide association study in offspring from preeclamptic pregnancies reported that variants in the fetal genome near FLT1 are associated with risk for preeclampsia. With the possible exception of thrombophilia genes, no genetic variants in the maternal genome have been robustly associated with preeclampsia.

Prophylaxis
Various strategies to prevent preeclampsia have been studied. These include antiplatelet drugs, metformin, antioxidant and calcium supplementation, and dietary sodium restriction among other lifestyle modifications. A 2014 systematic review by the U.S. Preventive Services Task Force found that low-dose aspirin use is associated with a 2% to 5% absolute reduction in the risk for preeclampsia (depending on baseline risk) and a 2016 ACOG practice advisory suggests that consideration should be given for initiating prophylactic low-dose aspirin between 12 and 24 weeks’ gestation in women at high risk for preeclampsia.

Clinical Presentation
Preeclampsia occurs more frequently in nulliparous women and most commonly presents during the third trimester, often near term. Women with early-onset disease (before 34 weeks’ gestation) have poorer outcomes than women with late-onset disease. The disease typically regresses rapidly after delivery, with resolution of symptoms within 48 hours. However, preeclampsia can also manifest postpartum with hypertension, proteinuria, or the occurrence of seizures (eclampsia). Postpartum preeclampsia usually presents within 7 days of delivery. Disease manifestations of severe preeclampsia occur in all body systems as the result of widespread endothelial dysfunction.

Identification of women at greatest risk for adverse maternal outcomes is potentially useful in guiding triage to high-risk centers and weighing the risks and benefits of expectant management. A 2011 multicenter prospective study involving 2023 women with preeclampsia admitted to tertiary care centers described a model (fullPIERS) for predicting which women will develop fatal or life-threatening complications. Unfavorable outcomes occurred in 261 patients. Predictors of unfavorable maternal outcome included early gestational age, chest pain or dyspnea, low oxygen saturation, low platelet count, and elevated creatinine and aspartate aminotransferase concentrations. The model showed excellent discrimination, with an area under the receiver operating characteristics (ROC) curve of 0.88 for adverse events within 48 hours of admission. It continued to perform well in predicting adverse events up to 7 days after admission. The fullPIERS model has recently been validated in low- and middle-income countries.

In further work on prediction of complications in early-onset preeclampsia, women were recruited from 53 maternity units in the United Kingdom to a large cohort study for the development of prognostic models for risk for complications. These models were externally validated in two large cohorts of patients and were found to be predictive of adverse maternal outcome risk, including preterm delivery. It was concluded that the models may have a role in triaging women who would benefit from referral for tertiary care.

A further advance in the prediction of disease severity relies on strong-ion analysis of maternal acid-base status. Early investigation suggests that preeclampsia is associated with greater offsetting of hypoalbuminemic alkalosis with hyperchloremic acidosis, although the overall base excess in severe preeclampsia is similar to that in healthy pregnancy. The magnitude of these opposing contributors may be a better indicator of disease severity than the overall base excess.
Central Nervous System

Although the term *preeclampsia* suggests that eclampsia is the end stage of preeclampsia, it is more accurate to consider eclampsia as the outward manifestation of disease progression in the brain, similar to other organ involvement. Central nervous system manifestations include severe headache, hyperexcitability, hyperreflexia, and coma. Visual disturbances can include scotoma, amaurosis, and blurred vision.

Noninvasive measurements of cerebral blood flow and resistance, along with other neuroimaging approaches, suggest that the loss of cerebral vascular autoregulation and vascular barotrauma occur with preeclampsia and eclampsia. Hyperperfusion of the brain, particularly in the setting of the endothelial dysfunction that is present in preeclampsia, causes vasogenic edema. Failure of autoregulation occurs most commonly in the posterior circulation; these changes may result in the posterior reversible leukoencephalopathy syndrome (PRES).

Other neurologic markers of disease severity are being examined. Optic nerve sheath diameter (ONSD) is being investigated as a marker for increased intracranial pressure. In a study that compared women with preeclampsia and healthy controls, the median ONSD was greater in women with disease. Nineteen percent of women with preeclampsia had ONSD of greater than 5.8 mm, a value that had previously been associated with a 95% risk for raised intracranial pressure in nonobstetric settings. However, this study found no association between ONSD and the severity of preeclampsia. Future investigations are necessary to understand whether the increase in ONSD is associated with raised intracranial pressure in preeclampsia or higher risk for eclampsia.

Regional cerebral hemoglobin oxygen saturation (rcSO₂) has been measured using near-infrared spectroscopy in women with severe preeclampsia and was found to be lower in women with preeclampsia compared with healthy women. The rcSO₂ increased after the administration of magnesium sulfate, with the percent increase indirectly correlating with blood pressure.

Airway

In pregnant women, the internal diameter of the trachea is reduced because of mucosal capillary engorgement. In women with preeclampsia, these changes can be exaggerated with upper airway narrowing as a result of pharyngolaryngeal edema; these changes may compromise visualization of airway landmarks during direct laryngoscopy. Signs of airway obstruction include dysphonia, hoarseness, snoring, stridor, and hypoxemia.

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by recurrent episodes of upper airway collapse leading to hypoxia and sleep disturbance. A meta-analysis of available cohort studies suggests that parturients with OSA have a twofold increase in risk for developing preeclampsia. This is plausibly a causal association, as recurrent nocturnal desaturations might result in placental hypoxia, hypertension, and maternal endothelial dysfunction, all of which are associated with preeclampsia.

Cardiovascular

Women with preeclampsia have increased vascular tone and increased sensitivity to vasoconstrictors and circulating catecholamines, which result in the clinical manifestations of hypertension, vasospasm, and end-organ ischemia. In preeclampsia without severe features, plasma volume may be normal; however, it may be reduced as much as 40% in women with severe disease.

Severe preeclampsia is usually a hyperdynamic state. Many studies have attempted to characterize the hemodynamic characteristics of preeclampsia using invasive monitoring techniques such as pulmonary artery catheterization or echocardiography. Interpretation and comparison of the results of these studies have been difficult because of variation in patient populations, definitions of preeclampsia, disease severity, prior treatment, and the presence or absence of concomitant comorbid disease. Hemodynamic characteristics in preeclamptic women are more complex than originally thought. This is partly because hemodynamic measurements change with treatment and disease progression. In a large prospective series of normotensive nulliparous women who were assessed with transthoracic echocardiography (TTE) at 24 weeks’ gestation, 107 women developed preeclampsia (75 early- and 32 late-onset). Mean (± standard deviation) total vascular resistance was 1605 ± 248 dyne · s · cm⁻⁵ and 739 ± 244 dyne · s · cm⁻⁵, and cardiac output was 4.49 ± 1.09 L/min and 8.96 ± 1.83 L/min in early- and late-onset preeclampsia, respectively, suggesting two different cardiovascular responses.

Overall, studies have found that the majority of affected women without clinical signs of pulmonary edema exhibit normal to increased cardiac output, hyperdynamic left ventricular function, and mild to moderately increased systemic vascular resistance, often associated with diastolic dysfunction. In severe preeclampsia, cardiac magnetic resonance imaging studies demonstrate that the myocardium may be edematous as well as hypertrophied.

Echocardiographic speckle-tracking is a new method of quantifying myocardial strain that appears to be a more sensitive marker of systolic dysfunction than the left ventricular ejection fraction in women with preeclampsia. Systolic dysfunction is more common in early- than late-onset disease and in some cases may present as severe cardiac failure with a low ejection fraction. This cardiac dysfunction is generally different from that which occurs in peripartum cardiomyopathy (see Chapter 41). The hypothesis that there are shared pathways of abnormal angiogenesis in preeclampsia and peripartum cardiomyopathy is controversial.

There is growing interest in the use of biomarkers such as brain natriuretic peptide (BNP) to identify cardiac dysfunction in preeclampsia. A systematic review found that serum BNP levels are higher in the third trimester in women with preeclampsia compared with healthy women. Studies
included in this review found that elevated BNP levels correlated with echocardiographically demonstrated cardiac dysfunction as well as increased systemic vascular resistance, decreased cardiac output, and left ventricular diastolic dysfunction. Future studies are needed, however, to define BNP threshold values that have high sensitivity and specificity for heart failure in preeclampsia.

**Pulmonary**

**Pulmonary edema** is a severe complication that occurs in approximately 3% of women with preeclampsia.\(^1\)\(^\text{141}\) It occurs infrequently in healthy, younger women; the risk increases in older multigravid women, in women with preeclampsia superimposed on chronic hypertension or renal disease, and among those whose preeclampsia leads to oliguria.

Plasma colloid osmotic pressure is reduced in normal pregnancy because of decreased plasma albumin concentration, and it is decreased even further in women with preeclampsia.\(^1\)\(^\text{142}\) Women with normal pregnancies have a mean osmotic pressure of approximately 22 mm Hg in the third trimester and approximately 17 mm Hg during the early postpartum period. In contrast, a study of women with preeclampsia demonstrated a mean colloid osmotic pressure of approximately 18 mm Hg before delivery and 14 mm Hg after delivery.\(^1\)\(^\text{143}\) Decreased colloid osmotic pressure, in combination with increased vascular permeability due to abnormalities of the pulmonary endothelial glycocalyx and the loss of intravascular fluid and protein into the interstitium, increases the risk for pulmonary edema.\(^1\)\(^\text{144}\) In addition, increased intravascular hydrostatic pressure due to fluid overload and/or increased left ventricular end-diastolic pressure, and occasional systolic heart failure, may cause pulmonary edema.\(^1\)\(^\text{145}\) All of these factors may coexist in a single patient.

Lung ultrasonography may be a useful adjunct to identify lung pathology. In a study of 20 asymptomatic women with severe preeclampsia and healthy controls,\(^1\)\(^\text{146}\) interstitial edema, which precedes alveolar edema, was identified by sonographic B-line artefacts in 25% of the cases. High lung “echo comet scores” were associated with increased left ventricular end-diastolic pressure. Another investigation in women with preeclampsia found echo comet scores were higher before delivery than 4 days after delivery, although tissue Doppler indices did not change after delivery.\(^1\)\(^\text{147}\) The authors concluded that increased extravascular lung water before delivery may be associated with increased pulmonary capillary permeability in addition to cardiac dysfunction.

**Hematologic**

**Thrombocytopenia** is the most common hematologic abnormality in women with preeclampsia, and preeclampsia is the most common cause of severe thrombocytopenia in the second half of pregnancy (see Chapter 44). Platelet counts less than 100,000/mm\(^3\) occur most commonly in women with severe disease or HELLP syndrome\(^1\)\(^\text{148}\) and correlate with the severity of the disease process.

Studies using thromboelastography have found that women with preeclampsia without severe features are hypercoagulable relative to women without preeclampsia and that those with severe disease are relatively hypocoagulable.\(^1\)\(^\text{149}\) In contrast to normal pregnancies and other hypertensive disorders, platelets are activated in preeclampsia\(^1\)\(^\text{145}\); subsequent platelet degranulation is believed to account for the decreases in platelet function, and aggregation appears to account for the decrease in platelet count.\(^1\)\(^\text{150}\)

The syndrome of **disseminated intravascular coagulation (DIC)** occurs in some women with preeclampsia, generally in the setting of severe liver involvement, intrauterine fetal demise, placental abruption, or postpartum hemorrhage.\(^1\)\(^\text{151}\) Activation of the coagulation system is marked by consumption of procoagulants, increased levels of fibrin degradation products, and end-organ damage secondary to microthrombi formation. In advanced DIC, procoagulants (e.g., fibrinogen, platelets) decrease to a level that may lead to spontaneous hemorrhage.

**Hepatic**

Hepatic manifestations of preeclampsia include periportal hemorrhage and fibrin deposition in hepatic sinusoids. Hepatic involvement frequently presents as right upper quadrant or epigastric pain. Damage ranges from mild hepatocellular necrosis to the more ominous HELLP syndrome and can be associated with subcapsular bleeding and risk for hepatic rupture. Spontaneous hepatic rupture is rare but is associated with a 32% maternal mortality rate.\(^1\)\(^\text{152}\)

**Renal**

Renal manifestations of preeclampsia include persistent proteinuria, changes in the glomerular filtration rate, and hyperuricemia. The presence of proteinuria is a defining element of preeclampsia but is no longer considered essential for diagnosis if other evidence of end-organ injury is present. The characteristic renal histologic lesion of preeclampsia is glomerular capillary endotheliosis, which manifests as glomerular enlargement and endothelial and mesangial cell swelling. Increasing urinary excretion of protein likely results from changes in the pore size or charge selectivity of the glomerular filter and impaired proximal tubular reabsorption.\(^1\)\(^\text{153}\)

During normal pregnancy, the **glomerular filtration rate (GFR)** increases by 40% to 60% during the first trimester,\(^1\)\(^\text{154,155}\) with a resulting decrease in the serum markers of renal clearance, including blood urea nitrogen (BUN), creatinine, and uric acid. In preeclampsia, this increase in GFR is blunted compared with normal pregnancy.\(^1\)\(^\text{155}\) Notably, women with preeclampsia may have BUN and creatinine measurements in the normal range for nonpregnant women despite significantly decreased GFR relative to healthy pregnant women.

The association between preeclampsia and hyperuricemia was recognized as early as 1917.\(^1\)\(^\text{156}\) Most evidence suggests that decreased renal clearance is the primary mechanism for elevated uric acid levels.\(^1\)\(^\text{157}\) Because levels of serum uric acid begin to increase as early as 25 weeks’ gestation,\(^1\)\(^\text{158}\) it has been investigated as a possible early predictor of preeclampsia.

**Oliguria** is a possible late manifestation of severe preeclampsia and parallels the severity of disease. Persistent
Uteroplacental Perfusion

Uteroplacental perfusion can be impaired in pregnancies complicated by preeclampsia. In contrast with normal pregnancy, fetal umbilical artery flow waveforms demonstrate an increase in downstream resistance, a decrease in diastolic flow velocity, and an increase in the systolic-to-diastolic flow velocity ratio. The systolic-to-diastolic ratio, calculated from Doppler ultrasonographic determination of blood flow velocities, reflects intrinsic arterial resistance in the chorionic plate of the placenta. Pathophysiologic changes can result in fetal growth restriction (the fetal syndrome) in some pregnancies complicated by severe preeclampsia.

Obstetric Management

Optimal management of the woman with preeclampsia requires a team approach. There is considerable overlap in areas of concern to the obstetrician and the anesthesia provider. Obstetric management of preeclampsia centers on (1) decisions regarding the timing and route of delivery, (2) fetal and maternal surveillance, (3) treatment of hypertension, and (4) seizure prophylaxis.

Delivery remains the only cure for preeclampsia. Obstetric care of women with preeclampsia without severe features differs little from routine management of healthy pregnant women, except for careful monitoring to detect the development of severe features. Data suggest that induction of labor for pregnancies beyond 37 weeks’ gestation in women with gestational hypertension or preeclampsia without severe features is associated with improved maternal outcomes compared with expectant management. Outcomes in these pregnancies are similar to those in uncomplicated pregnancies. In general, delivery is recommended for women presenting with preeclampsia with severe features at 34 weeks’ gestation or later.

For women with preeclampsia with severe features at less than 34 weeks’ gestation (Fig. 35.6), expectant management may improve fetal outcomes without substantially endangering the mother, but data are few. Delay of delivery for 24 to 48 hours allows for the administration of corticosteroids to facilitate fetal lung maturity and transfer to a facility with maternal and neonatal intensive care resources. Expedited corticosteroid administration is indicated for patients with eclampsia, pulmonary edema, DIC, placental abruption, abnormal fetal surveillance, a previable or nonviable fetus, or intrauterine fetal demise. If a woman develops refractory severe hypertension despite maximum doses of antihypertensive agents or persistent cerebral symptoms while receiving magnesium sulfate, delivery should occur within 24 to 48 hours, regardless of gestational age or corticosteroid administration. Expectant management before 34 weeks’ gestation should be undertaken at facilities with neonatal and maternal intensive care resources.

Maternal and Fetal Surveillance

Maternal surveillance is indicated for all preeclamptic women. In women with preeclampsia without severe features, the goal is early detection of severe disease. In women with severe disease, the goal is detection of worsening organ dysfunction. All women should be evaluated for signs or symptoms indicating end-organ involvement, including (1) severe headache, (2) visual disturbances, (3) altered mentality, (4) dyspnea, (5) right upper quadrant or epigastric pain, (6) nausea and vomiting, (7) decreased urine output, and (8) CNS hyperexcitability.

Initial laboratory investigations for the pregnant woman who develops hypertension after 20 weeks’ gestation are listed in Table 35.3. The admission platelet count is an excellent predictor of subsequent thrombocytopenia. For preeclamptic women with a platelet count exceeding 100,000/mm3, further coagulation testing is not required because coagulopathy is rarely present in severely preeclamptic women who have a normal platelet count. If the platelet count is less than 100,000/mm3, other hemorrhagic abnormalities (e.g., prolonged prothrombin time [PT] and activated partial thromboplastin time [aPTT], reduced fibrinogen concentration) may be present. Further coagulation studies may be useful, particularly if risk factors for DIC are present (e.g., placental abruption, liver dysfunction, HELLP syndrome). Liver

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin and hematocrit</td>
<td>Hemoconcentration supports diagnosis of preeclampsia and is an indicator of severity. Values are decreased if hemolysis is present.</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Thrombocytopenia suggests severe preeclampsia.</td>
</tr>
<tr>
<td>Urine protein-creatinine ratio or 24-hour urine protein excretion</td>
<td>Presence of proteinuria distinguishes preeclampsia from gestational hypertension. Abnormal or rising creatinine level suggests severe preeclampsia, especially in presence of oliguria.</td>
</tr>
<tr>
<td>Serum creatinine level</td>
<td></td>
</tr>
<tr>
<td>Serum aminotransferase levels</td>
<td>Elevated serum aminotransferase levels suggest severe preeclampsia with hepatic involvement.</td>
</tr>
</tbody>
</table>

Obstetric Complications

Evidence regarding its association with increased fetal or maternal risk for complications. In general, the frequency of subsequent laboratory evaluation will be guided by the initial findings and the severity of illness and disease progression. A diagnosis function tests are obtained in all women with preeclampsia because abnormal levels indicate more severe disease and may prompt delivery. Approximately 20% of women with preeclampsia have elevated serum aminotransferase levels. The value of uric acid testing is controversial, with conflicting evidence regarding its association with increased fetal or maternal risk for complications.

In general, the frequency of subsequent laboratory evaluation will be guided by the initial findings and the severity of illness and disease progression. A diagnosis
of preeclampsia without severe features should prompt at least weekly laboratory investigations, with the frequency modified based on subsequent clinical findings. In the expectant management of preeclampsia with severe features, hemoglobin, platelet count, liver function tests, creatinine, and coagulation parameters should be assessed daily or every other day. For women undergoing induction of labor for whom initial laboratory measurement or daily platelet counts demonstrate thrombocytopenia, serial platelet counts at least every 6 hours may be useful to detect declining platelet counts and to guide decision-making about the timing of delivery and analgesic or anesthetic technique. Finally, for women with indicated delivery, an active blood type and screen is indicated with consideration of type and cross-match of 2 units of packed red blood cells or more for patients with thrombocytopenia or other abnormalities in coagulation parameters.

Preeclampsia is a known risk factor for perinatal death. The ACOG Taskforce on Hypertension in Pregnancy recommends daily fetal movement counts with either nonstress testing or biophysical profile testing at the time of diagnosis and at regular intervals thereafter. Ultrasonography is used to estimate fetal weight and amniotic fluid volume. Doppler ultrasonography is used to measure fetal blood flow velocimetry if fetal growth restriction is suspected.

**Fluid Management**

Although preeclampsia is associated with intravascular volume depletion, the optimal approach to fluid management remains controversial, given potential dysfunction of the pulmonary endothelial glycocalyx and renal glomerulonephrosis. A 2011 systematic review found insufficient evidence of maternal or neonatal benefit of plasma volume expansion in preeclampsia. Given the heterogeneity of the disease, clinicians should restrict fluids in these patients unless monitoring is used (e.g., invasive blood pressure monitoring with or without noninvasive cardiac output monitoring, TTE) to assess response to fluid administration. Volume expansion is not recommended, and fluids should be limited to 80 mL/h or 1 mL/kg/h. In the case of hemorrhage, losses should be replaced appropriately. Administration of additional fluid may be considered before intravenous hydralazine, neuraxial anesthesia, or immediate delivery. Care must be taken not to overtreat oliguria with fluids; a fluid challenge is recommended in oliguric patients only if a volume deficit is suspected or can be confirmed.

**Treatment of Acute Hypertension**

Antihypertensive medications are used to treat severe hypertension (systolic blood pressure greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 110 mm Hg) with the goal of preventing adverse maternal sequelae such as hypertensive encephalopathy, cerebrovascular hemorrhage, myocardial ischemia, and congestive heart failure.

Although acute control of maternal blood pressure is critical, rapid changes in maternal perfusion pressure may adversely affect uteroplacental perfusion and oxygen delivery to the fetus. Antihypertensive medications should be carefully titrated to avoid abrupt changes in maternal blood pressure. The aim of therapy is to lower the mean arterial blood pressure by no more than 15% to 25%, with a target systolic blood pressure between 120 and 160 mm Hg and a diastolic blood pressure between 80 and 105 mm Hg.

TABLE 35.4  Treatment of Acute Severe Hypertension in Preeclampsia/Eclampsia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset of Action</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>5–10 min</td>
<td>20 mg IV, then 40–80 mg every 10 min up to maximum dose of 220 mg IV</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 min</td>
<td>5 mg IV every 20 min up to maximum dose of 20 mg IV</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10–20 min</td>
<td>10 mg PO every 20 min up to a maximum dose of 50 mg</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>10–15 min</td>
<td>Initial infusion 5 mg/h, increase by 2.5 mg/h every 5 min to a maximum dose of 15 mg/h</td>
</tr>
</tbody>
</table>

* Systolic blood pressure 160 mm Hg or greater, diastolic blood pressure 110 mm Hg or greater, or both, if sustained.

Labetalol

Labetalol is a combined alpha- and beta-adrenergic receptor antagonist with a 1:7 ratio of alpha- to beta-adrenergic receptor antagonism when administered intravenously. Labetalol should be avoided in women with severe asthma or congestive heart failure.179

A meta-analysis concluded that intravenous labetalol has efficacy similar to intravenous hydralazine but with fewer maternal side effects, although evidence was limited to four small randomized controlled trials.178 Neonates born to mothers exposed to beta-adrenergic receptor antagonists during delivery, including labetalol, demonstrate increased rates of neonatal hypoglycemia and bradycardia.180

Hydralazine

Hydralazine has been used safely in pregnant women for decades and is also considered a first-line drug for treating severe hypertension in pregnancy.175 Hydralazine exerts a potent direct vasodilating effect. Plasma volume expansion before administration decreases the risk for maternal hypotension. Other side effects include tachycardia, palpitations, headache, and neonatal thrombocytopenia. In a randomized clinical trial, hydralazine was associated with more maternal tachycardia and palpitations and less neonatal bradycardia and hypotension than labetalol,181 but both antihypertensive drugs are considered safe and effective for the treatment of severe hypertension in pregnant women.

Nifedipine

Nifedipine is a calcium entry–blocking agent that lowers blood pressure by relaxing arterial and arteriolar smooth muscle. It can be administered as a long-acting oral medication once the severe hypertension has stabilized. Nifedipine immediate-release capsules should not be administered to women with known coronary artery disease, long-standing diabetes mellitus or aortic stenosis, or to women older than 45 years of age because of an increased risk for sudden cardiac death.183 In the absence of contraindications, nifedipine is now recommended as a first-line agent in women for whom intravenous access is difficult to secure.175

Although earlier reports suggested that the co-administration of nifedipine with magnesium sulfate causes adverse effects in both the mother and fetus, including severe maternal hypotension,182 neuromuscular blockade,183 and nonreassuring fetal heart rate (FHR) patterns,182 subsequent data suggest that these drugs can be used together safely.184 Oral nifedipine has been found to be as efficacious and safe as intravenous labetalol.185

Other Agents

If labetalol, hydralazine, or nifedipine are not effective in controlling blood pressure, consideration may be given to using a nicardipine or labetalol infusion or other antihypertensive agents.175

Nicardipine is a calcium entry–blocking agent that can be administered by intravenous infusion and has been shown to achieve rapid decreases in systolic and diastolic blood pressures in pregnant women.186 It is an excellent option for treating severe hypertension that is not responsive to labetalol or hydralazine.175

Esmolol is a short-acting beta-adrenergic receptor antagonist that can be used to treat acute hypertension accompanied by maternal tachycardia. Concerns regarding the use of esmolol during pregnancy arose in 1989 after a report of dose-dependent prolonged fetal bradycardia in a study of gravid ewes receiving esmolol by stepped infusion.187 Subsequent human case reports have reported variable responses,188,189 but in most cases fetal bradycardia was transient and FHR returned to baseline after discontinuation of the drug. Placental transfer is rapid, and clinicians should expect to observe the effects of beta-adrenergic receptor blockade in the fetus. Maternal administration of esmolol produces a greater degree of beta-adrenergic receptor blockade in the fetal lamb than that observed after maternal administration of an equipotent dose of labetalol.187,190

Seizure Prophylaxis

The routine use of magnesium sulfate for seizure prophylaxis in women with preeclampsia with severe features is an established obstetric practice. There is clear evidence that magnesium sulfate is the best available agent for prevention of recurrent seizures in women with eclampsia91,192; thus, its use has been extended to seizure prophylaxis in women with preeclampsia with severe features.7

A meta-analysis of the available data identified six trials involving 11,444 women that compared magnesium sulfate for the treatment of preeclampsia with either placebo or no anticonvulsant.193 Magnesium decreased the risk for developing eclampsia (relative risk [RR], 0.41; 95% confidence interval [CI], 0.29 to 0.58); there was also a trend toward lower risk for maternal death (RR, 0.54; 95% CI, 0.26 to 1.10), but no effect on serious maternal morbidity.193 Additionally, magnesium therapy reduced the risk for placental abruption. It did not adversely affect fetal and/or neonatal outcomes, including stillbirth, perinatal death, or neurosensory disability.195 Treatment with magnesium increased the risk for maternal respiratory depression (RR, 1.98; 95% CI, 1.24 to 3.15) and cesarean delivery (RR, 1.05; 95% CI, 1.01 to 1.10).193 Other side effects that were significantly more common in those treated with magnesium included feeling warm or flushed, nausea/vomiting, muscle weakness, hypotension, dizziness, drowsiness/confusion, and headache.193

In general, magnesium sulfate is not indicated for seizure prevention in preeclampsia without severe features.2 Studies have failed to show a difference in the number of women who progressed to severe preeclampsia.194,195

The mechanism of the anticonvulsant effect of magnesium is not well understood. It was previously believed that eclamptic seizures were the result of cerebral vasospasm, and it was also believed that the cerebral vasodilating properties of magnesium reduced the rate of eclamptic seizures by relieving vasospasm.196 However, there is evidence that abrupt, sustained blood pressure elevation overwhelms
myogenic vasoconstriction and causes forced dilation of the cerebral vessels, hyperperfusion, and cerebral edema.  

This evidence raises the question of how magnesium sulfate—a vasodilator—could be effective in seizure prophylaxis; magnesium would be expected to worsen cerebral hyperperfusion and edema. Using a rat model, Euser and Cipolla demonstrated that the mesenteric vessels are more sensitive to magnesium-induced vasodilation than are cerebral vessels, suggesting that part of the effect may be mediated through decreasing peripheral vascular resistance. Further animal work suggests that magnesium may ameliorate neuroinflammation and brain edema in an eclampsia-like seizure model. Magnesium may also protect the blood-brain barrier, or act centrally at N-methyl-D-aspartate (NMDA) receptors to raise the seizure threshold.

No consensus exists regarding (1) the ideal time to initiate treatment with magnesium sulfate, (2) the best loading and maintenance doses, or (3) the optimal duration of therapy. Many obstetricians administer a loading dose of 4 to 6 g over 20 to 30 minutes, followed by a maintenance infusion of 1 to 2 g/h. The infusion is commonly initiated once the decision is made to deliver and is continued for 24 hours postpartum. Expert opinion recommends that women with preeclampsia with severe features undergoing cesarean delivery should receive magnesium sulfate at least 2 hours before the procedure, during surgery, and for 24 hours postpartum.

Magnesium sulfate is eliminated almost entirely by renal excretion, and serum levels may become dangerously high in the presence of renal insufficiency. Side effects of hypermagnesemia include chest pain and tightness, palpitations, nausea, blurred vision, sedation, transient hypotension, and, rarely, pulmonary edema. In untreated patients, the normal range for serum magnesium concentrations is 1.7 to 2.4 mg/dL. The therapeutic range lies between 5 and 9 mg/dL. Reflex testing is used as a clinical screen for hypomagnesemia; when deep tendon reflexes are preserved, the more serious side effects are usually avoided. Patellar reflexes are lost at serum magnesium levels of approximately 12 mg/dL. Respiratory arrest occurs at levels between 15 and 20 mg/dL, and asystole occurs when the level exceeds 25 mg/dL. Preeclamptic women with renal impairment should be monitored closely because magnesium toxicity can occur with usual dosing regimens. Serial measurement of serum magnesium levels may be helpful in the management of women with renal dysfunction.

Treatment of suspected magnesium toxicity includes immediate discontinuation of the infusion and the intravenous administration of calcium gluconate (1 g) over 10 minutes. In the rare event of respiratory compromise, the patient may require tracheal intubation and mechanical ventilation until spontaneous ventilation returns.

Route of Delivery

Vaginal delivery should be attempted in all women with preeclampsia without severe features, assuming no other indications for cesarean delivery exist. Vaginal delivery should also be attempted in most women with severe disease, especially those beyond 34 weeks’ gestation.

Cesarean delivery is appropriate when the maternal or fetal condition mandates immediate delivery or when other indications for cesarean delivery exist.

Corticosteroid Administration for Severe Preeclampsia or HELLP Syndrome

To accelerate fetal lung maturity, all women who develop preeclampsia with severe features or HELLP syndrome between 24 and 34 weeks’ gestation should receive a course of corticosteroid therapy. A randomized double-blind trial of 218 women with severe preeclampsia at 26 to 34 weeks’ gestation found that the infants of those receiving betamethasone, compared with the infants of those receiving placebo, exhibited a significant reduction in the rate of the neonatal respiratory distress syndrome and reduced rates of neonatal intraventricular hemorrhage, infection, and death. The available data also suggest that treatment with corticosteroids results in improvement in the maternal platelet count in women with HELLP syndrome, with dexamethasone being more efficacious than betamethasone. However, these studies do not show a clear benefit of corticosteroid treatment on the endpoints of severe maternal morbidity or mortality.

Complications

Preeclampsia is associated with an increased risk for maternal morbidity and mortality, including HELLP syndrome, cerebrovascular accident, pulmonary edema, renal failure, placental abruption, and eclampsia. In general, these complications are more common in women with early-onset preeclampsia and in women with prepregnancy medical conditions, including diabetes mellitus, chronic renal disease, and thrombophilia.

Cerebrovascular Accident

Although the absolute risk for cerebrovascular accident is low, preeclampsia confers markedly increased risk for intracerebral and subarachnoid hemorrhage and ischemic stroke. Stroke remains the leading cause of death in women with preeclampsia. A 2017 publication used multivariable analysis to delineate the risk factors for stroke in women with preeclampsia. Women with stroke were more likely to have severe preeclampsia or eclampsia, infections present on admission, prothrombotic states, coagulopathies, or chronic hypertension.

The endothelial dysfunction of preeclampsia contributes to edema, vascular tone instability, platelet activation, and local thrombosis. Reversible cerebral edema is the most common CNS feature of preeclampsia or eclampsia. The loss of cerebral autoregulation causes hyperperfusion that, compounded by endothelial disruption, leads to interstitial or vasogenic edema. The presence of HELLP syndrome or DIC increases the risk for a hemorrhagic event.

In the 2006–2008 Confidential Enquiry into Maternal and Child Health (CEMACH) report from the United Kingdom,
19 deaths were attributed to eclampsia and preeclampsia; 9 resulted from intracranial hemorrhage. Failure to adequately control hypertension was noted in most of these cases. The CEMACH report emphasized the importance of urgent treatment of women with a systolic blood pressure in excess of 150 to 160 mm Hg.214 A recent consensus bundle for the management of severe hypertension in pregnancy also emphasizes that, once confirmed, systolic blood pressure greater than or equal to 160 mm Hg, or diastolic blood pressure greater than or equal to 110 mmHg, should be treated within 30 to 60 minutes.5

Mean arterial blood pressure and diastolic blood pressure may not reflect the true risk for stroke. A review of 28 case histories of severely preeclamptic women who suffered a stroke revealed that (1) systolic blood pressure in excess of 160 mm Hg was a far superior predictor of stroke than diastolic hypertension or elevated mean arterial pressure, (2) the majority of strokes were hemorrhagic (93%) as opposed to thrombotic (7%), and (3) the majority of strokes (57%) occurred in the postpartum period.177 Close attention to blood pressure control throughout the peripartum period is the mainstay of stroke prevention.175 In keeping with this goal, ergot alkaloids should generally be avoided in hypertensive patients because their administration can result in severe hypertension.214

Pulmonary Edema
The clinical presentation of pulmonary edema is characterized by worsening dyspnea and orthopnea with concomitant signs of respiratory compromise, including tachypnea, rales, and hypoxemia. A large proportion of cases of pulmonary edema occur postpartum, usually within 2 to 3 days after delivery, and management is directed toward the underlying cause.218 TTE can be helpful in the diagnosis of heart failure with low ejection fraction, and in the identification of other cardiac comorbidities contributing to pulmonary edema.219 Initial treatment includes administration of supplemental oxygen, fluid restriction, and diuretic therapy (e.g., furosemide). A retrospective study of 86 women with peripartum pulmonary edema found that even in the presence of extensive radiographic infiltrates and severe hypoxemia, resolution was typically rapid, with a limited need for intensive care unit admission.220 Rarely, women with severe systolic heart failure with a low ejection fraction may develop precipitous hypoxemia and require urgent tracheal intubation and ventilatory support. Notably, in mortality reports from the United Kingdom in the current millennium,214,223 no deaths were attributed solely to cardiopulmonary causes. Presumably, this trend reflects improvements in the fluid management of women with severe preeclampsia. These results cannot be extrapolated to limited-resource environments. In the 6th Report on the Confidential Enquiries into Maternal Death in South Africa (2011–2013),224 pulmonary edema and respiratory failure were two of the most common causes of death in women with hypertensive disease, each accounting for approximately one-fourth of these deaths.

Renal Failure
Acute renal failure is a rare but serious complication of severe preeclampsia and HELLP syndrome.225 The true incidence remains unknown. Acute renal failure is divided into three categories: (1) prerenal, which refers to renal hypoperfusion; (2) intrarenal, which suggests intrinsic renal parenchymal damage; and (3) postrenal, which implies obstructive uropathy. The majority of cases (83% to 90%) of acute renal failure in preeclampsia result from prerenal and intrarenal pathologic processes (most commonly acute tubular necrosis) and resolve completely after delivery.224,225 In contrast, bilateral renal cortical necrosis is a rare and serious condition associated with considerable maternal and perinatal morbidity and mortality. It occurs most commonly in association with known renal parenchymal disease, chronic hypertension with superimposed preeclampsia, placental abruption, DIC, HELLP syndrome, sepsis, or fetal death.226,227

Placental Abruption
Placental abruption occurs in approximately 2% of women with preeclampsia and results in increased perinatal morbidity and mortality. A 2006 retrospective case-control study of 161 women with placental abruption and 2000 women without abruption found a threefold increased risk for placental abruption in women with preeclampsia.225 The incidence is also increased in women with underlying chronic hypertension. Management depends on the extent of abruption and associated hypotension, coagulopathy, or fetal compromise (see Chapter 37). Placental abruption is also associated with the development of DIC (see Chapter 44).

HELLP Syndrome
HELLP syndrome is characterized by hemolysis, elevated levels of liver enzymes, and a low platelet count. It may be a variant of severe preeclampsia, but this is controversial because a substantial fraction of women with HELLP syndrome do not have hypertension or proteinuria. It is associated with increased rates of maternal morbidities, including DIC, placental abruption, pulmonary edema, acute renal failure, liver hemorrhage or failure, acute respiratory distress syndrome, sepsis, stroke, and death (Table 35.5).229 Additionally, 70% of women with HELLP syndrome deliver preterm,229 contributing to prematurity-related perinatal morbidity and mortality. The onset of HELLP syndrome occurs antepartum in 70% of cases and postpartum in 30%.

Because of a lack of universally accepted diagnostic criteria for HELLP syndrome, its incidence cannot be determined accurately. The existence of a subset of preeclampsia complicated by abnormal peripheral blood smear, abnormal liver function tests, and thrombocytopenia has been recognized for decades; in 1982, Weinstein230 described a series of 29 cases and coined the acronym HELLP. Women who do not demonstrate one or more of these clinical features are said to have “partial” HELLP syndrome.

Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the classic hallmark of HELLP syndrome;
the peripheral blood smear demonstrates schistocytes, burr cells, and echinocytes. Common histopathologic findings are periportal hepatic necrosis and hemorrhage. Sibai proposed standardized laboratory diagnostic criteria, as outlined in Table 35.6. Maternal signs and symptoms include right upper quadrant or epigastric pain, nausea and vomiting, headache, hypertension, and proteinuria. Notably, clinical presentation varies; 12% to 18% of women may be normotensive, and proteinuria is absent in approximately 13% of affected women. Diagnosis can be especially challenging because numerous medical and surgical disorders, including acute fatty liver of pregnancy, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, and lupus, can mimic HELLP syndrome (Box 35.4). Pregnant women likely to have preeclampsia, but who demonstrate atypical symptoms, should be screened with a complete blood cell count, platelet count, and liver enzyme assessment.

In general, patients with HELLP syndrome are not considered candidates for expectant management; however, deferred delivery for 24 to 48 hours to allow for corticosteroid administration to accelerate fetal lung maturity may be appropriate for women less than 34 weeks’ gestation if the maternal and fetal condition remain stable. Women with HELLP syndrome who have not yet reached 34 weeks’ gestation should be managed in a tertiary care facility with a neonatal intensive care unit capable of caring for a compromised preterm neonate. Clinical management is similar to that for severe preeclampsia and includes intravenous magnesium sulfate for seizure prophylaxis and antihypertensive medications to maintain a systolic blood pressure below 160 mm Hg and a diastolic blood pressure below 110 mm Hg. The first priority is to assess and stabilize the maternal condition, with particular attention given to hypertension and coagulation abnormalities. Next, the fetal condition should be assessed with FHR monitoring, Doppler ultrasonography of fetal blood flow, a biophysical profile, or several of these options.

The platelet count can fall precipitously in the presence of HELLP syndrome, and it should be evaluated before the administration of neuraxial anesthesia. Women with a platelet count less than 50,000/mm³ are at significantly increased risk for bleeding, and general anesthesia is the method of choice for cesarean delivery. Data suggest treatment with dexamethasone may improve the platelet count in women with HELLP syndrome. If treatment with dexamethasone

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>92</td>
<td>21</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>69</td>
<td>16</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Severe ascites</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Subcapsular liver hematoma</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Maternal death</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Some women had multiple complications.


<table>
<thead>
<tr>
<th>Criteria</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>Abnormal peripheral blood smear</td>
</tr>
<tr>
<td>Elevated liver enzyme levels</td>
<td>Increased LDH greater than 600 IU/L</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count less than 100,000/mm³</td>
</tr>
</tbody>
</table>

LDH, Lactic dehydrogenase; AST, aspartate aminotransferase.


Acute fatty liver of pregnancy
- Appendicitis
- Cholestasis of pregnancy
- Diabetes insipidus
- Gallbladder disease
- Gastroenteritis
- Glomerulonephritis
- Hemolytic-uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Nephrolithiasis
- Peptic ulcer disease
- Systemic lupus erythematosus
- Thrombotic thrombocytopenic purpura
- Viral hepatitis

BOX 35.4 Differential Diagnosis of Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) Syndrome

CHAPTER 35 Hypertensive Disorders

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improves the patient’s platelet count, the decision as to whether to use neuraxial anesthesia must weigh the risk for recurrent thrombocytopenia against the risk for a difficult airway and hypertension during induction of general anesthesia.

Platelet transfusions are indicated in the presence of significant bleeding and in all parturients with a platelet count less than 20,000/mm³. For women with a platelet count less than 40,000/mm³ who are scheduled for cesarean delivery, the preincision administration of 6 to 10 units of pooled random-donor platelets (or 1 to 2 units of apheresis platelets) has been recommended. The risk for postpartum hemorrhage is significantly increased in patients with HELLP syndrome; large-bore intravenous access should be obtained, and identification of compatible red blood cell units should be considered.

Rupture of a subcapsular hematoma of the liver is a life-threatening complication of HELLP syndrome and severe preeclampsia that manifests as abdominal pain, nausea and vomiting, and headache; the pain worsens over time and becomes localized to the epigastric area or right upper quadrant. Hypotension and shock typically develop, and the liver is enlarged and tender. Diagnosis is confirmed with ultrasonography, computed tomography (CT), or magnetic resonance imaging of the liver (Fig. 35.7). Subcapsular hematoma rupture with shock is a surgical emergency that requires immediate multidisciplinary treatment that includes intravascular volume resuscitation and blood and plasma transfusions. In some circumstances, selective arterial embolization by an interventional radiologist may be useful. Patients with fulminant hepatic failure may require liver transplantation. Prompt surgical intervention and refinements in surgical technique have substantially reduced the maternal mortality rate associated with spontaneous hepatic rupture to less than 20% in the past decade. The most common causes of death are coagulopathy and exsanguination.

**Anesthetic Management**

The anesthetic management of the woman with preeclampsia without severe features differs little from the management of a healthy pregnant woman. However, the potential for rapid progression to the severe form of the disease mandates careful observation of the patient. The anesthesia provider must recognize the unpredictability of the development and progression of severe preeclampsia and should be prepared at all times for immediate cesarean delivery.

**Preanesthetic Evaluation**

The preanesthetic assessment of women with confirmed or suspected preeclampsia should focus on the airway examination, maternal hemodynamic and coagulation status, and fluid balance.

**Airway.** Generalized edema can involve the airway and obscure visualization of anatomic landmarks at laryngoscopy. The anesthesia provider should anticipate the possibility of difficult airway management (see Chapter 29).

**Hemodynamic monitoring.** Noninvasive blood pressure monitoring is appropriate in uncomplicated severe preeclampsia, although automated devices may underestimate blood pressure in preeclampsia. The most frequent indications for radial artery catheter insertion are (1) the need for continuous blood pressure monitoring during the induction of and emergence from general anesthesia in women with severe preeclampsia and poorly controlled hypertension; (2) a requirement for frequent arterial blood gas measurements, especially in the context of pulmonary edema; and (3) use of calculated systolic pressure variation to estimate intravascular volume status, particularly in the setting of hemorrhage.

In the past, guidelines recommended the placement of a pulmonary artery catheter and measurement of central pressures and cardiac output to inform fluid management decisions in women with pulmonary edema or renal failure. However, the causes of pulmonary edema are often multifactorial, and left ventricular compliance varies widely. This leads to poor correlation between pulmonary capillary wedge pressure and left ventricular end-diastolic volume. The placement of a pulmonary artery catheter is not a benign procedure; well-recognized risks include pneumothorax, venous air embolism, neuropathy, and cardiac arrhythmias. Additional risks for an indwelling pulmonary artery catheter include pulmonary artery hemorrhage, thromboembolism, sepsis, and endocardial damage. The 1991–1993 Report on Confidential Enquiries into Maternal Deaths in the United Kingdom described the postpartum death of a woman after several unsuccessful attempts at internal jugular vein line placement and a likely carotid artery puncture. In the 2003–2005 CEMACH report, an anesthesia-related maternal death occurred in a woman with fulminant preeclampsia and HELLP syndrome who developed a large right hemothorax after subclavian vein line insertion. Because both immediate and delayed maternal deaths have been attributed to the use of central venous catheters, insertion of these catheters should be done only after careful consideration of risks and
improvement in intervillous blood flow. Early initiation of hypertension during laryngoscopy; and (4) possible point-of-care TTE has become a useful technique for assessing cardiopulmonary status in the peridelivery period. Valuable information about volume status, chamber size and wall thickness, and ventricular function may be gleaned in critically ill patients with preeclampsia. Indeed, clinical examination, coupled with passive leg raising and TTE, have largely supplanted central venous and pulmonary artery catheters in the assessment of volume status. Research has shown that passive leg raising combined with TTE assessment of stroke volume changes accurately predicts fluid responsiveness. Pulse waveform analysis has been suggested as a minimally invasive method to measure cardiac output; cardiac output measurements using this approach have been shown to closely match those obtained from thermodilution in women with preeclampsia.

In summary, indications for invasive central monitoring are similar to those in other multisystem disorders such as severe sepsis, multisystem organ dysfunction, pulmonary edema, congenital heart disease, and cardiomyopathy. TTE and arterial waveform monitoring provide less invasive means of assessing hemodynamic parameters in these patients. Some women will require transfer to an intensive care unit for specialized nursing care and management directed by a critical care medicine specialist.

Neuraxial Analgesia for Labor and Delivery
The confirmation of the safety of neuraxial anesthesia for labor and cesarean delivery in women with preeclampsia is one of the most important developments in the past 25 years in obstetric anesthesia practice. The major advantages of neuraxial anesthesia are control of hypertension and avoidance of the need for airway management.

Continuous lumbar epidural analgesia or combined-spinal epidural (CSE) analgesia are the preferred methods of pain management during labor in women with preeclampsia. Advantages include (1) provision of high-quality analgesia, which attenuates the hypertensive response to pain; (2) a reduction in levels of circulating catecholamines and stress-related hormones; (3) provision of a means for rapid initiation of epidural anesthesia for emergency cesarean delivery, thus obviating the need for general anesthesia and its associated risk for airway catastrophe and critical hypertension during laryngoscopy; and (4) possible improvement in intervillous blood flow. Early initiation of neuraxial labor analgesia is recommended in the absence of contraindications in all patients with preeclampsia with severe features, particularly in women with HELLP syndrome, obesity, and when there is concern for fetal status. The advantages and disadvantages of a traditional epidural compared with a CSE technique are not different for women with preeclampsia compared with healthy women (see Chapter 23).

Continuous antepartum epidural infusion of local anesthetic has been suggested as a means to optimize uteroplacental blood flow and prolong pregnancy in women with preeclampsia remote from term. In one study, women with severe preeclampsia between 28 and 32 weeks' gestation who received an epidural local anesthetic infusion had delayed delivery and improved blood pressure and platelet counts compared with women who received standard treatment. A second study found a unilateral decrease in uterine artery vascular resistance (in the artery with highest baseline resistance) during the period of epidural ropivacaine infusion compared with saline infusion in women with early-onset preeclampsia. Although promising, this technique for prolonging pregnancy requires further study.

For the most part, the clinical administration of neuraxial labor analgesia to women with preeclampsia does not differ from that in healthy women (see Chapter 23). However, four special considerations exist: (1) assessment of coagulation status, (2) intravenous hydration before neuraxial administration of a local anesthetic, (3) treatment of hypotension, and (4) use of epinephrine-containing local anesthetic solutions.

Coagulation status. Platelets contribute to coagulation and hemostasis in two important ways. First, their adhesive and cohesive functions lead to the formation of the hemostatic plug. Second, they activate the coagulation process by exposing a phospholipid surface and acting as a catalytic site for subsequent coagulation and consolidation of the initial platelet plug. Activated platelets release adenosine diphosphate, serotonin, thromboxane A2, and other adhesive proteins, coagulation factors, and growth factors (see Chapter 44).

Women with preeclampsia without severe features are usually hypercoagulable relative to women with an uncomplicated pregnancy and should not be denied neuraxial labor analgesia. Women with preeclampsia with severe features (particularly those with HELLP syndrome) may develop thrombocytopenia, which increases the risk for bleeding into the epidural or spinal space during a neuraxial procedure (see Chapter 31). Neuraxial hematoma formation can result in permanent neurologic sequelae. Therefore, documentation of the platelet count is necessary before provision of neuraxial analgesia in women with severe preeclampsia. The incidence of neuraxial hematoma cannot be precisely determined because not all cases are reported and because there is no accurate method to determine the denominator of all preeclamptic women who have received neuraxial anesthesia. That said, the incidence of epidural hematoma in contemporary obstetric anesthesia practice is exceptionally low.

In the past, a platelet count greater than or equal to 100,000/mm³ was considered necessary for the safe administration of neuraxial anesthesia. This threshold probably originated from the results of a 1972 study that correlated platelet...
counts with bleeding times. Critical appraisal of 1083 human studies concluded that the bleeding time is not a reliable method of assessing the risk for bleeding in individual patients. Coagulopathy is rare in women with preeclampsia with a platelet count exceeding 100,000/mm³, and in the absence of other risk factors for coagulopathy, neuraxial anesthetic procedures are considered safe without further coagulation testing.

Currently, many anesthesia providers agree that neuraxial procedures may be initiated in pregnant women without other risk factors if the platelet count is higher than 80,000/mm³. There is general consensus among anesthesia providers that a platelet count less than 50,000/mm³ precludes the administration of neuraxial anesthesia. For women with a platelet count between 50,000 and 80,000/mm³, the risks and benefits of neuraxial anesthesia must be weighed against the risks associated with general anesthesia for the individual patient if emergency cesarean delivery is required, including whether anatomic features of the patient’s airway are favorable. A 2017 systematic review of retrospective case series of thrombocytopenic parturients receiving neuraxial techniques estimated the risk for epidural hematoma across a range of platelet counts (15 studies, 1524 women). No epidural hematoma was reported in any of the case series. The authors concluded that the risk remains poorly defined in parturients with a platelet count less than 70,000/mm³ due to the limited number of observations and the low absolute risk.

Two additional considerations in the decision to initiate neuraxial analgesia in women with preeclampsia include the platelet count trend over time and any coexisting coagulopathy. In certain cases, the platelet count decreases rapidly and the nadir in the platelet count cannot be identified prospectively. If serial platelet counts are stable and remain in the normal range, platelet count measurement every 24 to 48 hours is adequate to monitor women undergoing expectant management of severe preeclampsia remote from term. If a decision is made to induce labor, platelet count determination at least every 6 hours will ensure that a timely measurement has been obtained at the time of request for neuraxial analgesia. If the platelet count is low (80,000 to 100,000/mm³), early epidural catheter insertion is recommended in anticipation of worsening thrombocytopenia.

If the platelet count is less than 100,000/mm³, other hematologic abnormalities, including prolonged PT and aPTT and hypofibrinogenemia, may be present. Further coagulation studies may be useful, particularly if risk factors for DIC are present (e.g., placental abruption, HELLP syndrome). Thus, in the presence of thrombocytopenia or abnormal results of liver function tests, the PT and aPTT should be assessed before the initiation of neuraxial anesthesia.

Viscoelastic monitors of coagulation may expedite decision-making about neuraxial block administration for women with preeclampsia-related hematostatic dysfunction. Although thromboelastography (TEG) has shown some promise in the assessment of coagulation status in pregnant patients with thrombocytopenia, it has been criticized for its inability to diagnose specific coagulation defects, particularly impairment in primary hemostasis. Platelet function analysis (PFA-100) appears to be more sensitive to coagulation dysfunction in women with severe preeclampsia. However, with both TEG and PFA, the ability to predict the risk for epidural hematoma after the administration of neuraxial anesthesia is unproven and requires further study.

The risk for epidural hematoma formation exists not only at the time of epidural catheter placement but also at the time of its removal. In patients with thrombocytopenia, the catheter should not be withdrawn from the epidural space until there is evidence of an acceptable (and increasing) platelet count. A platelet count of 75,000 to 80,000/mm³ seems reasonable for epidural catheter removal. The platelet count in women with HELLP syndrome usually reaches a nadir on the second or third postpartum day and then gradually returns to the patient’s normal baseline. If the decision is made to proceed with a neuraxial technique when the platelet count is less than 100,000/mm³, the following suggestions may help reduce the risk for epidural hematoma and its sequelae:

1. The most skilled anesthesia provider available should perform the neuraxial procedure to minimize the number of needle passes and subsequent bleeding.
2. A single-shot spinal technique may be preferable to an epidural technique (when appropriate) because of the smaller needle size, although supporting data are lacking.
3. Use of a flexible wire–embedded epidural catheter, if available, may reduce epidural vein trauma.
4. The patient should be carefully monitored after delivery for neurologic signs that may signal bleeding into the epidural space.
5. The platelet count should be checked for evidence of a return toward normal measurements (at least 75,000 to 80,000/mm³) before removal of the epidural catheter. Epidural vein trauma at the time of catheter discontinuation can result in epidural bleeding and perhaps epidural hematoma.
6. Imaging studies and neurologic or neurosurgical consultation should be obtained immediately if there is any question of an epidural hematoma.

**Intravenous hydration.** In the past, when high concentrations of local anesthetic solution (e.g., 0.25% to 0.5% bupivacaine) were administered during labor, intravenous crystalloid hydration preceded epidural local anesthetic administration to prevent or ameliorate hypotension. In contemporary practice, lower concentrations of local anesthetic solutions are used (e.g., 0.0625% to 0.125% bupivacaine in combination with an opioid), hypotension is less common, and fluid administration at the time of analgesia initiation is of less clinical importance. Furthermore, the rapid administration of a large bolus of intravenous fluid (preload) results in only a transient increase in central venous pressure and has little impact on the risk for hypotension. The risk for maternal hypotension and FHR abnormalities after initiation of neuraxial analgesia may be reduced if fluid preload is administered to individuals with a narrow pulse pressure.
attention to intravenous fluid infusion rates is necessary in women with severe preeclampsia because of the increased risk for pulmonary edema in these patients; vasopressors should be used in preference to large fluid boluses to treat hypotension.

**Treatment of hypotension.** In a landmark study in which invasive hemodynamic monitoring was used during epidural analgesia in women with severe preeclampsia in labor, remarkable hemodynamic stability was observed.**264** Although the management of neuraxial labor analgesia–induced hypotension has not been formally studied, most clinicians treat hypotension with small bolus doses of phenylephrine or ephedrine. There is an often-expressed concern that women with severe preeclampsia may have an exaggerated response to vasopressors that might result in a sharp increase in blood pressure**262,263;** however, supportive data are lacking.**262,263** The anesthesia provider should initiate treatment with phenylephrine (25 to 50 µg) or ephedrine (5 to 10 mg), and assess maternal blood pressure response before administration of a larger dose. With careful titration, increased sensitivity to vasopressors is rarely a clinical problem.

**Epinephrine.** It has been suggested that local anesthetic solutions containing epinephrine (including the standard epinephrine-containing epidural test dose) should be avoided during the administration of epidural analgesia in women with preeclampsia. This concern arises from observations that preeclamptic women exhibit an increased sensitivity to vasopressors, including angiotensin II,**264,265** norepinephrine and epinephrine,**266,267** and a thromboxane A2-mimetic agent.**268** In addition, clinical studies have demonstrated that smaller doses of ephedrine and phenylephrine are required to restore maternal blood pressure during spinal anesthesia in preeclamptic women compared with healthy women.**262,263,269,270** An early study employing invasive hemodynamic monitoring in healthy human volunteers showed that epidural administration of 20 mL of 2% lidocaine containing epinephrine 5 µg/mL was followed predominantly by systemic beta-adrenergic-agonist effects (increased heart rate, decreased systemic vascular resistance and blood pressure, and increased cardiac output).**271** One case report described a hypertensive crisis in a preeclamptic woman after the incremental administration of 30 mL of freshly mixed 2% lidocaine with epinephrine 5 µg/mL for planned cesarean delivery.**272** However, the onset and duration of hypertension were atypical, and a drug error could not be excluded. In contrast, several other case series have used the same solution without adverse effects in women with preeclampsia.**273**

No randomized controlled trials have assessed the effects of epidural epinephrine in women with severe preeclampsia. In the absence of malignant hypertension, epinephrine is unlikely to pose a significant risk for hypertensive crisis, given the absence of confirmed reports after decades of its use in obstetric anesthesia practice. Although not necessarily harmful for women with preeclampsia, the use of epinephrine in epidural test doses or analgesic solutions may not be particularly helpful. Patients who have received beta-adrenergic receptor antagonists (e.g., labetalol) do not demonstrate the typical tachycardia after intravascular administration of epinephrine.**274** This lack of response decreases the sensitivity of the epinephrine test dose to detect intravascular administration of local anesthetic solution, and alternative testing strategies to detect intravascular catheter location may be preferred (see Chapter 12).**275** The addition of epinephrine to local anesthetic solutions results in a modest local anesthetic–sparking effect, at best, and increases the density of motor blockade.**276** Finally, consideration should be given to the consequences of an unintentional intravascular injection of an epinephrine-containing test dose in a patient with baseline hypertension. Given the available evidence, it seems prudent to avoid epinephrine during administration of labor epidural analgesia in women with preeclampsia with severe features.

**Anesthesia for Cesarean Delivery**

The administration of neuraxial anesthesia for cesarean delivery in women with preeclampsia does not differ greatly from the practice in healthy pregnant women (see Chapter 26). Hepatic dysfunction can result in reduced drug clearance but has little clinical impact on choice of anesthetic or analgesic agents. The choice of local anesthetic agent, technical aspects of neuraxial anesthesia, and maintenance of anesthesia are not affected by the presence of preeclampsia. However, there are three special considerations in women with preeclampsia undergoing cesarean delivery: (1) choice of anesthetic technique, (2) technique for induction of general anesthesia, and (3) the interaction between magnesium sulfate and nondepolarizing muscle relaxants.

**Neuraxial anesthesia.** In the Seventh and Eighth Reports of the Confidential Enquiries into Maternal Deaths in the United Kingdom,**214,221** the leading cause of death in women with preeclampsia was **intracranial hemorrhage.** Disadvantages of general anesthesia in the presence of preeclampsia include the risk for intracranial hemorrhage from the hypertensive response to both tracheal intubation and extubation. In a study involving more than 300,000 women in Taiwan, general anesthesia for cesarean delivery in preeclamptic women was associated with a greater than twofold increase in the risk for stroke after adjusting for confounders compared with neuraxial anesthesia.**279** However, despite attempting to statistically correct for confounding variables, it is difficult to overlook the major limitation of this study—it was not a randomized trial. It is likely that patients with more severe and complicated disease received general anesthesia. Neuraxial anesthesia does avoid the possibility of difficult tracheal intubation secondary to airway edema. Therefore, neuraxial anesthesia is preferred whenever clinical circumstances permit its use.

The traditional view was that spinal anesthesia is relatively contraindicated in severe preeclampsia because of the possibility of marked hypotension as a result of the rapid onset of spinal anesthesia–induced sympathetic blockade. However, this concern is not supported by evidence. Wallace et al.**279** randomized 80 women with severe preeclampsia who required cesarean delivery to receive general, epidural, or...
CSE anesthesia. There was no significant difference between the CSE and epidural anesthesia groups in maternal mean arterial pressure over time. Notably, the initial spinal dose in the CSE group (hyperbaric bupivacaine 11.25 mg) is a dose comparable to that often used for a single-shot spinal technique. Another small prospective study randomized women with severe preeclampsia to receive either spinal or epidural anesthesia, with similar results. Hood and Curry retrospectively reviewed cesarean delivery records for 138 women with severe preeclampsia who received either spinal or epidural anesthesia and found that the lowest mean blood pressure measurements did not differ between groups. Because of the retrospective study design, the possibility that the groups were dissimilar cannot be excluded (i.e., the anesthesia providers may have chosen to administer epidural anesthesia to more severely ill women). Nonetheless, the expected marked hypotension after spinal anesthesia did not occur.

In two prospective cohort studies of women undergoing cesarean delivery, Aya et al. compared women who had severe preeclampsia with healthy pregnant women (both preterm and term) and found that the risk for significant hypotension (defined as requiring the administration of ephedrine) was significantly lower in the preeclampsia groups than in the healthy control groups. The authors speculated that the known increased vascular sensitivity to vasoconstrictors may explain the infrequent incidence of hypotension after spinal anesthesia and the ease with which mean arterial blood pressure can be restored to baseline with small doses of vasopressor.

In contrast, a randomized multicenter study comparing the hemodynamic effects of spinal anesthesia with epidural anesthesia for cesarean delivery in women with severe preeclampsia found that significantly more women in the spinal anesthesia group experienced hypotension. However, the duration of hypotension was less than 1 minute in both groups and, although more ephedrine was used in the spinal group than in the epidural group, hypotension was easily treated in both groups. In addition, there was no significant difference in neonatal outcome between infants whose mothers received spinal anesthesia compared with those whose mothers received epidural anesthesia. Another study suggested that spinal anesthesia has little effect on cardiac output in severely preeclamptic women, and reduction in afterload was modest. These data, taken together, suggest that the use of spinal anesthesia for cesarean delivery in women with severe preeclampsia is appropriate.

Epidural anesthesia for cesarean delivery is often initiated with 2% lidocaine. In contrast to the lack of benefit of epinephrine for epidural labor analgesia, its addition to lidocaine for cesarean delivery likely has a more favorable risk/benefit ratio. Epinephrine enhances the quality of epidural lidocaine anesthesia for surgery, and when giving a large dose of lidocaine, the addition of epinephrine likely reduces the risk of local anesthetic systemic toxicity (LAST).

Disruption of the endothelial glycocalyx by fluid loading before spinal anesthesia occurs even in healthy parturients, which may reduce its effectiveness in expanding intravascular volume. The glycocalyx structure is altered in preeclampsia, fluid loading may result in exaggerated effects on the endothelium. The assumption that these changes also occur in the pulmonary endothelial glycocalyx supports a restrictive fluid management strategy and preferential use of vasopressors in managing spinal hypotension in women with preeclampsia.

Two randomized trials have shown that neonatal acid-base status is independent of the choice to use ephedrine or phenylephrine, whether administered by prophylactic infusion or used as a bolus to treat spinal hypotension in women with preeclampsia. Another randomized trial concluded that the maternal stroke volume response to colloid preload was variable, and phenylephrine 50 µg was more effective than ephedrine 15 mg in restoring systemic vascular resistance after spinal anesthesia. Therefore, in the absence of systolic heart failure, phenylephrine is preferred for the management of spinal hypotension during cesarean delivery in women with preeclampsia.

General anesthesia. General anesthesia is less desirable than neuraxial anesthesia because of (1) the possibility of difficult tracheal intubation secondary to airway edema and (2) the transient but severe hypertension that accompanies tracheal intubation and extubation. Nonetheless, there are situations in which general anesthesia is the best anesthetic option. Clinical indications include severe ongoing maternal hemorrhage, sustained fetal bradycardia with a reassuring maternal airway examination, and severe thrombocytopenia or other coagulopathy, or a combination of these indications. The platelet count can fall dramatically with rapidly progressive severe preeclampsia or HELLP syndrome and may mandate administration of general anesthesia. Major placental abruption, intrauterine fetal demise, and preeclampsia all increase the risk for DIC. However, placental abruption without maternal hemodynamic compromise or coagulation abnormalities is not an absolute contraindication to neuraxial anesthesia. The safe administration of general anesthesia in women with preeclampsia requires an advanced state of readiness and careful preparation.

Once the decision has been made to proceed with general anesthesia, the anesthesia provider faces three specific challenges: (1) the potential difficulty of securing the airway, (2) the hypertensive response to direct laryngoscopy and tracheal intubation, and (3) the effects of magnesium sulfate on neuromuscular transmission. A suggested technique for the administration of general anesthesia is outlined in Box 35.5.

Airway considerations. Before proceeding with general anesthesia, careful airway examination is mandatory. Airway edema may be present even with a relatively reassuring airway examination; thus, many anesthesia providers try to avoid emergent administration of general anesthesia if there is any suspicion of a difficult airway. Endotracheal tubes of various sizes, and difficult airway equipment should be immediately available (see Chapter 29). One of the dangers of repeated tracheal intubation attempts in the setting of preeclampsia is the risk for traumatic bleeding, which may make ventilation difficult or even impossible.

Given the potential for a difficult airway, use of video laryngoscopy should be considered. If tracheal intubation is not rapidly achieved, a supraglottic airway (SGA) should be placed. The reduction in oropharyngeal cavity dimensions due to edema, or a bitten tongue in the setting of eclampsia,
BOX 35.5 A Suggested Technique for Administration of General Anesthesia in Women with Severe Preeclampsia

1. Place a radial arterial cannula for continuous blood pressure monitoring in women with severe hypertension.
2. Verify that smaller-sized endotracheal tubes and supraglottic airway devices are immediately available. Equipment needed for difficult airway management should also be immediately available.
3. Consider the administration of an H2-receptor antagonist and metoclopramide IV between 30 and 60 minutes before induction of anesthesia.
4. Administer 0.3 M sodium citrate 30 mL PO immediately before induction of anesthesia.
5. Denitrogenate (3 minutes of tidal-volume breathing or 8 vital capacity breaths with an FiO2 of 1.0 and a tight-fitting face mask).
6. Give labetalol (10-mg bolus doses) IV to titrate systolic blood pressure between 140/90 and 160/110 mm Hg before the induction of anesthesia.
7. Continue to monitor FHR during labetalol administration.
8. Consider alternative antihypertensive agents for patients who do not respond to labetalol (or those with a contraindication to labetalol) (see Table 35.4). A remifentanil bolus (0.5 µg/kg) is an effective adjunct.
9. Perform rapid-sequence induction with propofol 2.0 to 2.8 mg/kg and succinylcholine 1.0 to 1.5 mg/kg (avoid ketamine as an induction agent given its sympathomimetic properties). For patients with severe heart failure, titrate propofol carefully or use etomidate. Consider the administration of a bolus dose of labetalol, esmolol, remifentanil, or magnesium sulfate to blunt the hemodynamic response to laryngoscopy. For patients with heart failure, carefully titrate small doses of propofol or use etomidate for induction of anesthesia, and avoid beta-adrenergic blocking agents.
10. Maintain anesthesia with a volatile halogenated agent and 40% to 50% oxygen as required, together with 50% to 60% nitrous oxide, before delivery. After delivery, decrease the concentration of the volatile halogenated agent to prevent uterine atony, and administer an opioid. Consider giving a propofol infusion and/or a benzodiazepine if there is concern for awareness and recall.
11. Avoid giving additional muscle relaxants; if absolutely required, administer a small repeat dose of succinylcholine with a small dose of anticholinergic agent, or a low dose of a short-acting nondepolarizing muscle relaxant because of the exaggerated effect of this class of drug when co-administered with magnesium.
12. At the end of surgery, reverse neuromuscular blockade and consider the administration of labetalol 5 to 10 mg IV bolus, titrated to effect, to prevent hypertension during emergence and tracheal extubation.

FHR, Fetal heart rate; IV, intravenously.

requires consideration. Guidelines for airway management in obstetric anesthesia provide a useful decision matrix to assess whether to wake the patient or continue the surgery using an SGA (see Chapter 29). In the setting of pre-eclampsia, where maternal or fetal factors lend urgency to delivery, there may be compelling reasons to proceed with surgery. An awake fiberoptic tracheal intubation may be necessary to secure the airway in rare circumstances, but thrombocytopenia and/or airway edema can make this procedure complex. In rare circumstances, it may be prudent to have a surgeon immediately available to establish a surgical airway, if needed.

Hypertensive response to laryngoscopy. The hemodynamic instability associated with rapid-sequence induction and tracheal intubation presents a serious problem in women with severe preeclampsia. The transient but severe hypertension that may accompany tracheal intubation can result in cerebral hemorrhage or pulmonary edema, both potentially fatal complications. Invasive arterial blood pressure monitoring is required for patients with poorly controlled and severe hypertension, to monitor the effects of antihypertensive drugs administered before and after tracheal intubation, and to allow rapid detection of adverse hemodynamic responses to laryngoscopy. The goal of treatment is to reduce the arterial blood pressure to less than 160/110 mm Hg before the induction of general anesthesia, and to maintain the systolic blood pressure between 140 and 160 mm Hg and the diastolic blood pressure between 90 and 100 mm Hg throughout laryngoscopy and tracheal intubation.

A 2014 narrative review discussed the pharmacology, efficacy, side effects, and the therapeutic range of beta-adrenergic receptor antagonists, opioids, vasodilators (e.g., sodium nitroprusside, nitroglycerin, hydralazine), and magnesium sulfate to blunt the hemodynamic response to laryngoscopy and tracheal intubation. None of these agents are problem-free: maternal beta-adrenergic receptor blockade may be associated with fetal bradycardia or hypoglycemia. Nitrites may cause precipitous hypotension in volume-depleted patients, hydralazine has a delayed onset and a prolonged effect, and remifentanil may be associated with respiratory depression in the neonate.

Many anesthesia providers consider labetalol to be the drug of choice for attenuating the hypertensive response to laryngoscopy in women with severe preeclampsia and preserved systolic function. Ramanathan et al. compared intravenously administered labetalol with no treatment in a randomized study of preeclamptic women who received general anesthesia for cesarean delivery. Mean arterial blood pressure increased after tracheal intubation in both study groups, but the hypertensive response was significantly less pronounced in the labetalol group. Women in the control group also developed tachycardia (in response to laryngoscopy and tracheal intubation), which did not occur in the labetalol group. Labetalol can be administered using either a bolus technique or a continuous intravenous infusion, or both.

There is also evidence of safe short-term administration of esmolol in this setting. A randomized double-blind study of 80 hypertensive women presenting for cesarean delivery
demonstrated that intravenous esmolol—in doses as high as 2 mg/kg, carefully titrated—can be safely used to dampen the hemodynamic response to laryngoscopy and tracheal intubation, particularly if hypertension and tachycardia are present.283

The short-acting opioid remifentanil is rapidly metabolized by both the mother and neonate by nonspecific blood and tissue esterases and has been administered to preeclamptic women. A clear advantage of remifentanil compared with other opioids is the rapid onset and short duration of the drug; the limited duration of action should not interfere with the resumption of spontaneous ventilation if tracheal intubation is unsuccessful. Ngan Kee et al.294 randomized 40 pregnant women without preeclampsia who required general anesthesia for cesarean delivery to receive either a one-time intravenous dose of remifentanil 1 µg/kg or saline immediately before induction of anesthesia. The primary outcome was the maximum increase in systolic blood pressure (compared with a baseline measurement). Administration of remifentanil significantly blunted the systolic blood pressure response. However, remifentanil crosses the placenta, and two neonates in the remifentanil group required naloxone administration for poor respiratory effort at birth. Park et al.295 randomized 48 patients with severe preeclampsia to receive remifentanil 0.5 µg/kg or 1 µg/kg before tracheal intubation. Both doses prevented a hypertensive response, but three patients treated with the higher dose required ephedrine to treat hypotension. Apgar scores and umbilical cord blood gas measurements were comparable in both groups, but a significant number of neonates in each group required tracheal intubation. The lower remifentanil dose, 0.5 µg/kg, is therefore likely preferable.

A bolus dose of magnesium sulfate 30 to 40 mg/kg administered immediately after the induction agent, with or without alfentanil, has been found to suppress maternal catecholamine release and effectively obtund the hypertensive response to tracheal intubation in women with preeclampsia.296–299 There were no maternal or neonatal adverse effects attributable to bolus magnesium, although caution is advised in women with renal insufficiency.

Sodium nitroprusside and nitroglycerin have been used in the past, but are seldom used in contemporary practice; the former can cause precipitous hypotension, and the hemodynamic effects of the latter are dependent on intravascular volume.

**Effects of magnesium sulfate.** Most women with severe preeclampsia will present to the operating room while receiving magnesium sulfate for seizure prophylaxis. The magnesium infusion should continue throughout surgery to minimize the risk for eclampsia. The primary anesthetic considerations for women receiving magnesium sulfate is the interaction with nondepolarizing muscle relaxants. Magnesium sulfate, when appropriately administered, is generally a safe drug, but systems should be in place to avoid inadvertent infusion of large boluses of the drug. Although magnesium sulfate has been used for tocolysis, it is relatively ineffective, and uterine tone is unlikely to be altered significantly.300

Magnesium inhibits the presynaptic release of acetylcholine at the neuromuscular junction, decreases the sensitivity of the postsynaptic receptor to acetylcholine, and depresses the excitability of the muscle fiber membrane. Magnesium sulfate increases the potency and duration of vecuronium, rocuronium, and mivacurium.301–303 Several case reports have described a requirement for overnight mechanical ventilation after administration of routine doses of vecuronium in women receiving magnesium sulfate.304 Thus, if nondepolarizing muscle relaxants are used, they should be administered in very small doses. Interpretation of responses to peripheral nerve stimulation may be difficult in this setting. Many practitioners avoid the use of nondepolarizing neuromuscular blocking agents in women with preeclampsia because of concern regarding residual postoperative neuromuscular blockade.

Airway guidelines discuss the use of sugammadex for the reversal of neuromuscular blockade when rocuronium has been used for rapid-sequence induction. Studies in nonpregnant populations showed that peri-induction administration of magnesium sulfate 40 to 60 mg/kg did not delay reversal of neuromuscular blockade with sugammadex.305,306 No cases of recurarization were observed. Although these studies did not address the patient with preeclampsia who is receiving magnesium, several case reports of magnesium use in women with severe preeclampsia support the contention that magnesium does not influence reversal with sugammadex.307

Even though succinylcholine mimics acetylcholine at the nerve terminal, the onset and duration of a single intubating dose is not prolonged when administered concurrently with a magnesium sulfate infusion;308 a routine intubating dose of 1 to 1.5 mg/kg should be used during rapid-sequence induction of anesthesia.

Although some reports have suggested that co-administration of a calcium entry–blocking agent and magnesium may cause hypotension and/or neuromuscular blockade,182–184,309 more recent information suggests that these medications can be used safely together.184

**Postoperative analgesia.** Multimodal options for postoperative analgesia are the same as for healthy pregnancies and include acetaminophen (paracetamol), nonsteroidal antiinflammatory drugs (NSAIDs), oral or intravenous opioids, neuraxial opioids (single injection), and continuous epidural infusion of analgesic agents. Many anesthesia providers prefer neuraxial opioid administration for postcesarean analgesia (see Chapter 27). For women whose postpartum hypertension persists longer than 1 day, the ACOG has suggested that NSAIDs be replaced by alternative analgesics, as these drugs may contribute to hypertension.2 However, more recent data have called this recommendation into question.310 In the rare case of a woman with continuing severe refractory hypertension, continuous epidural analgesia with a local anesthetic is an attractive option because of its blood pressure–modulating properties.

Regardless of the postoperative analgesic technique, all women should be carefully monitored for signs of respiratory depression, airway obstruction, and pulmonary edema.
**Postpartum Management**

The risks associated with severe preeclampsia do not end with delivery. Postpartum women are at significant risk for pulmonary edema, sustained hypertension, stroke, venous thromboembolism, airway obstruction, and seizures, and should receive close monitoring of oxygenation, blood pressure, fluid intake, and urinary output. In addition, severe preeclampsia, the HELLP syndrome, and eclampsia can present for the first time in the postpartum period, with delayed presentation as late as 4 weeks after delivery. A study of almost 4000 women diagnosed with preeclampsia found that the incidence of postpartum onset of disease was 5.7%, and hypertension is the leading indication for postpartum hospital readmission.

The risk for **pulmonary edema** is also highest in the postpartum period. The resolution of preeclampsia usually occurs within 5 days of delivery and is heralded by a marked diuresis that follows mobilization of extracellular fluid and an increase in intravascular volume. As a consequence, women with severe preeclampsia, particularly those with early-onset disease, renal insufficiency, or pulmonary capillary leak, are at increased risk for development of postpartum pulmonary edema.

In contrast with women with gestational hypertension, who typically become normotensive within 1 week of delivery, women with severe preeclampsia may have a longer duration of hypertension; the risk for **cerebrovascular accident** is highest during this time. Given the increased risk for postpartum cerebrovascular accident, the ACOG recommends antihypertensive therapy in the postpartum period when systolic blood pressure persistently exceeds 150 mm Hg or diastolic blood pressure exceeds 100 mm Hg. Antihypertensive therapy should be continued, started, or resumed for these women, and blood pressure should be closely monitored. For women in the postpartum period who develop new-onset hypertension associated with headache or other neurologic symptoms, or new-onset severe hypertension, a 24-hour course of magnesium sulfate administration may help prevent eclampsia or a cerebrovascular accident.

**Postpartum venous thromboembolism (VTE)** is a leading cause of maternal mortality in pregnancy. Both cesarean delivery and preeclampsia are independent risk factors for postpartum VTE. Prophylaxis and treatment of VTE are discussed in Chapter 38.

Preeclampsia has been associated with increased upper airway resistance and an increased risk for obstructive sleep apnea. A review of anesthesia-related maternal deaths in Michigan described a series of postoperative and postpartum deaths attributed to **airway obstruction** or **hypoventilation**, including the death of one woman with severe preeclampsia and sleep-disordered breathing who likely experienced opioid-related respiratory depression while receiving patient-controlled intravenous analgesia after cesarean delivery. Such findings highlight the need for close monitoring and consistent vigilance in the postoperative care of women with severe preeclampsia—particularly those with generalized edema, known airway swelling, snoring, and obesity.

**Long-Term Outcomes**

Although usually asymptomatic, a significant proportion of women who had preeclampsia have persistent moderate to severe abnormalities of left ventricular function as demonstrated using echocardiography 1 year postpartum. Women with a history of preeclampsia are at increased risk for chronic hypertension and cardiovascular disease, including ischemic heart disease, stroke, and diabetes, later in life, and an earlier onset of cardiovascular disease than women with healthy pregnancies. Risks for ischemic heart disease and stroke are elevated approximately twofold. There may also be an increased risk for chronic renal failure. In addition, there is evidence of a dose-response relationship between preeclampsia and cardiovascular disease. Women with severe and/or early-onset preeclampsia, and those whose pregnancies are complicated by both preeclampsia (the maternal syndrome) and fetal growth restriction (the fetal syndrome), are at higher risk than women with preeclampsia without severe features or gestational hypertension. Women with preeclampsia in both their first and second pregnancies are at even greater risk for future ischemic heart disease.

The mechanism of increased risk for cardiovascular disease in preeclampsia is unclear. It is possible that preeclampsia causes permanent damage to the endothelium and hastens the onset of cardiovascular disease. Women with a history of preeclampsia have persistent impairment of brachial artery endothelium-dependent vascular relaxation at 1 to 3 years after delivery compared with healthy control women. In addition, preeclampsia and cardiovascular disease probably have a common pathogenesis because of shared risk factors. Common risk factors for preeclampsia and atherosclerosis include hypertension, obesity, insulin resistance, advanced age, hypercholesterolemia, and dyslipidemia. Cigarette smoking is the notable exception in that it is an established risk factor for cardiovascular disease but is protective against preeclampsia. Preeclampsia may be a cardiovascular risk marker in women with an underlying predisposition to vascular disease; the hemodynamic and metabolic stress of pregnancy causes the predisposition to manifest as preeclampsia. After pregnancy, women return to a normal state until the threshold for disease development is exceeded in later life.

Regardless of the mechanism of increased risk, these observations represent a potential opportunity for primary disease prevention and risk factor modification. In a 2004 multinational study, 90% of the risk for a first myocardial infarction was attributed to potentially modifiable risk factors. Possible interventions include earlier cardiovascular disease screening and individual counseling regarding the importance of smoking cessation, regular exercise, and a diet low in saturated fat and high in antioxidants. It may also be beneficial for anesthesia providers to elicit a history of preeclampsia when conducting the preanesthesia evaluation for older women scheduled for nonobstetric surgery.

In contrast with the increased risk for cardiovascular disease, a history of preeclampsia has been associated with a...
decreased risk for cancer. Several earlier studies have suggested that women who have been diagnosed with preeclampsia have a slightly lower risk for breast cancer in later life compared with other parous women. However, a 2007 systematic review and meta-analysis of almost 200,000 women with a history of preeclampsia found no association between preeclampsia and future cancer risk.

Evidence indicates that preeclampsia may also result in psychological sequelae. The experience of severe preeclampsia (particularly with early-onset disease and preterm delivery) reflects a serious complication that threatens the mother’s life and the life of her child. In one study, approximately one-fourth of women developed posttraumatic stress disorder (PTSD) after early-onset preeclampsia. This association may be mediated by the condition of the offspring after preterm delivery. Further research is required to characterize women at risk for PTSD and to investigate strategies for PTSD prevention and intervention.

**ECLAMPSIA**

Eclampsia is defined as the new onset of seizures or unexplained coma during pregnancy or the postpartum period in a woman with signs and symptoms of preeclampsia and without a preexisting neurologic disorder.

**Epidemiology**

Findings from population-based studies in the past two decades suggest that the incidence of eclampsia varies from 0.1 to 5.9 per 10,000 pregnancies in developed countries. The variation in rates of eclampsia among studies likely reflects reporting differences among countries or differences in treatment for severe preeclampsia. On average, studies have shown a decrease in the incidence of eclampsia in developed countries over time; this decrease is likely attributable to an increase in the use of magnesium for seizure prophylaxis, or early initiation of antihypertensive therapy in combination with magnesium.

Eclampsia can occur suddenly at any point in the puerperium; however, most seizures occur intrapartum or within the first 48 hours after delivery. Late eclampsia is defined as seizure onset from 48 hours after delivery to 4 weeks postpartum. The majority of eclamptic women have evidence of severe preeclampsia, but in 10% to 15% of cases, hypertension is absent or modest and/or proteinuria is not detected. Reported risks include young maternal age, nulliparity, multiple gestation, molar pregnancy, triplody, preexisting hypertension, renal or cardiac disease, previous severe preeclampsia or eclampsia, nonimmune hydrops fetalis, and systemic lupus erythematosus. Major maternal complications of eclampsia include pulmonary aspiration, pulmonary edema, cerebrovascular accident, cardiopulmonary arrest, venous thromboembolism, acute renal failure, and death. Eclampsia is associated with a high perinatal death rate and has also been associated with placental abruption, severe fetal growth restriction, and extreme prematurity.

**Clinical Presentation and Diagnosis**

Any of the pathophysiologic changes of preeclampsia can be present in eclampsia. About 80% of patients will have premonitory neurologic symptoms, the most common of which are headache and visual disturbances. Other premonitory signs and symptoms can include photophobia, epigastric or right upper quadrant pain, hyperreflexia, and altered mental status; these symptoms can occur before or after the onset of seizures.

Seizures have an abrupt onset, typically beginning as facial twitching that is followed by a tonic phase that persists for 15 to 20 seconds. This phase progresses to a generalized clonic phase characterized by apnea, which lasts approximately 1 minute. Breathing generally resumes with a long stertorous inspiration, and the patient enters a postictal state with a variable period of coma. Cardiorespiratory arrest and pulmonary aspiration of gastric contents can complicate a seizure. Although the definitive diagnosis for eclampsia is a sudden seizure in a pregnant woman who has signs and symptoms of preeclampsia, a woman who lapses into coma without witnessed convulsions can also be classified as eclamptic.

The mechanism of eclamptic seizures remains poorly understood. It may involve a loss of the normal cerebral autoregulatory mechanism, resulting in hyperperfusion and leading to interstitial or vasogenic cerebral edema and decreased cerebral blood flow. Neurologic studies suggest that eclampsia might be a manifestation of PRES.

Until proven otherwise, the occurrence of seizures during pregnancy should be considered eclampsia. Conditions simulating eclampsia include seizure disorder, stroke, hypertensive encephalopathy, ischemia or hypoxia, cerebral space–occupying lesion, systemic disease (e.g., systemic lupus erythematosus, sickle cell anemia), infection (e.g., meningitis, encephalitis), electrolyte and endocrine disturbances, PRES, vasculitis or angiopathy, cerebral venous thrombosis, anemic fluid embolism, medications (withdrawal, substance use disorder), and organ failure.

**Obstetric Management**

Immediate goals are to stop convulsions, establish a patent airway, and prevent major complications (e.g., hypoxemia, aspiration). Further obstetric management includes antihypertensive therapy, induction or augmentation of labor, and expeditious (preferably vaginal) delivery. Fetal bradycardia typically begins during or immediately after a seizure but does not mandate immediate delivery unless it is persistent.

**Resuscitation and Seizure Control**

During the seizure, oxygenation may prove impossible, but supplemental oxygen should be delivered by means of a face mask (Box 35.6). Attempts to insert an oral airway should be withheld until the seizure abates. As soon as breathing resumes, ventilation may be gently augmented with a bag-and-mask device. Pulse oximetry should be used to assess maternal
oxygenation. Blood pressure and the electrocardiogram should be monitored to identify hypertension, arrhythmia, or cardiac arrest. While initial resuscitation is under way, an assistant may be used to raise the seizure threshold.

**Anesthetic Management**

The preanesthetic management of an eclamptic woman parallels that of a patient with severe preeclampsia. Considerations specific to the woman with eclampsia are as follows:

1. **Assessment of seizure control and neurologic function.**
   The possibility of increased intracranial pressure is not a cause for concern if the patient remains conscious, alert, and free of seizures. Persistent coma and localizing signs may indicate a major intracranial pathologic process that could affect anesthetic management.

2. **Maintenance of fluid balance.** Intake should be restricted to 75 to 100 mL/h to minimize the risk for exacerbating cerebral edema.

3. **Blood pressure control.** Antihypertensive therapy should be instituted if the systolic pressure is 160 mm Hg or higher, or if the diastolic pressure is 110 mm Hg or higher.

4. **Continuous pulse oximetry monitoring of maternal oxygen saturation.**

5. **Continuous FHR monitoring.**

6. **Laboratory investigations mimic those for preeclampsia.**
   Additionally, coagulation studies should be obtained regardless of the platelet count.

   The anesthetic plan is tailored to each individual case. In stable eclamptic women (fully conscious, no recent seizures, treated with magnesium sulfate, and no organ failure), neuraxial analgesia/anesthesia can be considered. In a retrospective review of 66 South African women with stable eclampsia, Moodley et al. found no difference in maternal and neonatal outcomes in women who received epidural anesthesia compared with general anesthesia for cesarean delivery. Another series describing spinal anesthesia in 12 stable eclamptic women reported only one episode of hypotension and no major complications. Eclamptic seizures are likely associated with an increase in intracranial pressure. Should operative delivery be required in a woman with ongoing seizures, a technique similar to that used for neuroanesthesia in patients with increased intracranial pressure should be considered. Intravenous induction agents such as propofol and thiopental will reduce the cerebral metabolic rate and cerebral blood flow, with a consequent decrease in cerebral blood volume and intracranial pressure. These agents are also effective in terminating seizures.

   Because hyperventilation reduces cerebral blood flow without a reduction in cerebral metabolic rate, it should be employed with caution. Conversely, hypoventilation should be avoided because hypercarbia can lower the seizure threshold. To prevent further neurologic injury, blood pressure should be carefully controlled to maintain cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure). Avoidance of hypoxemia, hyperthermia, and hyperglycemia is also important in avoiding an exacerbation of neurologic injury. Mechanical ventilation should be continued after cesarean delivery in patients who have not recovered neurologically, and these patients should be monitored in an intensive care unit. Sedation during ventilation should include a sedative with some anticonvulsant activity. Although benzodiazepine infusions have often been used in this setting, recent evidence in the nonobstetric population suggests that nonbenzodiazepine options are associated with less drug accumulation, a shorter period of mechanical ventilation, and reduced hospital stay. An infusion of propofol supplemented with judicious doses of an opioid is an acceptable alternative, carefully titrated to maintain adequate cerebral perfusion pressure in view of cerebral edema and raised intracranial pressure. If unconsciousness persists after discontinuation of sedation, further neurologic evaluation with electroencephalography and brain imaging may be required.
Long-Term Outcomes

Neurologic abnormalities occurring in patients with eclampsia (e.g., cortical blindness, focal motor deficits, coma) do not usually result in permanent neurologic deficits. However, studies suggest that formerly eclamptic women had significantly poorer neurocognitive function as well as an increase in visual impairment years after the index pregnancy, both of which may be attributable to permanent white matter changes caused by eclampsia.

**KEY POINTS**

- Preeclampsia is a multisystem disorder of pregnancy characterized by a maternal syndrome with or without a fetal syndrome.
- Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries.
- Disease pathophysiology involves superficial placentation related to abnormal angiogenesis, leading to placental hypoxia and the release of soluble substances toxic to vascular endothelium.
- Management of preeclampsia is supportive, and delivery of the fetus and placenta is the only definitive cure.
- Antihypertensive drugs should be used when systolic blood pressure is 160 mm Hg or higher, or the diastolic blood pressure is 110 mm Hg or higher.
- Preeclampsia likely consists of more than one disease; early-onset disease (earlier than 34 weeks’ gestation) carries a poorer prognosis than late-onset disease.
- Systemic disease manifestations result from widespread maternal vascular endothelial dysfunction.
- Complications of preeclampsia with severe features include severe refractory hypertension, cerebrovascular accident, pulmonary edema, placental abruption, renal failure, and the HELLP syndrome.

- Important hematogetic changes in severe preeclampsia include the potential for thrombocytopenia and disseminated intravascular coagulation.
- There are no indications for invasive central hemodynamic monitoring unique to preeclampsia; indications are similar to those in other multisystem disorders such as severe sepsis or multisystem organ dysfunction.
- Preeclamptic women are at risk for airway edema. The anesthesia provider should anticipate the possibility of difficult airway management.
- The hypertensive response to direct laryngoscopy and tracheal intubation can cause intracranial hemorrhage in women with severe preeclampsia.
- Spinal anesthesia is acceptable for women with severe preeclampsia, especially as an alternative to general anesthesia for emergency cesarean delivery.
- The risks for pulmonary edema, cerebrovascular accident, and venous thromboembolism are increased in the postpartum period.
- Preeclampsia poses considerable long-term future cardiovascular risks in many women.

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FEVER

Definition and Pathophysiology

In 1868, Carl Wunderlich analyzed more than 1 million axillary temperature measurements from 25,000 patients. He concluded that the average normal temperature of healthy adults was 37°C (98.6°F). However, he found a range of temperatures, with a nadir of 36.2°C between 2:00 and 8:00 am and a zenith of 37.5°C between 4:00 and 9:00 pm. A 1992 study using modern oral thermometers largely confirmed Wunderlich’s original data.

Well-regulated temperature results from hypothalamic integration of afferent thermal information from the skin, spinal cord, and other sites within the central nervous system (CNS). Hypothermia prompts vasoconstriction in peripheral tissues to decrease skin blood flow, decrease heat loss, and retain heat in the core compartment. If vasoconstriction is not adequate to prevent hypothermia, thermoregulatory shivering is triggered to increase heat production. Increased body temperature initially prompts vasodilation. It is mediated by the sympathetic nervous system, and it is observed in unanesthetized adults exposed to a hot environment before any significant change in central temperature occurs. If vasodilation is not adequate to prevent hyperthermia, thermoregulatory sweating occurs, which increases evaporative heat loss.

An abnormal body temperature can result from drugs or diseases that either change thermoregulatory thresholds or impair thermoregulatory responses. Hypothalamic activity and fever may be triggered by endogenous pyrogens released from immune effector cells in response to invasion by microorganisms (Fig. 36.1). Although no single endogenous pyrogen has been conclusively identified as the mediator of the febrile response, tumor necrosis factor seems capable of reproducing many components of the febrile response.

Endogenous pyrogen activity appears to depend largely on increased endothelial cell production of prostaglandins. Of interest, many of these substances help mediate uterine activity and parturition.

Clinically, temperature measurements greater than 38°C represent fever. During episodes of fever, the thermoregulatory set point is elevated, and the normal thermoregulatory mechanisms are used to maintain the elevated temperature. However, there are circumstances in which an abnormally
high temperature is measured in the absence of a change in thermoregulatory set point, such as when thermoregulatory responses to hyperthermia are prevented (e.g., block of sympathetically mediated sweating) or overwhelmed (e.g., immersion in hot water, malignant hyperthermia).

The fetus, by virtue of its intraabdominal location, has a unique problem with heat elimination. The only anatomic routes for egress of heat are the fetal skin surface (through the amniotic fluid) or the uteroplacental circulation. Evidence suggests that the fetus relies on heat exchange across the uteroplacental circulation to dissipate most of its metabolic heat. The normal fetus maintains a temperature that is approximately 0.5°C to 0.75°C higher than the maternal temperature.56

#### Neonatal Effects of Maternal Fever

Infection is the most common cause of fever and involves liberation of inflammatory cytokines, which are implicated in the pathogenesis of many fetal and neonatal injuries (see Chapter 10).14 The mechanism linking neonatal neurologic injuries to maternal fever likely involves the inflammatory cytokines.24 Animal models of chorioamnionitis suggest that fetal brain lesions can be induced by infection and blocked by antiinflammatory cytokines.10 Infants developing neonatal encephalopathy in the setting of maternal fever do not generally exhibit positive blood cultures, implying that it is neuroinflammation, rather than infection, that causes damage.11,12 Fever alone has a limited effect, but when combined with acidosis, inflammation, and/or infection, it appears to exacerbate neurologic injury.13

Early studies suggested that mild maternal intrapartum fever may not be benign. These studies focused only on the presence or absence of fever, and did not specifically comment on a clinical or pathologic diagnosis of chorioamnionitis. Macaulay et al.15 measured fetal scalp temperature in utero using a modified intrauterine pressure catheter. They concluded that maternal oral temperature is often an underestimation of fetal skin temperature. Lieberman et al.14 retrospectively reviewed the records of 1218 nulliparous women with singleton, term pregnancies in spontaneous labor who were afebrile on admission. They found fever (greater than 38°C) in 10% of the patients, nearly all of whom had received epidural analgesia. One-minute Apgar scores less than 7 and hypotonia were more common in the newborns of febrile mothers. Fever higher than 38.3°C was associated with more frequent requirement for bag-and-mask ventilation in the delivery room and need for supplemental oxygen in the nursery. There was also an increase in the incidence of neonatal seizures.14 The same group performed a case-control study of unexplained neonatal seizures in term infants and found a strong association with intrapartum fever and seizures (odds ratio [OR], 3.4).15 Perlman16 reported a high incidence of maternal fever among a cohort of infants with a 5-minute Apgar score less than or equal to 5 and those requiring resuscitation with chest compressions in the delivery room. Similarly, Greenwell et al.17 found an association between low-grade fever and adverse neonatal outcomes, including hypotonia and low 1-minute Apgar scores. More extreme fever (greater than 38.3°C) was also associated with low 5-minute Apgar scores and assisted ventilation.17 Lastly, a statistically significant association has been observed between maternal fever and neonatal encephalopathy.11

#### Hyperthermia

Hot tub and sauna use in pregnancy have been linked epidemiologically to neural tube defects in the fetus.18 Spontaneous abortion19 and major structural birth defects20 have similarly been associated with the frequency of use of hot tubs and saunas. Neonatal hypoxic encephalopathy has been observed after prolonged immersion in 39.7°C water during otherwise uncomplicated labor.21

#### Noninfectious Inflammatory Fever

Neuraxial labor analgesia is associated with intrapartum fever (so-called “epidural fever”). The predominant theory is that noninfectious inflammation is responsible for epidural analgesia–associated fever (see Chapter 23). The incidence of fever in parturients with neuraxial analgesia ranges from 20% to 30% compared with 5% to 7% in parturients without neuraxial analgesia.22 Why some women with neuraxial analgesia develop fever, but others do not, is not understood. It is not known whether epidural fever is associated with an increased risk for adverse maternal and fetal outcomes.

#### Fever Secondary to Infection

Maternal fever from chorioamnionitis that leads to neonatal infection is associated with both short- and long-term...
neonatal morbidity. In an observational evaluation of women with clinical chorioamnionitis, there was a higher incidence of prolonged positive-pressure ventilation in the delivery room, tracheal intubation, admission to a neonatal intensive care unit, and 5-minute Apgar score less than 6 in febrile versus afebrile newborns. Additional acute neonatal morbidity associated with chorioamnionitis includes neonatal pneumonia, meningitis, sepsis, and death. Importantly, the use of intrapartum antibiotic therapy given in response to maternal Group B streptococcal colonization or in response to signs of chorioamnionitis has significantly decreased the incidence of neonatal infection and sepsis. Clinical or pathologically diagnosed chorioamnionitis may also correlate with neonatal brain injury. In several large epidemiologic studies, there was an increased incidence of cerebral palsy in infants born to mothers with intrapartum fever (greater than 38°C) diagnosed with chorioamnionitis compared with those born to afebrile mothers.

Maternal Effects of Fever
Fever also produces significant maternal effects. Elevated temperature is associated with increased maternal heart rate, cardiac output, oxygen consumption, and catecholamine production. Women who develop fever are more likely to shiver and experience uncomfortable rigors. Not surprisingly, obstetricians fear infection are more likely to treat febrile women with antibiotics. While suspected chorioamnionitis in the setting of maternal fever is not an indication for immediate delivery, low-grade fever may prompt obstetricians to choose instrumental vaginal or cesarean delivery over expectant labor management.

INFECTIONS IN PREGNANT WOMEN
Chorioamnionitis (Intrauterine Inflammation and/or Infection)
In January 2015, an expert panel was convened by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to review the criteria for diagnosis and management of chorioamnionitis. They proposed that the phrase “intrauterine inflammation, infection, or both” (abbreviated “Triple I”) be used instead of the term “chorioamnionitis” because of the diverse range of conditions, both infectious and inflammatory, that it was used to describe. Triple I can be diagnosed when fever (diagnosed as maternal temperature greater than or equal to 39.0°C on one reading or greater than or equal to 38.0°C on two occasions separated by 30 minutes) is present with one or more of the following: (1) fetal tachycardia (greater than 160 bpm for 10 minutes or longer), (2) maternal white blood cell count greater than 15,000 × 10⁶ cells/L in the absence of corticosteroids, (3) purulent fluid from the cervix (cloudy or yellowish thick discharge confirmed visually on speculum examination to be coming from the cervical canal), and (4) biochemical or microbiologic amniotic fluid results consistent with microbial invasion of the amniotic cavity. It is stressed that maternal fever in the absence of other criteria should be categorized as “isolated maternal fever.” The new nomenclature of “intrauterine inflammation, infection, or both” (Triple-I) is in the process of being incorporated into practice to replace the term “clinical chorioamnionitis.”

Previously, the diagnosis of chorioamnionitis was made when any combination of the following elements was noted: maternal fever, maternal or fetal tachycardia or both, elevated maternal white blood cell count, uterine tenderness, and purulent fluid or discharge from the cervical os. Using this definition, it occurs with variable frequency in the literature with reported event rates ranging from 0.5% to 10%, depending on the means of ascertainment and the demographic and obstetric characteristics of the population. It may be seen in over 90% of deliveries before 24 weeks’ gestation, in almost 40% of women who deliver between 25 and 28 weeks, and in approximately 5% of deliveries at term. Independent risk factors include low parity, a history of chorioamnionitis in a prior delivery, the number of vaginal examinations, duration of total labor, duration of ruptured membranes, and use of internal monitors. Unfortunately, the laboratory diagnosis of chorioamnionitis is neither sensitive nor specific and may not correlate with the clinical presentation. Moreover, the classic clinical signs of chorioamnionitis are often absent. Goodman et al. reviewed the records of 531 women with pathologically proven chorioamnionitis. They found that only 10% of the patients had abdominal tenderness and only 1% had foul-smelling amniotic fluid.

In most cases, bacteria gain access to the amniotic cavity and the fetus by ascending through the cervix after rupture of the membranes. Alternatively, infectious agents present in the maternal circulation may undergo transplacental transport and gain access to the amniotic cavity. Similar to other pelvic infections, chorioamnionitis often is polymicrobial in origin, and bacteria normally present in the genital tract most likely are responsible for infections. Bacteroides species, Group B streptococci, Mycoplasma and Ureaplasma species, and Escherichia coli are organisms commonly isolated from the amniotic fluid of parturients with chorioamnionitis. Maternal bacteremia occurs in 5% to 12% of women with the clinical diagnosis of chorioamnionitis.

Maternal complications of chorioamnionitis include preterm labor, placental abruption, postpartum infection, uterine atony, postpartum hemorrhage, peripartum hysterectomy, adult respiratory distress syndrome, sepsis, intensive care unit (ICU) admission, and death. In addition, several studies have noted an increased incidence of cesarean delivery for dystocia in women with chorioamnionitis. Some investigators have suggested that infection adversely affects uterine contractility and contributes to an increased risk for cesarean delivery. However, in some cases, chorioamnionitis may represent an ascending infection developing late in a labor that is already prolonged and dysfunctional.

Neonatal complications of chorioamnionitis include pneumonia, meningitis, sepsis, and death. An association between chorioamnionitis and cerebral palsy has been identified. A recent meta-analysis also found an association with chorioamnionitis and cerebral palsy, but the association...
was much weaker than in previous meta-analyses. Once the studies were separated for analysis by gestational age, exclusion of studies without evaluation of postnatal causes of cerebral palsy, and potential sources of bias and confounding, the relative risk was much lower than in previous analyses.51,59,60 The link between maternal infection and neurologic injury in the neonate appears related to intra-amniotic infection or inflammation, particularly when there is evidence of fetal systemic inflammation or inflammation of the umbilical cord (funisitis).62

Historically, prompt delivery was the cornerstone of obstetric management of patients with chorioamnionitis. However, Gibbs et al.45 did not identify a correlation between poor maternal or neonatal outcome and the time interval from diagnosis of chorioamnionitis to delivery. They performed cesarean delivery only for standard obstetric indications and not for the diagnosis of chorioamnionitis alone.63 Similarly, a large prospective observational study found no relationship between the duration of infection and most measures of adverse neonatal outcome among 1965 gestations complicated by chorioamnionitis, although low 5-minute Apgar scores and neonatal mechanical ventilation were correlated with duration of chorioamnionitis.55 No recent studies have reinvestigated this practice as it relates to neonatal neurologic injuries. Many fetuses will exhibit tachycardia during maternal fever and infection, but this pattern is not highly predictive of neonatal acedia and, therefore, by itself, is not an indication for immediate delivery.61

Early antepartum treatment for chorioamnionitis results in decreased maternal and neonatal morbidity compared with delayed postpartum treatment.24,62,63 With chorioamnionitis, a combination of ampicillin and gentamicin should cover most relevant pathogens and is the recommended primary antibiotic regimen.24 The early use of antibiotics may affect the anesthesia provider’s decision regarding the administration of neuraxial labor analgesia or anesthesia (see later discussion). If a cesarean delivery is performed, additional anaerobic coverage with clindamycin or metronidazole may decrease the risk for endometritis.24 Continuation of antimicrobial agents postpartum should not be automatic, but rather based on risk factors for postpartum endometritis. In general, women who have a vaginal delivery are less likely to develop postpartum endometritis, and therefore may be candidates for discontinuing antimicrobial therapy after delivery. Even in women undergoing cesarean delivery, studies have shown only preoperative or one single postoperative dose appears to have the same efficacy as continuing antibiotics for a longer duration.24,64-66

Urologic Infection

Urinary tract infections are common during pregnancy, although the incidence of asymptomatic bacteriuria may not be higher than in nonpregnant women. Increased concentrations of progesterone cause the relaxation of ureteral smooth muscle. In addition, the gravid uterus causes partial ureteral obstruction. Both factors cause urinary stasis, which increases the risk for urinary tract infection.43,67,68 Furthermore, these physiologic changes increase the likelihood that asymptomatic bladder infection will ascend into the kidneys and produce pyelonephritis. Approximately 1.3% of pregnant women will develop symptomatic cystitis,69 and up to 25% of women with untreated bacteriuria in pregnancy may develop pyelonephritis.70

Acute pyelonephritis is a serious threat to maternal and fetal well-being and complicates approximately 1% to 2.5% of pregnancies.41 Symptoms of acute pyelonephritis include fever, chills, flank pain, and other symptoms of lower urinary tract infection. Approximately 14% to 17% of pregnant women with pyelonephritis will develop bacteremia during the course of this infection.71,72 Complications may also include anemia, renal insufficiency, and respiratory insufficiency.72 The most common causative organisms are E. coli, gram-positive organisms, Klebsiella, Enterobacter, and Proteus species.72

Hospitalization is indicated to initiate aggressive parenteral antibiotic treatment of this serious maternal infection, although limited data support outpatient treatment for carefully selected patients in the first and second trimester.73 Nevertheless, treatment failures and septic complications have been reported in patients randomized to outpatient therapy in clinical trials.74

Pyelonephritis may be associated with organ dysfunction. Nearly 20% of affected women have transient renal dysfunction,72 and the disease may also be complicated by pulmonary injury. Cunningham et al.76 suggested that “this syndrome was probably caused by permeability pulmonary edema, likely mediated by endotoxin-induced alveolar-capillary membrane injury.”76 Towers et al.77 compared 11 pregnant women who had pyelonephritis and pulmonary injury with 119 women who had pyelonephritis only. They observed that fluid overload and the use of tocolytic therapy were the most significant predictive factors associated with pulmonary injury. The authors suggested that “strict management of fluids should occur so that patients do not have fluid overload.”77 Contemporary authors, however, have questioned fluid restriction in pyelonephritis and instead suggest fluid administration sufficient to generate urine output of 30 to 50 mL/h, while observing respiratory rate, oxygen saturation, and symptoms of dyspnea to identify impending respiratory compromise. Respiratory failure should be investigated with chest radiography and arterial blood gas analysis and managed with appropriate respiratory support.43

Respiratory Tract Infection

Pregnancy results in a number of changes that may predispose the pregnant woman to the development of serious respiratory tract infection. Hyperemia and hypersecretion are characteristic of the respiratory tract mucosa during pregnancy, and these changes may intensify the effect of the initial infection.78 In the case of a viral infection, the excess secretions may predispose the patient to bacterial superinfection. Immunologic modulation during pregnancy may also predispose to pulmonary infection.79 Furthermore, the increased oxygen consumption, elevation of the diaphragm, and decreased functional residual capacity characteristic of...
pregnancy may increase the likelihood that infection will result in maternal hypoxemia.

Fortunately, most respiratory tract infections during pregnancy are upper respiratory tract viral infections that do not pose a serious threat to the mother or fetus. Most lower respiratory tract infections are also viral and self-limiting; pneumonia occurs during pregnancy with an incidence approximating that of the nonpregnant population.80

Benedetti et al.81 emphasized the importance of early diagnosis and treatment as well as the direct measurement of maternal oxygenation in cases of pneumonia during pregnancy. Most community-acquired pneumonias in healthy young women are bacterial in origin. *Streptococcus pneumoniae* is the most common pathogen.81 *Mycoplasma pneumoniae* and influenza are other common pathogens. *Legionella pneumophila, Chlamydia, and varicella* are less common pathogens in this population. Varicella pneumonia has been associated with maternal and fetal morbidity and up to 40% maternal mortality. *Acyclovir* has been used successfully to treat varicella pneumonia during pregnancy.82

Because morbidity and mortality from influenza are increased in pregnancy, influenza vaccination is strongly recommended for pregnant women or those who will be pregnant during influenza season.83 Notably, pregnant women are disproportionately represented when evaluating mortality from influenza, and a significant number of women were treated with extracorporeal membrane oxygenation (ECMO).84,85 In the Confidential Enquiries into Maternal Deaths and Morbidity in the United Kingdom and Ireland 2009 to 2012 report, of the women who died, one in eleven died from influenza and more than one-half of the deaths could have been prevented by vaccination.86 The risk for fetal death is increased by maternal influenza infection and is reduced by vaccination.87 The infant is also passively protected for up to 20 weeks after birth.88 Aggressive treatment with antiviral drugs (oseltamivir, zanamivir) reduces the severity of the ensuing illness; in the 2009 to 2010 H1N1 influenza pandemic, initiation of therapy in the first 2 days of the infection reduced hospitalization and ICU admission; however, benefits have also been seen if antiviral drugs were started up to 4 days after onset of symptoms.84,89 Antiviral drugs appear to be safe in pregnancy, with no reported increase in adverse pregnancy or neonatal outcomes.90,91

The Centers for Disease Control and Prevention (CDC) recommends the following: “droplet precautions should be implemented for patients with suspected or confirmed influenza for 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a healthcare facility.” It is also recommended that health care providers wear a fitted N95 respirator or its equivalent when performing aerosol-generating procedures (e.g., tracheal intubation and extubation).92

**Postpartum and Surgical Site Infection**

The most common source of postpartum infection is the **genital tract**. The urinary tract and less often the breasts or the lungs may also be infected.43 Postpartum uterine infection typically presents with a combination of fever, malaise, abdominal pain, and/or purulent discharge or lochia. Although obstetricians typically refer to postpartum uterine infection as *endometritis*, this infection involves the decidua, myometrium, and parametrial tissues. Bacteria that colonize the cervix and vagina gain access to the amniotic fluid during labor, and they may invade devitalized uterine tissue postpartum. Surgical site infection (SSI), defined by the CDC as infection related to an operative procedure that occurs at or near the surgical incision within 30 days of the procedure,93 is another increasingly common postpartum infection.

Cesarean delivery, prolonged rupture of membranes, and prolonged duration of labor are risk factors for postpartum endometritis.43 Similarly, risk factors for surgical site infection following cesarean delivery include patient-level factors such as obesity, prior cesarean delivery, hypertension, diabetes, and tobacco use; pregnancy-related factors such as emergency delivery, labor or rupture of membranes, and chorioamnionitis; and surgical factors such as operative time and surgeon experience.94 Prophylactic administration of antibiotics decreases the incidence of postpartum uterine infection and wound infection after cesarean delivery in all women, whether performed electively or emergently.92

Antibiotic prophylaxis should be administered 15 to 60 minutes before skin incision for cesarean delivery98 unless the patient is already receiving appropriate antibiotic coverage (e.g., for chorioamnionitis). A first-generation cephalosporin is effective against gram-positive bacteria, gram-negative bacteria, and some anaerobic bacteria, and is the first-line antibiotic for cesarean delivery prophylaxis. In women with a history of a significant penicillin or cephalosporin allergy, clindamycin with an aminoglycoside is an appropriate alternative.95 Extended-spectrum antibiotics, such as azithromycin, used in addition to first-generation cephalosporins for cesarean delivery prophylaxis, have been shown to reduce rates of endometritis and wound infection in women undergoing nonelective cesarean delivery during labor or after membrane rupture.98

A single intravenous dose of **cefazolin** is appropriate for most women undergoing cesarean delivery, as a therapeutic level is maintained for 3 to 4 hours. However, obese women may require a higher dose, although the specific appropriate dose has yet to be identified.97,99-101 Consistent with surgical prophylaxis principles, patients with prolonged surgical procedures or those with significant blood loss should receive an additional intraoperative dose of the antibiotic used for preincision prophylaxis.102

No important differences have been identified among various skin preparation solutions used before cesarean delivery.103 Vaginal preparation before cesarean delivery has been evaluated in a meta-analysis of 16 trials.104 These trials demonstrate an overall reduction in postcesarean endometritis, especially for women in labor or with ruptured membranes. More data are needed to evaluate the effect of this intervention on women not in labor or with intact membranes. A meta-analysis evaluating the effect of bundles of at least three evidence-based interventions (such as antibiotic prophylaxis
selection or dose, hair removal with clippers, and chlorhexidine skin preparation) showed a significant reduction in surgical site infection rates with a reduction in risk of 67%.105 Systematic reviews have found insufficient evidence to recommend prophylactic antibiotics for operative vaginal delivery or for manual removal of the placenta after vaginal delivery; however, consideration may be given to prophylactic antibiotics in the setting of complex perineal repairs.96,106–108

Parenteral, broad-spectrum antibiotic therapy with a combination of gentamicin and clindamycin is recommended to treat postpartum endometritis. Ampicillin is added in refractory cases and often in cases in which the patient was colonized with Group B streptococcus before delivery.109 Endometritis typically responds to the above antibiotic therapy, and outcomes are generally excellent. However, serious complications (e.g., peritonitis, abscess, septic thrombophlebitis) may rarely occur.10,111

## SEPSIS AND SEPTIC SHOCK

### Definition

In 2016, the definitions for sepsis and septic shock were updated. Sepsis is defined by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine as life-threatening organ dysfunction caused by a dysregulated host response to infection.112 The term “severe sepsis” is no longer used because of redundancy. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk for mortality than with sepsis alone.112

Sepsis remains an important cause of maternal mortality and morbidity. In the United States between 2006 and 2013, infection accounted for 13% of all maternal deaths, with a cause-specific mortality ratio of 2.2 deaths per 100,000 live births.113,114 In a population-based study of sepsis in delivery hospitalizations, Bauer et al.110 reported the most common infections were pneumonia, genitourinary infection, and chorioamnionitis. Although only 40.4% reported a specific organism, the most common organisms were *E. coli*, staphylococcus, streptococcus, and gram-negative organisms. Independent risk factors of congestive heart failure, chronic liver disease, chronic renal disease, cerclage, and retained products of conception were identified; however, the authors noted that sepsis often occurs in the absence of risk factors, and screening tools should be developed to enhance detection in pregnant women.110

In the United Kingdom and Ireland, sepsis was the reported cause of death in almost 25% of all maternal deaths in the Confidential Enquiries into Maternal Deaths and Morbidity 2009 to 2012 report owing to the large increase in maternal deaths from an H1N1 influenza epidemic.90 The most recent 2013 to 2015 report demonstrated a cause-specific mortality ratio of 0.6 per 100,000.115 In a United Kingdom case-control study, Acosta et al.116 reported the most common sources of infection were genital tract infection in 31.0% of cases, followed by urinary tract infection in 19.7% of cases. The most common organisms identified were *E. coli*, Group A streptococcus, and Group B streptococcus. No organism was identified in 36.2% of cases. Most cases of a Group A streptococcal infection were diagnosed with severe sepsis (using the previous definition) less than 9 hours from the first sign of the systemic inflammatory response syndrome (SIRS); one-half had less than 2 hours between first signs and diagnosis.116

### Screening and Diagnosis

Given the importance of early identification and treatment, prompt recognition is key. Clinically, sepsis is now defined as the combination of infection with end-organ injury. If end-organ injury is suspected, it is essential to screen for infection. If a patient has a suspected infection, it is essential to monitor closely for end-organ injury. Serial bedside evaluation is desirable to detect trends in vital signs and clinical status and to more rapidly assess and reassess for signs of sepsis.112

Several screening tools exist to help in the identification of end-organ injury. Organ dysfunction is characterized by a score of greater than or equal to 2 points on the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score (Table 36.1).112 Bedside screening for end-organ injury can be accomplished using an abbreviated set of criteria called quick SOFA (qSOFA). A nonobstetric patient screens positive with two or more of the following criteria: respiratory rate greater than or equal to 22 breaths/min, altered mentation, and systolic blood pressure less than or equal to 100 mm Hg.112 Previous diagnostic criteria using two or more abnormal values of the SIRS criteria were nonspecific; patients with noninfectious inflammatory processes exhibit these signs, including healthy pregnant women.117

It is not known how either SOFA or qSOFA will perform in the identification of sepsis in pregnant women. Parameters have not been adjusted for pregnancy; many healthy pregnant women have a systolic blood pressure less than or equal to 100 mm Hg and a respiratory rate greater than or equal to 22 breaths/min, especially during labor. Altered mentation is rare in pregnant women, even in the setting of severe disease, and can be considered a more specific sign of end-organ injury and sepsis in the presence of infection. Maternal Early Warning (MEW) criteria were proposed by the National Partnership for Maternal Safety as a set of criteria to identify impending maternal morbidity from a variety of causes (Table 36.2).118 In a case series study of maternal deaths caused by sepsis in Michigan by Bauer et al.,119 75% of patients met MEW criteria at the time of admission. The authors found that deaths were preceded by delays in recognition, administration of appropriate antibiotics, and escalation of care.119 Future research will help to determine the best screening tool to identify sepsis. Given the rarity of maternal sepsis, it seems prudent to use a screening tool to assess multiple types of morbidity at once rather than using a separate tool for each. It is recommended that if a patient meets any of the MEW criteria, she should receive prompt evaluation by a physician or other practitioner with ability to escalate care. A diagnosis of pulmonary, genital tract, or other systemic infection should prompt close monitoring for end-organ injury, and therefore sepsis.
TABLE 36.1 Sepsis-Related Organ Failure Assessment Score (SOFA)

<table>
<thead>
<tr>
<th>SOFA Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FIO₂, mm Hg</td>
<td>&lt; 400</td>
<td>&lt; 300</td>
<td>&lt; 200 with respiratory support</td>
<td>&lt; 100 with respiratory support</td>
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<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Platelets, × 10⁹/mm³</td>
<td>&lt; 150</td>
<td>&lt; 100</td>
<td>&lt; 50</td>
<td>&lt; 20</td>
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<tr>
<td><strong>Liver</strong></td>
<td></td>
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<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>1.2–1.9 (20–32)</td>
<td>2.0–5.9 (33–101)</td>
<td>6.0–11.9 (102–204)</td>
<td>&gt; 12.0 (&gt; 204)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
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<td></td>
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<tr>
<td>Hypotension</td>
<td>MAP &lt; 70 mm Hg</td>
<td>Dopamine ≤ 5 or dobutamine (any dose)ᵃ</td>
<td>Dopamine 6–15, epinephrine ≤ 0.1, or norepinephrine ≤ 0.1ᵃ</td>
<td>Dopamine &gt; 15 or epinephrine &gt; 0.1 or norepinephrine &gt; 0.1ᵃ</td>
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<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt; 6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (µmol/L)</td>
<td>1.2–1.9 (110–170)</td>
<td>2.0–3.4 (171–299)</td>
<td>3.5–4.9 (300–440)</td>
<td>&gt; 5.0 (&gt; 440)</td>
</tr>
<tr>
<td>or urine output</td>
<td>or &lt; 500 mL/day</td>
<td>or &lt; 200 mL/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIO₂, Fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen in arterial blood.
ᵃAdrenergic agents administered for at least 1 hour (doses given are in µg/kg/min)


TABLE 36.2 Maternal Early Warning Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>&lt; 90 or &gt; 160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>&gt; 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>&lt; 50 or &gt; 120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>&lt; 10 or &gt; 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation on room air, at sea level, %</td>
<td>&lt; 95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliguria, mL/h for ≥ 2 h</td>
<td>&lt; 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal agitation, confusion, or unresponsiveness; patient with preeclampsia reporting a nonremitting headache or shortness of breath</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

BP, Blood pressure.

These triggers cannot address every possible clinical scenario that could be faced by an obstetric clinician and must not replace clinical judgment. As a core safety principle, bedside nurses should always feel comfortable to escalate their concerns at any point.


The Sepsis in Obstetrics Score (SOS) may be useful for assessing the severity of illness, and to identify women requiring ICU admission (Table 36.3). In a retrospective cohort of 850 women with clinical suspicion of sepsis, an SOS score of greater than or equal to 6 was independently associated with ICU admission. A prospective validation study confirmed the threshold score of 6, making it the first score derived and validated in an obstetric population. The specificity of the score was 88%, but the sensitivity was only 64%. Additionally, given the low incidence of ICU admission, the negative predictive value of the score was excellent (98.6%), but the positive predictive value was poor (15%). It did not perform statistically better than other validated sepsis scoring systems. A screening tool that consistently facilitates rapid diagnosis of sepsis in pregnancy is therefore still an unmet need.

**Initial Treatment**

Once diagnosis has been established, prompt treatment is paramount. There is an increase in mortality of 7.6% for each hour delay in appropriate antibiotic administration in nonobstetric patients. Care should be escalated to accommodate the resources and requirements to treat critically ill patients. Surviving Sepsis Campaign (SSC) Guidelines were created to provide best practice guidelines in the management of sepsis based on available evidence, with strong recommendations worded as “recommended” and weak recommendations as “suggested.” SSC recommends IV antibiotic administration as soon as possible, within 1 hour, for sepsis and septic shock. Microbiologic cultures are recommended before antibiotic administration as long as there is no substantial delay in antibiotic administration. In a review of sepsis and septic shock in pregnancy by Barton and Sibai, the antibiotic regimen chosen should provide empiric coverage for the common obstetric infections and should include either a combination of gentamycin, clindamycin, and penicillin or a combination of vancomycin and piperacillin/tazobactam. Within the first 3 hours it is recommended to give 30 mL/kg of IV crystalloid fluid to treat sepsis-induced hypotension. It is recommended to use an initial target mean arterial blood pressure (MAP) of 65 mm Hg with norepinephrine used as the first-line vasopressor, and it is suggested to add either vasopressin or epinephrine as a second agent (if needed) to achieve hemodynamic goals. It is suggested to provide active resuscitation to normalize lactate.

In the Confidential Enquiries into Maternal Deaths and Morbidity in the United Kingdom and Ireland 2009 to 2012 report, it was also recommended to consult with an infectious disease specialist
TABLE 36.3 Sepsis in Obstetrics Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Abnormal Range</th>
<th>Normal Range</th>
<th>Low Abnormal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>+4</td>
<td>+3</td>
<td>+2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>&gt; 40.9</td>
<td>39–40.9</td>
<td>38.5–38.9</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>&gt; 90</td>
<td>70–90</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>&gt; 179</td>
<td>150–179</td>
<td>130–149</td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min)</td>
<td>&gt; 49</td>
<td>35–49</td>
<td>25–34</td>
</tr>
<tr>
<td>Spo₂ (%)</td>
<td>≥ 92%</td>
<td>90%–91%</td>
<td>85%–89%</td>
</tr>
<tr>
<td>White Blood Cell Count (per µL)</td>
<td>&gt; 39.9</td>
<td>25–39.9</td>
<td>17–24.9</td>
</tr>
<tr>
<td>% Immature Neutrophils</td>
<td>≥ 10%</td>
<td>&lt; 10%</td>
<td></td>
</tr>
<tr>
<td>Lactic Acid (mmol/L)</td>
<td>≥ 4</td>
<td>&lt; 4</td>
<td></td>
</tr>
</tbody>
</table>

Spo₂, Blood oxygen saturation.

specialist. For a further discussion beyond initial management, see Chapter 54.

Although the effects of maternal therapy on the fetus should be considered, treatment of the mother has first priority. Fetal status is best optimized by meeting maternal treatment goals. For nonreassuring fetal heart rate patterns in the setting of maternal sepsis, fetal resuscitation in utero and maternal medical therapy are frequently successful in delaying delivery. Nevertheless, in some cases, maternal sepsis may require delivery, even before the age of viability, particularly if chorioamnionitis is present. In a 2013 series of maternal admissions for sepsis, 40% of women diagnosed with severe sepsis and all with septic shock required delivery during the same hospitalization, most requiring emergent delivery for worsening maternal respiratory status. Maternal sepsis also increases the risk for perinatal mortality, with stillbirth approaching 33% when maternal sepsis requires ICU admission. A multidisciplinary team should consider the mother’s response to initial therapeutic interventions; vasopressor, oxygen, and ventilatory requirements; and the gestational age and fetal well-being when considering the optimal timing and route of delivery.

NEURAXIAL ANESTHESIA IN THE FEBRILE OR INFECTED PATIENT

Clinicians have long suspected an association between the performance of dural puncture during a period of bacteremia and the subsequent development of meningitis. Some clinicians have feared that diagnostic lumbar puncture may cause meningitis rather than aid in its diagnosis. They reasoned that lumbar puncture may disrupt the rich venous plexus surrounding the spinal cord and allow the direct introduction of infected blood into the CNS by the needle. Alternatively, others have speculated that disruption of the dural barrier may permit hematogenous spread of infection into the CNS without direct vessel trauma. Administration of continuous epidural analgesia often results in blood vessel trauma, and it includes the introduction of a foreign body. Theoretically, this technique could produce a nidus for subsequent infection.

This section focuses on the additional risk for CNS infection in the setting of bacteremia. The epidemiology of iatrogenic meningitis or epidural abscess as well as the discussion of lapses in sterile technique contributing to CNS infection are discussed in Chapter 31.

Laboratory Studies

Carp and Bailey performed a study to assess the risk for meningitis after the performance of dural puncture in bacteremic rodents. In this study, rats were made bacteremic by producing a flank abscess using E. coli bacteria. The bacteremia was similar in magnitude to that which occurs during the early phase of sepsis in humans. Cisternal dural puncture was performed after the onset of bacteremia. After 24 hours, the cisterna magna was drained surgically, and the cerebrospinal fluid (CSF) was cultured for evidence of meningitis. Of the 40 animals that underwent dural puncture during E. coli bacteremia, 12 developed meningitis. None of the 40 bacteremic animals not subjected to dural puncture developed meningitis. Furthermore, dural puncture did not result in infection in the 30 animals without bacteremia. Importantly, none of the 30 bacteremic animals given a dose of gentamicin 15 minutes before dural puncture developed meningitis.

This study is consistent with earlier laboratory studies that observed the development of meningitis after the performance of dural puncture in bacteremic laboratory animals. Although animal models of disease permit careful control of experimental conditions, these studies do not duplicate clinical conditions. Thus, there are limitations in the application of the rat study to clinical practice. First, the level of bacteremia produced in the rats exceeded the transient, low-grade bacteremia that often occurs clinically. Second, although E. coli is a common cause of bacteremia in surgical and obstetric patients, it is an uncommon cause of meningitis. Third, the relative size of the dural tear produced by the 26-gauge needle used in this study is greater in rats than in humans. Fourth, the cisternal site of dural puncture is not used clinically. Fifth, spinal and epidural anesthesia involves the injection of local anesthetics, and these drugs appear to be bacteriostatic. Finally, the investigators knew...
the identity of the organism (E. coli) and also knew that it was susceptible to gentamicin.

In summary, this study suggests that high-grade bacteremia may increase the risk for meningitis after dural puncture. However, antibiotic therapy before dural puncture appears to reduce, if not eliminate, this risk.

Clinical Studies

At least six retrospective clinical studies have evaluated diagnostic lumbar puncture and the risk for meningitis.133-138 (These studies did not evaluate the risk associated with neuraxial anesthesia or analgesia.) These reports provided conflicting conclusions regarding the risk for meningitis after the performance of dural puncture in bacteremic patients. Two studies suggested an association between dural puncture and meningitis.134,136 However both studies had serious methodologic flaws. A study performed during an epidemic of meningitis reported five cases of meningitis with initial negative CSF cultures (with positive blood cultures) and subsequent bacterial meningitis after lumbar puncture. However, they did not evaluate a comparable control group who did not undergo lumbar puncture.133 Teel et al.136 reported an association between lumbar puncture and meningitis only in bacteremic children younger than 1 year of age. Although there is a theoretical risk that a lumbar puncture seeder the meninges at the time of placement, it is also possible in both studies that diagnostic lumbar puncture was performed early in the progression of the disease before the CSF provided diagnostic evidence of infection. The remaining four studies clearly did not support an association between dural puncture and meningitis.134,135,137,138

Undoubtedly some parturients are bacteremic during the administration of epidural or spinal anesthesia, given the frequency with which parturients develop fever and infection during labor. For example, Blanco et al.139 found a 1% incidence of bacteremia in a random sample of patients on the labor ward. Other studies have noted an incidence of bacteremia ranging from 5% to 12% in parturients with chorioamnionitis.41,43-47 Although bacteremia is common, epidural abscess and meningitis rarely present after neuraxial blockade, and no epidemiologic study has clearly established a causal relationship between the performance of dural puncture during bacteremia and the subsequent development of meningitis or an epidural abscess.140

Bader et al.141 retrospectively observed no cases of CNS infection after the administration of epidural or spinal anesthesia for labor or cesarean delivery in 279 patients with chorioamnionitis. Only 43 of these 279 women received antibiotic therapy before the administration of neuraxial anesthesia. At least three women had positive blood cultures consistent with bacteremia, and none of these three women received antibiotics before the administration of anesthesia. Similarly, Goodman et al.31 found no cases of meningitis or epidural abscess among 531 patients with chorioamnionitis (proven by culture or pathologic examination) who received epidural (n = 517) or spinal (n = 14) anesthesia. Eleven of 45 patients with fever before initiation of the neuraxial procedure, and 174 of 229 patients with preexisting leukocytosis, received no antibiotics before instrumentation of the epidural or subarachnoid space.

Together, these clinical studies (combined with evidence in nonfebrile women, presented in Chapter 31) suggest that meningitis and epidural abscess are rare complications of epidural or spinal anesthesia. Furthermore, bacteremia itself does not appear to increase the risk for CNS infection after the administration of neuraxial anesthesia. However, published studies of neuraxial anesthesia in patients with chorioamnionitis were small and retrospective. Given the infrequent occurrence of CNS infection among noninfected patients undergoing neuraxial anesthesia, none of these studies was sufficiently large to exclude the possibility that chorioamnionitis increases the risk for meningitis or epidural abscess. Moreover, the retrospective study design introduces the possibility of selection bias; anesthesia providers may have avoided neuraxial anesthesia in the sickest patients with chorioamnionitis.

Recommendations

The 2017 American Society of Anesthesiologists Practice Advisory for the Prevention, Diagnosis, and Management of Infectious Complications Associated with Neuraxial Techniques recommends performing a complete history, physical examination (including vital signs), and review of laboratory studies to identify patients at risk for infectious complications.142 There is no specific laboratory parameter that precludes the use of neuraxial techniques. In pregnancy, C-reactive protein and erythrocyte sedimentation rate are elevated.143,144 In a meta-analysis of more than 4500 healthy pregnant women, many women had a white blood cell count of greater than 12,000 × 10^6 cells/L in the absence of infection (Fig. 36.2).117 These tests are unreliable to determine infection or severity of infection in pregnant women. We recommend evaluation of the patient’s entire clinical picture to weigh the risks and benefits for performing a neuraxial technique. In our judgment, the anesthesia provider may safely administer spinal or epidural anesthesia to healthy patients at risk for low-grade bacteremia. Appropriate antibiotic therapy may lessen the risk for meningitis or epidural abscess in patients with established infection. Thus, it often is appropriate for the anesthesia provider to request the initiation of antibiotic therapy before administration of neuraxial blockade in accordance with the American Society of Anesthesiologists practice advisory.142 Finally, although the choice of anesthesia must be individualized, it seems prudent to avoid spinal or epidural anesthesia in untreated patients with overt clinical signs of sepsis.

GENITAL HERPES INFECTION

Primary and Secondary Infection

Herpes simplex virus type 2 (HSV-2) causes locally recurring disease that is characterized by asymptomatic periods interrupted by episodes of viral reactivation from sites in the sensory ganglia, resulting in painful vesicular lesions on the
episodes of recurrent infection. However, recurrent infection may result in severe symptoms localized to the site of the lesions on the external genitalia. Prodromal symptoms, including vulvar pain or burning, often precede development of recurrent lesions. Unfortunately, asymptomatic shedding of the virus also may occur in the genital tract. 

**Primary maternal HSV-2 infection** is associated with transient viremia, and up to 2% of pregnant women will be primarily infected during gestation. Additionally, 10% of HSV-2 seronegative women are at risk for acquiring HSV-2 during pregnancy from a seropositive partner. Epidemiologic evidence suggests that HSV-1, formerly associated only with perioral lesions (herpes labialis), is the predominant cause of new genital herpes infections in some populations. Patients with primary infection may have systemic symptoms, including fever, headache, and lymphadenopathy, although asymptomatic primary infection is common. Hepatitis, aseptic meningitis, encephalitis, and cauda equina syndrome are uncommon complications of primary genital herpes infection. During recurrent (i.e., secondary) infection, maternal antibodies prevent the recurrence of viremia. Thus systemic symptoms are less severe—or do not occur at all—during episodes of recurrent infection. However, recurrent infection may result in severe symptoms localized to the site of the lesions on the external genitalia. Prodromal symptoms, including vulvar pain or burning, often precede development of recurrent lesions. Unfortunately, asymptomatic shedding of the virus also may occur in the genital tract.

### Interaction with Pregnancy

During the first 20 weeks of pregnancy, primary genital herpes infection may be associated with an increased risk for pregnancy loss, although cohort studies have disputed the risk for fetal death. The major obstetric concern is the potential for transmission of the virus to the infant at the time of birth. The infant may become infected in one of two ways: intrauterine infection can occur by ascent of the organism after rupture of membranes, or neonatal infection can occur as the fetus comes in direct contact with the virus during vaginal delivery.
delivery.\textsuperscript{146} Neonatal HSV is a life-threatening infection with the potential for permanent CNS sequelae.\textsuperscript{145,146,148,151}

Meta-analysis of seven randomized trials of antepartum antiviral therapy with \textit{acyclovir} or \textit{valacyclovir} demonstrated a reduction in the presence of active genital lesions at delivery (RR, 0.28) and requirement for cesarean delivery (RR, 0.30).\textsuperscript{152} However, these trials could not demonstrate a reduction in neonatal herpes infection (there were no cases in any trial), and failure of suppressive therapy to prevent such transmission has been reported.\textsuperscript{151}

Retrospective studies suggest that the risk for neonatal HSV infection associated with a primary maternal infection is much greater than that associated with recurrent maternal infection or asymptomatic viral shedding.\textsuperscript{148,153–155} The risk for transmission is 30–60\% in the setting of a primary HSV outbreak, 3\% in the setting of active recurrent HSV, and 0.02\% without genital lesions at the time of delivery.\textsuperscript{145} Most likely there is a greater risk that the infant will be exposed to the virus during episodes of primary maternal infection; the lower incidence in cases of recurrent herpes is likely caused by passive transfer of antibodies to HSV from the mother to the fetus.\textsuperscript{153}

\textbf{Obstetric Management}

A large epidemiologic study of 58,362 women provided direct evidence that cesarean delivery dramatically reduces the overall risk for HSV transmission to the neonate when HSV cultures of the cervix and external genitalia taken at the time of labor were positive (OR, 0.14).\textsuperscript{153} Other risk factors for neonatal transmission included primary maternal HSV infection, use of invasive obstetric monitoring, and HSV-1 (compared with HSV-2) infection.\textsuperscript{153}

The American College of Obstetricians and Gynecologists (ACOG) has reviewed the obstetric management of parturients with HSV infection and has concluded that cesarean delivery is indicated in women with active lesions or prodromal symptoms regardless of whether it is a primary or recurrent infection.\textsuperscript{145} In the setting of an active HSV lesion and rupture of membranes near term, a cesarean delivery should be performed as soon as logistically feasible. There is no consensus regarding when the risk for HSV outweighs the risk for preterm delivery in the setting of preterm premature rupture of membranes\textsuperscript{145}; however, in general, expectant management has become standard.

\textbf{Anesthetic Management}

There are at least five published retrospective studies of the use of neuraxial anesthesia in patients with genital HSV infection. These studies reported no serious neurologic sequelae related to the use of neuraxial anesthesia.\textsuperscript{156–160} However, most of the patients in these studies had recurrent (secondary) infection. Two studies\textsuperscript{157,158} were limited to patients with recurrent infection, a third report had a recurrent infection,\textsuperscript{160} and a fourth report\textsuperscript{156} did not indicate whether the patients had primary or recurrent infection. Bader et al.\textsuperscript{155} reported outcomes for 169 women with genital herpes infection who underwent cesarean delivery. Five of the 169 women in this study had primary infections, and three of these women received spinal anesthesia. Of the three women, one had transient, postoperative weakness of the left leg. The authors\textsuperscript{159} stated, “None of the cases of primary infection had associated systemic symptoms; it is therefore possible that some of these cases were actually misdiagnosed recurrent infections. The safety of regional anesthesia in patients with primary HSV infection remains unclear.”

Viremia may accompany primary episodes of genital herpes infection. However, viremia rarely complicates recurrent episodes of genital herpes infection. It is unlikely that a spinal or epidural needle could introduce virus into the CNS in patients with recurrent genital herpes infection. Thus, a consensus exists that it is safe to administer spinal or epidural anesthesia to women with recurrent genital herpes infection and no systemic symptoms. There are insufficient data to allow a definitive recommendation regarding the safety of neuraxial anesthesia in patients with primary infection who may be viremic. If the anesthesia provider is confronted with a patient with primary infection, the theoretical risk for CNS infection should be weighed against the risks associated with alternative methods of analgesia and anesthesia.

Finally, several studies have suggested that spinal or epidural administration of morphine, commonly administered for postcesarean delivery analgesia, increases the incidence of recurrence of oral HSV infection. This phenomenon was confirmed in prospective randomized trials for both epidural\textsuperscript{161} and intrathecal\textsuperscript{162} morphine. The cause is unknown, but some investigators have speculated that pruritus and scratching play a role in reactivation of oral lesions. Boyle\textsuperscript{163} concluded that facial pruritus is a marker of the migration of morphine to the trigeminal nucleus but not the cause of HSV recrudescence. He suggested that immunologic modulation by the opioid within this ganglion is the primary cause of the viral reactivation. Substantial evidence now supports this mechanism.\textsuperscript{164} A case of HSV-1 meningitis after unintentional dural puncture and passage of an intrathecal catheter has been reported.\textsuperscript{165} The patient underwent cesarean delivery with spinal bupivacaine, fentanyl, and morphine; the authors suggested that reactivation of HSV-1 caused by morphine, and the presence of the intrathecal catheter, may have contributed to the infection.\textsuperscript{165} To our knowledge, there are no reports suggesting that epidural or intrathecal administration of opioids increases the risk for recurrent genital herpes infection. However, a possible case of postnatal transmission secondary to maternal reactivation of oral HSV from intrathecal morphine has been reported.\textsuperscript{166}

\textbf{HUMAN IMMUNODEFICIENCY VIRUS}

\textbf{Pathophysiology}

Human immunodeficiency virus (HIV) is a member of the lentivirus subfamily of human retroviruses (i.e., it carries the enzyme reverse transcriptase). This enzyme converts the single-stranded viral RNA into double-stranded DNA, which subsequently can be integrated into the DNA of the infected
cell. This process is error prone, leading to rapid mutation of the virus, which significantly complicates drug therapy. Immune suppression is mainly caused by infection of helper T cells, CD4+ monocytes, and macrophages.\textsuperscript{167} Abnormalities of these elements of the immune system render the HIV patient vulnerable to bacterial, viral, fungal, parasitic, and mycobacterial infection. In addition, for reasons that are not entirely clear, patients infected with HIV are susceptible to several malignancies (e.g., Kaposi’s sarcoma, B-cell lymphoma, invasive cervical carcinoma). Clinical manifestations can result from the HIV infection itself, opportunistic infection, secondary malignancy, or long-term exposure to antiretroviral therapy.

**Clinical Manifestations**

**Neurologic involvement** can occur at any time during HIV infection. Viral particles can be isolated from the cerebrospinal fluid (CSF) at the time of primary infection.\textsuperscript{166} Patients with HIV infection typically have CSF abnormalities, including the local synthesis of HIV antibody and the presence of HIV particles or viral nucleic acid.\textsuperscript{169} This is an important consideration when one is determining the risk for introducing virus into the CNS during the performance of neuraxial anesthesia in an asymptomatic patient. It is almost certain that CNS infection has already occurred.

The manifestations of nervous system involvement vary with the stage of the disease. During initial systemic HIV infection, a variety of CNS disorders may occur. Headache, photophobia, and retro-orbital pain are common, while more severe disorders such as cranial and peripheral neuropathies, demyelinating polyneuropathy, and aseptic meningoencephalitis have been reported.\textsuperscript{170} The late stages of HIV infection are marked by significant neurologic deterioration in almost all patients caused by meningitis, encephalopathy, the AIDS dementia complex, or focal brain disorders. Underlying diagnoses include tuberculosis, Cryptococcus, metastatic lymphoma, cytomegalovirus (CMV), herpes simplex virus, toxoplasmosis, primary CNS lymphoma, and progressive multifocal leuкоencephalopathy, an opportunistic viral infection that causes selective destruction of white matter tracts. Myelopathy, peripheral neuropathy, chronic pain, and autonomic neuropathy may also occur.\textsuperscript{171} Finally, neurologic side effects such as headache and peripheral neuropathy of antiretroviral therapies also may occur. A baseline neurologic exam should be assessed and documented before performing neuraxial techniques.

**Pulmonary Abnormalities**

The pulmonary manifestations of HIV disease are caused not by a direct effect of the virus but, rather, by the opportunistic infections associated with the disease. The most prominent of these is Pneumocystis jiroveci (formerly known as Pneumocystis carinii), a fungal organism.\textsuperscript{172} Despite widespread exposure to the organism, symptomatic Pneumocystis pneumonia (PCP) is typically seen only in patients with severe immune suppression. Pneumonia is a leading cause of cause of death in HIV-infected pregnant women, with mortality as high as 50% for Pneumocystis jiroveci pneumonia.\textsuperscript{173,174} The impairment of humoral immunity is responsible for a higher incidence of bacterial pneumonia caused by encapsulated organisms (e.g., Streptococcus pneumoniae, Haemophilus influenzae).\textsuperscript{175} Finally, although less common than PCP, pneumonia secondary to other fungal organisms (e.g., Aspergillus, Cryptococcus, Coccidioides) is more common in patients infected with HIV than in the general population.\textsuperscript{175} Reactivation of latent tuberculosis is common in patients with HIV infection; immunosuppression may also increase susceptibility to acquiring tuberculosis from an infectious individual.\textsuperscript{176}

**Gastrointestinal Abnormalities**

Gastrointestinal disturbances occur at some time in almost all patients with HIV infection. Nausea and vomiting are common side effects of most antiretroviral medications. Painful or difficult swallowing is typically caused by herpetic, CMV, or candidal esophagitis; the contribution of these disorders to gastroesophageal reflux is unclear.\textsuperscript{177} Severe diarrhea resulting from infection with CMV, HSV, Shigella, Salmonella, Candida, Cryptosporidium, Giardia, Mycobacterium avium complex (MAC), or HIV itself can lead to significant cachexia and electrolyte abnormalities. Finally, hepatobiliary disease may also occur. Causes of parenchymal liver disease include hepatitis B and C, CMV, mycobacterial infection (both Mycobacterium tuberculosis and MAC), and Cryptococcus.

**Hematologic Abnormalities**

HIV infection is associated with hematologic abnormalities that affect each of the peripheral cell lines.\textsuperscript{178} Leukopenia is a hallmark of the disease, especially the depletion of CD4+ lymphocytes; qualitative alterations in the functions of neutrophils and macrophages also occur. Anemia is also quite common. Causes include direct HIV infection of erythroid precursors, suppression of erythropoiesis caused by inappropriate release of tumor necrosis factor, infiltration of bone marrow with MAC or malignancy, and occult gastrointestinal blood loss.

Additionally, coagulation disturbances are often seen in patients with HIV. Immune thrombocytopenia is common and typically is only mildly symptomatic. The activated partial thromboplastin time may be prolonged because of the presence of the lupus anticoagulant; this finding is linked to a higher incidence of major thromboembolic events in HIV-infected patients. Finally, many of the antiretroviral agents and other drugs used in these patients have hematologic toxicity.

**Cardiovascular Abnormalities**

Clinically significant cardiovascular disease is rare in patients with HIV. Pericarditis or pericardial effusion have been reported to be the most prevalent cardiovascular disorders seen in HIV-infected patients.\textsuperscript{179} The most common etiology appears to be mycobacterial infection; CMV, HSV, Kaposi’s sarcoma, malignant lymphoma, and HIV itself have also been implicated.\textsuperscript{180} Pulmonary hypertension can develop secondary
to repeated episodes of PCP and can also be a consequence of cytokine-mediated endothelial injury.79 Direct myocardial involvement—typically, focal myocarditis—is identified in 15% to 50% of autopsy studies, but clinical myocarditis or cardiomyopathy is rare.79 Infective endocarditis among patients with HIV occurs almost exclusively in intravenous drug users. Finally, the elevations in serum cholesterol and triglyceride concentrations produced by antiretroviral agents appear to increase the risk for coronary artery disease in patients receiving these drugs.181

### Endocrine Abnormalities

Patients with AIDS frequently have abnormal thyroid function test results, similar to the findings in patients with other chronic illnesses, yet clinical hypothyroidism is unusual. Insulin resistance and diabetes are increasingly recognized as consequences of HIV infection and antiretroviral treatment.182 There is a relatively high incidence of pathologic findings in the adrenal gland at autopsy, yet clinical evidence of glucocorticoid insufficiency is rare.

### Renal Abnormalities

Patients with HIV are at risk for acute renal failure secondary to sepsis, dehydration, and drug toxicity.183 A common cause of chronic renal insufficiency is proliferative glomerulonephritis secondary to deposition of immune complexes containing HIV antigen within the glomeruli. Renal failure may also occur because of HIV-associated nephropathy.184 This entity, seen almost exclusively in patients of African descent, is characterized by a focal segmental glomerulosclerosis. Hypertension is uncommon, deterioration of renal function is extremely rapid, and the long-term prognosis is worse than that seen in renal failure from other causes. The underlying cause appears to be direct infection of renal cells by HIV. Antiretroviral therapy appears to modify the course of the disease.184

### Interaction with Pregnancy

With the improvement in screening and treatment for HIV, the number of pregnancies in HIV-infected women is increasing.185 The estimated number of births to all women living with HIV (diagnosed or undiagnosed) in the United States in 2006 was 8700 (95% CI, 8400 to 8800).185 In the setting of opt-out HIV screening as well as risk-reducing strategies such as antiretroviral therapy (ART), scheduled cesarean delivery, and avoidance of breast-feeding, the number of perinatal transmissions of HIV in the United States has decreased from 216 (95% CI, 206 to 230) in 2002 to 69 (95% CI, 60 to 83) in 2013, with perinatal HIV infections now estimated at 1.75 per 100,000 live births.186,187

Available data are mixed whether HIV infection increases the risk for adverse pregnancy outcomes (e.g., low birth weight, small for gestational age, and preterm delivery).188,189 ART, especially protease inhibitor–based ART, may increase the risk for preterm delivery,190–192 but does not appear to lead to low birth weight, small for gestational age, or stillbirth.192,193 Likewise, no evidence suggests that pregnancy accelerates clinical deterioration in the HIV-infected patient or that the viral RNA load changes significantly during pregnancy.193,194,195

### Obstetric Management

Antenatal testing for HIV is part of routine prenatal screening, ideally completed in the first trimester of pregnancy, or as early as possible during the pregnancy, using an opt-out approach.196 Repeat HIV testing is recommended in the third trimester for patients at high risk for acquiring HIV infection. Women with undocumented HIV status should have rapid HIV testing upon presentation for delivery to guide appropriate treatment to prevent vertical transmission (Fig. 36.3).196 For those diagnosed with HIV, serial plasma HIV RNA levels, CD4+ T lymphocyte cell counts, and HIV drug-resistance assays are used to optimize antiretroviral therapy throughout pregnancy, and plasma HIV RNA levels repeated at 34 to 36 weeks’ gestation are used to guide decisions about mode of delivery and treatment in the newborn.

### Intrapartum Antiretroviral Therapy/Prophylaxis

Women should continue their antepartum ART drug regimen without interruption during labor and delivery to provide maximal virologic suppression and to minimize the chance of development of drug resistance.192

To minimize vertical transmission, IV zidovudine (AZT) should be administered as soon as possible upon arrival for delivery to HIV-infected women with a viral load that is high (HIV RNA greater than 1000 copies/mL) or unknown, with a goal of at least 3 hours of administration before delivery.192,197 For women with an HIV RNA less than or equal to 1000 copies/mL but still with a detectable viral load (50 to 1000 copies/mL), IV AZT is not necessary, but may be considered, especially in cases of unclear compliance with medications or a recent increase in viral load.192 Multiple studies have demonstrated that in the setting of virologic suppression (i.e., HIV RNA below 50 copies/mL), the addition of IV AZT did not provide additional protection against vertical transmission and therefore is not recommended.96–201 Irrespective of viral load, the clinician may use intrapartum IV AZT based on clinical judgment.192

### Mode of Delivery

For women with plasma HIV RNA greater than 1000 copies/mL near term, the ACOG recommends scheduled cesarean delivery at 38 weeks’ gestation to reduce the risk for labor or rupture of membranes before delivery.197 IV AZT administration (loading dose followed by infusion) should be started 3 hours before the scheduled cesarean delivery, allowing adequate time to reach equilibrium across the placenta, although cord blood zidovudine levels required to prevent perinatal transmission of HIV are currently unknown.202 Similar to women delivering vaginally, if the viral load is less than or equal to 1000 copies/mL at the time of cesarean delivery (i.e., the cesarean is not for the indication of maternal HIV), IV AZT is not necessary, but may be considered (see Fig. 36.3).
the use of methylergonovine maleate, which is a major substrate of cytochrome P (CYP) 450 3A4, should be avoided, if possible, in women receiving CYP450 3A4 enzyme inhibitors. CYP450 3A4 enzyme inhibitors include protease inhibitors (e.g., ritonavir, indinavir, nelfinavir), certain nonnucleoside reverse transcriptase inhibitors (e.g., delavirdine), and cobicistat. There have been reports of severe vasospasm leading to cerebral and extremity ischemia with concurrent use of ergot alkaloid drugs and CYP450 3A4 inhibitors. Conversely, in women taking a CYP450 3A4 enzyme inducer (e.g., nevirapine, efavirenz, or etravirine), the efficacy of methylergonovine may be decreased.

Finally, there is considerable evidence that breast-feeding may double the rate of perinatal transmission in women with established HIV infection. Thus, breast-feeding should be discouraged unless bottle-feeding is not a safe alternative, as is true in many developing countries (see Chapter 14).

**Anesthetic Management**

**Neuraxial Anesthesia**

Whether HIV-infected pregnant women are prone to the occurrence of infection after administration of neuraxial anesthesia is an important concern. Hughes et al. performed a study of 30 HIV-positive parturients, of whom 18 received neuraxial anesthesia and 12 did not. There was no evidence of accelerated disease progression in either group, and there were no neurologic or infectious complications in either group immediately after delivery and at 4 to 6 months postpartum. A later study demonstrated no postoperative
changes in viral load or CD4+/CD8+ lymphocyte ratio and no increased hemodynamic instability or blood loss in HIV-infected patients undergoing elective cesarean delivery with spinal anesthesia.213 The prevention of infectious complications of neuraxial anesthesia depends on strict aseptic technique, which should include handwashing with an alcohol-based antiseptic solution, removal of jewelry (e.g., rings, watches), and wearing sterile gloves, facemask, and hat (see Chapters 12 and 31). The CDC recommends that “universal blood and body-fluid precautions” should be used in the care of all patients including goggles when anticipating contact with blood or bodily fluids.216,217 For cases of occupational exposure, please refer to the CDC guidelines for the management of healthcare worker exposures to HIV and recommendations for postexposure prophylaxis.217,218

Some physicians may question whether it is prudent to administer neuraxial anesthesia to a patient who could develop neurologic deficits at some time in the future and whether these deficits might be ascribed to the neuraxial anesthetic technique. Because such deficits are unlikely to be temporally related to the anesthesia, this does not seem to be a significant concern. Further, it seems cruel to deny the most effective intrapartum analgesic techniques to HIV-positive women simply because of fear of future litigation.

Despite the use of small-gauge, pencil-point spinal needles, and despite careful technique during administration of epidural anesthesia, post-dural puncture headache (PDPH) remains a problem in pregnant patients (see Chapter 30). Clearly, the onset of headache and photophobia in an immunosuppressed patient who has recently received a major neuraxial anesthetic can be worrisome, but the typical postural nature of a PDPH should allay fears of bacterial meningitis. Once the diagnosis of PDPH is made, conservative therapy and pharmacologic interventions may be used. However, the “gold standard” for treatment of PDPH is an autologous epidural blood patch. Some physicians have expressed concern that the introduction of HIV-infected blood into the neuraxis might lead to the introduction of HIV into a previously uninfected CNS.219 Demonstration of subarachnoid extension of an epidural blood patch on magnetic resonance imaging heightens these concerns.220 Even though CNS infection occurs quite early in the course of HIV disease, even in asymptomatic patients, it seems prudent to acknowledge the possibility that an epidural blood patch could accelerate the CNS manifestations of the disease. This question was addressed in a study of six seropositive patients who experienced PDPH after diagnostic lumbar puncture and who subsequently received an epidural blood patch.221 These patients subsequently underwent serial neuropsychological testing for as long as 2 years. The investigators stated that “none of these six subjects had a decline in neurocognitive performance or other adverse neurologic or infectious sequelae” during the period of the study. Although these numbers are small and this study has never been repeated, it provides the best evidence to date of the safety of epidural blood patch in an HIV-infected patient.

General Anesthesia

As with neuraxial anesthesia, it is appropriate to ask whether patients with HIV might be more susceptible to the infectious (e.g., pulmonary) complications of general anesthesia. No published study has addressed this question. However, it seems appropriate to handle the endotracheal tube in a sterile manner as possible and to minimize the duration of postoperative ventilation. Care should also be taken to maintain sterility of intravenous lines by using a stopcock for injections, placing caps when the stopcock is not in use, and not allowing the IV line to touch the floor.

Another question involves the effect of general anesthesia on immune function. Several published studies suggest that general anesthesia can transiently depress immune function, but this depression appears to be clinically insignificant in healthy patients.222 It is appropriate to ask whether this effect might be exaggerated to the point of clinical significance in patients with HIV disease. Studies on this issue are lacking. At present, it would be inappropriate to recommend one anesthetic technique over another on the basis of their effects on immune function.223

EMERGING GLOBAL ILLNESS

Outbreaks such as the H1N1 influenza virus pandemic, the Zika virus in Brazil and surrounding areas, and the Ebola virus in West Africa have highlighted the vulnerability of pregnant women to epidemics of infectious disease. Pregnant women have altered immunity, which leads to increased susceptibility for infectious diseases as well as increased risk for poor outcomes in the setting of infection. This was highlighted in the H1N1 pandemic, as noted earlier in this chapter. Additionally, infection or treatment or both can have teratogenic effects. The possible teratogenic effect of infection itself was highlighted by the Zika virus pandemic and the association with fetal microcephaly.224,225 And unfortunately, a review by Beigi226 noted that in the recent Ebola outbreak, the high mortality rate in pregnancy may have been due in part to reluctance to care for pregnant women with Ebola. This reluctance may in part be from the knowledge that Ebola RNA has been isolated from amniotic fluid, cord blood, and the placenta, increasing the risk for health care worker infection at the time of delivery.226,227 In times of infectious disease epidemics, pregnant women are frequently among the most vulnerable populations.

**KEY POINTS**

- Fever may be produced by endogenous pyrogens released from immune effector cells in response to infection.
- Maternal fever, with or without infection, may cause fetal neurologic injury.
• Pyelonephritis and chorioamnionitis are the antepartum infections most likely to result in maternal and perinatal morbidity and mortality.
• Normal physiologic changes in pregnancy make it challenging to diagnose sepsis.
• Septic shock is an uncommon but devastating complication of maternal infection that demands broad-spectrum antibiotic therapy, aggressive hemodynamic support, and in some cases, surgical intervention.
• The anesthesia provider may safely administer epidural or spinal analgesia or anesthesia to patients at risk for transient bacteremia or with an established infection, provided there is no evidence of frank sepsis. However, it seems prudent to begin antibiotic therapy before the administration of anesthesia in patients with established infection.
• Recurrent genital herpes infection does not contraindicate the administration of neuraxial anesthesia.

• Spinal and epidural morphine administration is associated with reactivation of oral herpes simplex virus.
• HIV infection eventually can be expected to involve every organ system. Central nervous system involvement occurs as early as the period of initial infection and seroconversion.
• Highly active antiretroviral therapy during pregnancy can significantly reduce the rate of vertical transmission of HIV infection to the fetus.
• Utilization of AZT as well as scheduled cesarean delivery can provide further protection against vertical transmission in women with greater than 1000 copies of viral RNA per mL of plasma, and AZT may be of benefit in women with lower viral loads as well.
• Neuraxial anesthesia and autologous blood patch are safe in the HIV-infected parturient.

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1. Wunderlich C. Das verhalten der eigenwärme in krankheiten. Leipzig, Germany, Ott Wigard, 1868.


CHAPTER OUTLINE

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Obstetric hemorrhage is the most common cause of maternal mortality worldwide, accounting for roughly 15% of maternal deaths.1 The World Health Organization estimates that severe hemorrhage complicates 10.5% of live births globally and carries with it a case-fatality rate of 1%.1 The rates of maternal death and death caused by hemorrhage vary widely throughout various regions of the world (see Chapter 39).1 In the United States, hemorrhage accounts for 11.4% of pregnancy-related deaths (approximately 1.9 pregnancy-related deaths caused by hemorrhage per 100,000 live births).2 Hemorrhage is the most common cause for admission of an obstetric patient to an intensive care unit and is a risk factor for myocardial ischemia and infarction, and stroke.3,4 Organ dysfunction complicates 16% of cases of obstetric hemorrhage accompanied by transfusion of 5 or more units of packed red blood cells (PRBCs).5 Hemorrhage and severe morbidity caused by hemorrhage are increasing in the United States and other high-resource countries, primarily caused by increases in postpartum, rather than antepartum, hemorrhage.6,7 The explanation for this acceleration is not entirely clear but appears to be related to rising rates of postpartum uterine atony as well as increases in abnormal placentation coincident with the rise in cesarean delivery rates.6,8,11 The majority of hemorrhage-related adverse outcomes are considered preventable.12

MECHANISMS OF HEMOSTASIS

Uterine contraction, stimulated by endogenous oxytocic substances released after delivery, represents the primary mechanism for controlling blood loss at parturition. Uterine tetany creates shearing forces that cleave the placenta from the uterine wall through the layer of the uterine decidua (see Fig. 4.3). In addition, uterine contraction constricts the spiral arteries and placental veins supplying the myometrium and supplying the placental bed.

After disruption of vascular integrity, mechanisms of coagulation include (1) platelet aggregation and plug formation, (2) local vasoconstriction, (3) clot polymerization, and (4) fibrous tissue fortification of the clot. Platelet activation and aggregation occur rapidly after endothelial damage. Activated platelets release adenosine diphosphate, serotonin, catecholamines, and other factors that promote local vasoconstriction and hemostasis. These factors also activate the coagulation cascade. The end result of the cascade is conversion of fibrinogen to fibrin and stabilization of the blood clot (see Chapter 44).

ANTEPARTUM HEMORRHAGE

Antepartum vaginal bleeding may occur in as many as 25% of pregnant women; fortunately, only a fraction of these patients experience life-threatening hemorrhage.13 The majority of cases occur during the first trimester. The causes of antepartum hemorrhage range from cervicitis to abnormalities in placentation, including placenta previa and placental abruption. The greatest threat of antepartum hemorrhage is not to the mother but to her fetus. Several decades ago, vaginal bleeding during the second and third trimesters was associated with perinatal mortality rates as high as 80%. More
recent data suggest that antepartum bleeding secondary to placenta previa and placental abruption results in far fewer neonatal deaths than previously reported.14,15

### Placenta Previa

Placenta previa occurs when the placenta covers the cervix. In the past, classification was made on the basis of the relationship between the placenta and the cervical os, using terms such as total, partial, and marginal. With advances in transvaginal ultrasonography allowing for precise localization of the placental edge relative to the cervical os, these terms are being used less often. Instead, if any portion of the placenta overlies the os, it is referred to as a previa, and any placenta near the os is termed low-lying.16,17

### Epidemiology

The incidence of placenta previa varies throughout the world but is estimated to be 1 in 200 pregnancies at term, corresponding to a prevalence of 4.0 per 1000 births.18 The exact cause is unclear, but prior uterine trauma (e.g., scar from prior cesarean delivery) is a common finding. The placenta may implant in the scarred area, which typically includes the lower uterine segment. Conditions associated with placenta previa include multiparity, advanced maternal age, smoking history, male fetus, previous cesarean delivery or other uterine surgery, and previous placenta previa.16,17 Asian-American women are at increased risk for placenta previa compared with white women in the United States.20 The presence of placenta previa increases the likelihood of fetal anomalies, neurodevelopmental delay, sudden infant death syndrome, and the risk that the mother will require a peripartum hysterectomy.14,21,22

### Diagnosis

Transvaginal ultrasonography is the “gold standard” for diagnosis of placenta previa. Routine assessment of the relationship between the placenta and cervix has nearly eliminated the need for double setup examination (i.e., vaginal examination with all clinicians prepared for immediate cesarean delivery).17 Measuring the distance from the placental edge to the internal os predicts the likelihood of antepartum hemorrhage and need for cesarean delivery.23,24 Magnetic resonance imaging (MRI) is also useful for the diagnosis of placenta previa, but its use is not practical in most cases of antepartum hemorrhage.

The classic clinical sign of placenta previa is painless vaginal bleeding during the second or third trimester. All parturients with painless vaginal bleeding after 20 weeks’ gestation should be assumed to have placenta previa until proven otherwise. Digital or speculum examination should be avoided until ultrasonography excludes abnormal placentation. Placenta previa diagnosed in asymptomatic patients before the third trimester frequently resolves as pregnancy progresses. In fact, ninety percent of placentas identified as low lying in early pregnancy will normalize by the third trimester.25 The lack of abdominal pain and/or absence of abnormal uterine tone helps distinguish placenta previa from placental abruption. The absence of these factors does not exclude abruption, however, and patients with placenta previa are at risk for coexisting placental abruption.

### Obstetric Management

Obstetric management is based on the severity of vaginal bleeding and the maturity and status of the fetus. Active labor, persistent bleeding, a mature fetus (gestational age 36 weeks or greater), or nonreassuring fetal status should prompt delivery.26 The fetus is at risk from two distinct pathophysiologic processes: (1) progressive or sudden placental separation that causes uteroplacental insufficiency and (2) preterm delivery and its sequelae. The first episode of bleeding characteristically stops spontaneously and rarely causes maternal shock or fetal compromise. Expectant management in the hospital has been shown to prolong pregnancy by an average of 4 weeks after the initial bleeding episode.26 Maternal vital signs are assessed frequently, and the hemoglobin concentration is checked at regular intervals. Fetal evaluation involves frequent performance of a non-stress test or biophysical profile, and ultrasonographic assessment of fetal growth. Hemorrhage may be prevented by limitations on physical activity and avoidance of vaginal examinations and coitus, although the evidence supporting these measures is limited.

Outpatient management has resulted in good outcomes in carefully selected patients.27 Outpatient management is reserved for stable patients without bleeding in the previous 48 hours who have both telephone access and the ability to be transported quickly to the hospital. Expectant management requires immediate access to a medical center with 24-hour obstetric and anesthesia coverage and a neonatal intensive care unit.26

In most cases of placenta previa diagnosed between 24 and 34 weeks’ gestation, a corticosteroid (e.g., betamethasone) is administered to accelerate fetal lung maturity.26 A significant number of patients with placenta previa have preterm labor, which may provoke bleeding. The use of tocolysis in women with placenta previa is controversial. Some obstetricians may administer tocolytic therapy to decrease preterm uterine contractions with the goal to stabilize antepartum bleeding. Ritodrine has been shown to prolong pregnancy in women with placenta previa, but no studies have confirmed any decrease in the frequency or severity of vaginal bleeding.26,24 Obstetricians must balance the potential cardiovascular consequences of tocolytic therapy in the event of maternal hemorrhage against the consequences of preterm delivery. Tocolytic therapy is not recommended for patients with uncontrolled hemorrhage or those in whom placental abruption is suspected. Although expectant management reduces the risk for prematurity, it does not eliminate it from occurring.

Fetuses of women with placenta previa may be at risk for other complications, including fetal growth restriction (previously known as intrauterine growth restriction).28 Several factors may account for the association between placenta previa and fetal growth restriction. First, the lower uterine segment may be less vascular than normal sites of placental
implantation. Second, the placenta often is adherent to an area of fibrosis tissue. Third, patients with placenta previa have a higher incidence of first-trimester bleeding, which may promote a partial placental separation, reducing the surface area for placental exchange. Fourth, although the blood loss from placenta previa is almost entirely maternal, trauma to the placenta with vaginal examination or coitus may result in some fetal blood loss, which could restrict fetal growth. Additionally, a higher incidence of congenital anomalies in the fetuses of women with placenta previa may occur.

Experts recommend that women with a placental edge–to–internal os distance greater than 1 cm be offered a trial of labor because the risk for antepartum hemorrhage and need for cesarean delivery during labor are low in this setting. Parturients with a total previa, placental edge–to–internal os distance less than 1 cm, and/or significant bleeding will require abdominal delivery, as will some patients with nonreassuring fetal status.

**Anesthetic Management**

All patients admitted with vaginal bleeding should be evaluated by an anesthesiology provider on arrival. Special consideration should be given to the airway examination, intravascular volume assessment, and history of previous cesarean delivery or other procedures that create a uterine scar. Volume resuscitation should be initiated using a non–dextrose-containing balanced salt solution (e.g., lactated Ringer’s, normal saline). Women with placenta previa may remain hospitalized for some time before delivery, and at least one intravenous catheter should be maintained if bleeding is recurrent or imminent delivery is anticipated. Hemoglobin concentration measurement may be indicated after a bleeding episode. Availability of cross-matched blood should be ensured. The American Association of Blood Banks (AABB) recommends repeating such tests every 3 days in pregnant women because of the small but finite risk for developing a new alloantibody during pregnancy. The use of lower-extremity sequential compression devices may decrease the risk for venous thromboembolism in patients on bed rest. Pharmacologic prophylaxis may be withheld because of the risk for bleeding.

The choice of anesthetic technique depends on the indication and urgency for delivery, the severity of maternal hypovolemia, and the obstetric history (e.g., prior cesarean delivery and risk for placenta accreta). Few reliable data exist to guide anesthetic choice in the context of abnormal placentation. Survey data reveal that obstetric anesthesia providers prefer neuraxial anesthesia in patients with placenta previa without active bleeding or intravascular volume deficit. A randomized controlled trial comparing epidural with general anesthesia for cesarean delivery in women with placenta previa in the absence of active bleeding demonstrated that epidural anesthesia was associated with (1) more stable blood pressure after delivery and (2) lower transfusion rates and transfusion volumes with similar hematocrit measurements the day after surgery. Operative times, estimated blood loss, urine output, and Apgar scores were similar in the two groups. Combined spinal-epidural anesthesia, or even single-shot spinal anesthesia, is considered acceptable for patients without active bleeding.

Patients who have placenta previa—even without active preoperative bleeding—remain at risk for increased intrapartum blood loss for at least three reasons. First, the obstetrician may injure an anteriorly located placenta during uterine incision. Second, after delivery, the lower uterine segment implantation site, lacking uterine muscle compared with the fundus, does not contract as well as the normal fundal implantation site. Third, a patient with placenta previa is at increased risk for placenta accreta, especially if there is a history of previous cesarean delivery (see later discussion (Table 37.1)). For these reasons, it may be advisable to place two large-bore intravenous catheters before the start of either elective or emergent cesarean delivery. No consensus exists on the need for blood product availability in these patients, but it seems prudent to order a blood type and screen and ensure blood product availability. If preoperative imaging indicates the possibility of a placenta accreta, preparation for massive blood loss should be undertaken.

Patients with placenta previa and active preoperative bleeding represent a significant challenge for the anesthesiology care team. Frequently, such patients have just presented to the hospital and there is minimal time for evaluation. In these cases, patient evaluation, resuscitation, and preparation for operative delivery all proceed simultaneously. Because the placental site is the source of hemorrhage, the bleeding may continue unabated until the placenta is removed and the uterus contracts. Preoperative evaluation requires careful assessment of the parturient’s airway and intravascular volume. Two large-bore intravenous catheters should be placed, and blood products should be ordered as necessary. Blood administration sets, fluid warmers, and equipment for invasive monitoring should be immediately available. Initially, non–dextrose-containing crystalloid or colloid is infused rapidly. In some cases, the patient requires transfusion before cross-matched blood is available, and type-specific blood or type O, Rh-negative blood must be administered.

Rapid-sequence induction of general anesthesia is the preferred technique for bleeding patients. The choice of intravenous induction agent depends on the degree of cardiovascular instability. In patients with severe hypovolemic

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**TABLE 37.1 Risk for Placenta Accreta in Patients with Placenta Previa: Relationship to Number of Prior Cesarean Deliveries**

<table>
<thead>
<tr>
<th>Number of Prior Cesarean Deliveries</th>
<th>% of Patients with Placenta Accreta</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
</tr>
<tr>
<td>4 or more</td>
<td>67</td>
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</table>

shock, tracheal intubation may be accomplished without an induction agent, although this situation is rare. A low dose of propofol should be administered in women with ongoing hemorrhage. Ketamine and etomidate are useful alternative induction agents for hemodynamically unstable patients. Ketamine 0.5 to 1.0 mg/kg has an excellent record of safety and efficacy in obstetric anesthesia practice. Emergence phenomena such as hallucinations and nightmares are uncommon when the dose does not exceed 1 mg/kg. Ketamine may cause direct myocardial depression, which can result in hypotension in patients with severe hypovolemia. Etomidate 0.3 mg/kg causes minimal cardiac depression and is safe for use in obstetric patients. A low dose is appropriate in patients with severe hemorrhage. Disadvantages of etomidate include pain on administration, myoclonus, and possible adrenocortical suppression.

The agent(s) chosen for maintenance of anesthesia depends on maternal cardiovascular stability. In patients with modest bleeding and no fetal compromise, 50% nitrous oxide in oxygen can be administered with a low concentration of a volatile halogenated agent before delivery to prevent maternal awareness. The concentration of nitrous oxide or halogenated agent can be reduced or omitted in cases of severe maternal hemorrhage or fetal compromise. In these cases, a benzodiazepine such as midazolam may be administered to provide amnesia.

Oxytocin should be administered by intravenous infusion immediately after delivery. The relatively amuscular lower uterine segment implantation site does not contract as efficiently as the uterine fundus. If bleeding continues, it may be best to discontinue the volatile halogenated agent completely after delivery and to substitute 70% nitrous oxide and an intravenous opioid or ketamine. These drugs, along with small doses of midazolam, can be administered without causing significant uterine relaxation or cardiovascular depression. A low-dose infusion of propofol and/or ketamine may be considered, with the caution that propofol causes decreased uterine contractility in a dose-dependent manner. Some anesthesia providers contend that bispectral index (BIS) monitoring may be useful in lowering the risk for intraoperative awareness in cases in which the volatile anesthetic agent has been discontinued, although this issue is a matter of some dispute.

If the placenta does not separate easily, placenta accreta may exist. In such cases, massive blood loss and the need for cesarean hysterectomy should be anticipated (see later discussion). The need for invasive hemodynamic monitoring varies among patients. An indwelling arterial catheter is useful for patients with hemodynamic instability or for those who require frequent determination of hematocrit and blood gas measurements.

**Placental Abruption**

Placental abruption is defined as complete or partial separation of the placenta from the decidua basalis before delivery of the fetus. Maternal hemorrhage may be revealed by vaginal bleeding or may be concealed behind the placenta. Fetal compromise occurs because of the loss of placental surface area for maternal-fetal exchange of oxygen and nutrients.

**Epidemiology**

Placental abruption complicates 0.4% to 1.0% of pregnancies. The United States incidence increased through the 1990s, particularly among African-American women, and then stabilized after 2000. The causes of abruption are not well understood, but several conditions are known risk factors for abruption (Box 37.1).

**Diagnosis**

The classic presentation of abruption consists of vaginal bleeding, uterine tenderness, and increased uterine activity, but not all symptoms are always present. In cases of concealed abruption, vaginal bleeding may be absent, and gross underestimation of maternal hypovolemia can occur. Bleeding may be painless. In some cases, abruption may manifest as idiopathic preterm labor. Patients may have a variety of nonreassuring fetal heart rate (FHR) patterns, including bradycardia, late or variable decelerations, and loss of variability. The diagnosis of placental abruption is primarily clinical, but in a subset of cases, ultrasonography may help confirm it. Ultrasonography is highly specific for placental abruption (96%), but it is not very sensitive (24%). It is also useful for determining placental location, which can exclude placenta previa as a cause of vaginal bleeding. The ultrasonographic examination can ascertain whether a retroplacental or subchorionic hematoma is present. Normal findings do not exclude the diagnosis of placental abruption.

**Pathophysiology**

Complications of placental abruption include hemorrhagic shock, coagulopathy, and fetal compromise or demise. One-third of coagulopathies in pregnancy are attributable to abruption, and coagulopathy is associated with fetal demise. Placental tissue displays tissue factor and other procoagulant pathways.

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**BOX 37.1 Conditions Associated with Placental Abruption**

<table>
<thead>
<tr>
<th>Obstetric Conditions</th>
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<tbody>
<tr>
<td>Advanced maternal age</td>
</tr>
<tr>
<td>Multiparity</td>
</tr>
<tr>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
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<table>
<thead>
<tr>
<th>Maternal Comorbidities</th>
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<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Acute or chronic respiratory illness</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Maternal cocaine use</td>
</tr>
<tr>
<td>Maternal or paternal tobacco use</td>
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<table>
<thead>
<tr>
<th>Trauma</th>
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<tbody>
<tr>
<td>Direct (i.e., blunt abdominal)</td>
</tr>
<tr>
<td>Indirect (e.g., acceleration/deceleration injury)</td>
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</table>
substances on cell membranes, and it is surmised that when bleeding at the decidual-placental interface (i.e., abruption) occurs, these thromboplastic substances are released into the central circulation, resulting in consumptive coagulopathy and disseminated intravascular coagulation (DIC).

Although some cases of abruption occur acutely (e.g., in the setting of trauma), many abruptions complicate chronic, long-standing placental abnormalities. Investigators have noted strong associations between abruption, fetal growth restriction, and preeclampsia, and all three conditions share similar risk factors. Histologic evidence of shallow trophoblastic invasion of the spiral arteries supports the conclusion that “ischemic placental disease” may underlie chronic placental hypoxia, leading to preeclampsia, fetal growth restriction, and abruption. Decidual necrosis at the placental margin and large placental infarcts are the most common abnormalities among women who suffer placental abruption and fetal demise. Infants who die typically have 14% less placental weight, 8% less body weight, and 3% shorter body length than surviving control infants of the same gestational age. The major risks for the fetus are hypoxia and prematurity. Separation of all or part of the placenta reduces gas exchange surface area and can lead to fetal death. The risk for intrauterine fetal demise increases as the detachment area increases, particularly when the location of bleeding is retroplacental rather than subchorionic. Inadequate transplacental oxygen exchange is exacerbated by maternal hypotension, which decreases uteroplacental blood flow. The increased perinatal mortality rate associated with placental abruption reflects both a high risk for fetal death and the consequences of preterm birth.

**Obstetric Management**

The definitive treatment is delivery of the infant and placenta, but the degree of maternal and fetal compromise and estimated gestational age determine the timing and route of delivery. If the fetus is at or near term and both maternal and fetal status are reassuring, vaginal delivery may be appropriate. If the patient is preterm, the extent of abruption is minimal, and the mother and fetus show no signs of compromise, the patient may be hospitalized and the pregnancy allowed to continue to optimize fetal maturation. The obstetrician may administer a corticosteroid to promote fetal lung maturity. If the mother develops hemodynamic instability or coagulopathy, or the fetal status becomes nonreassuring, urgent cesarean delivery may become necessary. Vaginal delivery is preferred for patients with intrauterine fetal demise.

**Anesthetic Management**

If abruption is suspected, the anesthesia provider should insert a large-bore intravenous catheter and assess hemoglobin, coagulation status, and blood product preparation. When gauging volume status, the clinician must remain aware of the possibility of hemorrhage concealed behind the placenta. Placement of a urethral catheter to monitor urine output may help the physician assess adequacy of renal perfusion.

**Labor and vaginal delivery.** Neuraxial labor analgesia may be offered in the setting of abruption provided that hypovolemia has been treated and coagulation status is normal. The appropriateness of neuraxial analgesia with its accompanying sympathotony in patients at risk for extension of abruption and further hemorrhage has been questioned; however, the risk that neuraxial analgesia will worsen hemorrhage-associated tachycardia and hypotension can be mitigated by appropriate intravascular volume replacement and use of vasopressors. A patient with abruption presenting for vaginal delivery may have a severe coagulopathy, particularly in the setting of fetal demise. In this case, intravenous patient-controlled opioid analgesia should be offered.

**Cesarean delivery.** Spinal, combined spinal-epidural, or epidural anesthesia may be administered in stable patients in whom intravascular volume status is adequate and coagulation studies are normal. General anesthesia is preferred for most cases of urgent cesarean delivery accompanied by unstable maternal status, a nonreassuring FHR pattern, or both. Propofol may precipitate severe hypotension in patients with unrecognized hypovolemia; ketamine and etomidate represent alternatives for the patient with decreased intravascular volume.

Aggressive volume resuscitation is critical. In cases of severe hemorrhage, insertion of an intra-arterial catheter may aid prompt recognition of hypotension and allow for frequent blood sampling and assessment of anemia and coagulation status. Patients with abruption are at risk for postpartum hemorrhage from uterine atony and coagulopathy; after delivery, oxytocin should be infused promptly. Persistent uterine atony requires the administration of other uterotonic drugs (see later discussion). Red blood cells (RBCs) and coagulation factors should be replaced as indicated by laboratory studies. Experts recommend aggressive monitoring and early replacement of coagulation factors, especially fibrinogen, to minimize the risk for developing a coagulopathy.

Most parturients recover quickly and completely after delivery. A minority of postpartum patients, notably those who have prolonged hypotension or coagulopathy, and who need massive blood volume and blood product replacement, are best monitored in a multidisciplinary intensive care unit.

**Uterine Rupture**

Rupture of the gravid uterus can be disastrous for both the mother and the fetus. Because of variation in nomenclature and severity, accurate determination of maternal and fetal morbidity secondary to uterine rupture is difficult. The most common variety of uterine scar disruption is separation or dehiscence; some cases are asymptomatic. **Uterine scar dehiscence** is defined as a uterine wall defect that does not result in excessive hemorrhage or FHR abnormalities and does not require emergency cesarean delivery or postpartum laparotomy. In contrast, **uterine rupture**, less common than dehiscence, refers to a uterine wall defect with maternal hemorrhage and/or fetal compromise sufficient to require emergency cesarean delivery or postpartum laparotomy.
Risk, but the incidence of true uterine rupture after cesarean surgery (e.g., cesarean delivery or myomectomy) increases the risk, and induced/augmented labors are longer than those not induced/augmented. Additional risk factors for uterine rupture include the induction/augmentation process itself, prolonged labor, and placental implantation. Lateral extension of the rupture can involve the major uterine vessels and is typically associated with massive bleeding. Maternal death secondary to uterine rupture is rare, although there were three deaths attributed to uterine rupture in the 2006 to 2008 triennial report from the United Kingdom. Rupture-associated neonatal hypoxic-ischemic encephalopathy or mortality occurs at rates of less than one per 1000 trials of labor after cesarean delivery in the United States.

### Conditions Associated with Uterine Rupture

**Obstetric Conditions**
- Prior uterine surgery
- Induction of labor
- High-dose oxytocin induction
- Prostaglandin induction
- Grand multiparity (> 5)
- Morbidly adherent placenta
- Congenital uterine anomaly (e.g., bicornuate uterus)

**Maternal Comorbidities**
- Connective tissue disorder (e.g., Ehlers-Danlos syndrome)

**Trauma**
- Forceps application/rotation
- Internal podalic version
- Excessive fundal pressure

**Obstetric**
- Cesarean delivery
- Prior uterine surgery
- High-dose oxytocin induction
- Prostaglandin induction
- Internal podalic version
- Forceps application/rotation
- Excessive fundal pressure

**Nonobstetric**
- Blunt
- Penetrating

### Epidemiology

Fortunately, uterine rupture occurs very rarely in the woman with an unscarred uterus, but it does occur. Previous uterine surgery (e.g., cesarean delivery or myomectomy) increases the risk, but the incidence of true uterine rupture after cesarean delivery is still low, occurring at a rate of less than 1%. Box 37.2 lists additional conditions that have been associated with uterine rupture.

Although rupture of a previous uterine scar may occur in the absence of labor, it occurs more commonly during labor (see Chapter 19). A population-based retrospective analysis of more than 20,000 women who had undergone one previous cesarean delivery demonstrated the risk for uterine rupture among nonlaboring women was 1.6 per 1000, whereas among women in spontaneous labor the risk increased approximately threefold to 5.2 per 1000. Among women undergoing induction of labor, the risk increased nearly fivefold to 7.7 per 1000, and among women undergoing prostaglandin induction the risk increased almost 16-fold to 24.5 per 1000. This apparent risk escalation may not result from the induction/augmentation process per se, but may reflect the fact that prolonged labor increases rupture risk, and induced/augmented labors are longer than those not induced/augmented. Additional risk factors for uterine rupture during a trial of labor after cesarean (TOLAC) include an interdelivery interval of less than 12 to 16 months, multiple previous cesarean deliveries, postterm gestation, birth weight greater than 4000 g, maternal age older than 35 years, and previous delivery with severe postpartum hemorrhage. Previous vaginal delivery and prior successful vaginal delivery after cesarean confer decreased rupture risk. Evidence of decreased lower uterine segment thickness on ultrasound examination increases rupture risk, but a precise clinically applicable threshold value below which a TOLAC should not be offered has not been determined.

The rupture of a classical uterine incision scar (a vertical incision involving the muscular uterine fundus) is associated with greater morbidity and mortality than rupture of a low transverse uterine incision scar because the anterior uterine wall is highly vascular and may include the area of placental implantation. Lateral extension of the rupture can involve the major uterine vessels and is typically associated with massive bleeding. Maternal death secondary to uterine rupture is rare, although there were three deaths attributed to uterine rupture in the 2006 to 2008 triennial report from the United Kingdom. Rupture-associated neonatal hypoxic-ischemic encephalopathy or mortality occurs at rates of less than one per 1000 trials of labor after cesarean delivery in the United States.

### Diagnosis

The variable presentation of uterine rupture may cause diagnostic difficulty. An FHR abnormality is the first sign of uterine rupture in more than 80% of patients (see Chapter 19). The triad of abdominal pain, abnormal FHR pattern, and vaginal bleeding is seen less frequently (9% of patients with rupture). Other presenting signs include vaginal bleeding, uterine hypertonia, cessation of labor, maternal hypotension, loss of the fetal station, decrease in cervical dilation, or a change in fetal presentation. Breakthrough pain and need for frequent redosing during neuraxial labor analgesia may also indicate impending or evolving uterine rupture.

### Obstetric Management

Treatment options for uterine rupture include repair of the uterus, arterial ligation, and hysterectomy. Uterine repair is appropriate for most cases of separation of a prior low transverse uterine scar and for some cases of rupture of a classical incision. However, the risk for rupture in a future pregnancy remains. A disadvantage of arterial ligation is that it may not control the bleeding and may delay definitive treatment. Hysterectomy may become necessary, albeit rarely.

### Anesthetic Management

Patient evaluation and resuscitation are initiated while the patient is being prepared for emergency laparotomy. If rupture has occurred antepartum, fetal compromise is likely. General anesthesia may be necessary, but surgery can proceed under neuraxial anesthesia in stable patients with preexisting epidural labor analgesia. Aggressive volume replacement is essential, and transfusion may be necessary. Urine output should be monitored. Focused cardiac ultrasound monitoring may be appropriate whenever there is uncertainty about the intravascular volume status.

### Vasa Previa

Vasa previa occurs when the fetal blood vessels traverse the fetal membranes covering the internal cervical os. Consequently, the fetal vessels are not protected by the placenta or the umbilical cord, and rupture of membranes can be accompanied by tearing of a fetal vessel and exsanguination of the fetus.
Two types of vasa previa exist: type 1, when the vessels are associated with a velamentous umbilical cord, and type 2, when the vessels connect the lobes of a multilobed placenta or the placenta and a succenturiate lobe. Although no universal definition exists regarding the exact distance between fetal vessels and internal os that constitutes vasa previa, many clinicians use a threshold of 2 cm. This cutoff is based on a case series that demonstrated that all emergent deliveries caused by vasa previa had a fetal vessel within 2 cm of the cervical os.

### Epidemiology

Vasa previa occurs rarely (1 in 2500 to 1 in 5000 deliveries). Because it involves the loss of fetal blood, vasa previa is associated with a high fetal mortality rate (nearly 60% if vasa previa is unrecognized). The blood volume of the fetus at term is approximately 80 to 100 mL/kg. Therefore, the amount of blood that can be lost without leading to fetal death is small. In addition, the presence of vasa previa exposes the vulnerable fetal vessels to compression by the fetal presenting part, resulting in fetal hypoxia and death. Risk factors for vasa previa include the presence of velamentous cord insertion, placenta previa or low-lying placenta in the second trimester, placental accessory lobes, in vitro fertilization, and multiple gestation.

### Diagnosis

Ultrasonography can be used to visualize the velamentous insertion of the vessels, but vasa previa should be suspected whenever bleeding occurs with rupture of membranes, particularly if the rupture is accompanied by FHR decelerations or fetal bradycardia. Hemorrhage can also occur without rupture of membranes, making the diagnosis more difficult.

### Obstetric Management

Prenatal diagnosis confers a neonatal survival benefit: neonatal mortality is 3% when vasa previa is diagnosed antenatally but increases to 56% when it is not. Any woman at risk for vasa previa should have an ultrasonographic examination with transvaginal color Doppler. The management of vasa previa is directed toward ensuring fetal survival.

Timing of delivery reflects a balance between the risks associated with preterm delivery and the risk for vessel rupture if the pregnancy is allowed to continue. Experts advocate antenatal steroid administration between 30 and 32 weeks’ gestation to promote fetal lung maturity, and hospitalization of the patient between 30 and 34 weeks’ gestation to ensure prompt delivery should rupture of membranes occur. Mathematical modeling comparing delivery timing strategies for women with vasa previa reveals that the best fetal outcomes will occur with elective delivery between 34 and 35 weeks’ gestation. Amniocentesis to evaluate fetal lung maturity is not recommended because delaying delivery is typically not an option.

Ruptured vasa previa is a true obstetric emergency that requires immediate delivery of the fetus by cesarean delivery. Neonatal resuscitation requires attention to neonatal volume status.

### Anesthetic Management

The choice of anesthetic technique depends on the urgency of the cesarean delivery. In many cases, general anesthesia is necessary for prompt delivery.

### POSTPARTUM HEMORRHAGE

Conflicting definitions of postpartum hemorrhage exist; however, the most commonly accepted definition is blood loss more than 500 mL after vaginal delivery or more than 1000 mL after cesarean delivery. The American College of Obstetricians and Gynecologists (ACOG) defines hemorrhage as blood loss greater than or equal to 1000 mL, or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours of birth. Primary postpartum hemorrhage occurs during the first 24 hours, and secondary postpartum hemorrhage occurs between 24 hours and 6 weeks after delivery. Primary postpartum hemorrhage is more likely to result in maternal morbidity or mortality. Fig. 37.1 provides an overview of the obstetric management of postpartum hemorrhage.

Postpartum hemorrhage is the most common cause of maternal mortality worldwide and an important contributor to maternal death in the United States. The incidence of postpartum hemorrhage varies widely throughout different regions of the world; in the United States the current rate of postpartum hemorrhage is approximately 3%. Postpartum hemorrhage increased in incidence between 1994 and 2006 during this period, the transfusion rate for postpartum hemorrhage more than doubled, indicating hemorrhage also became more severe. The explanation for this acceleration in incidence and severity is not entirely clear but appears to be related to rising rates of postpartum uterine atony as well as increases in the incidence of abnormal placentation, both coincident with the rise in cesarean delivery rates. Other factors may include the rising rates of obstetric interventions, such as induction and augmentation of labor, and the increasing prevalence of obesity, multiple gestation, hypertensive diseases of pregnancy, and advanced maternal age. However, the rising prevalence of these risk factors does not entirely explain the upward trend in postpartum hemorrhage that has been observed.

### Uterine Atony

#### Epidemiology

Uterine atony is the most common cause of severe postpartum hemorrhage, accounting for approximately 80% of cases; the incidence is increasing in the United States. Box 37.3 lists conditions associated with uterine atony. In addition to normal hemostatic mechanisms, postpartum hemorrhage involves the release of endogenous uterotonic agents—primarily oxytocin and prostaglandins—that contract the uterus and constrict uterine vessels. Uterine atony represents a failure of this process. In addition, parturients with obstetric...
hemorrhage may have uterine arteries that are relatively unresponsive to vasoconstrictor substances. 

Diagnosis
An atonic, poorly contractile uterus and vaginal bleeding are the most common findings in patients with uterine atony. The absence of vaginal bleeding does not exclude this disorder because the atonic, engorged uterus may contain more than 1000 mL of blood. Unrecognized bleeding may manifest initially as tachycardia; worsening hypovolemia eventually leads to hypotension (Table 37.2).  

Obstetric and Anesthetic Management

**Prophylaxis.** The ACOG recommends active management of the third stage of labor, including uterine massage and prophylactic oxytocin administration to decrease blood loss and transfusion requirements compared with expectant management.  

Oxytocin is the first-line drug for prophylaxis of uterine atony after delivery of a third-trimester pregnancy. (The number of high-affinity receptors for oxytocin increases greatly near term; alternative uterotonic agents are more effective in the first and second trimesters of pregnancy.) Endogenous oxytocin is a nine–amino acid polypeptide produced in the posterior pituitary gland. The exogenous form
of the drug (Pitocin, Syntocinon) is a synthetic preparation with a rapid onset and short half-life.

Unfortunately, exogenous oxytocin can be associated with serious side effects, including vasodilation, tachycardia, hypotension, coronary vasoconstriction, myocardial ischemia, and, rarely, even death, especially in hypovolemic or other hemodynamically compromised women. Many of these adverse effects are directly related to the dose of oxytocin. Administration of phenylephrine with oxytocin can mitigate the adverse hemodynamic consequences of oxytocin, but phenylephrine may not be necessary as long as an oxytocin bolus dose is avoided and the infusion rate is maintained below 1 IU/min, the threshold at which hemodynamic consequences become apparent. High doses of oxytocin administered concomitantly with large volumes of intravenous fluids, especially those containing free water, can lead to hyponatremia, seizures, and coma because of oxytocin’s structural similarity to vasopressin.

Oxytocin is rapidly metabolized by hepatic oxytocinases and cleared in the urine and bile, resulting in a half-life of less than 6 minutes. Consequently, a prolonged intravenous infusion is more effective than bolus administration in preventing uterine atony. Administering a 5-IU bolus of oxytocin before an infusion does not provide benefit compared with an infusion without a bolus, and may cause more hemodynamic perturbations. The dose of oxytocin required to generate satisfactory uterine tone after delivery is lower than previously thought (see Chapter 26). The ED₉₀ of bolus-dose oxytocin for satisfactory uterine tone within 3 minutes of cesarean delivery in nonlaboring women is 0.35 IU; the ED₉₀ is almost ten times higher, approximately 3 IU, in women undergoing cesarean delivery for labor arrest after labor augmentation or induction with oxytocin. Similarly, the ED₉₀ of oxytocin administered via infusion without a bolus dose is approximately 0.3 IU/min in nonlaboring women, but approximately 0.7 IU/min in women exposed to oxytocin during labor before cesarean delivery.

Munn et al. randomized women undergoing intrapartum cesarean delivery to receive a prophylactic infusion of oxytocin at 2.67 IU/min or 0.33 IU/min for 30 minutes after delivery. The higher dose was associated with less need for secondary uterotonic (19% versus 39%, respectively; P < .001); however, this high dose of oxytocin may be associated with clinically significant tachycardia and hypotension, and other authors have not demonstrated any differences in bleeding-related outcomes after introducing protocols that employ oxytocin doses in the lower range. Awareness of the dangers of high-dose administration and data demonstrating the effectiveness of lower oxytocin doses than used historically call into question the safety of the practice of injecting 10 to 40 IU of oxytocin into a 1-liter crystalloid solution and infusing the solution at an unspecified rate, often “wide open” (i.e., gravity-dependent flow). The doses administered with this method may approach those achieved with bolus administration. Box 37.4 contains a suggested protocol for third-stage oxytocin administration.

### TABLE 37.2 Advanced Trauma Life Support (ATLS) Classification of Shock

<table>
<thead>
<tr>
<th>Class</th>
<th>Blood loss (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Heart rate (bpm)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Pulse pressure</th>
<th>Respiratory rate (breaths/min)</th>
<th>Mental state</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>15–30</td>
<td>&gt; 100</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>14–20</td>
<td>Slightly anxious</td>
</tr>
<tr>
<td>15–30</td>
<td>30–40</td>
<td>&gt; 120</td>
<td>Decreased</td>
<td>Decreased</td>
<td>20–30</td>
<td>Mildly anxious</td>
</tr>
<tr>
<td>30–40</td>
<td>&gt; 40</td>
<td>&gt; 140</td>
<td>Decreased</td>
<td>Decreased</td>
<td>&gt; 35</td>
<td>Anxious, confused</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percent total blood volume.

Modified from American College of Surgeons Trauma Committee. Advanced Trauma Life Support for Doctors. 9th ed. Chicago, IL: American College of Surgeons; 2012.

### BOX 37.4 University of Chicago Family Birth Center Postpartum Oxytocin Protocol

**Cesarean Delivery without Previous Oxytocin Exposure or Vaginal Delivery**
- Start infusion: 300 mL/h = 0.3 IU/min = 18 IU/h
- If uterine atony: increase to 600 mL/h = 0.6 IU/min = 36 IU/h
- If continued atony: increase to 900 mL/h = 0.9 IU/min = 54 IU/h

**Cesarean Delivery with Previous Intrapartum Oxytocin Exposure**
- Start infusion: 600 mL/h = 0.6 IU/min = 36 IU/h
- If uterine atony: increase to 900 mL/h = 0.9 IU/min = 54 IU/h

**For Continued Atony, Consider:**
- Methylergonovine 0.2 mg IM × 1
- 15-methylprostaglandin F₂α 0.25 mg IM (may repeat every 15 min for 8 doses)

**After Atony Is Resolved:**
- Decrease oxytocin to 60 mL/h = 0.06 IU/min = 3.6 IU/h

IM, Intramuscular.

Hypertension

Because ergot alkaloids rapidly produce tetanic uterine contractions, their use is restricted to the postpartum period. The mechanism of action is poorly understood, but the uterotonic effect is most likely mediated by serotonergic agonism; the ergot alkaloids are also weak dopamine and alpha-adrenergic receptor agonists. Parenteral administration of an ergot alkaloid is associated with a high incidence of nausea and vomiting. Bolus intravenous administration is not recommended because of the propensity to cause serious cardiovascular system derangements; even intramuscular administration may cause vasoconstriction, hypertension, myocardial ischemia and infarction caused by coronary vasospasm, cerebrovascular accident, seizures, and death. Fortunately, these serious adverse effects occur rarely. Patients at greatest risk are those with preexisting hypertension; however, sudden and marked hypertension may also occur in previously normotensive patients. The combination of an ergot alkaloid followed by a vasopressor may lead to exaggerated hypertension. Relative contraindications to the use of ergot alkaloids include hypertension, preeclampsia, peripheral vascular disease, and ischemic heart disease. Treatment of ergot-induced vasoconstriction and hypertension may require administration of a potent vasodilator such as nitroglycerin or sodium nitroprusside; blood pressure and the electrocardiogram should be monitored closely after administration, especially in the setting of hemorrhage.

Prostaglandins of the E and F families have gained wide acceptance as escalation therapy when high-dose oxytocin is inadequate. Concentrations of endogenous prostaglandins increase during labor, and levels peak at the time of placental separation. It is hypothesized that uterine atony may represent a failure of prostaglandin concentrations to increase during the third stage of labor in some women.

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**TABLE 37.3 Drug Therapy for Uterine Atony**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose and Route</th>
<th>Relative Contraindications</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>0.3–0.9 IU/min IV infusion</td>
<td>None</td>
<td>Tachycardia, Hypotension, Myocardial ischemia, Free water retention</td>
<td>Short duration of effect</td>
</tr>
<tr>
<td>Ergonovine or methylergonovine</td>
<td>0.2 mg IM</td>
<td>Hypertension, Preeclampsia, Coronary artery disease, Reactive airway disease, Pulmonary hypertension, Hypoxemia</td>
<td>Nausea and vomiting, Arteriolar constriction, Hypertension, Fever, Chills, Nausea and vomiting, Diarrhea</td>
<td>Long duration of action, May be repeated once after 30 minutes, May be repeated every 15 minutes up to 2 mg</td>
</tr>
<tr>
<td>15-Methylprostaglandin F₂α</td>
<td>0.25 mg IM</td>
<td>None</td>
<td>Nausea and vomiting, Diarrhea</td>
<td>Bronchoconstriction, Fever, Chills, Nausea and vomiting, Diarrhea</td>
</tr>
<tr>
<td>Misoprostola</td>
<td>600–1000 µg PR, sublingual, or buccal</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM, Intramuscular; IV, intravenous; PR, per rectum.

*Meta-analysis indicates that misoprostol does not provide benefit and increases adverse effects when administered to women with postpartum hemorrhage who are already being treated with high-dose oxytocin.*

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Prostaglandins increase myometrial intracellular free calcium concentration, ultimately leading to an increase in myosin light-chain kinase activity. Common side effects noted after prostaglandin administration include fever, chills, diarrhea, nausea, and vomiting. 

15-methyl prostaglandin F₂α, or carboprost, is commonly employed. Its administration may succeed in controlling hemorrhage when all other pharmacologic treatments have failed. The recommended dose is 0.25 mg (250 µg) administered intramuscularly, which may be repeated every 15 to 30 minutes; the total dose should not exceed 2 mg (eight doses). Unfortunately, this valuable agent requires refrigeration and may rarely cause bronchospasm, abnormal ventilation-perfusion ratio, increased intrapulmonary shunt fraction, and hypoxemia in susceptible patients. Methylergonovine may be a more effective second-line agent than carboprost. Retrospective data from the Maternal-Fetal Medicine Units Network demonstrated that women treated with methylergonovine were less likely to suffer hemorrhage-related morbidity than those given carboprost. 

Misoprostol is a prostaglandin E₅ analogue that has been used successfully for cervical ripening and induction of labor. Although it is not as effective as oxytocin, prophylactic misoprostol administration reduces the incidence of postpartum hemorrhage compared with placebo. Furthermore, misoprostol is thermostable in tropical conditions and does not require intravenous access for administration. These characteristics make it an attractive alternative to oxytocin and ergot alkaloids in low-resource areas, where the rate of maternal mortality from hemorrhage is high.

A large multinational randomized controlled trial and a subsequent meta-analysis indicate that misoprostol does not provide benefit and increases adverse effects when administered to women with postpartum hemorrhage who are already being treated with high-dose oxytocin. Unlike other prostaglandins, misoprostol may be associated with fever, chills, nausea, vomiting, and diarrhea. Misoprostol’s prolonged half-life may make it an attractive choice for patients who experience late postpartum hemorrhage. A dose of 600 to 1000 µg per rectum is commonly administered; administration via the oral, buccal, and sublingual routes has been described.

If hemorrhage and atony persist despite aggressive administration of multiple classes of uterotonic drugs, invasive techniques must be considered. Invasive techniques include intrauterine balloon tamponade, uterine compression sutures, embolization of the arteries supplying the uterus, surgical ligation of arteries, and cesarean hysterectomy (see later discussion).

Genital Trauma

The most common childbirth injuries are lacerations and hematomas of the perineum, vagina, and cervix. Most injuries have minimal consequence, but some puerperal lacerations and hematomas are associated with significant hemorrhage, either immediate or delayed. Prompt recognition and treatment can minimize morbidity and mortality. Genital tract lacerations should be suspected in all patients who have vaginal bleeding despite a firm, contracted uterus. The cervix and vagina must be inspected carefully in these patients. Computed tomography (CT) and/or MRI may be useful in detecting the presence, location, and extent of suspected hematoma.

Pelvic hemATOMas may be divided into four types: vaginal, vulvar, vulvovaginal, and retroperitoneal. Vaginal hemATOMas result from soft tissue injury during delivery, and they may involve bleeding from the descending branch of the uterine artery.

Pelvic hemATOMas are the least common and most dangerous hemATOMas associated with childbirth. A retroperitoneal hemorrhage occurs after laceration of one of the branches of the hypogastric artery. Injury typically occurs during cesarean delivery or rarely after rupture of a low transverse uterine scar during labor. A hematoma that originates in the broad ligament may dissect into the retroperitoneal space along the lateral pelvic sidewalls and may extend as far as the kidneys.

The symptoms of concealed bleeding depend on the size of the hematoma and the rate at which it forms. In some instances, progressive tachycardia or abrupt hypotension may be the first sign of bleeding. The diagnosis of a retroperitoneal hematoma must be considered whenever a postpartum patient has an unexpected decrease in hematocrit or unexplained tachycardia and hypotension. Other signs and symptoms are restlessness, lower abdominal pain, a tender mass above the inguinal ligament that displaces a firm uterus to the contralateral side, and vaginal bleeding with hypotension out of proportion to the external blood loss. Ileus, unilateral leg edema, urinary retention, and hematuria also may occur.

A high index of suspicion is needed; in obese women it may be especially difficult to examine the abdomen for signs of retroperitoneal hematoma.

Occasionally, a retroperitoneal hematoma may be self-limiting and need no surgical intervention. Life-threatening
hematomas require exploratory laparotomy and ligation of the hypogastric vessels. Fliegner\textsuperscript{116} reported that 38 of 39 patients with a broad ligament hematoma received a blood transfusion. Eight (21\%) of the patients required a hysterectomy.

Anesthetic Management

Choice of anesthetic technique for the repair of genital lacerations and evacuation of pelvic hematomas depends on the affected area, surgical requirements, volume/hemodynamic status of the patient, and urgency of the procedure. Local infiltration and a small dose of intravenous opioid suffice for drainage of some vulvar hematomas; however, repair of extensive lacerations and drainage of vaginal hematomas require significant levels of analgesia or anesthesia. A pudendal nerve block may not be technically feasible because of anatomic distortion or severe pain from the hematoma. Spinal or epidural anesthesia may be necessary, although the clinician should exercise caution initiating (or extending) a neuraxial block in a hypovolemic patient. In some cases, general anesthesia with tracheal intubation may be necessary. Exploratory laparotomy for a retroperitoneal hematoma typically requires the administration of general anesthesia.

Retained Placenta

Retained placenta is defined as failure to deliver the placenta completely within 30 minutes of delivery of the infant and occurs in approximately 3\% of vaginal deliveries.\textsuperscript{117,119} Retained placenta typically results from one of three causes: (1) the placenta may be blocked behind a contracted lower uterus/cervix (incarcerated placenta), (2) the placenta may be adhered to the uterine wall (placenta adherens), or (3) it may be invading the myometrium (placenta accreta). The severity of bleeding ranges from minimal to severe and can be life-threatening and require transfusion.\textsuperscript{118} The risk for postpartum hemorrhage increases significantly if the interval between delivery of the infant and the placenta exceeds 30 minutes.\textsuperscript{117,119} Prophylactic oxytocin facilitates placental separation from the uterine wall, and, on balance, prophylactic oxytocin administered before delivery of the placenta is not associated with retained placenta after vaginal birth.\textsuperscript{120,121} Risk factors for retained placenta include history of retained placenta, preterm delivery, oxytocin use during labor, preeclampsia, and nulliparity.\textsuperscript{117,118}

Obstetric Management

Treatment of retained placenta during the early postpartum period often involves gentle cord traction, uterine massage, manual removal, and inspection of the placenta. If manual extraction is not successful, curettage may be required. The clinician may need to discontinue oxytocin during curettage and then, once the placenta has fully delivered, restart it to augment uterine tone. The eventual removal of the placenta typically promotes uterine contraction and a reduction in bleeding, but close observation for evidence of recurrent hemorrhage is warranted. Because manual extraction of the placenta increases the risk for endometritis, the World Health Organization recommends prophylactic antibiotic administration,\textsuperscript{122} but published studies neither support nor refute this recommendation.\textsuperscript{123}

Anesthetic Management

Manual extraction of the placenta can be painful, requiring analgesia. In some cases, the administration of small amounts of sedatives and analgesics is adequate to allow examination and manual placental extraction by a skilled obstetrician. Administration of local anesthetic through an indwelling epidural catheter may prove helpful.\textsuperscript{124} In the absence of an indwelling catheter, \textit{de novo} neuraxial anesthesia may be considered in patients who are not bleeding severely and are hemodynamically stable. General anesthesia sometimes becomes necessary, particularly in patients who are hemodynamically unstable.

In cases in which lower uterine or cervical contraction prevents placental passage, manual removal requires uterine relaxation. Historically, anesthesia providers performed rapid-sequence induction of general anesthesia, followed by the administration of a high dose of a volatile halogenated agent to relax the uterus. However, induction of general anesthesia in a parturient entails risk for failed tracheal intubation, failed ventilation, and/or aspiration of gastric contents.

Alternatively, \textit{nitroglycerin} may be administered for uterine relaxation. Nitroglycerin provides a rapid onset of reliable smooth muscle relaxation and a short plasma half-life (2 to 3 minutes).\textsuperscript{125} Nitroglycerin has been administered for various obstetric emergencies without clinically significant side effects.\textsuperscript{123} Peng et al.\textsuperscript{126} described successful removal of retained placenta in 15 parturients after administration of intravenous nitroglycerin 500 \textmu g. Others have used a substantially lower dose of nitroglycerin (50 to 100 \textmu g) with similar results.\textsuperscript{127} Nitroglycerin may also be administered sublingually via spray or tablet. A double-blind, randomized controlled study compared sublingual nitroglycerin with placebo for management of retained placenta; the placenta was delivered successfully within 5 minutes in all 12 of the parturients who received nitroglycerin compared with only 1 of the 12 who received placebo.\textsuperscript{128} Nitroglycerin most likely produces uterine smooth muscle relaxation by releasing nitric oxide, which temporarily decreases the patient’s systemic blood pressure. Because of nitroglycerin’s short plasma half-life, boluses rarely lead to sustained hypotension. Nevertheless, administration of nitroglycerin necessitates vigilant blood pressure monitoring.

Uterine Inversion

Uterine inversion, or the turning inside-out of all or part of the uterus, is a rare but potentially disastrous event. It is associated with severe postpartum hemorrhage, and hemodynamic instability may be worsened by concurrent vagal reflex–mediated bradycardia. The reported incidence of this disorder varies widely; recent reports suggest an incidence of approximately 1 in 3400 deliveries.\textsuperscript{129}
Risk factors for uterine inversion include uterine atony, a short umbilical cord, uterine anomalies, and overly aggressive management of the third stage of labor, including inappropriate fundal pressure or excessive umbilical cord traction.125 Uterotonic therapy can convert a partial inversion to a complete inversion. An abnormally implanted placenta (i.e., placenta accreta) may be first recognized when uterine inversion occurs.

**Diagnosis**

Many cases of uterine inversion are obvious because of hemorrhage and a mass in the vagina, but others may not be readily apparent. Inversion should be suspected in all cases of postpartum hemorrhage. Ultrasonographic examination may show characteristic findings, such as an echoluent zone within an echogenic mass filling the uterine cavity on transverse view.130 Historically, obstetricians have stated that the shock is out of proportion to the blood loss, but an underestimation of obstetric hemorrhage is more likely. An incomplete inversion not protruding through the introitus is more likely to result in missed or delayed diagnosis.112

**Obstetric Management**

Immediate replacement of the uterus, even before removal of the placenta, is the treatment goal, but it may be difficult to achieve. All uterotonic drugs should be discontinued immediately. The obstetrician should attempt to right the inversion by applying pressure through the vagina to the uterine fundus; ring forceps may be used on the cervix to apply countertraction. Insertion of an intrauterine balloon may prove useful during treatment of uterine inversion, preventing reinversion.131

**Anesthetic Management**

Often, uterine tone precludes replacement of the uterus, and uterine relaxation is necessary for successful uterine reduction. The use of nitroglycerin to facilitate relaxation and replacement of the uterus has been reported.132,133 Fairly large intravenous doses (200 to 250 µg) may be required, and the anesthesia provider typically will need to support the circulation with intravenous fluids and vasopressors. Administration of general anesthesia with a volatile halogenated agent may become necessary, not only for uterine relaxation but also to prepare for laparotomy should it become necessary to correct the inversion. Once the uterus has been replaced, a firm, well-contracted uterus is desired. Oxytocin should be infused, and additional uterotonic drugs may be needed.

**Placenta Accreta Spectrum**

Placenta accreta is defined as a placenta that in whole or in part invades the uterine wall and is inseparable from it.134 Three types of placenta accreta (together referred to as **placenta accreta spectrum**) occur (Fig. 37.2). Placenta accreta vera is defined as adherence of the basal plate of the placenta directly to uterine myometrium without an intervening decidual layer. Placenta increta refers to a placenta in which chorionic villi invade the myometrium. Placenta percreta represents invasion through the myometrium into serosa and sometimes into adjacent organs, most often the bladder.134

**Epidemiology**

The increased incidence of placenta accreta mirrors the increased cesarean delivery rate, with a lag time of approximately 6 years.135 Between 1994 and 2007, the rate of peripartum hysterectomy for abnormal placentation increased by 20% in the United States, an increase entirely explained by adjustment for the rising prevalence of previous cesarean delivery among childbearing women.11 The percentage of U.S. cesarean deliveries increased from 20.7% in 1997 to 32.9% in 2009, as a result of an increase in both primary and repeat cesarean deliveries and a decrease in the TOLAC rate.136,137 Fortunately, the cesarean delivery rate stabilized after 2009 and declined to 31.9% in 2016.138

Previous cesarean delivery or other uterine surgery increases the risk for both placenta previa and placenta accreta. The combination of placenta previa with previous cesarean delivery synergistically increases the risk for coexisting placenta accreta, particularly if the placenta is anterior and overlies the uterine scar. A prospective multicenter observational study determined the relationship between placenta previa, previous cesarean delivery, and placenta accreta.19 Placenta previa with no prior uterine surgery conferred a 3% risk for placenta accreta. In women with placenta previa and one previous cesarean delivery, the risk for placenta accreta was 11%. In patients with placenta previa and a history of two previous cesarean deliveries, the incidence of placenta accreta increased to 40%. The incidence of placenta accreta was more than 60% in women with placenta previa and a history of three or more previous cesarean deliveries (see Table 37.1). Another study documented a positive relationship between the extent of uterine wall invasion and the number of previous cesarean deliveries.139

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Diagnosis

In some cases of placenta accreta the condition is first suspected at vaginal delivery, when the obstetrician notes difficulty in separating the placenta from the uterine wall. The definitive diagnosis is then made at laparotomy. Antenatal diagnosis of placenta accreta facilitates effective planning. Antenatal diagnosis is associated with less maternal and neonatal morbidity, including decreased blood loss at delivery and transfusion of fewer units of blood products. Ultrasoundography is a useful screening tool in patients with placenta previa and/or previous cesarean delivery and is the primary imaging modality used for making the diagnosis of placenta accreta. However, among women at risk for placenta accreta, ultrasoundography has imperfect sensitivity and specificity. MRI may help confirm the diagnosis in at-risk patients with inconclusive ultrasonographic examinations. Mathematical modeling using the presence or absence of placenta previa, number of previous cesarean deliveries, and strength of ultrasound evidence of placenta accreta can increase the sensitivity and specificity of accreta diagnosis.

Obstetric Management

The ACOG advises that clinicians working at small hospitals without adequate blood bank supplies transfer patients with placenta accreta to a tertiary care facility because there is a predictable need for massive transfusion. Patients treated at institutions with a 24-hour in-house obstetrician and anesthesia provider, immediate availability of a gynecologic oncologist, a fully stocked blood bank, and interventional radiology services suffer less morbidity than those treated at hospitals without these services. Planned delivery with all of the necessary multidisciplinary collaborators present compared with emergency delivery is associated with less maternal morbidity, including fewer transfusions, complications, and intensive care unit admissions. However, circumstances may dictate emergency delivery, and institutions that manage women with suspected placenta accreta expectantly must have the capacity to mobilize the entire perioperative team at any time. Some cases of vaginal bleeding remote from term resolve spontaneously, and expectant management may prolong the duration of pregnancy, at least into the third trimester. However, the risk for severe antenatal bleeding increases as gestational age increases. Timing of delivery, therefore, involves balancing this risk against the neonatal risks associated with preterm delivery. Decision analysis indicates that 34 weeks' gestational age is the preferred time for planned delivery in most clinical circumstances involving placenta previa and evidence of placenta accreta.

Most patients with known placenta accreta should undergo planned preterm cesarean delivery and hysterectomy with the placenta left in situ because attempts to remove the placenta are likely to initiate hemorrhage. Because the positive predictive value of ultrasonography may be low, it is reasonable to await spontaneous placental delivery or even attempt manual extraction in cases in which the diagnosis is unclear, although manual extraction may increase the risk for bladder injury. Preoperative placement of ureteral stents may minimize urinary tract injury. A midline vertical skin incision may provide optimal surgical exposure, and it may be necessary to modify the uterine incision to avoid cutting through the placenta.

The preoperative insertion of internal iliac artery balloon catheters is controversial. Optimally, the balloons are inflated after delivery as a means to minimize blood in the surgical field and decrease blood loss and transfusion requirements. Retrospective cohort studies have reported conflicting data regarding the effects of balloon catheter placement on blood loss, transfusion requirements, and duration of the surgical procedure.

Multiple complications can arise from the placement of these devices, some of them involving serious disruptions of the vasculature and lower extremity ischemia. Introduction of the arterial catheters, even without inflation, can cause fetal bradycardia, necessitating emergency delivery. If employed, therefore, internal iliac artery balloon catheters should be placed in the operating room to avoid dislodgement during transport and to allow for rapid delivery should fetal compromise occur. Authors of a 2012 review article opined that current evidence, confined to case reports, case series, and small retrospective studies, is inadequate to guide clinical decision-making. The Society for Maternal-Fetal Medicine (SMFM) recommends reserving the use of prophylactic intra-arterial balloon catheters for well-counseled women with a strong desire for fertility preservation, those who decline blood products, and those with unresectable placenta percreta. Prophylactic use of resuscitative endovascular balloon occlusion of the aorta (REBOA) reduces blood loss during placenta accreta surgery, based on meta-analysis of observational studies.

Two forms of conservative therapy for placenta accreta have been described. In selected patients with a partial placenta accreta, small focal areas of placental invasion may be managed by curettage and oversewing. Alternatively, it may be possible to leave the intact placenta in situ, close the uterus and abdomen, and await spontaneous placental involu-

Anesthetic Management

Anesthetic management is similar to other cases of severe postpartum hemorrhage and peripartum hysterectomy (see later discussion). Preoperative suspicion for placental implantation abnormalities should alert the anesthesia provider to the potential for massive blood loss and transfusion.
Invasive Treatment Options

Regardless of the cause of obstetric hemorrhage, first-line conservative measures may fail to control bleeding. In these cases, invasive procedures must be performed promptly once delivery has occurred to avoid severe morbidity and mortality. Second-line options, including intrauterine balloon tamponade, uterine compression sutures, angiographic arterial embolization, and uterine artery and/or internal iliac artery ligation, may help to avoid hysterectomy. Unfortunately, no randomized controlled trials assessing relative efficacy and safety of these options exist to guide management. In cases of intractable hemorrhage, hysterectomy may become necessary.

Intrauterine balloon tamponade is a conservative method for controlling postpartum hemorrhage, especially when uterine atony or lower uterine segment bleeding is suspected. The technique can reduce rates of hysterectomy. An intrauterine balloon can be deployed quickly, requires minimal analgesia for both insertion and removal, and preserves fertility. Continued bleeding may be concealed behind the balloon. Failure may also be attributed to prolapse through a partially open cervix. In such cases, the balloon may be replaced and secured by applying bilateral ring forceps to the cervix or by placing a cervical cerclage. Few complications have been reported, although concerns for infection exist.

Uterine compression sutures (e.g., B-Lynch suture) are most useful in cases of refractory uterine atony but have also been used in cases of retained placenta and accreta. A systematic review—based mostly on case reports and case series and therefore subject to reporting bias—estimated a 92% success rate for this procedure, but the success rate (avoidance of hysterectomy) in a prospective population-based trial was more modest (75%). The suture may slip off of the uterine fundus and fail to provide compression. Placement of compression sutures may preserve fertility, but data on the long-term effects on fertility and pregnancy outcomes are lacking. Complications include infection, uterine necrosis, and suture erosion. A case report describes placenta accreta and uterine rupture presumably caused by a uterine compression suture that had been placed after a previous delivery.

Angiographic arterial embolization may be appropriate if moderate blood loss continues and if the patient is stable for transport to the interventional radiology suite. The uterine arteries, which are branches of the anterior trunk of the internal iliac arteries, provide the primary blood supply to the uterus. The ovarian and vaginal arteries also make a sizable contribution to uterine blood flow during pregnancy. During angiography, the radiologist can identify the vessels responsible for bleeding and embolize these vessels with gelatin sponge pledges (Gelfoam). A small percentage of cases may require placement of a metallic coil in addition to gelatin sponges. The gelatin sponge is a temporary occlusive agent, and flow through these vessels returns over time, preserving both the uterus and fertility. Published success rates in emergently controlling postpartum hemorrhage with this approach vary between 70% and 100%. Successful treatment of acute postpartum hemorrhage with this modality requires rapid access to an angiography facility and a skilled interventional radiologist. The patient must be observed and monitored carefully while undergoing the procedure. Ischemic complications of embolization therapy have been reported, but the risk is reduced with the use of selective techniques.

Bilateral surgical ligation of the uterine arteries (O’Leary sutures) may be used to control bleeding at laparotomy. In the case of failure to control bleeding, the surgeon may proceed with a more complex procedure that involves ligation of the tubo-ovarian and ascending and descending uterine arteries. Internal iliac artery ligation may also be considered, although it is more difficult to perform. Reported success rates are highly variable, and it appears that arterial ligation is being used less often than in the past. The rich collateral circulation of the uterus at term most likely contributes to failure to control bleeding, as does the challenging nature of the procedure itself. Engorgement of pelvic viscera, variability in vascular anatomy, and the increased blood flow during pregnancy contribute to the risk for complications when this approach is used. Successful surgical ligation permits preservation of fertility. Ischemic complications and neuropathy have been reported.

Peripartum hysterectomy is the definitive treatment for postpartum hemorrhage unresponsive to medical and other invasive therapies. The two most common indications for this procedure are uterine atony and placenta accreta. Between 1994 and 2007, the overall rate of peripartum hysterectomy increased by 15% in the United States, because of a 130% increase in hysterectomy for atony and a 20% increase in hysterectomy for placental implantation abnormalities. The increase in hysterectomy for placental abnormalities is entirely explained by an increase in the cesarean delivery rate. Parturients with a history of previous cesarean delivery are more than five times as likely to require a peripartum hysterectomy as those without this history, and the risk for hysterectomy rises progressively with an increasing number of previous cesarean deliveries. The incidence of peripartum hysterectomy caused by uterine rupture has declined in the United States because the rate of TOLAC has declined. Elective peripartum hysterectomy may also be undertaken for concurrent gynecologic abnormalities, especially malignancies.

Peripartum hysterectomy is a technically challenging operation; the uterus is enlarged, exposure may be difficult, the vessels are engorged, and the pregnant uterus receives a rich collateral blood supply. The presence of dense adhesions from previous surgeries can further complicate the procedure. Compared with nonobstetric hysterectomy, patients undergoing obstetric hysterectomy are more likely to suffer postoperative hemorrhage and require blood transfusion, have intraoperative urinary tract injury, and experience
Effective aortic compression against a vertebral body in the upper abdomen should decrease blood flow to the pelvis, thereby allowing hemodynamic and hemostatic resuscitation and surgical control. An aortic cross-clamp requires vascular surgery expertise and retroperitoneal dissection but may be necessary to achieve hemostasis. Mild cardiac and renal dysfunction have been noted in nonobstetric patients if the aortic cross-clamp time exceeds 50 minutes.177 If a prolonged clamp time is required, the anesthesia provider should prepare for lactic acidosis and hypotension at the time the clamp is released. An endovascular aortic balloon may be inserted emergently via the femoral artery, and partial inflation just below the renal arteries may be sufficient to facilitate surgical visualization while preserving distal blood flow.178 Advanced surgical techniques to control friable, engorged blood vessels include felt or Teflon pledgets to buttress sutures, the rapid application of straight clamps, and the application of high-pressure surgical sealants.179,180

Anesthesia for peripartum hysterectomy is frequently challenging because massive blood loss may occur unpredictably.161 An experienced, skilled team is invaluable and critical to a successful outcome (see later discussion). Anesthesia providers may elect neuraxial anesthesia in a properly prepared patient. Intraperitoneal manipulation, dissection, and traction exceed similar maneuvers required with cesarean delivery alone. Maintenance of a T4 sensory level of anesthesia and judicious sedation may reduce the need for intraoperative conversion to general anesthesia. In a multicenter

### TABLE 37.4 Operative Management and Complications of Elective versus Emergency Obstetric Hysterectomies

<table>
<thead>
<tr>
<th></th>
<th>Elective (N = 21)</th>
<th>Emergency (N = 21)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anesthesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Operative time (minutes)</strong></td>
<td>137 ± 55</td>
<td>148 ± 62</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Hysterectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated blood loss (mL)</strong></td>
<td>1319 ± 396</td>
<td>2526 ± 1240</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Intraoperative hypotension</strong></td>
<td>6 (29%)</td>
<td>13 (62%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Intraoperative crystalloid (mL)</strong></td>
<td>4062 ± 1512</td>
<td>5274 ± 2340</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Intraoperative transfusion</strong></td>
<td>7 (33%)</td>
<td>17 (81%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Intraoperative or postoperative transfusion</strong></td>
<td>10 (48%)</td>
<td>18 (86%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Total units transfused</strong></td>
<td>1.6 ± 1.9</td>
<td>6.6 ± 5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Discharge hematocrit (%)</strong></td>
<td>30 ± 4</td>
<td>30 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Intraoperative injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteral</td>
<td>1 (5%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Cystotomy</td>
<td>1 (5%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Reoperation required</td>
<td>0</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>5.5 ± 1.3</td>
<td>7.3 ± 4.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

study of peripartum hysterectomy, none of the 12 patients who received continuous epidural anesthesia for elective or emergency hysterectomy required intraoperative induction of general anesthesia. In a single-center retrospective review, 79 patients underwent cesarean hysterectomy with neuraxial anesthesia, of whom 21% required conversion to general anesthesia. Longer surgical duration and a history of three or more prior cesarean deliveries increased the odds of requiring conversion to general anesthesia.

Single-shot spinal anesthesia is unlikely to provide anesthesia of sufficient duration for an unanticipated hysterectomy. Patients who have delivered vaginally with preexisting epidural labor anesthesia may be managed successfully with extension of epidural blockade, but careful consideration of hemodynamic status should precede the administration of local anesthetics into the epidural space. Animal models suggest that sympatholysis established before the onset of hemorrhage reduces excessive catecholamine response to blood loss and may improve survival. However, the induction of sympatholysis during hemorrhage may compromise end-organ perfusion and even precipitate cardiopulmonary arrest.

As the magnitude of blood loss increases, general anesthesia becomes the anesthetic technique of choice. First, severely hypotensive patients may require tracheal intubation for airway protection. Second, large fluid shifts and massive transfusion may adversely affect oxygenation so that control of ventilation via an endotracheal tube becomes necessary. Third, these same fluid shifts increase airway edema, potentially making failed ventilation/failed tracheal intubation more likely as the surgery proceeds. Fourth, the massive transfusion of blood products often results in the need for co-administration of potent vasopressors and calcium chloride and, thus, central venous access; the placement of a central venous catheter may be more easily accomplished after the induction of general anesthesia. In all cases, patients at risk for peripartum hysterectomy managed with neuraxial anesthesia should be informed in advance that intraoperative discomfort or severe hemorrhage may mandate the intraoperative induction of general anesthesia.

The induction of general anesthesia in the setting of severe hemorrhage may require careful use of small doses of noncardiodepressant induction agents such as ketamine or etomidate. The circulation should be supported with replacement of intravascular volume and vasopressors as needed. A review of maternal deaths from postpartum hemorrhage in France revealed that 5 of 38 deaths followed cardiac arrest on induction of general anesthesia.

Regardless of the anesthetic technique used, two or more large-bore intravenous catheters should be inserted. Invasive blood pressure monitoring may aid in the prompt recognition of hypotension and provide access for frequent blood draws. The blood bank should be alerted to the possible need for massive transfusion. At least 4 units of PRBCs should be immediately available, with additional blood products, including plasma and cryoprecipitate, readily available without delay. The ACOG recommends consideration of intraoperative blood salvage in cases with massive transfusion potential (see later discussion). Vasoactive drugs (e.g., phenylephrine, epinephrine), fluid warmers, a forced-air body warmer, and equipment for rapid infusion of fluids and blood products should be accessible if the care team is anticipating and managing significant blood loss.

**TEAM RESPONSE TO HEMORRHAGE**

**Prevention of Mortality**

Data from the UK Confidential Enquiry into Maternal and Child Health and the French Confidential Enquiry into Maternal Death reveal that maternal deaths from hemorrhage in high-resource settings are often preventable and associated with substandard care. In one state-level study, 93% of hemorrhage-related deaths were found to be preventable, compared with 40% of all-cause pregnancy-related deaths.

Delays in diagnosis and treatment of postpartum hemorrhage increase the severity of hemorrhage. Among women who develop postpartum hemorrhage from uterine atony after vaginal birth, risk factors for progressing to severe hemorrhage (defined as a decrease in hemoglobin concentration greater than 4 g/dL) include delaying the administration of oxytocin and delaying manual exploration of the uterus. Delays of more than 10 minutes in summoning either an obstetrician or an anesthesia provider to help manage hemorrhage also increase the odds of severity, presumably by delaying treatment. Interestingly, epidural labor analgesia protects against severe hemorrhage, in all likelihood by allowing for more rapid and thorough uterine exploration.

Delays in care most likely result from several factors, including difficulties in accurately estimating blood loss and in diagnosing maternal hypovolemia and shock, lack of aggressive monitoring and treatment of coagulopathy, and poor coordination of team responses. Practitioners often underestimate the amount of hemorrhage, with the degree of underestimation increasing as volume of blood loss increases (Fig. 37.3). Accuracy of blood loss estimation can be improved with the use of calibrated collection drapes. Clinician education using simulated scenarios with known blood volumes enhances estimation accuracy. Separation of nonblood fluids (i.e., switching the suction canister after evacuation of amniotic fluid) and weighing pads and bedding improves assessment. It is imperative that clinicians have a low threshold for the diagnosis of postpartum hemorrhage.

A second potential explanation for delays in diagnosis and treatment relates to difficulties in diagnosing hypovolemic shock in healthy young patients. The American College of Surgeons’ Trauma Committee’s Advanced Trauma Life Support (ATLS) system defines four stages of hypovolemic shock based on degree of blood loss (see Table 37.2). Obstetric patients are often mildly tachycardic, and worrisome rates of tachycardia (greater than 120 bpm) may not develop until the patient has lost 30% to 40% of her total blood volume. Similarly, hypotension and mental status changes are late signs. Findings such as these have led to the
and rapid treatment of hemorrhage. The National Partnership for Maternal Safety, sponsored by the ACOG Council on Patient Safety in Women’s Healthcare, has published a patient safety bundle, a collection of evidence-based practices designed to enhance early detection of, and response to, hemorrhage and decrease hemorrhage-related morbidity and mortality. It emphasizes team approaches; employment of multidisciplinary protocols, education, and drills; and review of cases of severe hemorrhage. The bundle also calls for quantification of blood loss, recognition of early signs of hypovolemia, early monitoring for anemia and coagulopathy, and appropriate transfusion of blood products.

The obstetric hemorrhage bundle is divided into four sections: readiness, recognition and prevention, response, and reporting and systems learning (Fig. 37.4). It recommends that every maternity unit maintain a hemorrhage cart with access to important supplies, surgical instruments, and medications. It advises partnering with the local blood bank to ensure rapid availability of blood products and encourages creation of a massive transfusion protocol. Clinicians are advised to assess hemorrhage risk at multiple time points, including prenatally, on admission to the delivery unit, at the beginning of the second stage of labor, and postpartum. The bundle emphasizes quantitative cumulative blood loss measurement rather than visual estimation, and recommends that each obstetric unit develop a protocol to manage all stages of obstetric hemorrhage. Finally, it encourages the use of huddles, debriefing sessions, multidisciplinary reviews, and quality improvement committees.

The effectiveness of such approaches has been evaluated. Investigators examined outcomes before and after introduction of a comprehensive hemorrhage program, and
CHAPTER 37  Antepartum and Postpartum Hemorrhage

COUNCIL ON PATIENT SAFETY
IN WOMEN’S HEALTH CARE
safe health care for every woman

PATIENT SAFETY BUNDLE
Obstetric Hemorrhage

READINESS

Every unit
- Hemorrhage cart with supplies, checklist, and instruction cards for intrauterine balloons and compressions stitches
- Immediate access to hemorrhage medications (kit or equivalent)
- Establish a response team - who to call when help is needed (blood bank, advanced gynecologic surgery, other support and tertiary services)
- Establish massive and emergency release transfusion protocols (type-O negative/uncrossmatched)
- Unit education on protocols, unit-based drills (with post-drill debriefs)

RECOGNITION & PREVENTION

Every patient
- Assessment of hemorrhage risk (prenatal, on admission, and at other appropriate times)
- Measurement of cumulative blood loss (formal, as quantitative as possible)
- Active management of the 3rd stage of labor (department-wide protocol)

RESPONSE

Every hemorrhage
- Unit-standard, stage-based, obstetric hemorrhage emergency management plan with checklists
- Support program for patients, families, and staff for all significant hemorrhages

REPORTING/SYSTEMS LEARNING

Every unit
- Establish a culture of huddles for high risk patients and post-event debriefs to identify successes and opportunities
- Multidisciplinary review of serious hemorrhages for systems issues
- Monitor outcomes and process metrics in perinatal quality improvement (QI) committee

Fig. 37.4 The Council on Patient Safety in Women’s Healthcare/National Partnership for Maternal Safety Patient Safety Bundle for Obstetric Hemorrhage. (Copyright © American College of Obstetricians and Gynecologists, 2015. Reprinted with permission.)
observed a reduction in hemorrhage severity, fewer cases of coagulopathy, a decrease in blood products transfused, and a nonsignificant reduction in the number of puerperal hysterectomies performed in the postprotocol period.\textsuperscript{198,199} The state of California witnessed a dramatic decrease in the rate of hemorrhage-related severe maternal morbidity after implementation of a hemorrhage bundle.\textsuperscript{200} These types of programs have positive effects on sentinel events and malpractice payments.\textsuperscript{201}

**TRANSFUSION THERAPY**

Despite advances in the prevention, diagnosis, and treatment of the hemorrhagic complications of pregnancy, the potential for significant blood loss remains. All physicians who provide care for pregnant women should understand the indications, risks, and benefits of transfusion. Transfusion may be indicated for treatment of severe anemia after moderate obstetric hemorrhage or to preserve life during massive hemorrhage.\textsuperscript{202}

**Risks and Benefits**

**Risk for Anemia**

Anemia is common during pregnancy and carries many adverse effects (see Chapter 44). Blood oxygen content and oxygen delivery to the tissues depend on hemoglobin concentration. Several compensatory physiologic responses can offset the negative effect of anemia on oxygen transport, especially if euolemia is maintained with intravascular volume expansion after moderate hemorrhage. Tachycardia and increased stroke volume combine to increase cardiac output, augmenting oxygen delivery. Anemia decreases blood viscosity and systemic vascular resistance, enhancing blood flow to the tissues. Tissue oxygen extraction increases during anemic states. Three lines of evidence support the safety of normovolemic, normotensive anemia. Weiskopf et al.\textsuperscript{203} studied the effects of acute normovolemic hemodilution on oxygen delivery and extraction. As hemoglobin concentration fell, systemic vascular resistance decreased and heart rate, stroke volume, and cardiac index increased. Oxygen transport rate and mixed venous oxyhemoglobin saturation did not decrease, and plasma lactate did not accumulate until hemoglobin concentration reached 5.0 g/dL. Second, experience with patients who refuse blood transfusion confirms that rates of morbidity and mortality are comparable to the general surgical population until hemoglobin concentrations fall below 5.0 g/dL.\textsuperscript{204} Finally, postoperative wound tissue oxygenation and wound collagen deposition are preserved with mild anemia, showing no impairment until the postoperative hemoglobin concentration falls below 5.0 g/dL.\textsuperscript{204} These data have been observed in healthy, nonpregnant patients and volunteers who were at rest. Extrapolation of these results to sick or pregnant patients may not be warranted, as anemia carries increased risks in patients with cardiovascular disease.\textsuperscript{205}

Moderate levels of postpartum anemia are associated with fatigue. However, fatigue is transient, and within 1 week fatigue and health-related quality of life scores are similar between postpartum patients who were anemic at discharge and those who were not.\textsuperscript{206} Transfusion of 1 or 2 units of PRBCs to hemodynamically stable, moderately anemic parturients has no effect on length of hospital stay.\textsuperscript{207} The effect of moderate anemia on breast-feeding is unknown.

**Risks Associated with Transfusion**

Blood product transfusion is associated with known risks including transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), immunologic reactions, infectious complications, and clerical error resulting in ABO incompatibility (see Table 54.2).

**Transfusion-associated circulatory overload** (TACO) occurs in approximately 1% of transfused patients.\textsuperscript{208} It may follow the transfusion of as little as 1 unit of PRBCs,\textsuperscript{209} but the likelihood of TACO increases as the volume of transfused plasma increases.\textsuperscript{208}

**Transfusion-related acute lung injury** (TRALI) is defined as a new acute lung injury (ALI) that occurs within 6 hours of transfusion in a patient without an alternative risk factor for ALI.\textsuperscript{210} It is usually accompanied by hypoxemia, transient leukopenia, and radiographic evidence of pulmonary edema in the absence of circulatory overload (Box 37.5).\textsuperscript{210} TRALI results when human leukocyte antigen (HLA) class I and II neutrophil or possibly monocyte antibodies in donor plasma react with recipient white blood cells, leading to increased pulmonary microvascular permeability, interstitial and alveolar edema, and extravasated neutrophils in the alveolar

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**BOX 37.5 Recommended Criteria for TRALI and Possible TRALI**

**TRALI Criteria**

- Acute lung injury
- Acute onset
- Hypoxemia
- Research setting: $\text{PaO}_2/\text{FiO}_2 \leq 300$ or $\text{SpO}_2 < 90\%$ on room air
- Nonresearch setting: $\text{PaO}_2/\text{FiO}_2 \leq 300$ or $\text{SpO}_2 < 90\%$ on room air or other clinical evidence of hypoxemia
- Bilateral infiltrates on frontal chest radiograph
- No evidence of left atrial hypertension (i.e., circulatory overload)
- No preexisting acute lung injury before transfusion
- Occurs during or within 6 h of transfusion
- No temporal relationship to an alternative risk factor for acute lung injury

**Possible TRALI Criteria**

- Acute lung injury
- No preexisting acute lung injury before transfusion
- Occurs during or within 6 h of transfusion
- A clear temporal relationship to an alternative risk factor for acute lung injury

TRALI, Transfusion-related acute lung injury.

space. These consequences are more likely to affect young obstetric patients than older patients. Leukoreduction may have a modest role in mitigating TRALI. In addition, microchimerism, whereby donor cells/DNA persist in the host for several years, occurs and predisposes the recipient to autoimmune illnesses. There is some suggestion that TRIM increases the lifetime risk for nonsolid cell malignancies. These consequences are more likely to manifest as time passes and therefore may be more likely to affect young obstetric patients than older patients. Leukoreduction may have a modest role in mitigating TRALI.

The risk for viral transmission because of allogeneic blood transfusion continues to decrease with thorough donor screening and use of nucleic acid amplification testing (nucleic acid technology [NAT]). The residual risk for transmission after both NAT and serologic testing of donor blood is approximately 1 in 2 million for both human immunodeficiency virus (HIV) and hepatitis C virus (HCV). NAT is not routinely used to test for hepatitis B virus (HBV). Instead, donor screening for hepatitis B surface antigen (HBsAg) and anti-core (Hbc) antibody has greatly reduced the risk for transmission of HBV, with the current risk for transmission with a blood transfusion being 1 in 350,000. The transfusion transmission of Creutzfeldt-Jakob disease also has been reported. Levels of infectivity are very low, but because of the long incubation period of this prion, symptoms may not be evident for several years after transfusion. The first case of West Nile virus transmitted via a blood transfusion was identified in 2002; since 2003, routine blood screening has been implemented, virtually eliminating this risk. Cytomegalovirus (CMV) is carried in the monocytes of asymptomatic donors and may be transmitted to uninfected recipients of blood transfusions. Most of the subsequent infections are asymptomatic or mild, but CMV infection of an immunocompromised patient and/or fetus or neonate can lead to serious sequelae. The transmission rate may be as high as 30% without preventive techniques. Transmission of CMV is reduced by administering seronegative or leukodepleted PRBCs.

Bacterial contamination occasionally occurs, most often during platelet transfusion. Because platelets may undergo conformational changes at temperatures below 18°C, they are typically stored at 20°C to 24°C. This warmer storage temperature (compared with that used for PRBCs) increases the risk for bacterial proliferation. In 2004, the AABB mandated testing of all platelets for bacterial contamination. Use of culture-negative platelets has resulted in a reduction in the risk for septic transfusion to 1 in 75,000.

Hemolytic transfusion reaction is a rare complication; it occurs most commonly as a result of accidental administration of ABO-incompatible blood. Acute intravascular hemolysis typically results in fever, chills, nausea, flushing, and chest and flank pain. Signs that may manifest during general anesthesia include hypotension, tachycardia, DIC, and hemoglobinuria. Immediate supportive care consists of discontinuation of the transfusion, treatment of hypotension and hyperkalemia, administration of a diuretic, and alkalinization of the urine. Assays for urine and plasma hemoglobin concentration and antibody screening confirm the diagnosis. A second cross-match must be performed.

The biochemical and additional changes that occur during blood storage can lead to complications in the recipient, particularly when blood products are infused rapidly, as during massive transfusion for severe hemorrhage. The anticoagulant used for blood collection and storage contains citrate, which binds ionized calcium. Citrate is rapidly metabolized in the liver and typically does not lead to significant hypocalcemia. However, in patients who are hypothermic, have liver disease, or require rapid infusion of multiple units of blood products, citrate may accumulate and cause a decrease in ionized calcium. Hypocalcemia results in reduced cardiac contractility, hypotension, and elevated central venous pressure. The concentration of citrate is seven times higher in fresh frozen plasma (FFP) and platelets than in PRBCs.

Transfusion of stored blood may lead to acidosis, hyperkalemia, and hypothermia. Stored blood develops low pH caused by the addition of acidic citrate-phosphate-dextrose and the accumulation of lactic and pyruvic acids that result from RBC metabolism and glycolysis. Despite the lower pH, transfusion of blood rarely causes significant acidosis as long as tissue perfusion remains adequate. Potassium concentration increases in stored blood. Typically, transfused potassium moves intracellularly or is excreted in the urine and does not accumulate in the recipient, but hyperkalemia may develop as blood is transfused rapidly to a hypothermic and acidotic patient. PRBCs and plasma are maintained at 4°C and should be administered through a warming device to prevent development of hypothermia.

Transfusion Strategies

Several randomized controlled trials have compared the use of restrictive and liberal transfusion practices, based on lower or higher hemoglobin triggers, mostly in nonpregnant patients; these trials uniformly failed to demonstrate benefit to a liberal strategy and suggested that using higher hemoglobin triggers may cause harm. In fact, the use of lower hemoglobin triggers reduces the risk for receiving an RBC transfusion (relative risk [RR], 0.61; 95% confidence interval [CI], 0.52 to 0.72), reduces the volume of RBC transfused, and does not affect the rate of adverse events such as myocardial infarction, other cardiac events, or stroke. Furthermore, restrictive strategies are associated with a reduction of in-hospital
mortality (RR, 0.77; 95% CI, 0.62 to 0.95) and a trend toward lower 30-day mortality (RR, 0.85; 95% CI, 0.70 to 1.03).287 In a 2014 multicenter randomized trial, stable obstetric patients who suffered postpartum hemorrhage and developed acute anemia (4.8 to 7.9 g/dL) were randomized to receive RBC transfusion or no intervention.286 No differences were apparent between the two groups, other than a slight difference in fatigue scores at 1 week. Both the AABB and the American Society of Anesthesiologists (ASA) recommend restrictive transfusion strategies.287

The AABB further advises that transfusion not be guided by hemoglobin concentration triggers alone.287 Physicians should consider the patient’s symptoms and physiologic triggers such as mentation, blood pH, lactate concentration, urine output, and, if central access is present, central venous oxygen saturation, to guide transfusion. Every patient will have a different critical oxygen threshold, the point at which metabolism shifts from aerobic to anaerobic. Utilizing symptomatic and physiologic transfusion triggers rather than an absolute hemoglobin level can target blood transfusion to the needs of the individual patient.

Transfusion practices vary widely288 and often deviate from both national and institutional guidelines.228–231 Given current evidence, it seems reasonable that transfusion should be considered in obstetric patients with a hemoglobin concentration less than 7 g/dL and those with clinical evidence of inadequate oxygen-carrying capacity. Active hemorrhage may prompt transfusion in some patients with a hemoglobin concentration greater than 7 g/dL.65

The optimal preparation for possible transfusion in the peripartum period is controversial. Many anesthesia providers believe that the potential need for transfusion, and the occasional patient who develops an antibody from fetal antigen exposure during pregnancy, warrant the routine performance of a blood type and screen on admission to the hospital for childbirth. Others suggest that this test is unnecessary in healthy women without risk factors for peripartum hemorrhage and negative antibody screens throughout the pregnancy. Given the low rate of transfusion in this group, the number-needed-to-treat is high. The ASA Practice Guidelines for Obstetric Anesthesia state that the decision to perform a type and screen should be based on maternal history, anticipated hemorrhagic complications, and local institutional policies.232 Patients with a positive antibody screen should have a cross-match performed to avoid a delay in obtaining blood products should the need arise.

If blood is required quickly and the results of antibody screening are not available, the safest option is to administer ABO- and Rh-specific blood. If the blood type is unknown and blood products are required immediately, type O Rh-negative RBCs and type AB plasma can be administered.

**Blood Conservation Techniques**

**Iron deficiency anemia** is the most common cause of anemia during pregnancy because fetal erythropoiesis occurs at the expense of maternal iron stores (see Chapter 44). Oral iron therapy is a mainstay of anemia prevention and treatment in pregnant women, but unfortunately, oral therapy is not well-tolerated and iron may be poorly absorbed through the gastrointestinal tract. Intravenous therapy corrects anemia more quickly and reliably than oral iron therapy.233–235

The potential advantages of autologous blood transfusion include avoiding the risk for some transfusion-related adverse events and reducing demands on the blood supply. The three methods of autologous transfusion are (1) preoperative (antepartum) donation, (2) normovolemic hemodilution, and (3) intraoperative blood salvage. The first two options are not recommended in pregnancy. Preoperative autologous donation causes anemia, may not reduce the risk for alloimmune transfusion, cannot be used in emergencies, and is not cost-effective because of difficulties in predicting transfusion need in obstetric patients, even those with traditional risk factors for hemorrhage.236 Normovolemic hemodilution may also induce anemia and may not reduce the risk for alloimmune transfusion.237 The third option, intraoperative blood salvage, is a technique whereby blood shed during surgery is scavenged, processed by centrifugation, washed, and filtered before transfusion to the patient. RBCs processed in this way have an excellent survival rate.

Historically, there was concern that the processing of salvaged blood collected from the surgical field did not adequately remove amniotic fluid, fetal debris, or fetal cells, and that reinfusion might precipitate amniotic fluid embolism. However, these concerns are unfounded, as modern salvaging processes efficiently remove these contaminants.238,239 Washing and filtration remove tissue factor, which is implicated in the pathophysiology of amniotic fluid embolism.240 Combining these processes with the use of a leukocyte-depletion filter greatly reduces fetal debris.241,242 Fetal squamous cell concentration in postfiltration scavenged blood is equal to that in maternal venous blood.242 In all cases of potential contamination, a double suction setup is recommended, although this increases the volume of unprocessed blood, and decreases the cost-effectiveness of the technique.243 One suction line is connected to the general suction system and is used to remove grossly contaminated fluid immediately after amniotomy and delivery; a second suction line is used after delivery to transfer shed blood to the salvaging system.

Reports of clinical experience with cell salvage in obstetric patients have accumulated over recent years; no reports of acute respiratory distress syndrome, DIC, or other complications have been described.244–251 The authors of one case report attributed maternal death to cell salvage–induced amniotic fluid embolism,252 but many authorities do not accept the cause of death in this case as amniotic fluid embolism because the patient was quite ill with preeclampsia with severe features—hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome—and coagulopathy, and the postmortem examination was inconclusive concerning the diagnosis of amniotic fluid embolism.231

Some minimal maternal risks exist. The cell scavenging system does not distinguish between maternal and fetal RBCs, and the transfusion of washed blood is likely to expose the
mother to a greater amount of fetal RBCs than commonly occurs during delivery.241,242 Isomunization of the mother is possible, and anti-D immune globulin should be administered as guided by Kleihauer-Betke testing in the postpartum period.238,239,244

Despite the potential risks, intraoperative blood salvage during cesarean delivery is widely regarded as safe. The ACOG has stated that in cases of suspected placenta accreta, “cell saver technology should be considered if available.”243 The ASA Practice Guidelines for Obstetric Anesthesia recommend: “In cases of intractable hemorrhage, when banked blood is not available or the patient refuses banked blood, consider intraoperative cell salvage if available.”241 Many authorities advocate this technique as a potential solution to the worsening shortage of banked blood, increased cost of allogeneic blood transfusion, and concern about transfusion-related infections and clerical errors.238,239,241 An economic analysis of the use of cell salvage in obstetrics demonstrates that its cost-effectiveness may depend, in part, on an institution’s case volume and the anticipated volume of blood loss. This procedure may therefore prove useful in cases of massive transfusion. Furthermore, transfusion of salvaged blood is acceptable to many Jehovah’s Witness patients.233

**Treatment of Massive Blood Loss**

During initial resuscitation of the hemorrhaging patient, warmed non–dextrose-containing crystalloid (e.g., lactated Ringer’s, normal saline) and/or colloid (e.g., 5% albumin) solutions are acceptable choices for volume replacement. During massive hemorrhage, blood replacement therapy becomes necessary. Coagulopathy can develop rapidly in the bleeding patient because of dilution from replacement of blood with crystalloid and PRBCs, and hemostatic factor consumption. Furthermore, obstetric hemorrhage may be associated with accelerated factor consumption, especially during bleeding from the placental bed.43,254 Fibrinolysis may also play a role during uterine bleeding.252 DIC further worsens hemorrhage (see later discussion). Pregnancy-related pathologic processes commonly associated with DIC include amniotic fluid embolism, placental abruption, uterine infection, intrauterine fetal demise, and severe postpartum hemorrhage.43 Transfusion endpoints include cessation of bleeding, hemodynamic stability, urine output of 0.5 mL to 1 mL/kg/h, decreasing serum lactate, demonstrating improved end-organ perfusion, and stabilization of laboratory measures of coagulation.

Standardized laboratory tests such as the prothrombin time (PT), partial thromboplastin time (aPTT), international normalized ratio (INR), and Clauss fibrinogen assay require relatively long turnaround times, rendering them impractical to guide transfusion therapy during massive hemorrhage. Viscoelastic monitoring with thromboelastography (TEG) and rotational thromboelastometry (ROTEM) graphically displays the kinetics of clot formation and fibrinolysis in real time.256 In some studies, transfusion therapy guided by viscoelastic monitoring, rather than transfusion using a fixed ratio of blood products, reduced the administration of blood products, specifically plasma and platelets, without increasing blood loss or coagulation abnormalities.257–259

**Blood Products**

Either whole blood or component products are transfused. Whole blood is an ideal choice for maintaining intravascular volume in the setting of massive hemorrhage. A population-based observational study of 1540 obstetric patients who required transfusion compared outcomes among patients who received only whole blood (43%), only PRBCs (39%), or multicomponent therapy (19%).260 Whole blood was associated with lower rates of acute tubular necrosis than the two other transfusion practices. However, few donor units are stored as whole blood in the modern blood bank. The high demand for blood components such as platelets, plasma, and cryoprecipitate requires fractionation of more than 90% of donor blood into blood components. Blood component therapy provides the patient with only those products that are required and helps extend the shelf-life of each unit of donor blood because derivatives from one unit of blood can be used to treat several patients. Characteristics of commonly administered blood products are summarized in Table 37.6. During massive resuscitation, care must be taken to avoid hypothermia, acidosis, and hypocalcemia, because these conditions contribute to coagulopathy.

**Packed red blood cells.** PRBC units are prepared by removing plasma from whole blood and replacing it with additives to improve RBC survival. These units are packaged with preservatives and anticoagulant (citrate, phosphate, dextrose, adenine) and have a 42-day shelf-life. Each unit has a volume of approximately 300 mL with a hematocrit of 70%. Transfusion of 1 unit of PRBCs increases the hemoglobin concentration by approximately 1 mg/dL in the absence of ongoing bleeding.

**Plasma.** A unit of plasma has a volume of approximately 250 mL and contains coagulation factors. Components of plasma replace coagulation factors when they are depleted, as may occur during massive transfusion or in the presence of DIC. Administration of plasma may be considered for correction of microvascular bleeding if the PT is more than 1.5 times normal, the INR is greater than 2.0, or the aPTT is more than two times normal. Plasma should not be used to treat hypovolemia or as a protein supplement. One unit of plasma per 20 kg of body weight is an appropriate initial dose. The prophylactic use of plasma is not effective for decreasing blood loss in patients at risk for massive blood loss.261

**Cryoprecipitate.** Cryoprecipitate is prepared from thawed plasma and contains fibrinogen, factor VIII, von Willebrand factor, fibronectin, and factor XIII. In the setting of postpartum hemorrhage, cryoprecipitate is used to replace fibrinogen, which is rapidly consumed during obstetric hemorrhage. Normal pregnancy is a hypercoagulable state, and coagulation activity peaks at the time of parturition,260,262 possibly because of an increase in circulating tissue factor concentration and enhancement of the tissue factor–dependent coagulation pathway.263 It is postulated that tissue factor and other procoagulant substances are released.
from the placental implantation site at the time of placental separation, augmenting thrombin formation and serving an important hemostatic function after delivery.\(^{42,43}\) In the setting of continued bleeding from the placental bed, these thromboplastic substances may continue to enter the circulation and, in severe cases, may lead to a consumptive coagulopathy and DIC.\(^{254}\)

The consumption of fibrinogen appears to play a central role in the pathophysiology of peripartum hemorrhage. Charbit et al.\(^{96}\) prospectively identified 128 patients who had postpartum hemorrhage and classified the hemorrhage as severe (decline in hemoglobin concentration more than 4 g/dL, transfusion of 4 units PRBCs or more, or invasive hemostatic intervention required) or nonsevere. Patients who developed severe hemorrhage had lower fibrinogen, prothrombin, factor V, and antithrombin levels compared with patients without severe hemorrhage. These early differences were most striking for fibrinogen; a fibrinogen concentration less than 200 mg/dL at the time hemorrhage was diagnosed had a 100% positive predictive value for severe hemorrhage, whereas a fibrinogen concentration greater than 400 mg/dL had a 79% negative predictive value for subsequent severe hemorrhage. The coagulation changes were consistent with a consumptive coagulopathy because they were accompanied by increases in thrombin-antithrombin complexes and D-dimer levels, both markers of excessive coagulation. Furthermore, because the fall in fibrinogen concentration was twice the fall in hemoglobin concentration, dilution did not account for the difference in fibrinogen levels between the two groups. Other investigators have confirmed that decreases in fibrinogen correlate better than other hemostatic measures with the severity of hemorrhage.\(^{264,265}\)

The rapid consumption of fibrinogen during obstetric hemorrhage calls for early monitoring for, and aggressive treatment of, hypofibrinogenemia. During active hemorrhage, clinicians should attempt to maintain the fibrinogen concentration greater than 150 to 200 mg/dL.\(^{196}\) Each dose of cryoprecipitate supplied by most blood banks contains 5 to 10 single-donor units of cryoprecipitate, and each unit of cryoprecipitate contains approximately twice the fibrinogen of 1 unit of plasma. Therefore, the most efficient method to replace fibrinogen during obstetric hemorrhage may be to administer cryoprecipitate.\(^{266}\) In a multicenter prospective cohort study of trauma victims (n = 1175), administration of cryoprecipitate compared with large doses of plasma was associated with a decreased risk for multiorgan failure.\(^{267}\)

Fibrinogen concentrate is an alternative source of fibrinogen, and has been used to restore fibrinogen levels in patients with postpartum hemorrhage.\(^{268}\) Fibrinogen concentrate does not appear to improve hemostasis unless fibrinogen levels have fallen below 200 mg/dL.\(^{257}\) This product is currently approved in the United States for the treatment of acute bleeding in individuals with congenital hypofibrinogenemia, but in some countries it has replaced the use of cryoprecipitate for the treatment of acquired hypofibrinogenemia.

**Platelets.** Thrombocytopenia may develop after massive transfusion secondary to dilution, and platelet transfusion may become necessary when hemorrhage is accompanied by a platelet count less than 50,000/mm\(^3\). This degree of thrombocytopenia is unusual unless blood loss exceeds 5000 mL or consumptive coagulopathy is present.\(^{269}\) Thrombocytopenia may also occur in association with obstetric comorbidities such as HELLP syndrome. In nonbleeding patients, a transfusion trigger of 20,000/mm\(^3\) has traditionally been suggested, although many clinicians prefer to administer platelets before the platelet count decreases to this value. Platelet dysfunction associated with bleeding may also necessitate platelet administration. One unit of donor platelets increases the platelet count by 5000 to 10,000/mm\(^3\) in the average adult. The blood bank typically provides pooled random-donor platelets or

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**TABLE 37.6 Characteristics of Blood Components**

<table>
<thead>
<tr>
<th>Component</th>
<th>Dose</th>
<th>Volume Per Dose</th>
<th>Shelf Life</th>
<th>Storage Conditions</th>
<th>Expected Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed red blood cells</td>
<td>1 unit</td>
<td>250–325 mL</td>
<td>21–42 days</td>
<td>1 °C to 6 °C</td>
<td>1 g/dL increase in hemoglobin concentration</td>
</tr>
<tr>
<td>Plasma</td>
<td>10–15 mL/kg</td>
<td>200 mL</td>
<td>Frozen: 1 year</td>
<td>Frozen: ≤ −18° C</td>
<td>Correction of PT, aPTT, INR by replacement of coagulation factors</td>
</tr>
<tr>
<td>Platelets</td>
<td>4–6 units of pooled whole blood–derived platelets or 1 unit of apheresis platelets</td>
<td>200–250 mL</td>
<td>5 days</td>
<td>20° C to 24° C with continuous and gentle agitation</td>
<td>Increase in platelet count of 30,000–60,000/mm(^3)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>10 pooled units</td>
<td>100 mL</td>
<td>Frozen: 1 year</td>
<td>Frozen: ≤ −18° C</td>
<td>Increase in levels of fibrinogen, von Willebrand factor, factor VIII, factor XIII</td>
</tr>
</tbody>
</table>

*aPTT, Activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.*

single-donor apheresis platelets obtained from an ABO- and Rh-compatible donor, although ABO compatibility is not essential. One unit of apheresis platelets is equivalent to 4 to 6 units of pooled platelets.

**Fixed-Ratio Transfusion**

The optimal plasma:PRBC transfusion ratio remains a topic of research and debate. Borgman et al. sought to characterize the relationship between this ratio and survival in a retrospective review of combat victims in Iraq between 2003 and 2005. The investigators identified 246 patients who required massive transfusion and separated them into low (median ratio 1:8), medium (median ratio 1:2.5), and high (median ratio 1:1.4) plasma:PRBC ratio groups. A high ratio was independently associated with increased odds of survival after correcting for confounders (OR, 8.6; 95%, CI, 2.1 to 35.2). After publication of these data, some experts recommended a 1:1 plasma:PRBC ratio during massive hemorrhage. However, many authors, including Borgman et al., point out the well-known limitations of retrospective data, which include the potential existence of unidentified confounders. These authors articulated that deaths in the low-ratio group occurred much earlier than deaths in the high-ratio group, raising the possibility that those in the low-ratio group had more severe injuries and died before plasma could be thawed and administered (e.g., survivor bias). Indeed, if the analysis is adjusted for survivor bias, the survival benefit associated with the high plasma:PRBC ratio disappears. Furthermore, a study in civilian trauma victims identified a plasma:PRBC ratio of 1:2 to 1:3 as optimal for survival. The extrapolation of data from young male trauma victims to bleeding parturients seems fraught with potential for error.

A 2013 publication described the retrospective review of records from 142 women who had postpartum hemorrhage and required transfusion within 6 hours of delivery. Patients were divided into two groups based on their response to sulprostone therapy: those in whom bleeding was controlled with sulprostone alone and those who required advanced interventional procedures. Propensity score analysis revealed that a high plasma:PRBC ratio (greater than 1:2) was associated with fewer requirements for interventional procedures. Retrospective studies such as these can only demonstrate an association between the plasma:PRBC ratio and outcome and cannot determine causation. Investigators have uniformly called for high-quality randomized trials to adequately define the optimal plasma:PRBC ratio during resuscitation for massive hemorrhage.

Many blood banks and hospitals have **massive transfusion protocols** whereby blood products are delivered to the operating room in fixed ratios. Such protocols allow the blood bank to more quickly provide component products and may encourage clinicians to more effectively prevent and/or treat coagulopathy. Routine blood loss quantification, early uterotonic therapy, timely physician evaluation, and early fixed-ratio transfusion may reduce the transfusion requirement by ensuring treatment at an earlier stage of bleeding. Viscoelastic monitoring may accelerate the transition from fixed-ratio to goal-directed transfusion, and thereby avoid unnecessary transfusion of plasma and platelets.

**Pharmacologic Treatment**

**Recombinant activated factor VII.** Factor VIIa binds not only to tissue factor, but also with low affinity to the thrombin-activated platelet. This low-affinity binding to the activated platelet allows direct activation of factor X to Xa on the surface of the activated platelet, bypassing the normal need for factors VIIIa and IXa. Activation of factor X leads to a small thrombin burst. This thrombin, in turn, activates more platelets. Additionally, factor VIIa enhances platelet aggregation and adhesion. Recombinant activated factor VII (rFVIIa) is currently approved in the United States for the treatment and prophylaxis of bleeding in patients with hemophilia A and B with inhibitors to factors VIII and IX, acquired hemophilia, and congenital factor VII deficiency. However, its off-label use has been reported in multiple clinical scenarios, including postpartum hemorrhage.

Most recommendations regarding rFVIIa are based on case report or case series data, which are difficult to interpret because there is a lack of standardized administration and adequate control groups against which to judge the therapeutic response. There is concern that rFVIIa may increase the likelihood of thromboembolic events, especially because severe obstetric hemorrhage and peripartum hysterectomy increase the risk for thrombotic complications. The incidence of such events is not known. Arterial events (e.g., myocardial infarction, cerebral thrombosis) are more likely than venous events and are dose and age dependent. Leighton et al. advise against rFVIIa administration in the setting of amniotic fluid embolism because tissue factor may play a role in its pathophysiology and thrombotic complications may be increased.

Given the unknown efficacy and safety of rFVIIa, as well as its high cost, rFVIIa is not recommended for routine use in obstetric practice. In 2005, an American expert consensus panel judged the use of rFVIIa for treatment of postpartum hemorrhage as appropriate only when bleeding continues despite clotting factor replacement. The ASA guidelines recommend consideration of rFVIIa therapy “when traditional options for treating excessive bleeding due to coagulopathy have been exhausted.” Importantly, maintenance of normothermia and correction of acidosis are necessary for optimal rFVIIa activity; optimization of platelet count, fibrinogen, and serum calcium are also advisable as rFVIIa requires these substances to be effective. Several authors have called for randomized placebo-controlled trials of rFVIIa use for postpartum hemorrhage, but such a trial will be difficult to undertake given the unpredictability of massive obstetric hemorrhage.

**Antifibrinolytic therapy.** Tranexamic acid binds to plasminogen, blocking its activation, thus inhibiting fibrinolysis. Administration of tranexamic acid decreases blood loss and transfusion risk and does not increase rates of thromboembolic
Fig. 37.5 Sample transfusion algorithm for obstetric hemorrhage that integrates a massive transfusion protocol with goal-directed therapy. \( ^a \)FFLEV and FIBTEM A5: TEG and ROTEM tests, respectively, that evaluate contribution of fibrin to clot formation by eliminating platelet contribution during testing. \( ^b \)TEG Ly30 and ROTEM EXTEM ML are tests that evaluate clot fibrinolysis. INR, international normalized ratio; IV, intravenous; MTP, massive transfusion protocol; PLT, platelet; RBC, red blood cells; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TXA, tranexamic acid.
events in high–blood loss surgical patients. In trauma patients, it lowers the risk for death from bleeding without increasing the risk for thromboembolic events or deaths.

In low-risk obstetric patients, prophylactic use of tranexamic acid very modestly decreases blood loss, but fibrinolysis may play a larger role during postpartum hemorrhage. Bleeding postpartum patients display elevated levels of D-dimer and plasmin-antiplasmin complexes, both markers of fibrinolysis, compared with nonbleeding patients, and administration of tranexamic acid attenuates these increases. The results of a large multinational placebo-controlled trial of tranexamic acid therapy in the setting of postpartum hemorrhage, the WOMAN trial, were published in 2017. Hemorrhaging patients who received tranexamic acid therapy within 3 hours of the diagnosis of hemorrhage suffered fewer deaths caused by bleeding than those given placebo. No differences in adverse events (including venous and arterial thromboembolic events) between the two groups were apparent. However, most patients included in the WOMAN trial were from low- and middle-resource countries; extrapolation of these results to high-resource settings such as U.S. hospitals may not be valid. More than 7% of those who died from hemorrhage in the study did so without having received any blood products. Uterine tamponade was used in only 7% of study subjects, and uterine suture sutures in just 3%. Furthermore, the overall case fatality ratio (deaths per hemorrhage) in the control group was 2.6%, which greatly exceeds the ratio in high-resource countries (most likely less than 1:10,000). These factors make it extremely unlikely that the United States will witness similar survival benefits from tranexamic acid. The effect of tranexamic acid on hysterectomy rates and preservation of fertility among hemorrhaging women remains unknown. Nevertheless, tranexamic acid administration likely decreases blood loss and transfusion rates, similar to its effects in other nonobstetric, high–blood loss circumstances.

Against these potential benefits, one must weigh the potential risks associated with administration of tranexamic acid. Although data on thromboembolic events from nonobstetric and obstetric patients are reassuring, parturients are hypercoagulable, and caution may be warranted. A case cluster of renal cortical thrombosis and irreversible kidney damage developed among 18 women treated with tranexamic acid for postpartum hemorrhage in France. The doses of tranexamic acid used in these cases were higher than those employed in the WOMAN trial and included prolonged infusion of the drug. Practitioners are cautioned not to exceed doses of 1 g administered slowly over 10 minutes; this dose may be repeated once if bleeding continues after 30 minutes. Continuous infusion is not recommended. Aortoiliac thrombosis was reported after the concomitant use of tranexamic acid and an intra-arterial balloon catheter during urgent cesarean hysterectomy. Dose-dependent seizures may occur. Tranexamic acid crosses the placenta. Lastly, multiple reports exist of accidental injection of tranexamic acid into the intrathecal space, leading to uncontrollable seizures and death within 24 hours.

The role of tranexamic acid in hemorrhage protocols in high-resource settings remains to be determined. It seems plausible that tranexamic acid may benefit women who demonstrate hyperfibrinolysis on viscoelastic monitoring. The ACOG states that “tranexamic acid should be considered in the setting of obstetric hemorrhage when initial medical therapy fails. Earlier use is likely to be superior to delayed treatment.”

### KEY POINTS

- Obstetric hemorrhage is the most common cause of maternal mortality worldwide and a leading contributor to maternal mortality in developed nations.
- Most severe morbidity and mortality that occurs secondary to obstetric hemorrhage is preventable and is caused by delays in recognition and treatment.
- The visual estimate of vaginal bleeding often underestimates true blood loss; training clinicians, separation of amniotic fluid, use of calibrated drapes, and weighing pads and bedding improves estimation accuracy.
- Hypotension and tachycardia are late signs in hypovolemic shock.
- Antepartum hemorrhage usually represents a greater threat to the fetus than to the mother.
- Postpartum hemorrhage is increasing in both rate and severity in the developed world, mostly resulting from an increase in the incidence of uterine atony.
- Uterine atony is the most common cause of postpartum hemorrhage.
- The incidence of placenta accreta is increasing because of the higher cesarean delivery rate.
- Peripartum hysterectomy is increasing in frequency because of an increase in the incidence of both uterine atony and placenta accreta.
- Patients with placenta accreta are at high risk for massive hemorrhage and should be managed only in facilities with multidisciplinary specialists, including interventional radiologists and a well-staffed blood bank.
- Multidisciplinary team responses that emphasize the accurate estimation of blood loss, early warning signs of shock, and rapid response to blood loss and coagulopathy are associated with less maternal morbidity.
- Coagulopathy develops quickly during bleeding from the placental bed, and may be out of proportion to blood
loss or dilution because of the rapid consumption of fibrinogen.

- Intraoperative blood salvage may be lifesaving in cases of intractable hemorrhage if allogeneic blood is not available, or if the patient refuses allogeneic blood.

- Administration of tranexamic acid during postpartum hemorrhage decreases deaths caused by bleeding in low-resource settings. Its effect in high-resource settings is unknown, but it may decrease blood loss and transfusion risk.

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CHAPTER 37  Antepartum and Postpartum Hemorrhage


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Embolic disease during pregnancy includes venous thromboembolism, amniotic fluid embolism, and venous air embolism. Each of these entities varies in its incidence, clinical course, and consequences. Embolic events account for almost one-sixth of all maternal deaths in the United States.1 Early recognition, diagnosis, and treatment are necessary to reduce associated morbidity and to avoid mortality.

**THROMBOEMBOLIC DISORDERS**

**Incidence**

Venous thromboembolic events (VTE) in pregnancy refer to deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). Analysis of administrative data from a nationally representative sample of U.S. hospital admissions that included 64,413,973 pregnancy-related hospitalizations (1994 to 2009) suggests a VTE event rate of 1.99 events per 1000 pregnancies.2 Among these events, the DVT event rate (1.26 per 1000 deliveries) is higher than the PTE event rate (0.73 per 1000 deliveries).2

Compared with nonpregnant patients, pregnant women are at fivefold greater odds of thromboembolic events during pregnancy (odds ratio [OR], 4.6; 95% CI, 2.7 to 7.8) and at 60-fold greater odds during the postpartum period (OR 60.1, 95% CI, 26.5 to 135.9).1 The highest risk occurs immediately postpartum. Analysis from a 30-year population-based cohort (n = 50,080 births) revealed the risk for both DVT and PTE was highest in the first week postpartum (incidence rate, 3573 per 100,000 woman-years; 95% CI, 2475 to 4993 per 100,000), with a progressive decline thereafter.4 Compared with 1 year postpartum, the odds of a thrombotic event in the first 6 weeks postpartum are tenfold higher (OR, 10.8; 95% CI, 7.8 to 15.1); the period of elevated risk persists until at least 12 weeks after delivery.5

Multiple studies have demonstrated an increasing trend in VTE-associated hospitalizations.2,6,7 According to data from the Nationwide Inpatient Sample (a stratified sample of inpatients from hospitals in the United States representing approximately 20% of discharges), the incidence increased by 72% between 1998 and 2009.7 Although VTE-related mortality, as reported by the Confidential Enquiries into Maternal Deaths and Morbidity in the United Kingdom and Ireland, appeared to have been decreasing (0.85 deaths per 100,000 births in 2012 to 2014, compared with 1.26 per 100,000 births in 2009 to 2011),8 in the most recent report (2013 to 2015), the incidence of VTE-related mortality was 1.13 deaths per 100,000 births,9 making VTE the leading cause of direct maternal deaths. VTE-related maternal mortality appears to be stable in the United States, at 1.49 deaths per 100,000 births.1

**Risk Factors**

The two most important risk factors for thromboembolic events in pregnancy and the postpartum period are a previous history of thromboembolism and a diagnosis of thrombophilia.10-13 Essentially all known thrombophilias increase the risk for VTE in pregnancy, with the greatest risk increase noted in women homozygous for the factor V Leiden
Postpartum hemorrhage and postpartum infections, are also associated with increased risk; this is likely mediated through their effects on maternal coagulation and inflammation. Cesarean deliveries increases the risk for postpartum venous thromboembolism. In a meta-analysis of 28 studies (pooled n greater than 53,000 postpartum VTE events), the odds ratio of postpartum VTE after a cesarean delivery compared with a vaginal delivery was 3.7 (95% CI, 3.0 to 4.6). Greater increases were noted after emergency compared with elective cesarean deliveries. The American College of Chest Physicians has defined major and minor risk factors for postcesarean VTE (Box 38.1). The American College of Obstetricians and Gynecologists (ACOG) recommends that all pregnant women should be screened for risk factors for VTE early in pregnancy.

**Pathophysiology**

Virchow’s triad describes three factors that contribute to an increased risk for thromboembolism: (1) **venous stasis**, (2) **vascular damage**, and (3) **hypercoagulability**. The incidence of each factor is increased during pregnancy or in the postpartum period. Venous stasis occurs as a result of venocaval compression and possibly decreased mobility later in pregnancy. Separation of the placenta from the uterine wall traumatizes the endometrium, which accelerates the coagulation cascade. Additionally, pregnancy is a relatively hypercoagulable state, associated with enhanced platelet turnover, coagulation, and fibrinolysis. Thrombin generation and the concentration of clotting factors increase during pregnancy, including factors I (fibrinogen), V, VII, VIII, IX, X, and XII. Platelet count typically remains unchanged or is decreased during pregnancy. Fibrinolytic activity decreases during the 48 hours after delivery and enhances clot stability in the early postpartum period.

The prognosis of PTE depends on the following factors: (1) the size and number of emboli, (2) concurrent cardiopulmonary function, (3) the rate of clot fragmentation and lysis, (4) the presence or absence of a source for recurrent emboli, and (5) the location of the embolism (proximal or main pulmonary artery embolism is more symptomatic than segmental embolization). Massive PTE can occlude the pulmonary vasculature and precipitate cardiopulmonary arrest; smaller emboli may also lead to cardiopulmonary failure by triggering pulmonary arterial vasospasm and secondary pulmonary edema. Local platelets embedded in the clot release serotonin, adenosine diphosphate, and thrombin, factors that promote both vasoconstriction and bronchoconstriction. Redistribution in pulmonary blood flow leads to “hyperperfusion” of otherwise low V/Q zones in unaffected areas of the lung; the resulting intrapulmonary shunts cause hypoxemia disproportionate to the cross-sectional area occluded by clot. At the same time, regional hypoxic pulmonary vasoconstriction exacerbates pulmonary hypertension initiated by mechanical and humoral factors. Intracardiac shunting may develop when elevated right ventricular pressure forces blood across a probe-patent foramen ovale. The increase in right ventricular pressure leads to right ventricular dilation, with increased wall tension and oxygen demand, and a leftward shift of the interventricular septum. Compression of the left ventricle combined with a decrease in preload impairs left ventricular function, cardiac output, and coronary arterial perfusion, with eventual myocardial ischemia and cardiopulmonary failure.

**Deep Vein Thrombosis**

**Clinical Presentation**

The signs and symptoms of DVT are nonspecific and often mimic normal symptoms of pregnancy, specifically lower leg edema and pain. A systematic review of the anatomic distribution of DVT in symptomatic pregnant patients (six studies, pooled n = 124) identified left leg thrombus in 88% of pregnant women in whom the side of the DVT was
Most thrombi were proximally located in the iliac or femoral veins, or both. This distribution is different from the anatomic distribution in nonpregnant patients, who are more likely to have thrombi in the distal calf vessels.\(^{24}\) A prospective observational study of serial ultrasonographic examinations in pregnant women (n = 24) found an increase in vessel diameter and a decrease in flow velocity in the proximal deep leg veins with increasing gestation; this finding was most notable in the common femoral vein.\(^{25}\) The flow velocity was slower in the left leg than in the right leg, presumably caused by uterine compression of the left iliac vein.\(^{25}\)

**Diagnosis**

For patients with new-onset signs or symptoms suggestive of DVT, the ACOG recommends compression ultrasonography of proximal veins as the initial diagnostic test.\(^{2}\) If the test is negative, and involvement of the iliac vessels is not suspected, no further action other than routine surveillance is necessary. A positive result warrants treatment (see later discussion). If the results are negative or equivocal, and iliac vein thrombosis is suspected, clinicians may opt for Doppler ultrasonography of the iliac vein, venography, or magnetic resonance imaging or presumptive anticoagulation.\(^{13}\)

The d-dimer test is useful in nonpregnant patients because it has a high sensitivity and a high negative predictive value. Unfortunately, d-dimer levels are increased in pregnancy, making interpretation of elevated levels difficult in pregnant women. In one prospective, longitudinal study, serial d-dimer levels were evaluated in 89 healthy pregnant women; values exceeded the normal nonpregnant reference range in all but one woman in the third trimester.\(^{26}\) Therefore, the d-dimer test is not currently recommended for diagnosis of DVT in pregnancy,\(^{27,28}\) although future work may delineate pregnancy-specific thresholds.

**Pulmonary Thromboembolism**

**Clinical Presentation**

Clinical suspicion for PTE is critical to ensure timely diagnosis and treatment. Physical signs and symptoms may be subtle and limited to symptoms (e.g., shortness of breath) that mimic normal pregnancy (Table 38.1). Palpitations, anxiety, pleuritic chest pain, cyanosis, diaphoresis, and cough with or without hemoptysis may all indicate PTE. Physical examination of the patient commonly reveals tachypnea, crackles, decreased breath sounds, and tachycardia. Signs of right ventricular failure, including an accentuated or split-second heart sound, jugular venous distention, a parasternal heave, and hepatic enlargement, may be apparent. Although the Pao\(_2\) is generally low (less than 80 mm Hg), as many as 30% of all patients with a pulmonary embolus have an arterial Pao\(_2\) greater than 80 mm Hg; thus, the diagnosis of PTE cannot be excluded on the basis of an apparently normal Pao\(_2\).\(^{19,20}\) Left ventricular failure may occur secondary to poor left ventricular filling and arterial hypoxemia. One or more signs of DVT (calf or thigh edema, erythema, tenderness, palpable cord) generally accompanies the pulmonary or cardiovascular findings.\(^{18}\) The electrocardiogram may show signs of right ventricular strain, including a right-axis shift, P pulmonale, ST-segment abnormalities, and T-wave inversion, as well as supraventricular arrhythmias. Transthoracic echocardiography may reveal signs of right ventricular dysfunction or other findings consistent with acute pulmonary embolism, such as hypokinesis of the right ventricular free wall with normal contraction of the apical segment (McConnell’s sign).\(^{30}\)

**Diagnosis**

Diagnosing PTE in pregnancy is challenging given the lack of validated criteria specific for the peripartum period. The American Thoracic Society developed an evidence-based guideline for the evaluation of suspected PTE in pregnancy,\(^{28}\) which has been endorsed by the ACOG.\(^{27}\) A diagnostic algorithm for suspected PTE is shown in Fig. 38.1. If the pregnant patient has signs or symptoms suggestive of DVT, in addition to the signs or symptoms of PTE, compression ultrasonography should be done. If the results are positive, treatment should ensue. However, if the results are negative, further imaging is necessary. If there are no signs or symptoms of DVT, a chest radiograph should be performed, both to exclude alternative diagnoses, and to guide decision-making for the next most appropriate test. If the chest radiograph is normal, V/Q scanning should be performed.\(^{13}\) A retrospective study of 304 women who underwent computed tomographic angiography (CTA) or V/Q scanning at a single institution between 2001 and 2006 demonstrated that pregnant women with a normal chest radiograph have a fivefold higher rate of a nondiagnostic result from a CTA compared with a V/Q scan (relative risk [RR], 5.3; 95% CI, 2.1 to 13.8).\(^{21}\) The use of chest radiography as a screening procedure may also minimize the amount of radiation to which a pregnant woman and her fetus are exposed if the pregnant patient is a candidate for V/Q scanning.\(^{28}\) If the chest radiograph is abnormal, CTA is the next appropriate test because the proportion of nondiagnostic V/Q scans in the presence of an abnormal chest radiograph has been reported to be as high as 48%.\(^{32}\) If either the V/Q scan or CTA is positive, anticoagulation should ensue.

### TABLE 38.1 Symptoms and Signs of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Finding</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>79</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>47</td>
</tr>
<tr>
<td>Cough</td>
<td>43</td>
</tr>
<tr>
<td>Calf or thigh pain</td>
<td>42</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>57</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>26</td>
</tr>
<tr>
<td>Localized rales</td>
<td>21</td>
</tr>
<tr>
<td>Accentuated second heart sound</td>
<td>15</td>
</tr>
</tbody>
</table>

The use of magnetic resonance pulmonary angiography has not been validated in the pregnant population.

Single-photon emission computed tomography (SPECT) is another diagnostic modality that has been evaluated in pregnant women. In a nonpregnant patient population, the V/Q SPECT demonstrated 100% sensitivity and 94% specificity compared with CTA as the "gold standard." A retrospective analysis of 127 women who underwent evaluation for PTE with V/Q SPECT identified PTE in 11 women (9%). The negative predictive value was 100%, and the calculated fetal and breast absorbed radiation doses were low (less than 0.014 mGy and 0.25 mGy, respectively).

Perhaps the greatest concern with diagnostic imaging for PTE is maternal and fetal exposure to ionizing radiation. The teratogenic effects of ionizing radiation are discussed in Chapter 17. Both V/Q scanning and CTA are associated with low doses of fetal radiation exposure (less than 1 mGy). V/Q scanning delivers a higher fetal dose of radiation than CTA; however, the maternal radiation exposure is higher with CTA, particularly radiation to the breast tissue. A patient’s lifetime breast cancer risk may increase as much as 14% after CTA. Maternal radiation exposure is lower with V/Q SPECT than with CTA.

### Management of Thromboembolic Disorders

#### Anticoagulation

All women with a new-onset thromboembolic event in pregnancy should be therapeutically anticoagulated. Patients with a previous history of thrombosis, certain high-risk populations (e.g., patients with acquired or inherited thrombophilies), or patients with a mechanical heart valve should be anticoagulated during pregnancy as well as the postpartum period. The ACOG practice bulletin on thromboembolism in pregnancy summarizes which patients should receive prophylactic versus therapeutic anticoagulation. Given the significant morbidity and mortality associated with VTE, the National Partnership for Maternal Safety, a multidisciplinary body that develops evidence-based safety bundles, published a consensus bundle on VTE in 2016. This bundle broadens the indications for antepartum and postpartum pharmacologic anticoagulation beyond the ACOG practice guidelines, including recommending daily thromboprophylaxis for antepartum patients hospitalized for greater than 72 hours.

Although the exact dose and regimen for anticoagulation remain controversial, two classes of drugs are typically used to initiate anticoagulation: unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Table 38.2 lists anticoagulation regimens commonly used in pregnancy. Both the ACOG and the American College of Chest Physicians recommend LMWH rather than UFH for prophylactic and therapeutic anticoagulation for pregnant women. No differences in symptomatic thrombotic events (RR 0.47; 95% CI, 0.09 to 2.49) were identified in a 2014 Cochrane review that compared antenatal prophylaxis with UFH or LMWH (four trials, pooled n = 404). LMWH has an enhanced ratio of antithrombotic (anti-factor Xa) to anticoagulant (anti-factor IIa) activity compared with UFH and does not affect activated partial thromboplastin time (aPTT) measurement. A 2005 systematic review (64 studies, pooled n = 2777) evaluated the efficacy and safety of LMWH in pregnancy. The rate of VTE in women receiving LMWH for thromboprophylaxis, prevention of adverse pregnancy outcome, or for unspecified indications was 0.9% (95% CI, 0.6% to 1.3%), and the rate of significant maternal bleeding was 2.0% (95% CI, 1.5% to 2.6%). There were no reported cases of heparin-induced thrombocytopenia when LMWH was used for any indication in pregnancy. An older systematic review (1999) did not identify any increase in osteoporosis in pregnant women treated with LMWH compared with nonpregnant controls.

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When LMWH is used for therapeutic anticoagulation,
dosing can be adjusted based on anti–factor Xa activity. The desired peak level is 0.6 to 1.0 U/mL measured 4 hours after injection; however, because of the cost of the assays, routine monitoring of anti–factor Xa activity is not recommended during therapy in pregnancy. Viscoelastic monitoring provides an alternative method to assess LMWH activity. Carroll et al. demonstrated that the delta reaction time (ΔR) measured by thromboelastography correlates with anti–factor Xa levels in the pregnant woman and allows LMWH doses to be adjusted to ensure anticoagulation or, conversely, confirms the absence of anticoagulation. LMWH is cleared by the kidney; therefore, dose reduction may be required in patients with renal failure.

UFH therapy may be used to initiate anticoagulation or to maintain therapy as the patient nears delivery (see later discussion). UFH exerts its anticoagulant activity by binding to antithrombin III and potentiates inactivation of other coagulation factors, including thrombin (factor IIa); factors IXa, Xa, Xla, and XIIa; and kallikrein. Typically, UFH is administered as a subcutaneous injection for both prophylactic and therapeutic therapy. The aPTT measured 6 hours after an injection or dose adjustment should be maintained at 1.5 to 2.5 times the normal range. In pregnancy, the bioavailability of UFH decreases as a result of an increase in heparin-binding proteins, increased plasma volume, increased renal clearance, and increased degradation by plasma heparinases. Based on pharmacodynamic studies, even a twice-daily dose of subcutaneous UFH is often inadequate to achieve prophylactic plasma heparin concentrations in the second half of pregnancy, possibly because of the presence of a heparin-neutralizing protein or the presence of increased factor VIII and fibrinogen levels in pregnancy. For therapeutic anticoagulation, the ACOG currently recommends a subcutaneous, twice-daily UFH dose of 10,000 units or greater, with aPTT monitoring and dose adjustment. In the event of an antepartum massive PTE resulting in hemodynamic instability, thrombolytic therapy should be considered as it is associated with high maternal and fetal survival. However, in the postpartum period, other options, including thrombectomy, should be considered because thrombolysis is associated with a significant risk for hemorrhage. In patients who develop heparin–induced thrombocytopenia, or severe cutaneous reactions to heparin, fondaparinux is the preferred anticoagulant because it has minimal cross-reactivity with UFH. Anticoagulation with other classes of drugs such as vitamin K antagonists, thienopyridines, direct factor Xa inhibitors, and direct thrombin inhibitors is possible in pregnancy, but the use of these medications is less common. Animal studies with rivaroxaban, a direct factor Xa inhibitor, and dabigatran, a direct thrombin inhibitor, have found teratogenic effects, reduced fetal viability, hemorrhagic changes, and placental abnormalities; thus, their use in pregnancy is not recommended.

**Antithrombotic Therapy and Anesthetic Implications**

In 2018, the American Society of Regional Anesthesia and Pain Medicine (ASRA) published updated guidelines for regional anesthesia in patients receiving antithrombotic or thrombolytic therapy. Owing to the relative paucity of outcome data in pregnant women, the ASRA suggests following the guidelines for surgical patients when developing clinical policy for obstetric patients with regard to initiation of neuraxial procedures and postpartum thromboprophylaxis. The ASRA-recommended time intervals between anticoagulant administration and the initiation of neuraxial anesthesia are summarized in Table 38.3.

Before the ASRA guideline release, the Society for Obstetric Anesthesia and Perinatology (SOAP) released a consensus statement with pregnancy-specific recommendations regarding neuraxial procedures in obstetric patients receiving thromboprophylaxis or therapeutic anticoagulation. The SOAP consensus statement integrates the ASRA guidelines, pharmacokinetic parameters of anticoagulants in pregnancy, and the risks associated with maternal airway management into decision-making algorithms intended to guide clinicians. The consensus statement emphasizes the importance of

| Table 38.2 Commonly Used Anticoagulation Regimens during Pregnancy |
|-------------------------------|-------------------------------|
| **Drug**                      | **Dose**                      |
| Prophylactic LMWH             | Enoxaparin 40 mg SC once daily |
|                               | Dalteparin 5000 units SC once daily |
|                               | Tinzaparin 4500 units SC once daily |
|                               | Nadroparin 2850 units SC once daily |
| Intermediate-dose LMWH        | Enoxaparin 40 mg SC every 12 hours |
|                              | Dalteparin 5000 units SC every 12 hours |
| Therapeutic LMWH (weight-adjusted treatment dose)* | Enoxaparin 1 mg/kg q12h |
|                               | Dalteparin 200 units/kg once daily |
|                               | Tinzaparin 175 units/kg once daily |
|                               | Dalteparin 100 units/kg q12h |
| Prophylactic UFH in the first trimester | UFH 5000–7500 units SC every 12 hours |
| Prophylactic UFH in the second trimester | UFH 7500–10,000 units SC every 12 hours |
| Prophylactic UFH in the third trimester | UFH 10,000 units SC every 12 hours (unless aPTT is elevated) |
| Therapeutic (adjusted-dose) UFH | UFH 10,000 units or more SC every 12 hours |
| Postpartum anticoagulation†   | Prophylactic LMWH for 6–8 weeks |

aPTT, Activated partial thromboplastin time; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.
*Target anti-Xa level 4 hours after last injection for twice-daily regimen: 0.6–1.0 unit/mL. Slightly higher doses may be necessary for once-daily dosing.
†Adjust dose to target aPTT (1.5–2.5 times the normal range 6 h after injection).
‡Oral anticoagulants may be considered based on planned duration of therapy, lactation, and patient preference.
TABLE 38.3  Recommended Time Intervals for Administration of Neuraxial Anesthesia after Anticoagulation and Initiation of Postpartum Anticoagulation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Administration of Neuraxial Anesthesia after Anticoagulation</th>
<th>Initiation of Postpartum Anticoagulation</th>
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<tbody>
<tr>
<td>SC UFH, low-dose prophylactica</td>
<td>Greater than or equal to 4 h or assessment of coagulation statusb</td>
<td>Greater than or equal to 1 h after neuraxial block or epidural catheter removal</td>
</tr>
<tr>
<td>SC UFH, intermediate dose</td>
<td>Greater than or equal to 12 h, and verify normal coagulation statusb</td>
<td>Greater than or equal to 1 h after neuraxial block or epidural catheter removal</td>
</tr>
<tr>
<td>SC UFH, therapeuticc</td>
<td>Greater than or equal to 2 h, and verify normal coagulation statusb</td>
<td>Greater than or equal to 1 h after neuraxial block or epidural catheter removal</td>
</tr>
<tr>
<td>IV UFH</td>
<td>4–6 h, and verify normal coagulation statusb</td>
<td>Greater than or equal to 1 h after neuraxial block or epidural catheter removal</td>
</tr>
<tr>
<td>LMWH, prophylactic</td>
<td>Greater than or equal to 12 h</td>
<td>Greater than or equal to 12 h after neuraxial block and epidural catheter removal</td>
</tr>
<tr>
<td>LMWH, therapeutic</td>
<td>Greater than or equal to 24 h</td>
<td>Greater than or equal to 24 h after neuraxial block and epidural catheter removal</td>
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TIME INTERVAL

TABLE 38.3  Recommended Time Intervals for Administration of Neuraxial Anesthesia after Anticoagulation and Initiation of Postpartum Anticoagulation

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</tr>
</tbody>
</table>

IV, Intravenous; LMWH, low-molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin.

*aUFH regimens of 5000 units SC two or three times a day.

*bCheck platelet count if either UFH or LMWH therapy for more than 4 days.

*cUFH regimens of 7500 to 10,000 units twice a day.

*dIf less than 12 hours and aPTT is within normal range, may consider neuraxial procedure based on assessment of risks and benefits.

*eUFH individual dose greater than 10,000 units SC or greater than 20,000 total units per day.


Clinicians weighing the risk associated with potential spinal or epidural hematoma against the risk associated with general anesthesia in decision-making.

The following anticoagulation strategies will help to facilitate safe and timely neuraxial analgesia/anesthesia for parturients:60,50:

1. Consider transitioning women taking LMWH to UFH at 36 weeks’ gestation, particularly if they are at risk for urgent delivery.

2. LMWH should be discontinued before planned delivery; the interval depends on the dose (see Table 38.3). LMWH therapy should be converted to UFH if necessary.

3. Intravenous UFH should be discontinued 4 to 6 hours before planned neuraxial procedure/delivery.

4. For patients being treated with either UFH or LMWH for more than 4 days, a platelet count should be assessed before initiation of neuraxial anesthesia procedures.

5. Aspirin should be discontinued at 35 to 36 weeks’ gestation in patients receiving pharmacologic thromboembolism prophylaxis.

Other anticoagulant medications sometimes administered to pregnant women include aspirin, warfarin, and newer anticoagulant medications. In patients receiving warfarin therapy, the ASRA recommends discontinuing warfarin therapy for 5 days and waiting for normalization of the international normalized ratio (INR).50 Neuraxial catheters are not recommended in patients receiving fondaparinux, and neuraxial techniques are not recommended in patients anticoagulated with direct thrombin inhibitors. Treatment with thrombolytics is an absolute contraindication to neuraxial anesthesia.50 By contrast, there is no contraindication to neuraxial anesthesia in patients who have received non-steroidal antiinflammatory drugs or aspirin, if these drugs are used alone.50

If a patient is not a candidate for neuraxial anesthesia, noninvasive analgesic methods (e.g., intravenous opioid analgesia) should be offered for labor, and general anesthesia should be performed for operative procedures, including cesarean delivery. Risks associated with general anesthesia in the anticoagulated patient include airway bleeding. Laryngoscopy and tracheal intubation should be as atraumatic as possible. The anesthesia provider should be aware that placement of nasopharyngeal and oropharyngeal airways, gastric tubes, and other devices (e.g., temperature probes, stethoscopes) carries a tangible risk for traumatic hemorrhage. Emergency surgery may necessitate the administration of protamine or the transfusion of blood products (e.g., plasma, platelets) to reverse anticoagulation and reduce the risk for hemorrhage during and after surgery.

The timing of initiation of pharmacologic prophylaxis postpartum varies according to which drug is chosen and the dose. Both the ASRA and the SOAP consensus statements recommend at least a 1-hour delay after neuraxial blockade or epidural catheter removal before starting or restarting UFH, regardless of dose; at least a 12-hour delay after neuraxial blockade before the initiation of low-dose LMWH; and at least a 24-hour delay after neuraxial blockade before initiating therapeutic LMWH doses (see Table 38.3).50,31
The greatest concern with neuraxial procedures in anticoagulated patients is spinal or epidural hematoma. A meta-analysis estimated the incidence of epidural hematoma in obstetric patients (8 studies, pooled \( n = 1.1 \) million) to be \( 1:183,000 \). An incidence of \( 1:251,643 \) (95% CI, \( 1:46,090 \) to \( 1:10,142,861 \)) was identified in the SOAP Serious Complication Repository Project (SCORE).\(^{53}\) Notwithstanding the very low incidence, the consequences of a spinal-epidural hematoma can be devastating. The ASRA guidelines include a summary of 15 cases of spinal hematoma after neuraxial anesthesia in obstetric patients; approximately one-third of the cases had some form of permanent motor or sensory deficit, and the interval between symptom onset and surgery; severity of preoperative deficits, the duration of maximum decompression. Neurologic recovery is a function of the age of the hematoma and symptoms of epidural hematoma (see Chapter 31). These include (1) severe, unremitting backache; (2) neurologic deficit, including bowel or bladder dysfunction or radiculopathy; (3) tenderness over the spinous or paraspinal area; and (4) unexplained fever.\(^{56}\) Suspicion of epidural hematoma should lead to immediate diagnostic imaging of the spinal cord and neurosurgical consultation for possible spinal cord decompression. Neurologic recovery is a function of the severity of preoperative deficits, the duration of maximum deficit, and the interval between symptom onset and surgery; better outcomes are associated with a shorter symptom onset-to-surgery interval.\(^{57}\) A high index of suspicion is necessary because neurologic dysfunction may mimic local anesthetic–induced effects.\(^{58}\)

**Prevention of Thromboembolic Events**

Anesthesia providers should work with obstetricians to develop and implement strategies to reduce VTE. Systems should be developed to identify at-risk women for whom peripartum mechanical or pharmacologic thromboprophylaxis is indicated. Given the recent expansion of indications for pharmacologic thromboprophylaxis,\(^{40}\) it is imperative that communication occur between anesthesia providers and obstetricians with regard to the timing of delivery, plans for the use of neuraxial analgesia and/or anesthesia, and plans for postpartum anticoagulation. Mechanical thromboprophylaxis should be initiated in women with contraindications to pharmacologic anticoagulation, and after all cesarean births.\(^{16,27}\) The use of intermittent pneumatic compression stockings have been shown to be cost-effective when compared with no thromboprophylaxis after cesarean delivery\(^{59}\); however, compliance with their use has been shown to be suboptimal.\(^{60}\) For women in whom significant risk factors persist after delivery, extended prophylaxis (6 to 8 weeks postpartum) is recommended.\(^{16,27,40}\) Women are at the highest risk for thrombotic events in the first week postpartum; therefore, careful postdischarge planning and evaluation of VTE risk are equally as important as inpatient management.

**AMNIOTIC FLUID EMBOLISM**

Death attributable to amniotic fluid embolism (AFE) was first reported by Meyer in 1926.\(^{61}\) Early reports described a syndrome of fatal peripartum shock attributed to emboli of amniotic fluid mechanically obstructing the maternal pulmonary circulation.\(^{62}\) Although the pathophysiology of this disease remains poorly understood, current evidence suggests that emboli alone are insufficient to precipitate this infrequent, idiosyncratic, and devastating condition. Rather, fetal material in the maternal circulation has the potential to trigger a massive cascade of inflammatory and hemostatic reactions that culminate in cardiopulmonary collapse and disseminated intravascular coagulation (DIC).

**Epidemiology**

The incidence of amniotic fluid embolism is difficult to establish because (1) there is no universally accepted definition for identifying cases of AFE, (2) differing ascertainment methods yield divergent rates of AFE, and (3) AFE is ultimately a diagnosis of exclusion. The lack of uniform diagnostic criteria is a significant barrier to furthering our understanding of AFE. A Japanese retrospective observational study\(^{66}\) reviewed 26 registered AFE cases and compared diagnosis agreement using three commonly used diagnostic criteria for AFE (the U.S. AFE Registry entry criteria,\(^{63}\) the UK Obstetric Surveillance System [UKOSS] entry criteria,\(^{64}\) and the Japanese consensus criteria\(^{65}\)). Table 38.4 summarizes the diagnostic criteria used for identifying AFE. Only 10 of the 26 cases were given a diagnosis of AFE by all three criteria.\(^{66}\) In 2016, the Society for Maternal-Fetal Medicine (SMFM) and the Amniotic Fluid Foundation convened a task force to develop uniform diagnostic criteria for research reporting of AFE.\(^{67}\) The newly published definition requires documentation of coagulopathy to confirm the diagnosis of AFE.\(^{67}\) When this definition was applied to maternal deaths caused by AFE from the French Confidential Enquiry into Maternal Deaths (2007 to 2011), documentation of coagulopathy was missing for 14 of the 39 deaths.\(^{68}\) It is important for clinicians to recognize that clinical variants of AFE exist and treatment should not be withheld if a patient is missing any of the required elements of the definition.\(^{69,70}\)

Currently, the UKOSS provides the most comprehensive prospective surveillance for amniotic fluid embolism in the world. All hospitals in the United Kingdom with a consultant-led maternity unit report all suspected cases of AFE, along
1.4 to 2.1). Cross-sectional analyses of administrative data suggest an event rate of 1.7 per 100,000 deliveries (95% CI, or hair in the maternal lungs. Registry data from the UKOSS or potential explanation for the symptoms and signs observed, hypoxemia, and/or coagulopathy in the absence of any other that include acute hypotension, cardiac arrest, acute hypotension, maternal hemorrhage, premonitory symptoms, seizures, shortness of breath OR: 2. Pathologic diagnosis of fetal squames or hair in the maternal lungs

### Risk Factors

Maternal demographic factors such as older age and race or ethnicity have been associated with AFE in population-based studies. Other obstetric factors such as abnormal placentation, placental abruption, eclampsia, multiple gestation, induction of labor, artificial or spontaneous rupture of membranes, and operative delivery have also been associated with AFE. Because nonreassuring fetal heart rate (FHR) tracings can complicate AFE in labor, cesarean delivery may be a consequence, rather than a cause, of intrapartum AFE. Nonetheless, a strong association between cesarean birth and postpartum AFE persists among women in the UKOSS dataset. Of the 55 women who presented postpartum, 71% delivered via cesarean. The adjusted odds ratio of postpartum AFE after cesarean delivery compared with other modes of delivery was 16.15 (95% CI, 6.20 to 42.05).

### Pathophysiology

In 1941, Drs. Steiner and Lushbaugh, two pathologists from the University of Chicago, described a case series of eight autopsies after fatal intrapartum shock. Examination of lung tissue from these cases revealed embolic material of squamous cells, mucin, meconium, and amorphous eosinophilic material. Because all of these patients were described as having tumultuous labors with stronger than usual uterine contractions, it was presumed that the forceful contractions loosened or tore the placenta and forced the emboli into the maternal circulation. Yet, periods of uterine tachysystole are the least likely times for maternal-placental exchange of embolic material to occur as uterine blood flow ceases. The tachysystole is probably a result of endogenous norepinephrine release and, therefore, is likely temporally related to, but not causative for, embolic material transfer.

### TABLE 38.4 Commonly Used Amniotic Fluid Embolism Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>United States Amniotic Fluid Embolism Registry Entry Criteria</th>
<th>United Kingdom Obstetric Surveillance System Criteria</th>
<th>Society for Maternal-Fetal Medicine and the Amniotic Fluid Foundation Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acute hypotension or cardiac arrest</td>
<td>In the absence of any other clear cause, either: 1. Acute maternal collapse with one or more of the following features: acute fetal compromise, cardiac arrest, cardiac arrhythmias, coagulopathy, hypotension, maternal hemorrhage, premonitory symptoms, seizures, shortness of breath OR: 2. Pathologic diagnosis of fetal squames or hair in the maternal lungs</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Acute hypoxia (dyspnea, cyanosis, respiratory arrest)</td>
<td></td>
<td>1. Sudden onset of cardiorespiratory arrest, or both hypotension and respiratory compromise</td>
</tr>
<tr>
<td>3.</td>
<td>Coagulopathy (laboratory evidence or hemorrhage without an alternative explanation)</td>
<td></td>
<td>2. Documentation of overt DIC, after the appearance of initial signs or symptoms, using the scoring system of Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Hemostasis (ISTH), modified for pregnancy. The coagulopathy must be detected before sufficient blood is lost to account for dilutional or shock-related consumptive coagulopathy</td>
</tr>
<tr>
<td>4.</td>
<td>Onset of the above during labor, cesarean delivery, dilation and evacuation, or within 30 minutes postpartum</td>
<td></td>
<td>3. Clinical onset during labor or within 30 minutes of delivery of the placenta</td>
</tr>
<tr>
<td>5.</td>
<td>Absence of an alternative explanation for the observed signs/symptoms</td>
<td></td>
<td>4. No fever (greater than or equal to 38.0°C) during labor</td>
</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulation.

Large intravenous boluses of human meconium suspended in human amniotic fluid can precipitate cardiovascular collapse in rabbits and dogs, but injection of autologous amniotic fluid fails to reproduce the AFE syndrome in many animal models. The passage of fetal squames, lanugo hair, and mucin into the maternal pelvic vasculature appears to be a common event at term, and fetal material has been identified in pulmonary arterial samples aspirated from critically ill women who did not have AFE.

The exact trigger for the reaction in women with AFE is not known but may be a rare pathologic fetal antigen or a common antigen presented in an unusual way—in amount, timing, or frequency of entry into the maternal circulation. AFE appears to be a systemic inflammatory response associated with the inappropriate release of endogenous inflammatory mediators. Whatever the trigger, several maternal endogenous mediators appear to play an important role in the initial reaction, including arachidonic acid metabolites (thromboxane, prostaglandins, leukotrienes, endothelins).

Approximately 40% of women in a U.S. national AFE registry had a history of allergy or atopy, leading some authors to suggest an anaphylactoid mechanism. In support of this theory, the symptoms of AFE could be blocked by the administration of a leukotriene inhibitor in a rabbit model. However, a series of case reports now suggests that levels of tryptase and histamine are not dramatically or universally elevated among women experiencing the AFE syndrome. Although mast cell degranulation may contribute to the pathophysiology of AFE, this effect may be a secondary product of the inflammatory cascade, rather than causal, and thus the term anaphylactoid syndrome of pregnancy may be a misnomer.

Other immune-mediated mechanisms have also been implicated in AFE. A case-control study demonstrated low levels of the complement components C3 and C4 among women diagnosed with AFE compared with controls, suggesting that complement activation may also contribute to the inflammatory cascade. Whether complement plays a primary or secondary role in the AFE syndrome is unknown. A heat-stable pressor agent in meconium has been suggested as another possible mediator of AFE; in a goat model, this agent caused a circulatory response similar to that seen in human AFE.

Alternatively, the hemodynamic consequences of AFE could derive from activation of the coagulation system, mediated through platelet activation. Fetal squamous cells and syncytiotrophoblasts display high concentrations of tissue factor and phosphatidylserine. Tissue factor irreversibly aggregates platelets, leading to platelet degranulation, which releases thromboxane, serotonin, and additional mediators that amplify the immunologenic systems. Serotonin is a potent pulmonary vasoconstrictor that produces vasodilation in the systemic vasculature and may lead to early right-sided heart failure in the AFE syndrome.

Coagulopathy develops in the majority of women who survive the initial cardiovascular collapse. One proposed mechanism involves tissue factor. As pregnancy progresses, increasing amounts of tissue factor, a potent procoagulant, accumulates in the amniotic fluid. Tissue factor binds factor VII, thus activating the extrinsic pathway and triggering clotting by activating factor X, with the subsequent development of a consumptive coagulopathy. A second possible mechanism is that amniotic fluid has a thromboplastin-like effect, which induces platelet aggregation, releases platelet factor III, and activates the clotting cascade. Other components of amniotic fluid, the amniochorion, and the placenta have also been implicated in contributing to the coagulopathy. Uterine atony, whether resulting from a specific myometrial depressant or from uterine hypoperfusion, may exacerbate hemorrhage and the consumptive coagulopathy seen in AFE. There is conflicting evidence regarding whether the bleeding seen in AFE is due primarily to a consumptive coagulopathy or massive fibrinolysis. A rapid and severe hypofibrinogenemia has been observed during AFE.

Future work is necessary to further refine our understanding of the coagulopathy that accompanies AFE.

Clinical Presentation

Whereas the classic presentation of AFE includes acute respiratory distress, cardiovascular collapse, and coagulopathy near the time of delivery, a broad range of AFE syndromes have been described in situations in which other diagnoses were excluded.

AFE most often occurs during labor; intrapartum events comprise 53% of cases in the UKOSS registry and 70% in the U.S. registry. In the U.S. registry, seizure and dyspnea were the two most common presenting symptoms in women who collapsed before delivery. In a more recent multicenter retrospective cohort study, loss of consciousness was the most common presenting symptom. Maternal symptoms may precede FHR changes. Fetal bradycardia, or the abrupt onset of variable decelerations that progress to fetal bradycardia, may also herald AFE in labor.

AFE can present after abdominal trauma, after first-trimester abortion, in the second trimester, at the time of delivery, and in the postpartum period. Although acknowledging that AFE has been reported up to 48 hours postpartum, the newly published criteria by the SMFM and the Amniotic Fluid Foundation require the diagnosis of AFE to be made within 30 minutes of placental delivery.

Close inspection of hemodynamic data reveals a biphasic cardiovascular response during AFE. During the initial phase, acute pulmonary hypertension results in right ventricular dilation, a decrease in cardiac output, and ventilation-perfusion (V/Q) mismatch resulting in oxygen desaturation. In the U.S. registry, 11 of 17 patients with an arterial blood gas sample drawn within 30 minutes of the acute event demonstrated an initial PaO2 less than 30 mm Hg while breathing an FiO2 of 100%. Release of endogenous catecholamines may produce a brief period of systemic hypertension and uterine tachysystole that precedes hypotension or cardiac arrest. In a minority of cases, there is massive hemorrhage and DIC without preceding cardiopulmonary collapse.
Electrocardiographic findings are nonspecific and vary from ST-segment and T-wave abnormalities to arrhythmias or asystole. A chest radiograph may show diffuse bilateral heterogeneous or homogenous areas of opacity. Echocardiography typically demonstrates a dilated, akinetic right ventricle, pulmonary hypertension, and a normally contracting left ventricle with a nearly obliterated cavity. Initially, right ventricular failure leads to right ventricular dilation, which compresses the left ventricle and impedes left ventricular filling and cardiac output. A second phase commences when right ventricular function improves, typically 15 to 30 minutes after the initial event. At this point, left ventricular failure may persist as a result of ischemic injury to the left ventricle or direct myocardial depression, and it is accompanied by decreased systemic ventricular resistance, decreased left ventricular stroke index, and pulmonary edema. Women who survive to the second phase may also experience hemorrhage and DIC. Laboratory analysis may reveal anemia, thrombocytopenia, prolonged prothrombin time or aPTT or both, and significant hypofibrinogenemia. Viscoelastic blood testing may demonstrate early hyperfibrinolysis and hypofibrinogenemia.

Because many of the signs and symptoms are nonspecific, the differential diagnosis for AFE is extensive and should include nonobstetric, obstetric, and anesthetic causes (Box 38.2). Even though the time course and clinical presentation of many of these competing diagnoses are similar, only amniotic fluid embolism and placental abruption result in a relatively sudden onset of coagulopathy after maternal collapse.

**Confirmatory Tests**

To date, there is no definitive test to confirm the diagnosis of AFE, although the UKOSS considers the finding of fetal material in the maternal pulmonary vasculature at autopsy to be pathognomonic for AFE. However, fetal squamous cells and trophoblasts are commonly found in the maternal circulation of healthy parturients. Furthermore, differentiating between maternal and fetal cells histologically is challenging. Clinicians should therefore not place invasive monitors solely for the purpose of aspirating cells of fetal origin.

Several biochemical markers have been suggested. Although some of these may be promising based on preliminary data and the proposed pathophysiology of AFE, studies of test performance are limited by delayed sample acquisition and small sample size because of the rarity and unpredictability of the AFE syndrome.

Several markers suggest an anaphylactic/anaphylactoid mechanism. Mast cells release tryptase and histamine during degranulation; tryptase has been used as a marker for anaphylaxis because its half-life is longer than that of histamine. Elevations in serum tryptase have been reported in some parturients with AFE. However, a case series found normal tryptase and urinary histamine levels in nine women with

**BOX 38.2 Differential Diagnosis of Amniotic Fluid Embolism**

<table>
<thead>
<tr>
<th>Nonobstetric</th>
<th>Obstetric</th>
<th>Anesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Placental abruption</td>
<td>High neuraxial blockade (“total spinal”)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Eclampsia</td>
<td>Local anesthetic systemic toxicity</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Uterine rupture or laceration</td>
<td>Medication error</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Obstetric hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>
The optimal threshold value for SCC antigen levels was associated with autopsy-proven AFE compared with healthy controls. Serum SCC antigen levels were higher in women who were diagnosed with AFE compared with nonfatal cases (23% versus 32%, \( P < .05 \)).

Complement activation may cause mast cell degranulation, and there is some evidence supporting widespread complement activation, and depressed C3 and C4 levels in AFE. However, because complement activation is not specific for AFE, levels are not elevated with infections, and other inflammatory states. Therefore, results are not specific for AFE. C1 esterase inhibitor (C1INH), which inhibits C1 as well as kallikrein and factors XIa and XIIa, has been suggested as a possible biomarker to support the clinical diagnosis of AFE. C1INH levels were lower in women who were diagnosed with AFE compared with healthy pregnant controls (30% versus 62%, \( P < .001 \)). C1INH levels were further decreased in fatal AFE cases compared with nonfatal cases (23% versus 32%, \( P < .05 \)).

Zinc coproporphyrin and sialyl Tn antigen are two biomarkers that are components of meconium and have been associated with the AFE syndrome. Sialyl Tn is a mucinous glycoprotein that originates in the fetal gastrointestinal tract and is also associated with mucinous gastrointestinal tumors. Insulin-like growth factor–binding protein-1 (IGFBP-1) has been identified as a sensitive and specific biomarker for AFE in a case-control study conducted in 13 delivery centers in France. IGFBP-1 levels exceeded 104.5 \( \mu \)g/L in all patients who died of AFE but was 95 \( \mu \)g/L in 23 of 25 women who were diagnosed with AFE and remained below 95 \( \mu \)g/L in all patients with postpartum hemorrhage caused by atony, thrombotic pulmonary embolism, or uncomplicated labor. Finally, squamous cell carcinoma (SCC) antigen, a gene product present only in the amniotic fluid and not in the maternal serum, has been suggested as a potential candidate marker for diagnosing AFE. Serum SCC antigen levels were higher in women who autopsy-proven AFE compared with healthy controls. The optimal threshold value for SCC antigen levels was 7.15 ng/mL; sensitivity was 60% and specificity was 89%.

Confirmatory studies are necessary.

### Management

Although no single intervention has been shown to reliably reverse the AFE syndrome, prompt recognition and aggressive resuscitation may improve maternal and fetal outcomes. Maternal resuscitation should focus on three priorities: (1) maintenance of oxygenation, (2) hemodynamic support, and (3) correction of coagulopathy (Box 38.3).

At the time the diagnosis of AFE is suspected, 100% oxygen should be delivered to the patient. Given the risk for coagulopathy and hemorrhage, large-bore intravenous access is warranted. An arterial line and central venous pressure catheter may facilitate hemodynamic monitoring, blood sampling, and vasopressor administration. Transesophageal echocardiography may be useful to guide volume resuscitation and selection of appropriate vasopressor therapy.

In addition to standard resuscitative measures, other management strategies have been reported for AFE. The use of cardiopulmonary bypass, extracorporeal membrane oxygenation, continuous hemofiltration, exchange transfusions, and intra-aortic balloon counterpulsation have all been described. It is speculated that filtration technologies may filter amniotic fluid or vasoactive mediators from the systemic circulation. Strategies for management of right-sided heart failure include inhaled nitric oxide, prostacyclin, right ventricular assist devices, and vasopressors such as vasopressin, dobutamine, and milrinone.

Intact neonatal survival is related to the time interval from the onset of maternal compromise to delivery. In the event of maternal cardiopulmonary arrest, immediate high-quality cardiopulmonary resuscitation should be initiated (see Chapter 54). The American Heart Association recommends that delivery of the fetus should occur within 5 minutes to increase the probability of favorable outcomes for both the mother and her neonate. Although the operating room may provide a more favorable environment for surgery...
and resuscitation, simulation studies have suggested that resuscitation quality and the arrest-to-delivery interval both suffer with maternal transport\(^{128,129}\); therefore, if obstetric conditions do not support an immediate operative vaginal delivery (i.e., forceps or vacuum), a bedside perimortem cesarean delivery is indicated. After cardiac arrest, mild therapeutic hypothermia (temperature between 32° C and 34° C), when maintained for 12 to 24 hours, is associated with improved neurologic outcomes and reduced mortality in the nonpregnant patient population.\(^{130}\) In the setting of severe coagulopathy, the effects on the coagulation system must be balanced against any neurologic benefit of mild hypothermia.

Because coagulopathy will likely ensue for the majority of AFE survivors, early assessment of coagulation status is indicated, and the massive transfusion protocol should be activated as soon as AFE is suspected.\(^{99}\) Blood and component therapy should be guided by the clinical presentation (see Chapter 37). Close communication with the blood bank is paramount because large quantities of blood products may be needed. Although the optimal transfusion strategy is not known, one case-control study has shown improved survival with a higher (≥ 1) FFP : RBC transfusion ratio compared with lower ratios (adjusted odds ratio [aOR], 28.32; 95% CI, 4.26 to 188.37).\(^{131}\) Potential pharmacologic therapies for the coagulopathy associated with AFE include antifibrinolytic agents (e.g., tranexamic acid), recombinant factor VIIa (rVIIa), prothrombin thrombin concentrate, and fibrinogen concentrate.\(^{100,114,132}\)

The use of rVIIa to treat intractable hemorrhage in the AFE syndrome remains controversial. Use of rVIIa for obstetric hemorrhage is off-label (see Chapter 37). Recombinant factor VIIa binds to tissue factor and initiates clotting via the extrinsic pathway. Although individual case reports have described improvement in hemostasis, rVIIa has been associated with thrombotic complications. A meta-analysis of 25 trials involving 3849 nonobstetric bleeding patients without hemophilia found a significant increase in arterial thromboembolic events among patients who received rVIIa (RR 1.45; 95% CI, 1.02 to 2.05).\(^{133}\)

A case-control study based on a systematic review of case reports of women with the AFE syndrome identified a twofold increase in risk for death or permanent disability among 16 women treated with rVIIa compared with 28 control patients who underwent surgery to control bleeding but did not receive rVIIa.\(^{132}\) Among survivors, treatment with rVIIa was associated with more permanent disability (RR, 4.0; 95% CI, 1.5 to 10.4), largely attributed to thrombosis in major organs.\(^{132}\) An unmeasured increase in severity of disease in the treatment group compared with the control group could explain these dismal results because the population of patients who did not survive to the time of operation was excluded from the analysis. In this case-control study of case reports,\(^{132}\) 50% of parturients treated with rVIIa survived, whereas in the 2010 UKOSS dataset,\(^{46}\) 93% of the parturients treated with rVIIa survived (n = 14).\(^{64}\) However, the 2016 UKOSS summary did not report differences in survival or neurologic outcomes in AFE patients treated with and without rVIIa.\(^{72}\)

Recombinant factor VIIa should be considered as a last resort should component replacement and other surgical interventions fail.\(^{99}\)

### Maternal and Perinatal Outcomes

The maternal mortality ratio associated with AFE has been reported between 0.5 and 1.7 deaths per 100,000 live births.\(^{134}\) The pooled AFE-related case-fatality rate from 12 population-based studies published between 1999 and 2016 (n = 17,451,646 deliveries) is 20.4%.\(^{135}\) This rate is significantly lower than the 61% fatality rate reported in the 1988 to 1994 analysis of the U.S. AFE registry.\(^{72}\) Suboptimal care was identified in 20 of the 36 AFE mortalities in the French Confidential Enquiry into Maternal Deaths (2007 to 2011), with contributing factors including delays in, or suboptimal, transfusion management, as well as delays or lack of performing indicated hysterectomies.\(^{48}\)

Cardiac arrest complicated 87% of AFE cases reported to the U.S. registry but only 46% of cases identified by UKOSS.\(^{13,72}\) This difference may reflect more comprehensive ascertainment in the United Kingdom that captures less severe cases; alternatively, improvements in early recognition and management of AFE over the past 20 years may explain improved outcomes reported more recently from the United Kingdom compared with those previously published from the U.S. registry. Interestingly, in the UKOSS dataset, women with AFE who died were more likely than those who survived to present with cardiac arrest (87% versus 36%, \(P < .001\)).\(^{72}\) Patients who died of AFE were more likely to be from ethnic minority groups than were survivors, even after adjusting for confounders such as age, socioeconomic status, body mass index, parity, and induction of labor (aOR, 2.85; 95% CI, 1.02 to 8.00).\(^{72}\) Similar racial/ethnic disparities in maternal mortality have been observed in the United States.\(^{136}\) Improvements in the management of critically ill parturients may have contributed to the decline in the case-fatality rate observed in the two studies, but the disparity in outcomes by race/ethnicity suggests further systems improvements are necessary. Multidisciplinary reviews are currently recommended for all severe obstetric hemorrhages to identify systems issues or breakdowns that contributed to the outcome\(^{137}\); implementation of such reviews could be employed for AFE cases, and may reduce current racial/ethnic disparities.\(^{138}\)

Neurologic outcomes for survivors appear to be improving. The 1995 analysis of the U.S. registry reported a 15% overall rate of intact neurologic survival\(^{139}\); by contrast, only 7% of AFE survivors suffered permanent neurologic injury in the 2016 UKOSS dataset.\(^{72}\)

Neonates have a high overall survival rate, with greater than 90% of infants surviving.\(^{72,73}\) Intact neurologic survival for infants is related to the cardiac arrest-to-delivery interval; delays of greater than 15 minutes are associated with poor outcomes.\(^{43}\)

Verified recurrent AFE has not been reported; however, this may be attributable to reproductive choices of AFE survivors.\(^{139}\) A survey of Amniotic Fluid Embolism Registry
survivors revealed that only 30% subsequently conceived, and 57% of survey participants reported that the diagnosis of AFE affected their decisions about future childbearing.\textsuperscript{139}

**VENOUS AIR EMBOLISM**

Venous air embolism (VAE) is a recognized complication of many surgical procedures.\textsuperscript{140} The first study of VAE during cesarean delivery was published in 1987.\textsuperscript{141} Subsequent research has revealed that VAE is a common occurrence during cesarean delivery. Most air emboli are small, but volumes greater than 200 to 300 mL, or 3 to 5 mL/kg, may be lethal.\textsuperscript{142} Early recognition and appropriate management are necessary for avoiding unfavorable outcomes.

**Incidence**

The reported incidence of VAE during cesarean delivery varies depending on the method used to ascertain the presence of air (Table 38.5). The most sensitive monitors detect volumes of air as low as 0.02 mL/kg.\textsuperscript{140} Studies that have used precordial Doppler monitoring in patients undergoing cesarean delivery with neuraxial anesthesia have found incidence rates ranging from as low as 10\%\textsuperscript{142} to as high as 65\%.\textsuperscript{143} One study used precordial Doppler monitoring to detect VAE and correlated the Doppler findings with transthoracic echocardiographic evidence of intracardiac air. Of the 42 patients who underwent cesarean delivery with neuraxial anesthesia, 11 (26\%) had evidence of VAE, with perfect agreement between the Doppler and the echocardiographic monitoring (kappa = 1.0).\textsuperscript{144} Another study of healthy parturients undergoing elective cesarean delivery with general anesthesia found that 29 of 30 parturients had evidence of intraoperative VAE.\textsuperscript{145} The authors defined VAE as a 0.1\% increase from the baseline of expired nitrogen concentration (equivalent to 0.25 to 1.0 mL/kg venous air).\textsuperscript{145} Although the volume of entrained air may be lower with general anesthesia using positive-pressure ventilation than spontaneous ventilation,\textsuperscript{146} the use of prophylactic positive end-expiratory pressure has not been shown to decrease the incidence of VAE in a neurosurgical population.\textsuperscript{147}

The incidence of VAE does not appear to vary with maternal position. Although the Trendelenburg position could produce a pressure gradient between the right side of the heart and open venous sinuses in the surgical field, a meta-analysis of two randomized controlled trials, which compared 5 to 10 degrees reverse Trendelenburg positioning with supine positioning for cesarean delivery (pooled n = 130) found no difference in the incidence of air embolism (RR 0.85; 95\% CI, 0.28 to 2.57).\textsuperscript{146}

The majority of VAE episodes are subclinical. The true incidence of fatal VAE in the obstetric population is unknown. One estimate using data on maternal deaths from the National Center for Health Statistics from 1974 to 1978 found that 25 of 2475 deaths were attributable to air embolism.\textsuperscript{145} In recent Confidential Enquiries into Maternal Deaths and Morbidity reports from the United Kingdom, no VAE-related deaths were reported.\textsuperscript{139}

**Pathophysiology**

A pressure gradient as small as –5 cm H\textsubscript{2}O between the surgical field and the heart allows a significant amount of air to be entrained into the venous circulation. Immediately after placental separation, the raw endometrial surface appears to be a location of significant air entrainment; almost all episodes of VAE during cesarean delivery are noted after delivery of the placenta.\textsuperscript{143} In the noncesarean delivery setting, pressurized air in the vagina is believed to traverse the cervical canal, dissect around fetal membranes (if present), and enter the maternal circulation via subplacental sinuses.\textsuperscript{150} Venous air embolism has been reported during pregnancy during vaginal examinations and orogenital sex,\textsuperscript{151–153} as well as postpartum during manual repositioning of an inverted uterus.\textsuperscript{154}

Small volumes of air can precipitate pulmonary vasospasm via a pathophysiologic process that mimics that of other embolic phenomena. Vasoactive mediators or mechanical obstruction of small vessels appear to induce pulmonary vasoconstriction that leads to V/Q mismatch, hypoxemia, right-sided heart failure, arrhythmias, and hypotension. Fluid resuscitation and increased hydrostatic pressure may provoke interstitial pulmonary edema. A paradoxical air embolus into the arterial circulation (by means of a patent foramen ovale) can lead to cardiovascular and neurologic sequelae and morbidity. Large volumes of air (greater than 3 mL/kg) can generate cardiovascular collapse by creating an “air lock” that causes right-ventricular outflow tract obstruction.

**Clinical Presentation**

Most air emboli are subclinical with no sequelae; however, massive VAE can manifest as a sudden, dramatic, and devastating event with hypotension, hypoxemia, and even cardiac arrest.\textsuperscript{155} In awake patients receiving neuraxial anesthesia, transient episodes of hypoxemia, dyspnea, or chest pain during uterine repair suggest VAE.\textsuperscript{142,143,156} In the patient receiving general anesthesia, evidence of VAE may be limited to hypoxemia and a slight decrease in end-tidal CO\textsubscript{2}.\textsuperscript{140} VAE may be more frequent when the uterus is exteriorized than when it is repaired within the abdomen, either caused by

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**TABLE 38.5** Methods to Detect Venous Air Embolism

<table>
<thead>
<tr>
<th>Method of Detection</th>
<th>Sensitivity</th>
<th>Volume of Air Detected (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transesophageal echocardiography</td>
<td>High</td>
<td>0.02</td>
</tr>
<tr>
<td>Precordial Doppler</td>
<td>High</td>
<td>0.05</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>High</td>
<td>0.25</td>
</tr>
<tr>
<td>Expired CO\textsubscript{2}</td>
<td>Moderate</td>
<td>0.5</td>
</tr>
<tr>
<td>Expired nitrogen</td>
<td>Moderate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

vertical elevation relative to the heart or traction on the uterus that opens venous sinuses. A precordial stethoscope may detect a pathognomonic “millwheel murmur.” Transesophageal echocardiography may detect air in the right atria or the pulmonary artery. Clinically significant air emboli may be associated with hypotension, heart rate or rhythm changes, evidence of right-sided heart strain on the electrocardiogram, an increase in central venous pressure, and/or an increase in pulmonary artery pressure. Although isolated ST-segment depression during cesarean delivery was once common and thought to be possibly related to VAE, more recent evidence suggests that ST-segment depression in the immediate postdelivery period may be associated with rapid oxytocin administration. One small prospective observational study failed to identify VAE using echocardiography at the time of ST-segment depression during cesarean deliveries.

Management

The clinician should consider VAE in women who complain of intraoperative chest pain or dyspnea or experience sudden hypoxemia, hypotension, or arrhythmia during cesarean delivery. Although continuous precordial Doppler monitoring has been recommended by some experts, the rarity of hemodynamically significant VAE suggests that targeted use in high-risk patients (e.g., women with a known intracardiac shunt) may be more appropriate than routine application. Transthoracic or transesophageal echocardiography may help to confirm a diagnosis of VAE, to exclude alternative causes of hemodynamic instability, and to guide appropriate clinical management. Regardless, clinical suspicion of VAE should prompt appropriate management (Box 38.4).

Currently, there are no data to support central line insertion for air aspiration from the right side of the heart, but central line placement may be indicated to deliver potent vasopressors. Maternal position changes to limit air entrainment are recommended; however, to date, no human data support placing the patient in the left lateral decubitus position to relieve the “air lock.” In a canine study of resuscitation positioning after a 2.5-mL/kg VAE, repositioning animals to direct air to the nondependent portion of the right side of the heart did not improve cardiac function or survival. The use of the Valsalva maneuver and positive-end expiratory pressure should be avoided because an increase in right atrial pressure may result in a paradoxical embolism. In patients with delayed emergence from anesthesia, computed tomography or magnetic resonance imaging may be considered to evaluate for intracerebral air. Hyperbaric oxygen may improve neurologic outcomes if instituted within 6 hours of intracerebral air embolism.

**BOX 38.4 Resuscitation of the Obstetric Patient with Massive Venous Air Embolism**

**Air**
- Prevent further air entrainment (e.g., flood the surgical field with saline solution, lower the surgical field relative to the heart, if tolerated).

**Airway**
- Administer 100% oxygen, discontinue nitrous oxide, intubate the trachea, and support ventilation as needed.

**Cardiovascular Support**
- Support circulation with chest compressions, intravascular volume expansion, and vasopressors as needed.

**Fetus**
- Expedite delivery.

**Postresuscitation Care**
- Evaluate for intracerebral air, and consider hyperbaric oxygen therapy if indicated.
- Consider initiation of mild therapeutic hypothermia after cardiac arrest.

**KEY POINTS**

- Embolic disorders are a major cause of maternal morbidity and mortality.
- Early recognition, diagnosis, and therapy may reduce the incidence of morbidity and mortality associated with embolic disorders.
- During pulmonary embolic phenomena, hemostatic and immunologic mediators may trigger a cascade of physiologic derangements disproportionate to the cross-sectional area of occluded lung tissue.
- Pregnant patients are at a fivefold higher risk than non-pregnant patients for thromboembolic events. The third trimester and first postpartum week are the periods of highest risk.
- Several prophylactic and therapeutic anticoagulation regimens exist for patients with venous thromboembolism or those at increased risk for thromboembolism; anesthesia providers should be aware of the safety implications of anticoagulation therapy on the timing of initiation of neuraxial anesthesia and neuraxial catheter removal.
- Amniotic fluid embolism is a diagnosis of exclusion. It may occur at any time during labor or delivery, as well as antepartum or postpartum.
- Venous air embolism is a common occurrence during cesarean delivery. Most of the emboli are small, transient, and benign. Massive venous air embolism is rare during vaginal or cesarean delivery but can be fatal.
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135. Vartikar JV, Johnson MD, Datta S. Precordial Doppler monitoring and pulse oximetry during cesarean delivery:


Globally in 2015, an estimated 303,000 women died while pregnant or within 42 days of the end of pregnancy. This number corresponds to a ratio of 216 maternal deaths per 100,000 live births and to a 1-in-180 lifetime risk for pregnancy-related death for each girl entering her childbearing years (Table 39.1). According to the World Health Organization (WHO), “No issue is more central to global well-being than maternal and perinatal health. Every individual, every family and every community is at some point intimately involved in pregnancy and the success of childbirth.”

Definitions for maternal death are listed in Table 39.2, and measures of maternal mortality are listed in Table 39.3. More than 99% of maternal deaths occur in low- and middle-income countries, with 84% in either sub-Saharan Africa or South Asia (Fig. 39.1). Between 1990 and 2015, the global maternal mortality ratio (MMR) fell by 44%, an impressive improvement, but less than the 75% reduction targeted by the Millennium Development Goals. In 2015, the United Nations issued 17 Sustainable Development Goals, including a commitment to reduce the global MMR to less than 70 per 100,000 live births by 2030, with no single country having an MMR of more than 140. Several regions will require substantial investment to meet this goal, most notably sub-Saharan Africa, where the lifetime risk for maternal death remains remarkably high, at 1 in 36. There is considerable regional variation. Within sub-Saharan Africa, the highest MMRs are in Sierra Leone (1360), Central African Republic (882), and Chad (856) and represent rates that are 10-fold higher than the lowest ratios in the region. Throughout the world, war, natural disaster, and political conflict can degrade health systems and trigger a rise in deaths caused by complications that would be treatable under stable conditions.

**Leading Causes**

Hemorrhage, hypertensive disorders of pregnancy, and sepsis account for more than one-half of global maternal deaths and for slightly more than one-third of deaths in the developed world. Hemorrhage is the leading direct cause of maternal death worldwide, followed by hypertensive disorders, causing an estimated 27.1% and 14.0% of all deaths, respectively (see Fig. 39.1). Infection and sepsis may be substantially underestimated in regions where laboratory diagnostic tests are unavailable. In one Malawi hospital with full laboratory capabilities, infection played a primary role in almost three-fourths of all maternal deaths.

Rarely, anemia can cause lethal congestive heart failure in pregnancy, but more commonly, it increases the risk for maternal death from other complications, particularly hemorrhage and infection. Risk factors associated with anemia include (1) iron and other micronutrient deficiencies, (2) pregnancy intervals of less than 1 year, (3) adolescent pregnancy, (4) hemoglobinopathy, (5) urinary tract infection, (6) human immunodeficiency virus (HIV) infection, (7) parasitic infections including malaria, and (8) recurrent antepartum hemorrhage.

Obstructed labor causes less than 10% of maternal deaths worldwide, but it is an important cause of mortality in communities where early adolescent pregnancy is common, childhood malnutrition leads to small maternal pelvices, and operative delivery is unavailable. Death from obstructed labor is largely the result of hemorrhage caused by uterine rupture, or sepsis caused by ascending genital tract infection, and deaths may be coded under those categories. Prolonged pressure on the pelvic outlet can lead to tissue necrosis and obstetric fistula, which is thought to affect between 2 and 3.5 million women worldwide.

<table>
<thead>
<tr>
<th>Region</th>
<th>MMR</th>
<th>Lower Estimate</th>
<th>Upper Estimate</th>
<th>Number of Maternal Deaths</th>
<th>Lifetime Risk for Maternal Death, 1 in</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>215</td>
<td>207</td>
<td>249</td>
<td>303,000</td>
<td>180</td>
</tr>
<tr>
<td>Developed Regions</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>1700</td>
<td>4900</td>
</tr>
<tr>
<td>Developing Regions</td>
<td>239</td>
<td>229</td>
<td>275</td>
<td>302,000</td>
<td>150</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>70</td>
<td>56</td>
<td>92</td>
<td>3100</td>
<td>450</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>546</td>
<td>511</td>
<td>652</td>
<td>201,000</td>
<td>36</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>27</td>
<td>23</td>
<td>33</td>
<td>4800</td>
<td>2300</td>
</tr>
<tr>
<td>Southern Asia</td>
<td>176</td>
<td>153</td>
<td>216</td>
<td>66,000</td>
<td>210</td>
</tr>
<tr>
<td>Southeastern Asia</td>
<td>110</td>
<td>95</td>
<td>142</td>
<td>13,000</td>
<td>380</td>
</tr>
<tr>
<td>Western Asia</td>
<td>91</td>
<td>73</td>
<td>125</td>
<td>4700</td>
<td>360</td>
</tr>
<tr>
<td>Caucasus and Central Asia</td>
<td>33</td>
<td>27</td>
<td>45</td>
<td>610</td>
<td>1100</td>
</tr>
<tr>
<td>Latin America</td>
<td>60</td>
<td>57</td>
<td>66</td>
<td>6600</td>
<td>760</td>
</tr>
<tr>
<td>Caribbean</td>
<td>175</td>
<td>130</td>
<td>265</td>
<td>1300</td>
<td>250</td>
</tr>
<tr>
<td>Oceania</td>
<td>187</td>
<td>95</td>
<td>381</td>
<td>500</td>
<td>150</td>
</tr>
</tbody>
</table>

1Numbers of maternal deaths and lifetime risk numbers have been rounded according to the following scheme: < 100 rounded to nearest 1; 100–999 rounded to nearest 10; 1000–9999 rounded to nearest 100; and ≥ 10,000 rounded to nearest 1000.

HIV/acquired immune deficiency syndrome (AIDS) increases vulnerability to both nonobstetric infection (e.g., tuberculosis, malaria) and obstetric complications (e.g., hemorrhage, pregnancy-related sepsis, septic abortion). Global mortality attributed to HIV/AIDS peaked in 2004, and the WHO attributed 1.6% of maternal deaths in 2015 to HIV/AIDS. In countries most severely affected (e.g., Botswana, Malawi, South Africa), MMRs increased between 1990 and 2000, but they have subsequently declined with increasing availability of antiretroviral therapy.

Maternal deaths attributed to unsafe abortion account for 5% to 13% of maternal deaths worldwide. The WHO defines unsafe abortion as “a procedure for terminating an unintended pregnancy either by individuals without the necessary skills or in an environment that does not conform to minimum medical standards, or both.” Worldwide, 45% of abortions were unsafe between 2010 and 2014, compared with 44% in 1995. The case-fatality rate (460 maternal deaths per 100,000 unsafe abortions) and the absolute number of maternal deaths per year (28,500) are highest in sub-Saharan Africa.

Early marriage (before 18 years of age) has been identified as a major health risk for girls, increasing their exposure to domestic violence, coercion, pregnancy, and sexually transmitted diseases such as HIV/AIDS. Girls younger than 15 years of age are four times more likely to die in childbirth than women in their 20s, and pregnancy is among the leading causes of death worldwide for girls 15 to 19 years of age. Early childbearing also increases the likelihood of high parity birth (greater than or equal to 5) later in life. With a threefold increase in the MMR, high parity is the most important demographic risk for maternal death because it remains so common, accounting for 29% of births globally between 1990 and 2005.
delivery is the most common major surgical procedure in Africa. Perioperative maternal mortality is estimated to be between 1.2% and 2%, with one in seven deaths associated with cesarean delivery attributed to anesthesia. Although general anesthesia is associated with a threefold increased risk for death (5.9 per 1000 general anesthetics versus 1.2 per 1000 neuraxial anesthetics), reports of high spinal anesthesia and hemodynamic collapse highlight potential hazards with neuraxial anesthesia. Failed airway management (including bronchospasm and aspiration of gastric contents) accounts

Anesthesia providers working in the developing world must contend with profound limitations in staffing, equipment, and other resources. In addition, patients who labor at home may face a variety of social and environmental obstacles to reach a facility with the capacity to provide comprehensive emergency obstetric care, and many arrive at these facilities in septic or hemorrhagic shock. Cesarean

### TABLE 39.2 Glossary of Terms Used in Discussions of Maternal Mortality

<table>
<thead>
<tr>
<th>Source</th>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization</td>
<td>Maternal death</td>
<td>Death while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. ICD-10 A34, O00-O95, O98-O99.</td>
</tr>
<tr>
<td></td>
<td>Direct maternal death</td>
<td>Death resulting from obstetric complications of the pregnant state (pregnancy, labor, and the puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above. A34, O00-O95.</td>
</tr>
<tr>
<td></td>
<td>Indirect maternal death</td>
<td>Death resulting from previous existing disease or disease that developed during pregnancy and that was not a result of direct obstetric causes but was aggravated by physiologic effects of pregnancy. O98-O99.</td>
</tr>
<tr>
<td>U.S. Centers for Disease Control and Prevention, Pregnancy Mortality Surveillance System</td>
<td>Late maternal death</td>
<td>Death of a woman from direct or indirect obstetric causes more than 42 days but less than 1 year after termination of pregnancy. O96-O97.</td>
</tr>
<tr>
<td></td>
<td>Pregnancy-associated death</td>
<td>Death while pregnant or within 1 year of termination of pregnancy, irrespective of cause.</td>
</tr>
<tr>
<td></td>
<td>Pregnancy-related death</td>
<td>Death while pregnant or within 1 year of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.</td>
</tr>
<tr>
<td></td>
<td>Non–pregnancy-related death</td>
<td>Death while pregnant or within 1 year of termination of pregnancy, from a cause unrelated to pregnancy.</td>
</tr>
</tbody>
</table>

*Numbers after some definitions indicate cause of death codes.


### TABLE 39.3 Measures of Maternal Mortality

<table>
<thead>
<tr>
<th>Maternal Mortality Measure</th>
<th>Definitions</th>
<th>Reports Using the Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mortality ratio (MMR)</td>
<td>Direct and indirect maternal deaths, but not late maternal deaths, per 100,000 live births</td>
<td>WHO</td>
</tr>
<tr>
<td>Maternal mortality rate</td>
<td>Direct and indirect maternal deaths, but not late maternal deaths, per 100,000 maternities (pregnancies resulting in a live birth or stillbirth ≥ 20 weeks gestational age)</td>
<td>UK CEMD</td>
</tr>
<tr>
<td>Pregnancy-related mortality ratio (PRMR)</td>
<td>Pregnancy-related deaths per 100,000 live births</td>
<td>U.S. CDC PMSS</td>
</tr>
<tr>
<td>Lifetime risk for maternal death</td>
<td>The lifetime risk for maternal death takes into account both the probability of becoming pregnant and the probability of dying as a result of that pregnancy cumulated across a woman’s reproductive years</td>
<td>WHO</td>
</tr>
</tbody>
</table>

Deaths include those from induced abortion, miscarriage, and ectopic pregnancy. First-trimester deaths include those from induced abortion, miscarriage, and ectopic pregnancy. (Data from Say L, Chou D, Gemmil, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2:e323–e333.)

Fig. 39.1 Estimated distribution for the main causes of maternal death worldwide, and in selected regions. The relative size of each circle is illustrative but not directly proportional to the relative numbers of deaths in the three illustrated regions. *First-trimester deaths include those from induced abortion, miscarriage, and ectopic pregnancy.

for three-fourths of anesthesia-related deaths reported from low- and middle-income countries. Peripartum deaths have also been attributed to limited availability or affordability of blood products, cardiac arrest at induction of anesthesia, drug overdose, adverse medication reaction, and drug error. The number of maternal perioperative deaths likely pales in comparison with maternal deaths that result from the unmet need for lifesaving obstetric procedures, including cesarean delivery.

Strategies to reduce global maternal mortality include (1) improvement in family planning services and a reduction in the performance of unsafe abortion; (2) community-based education focused on safe birth practices and indications for transfer to a higher level of care; and (3) development of the infrastructure needed to provide timely emergency obstetric care, including the performance of indicated cesarean delivery (and safe administration of anesthesia) by trained care providers, who can also provide resuscitation of women in whom shock develops secondary to hemorrhage or infection. Cluster randomized trials and cost-effectiveness analyses to evaluate these strategies are beginning to appear. When deployed as part of an integrated, context-specific, and culturally sensitive program, interventions to reduce maternal and fetal mortality can be highly cost-effective.

MATERNAL MORTALITY IN THE DEVELOPED WORLD

In developed regions of the world, the MMR decreased 48% from 23 in 1990 to 12 (95% confidence interval [CI], 11 to 14) in 2015. The United States was the only high-income country where the MMR increased over this time period.

The most comprehensive maternal surveillance system in the world is the Confidential Enquiry into Maternal Deaths (CEMD) in the United Kingdom. Triennial reports of CEMD in England and Wales extend back to 1952 and have covered the entire United Kingdom since the 1985 to 1987 report. Since 2014, annual reports summarize overall mortality statistics and focus on clinical diagnoses on a rolling basis that covers all clinical conditions every 3 years. By government mandate, all maternal deaths are subject to this enquiry, and health professionals have a duty to provide all requested information. Once a case is identified, practitioners are asked to provide (1) a full account of the circumstances leading up to the woman's death, (2) all supporting records, (3) any clinical or other lessons that have been learned, and (4) details of any actions that may have been taken as a result. Regional assessors review the files to ensure completeness before removing identifying information. Once data are complete, central assessors review the anonymized cases and produce the reports. The reports focus on both medical and nonmedical recommendations for action to improve safety for future pregnant women.

The CEMD reports include both the internationally defined MMR and the UK-defined maternal mortality rate (see Table 39.3). The numerator for the UK-defined maternal mortality rate includes all deaths that in the opinion of the central assessors are related to pregnancy, including some causes that are not internationally coded as maternity related (e.g., suicide attributed to postpartum depression). The denominator includes all pregnancies that resulted in a live birth or stillbirth after 24 weeks' gestation. The international MMR is calculated strictly from data coded on death certificates; the UK maternal mortality rate includes all deaths identified through active surveillance. Over time, these numbers have converged.

National confidential enquiry reports are now published by many other countries, including France, the Netherlands, New Zealand, and South Africa. In the United States, the National Center for Health Statistics (NCHS) has provided maternal death counts since 1990 and MMRs since 1915. Accuracy is limited because (1) the system relies on death certificates rather than active surveillance, (2) the certification of death is the legal responsibility of individual states, and (3) the process of maternal death ascertainment varies by state.

The U.S. MMR reported by the NCHS declined from more than 600 deaths per 100,000 live births in 1915 to
fewer than 10 deaths per 100,000 live births by 1980 (Fig. 39.2).71 Throughout the 1980s and 1990s, the MMR oscillated between 6.6 and 9.2. Then in 1999, the MMR began to increase, reaching 21.0 in 2015 (Fig. 39.3).72 Improvements in ascertainment explain some of the increase. In 1999, the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) replaced the ICD-9 as the coding system for U.S. death certificates and liberalized the criteria by which pregnancy could be linked with death. Growing numbers of states perform electronic matches among women’s death certificates, live birth certificates, and fetal death files. In addition, increasing numbers of states have adopted the 2003 revision of the U.S. Standard Certificate of Death, which introduced questions about pregnancy status at the time of death (Box 39.1). By 2005, 19 states had adopted the standard pregnancy questions; the MMR calculated from vital records in these states was 17.3, compared with 10.7 from states without any questions about pregnancy on the state death certificate.73 Subsequent analyses confirmed improved ascertainment with the pregnancy checkbox, but also evidence of misclassification of nonmaternal deaths as maternal, particularly among older women.74

In 1987, the U.S. Centers for Disease Control and Prevention (CDC) partnered with state health departments and the American College of Obstetricians and Gynecologists (ACOG) to form the Pregnancy Mortality Surveillance System (PMSS).75 To capture maternal deaths more completely, the PMSS recommended that states develop an active

![Figure 39.2](image-url) **Fig. 39.2** U.S. maternal mortality ratios by race, 1915 to 2015.71,72 *Includes races other than white and black.†For 1915 to 1934, data on black race not available.

![Figure 39.3](image-url) **Fig. 39.3** U.S. maternal mortality ratios by race, 1970 to 2015.71,72 *Includes races other than white and black.†Beginning in 1989, race for live births tabulated according to race of mother, not child.
surveillance system and collect death certificates and matching live birth or fetal death certificates for all pregnancy-associated deaths (defined in Table 39.2). These certificates are forwarded to the CDC, where clinically experienced epidemiologists manually review the certificates to identify all pregnancy-related deaths (defined in Table 39.2). Similar surveillance enhancement procedures have been estimated to improve case ascertainment by between 22% and 93%. The pregnancy-related mortality ratio (PMR) includes deaths that took place up to 1 year after the end of pregnancy and, according to the PMSS, increased from 10.3 in 1991 to 17.0 in 2013. Documentation of pregnancy on the death certificate increases ascertainment further. In 2005, among the 19 states with death certificates that include the standard pregnancy questions, the combination of data from the NCHS and the PMSS suggests an MMR of 19.7 and a PRMR of 22.3.

In response to an apparent doubling of the U.S. MMR over two decades, a growing number of states have established maternal mortality review committees to analyze case records in detail, and to publish recommendations to improve safety for future women. Ascertainment and review procedures vary by state, so the CDC has created a national database to facilitate standardized review. To move recommendations into practice, the U.S. Council on Patient Safety in Women's Health Care has partnered with state and regional health care collaboratives to identify and implement evidence-based practices and systems solutions that will improve outcomes for the leading causes of maternal death. Ongoing surveillance will determine whether these efforts are effective.

### Leading Causes

According to a 2010 systematic review of data from high-income countries, hypertensive disorders of pregnancy, embolic disorders, and hemorrhage together account for 43% of maternal deaths in the developed world (see Fig. 39.1). Indirect deaths account for another 25%. Indirect deaths have exceeded direct deaths in the United Kingdom since 1997, with cardiac disease being the most common category of death. Similar patterns are seen in the United States, where the combination of cardiovascular conditions and cardiomyopathy comprised 26.4% of all pregnancy-related deaths between 2011 and 2013, and cerebrovascular accidents and noncardiovascular medical conditions represented another 21%. Cardiomyopathy, including both peripartum and other types of cardiomyopathy, is the leading diagnosis underlying maternal cardiac death in the United States. In the United Kingdom, sudden arrhythmia, ischemic cardiac disease, and cardiomyopathy are the leading causes of maternal cardiac death.

Detailed descriptions of hypertensive disorders of pregnancy, obstetric sepsis, maternal hemorrhage, embolic disorders, and cardiovascular diseases in pregnancy are provided in Chapters 35, 36, 37, 38, and 41, respectively. Injury-related deaths are considered pregnancy-associated but not pregnancy-related; they are discussed in Chapter 54. Common clinical and sociodemographic factors that increase the risk for maternal death from all of these complications are discussed in the following sections.

### Risk Factors

**Advanced maternal age** increases maternal risk, with a linear trend evident for each 5-year increase in maternal age beyond 34 years. In the United States between 2011 and 2013, the PRMR among women 40 years of age and older was 191.6 for black women (compared with 27.5 for black women 20 to 24 years of age) and 53.9 for white women (compared with 9.9 for white women 20 to 24 years of age). Based on data from the PMSS for 1991 to 1999, the association between age and mortality persisted after data were controlled for parity, prenatal care, race, and education. Among older black women (greater than or equal to 40 years), the excess risks were greatest for hypertensive disorders of pregnancy, infection, cerebrovascular accident, and other medical conditions. Among older white women, the greatest excess risks for death were caused by hemorrhage, cardiomyopathy, embolic disorders, and other medical conditions.

In the United States, black or African-American race significantly correlates with the risk for death. Non-Hispanic black women experience a PRMR that is 3.5-fold higher than non-Hispanic white women. In a case series of anesthesia-related maternal deaths in Michigan published in 2007, six of eight deaths occurred among non-Hispanic black women in Detroit, suggesting a profound concentration of maternal risk. The disparity in maternal mortality between black women and white women persists after data are controlled for maternal age, income, and receipt of prenatal care and appears to be related to a higher case-fatality rate.

**Other racial and ethnic groups** also experience increased risk. In the United States between 2005 and 2014, in comparison with non-Hispanic white women, the MMR was 80% higher for American Indian or Alaskan Native women. In England, black African, black Caribbean, Indian, Pakistani, and Chinese women have higher relative risks for death than white women.

**Immigrants, asylum seekers, and non-native speakers** appear to be particularly vulnerable to both maternal death and substandard care, based on data from the United Kingdom and the Netherlands. In the United States, Hispanic and Asian/Pacific Islander immigrants face increased risk compared with women of these same racial/ethnic groups born in the United States. Significant regional variation

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If female:
- Not pregnant within the past year
- Pregnant at the time of death
- Not pregnant, but pregnant within 42 days of death
- Not pregnant, but pregnant 42 days to 1 year before death
- Unknown if pregnant within the past year

Maternal obesity increases the risk for maternal death from a variety of causes, including pulmonary embolism, infection, preeclampsia, and anesthesia-related complications. Remarkably, there are limited epidemiologic data to establish this connection. Obesity is a common feature in case series of maternal deaths. In the 2012 to 2014 CEMD report from the United Kingdom, 51% of women who died were overweight or obese. Among the subset of women experiencing severe obstetric complications (including eclampsia, pulmonary embolism, amniotic fluid embolism, acute fatty liver of pregnancy, and antenatal stroke), obesity (body mass index greater than or equal to 30 kg/m\(^2\)) was associated with maternal death [AOR, 5.26; 95% CI, 1.15 to 6.46].

Multifetal pregnancies increase maternal risk for a variety of complications, including preeclampsia, venous thromboembolism, heart failure, myocardial infarction, peripartum hemorrhage, and maternal death. Compared with twin pregnancies, triplet and higher-order multiple pregnancies further increase maternal risk for preeclampsia, hemorrhage, and emergency peripartum hysterectomy. In the United States between 1979 and 2000, the relative risk for death associated with a multifetal pregnancy was 3.6 (95% CI, 3.1 to 4.1) with threefold to fourfold increases in the cause-specific relative risk for death for embolism, hemorrhage, hypertensive disorders of pregnancy, infection, cardiomyopathy, and other medical conditions.

Cesarean delivery has also been associated with an increased risk for maternal death; however, the association does not always reflect a causal relationship. Death can be a consequence of the indication for the operation rather than the mode of delivery itself. In an attempt to estimate the relative risk for death caused by cesarean delivery, a population-based case-control study from France focused on 65 maternal deaths after singleton births among low-risk women in whom complications developed only after delivery. Cases were identified by the French National Confidential Enquiry on Maternal Deaths from 1996 through 2000. These cases were compared with 10,244 singleton births to low-risk women identified through the French National Perinatal Survey conducted in 1998. After data were controlled for maternal age, nationality, parity, and preterm delivery, the AOR for increased risk for death with cesarean delivery was 3.45 (95% CI, 1.25 to 6.19). The increased risk was most dramatic for intrapartum cesarean deliveries (AOR, 4.58; 95% CI, 2.30 to 9.09) but persisted when cesarean delivery preceded labor (AOR, 2.42; 95% CI, 1.14 to 5.13). Among women who underwent cesarean delivery, there was an increased risk for cause-specific maternal mortality from venous thromboembolism, puerperal infection, and complications of anesthesia.

There was no difference in risk for death from postpartum hemorrhage or amniotic fluid embolism.

A cohort study of deliveries in Canada between 1991 and 2005 compared 46,766 planned cesarean deliveries for breech presentation with 2,292,420 planned vaginal deliveries in which labor was either spontaneous or induced. Planned cesarean delivery increased the risk for postpartum cardiac arrest (AOR, 5.1; 95% CI, 4.1 to 6.3), major puerperal infection (AOR, 3.0; 95% CI, 2.7 to 3.4), anesthetic complications (AOR, 2.3; 95% CI, 2.0 to 2.6), and puerperal venous thromboembolism (AOR, 2.2; 95% CI, 1.5 to 3.4), but did not increase the risk for in-hospital maternal death.

A medical record review of all in-hospital maternal deaths that occurred in a sample of U.S. hospitals between 2000 and 2006 sought to identify evidence for a causal connection between mode of delivery and the mechanism of maternal death. Among 1,461,270 live births, there were 95 maternal deaths (6.5 per 100,000). Although 61% of the deaths were associated with cesarean delivery, one-third of these were perimortem cesarean deliveries in which the surgical procedure followed maternal cardiac arrest. Four deaths were thought to have been directly caused by cesarean delivery (attributed to hemorrhage or infection), with an additional seven deaths attributed to pulmonary thromboembolism after cesarean delivery. Two deaths were thought to have been causally related to vaginal delivery (one case of uterine inversion and one case of rupture of an unrecognized cerebral berry aneurysm during labor), and two deaths were attributed to pulmonary thromboembolism after vaginal delivery. Another 16 deaths were thought to have been potentially preventable had a cesarean delivery or an earlier cesarean delivery been performed (12 caused by preeclampsia, 3 caused by hemorrhage, and 1 caused by sepsis). The investigators concluded that a policy of universal thromboprophylaxis for all patients undergoing cesarean delivery would eliminate the increased risk for maternal death caused by cesarean delivery as opposed to vaginal delivery.

Regardless of mode of delivery, risk appears to be particularly concentrated in women with preexisting medical conditions; pulmonary hypertension, malignancy, systemic lupus erythematosus, sickle cell disease, and major cardiovascular and renal disease all confer substantially increased risk for maternal death or end-organ injury. Given the preponderance of indirect deaths documented in recent CEMD reports, central assessors have repeatedly recommended both preconception counseling and intensive multidisciplinary antepartum and intrapartum care for women with serious medical or mental health conditions that may be aggravated by pregnancy. Some health system characteristics have been associated with a higher risk for maternal death; they include (1) low
Severe and Near-Miss Morbidity

Death is considered the extreme outcome of the following continuum of adverse pregnancy events: normal pregnancy → morbidity → severe morbidity → near-miss → death. Approximately one-half of women experience some morbidity during pregnancy, most commonly anemia, urinary tract infection, mental health conditions, hypertensive disorders, and pelvic or perineal trauma. Research has focused on severe morbidity, near-miss events, and maternal deaths to elucidate the patient, provider, and health system factors that lead to these adverse outcomes.

Severe maternal morbidity includes unexpected complications of childbirth that result in significant short- or long-term consequences to a woman’s health; its estimated incidence depends on the health system evaluated, the method of ascertainment, and the definition of severe morbidity used. Waterstone et al. evaluated pregnancies in France between 1997 and 1998 for the presence of severe preeclampsia, severe hemorrhage, or sepsis; the combined incidence for these three conditions was 12.0 per 1000 deliveries (95% CI, 11.2 to 13.2). Zhang et al. applied the same criteria across Western Europe and identified a combined European incidence for these three conditions of 9.5 per 1000 deliveries (95% CI, 9.1 to 9.9). Analyses of administrative codes (ICD-9 or ICD-10) for conditions that indicate severe obstetric morbidity in population-level data suggest rates of 8.1 per 1000 hospitalizations in the United States from 2004 to 2005, 13.8 per 1000 in Canada from 2003 to 2007, and 13.8 per 1000 deliveries in Australia in 2004.

Near-miss morbidity occurs when a woman survives a life-threatening complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy. The concept of a near-miss event evolved from early studies of pregnant patients who required intensive care. Mantel et al. proposed a definition that requires evidence of severe organ dysfunction, intensive care unit admission, emergency hysterectomy, or an anesthetic accident such as failed intubation. Based on these criteria, a meta-analysis of 11 studies suggests a ratio of 4.2 near-misses per 1000 deliveries (95% CI, 4.0 to 4.4). Geller et al. validated a five-factor scoring system consisting of organ system failure (5 points), intensive care unit admission (4 points), transfusion of more than 3 units of blood products (3 points), extended intubation (2 points), and surgical intervention (1 point); a total score higher than 7 points defines a near-miss event. According to this scoring system, the incidence of a near-miss event was approximately 0.2 per 1000 deliveries in a perinatal tertiary care center in Chicago between 1995 and 2001.

Maternal near-miss morbidity has also been defined using administrative data by combining ICD-9 codes for diagnoses indicating end-organ injury with either a prolonged length of stay (greater than 99th percentile) or transfer to a second health care facility. Based on this administrative data definition, the incidence of near-miss maternal morbidity or maternal death in the United States between 2003 and 2006 was 1.3 per 1000 hospitalizations for delivery. The WHO Working Group on Maternal Mortality and Morbidity Classification determined that end-organ injury represents the most epidemiologically sound way to identify near-miss morbidity. In 2009 the WHO proposed a panel of clinical, laboratory-based, or management-based criteria to identify maternal end-organ injury (see Box 39.e1 available at ExpertConsult.com). Cecatti et al. applied the WHO near-miss criteria to all intensive care unit admissions in a tertiary care facility in Brazil between 2002 and 2007 and found a near-miss morbidity ratio of 14.7 events per 1000 live births, an MMR of 125 deaths per 100,000 live births, and a maternal near-miss-to–mortality ratio of 10.7:1.

Preventability has emerged as an important concept in maternal mortality and near-miss morbidity reviews because the opportunities for prevention identified from these reviews can be used to prioritize changes in clinical policy and health system improvements. The Perinatal and Maternal Mortality Review Committee in New Zealand proposed a comprehensive list of contributory factors, including those attributed to the health care organization, personnel, technology and equipment, the environment and geography, and patient-level barriers to accessing or engaging with care. Although contributory factors may be identified in the majority of maternal deaths, multiple reviews suggest that only 20% to 45% were likely preventable. In a case-control study of maternal death, near-miss events, and severe morbidity, Geller et al. identified a higher proportion of preventability among deaths and near-miss events compared with cases of severe morbidity (41% and 45% versus 17%) and suggested that provider-level improvements in medical care among women who develop severe morbidities represent the most frequent opportunities to prevent both near-miss events and maternal deaths. Across various reviews, the highest rates of preventability are noted among ethnic minorities and among deaths attributed to hemorrhage, hypertensive disorders of pregnancy, and sepsis or infection.

Anesthesia-Related Maternal Mortality

Anesthesia-related maternal mortality has been defined as “death attributable to anesthesia, either as the result of medications used, method chosen, or the technical maneuvers performed, whether iatrogenic in origin or resulting from an abnormal patient response.” A death may be considered anesthesia-related if it can be uniquely attributed to an anesthetic complication. Actual case reports often include layers of comorbidities, anesthetic complications, and problems with nonanesthetic care; these cases may be considered anesthesia-related if optimal anesthetic care would likely have averted the death. If optimal anesthetic care in combination with improvements in obstetric or medical management would likely have saved the woman’s life, then the death may be considered anesthesia-contributing. In some cases, the
### Clinical Criteria
- Acute cyanosis
- Gasping\(^a\)
- Respiratory rate > 40 or < 6/min
- Shock\(^b\)
- Oliguria nonresponsive to fluids or diuretics\(^c\)
- Clotting failure\(^d\)
- Loss of consciousness lasting ≥ 12 hours\(^e\)
- Loss of consciousness and absence of pulse/heartbeat
- Stroke\(^f\)
- Uncontrollable fit/total paralysis\(^g\)
- Jaundice in the presence of preeclampsia\(^h\)

### Laboratory-Based Criteria
- Oxygen saturation < 90% for ≥ 60 minutes
- \(\text{PaO}_2/\text{FiO}_2\) < 200 mm Hg
- Creatinine ≥ 300 \(\mu\)mol/L or ≥ 3.5 mg/dL
- Bilirubin > 100 \(\mu\)mol/L or > 6.0 mg/dL
- pH < 7.1
- Lactate > 5
- Acute thrombocytopenia (< 50,000 platelets)
- Loss of consciousness and the presence of glucose and ketoacids in urine

### Management-Based Criteria
- Hysterectomy after infection or hemorrhage
- Use of continuous vasoactive drugs\(^i\)
- Transfusion of ≥ 5 units of red blood cells
- Intubation and ventilation for ≥ 60 minutes not related to anesthesia
- Dialysis for acute renal failure
- Cardiopulmonary resuscitation

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\(^a\) Gasping is a terminal respiratory pattern and the breath is convulsively and audibly caught.
\(^b\) Shock is a persistent severe hypotension, defined as a systolic blood pressure < 90 mm Hg for ≥ 60 minutes with a pulse rate at least 120 despite aggressive fluid replacement (> 2 L).
\(^c\) Oliguria is defined as a urinary output < 30 mL/h for 4 h or < 400 mL/24 h.
\(^d\) Clotting failure can be assessed by the bedside clotting test or absence of clotting from the IV site after 7 to 10 minutes.
\(^e\) Loss of consciousness is a profound alteration of mental state that involves complete or near-complete lack of responsiveness to external stimuli. It is defined as a Coma Glasgow Scale < 10 (moderate or severe coma).
\(^f\) Stroke is a neurologic deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours.
\(^g\) Condition in which the brain is in a state of continuous seizure.
\(^h\) Preeclampsia is defined as the presence of hypertension associated with proteinuria. Hypertension is defined as a blood pressure of at least 140 mm Hg (systolic) or at least 90 mm Hg (diastolic) on at least two occasions and at least 4 to 6 h apart after the 20th week of gestation in women known to be normotensive before pregnancy. Proteinuria is defined as excretion of 300 mg or more of protein every 24 hours. If 24-h urine samples are not available, proteinuria is defined as a protein concentration of 300 mg/L or more (≥ 1+ on dipstick) in at least two random urine samples taken at least 4 to 6 hours apart.

For instance, continuous use of any dose of dopamine, epinephrine, or norepinephrine.

Anesthetic complication is tragic but incidental (e.g., failed intubation during advanced cardiac life support for massive pulmonary embolism).

Anesthesia-related maternal death is extremely rare in the developed world. Table 39.4 shows recent MMRs attributed to anesthesia in the United States and the United Kingdom. Comparable ratios reported elsewhere in recent years include 1.4 per million live births in France for 2001 to 2006 and 1.0 per million in the Netherlands for 1993 to 2005. Active surveillance in the United Kingdom may be particularly effective at comprehensive identification of anesthesia-related maternal deaths.

A number of clinical and sociodemographic factors commonly appear among cases of anesthesia-related maternal death and may play a causal role in the mechanism of death. These include (1) maternal obesity; (2) patient refusal of neuraxial anesthesia; (3) remote anesthetic location; (4) delay in anesthesia provider consultation; (5) insufficient multidisciplinary planning, communication, and coordination; and (6) inadequate supervision of care. In the United States, the relative risk for anesthesia-related maternal death appears to be increased for African-American women.

Anesthesia-related maternal deaths are distributed throughout the perioperative period and follow both neuraxial and general anesthesia, primarily administered for cesarean delivery, but occasionally for vaginal delivery or another obstetric or nonobstetric surgical procedure. Case-fatality rates according to mode of anesthesia for cesarean delivery are presented in Table 39.5. To generate these estimates, the authors identified cases from death certificate data collected by the PMSS and estimated the total number of anesthetics delivered based on the national incidence of cesarean delivery and the proportions of cesarean deliveries completed with neuraxial and general anesthesia according to national surveys of anesthesia providers.

Anesthesia-related maternal deaths are almost always preventable, as evidenced by both individual case analysis and review of historical trends. The relative risks of general and neuraxial anesthesia for cesarean delivery in the United States have shifted over time (see Table 39.5), reflecting three major safety initiatives in anesthesia practice. The first initiative addressed the hazard of local anesthetic systemic toxicity (LAST), identified as a major problem in a series of editorials published in the early 1980s. In response, in 1984, the U.S. Food and Drug Administration recommended that bupivacaine 0.75% not be used for epidural anesthesia in obstetric patients. Also, anesthesiologists developed a series of safety procedures to avoid the unintentional intravascular administration of a toxic dose of local anesthetic through an epidural catheter. Case-fatality rates for neuraxial anesthesia subsequently declined 78% between 1979 to 1984 and 1985 to 1990 (see Table 39.5). Despite this improvement in prevention, LAST remains a rare and potentially lethal complication in obstetric anesthesia, with recent events attributed to drug error by nonanesthesia providers, cumulative dosing above the toxic threshold, epidural catheter migration, and single-shot transversus abdominis plane (TAP) blocks. Lipid emulsion is now recommended as part of a comprehensive resuscitation strategy.

The second initiative involved a shift toward greater use of neuraxial anesthesia for cesarean delivery. Between 1985 and 1990, the relative risk associated with general anesthesia compared with neuraxial anesthesia for cesarean delivery was 16.7 (see Table 39.5), and much of the increase in risk was attributed to failed intubation or aspiration of gastric contents during induction of general anesthesia, or both. In response, anesthesia providers now reserve general anesthesia for specific indications, including (1) emergency cesarean delivery with insufficient time to establish neuraxial anesthesia; (2) medical conditions that make neuraxial anesthesia unsafe, such as maternal coagulopathy, hemorrhagic shock, and septic shock; and (3) failed neuraxial anesthesia with intraoperative pain.
The third initiative introduced a series of protocols and devices to improve the safety of general anesthesia. Pulse oximetry and capnography have been widely credited with the decline in the incidence of unrecognized esophageal intubation. Failed intubation algorithms, extraglottic airway devices (particularly the laryngeal mask airway), and a heightened focus on simulation and practice have impelled a transformation in airway management toward a clear focus on effective oxygenation and ventilation as well as ongoing preparation for airway emergencies. Consequently, the case-fatality rate for general anesthesia decreased by 80% between 1985 to 1990 and 1997 to 2002 (see Table 39.5). Nevertheless, recent series continue to report deaths from difficult intubation, unrecognized esophageal intubation, pulmonary aspiration of gastric contents (both with anesthetic induction and emergence), postextubation airway obstruction, and postoperative respiratory arrest attributed to opioids or other respiratory depressants. Strategies to limit the risk for airway complications are discussed in Chapters 28 and 29.

The relative risk associated with general anesthesia in comparison with neuraxial anesthesia has fallen since 1990 and was estimated to be 1.7 (95% CI, 0.6 to 4.6) between 1997 and 2002. In contemporary anesthesia practice, both general anesthesia and neuraxial anesthesia carry remote, but tangible risks for maternal death.

Why do women die of neuraxial anesthesia? High neuraxial block was the leading cause of anesthesia-related maternal death among women receiving neuraxial anesthesia for cesarean delivery in the United States between 1997 and 2002. It was also the leading cause of legal claims for maternal death or permanent brain injury filed between 1990 and 2003 (n = 15/25; 60%), with the majority of these attributed to unrecognized intrathecal catheters intended for the epidural space. Single-shot spinal anesthesia administered after failed epidural anesthesia for cesarean delivery represents a second clinical scenario associated with high neuraxial block. More details on high neuraxial block and its management may be found in Chapters 23 and 26.

Potentially lethal infectious complications of neuraxial block include meningitis, encephalitis, and neuraxial abscess. The CEMD 2006 to 2008 report included a case of acute hemorrhagic disseminated leuкоencephalitis attributed to thoracolumbar spinal canal empyema. Current guidelines stress the importance of strict aseptic technique during neuraxial block administration, as well as appropriate monitoring and management for any infectious complications that may develop. Further details are available in Chapter 31.

Other series suggest that neuraxial cardiac arrest and hypotensive arrest may be important mechanisms by which neuraxial anesthesia can lead to maternal death. Prevention likely depends on careful attention to intravascular volume status, as well as the prompt, aggressive treatment of maternal hypotension to prevent reflex-mediated bradycardia and cardiovascular collapse. Finally, perioperative respiratory arrest can result from neuraxial opioids or intravenous opioids or other respiratory depressants administered during or after neuraxial anesthesia.

Further efforts to improve maternal safety must include a comprehensive approach to high-quality perioperative patient care. Timely preanesthesia evaluation and ongoing communication with obstetric providers are essential to limit the number of patients who require emergency administration of anesthesia without sufficient evaluation and preparation. Problems with postoperative care have long been recognized but appear to account for a growing proportion of perioperative maternal deaths, particularly those attributed to respiratory events, hemorrhage, and maternal sepsis. The physiology of pregnancy and the compensatory physiologic responses that occur in young pregnant women may obscure early signs of septic or hemorrhagic shock. Early warning scoring systems may facilitate the early identification of women who have, or are beginning to develop, a critical illness. Postanesthesia and postpartum care are commonly provided by labor and delivery nurses (as opposed to perianesthesia care nurses) with limited training and experience with major anesthetic complications, noninvasive ventilation, and advanced cardio-pulmonary life support.

Fortunately, severe morbidity and mortality are rare in obstetrics; as an unfortunate consequence of this rarity, individual clinical experience with serious adverse events will always be limited. Simulation may be an effective strategy for all obstetric and anesthesia providers to prepare for a wide variety of obstetric emergencies, including postoperative airway obstruction, failed intubation, eclampsia, anaphylaxis, maternal cardiac arrest, and maternal hemorrhage. Chapter 11 details additional strategies to enhance patient safety.

**KEY POINTS**

- Ninety-nine percent of maternal deaths worldwide occur in developing countries. More than one-half of global maternal deaths are attributed to direct obstetric causes, including maternal hemorrhage, hypertensive disorders of pregnancy, and infection.
- In the developed world, 12 women die per 100,000 live births. In the United States, the maternal mortality ratio is increasing; in 2015, 21 women died per 100,000 live births.
- Advanced maternal age, maternal obesity, multiple gestation, cesarean delivery, and nonwhite race increase the risk for maternal death.
- Hypertensive disorders of pregnancy, embolic disorders, and hemorrhage together account for just under one-half
of maternal deaths in the developed world but appear to be eclipsed by indirect deaths in some countries.

• Death is considered the extreme outcome of the following continuum of adverse pregnancy events: normal pregnancy → morbidity → severe morbidity → near-miss → death.

• In the developed world, the anesthesia-related maternal mortality ratio is estimated to range between 1 and 3 per million live births.

• Anesthesia safety for obstetric patients depends on the provision of high-quality perioperative patient care.

REFERENCES


In the late 19th century, Ehrlich proposed the dictum of *horror autotoxicus*, the belief that immunity is directed against foreign material and never against one’s own body. The demonstration of autoantibodies in the 1950s disproved the theory and demonstrated the failure of self-tolerance.1

Autoimmunity has been described in more than 40 disorders, and may result in chronic illness and severe disability. The classification of autoimmune diseases has been controversial since it is recognized that both genetic and epigenetic (potentially heritable changes in gene expression that are not associated with changes in DNA sequencing) factors play a role. The traditional clinical classification recognizes immune responses that are directed against a particular antigen and are limited to a particular organ or cell type (organ-specific disease), and those that are directed against a range of antigens that produce multisystem involvement (systemic disease). Some examples are shown in Box 40.1. Classification now incorporates a “spectrum of autoimmunity” from low-level (possibly beneficial to self) to high-level (clearly detrimental to self) autoimmunity.7

The pathogenesis of autoimmunity is complex. A genetic predisposition underlies abnormal reactivity of B cells and immunoglobulins, T-cell receptors, and genes within the major histocompatibility complex (MHC).1 Specific allotypes within the MHC are associated with certain diseases; for example, HLA-DR2 is strongly positively associated with systemic lupus erythematosus (SLE) but negatively associated with diabetes mellitus type 1. Genome-wide association studies have identified genetic associations between single-nucleotide polymorphisms (SNPs) and some autoimmune conditions.4 Meta-analyses of HLA subclasses show similar associations with autoimmunity.5 More recently, epigenetic factors, including dysregulation of DNA expression (but not of its sequencing), noncoding RNA, histone (a nucleosomal protein) modification, and immunoendocrine status, have been shown to influence immune status.6,7

Other factors (e.g., environmental conditions) may predispose to autoimmunity. Parasitic infection may reduce the incidence of autoimmunity, whereas bacterial infection with *Klebsiella* may predispose to ankylosing spondylitis. Drug-induced SLE is well described.

Sex hormones, notably the androgen-estrogen balance and its effect on cytokine production, have been implicated in the development of autoimmunity.8 Autoimmune
disorders are more common in women than in men, with the highest incidence of several conditions occurring during the childbearing years,9 and occasionally the initial diagnosis is made during pregnancy. During normal pregnancy, altered immune function allows maternal tolerance of the fetal alloantigen. It has been known for decades that both mother and fetus produce immunologic factors that inhibit maternal cell-mediated immunity,10 prevent rejection of the fetus, and limit the expression of autoimmunity. The high estrogen environment of pregnancy may enhance immune function allows maternal tolerance of the fetal antigens. Impaired clearance of apoptotic cells and produces immunologic factors that inhibit maternal cell-mediated immunity,10 prevent rejection of the fetus, and limit the expression of autoimmunity. The high estrogen environment of pregnancy may enhance immune function allows maternal tolerance of the fetal antisera, leading to aberrant sensitization against these antigens. Impaired clearance of apoptotic cells and prolonged exposure to nuclear autoantigens may be involved.14

**Systemic lupus erythematosus, lupus anticoagulant, scleroderma, and polymyositis/dermatomyositis** are discussed elsewhere in this text, including **diabetes mellitus type 1** (see Chapter 43) **autoimmune thrombocytopenic purpura** and **autoimmune hemolytic anemia** (see Chapter 44), **rheumatoid arthritis** and **ankylosing spondylitis** (see Chapter 47), and **myasthenia gravis** (see Chapter 48.)

**SYSTEMIC LUPUS ERYTHEMATOSUS**

**Definition and Epidemiology**

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease of unknown etiology that is characterized by the production of autoantibodies against nuclear, cytoplasmic, and cell membrane antigens. Although its overall prevalence is about 50 per 100,000 population,12 it is recognized most commonly in women during their childbearing years, with a female-to-male ratio of 9:1. Certain groups have a higher prevalence, including African-Americans (2- to 3-fold risk), Asians, and Native Americans.13 An estimated 1 in 1200 deliveries occurs in women with SLE.13

**Pathophysiology**

The etiology of SLE remains unclear. The principal mechanism is thought to be an immune complex disease involving IgG antibodies to double-stranded DNA and other nuclear proteins. Intracellular autoantigens are released by necrotic and apoptotic cells, leading to aberrant sensitization against these antigens. Impaired clearance of apoptotic cells and prolonged exposure to nuclear autoantigens may be involved.14 Affected individuals have both hyperactivity of the antibody-producing B cells and defects of the helper and suppressor T cells.15 Genetic defects of immune regulation and possibly environmental triggers including viruses and bacteria lead to a proliferation of B cells capable of producing autoantibodies that may target more than 30 classes of antigens. A variety of antigen-antibody immune complexes are formed, followed by secondary inflammatory responses. Deposits may occur within the skin, choroid plexus, and other endothelial surfaces, with or without an inflammatory response. In certain locations (e.g., the renal glomerulus), deposition of immune complexes and continued inflammation may lead to irreversible injury. However, SLE is not simply an immune complex disorder because some autoantibodies actively bind to erythrocytes, granulocytes, lymphocytes, and macrophages, leading to their removal from the circulation.16

**Diagnosis**

Clinical manifestations of SLE are diverse, owing to the widespread antigenic targets. **Box 40.2** outlines objective criteria.
for the diagnosis of SLE. Although epidemiologic studies require the presence of four or more of these criteria, the clinical diagnosis may be suspected if fewer features are present without another explanation. Typically, the diagnosis of SLE is made before conception, but in 20% of cases the initial diagnosis is made during pregnancy.

**Effect of Pregnancy**

SLE disease activity may increase during pregnancy, and some pregnancy-related complications may have long-term effects on women with SLE. The PROMISSE study, an observational prospective outcome study of 385 women with SLE with or without antiphospholipid antibodies (aPL), used formal measurements of disease activity to delineate risk. Renal disease, SLE disease activity, and the presence of aPL are considered significant risk factors for maternal deterioration during pregnancy. Assessments using the SLE Disease Activity Index found that 50% to 65% of women with active disease had deterioration during pregnancy in both retrospective and prospective studies. Such flares occur more commonly in the second and third trimesters and the puerperium, are not more severe than those in nonpregnant patients, and mostly respond to conservative management. The risk for significant disease activity during pregnancy is increased sevenfold if active disease is present in the 6 months before conception, and a preconception history of nephritis predicts adverse maternal outcome.

Women with SLE have a 2- to 4-fold increase in the overall rate of pregnancy complications, with increased rates of hypertension, renal disease, preeclampsia, preterm delivery, cesarean delivery, and maternal and neonatal death. Nevertheless, maternal and fetal outcomes have improved with advances in disease management.

**Effect on the Fetus**

Maternal SLE impairs fetal survival and increases the risk for preterm delivery. The primary predictor for adverse pregnancy outcomes is the presence of lupus anticoagulant (LAC). A systematic review of papers published between 1980 and 2009 showed that preterm delivery occurred in 39.4% of 2751 pregnancies in 1842 patients. In the Hopkins Lupus Pregnancy Cohort, preterm birth occurred in 38 of 57 (67%) pregnancies in women with moderate to severe active SLE, compared with 68 of 210 (32%) pregnancies in women with inactive or mild active SLE. Improved perinatal management and control of disease activity have reduced the rate of fetal loss from 43% (between 1960 and 1965) to 17% (between 2000 and 2003). Data from California showed a preterm delivery rate in SLE that was six times higher than that found in the general population.

**Neonatal lupus erythematosus (NLE)** is a syndrome that results from maternal autoantibodies against Ro (SS-A) or La (SS-B) crossing the placenta and binding to fetal tissue. These autoantibodies are found in up to 87% of patients with SLE, but NLE occurs in only a small proportion of patients. The condition is generally benign and self-limiting, and reversible manifestations such as cutaneous lupus, elevation in amino-transferase levels, and thrombocytopenia resolve as maternal antibodies disappear from the neonatal circulation within 8 months of birth. Anti-Ro/anti-La antibodies may bind to fetal cardiac conduction cells in utero, leading to cell death and irreversible fetal heart block. Neonatal congenital heart block occurs in 2% of neonates when anti-Ro antibody is detected in the mother, and mortality occurs in about 18% of affected babies. Fetal echocardiography reveals atrophicventricular dissociation, cardiac dilation, and pericardial effusion. Treatment includes prompt delivery, newborn cardiac pacing, antepartum administration of dexamethasone, and consideration of apheresis to remove maternal antibodies.

**Medical Management**

Optimally, women with SLE should delay pregnancy until their disease has been quiescent for at least 6 months, and they should be taking “acceptably safe” medications at the time of conception. Medications with acceptable safety are used to minimize disease activity during gestation. Disease-modifying antirheumatic drugs (DMARDs) and immunosuppressive agents form the mainstay of treatment.
Antimalarial drugs, most notably hydroxychloroquine (HCQ), are frequently used to reduce SLE activity. Discontinuation of HCQ just before conception or in early pregnancy leads to a significant increase in disease activity. A systematic review of English literature (1982 to 2007) found that antimalarial drugs, particularly HCQ, prevent lupus flares; increase long-term survival; contribute to protection against irreversible organ damage, thrombosis, and bone loss; and have low toxicity. HCQ should be continued in all women who were taking it before conception, and it may be used to treat flares during gestation. In contrast, mycophenolate mofetil should be discontinued before conception owing to the risk for teratogenicity.

Immunosuppressive agents such as azathioprine, cyclosporine, and tacrolimus are considered safe for use in pregnancy and may be considered if corticosteroid avoidance is desirable. Azathioprine should be continued if used before conception. The fetal liver does not express the enzyme necessary to convert azathioprine to its active form, but maternal use of azathioprine has been associated with reversible neonatal lymphopenia, depressed serum immunoglobulin levels, and decreased thymic size in the newborn. Transplant registries do not report increased risk for congenital abnormalities after its use.

Corticosteroids may be used to treat flares of SLE disease activity. Antenatal exposure to low-dose prednisone (less than 20 mg daily) appears to be safe, and most children born to mothers who have used antenatal corticosteroids develop normally. However, fluorinated glucocorticoids such as dexamethasone or betamethasone readily cross the placenta and may cause fetal growth restriction and abnormal neuronal development, although orofacial cleft abnormalities are not associated with their use. Corticosteroid therapy may precipitate gestational diabetes, and patients should be monitored for evidence of glucose intolerance. Striae, gastrointestinal ulceration, and bone demineralization may complicate long-term corticosteroid therapy. Regular use of antacids may be required. The pediatrician should be alerted to the possibility of neonatal adrenal suppression.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and stronger analgesics may be used to manage lupus arthritis. Although there is no evidence of teratogenicity with these agents, concern exists that NSAIDs may cause premature closure of the fetal ductus arteriosus, and high-dose aspirin and NSAIDs ideally should be discontinued by 30 weeks’ gestation.

Biologic agents such as rituximab and belimumab are being used more frequently, but assessment of their efficacy has been limited by the heterogenous nature of SLE and the connective tissue disorders. There is little consensus on their use at present.

Obstetric Management

Patients with SLE are at increased risk for intrauterine fetal death and preterm delivery. Estimation of the gestational age is obtained with ultrasonography at the first prenatal visit and again at 20 weeks’ gestation. Continued surveillance consists of nonstress testing, biophysical profile measurement, and/or umbilical artery Doppler velocimetry beginning at 26 to 28 weeks’ gestation and performed weekly until delivery.

The coexistence of antiphospholipid antibodies (either lupus anticoagulant or triple-positive antiphospholipid antibody; see later discussion) predicts a much higher maternal and fetal risk. Maternal serologic markers are checked regularly, together with platelet count, creatinine clearance, 24-hour urine protein level, uric acid, and complement levels. In normal pregnancy, serial complement levels gradually increase. However, declining levels of C3 and C4 suggest active disease and lupus nephritis. Thromboprophylaxis is important in patients with antiphospholipid syndrome (see later discussion). Aspirin resistance may predict adverse maternal and neonatal outcomes. Regular assessment of blood pressure, weight gain, and proteinuria is performed to detect the development of preeclampsia. Prediction of cardiovascular risk in women with SLE may be possible using the Pulse-Mass Index.

The timing and route of delivery are individualized. Although vaginal delivery is preferred, a cesarean delivery rate of 40% has been reported in parturients with SLE.

Anesthetic Management

The obstetrician, rheumatologist, and anesthesia provider should formulate a joint plan for delivery. Maternal organ system involvement, current disease severity, and particularly the presence of flares must be assessed. Pericarditis is common in patients with SLE and is typically asymptomatic. A history of dyspnea on exertion or unexplained tachycardia may suggest pericarditis or myocarditis. Cardiac tamponade has been reported. Prolongation of the PR interval or nonspecific T-wave changes may be seen on the electrocardiogram. Coronary artery vasculitis, accelerated atherosclerosis leading to myocardial ischemia, and even myocardial infarction in young women have been reported.

An echocardiographic study in 69 patients with SLE showed a high incidence of valvular abnormalities, including valvular thickening in 51%, vegetation in 43%, regurgitation in 25%, and stenosis in 4%. Current American Heart Association guidelines recommend antibiotic prophylaxis only for patients at highest risk for infective endocarditis in whom there is both significant risk and consequence of infection. Prophylactic antibiotics are not recommended for women with common valvular lesions undergoing genitourinary procedures, including vaginal delivery, but are specifically indicated for those with previous infective endocarditis, un repaired cyanotic congenital heart disease, implanted prosthetic material or devices, or a history of cardiac transplantation with cardiac valvulopathy.

The prevalence and progression of pulmonary hypertension in 28 patients with SLE has been studied. The prevalence increased from 14% at initial evaluation to 43% 5 years later. Epidural anesthesia for cesarean delivery in parturients with pulmonary hypertension has been reported (see Chapter 41). The abrupt onset of sympathetic blockade and decreased
venous return may cause precipitous systemic hypotension and hypoxemia. One report described the administration of general anesthesia in a parturient with SLE and pulmonary hypertension, with coexisting SLE-related restrictive lung disease, pulmonary edema, and orthopnea.27 In one report of three parturients with pulmonary hypertension secondary to SLE and antiphospholipid syndrome, two died of right-sided heart failure within 48 hours of delivery.28

Subclinical pleuritis is common, but significant pleural effusions are rare. Patients may suffer from infectious pneumonia or lupus pneumonitis. The latter condition is characterized by fleeting hemorrhagic infiltrates that may become consolidated. Pulmonary embolism and diaphragmatic dysfunction have been reported.31

Central and peripheral sensorimotor and autonomic neuropathies are observed in as many as 25% of patients with SLE,36 and vocal cord palsy has been reported.39,40 These deficits should be documented before the administration of either neuraxial or general anesthesia. Migraine headache and cerebral vasculitis resulting from SLE must be considered in the differential diagnosis of a postpartum headache. Psychological disorders and frank psychosis can occur during pregnancy.61 Seizures can occur, especially if chronic anticonvulsant medications are discontinued inadvertently.

Hematologic abnormalities, including anemia, thrombocytopenia, and coagulopathy, should be documented. An abnormality of the activated partial thromboplastin time (aPTT), which is not corrected with a 1:1 control plasma mix, suggests the presence of either lupus anticoagulant (a coexistent but separate disease entity) or, more rarely, true autoantibodies against specific coagulation factors (e.g., VIII, IX, XII). Lupus anticoagulant is a laboratory artifact that does not cause clinical coagulopathy. True coagulation factor autoantibodies (or inhibitors) may result in a significant bleeding diathesis, which contraindicates the administration of neuraxial anesthesia.

Long-term use of NSAIDs leads to qualitative platelet abnormalities, but their role in causing spinal epidural hematoma remains conjectural. In prospective studies of patients undergoing orthopedic procedures (924 patients receiving spinal or epidural anesthesia, and with preoperative anti-platelet medications taken by 39% of patients)62 and epidural steroid injection for chronic pain management (1035 patients, with NSAID use reported by 32% of patients),63 no cases of spinal epidural hematoma were observed. In the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), a large, multicenter randomized trial, 9364 pregnant women received either low-dose aspirin (60 mg daily) or placebo for prevention and treatment of preeclampsia.64 Of 5000 enrollees, at least 1069 patients received epidural analgesia, and no cases of epidural hematoma were observed.65 Measurement of the bleeding time before neuraxial injection in patients taking aspirin or NSAIDs is not indicated. Thromboelastography has been suggested as an alternative but is not widely available.66 One case report described administration of general anesthesia for cesarean delivery in a patient with SLE and antiphospholipid syndrome who had suffered a thrombotic cerebrovascular event; thromboelastography was used as an adjunct to coagulation studies.67 Atypical blood antibodies may complicate cross-matching of blood for patients with SLE, and additional time may be required.

Prosthetic orthopedic joints should be positioned carefully during vaginal or cesarean delivery. Lupus arthritis rarely involves the cervical spine. Women who have undergone long-term corticosteroid therapy should receive a peripartum stress dose of a corticosteroid.

**ANTIPHOSPHOLIPID SYNDROME**

**Definition and Epidemiology**

Antiphospholipid syndrome (APS, also known as Hughes’ syndrome) was first recognized in the early 1980s68,69 and classified by international consensus in 2005.70 It is an autoimmune prothrombotic disorder characterized by the presence of aPL, namely lupus anticoagulant, anticardiolipin antibodies (aCL), and anti-beta2-glycoprotein I (aβ2GPI). Affected patients are at risk for arterial and venous thrombosis and pregnancy-related complications.71

Although initially described as a subset of patients with SLE, it is now accepted that APS is a distinct and separate disease entity from SLE.72 About 40% of patients with SLE may have aPL (lupus anticoagulant in 34% and aCL in 44%),73 but few of these will progress to develop thrombotic events. Long-term follow-up suggests that more than one-half of patients with SLE and aPL will progress to APS, but few patients with APS progress to SLE.72

The population prevalence of APS is unclear. Most information has been derived from the “Euro Phospholipid” cohort of 1000 patients.74 Prevalence of aPL in the general population is 1% to 5%, but APS occurs in only a small proportion of people with aPL; the estimated population prevalence is 20 to 50 per 100,000 people.75 In 1990, commenting on the volume of publications on APS, Harris remarked that the syndrome “probably occurs less frequently than the number of papers published on the subject.”76 However, with greater clinical recognition, Hughes predicted that the prevalence of APS will exceed that of SLE.68

**Pathophysiology**

APS is associated with two important misnomers. First, the antiphospholipid antibodies do not bind directly to phospholipids but to phospholipid-binding plasma proteins such as β2GPI, prothrombin, and annexin V. Second, the lupus anticoagulant has no true anticoagulant activity in vivo but is a laboratory artifact that affects phospholipid-dependent coagulation assays: the aPTT, the kaolin clotting time (KCT), the tissue thromboplastin inhibition (TTI) test, and the dilute Russell viper venom time (dRVVT). These times remain prolonged even when the tests are repeated with a 1:1 mixture of the patient’s plasma and control plasma. Typically the prothrombin time (PT) is normal. Lupus anticoagulant appears to block in vitro assembly of prothrombinase (a phospholipid complex), thus preventing the conversion of prothrombin to thrombin. True bleeding associated with lupus anticoagulant is extremely rare and, in most cases, is caused by an underlying factor deficiency or inhibitor.77
Contrary to expectation, lupus anticoagulant and aCL are associated with both arterial and venous thrombotic events. The current model by which this thrombotic tendency occurs involves aPL antibodies binding to β2GPI, which then bind to glycoprotein Ibα on platelets, monocytes, and endothelial cells. These complexes cause platelet adhesion, expression of prothrombotic molecules, and local complement activation. Complement activation may lead to inflammation, placental insufficiency, and fetal loss, while aPL interference with fibrinolysis may predispose to thrombotic events.

**Diagnosis**

The diagnosis of APS depends on a clinical history of unexplained recurrent venous or arterial thrombosis, pregnancy loss, and laboratory evidence of aCL or lupus anticoagulant. The latter is demonstrated by (1) evidence of abnormal phospholipid-dependent coagulation (elevated aPTT); (2) evidence that this abnormality is caused by an inhibitor rather than a factor deficiency (elevated aPTT with 1:1 mix); and (3) proof that the inhibitor is directed against phospholipid rather than specific coagulation factors. Antibodies should be demonstrable on two occasions separated by 12 weeks. The presence of lupus anticoagulant, aCL, and β2GPI antibodies (triple positivity) with a clinical diagnosis of APS predicts severe disease. Results from different laboratories show considerable variability, and guidelines on diagnostic criteria have been published. Tests for syphilis detect the antiphospholipid antibodies present in syphilis, and consequently the Venereal Disease Research Laboratory (VDRL) and Wasserman test results may be falsely positive. Some 20% of patients with APS may present with an initial diagnosis of idiopathic thrombocytopenic purpura.

**Effect on the Mother**

Pregnant women with APS are at risk for venous and arterial thrombosis, pulmonary embolism, myocardial infarction, cerebral infarction, and fetal loss. Cohort studies suggest that contemporary management strategies may improve maternal outcome. The PROMISSE study showed that higher risk was indicated by African or Hispanic descent, presence of lupus anticoagulant, moderate clinical disease activity when pregnancy was diagnosed, thrombocytopenia, and flare activity.

Silver et al. reported that of 130 women with APS followed over a 3-year period, 48% experienced at least one of the following disorders: transient ischemic attack, peripheral thrombosis (of which one-fourth occurred in pregnancy and the puerperium), stroke, amaurosis fugax, autoimmune thrombocytopenia, and SLE. Clark et al. reported that women diagnosed with APS on the basis of recurrent pregnancy loss and evidence of aPL, but without prior thrombotic events, rarely suffered thrombosis during pregnancy. A history of thromboembolic events significantly worsens prognosis and increases the likelihood of future events, an effect ameliorated by the use of oral anticoagulants. Thrombocytopenia, present in one-fourth of patients with APS, is generally mild and responds to prednisone therapy. More recently, rituximab and rivaroxaban have been used, and occasionally splenectomy may be required. The use of HCQ for women with pregnancies at particular risk has, in the absence of study findings, been the subject of expert consensus, with the conclusion that its use may be justified in certain cases or when treatment with aspirin and heparin has been ineffective. Catastrophic antiphospholipid syndrome (CAPS or Asherson's syndrome), an accelerated form of the condition that results in multisystem organ thrombosis and failure, may be triggered by pregnancy in 1% of cases.

**Effect on the Fetus**

Pregnant women with APS are at high risk for intrauterine fetal death. Early studies showed that only 7.5% of pregnancies resulted in the delivery of a live newborn, whereas recent reports have shown live-birth rates up to 100%. Pregnant women with so-called triple positivity (lupus anticoagulant, aCL, and β2GPI antibody titers greater than four times the upper limit of normal) have a twofold increase in risk for fetal loss compared with women with positive titers only (35% live-birth rate versus 77%). The PREGNANTS study, a retrospective cohort study, recorded that only 30% of women with triple positivity had a live born neonate. Placental infarction is the apparent mechanism of mortality, and most fetal deaths occur during mid- and late pregnancy. There is no high-level evidence to guide management of pregnant women with high antibody titers.

Most infants born to women with APS do not have an increased rate of neonatal or childhood complications, although cases of antiphospholipid-related fetal and neonatal thrombosis (mainly cerebral thrombosis) have been reported.

**Medical and Obstetric Management**

The mainstay of obstetric management is thromboprophylaxis. Fetal survival and maternal thrombotic risk may be improved when affected pregnant women are treated with low-dose aspirin and heparin. A 2005 meta-analysis found that combined treatment with unfractionated heparin and aspirin can reduce pregnancy loss by 54%. Recommendations on investigation and management of APS have been made. Women with more than three unexplained pregnancy losses before 10 weeks’ gestation should be tested for antiphospholipid antibodies; women with APS and recurrent pregnancy loss should receive prophylactic doses of heparin and low-dose aspirin throughout pregnancy, and administration for 6 to 8 weeks postpartum should be considered. A history of APS with thrombosis may require full anticoagulation throughout pregnancy and the postpartum period. A meta-analysis suggested that unfractionated heparin in combination with aspirin increases the live-birth rate in women with APS, but the benefit of low-molecular-weight heparin (LMWH) is unclear; neither type of heparin crosses the placental barrier.

Catastrophic antiphospholipid syndrome occurs in 1% of patients with APS. It is characterized by rapidly progressive thromboses with organ damage, thrombotic microangiopathy, and a systemic inflammatory response syndrome.
Diagnosis requires the presence of antiphospholipid antibodies with involvement of at least three organs and rapid onset and progression of disease. Urgent management strategies include elimination of precipitating causes, antibiotic cover for a precipitating bacterial infection, full anticoagulation, intravenous corticosteroids and immunoglobulin, and plasma exchange. HCQ and rituximab are increasingly used.

Mortality is as high as 50%.

Anesthetic Management

There are no large scale studies describing anesthetic management of patients with APS, and management is similar to that of the patient with SLE. Coexisting autoimmune disorders, secondary organ involvement, and thrombotic phenomena should be evaluated. The term lupus anticoagulant is a misnomer (as discussed earlier) and does not warrant withholding neuraxial anesthesia. Infrequently, antiphospholipid antibodies can cause coagulation factor deficiencies, and in such patients neuraxial anesthesia is relatively contraindicated. In the absence of an underlying coagulation deficit or anticoagulant therapy, the prolonged aPTT does not suggest a bleeding tendency, and neuraxial anesthesia may be administered safely.

The anesthetic management of pregnancies complicated by APS has been reviewed. All subjects received aspirin (75 to 150 mg daily) throughout pregnancy, and aspirin therapy alone was not considered a contraindication to neuraxial anesthesia. In parturients who received thromboprophylaxis with standard unfractionated heparin, spinal or epidural anesthesia was administered 4 hours after the last dose of heparin. The use of LMWH for thromboprophylaxis precludes administration of neuraxial anesthesia until at least 12 hours have elapsed since the time of the last dose. Further, therapeutic anticoagulation with high-dose LMWH precludes the administration of neuraxial anesthesia until at least 24 hours have elapsed since the time of the last dose (see Chapters 38 and 44). The use of thromboelastography to document clearance of heparin before administration of neuraxial anesthesia in parturients with lupus anticoagulant has been described.

If fetal compromise secondary to multi-infarct placental insufficiency exists, hypotension from sympathetic blockade should be prevented. Neuraxial anesthesia with an epidural, intrathecal, or combined spinal-epidural technique is not contraindicated provided that blood pressure is closely controlled. Parturients with APS who undergo general anesthesia are at risk for venous thrombosis. Compression stockings, warm intravenous fluids, and early ambulation should be used, whereas hypothermia and dehydration should be avoided. There is no evidence that a “walking epidural” confers benefit.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Definition and Epidemiology

Systemic sclerosis or scleroderma is a chronic progressive autoimmune disease of unknown etiology characterized by deposition of fibrous connective tissue in the skin and other tissues, microvascular changes, and chronic inflammation. It is a heterogeneous disorder and may be in the form of limited or diffuse cutaneous scleroderma. A subset of patients exhibit systemic sclerosis without cutaneous involvement. The annual incidence of scleroderma in the United States is 19 per million. The prevalence is 240 per million, which is four to nine times greater than the reported global prevalence. Scleroderma is almost five times more common in women than in men and occurs primarily between 30 and 50 years of age.

Pathophysiology

Epigenetic regulation of gene expression through cellular transcription, without changes in gene sequence, plays a key role in phenotypic expression, and is a possible mechanism by which the same genotype can be expressed as different phenotypes. Possible mechanisms include chemical modification of DNA (particularly methylation), histone coding, modification of RNA, and environmental influences. Although the stimulus for fibroblasts to produce excessive collagen and other matrix constituents is unknown, their accumulation leads to microvascular obliteration and fibrosis in the skin and other target organs. Endothelial cells undergo vasomotor and permeability changes, producing cyclic vasoconstriction-vasodilation and edema. Patients with scleroderma produce autoantibodies against nuclear and centromere structures, although their significance is unclear. Scleroderma exhibits a strong female predilection, a steep rise in incidence after the childbearing years, and features that are similar to graft-versus-host disease after bone marrow transplantation, prompting some to postulate that microchimerism may be involved in its pathogenesis. Fetal cells gain access to the maternal circulation during gestation and may be detected in maternal blood for decades after delivery. After some unknown stimulus but possibly including environmental factors, they may differentiate and initiate a reaction similar to graft-versus-host disease.

Diagnosis

Raynaud’s phenomenon, characterized by cyclic pallor and cyanosis of the digits in response to cold or emotion, may be a prodrome to scleroderma, with 1% of patients progressing to scleroderma. The triad of Raynaud’s phenomenon, nonpitting edema, and hidebound skin establishes the diagnosis of scleroderma.

Limited cutaneous scleroderma, also termed CREST syndrome, involves calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. Skin involvement is limited to the hands, face, and feet in this form of the disease. The more extensive clinical manifestations of diffuse cutaneous scleroderma are summarized in Box 40.3.

Effect of Pregnancy

Progression of scleroderma tends to be slow. More than 70% of patients with diffuse cutaneous scleroderma and more than 90% of those with limited cutaneous scleroderma are...
**Effect on Pregnancy and the Fetus**

The frequency of preterm births and small-for-dates infants is higher in pregnant women with scleroderma. Preterm birth occurs in 25% of pregnancies (compared with 5% in control pregnancies), and most preterm deliveries occur in women with unstable diffuse scleroderma of less than 4 years’ duration. Miscarriage occurs more commonly in women with long-standing diffuse scleroderma.

**Medical Management**

Management is symptomatic rather than curative, and is directed toward slowing end-organ damage. When lifestyle alterations (e.g., avoidance of cold, cessation of smoking) are no longer effective, management may include calcium entry–blocking agents for skin manifestations; proton-pump inhibitors, and occasionally esophageal dilation for gastrointestinal tract symptoms; and phosphodiesterase inhibitors and prostaglandins for pulmonary arterial hypertension. No disease modification benefits have been shown by administration of penicillamine, methotrexate, or other immunosuppressive agents (other than the use of glucocorticoids for inflammatory myositis).

Drugs with unproven or potential teratogenicity are relatively contraindicated during pregnancy. However, angiotensin-converting enzyme (ACE) inhibitors are the agents of choice for treating scleroderma-associated renal crisis and malignant hypertension, despite the potential for fetal teratogenicity, renal atresia, pulmonary hypoplasia, anhydramnios, and fetopathy. ACE inhibitors provide the only effective control of hypertension during scleroderma-associated renal crisis and should be started immediately if maternal hypertension occurs. Their use should be avoided if hypertension or overt renal crisis are not present. Nitric oxide donors and possibly heparin may provide some protection against placental dysfunction in pregnant women with scleroderma.

**Obstetric Management**

Pregnant women with scleroderma should be specifically evaluated for evidence of renal, pulmonary, and cardiac dysfunction. Preterm delivery or termination of pregnancy may be required in the presence of advanced or rapidly progressive disease. Frequent assessment of renal function and intensive observation for the onset of systemic or pulmonary hypertension, cardiac dysfunction, and fetal compromise, combined with improvements in monitoring and treatment, allow most mothers to deliver healthy infants. Although the prevalence of left ventricular diastolic dysfunction is known to be higher in patients with scleroderma than in the general population, an association with pregnancy has not been noted. However, additional monitoring based on clinical findings may be indicated. Obstructive uropathy may result from an enlarging uterus trapped within a noncompliant abdomen. Uterine and cervical wall thickening may lead to ineffective uterine contractions or cervical dystocia at delivery. Even the tightest abdominal skin usually heals if cesarean delivery is necessary.
Anesthetic Management

The pregnant woman with scleroderma presents several challenges to the anesthesia provider and should be assessed before labor and delivery. Early multidisciplinary involvement is required. History and physical examination should be directed toward detection of underlying systemic dysfunction. Laboratory tests include complete blood cell count, coagulation screen, electrolyte concentrations and creatinine clearance, arterial blood gas analysis, urinalysis, and urine protein determination. An electrocardiogram and pulmonary function testing should be performed in all patients. Echocardiography is increasingly used to assess ventricular dysfunction, pericardial and pleural effusions, and pulmonary hypertension. Particular attention should be paid to arterial pulses, noninvasive blood pressure measurement, peripheral venous access, extent of Raynaud’s phenomenon involvement, and special positioning requirements.

Severe limitation of mouth opening caused by hidebound perioral skin may make direct laryngoscopy impossible and mandates careful airway assessment. The patient should be prepared for the possibility of an awake intubation. Specialized airway equipment (e.g., fiberoptic laryngoscope, videolaryngoscope, emergency cricothyrotomy set) should be immediately available. The changes in airway assessment scores that occur during labor should also be borne in mind.

Patients with scleroderma may develop pulmonary hypertension as a consequence of vascular changes, fibrosis, or left ventricular dysfunction. Administration of a pulmonary vasodilator may increase the likelihood of a favorable outcome.

If cesarean delivery is required, the decision to use neuraxial or general anesthesia depends on the urgency of delivery, anticipated airway difficulty, and operator skills. One report of two pregnant women with scleroderma and pulmonary hypertension described administration of neuraxial anesthesia in one patient and general anesthesia in the other patient, highlighting the complexity of management choices. Gastric hypomotility increases the risk for esophageal reflux and aspiration. Epidural anesthesia has been used successfully. Early administration of epidural analgesia in laboring women in whom tracheal intubation is likely to be difficult is encouraged. Even when severe diffuse cutaneous involvement is present, the skin of the lumbar back is spared. Spinal anesthesia for cesarean delivery complicated by precipitous hypotension in a parturient with scleroderma has been reported; recovery was uneventful with full return of motor function within 3.5 hours.

Prolonged duration of regional anesthesia has been observed in some patients with scleroderma, and may be caused by reduced uptake of the local anesthetic agent as a consequence of microvasculature changes. These cases have included (1) an axillary block performed with 1% lidocaine with epinephrine (reported to have persisted for 24 hours); (2) a digital nerve block performed with 1% lidocaine without epinephrine (10-hour duration); (3) a sciatic nerve block that persisted for 16 hours; and (4) prolonged epidural anesthesia with 2% 2-chloroprocaine. This is not a contraindication to neuraxial techniques but should prompt the use of small incremental boluses of the local anesthetic agent, and the patient should be warned of the possibility of prolonged neural blockade. Incremental bolus or patient-controlled injection techniques may be preferable to continuous infusion techniques that may result in the administration of an excessive dose with prolonged neural blockade. Whether this consideration makes epidural (with the ability to titrate the dose) rather than spinal anesthesia preferable for cesarean delivery is unclear.

Venous access may be difficult. Diffuse cutaneous involvement may indicate the need for central venous catheterization, and for invasive arterial monitoring if noninvasive blood pressure measurement is inaccurate. Radial artery catheterization is contraindicated in patients with Raynaud’s phenomenon because of the risk for hand ischemia. Brachial artery catheterization may be necessary. Pulmonary artery catheterization may be indicated in the presence of cardiac dysfunction or pulmonary hypertension. The use of noninvasive assessment of cardiac function with transthoracic echocardiography is likely to increase. Warming of the patient, and especially of the extremities affected by Raynaud’s phenomenon, is required. Scleroderma reduces tear production, and the eyes should be protected against corneal abrasions.

POLYMYOSITIS AND DERMATOMYOSITIS

Definition and Epidemiology

Polyomyositis and dermatomyositis represent two members of a larger disease group, the idiopathic inflammatory myopathic diseases. Polyomyositis is characterized by nonsuppurative inflammation of muscle, primarily skeletal muscles of the proximal limbs, neck, and pharynx. This inflammation leads to symmetric weakness, atrophy, and fibrosis of affected muscle groups. Dermatomyositis represents the same disorder, with the addition of a characteristic heliotrope eruption (blue-purple discoloration of the upper eyelid) and Gottron’s papules (raised, scaly, violet eruptions over the knuckles). These disorders are quite rare, with a prevalence of 10 per million and an annual incidence of 5.5 per million. Women are affected twice as often as men. The age at onset is bimodal, with peaks before puberty and during the fifth decade.

Pathophysiology

Both polyomyositis and dermatomyositis are associated with other autoimmune disorders, notably scleroderma. The etiology of inflammatory muscle disease is unknown and probably multifactorial. An initial insult mediated by viral or other infectious agent, or exposure to environmental substances, may lead to initial muscle damage in genetically susceptible individuals. This initial process may then trigger an autoimmune response involving chronic muscle inflammation. A viral etiology is suggested by seasonal and geographic clustering of new cases. However, viral genomic material has
Pregnancy-associated form of dermatomyositis has been documented, with renal or hematologic involvement being rare. The onset of a dermatomyositis flare generally involves the small joints of the hands and fingers. For dermatomyositis, reports of primary cardiac involvement, including nonspecific repolarization abnormalities, conduction disturbances, arrhythmias, coronary artery vasculitis, and, rarely, heart failure, have been described. The presence of cellular infiltrates within affected muscle tissue and complement-mediated capillary damage are features of inflammatory muscle diseases. More than 12 autoantibodies have been identified in affected individuals. Underlying malignancy has been associated with both conditions, although causality is unclear; the association is stronger for dermatomyositis than polymyositis.

Diagnosis

The diagnostic criteria proposed by Bohan and Peter remain the standard for classification of polymyositis and dermatomyositis (Box 40.4). After exclusion of other conditions that can mimic polymyositis or dermatomyositis, clinical features together with electromyographic and laboratory evidence of myositis (both through blood tests and muscle biopsy) establish the diagnosis. Serum creatine kinase concentration correlates with disease activity. Systemic involvement may be variable. Pharyngeal muscle involvement leads to dysphagia and reflux, and most patients exhibit impairment of gastric and esophageal motility. Pulmonary involvement is present in 50% of patients with polymyositis/dermatomyositis, and chronic aspiration pneumonitis and pneumonia are the most common pulmonary manifestations. Pulmonary fibrosis is present in 30% of patients and may rarely lead to pulmonary hypertension. Myositis of the respiratory muscles may cause respiratory insufficiency. Cardiac involvement includes nonspecific repolarization abnormalities, conduction disturbances, arrhythmias, coronary artery vasculitis, and, rarely, heart failure. Arthritis generally involves the small joints of the hands and fingers. Renal or hematologic involvement is rare. The onset of a pregnancy-associated form of dermatomyositis has been described postpartum.

Effect of Pregnancy

Reports of polymyositis or dermatomyositis during pregnancy are rare. Ishii et al. reviewed 12 reports of 29 pregnancies during a 30-year period. In 11 (40%) of the patients, the initial diagnosis was made during gestation or the immediate postpartum period. Among the 18 patients with previously diagnosed disease, the disease remained inactive in 11 (61%) of the patients, and 2 (11%) had an exacerbation of disease activity. Pregnancy may be a trigger for induction of dermatomyositis in some women.

Effect on the Fetus

Fetal outcome is influenced by disease activity; it has been reported that 60% of women with minimal activity delivered healthy newborns at term, but fetal survival is affected by concurrent polymyositis/dermatomyositis. Consequences may include fetal growth restriction, preterm delivery, and fetal death. A similar correlation was noted between outcome and disease activity in four pregnant women with polymyositis/dermatomyositis: two with active disease and fetal death and two with disease remission and uneventful outcome. A large cohort study from Brazil documented 98 female patients (60 with dermatomyositis and 38 with polymyositis), of whom 78 women had an obstetric history; 57 women had been pregnant before their myositis diagnosis; 15 women became pregnant after the diagnosis was made; and 6 women were diagnosed with myositis while pregnant or in the postpartum period. Adverse pregnancy outcomes (either as worsening of maternal condition or of fetal compromise) were associated with intercurrent clinical conditions such as diabetes mellitus, hypertension, and hypothyroidism, rather than as a direct consequence of dermatomyositis or polymyositis.

Medical and Obstetric Management

Pregnancy should be planned during periods of disease inactivity. Serum creatine kinase, glutamic oxaloacetic transaminase, and aldolase determinations can guide this decision. Obstetric management involves frequent monitoring of disease activity and fetal well-being.

Glucocorticoid treatment remains the mainstay of medical management of active disease. Efficacy of steroids has not been demonstrated in controlled studies, but improvement in muscle strength and decreased creatine kinase concentrations are usually seen after 1 to 2 months of either continuous or pulsed steroid therapy. Methotrexate, azathioprine, and intravenous immunoglobulin may be beneficial; there is limited evidence for their use and safety in pregnant patients. A recent systematic review suggested, but could not confirm, benefit from methotrexate, azathioprine, cyclosporine, rituximab, and intravenous immunoglobulin, but very few data relate to pregnant patients. The first-line drug for treatment of skin manifestations is HCQ.

Anesthetic Management

Anesthetic management of the pregnant woman with polymyositis/dermatomyositis begins with the evaluation of disease activity and underlying cardiopulmonary involvement. If muscle weakness is present, spirometry should be performed to determine whether respiratory muscles are affected. Maximum breathing capacity and peak expiratory flow rate are the most helpful measurements. Pharyngeal

**BOX 40.4 Diagnostic Criteria for Polymyositis and Dermatomyositis**

**Polymyositis**
- Symmetric weakness of proximal muscles
- Histologic evidence of muscle inflammation and necrosis
- Elevation of serum skeletal muscle enzymes
- Electromyographic evidence of myopathy

**Dermatomyositis**
- Three or four of the above, plus heliotrope eruption or Gottron’s papules

weakness may cause chronic aspiration and pulmonary diffusion defects. Arterial blood gas analysis and a chest radiograph should be obtained in patients with a history of aspiration. An electrocardiogram should be obtained to exclude conduction abnormalities and arrhythmias.

Although neuraxial anesthesia has been used safely, its use in patients with muscle weakness requires caution because excessive cephalad spread may further impair intercostal muscle function and lead to ventilatory failure. Abdominal muscle paralysis may slow progress of the second stage of labor. Careful epidural administration of a dilute solution of local anesthetic may provide effective pain relief without muscle paralysis and lead to ventilatory failure. Abdominal excessive cephalad spread may further impair intercostal muscle function and lead to ventilatory failure. Abdominal muscle paralysis may slow progress of the second stage of labor. Careful epidural administration of a dilute solution of local anesthetic may provide effective pain relief without adverse effect on the progress of labor. Intrathecal opioid administration is an attractive alternative method of labor analgesia in these patients.

Patients with polymyositis/dermatomyositis may exhibit an atypical response to muscle relaxants. A short-lived thumb contracture after succinylcholine administration in a child with dermatomyositis has been reported. Direct laryngoscopy was not impaired, the contracture resolved within 3 minutes, and normal neuromuscular recovery occurred. Prolonged paralysis of 50 minutes after succinylcholine administration in a patient with dermatomyositis has been noted. The patient was found to be homozygous for an atypical pseudocholinesterase. Of four other patients with dermatomyositis in whom the dibucaine number was measured, one was heterozygous for atypical pseudocholinesterase. The occurrence of benign contractures and the possibility of atypical pseudocholinesterase do not preclude the use of succinylcholine if it is required for cesarean delivery. Rocuronium may be an alternative agent for rapid-sequence induction.

An atypical response to nondepolarizing muscle relaxants may also occur. A case of prolonged paralysis (9.5 hours) after administration of vecuronium in a patient with polymyositis has been reported. However, underlying malignancy, to which patients with dermatomyositis and polymyositis are prone, may have an associated myasthenic syndrome that can prolong neuromuscular blockade. Other reports of nondepolarizing neuromuscular blockade in patients with polymyositis/dermatomyositis have described a normal response and recovery. Parturients who have undergone long-term corticosteroid therapy should receive a peripartum stress dose of a corticosteroid.

Neuromuscular recovery should be verified before tracheal extubation. Some investigators have advocated the avoidance of agents known to trigger malignant hyperthermia in patients with polymyositis/dermatomyositis and elevated creatine kinase levels, but the association is speculative and is not supported by published clinical experience.

**KEY POINTS**

- Pregnancy does not worsen the long-term course of autoimmune disorders.
- Autoimmune disorders can lead to renal, cardiac, and pulmonary dysfunction.
- Systemic lupus erythematosus can result in maternal thrombocytopenia.
- Systemic lupus erythematosus is associated with a higher incidence of spontaneous abortion, intrauterine fetal demise, and preterm delivery.
- Antiphospholipid syndrome is characterized by the presence of the autoantibodies lupus anticoagulant and anti-cardiolipin antibody.
- The term lupus anticoagulant is a misnomer because it has no true anticoagulant activity in vivo.

**REFERENCES**


Cardiovascular Disease

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Evidence suggests that an individual’s sex has a significant impact on cardiovascular disease. The etiology of coronary thrombosis causing acute myocardial infarction is different in women than in men. Plaque erosion, rather than plaque rupture, occurs at a higher rate in women than in men. Coronary artery diameter is smaller in women,1 and women frequently develop more diffuse atherosclerosis than men. Female aortas appear to be stiffer because of underlying fibrosis or remodeling. Women have more microvascular coronary artery dysfunction than men and frequently demonstrate impaired coronary artery vasodilator response.

Autoimmune rheumatic diseases are associated with premature atherosclerosis; vasculitides such as Takayasu’s arteritis, temporal arteritis, rheumatoid vasculitis, lupus vasculitis, and polymyalgia rheumatica are all more common in women than in men. During exercise stress testing, women more often have atypical and nonanginal pain than men, who more often have typical angina.2 Women with acute myocardial infarction more frequently do not have chest pain, especially those who have the infarction at a younger age. In-hospital mortality for acute myocardial infarction is higher for women than for men.3 Although women who have non–ST-segment elevation myocardial infarction have a poorer risk profile than men, the infarction is frequently treated less aggressively.4 Yet women are more likely than men to summon emergency medical services during a myocardial infarction.

Whether women have poorer outcome after percutaneous coronary intervention has been a matter of debate.5 At the time of presentation for both percutaneous and surgical coronary revascularization procedures, women are older than men and have more cardiovascular risk factors and comorbid conditions.5 Older studies demonstrated poorer overall outcome in women than in men; however, more recent studies have demonstrated a narrowing or disappearance of the sex-related outcome gap. Similarly, several studies have demonstrated that female sex was an independent predictor of coronary artery bypass grafting (CABG) operative mortality. However, after extensive baseline risk adjustment, outcomes after CABG or aortic valve replacement have been reported to be similar for men and women.

Number of pregnancies has been associated with the future risk for coronary artery disease6 and progression of atherosclerosis.7 Hypertensive disorders of pregnancy, pre-eclampsia, and gestational diabetes mellitus are risk factors for future development of cardiovascular disease.8,9 Earlier identification of these women with an increased lifetime risk for developing cardiovascular disease may present a unique opportunity for prevention of subsequent cardiovascular events.

Historically, rheumatic mitral stenosis represented the most common cardiac condition encountered in pregnant women. This disease continues to be a major problem in the developing world and in certain immigrant populations in the United States. In industrialized countries, congenital heart disease has become the most common cardiac condition complicating pregnancy. This demographic change is a result of significant advances in the treatment of complex congenital heart conditions and survival of these patients into childbearing age. In the United States, maternal mortality caused by hemorrhage and hypertensive disorders of pregnancy has declined, whereas mortality caused by cardiovascular conditions has steadily increased.10

The optimal management of women with cardiovascular disease begins before conception. Normal physiologic changes of pregnancy may exacerbate preexisting cardiovascular disease. For most women with heart disease, pregnancy is associated with favorable outcome; however, even with modern advances in treatment and monitoring, there remains a high incidence of morbidity and mortality for some conditions. Thus, for some women, it may be advisable to avoid pregnancy.

There is significant individual variability in the severity of specific cardiovascular disease entities. Additionally, several cardiovascular conditions may be simultaneously present in one individual. Management may be further complicated by the presence of noncardiovascular pathologic processes. The anesthetic management of the parturient with cardiovascular disease should be individualized, and a multidisciplinary team should plan peripartum care. Some case reports and small series have described the anesthetic management of these patients, but, in general, few data justify choosing one anesthetic technique over another. Therefore, the anesthesiologist must have a thorough understanding of the normal physiologic changes of pregnancy as well as the individual parturient’s pathophysiology, and then plan anesthetic management that best achieves the desired hemodynamic goals. Optimal analgesia is often an important part of safe childbirth in these patients.

The anesthetic care of women with cardiovascular disease does not end with labor and delivery; rather, it continues postpartum when the physiologic changes of pregnancy may be at their greatest. Inadequate postpartum analgesia may be associated with hypertension and tachycardia. Postoperative shivering increases oxygen consumption and may cause myocardial ischemia in patients with limited cardiac reserve.

**CARDIOVASCULAR PHYSIOLOGIC CHANGES OF PREGNANCY**

The electrocardiogram (ECG) typically changes during pregnancy. During the third trimester, the enlarging gravid uterus causes upward and lateral rotation of the heart, which may result in left-axis deviation of 13 to 20 degrees. Overall, however, the QRS axis is quite variable during pregnancy. At rest, nonspecific ST-segment and T-wave changes are very common during normal pregnancy.11 Exercise in healthy pregnant women does not cause distinctive ECG changes compared with nonpregnant subjects.

No repolarization abnormalities are observed with uncomplicated vaginal delivery. ST-segment elevation is never seen in normal pregnancy and should always be considered pathologic. ST-segment depression is seen in 25% to 81% of parturients undergoing cesarean delivery, regardless of the type of anesthesia. Oxytocin administration during the third
stage of labor has been associated with ST-segment depression.12,13 However, these oxytocin-associated ECG changes are not associated with myocardial damage. Whether these ECG changes are caused by underlying ischemia or some other mechanism remains unclear.

Left ventricular mass increases during normal pregnancy.14 The increase in left ventricular mass is greater in multiple gestation than in singleton gestation.15 Preeclampsia also results in a greater increase in left ventricular mass.16

Plasma lipid concentrations, including total serum cholesterol, triglycerides, and low-density lipoprotein cholesterol concentrations, increase during pregnancy.17 Obese pregnant women have an even greater increase in plasma lipids. This increase in plasma lipids results in part from insulin resistance and an increase in estrogen levels during pregnancy. The effects of these physiologic changes in plasma lipid concentrations on long-term cardiovascular outcomes are unclear.

Brain natriuretic peptide (BNP) is a natriuretic hormone synthesized primarily in the heart ventricles. BNP levels increase as a response to increased filling pressures in patients with heart failure. Physiologically, BNP has hypotensive, diuretic, and natriuretic effects. During uncomplicated normal pregnancy, BNP levels are double the nonpregnant level with return to baseline approximately 3 days after delivery. The BNP level appears to be unchanged between the trimesters.18 BNP levels are increased in preeclamptic women19 and in pregnant women with heart disease.20 A correlation exists between BNP and the increases in left ventricular mass and end-diastolic and end-systolic volumes observed in preeclampsia.16 The increase in BNP with fluid administration in preeclamptic women further confirms that this hormone is secreted in response to increased intracavitary pressures. Intravenous fluid administration does not increase BNP levels in healthy women.21 BNP is elevated in women with complex congenital heart disease, but it varies considerably among anomalies. Therefore, its role for individual patient management remains unclear.22

Cardiac enzyme levels may be altered by pregnancy or pregnancy-associated disease. Myocardial cell death is associated with elevation of sensitive and specific cardiac biomarkers—creatinine kinase MB fraction (CK-MB) and cardiac troponins.23 Cardiac troponin levels are not elevated above the upper limits of normal during uncomplicated pregnancy. Troponin levels are elevated in women with gestational hypertension or preeclampsia.24,25 By contrast, CK-MB pregnancy. Troponin levels are elevated in women with gestation above the upper limits of normal during uncomplicated pregnancy.24,25 By contrast, CK-MB

**Cardiac output** increases as early as 5 weeks’ gestation and continues to increase throughout the second trimester until it is approximately 50% greater than nonpregnant values (see Fig. 2.2). Cardiac output does not change from this level during the third trimester; it may actually be reported as decreased in the third trimester if measurements are made in the supine position, which causes aortocaval compression. Both an increase in heart rate and stroke volume contribute to the increase in cardiac output. Distribution of cardiac output to the uterine circulation increases from 1% in the nonpregnant state to 12% during the second half of pregnancy (see Chapter 2).

**CARDIAC EXAMINATION DURING PREGNANCY**

Pregnant women frequently complain of mild dyspnea at rest and exertion; on occasion, exercise tolerance is decreased. Therefore, it is important to recognize normal changes in the physical examination associated with pregnancy (Table 41.1).

Resting heart rate is higher in pregnancy, and peripheral pulses are “well filled” with rapid upstroke and collapse, primarily owing to lower systemic vascular resistance (SVR). Central venous pressure remains unchanged during pregnancy, and any elevation of jugular venous pressure is an abnormal finding. Basilar rales may be heard on lung auscultation; however, these are no longer heard after deep inspiration, a brief breath-hold, or a cough. These evanescent rales likely result from basilar atelectasis.

The heart examination during pregnancy is altered as a result of uterine enlargement. Consequently, the point of maximum impulse (left ventricular apex) is displaced superiorly and laterally during advanced pregnancy. It remains crisp, well defined, and hyperdynamic. In thin women, the right ventricular impulse may become visible owing to an increase in circulating blood volume and the proximity of this chamber to the anterior chest wall.

Recognition of normal auscultatory changes helps distinguish pathologic from physiologic changes. New murmurs are heard in more than 90% of pregnant women. The loudest murmurs are heard between 15 and 25 weeks’ gestation; murmur intensity decreases toward term and increases again during labor and the early postpartum period. This peripartum increase in murmurs is followed by a gradual decrease; most of these pregnancy-associated murmurs are no longer appreciated by 6 weeks postpartum.24 Importantly, there is no correlation between the disappearance of physiologic murmurs of pregnancy and the return of cardiac output and blood volume to pregestational levels.29

The first heart sound (S1) becomes louder and is widely split owing to early closure of the mitral valve during pregnancy. The second heart sound (S2) is unchanged. It is quite common to appreciate the third heart sound (S3), although considerable expertise and a quiet environment are necessary because of the presence of underlying tachycardia and an increased basal respiratory rate. The fourth heart sound (S4) is rarely appreciated. Owing to increased cardiac output and
edema is symmetric and decreases with leg elevation and the left lateral decubitus position. The pathologic edema of pre-eclampsia should be differentiated from the physiologic edema of pregnancy. Asymmetric lower extremity edema is almost invariably pathologic. A tender and warm lower extremity may suggest deep vein thrombosis or cellulitis.

Funduscopic examination in pregnancy may help differentiate chronic hypertension from hypertensive disease of pregnancy (preeclampsia/eclampsia) and may identify changes caused by long-standing diabetes. It is important to look for stigmata of Marfan syndrome. Tall stature, large arm span, or other stigmata may alert the practitioner to the presence of a previously undiagnosed condition. Patients with Marfan syndrome frequently demonstrate scoliosis and may have dural ectasia. Turner syndrome is characterized by short stature and webbed neck. Both conditions predispose pregnant women to aortic dissection (see later discussion).

**CARDIAC RISK PREDICTION**

The New York Heart Association (NYHA) and Heart Failure Stage classifications describe symptoms and predict risk in the nonpregnant population (Box 41.1). Several classifications have been proposed to specifically predict cardiac risk during pregnancy, including the ZAHARA I (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking), CARPREG (CARdiac disease in PREGnancy), and modified World Health Association (WHO) risk scores (Box 41.2).
Echocardiography allows for safe and noninvasive assessment of heart structure and function. Both transthoracic and transesophageal echocardiography can be performed at any stage of pregnancy. Echocardiography helps predict overall cardiovascular risk and guides anesthetic management in pregnant women with cardiac disease. Echocardiography also allows assessment of intravascular volume and may obviate the need for right-sided heart catheterization to determine ventricular
filling pressures. Contemporary evidence suggests that for most common cardiac conditions, handheld transthoracic echocardiography provides more accurate diagnosis than physical examination.\textsuperscript{40}

One of the most commonly used echocardiographic assessments of left ventricular function—left ventricular ejection fraction—remains unchanged during pregnancy. Echocardiographic measurements of cardiac output increase during pregnancy owing to increases in stroke volume and heart rate. Importantly, stroke work is increased during pregnancy, which is consistent with augmented myocardial fiber function. Both the right and left ventricular chamber size are increased in end-diastole and end-systole, and the heart becomes more globular. This increase in chamber size results in increased left ventricular end-systolic and end-diastolic volumes and is accompanied by an increase in left ventricular wall thickness (eccentric left ventricular hypertrophy). These parameters return to baseline within 3 to 6 months postpartum.\textsuperscript{41} Left ventricular end-diastolic and end-systolic volumes are further increased with multiple gestation; the stroke volume is increased an additional 15%. Combined with a small additional increase in heart rate, this change results in a 20% greater increase in maternal cardiac output with multiple gestation compared with singleton gestation.\textsuperscript{15}

Left atrial size is increased during pregnancy;\textsuperscript{14} the increase is even greater with multiple gestation than with singleton gestation.\textsuperscript{15} Preeclampsia results in an adaptive concentric hypertrophy and an increase in left ventricular mass caused by increased afterload.

In normal pregnancy, left ventricular diastolic function is increased in the first two trimesters and declines in the third trimester.\textsuperscript{42} Twenty percent of women with preeclampsia have evidence of global diastolic dysfunction.\textsuperscript{43} Diastolic function is most commonly assessed echocardiographically by evaluating mitral valve inflow, pulmonary venous flow, and myocardial tissue motion (tissue Doppler imaging).

**Cardiac Magnetic Resonance Imaging**

The risks associated with magnetic resonance imaging (MRI) in pregnant women are similar to those in nonpregnant patients, and there is no evidence that MRI causes harm to the fetus.\textsuperscript{44} Similar to the use of all imaging modalities during pregnancy, cardiac magnetic resonance (CMR) imaging should be performed during pregnancy only after consideration of both the maternal and fetal benefits and risks. However, given the quality of images and diagnostic yield, CMR is preferable to any modality that uses ionizing radiation. Gadolinium crosses the placenta and has been found to be teratogenic in animal models. Currently available human data suggest that gadolinium should be used in pregnant women only if it significantly improves diagnostic performance and is expected to improve maternal or neonatal outcome.\textsuperscript{44}

**Cardiac Catheterization**

Coronary angiography remains the “gold standard” for diagnosis of coronary artery disease, and it can be performed at any time during pregnancy. Radial arterial access is preferable to femoral access because it is associated with earlier ambulation, increased patient comfort, and a significant reduction in access-related bleeding complications. Additionally, during the procedure, the left lateral decubitus position can be more easily maintained with radial access. Cardiologists should strictly adhere to the ALARA principle (as low as reasonably achievable) to limit both maternal and fetal ionizing radiation exposure.

The use of pulmonary artery catheterization has significantly declined in the United States in recent years. Similar information can be obtained noninvasively by transthoracic or transesophageal echocardiography. However, thermodilution and Fick cardiac output measurements can be obtained only with the use of a pulmonary artery catheter. Similarly, right-sided heart catheterization is required for vasoreactivity testing in patients with pulmonary hypertension.

**Iodinated Contrast Use during Pregnancy**

The use of iodinated contrast media in pregnant women appears safe.\textsuperscript{45} To date, there has been no report of fetal teratogenic or mutagenic effects after maternal administration of iodinated contrast media. Free iodide in the contrast medium administered to the mother may depress fetal, and subsequently neonatal, thyroid function. Therefore, it has been suggested that neonatal thyroid function be checked during the first week postpartum. Minimal amounts of iodinated contrast media are excreted in breast milk; even smaller amounts are absorbed by the neonate’s gastrointestinal tract. The slight potential risk associated with absorption of contrast medium is thought to be insufficient to recommend interruption of breast-feeding after maternal administration of iodinated contrast media.

**Computed Tomographic Angiography**

Multidetector computed tomography (CT) allows noninvasive imaging of the coronary arteries along with cardiac structure and function. Use of contemporary CT with aggressive dose-reduction techniques can significantly limit the radiation dose. The overall radiation dose of coronary CT angiography may be equivalent to, or even lower than, radiation doses delivered with conventional invasive coronary angiography. Although soft cardiac structures not seen by conventional coronary angiography are well visualized by CT angiography, the intravenous contrast medium load is greater with CT angiography, and coronary intervention cannot be performed at the time of imaging. Thus, in pregnancy, invasive coronary angiography appears preferable under most circumstances.

**Ionizing Radiation Risks to the Fetus**

The ionizing radiation dose to the fetus can be limited by the use of echocardiography, intracardiac echocardiography, reduced fluoroscopy frame rates, and contemporary image noise-reduction technology. Because the fetus is not directly within the radiation beam for cardiac procedures, the fetal exposure occurs through indirect scatter radiation. Therefore,
external shielding of the fetus is ineffective. The fetal radiation dose cannot be measured and is therefore estimated; however, it is reassuring that the estimated fetal doses are low. Nonetheless, the safest approach is to avoid ionizing radiation during pregnancy if possible, and to assess both the maternal and fetal risks and benefits before deciding on the most appropriate imaging modality.

**CARDIAC DRUGS AND PREGNANCY**

**Angiotensin-Converting Enzyme Inhibitors**
Angiotensin-converting enzyme (ACE) inhibitors are the mainstay treatment of coronary artery disease, left ventricular dysfunction, and hypertension in nonpregnant patients. These drugs are particularly useful in nonpregnant patients with diabetes mellitus.

In the first trimester, the use of ACE inhibitors has been associated with an increased risk for fetal cardiovascular and central nervous system malformations. Use of ACE inhibitors during the second and third trimesters of pregnancy has also been associated with adverse fetal and neonatal outcomes as a result of the ACE inhibitors’ effect on fetal renal vascular tone. These drugs cause fetal kidney malfunction and decreased fetal urine output, which results in oligohydramnios. Positional limb deformities, skull ossification retardation, and lung hypoplasia are seen with ACE inhibitor–associated oligohydramnios. Thus, despite the exceptionally useful profile of ACE inhibitors in nonpregnant patients with cardiovascular disease, their use in pregnancy is contraindicated (see Chapter 14).45

**Angiotensin Receptor–Blocking Agents**
Fewer data are available on the use of angiotensin receptor–blocking agents in pregnancy. Nonetheless, given the adverse outcomes associated with use of ACE inhibitors in pregnancy and the mechanism of action of angiotensin receptor–blocking agents, the use of these drugs is not recommended in pregnancy.45

**Beta-Adrenergic Receptor Antagonists**
Beta-adrenergic receptor antagonists are often used for treatment of coronary artery disease, myocardial infarction, hypertension, many arrhythmias, and a wide spectrum of cardiomyopathies. There is no evidence that beta-adrenergic receptor antagonists are teratogenic. Prolonged and high-dose use of these drugs has been associated with fetal growth restriction; however, the overall risk is likely small.45 Neonatal bradycardia, hypotension, and hypoglycemia are rarely encountered.

**Calcium Entry–Blocking Agents**
First-trimester maternal use of verapamil and diltiazem is likely not teratogenic. Both drugs appear to be safe and effective treatments for cardiac arrhythmias in the second and third trimesters.45 The use of amlopidine, a dihydropyridine calcium entry–blocking agent, appears safe during pregnancy.45

**Other Drugs**

**Hydralazine** is used in the treatment of cardiomyopathy and is also an excellent antihypertensive agent. It has a long track record of safe use during pregnancy.45

The use of **nitrates** for treatment of angina during pregnancy appears safe. Nitrates likely can be safely used long term in pregnant women with cardiomyopathy.45

**Digoxin** may be useful for the treatment of various cardiomyopathies and some arrhythmias. Digoxin freely crosses the placenta, but its use has not been associated with congenital abnormalities or untoward fetal effects.45 Digoxin’s pharmacokinetics are altered during pregnancy, and monitoring of blood levels is recommended.

**Eptifibatide, tirofiban,** and **abciximab** are potent intravenous platelet aggregation inhibitors (IIB/IIIA receptor inhibitors) used to inhibit platelet aggregation during percutaneous coronary intervention. Both the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the European Society of Anaesthesiology (ESA) guidelines strongly advise avoidance of neuraxial anesthesia until platelet function has recovered after administration of these agents.46,47

**Statins** interrupt cholesterol synthesis and result in a lowering of plasma cholesterol levels. The widespread use of statins (which are associated with exceptionally robust cardiovascular outcome data) has transformed the treatment of coronary artery disease. Nonetheless, given the critical importance of cholesterol synthesis in the normal development of the embryo and placenta, and thus their potential for teratogenicity, statins are contraindicated in pregnancy.45

**Thiazide diuretics** do not appear to be teratogenic. Long-term use may result in a reduction in uteroplacental perfusion, which may be associated with fetal growth restriction and oligohydramnios.45 Neonatal hypoglycemia and thrombocytopenia have been reported.

**Loop diuretics** are likely not teratogenic.45 Similar to thiazide diuretics, fetal growth restriction may be associated with long-term use during pregnancy. **Spironolactone** is an aldosterone antagonist frequently used in the treatment of patients with congestive heart failure and cardiomyopathy, but because of its antiandrogenic potential its use during pregnancy is not recommended.45

**AORTIC DISEASES AND AORTIC DISSECTION**

The cardiovascular changes of pregnancy may lead to increased arterial wall tension and intimal shear forces. However, the full impact of pregnancy on changes in aortic wall structure is not fully understood. Estrogen-induced changes in collagen deposition, as well as circulating elastases and relaxin, may weaken the aortic media and thus predispose the aorta to dissection during pregnancy. Approximately one-half of aortic dissections and ruptures in women younger than 40 years of age are associated with pregnancy.46 Dissection of the ascending aorta (Stanford type A or DeBakey type I or II) is a surgical emergency, whereas dissection of the
descending aorta (Stanford type B or DeBakey type III) is predominantly treated medically.

Conditions that predispose women to aortic dissection during pregnancy include Marfan syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve, Turner syndrome, and non–Marfan syndrome–associated familial thoracic aneurysms. Aortic dissection has been associated with pre-eclampsia and chronic hypertension in pregnancy. Most aortic dissections that occur during pregnancy are type A (ascending aorta); the average aortic diameter at the time of dissection is 4.8 cm. The majority of dissections occur in the third trimester of pregnancy, but aortic dissections may also occur at the time of delivery or in the early postpartum period. It has been hypothesized that contraction of the uterus causes outflow resistance, thus predisposing to aortic dissection after delivery.

Marfan Syndrome
Marfan syndrome is an autosomal-dominant connective tissue disorder. The penetrance is high, but the expression is variable. Marfan syndrome is caused by a mutation in the FBN1 gene encoding fibrillin-1, a glycoprotein. Sporadic mutations are seen in approximately 25% of patients without a family history of this syndrome. Aortic dilation and aortic dissection contribute significantly to cardiovascular complications in these patients. In addition to aortic disease, affected patients often have valvular disease (e.g., aortic regurgitation, mitral regurgitation, mitral valve prolapse). Aortic dissection has been observed during pregnancy and in the peripartum period. Most patients have type A aortic dissection; type B aortic dissection and abdominal aortic aneurysm are less commonly seen.

Based on observational studies, current guidelines recommend that women with Marfan syndrome who are planning pregnancy undergo replacement of the ascending aorta and the aortic root if the diameter is greater than 4.0 cm (class IIa, level of evidence C). The aortic root dilation rate increases during pregnancy and does not return to baseline after delivery. Subsequent pregnancies further increase the aortic dilation rate.

Aortic Disease Associated with a Bicuspid Aortic Valve
Bicuspid aortic valve has been associated with dissection during pregnancy. Affected women are slightly younger, and the dissection occurs earlier in pregnancy than in patients with Marfan syndrome. Because the disease is familial, first-degree relatives of patients with a bicuspid aortic valve should be screened for this disease.

Ehlers-Danlos Syndrome
Ehlers-Danlos syndrome is an inherited connective tissue disorder. Ehlers-Danlos syndrome type IV has been associated with severe complications and maternal mortality. Rupture of the bowel, aorta, vena cava, and uterus may occur. Pregnancy outcomes in patients with Ehlers-Danlos syndrome types I, II, and III are generally favorable, although these women may have a higher incidence of pelvic instability, preterm delivery, perineal lacerations, and postpartum hemorrhage than the general population.

Turner Syndrome
Turner syndrome is caused by complete or partial absence of an X chromosome. In addition to short stature, webbed neck, and characteristic facial features, Turner syndrome is associated with aortic coarctation and hypertension. Approximately 30% of patients with Turner syndrome have a bicuspid aortic valve. During pregnancy, the syndrome is associated with aortic dissection. Preconception echocardiographic evaluation of patients with Turner syndrome is recommended. Given the frequent aortic abnormalities in these patients, preconception MRI is also recommended. Because of short stature in some patients with Turner syndrome, absolute aortic root measurements may not accurately predict the risk for aortic dissection. Cesarean delivery is frequently required in these patients because of cephalopelvic disproportion.

Aneurysm-Osteoarthritis Syndrome
Aneurysm-osteoarthritis syndrome is a recently described autosomal-dominant condition caused by mutations in the SMAD3 gene. Mutations in the SMAD3 gene lead to increased aortic expression of several components in the TGF-β pathway and subsequent aneurysm formation. In addition, visceral and iliac aneurysms, arterial tortuosity, and early-onset joint abnormalities may be present. In a cohort of 17 patients and 34 pregnancies, no maternal mortality or aortic dissection was observed. Cesarean delivery was performed for mainly obstetric indications without increased bleeding complications. The type of anesthesia was not reported.

Obstetric and Anesthetic Management
Given the inherent risk for aortic dissection, parturients with aortic disease should deliver in a center that has immediate access to a cardiothoracic surgeon with expertise in aortic endovascular repair techniques. Current guidelines are based on expert opinion, case reports, and current standard of care (level C evidence) (Box 41.3; Table 41.2). The 2010 American College of Cardiology (ACC) Foundation/American Heart Association (AHA) guidelines recommend the following for pregnant women with chronic aortic dilation: (1) strict blood pressure control; (2) monthly or bimonthly echocardiographic measurement of aortic dimension; (3) cesarean delivery in women with significant aortic enlargement, dissection, or severe aortic valve regurgitation; and (4) prophylactic surgery in the setting of progressive aortic dilation and/or advancing aortic valve regurgitation.

All patients with Marfan syndrome should receive beta-adrenergic receptor antagonist therapy throughout pregnancy to decrease the rate of aortic dilation. The risk for major aortic complications during pregnancy appears low if the aortic root diameter is less than 4.0 cm. In the event of a type A aortic dissection in the first or second trimester,
surgical repair should be performed with the knowledge of fetal risk during hypothermic circulatory arrest. If the dissection occurs in the third trimester and the fetus is deemed viable, an urgent cesarean delivery followed by aortic surgery may be performed.

Both neuraxial and general anesthesia may be safely performed in these patients, with emphasis on meticulous blood pressure stability and control. Invasive blood pressure monitoring is recommended to facilitate tight hemodynamic control. Dural ectasia and scoliosis may complicate neuraxial anesthesia in parturients with Marfan syndrome. The increase in lumbar cerebrospinal fluid volume associated with dural ectasia may cause unpredictable and inadequate spread of intrathecal local anesthetic solutions; thus, it may be prudent to obtain lumbar spine MRI before planned pregnancy.

**CONGENITAL HEART DISEASE**

**Atrial Septal Defect**

Patients with an atrial septal defect may remain asymptomatic until the fourth decade of life. Not infrequently, women with an atrial septal defect may become symptomatic during pregnancy. The most common defect is the secundum-type atrial septal defect (80%), whereas the primum, sinus venosus, and coronary sinus types of atrial septal defect are less common. Right ventricular overload leads to pulmonary hypertension and Eisenmenger syndrome in less than 5% of patients with an atrial septal defect. In women with both an atrial septal defect and Eisenmenger syndrome, pregnancy carries a significant risk for both maternal and fetal mortality, and is not recommended. In the absence of pulmonary hypertension, pregnancy is overwhelmingly well tolerated in women with an atrial septal defect.

Cardiac complications are similar in women with unrepaired or repaired atrial septal defects. Preeclampsia, fetal demise, and small-for-gestational-age infants are more common in pregnant women with an unrepaired atrial septal defect than in the general obstetric population. Pregnant women with an atrial septal defect are more likely to develop supraventricular and ventricular arrhythmias than women who are not pregnant.

The risk for paradoxical embolism is increased in patients with an unrepaired atrial septal defect. It is critically important to ensure that intravenous catheters are de-aired. Transesophageal echocardiography demonstrates the presence of microbubbles in the right-sided cardiac chambers within 15 seconds of the epidural injection of air or fluid. Therefore, it seems prudent to avoid using the loss-of-resistance-to-air technique to identify the epidural space (see Table 41.2). Both neuraxial and general anesthesia are appropriate for patients with a repaired or unrepaired atrial septal defect.

**Ventricular Septal Defect**

There are four types of ventricular septal defects; the most common type is a perimembranous ventricular septal defect. Pregnancy is well tolerated in women with a repaired ventricular septal defect or a small ventricular septal defect in the absence of pulmonary hypertension. An unrepaired ventricular septal defect with Eisenmenger syndrome is associated with a high risk for maternal cardiac complications (see later discussion). Pregnancy is not recommended in patients with a ventricular septal defect and Eisenmenger syndrome. Preeclampsia is encountered more frequently in women with an unrepaired ventricular septal defect. Echocardiography allows assessment of right-sided pressures and shunt fraction.

**Patent Ductus Arteriosus**

Pregnancy is well tolerated in patients with patent ductus arteriosus, and complications are rare. A left-to-right shunt may cause pulmonary hypertension. Pregnancy is not recommended in women with patent ductus arteriosus with Eisenmenger syndrome.
<table>
<thead>
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<th>Monitoring</th>
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<td>Turner syndrome</td>
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<td>Positive-pressure ventilation decreases preload and increases intrathoracic pressure, which is deleterious to RV function</td>
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<tr>
<td>Repaired ASD</td>
<td>PAP &lt; 40 mm Hg</td>
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<tr>
<td>Disease</td>
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<td>Anesthetic Considerations</td>
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<td>Prevent/treat pain, hypoxemia, hypercarbia, and acidosis</td>
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<td>Aortic stenosis</td>
<td>Transvalvular gradient &lt; 25 mm Hg, valve area &gt; 1.5 cm², normal LV function</td>
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<td>Low threshold for invasive blood pressure monitoring</td>
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<td>Attentive preservation of preload and afterload</td>
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<td></td>
<td></td>
<td>Monitor closely for volume overload during the first 24 hours after delivery</td>
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<tr>
<td></td>
<td>Transvalvular gradient ≥ 25 mm Hg, valve area &lt; 1.0 cm², LV dysfunction</td>
<td>High-risk group</td>
<td>Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider risks/benefits of neuraxial versus general anesthesia</td>
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<tr>
<td></td>
<td></td>
<td>Avoid myocardial depressants and vasodilators</td>
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<td></td>
<td></td>
<td>Meticulously maintain preload and afterload</td>
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<td></td>
<td></td>
<td>Avoid abrupt decrease in SVR with sympathectomy</td>
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<td></td>
<td></td>
<td>Maintain sinus rhythm</td>
<td></td>
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<td></td>
<td></td>
<td>Address new-onset atrial fibrillation (rate control, consider cardioversion)</td>
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<td></td>
<td></td>
<td>Monitor very closely for volume overload during first 24 hours after delivery</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Valve area &gt; 1.5 cm², no pulmonary hypertension</td>
<td>Neuraxial anesthesia generally well tolerated</td>
<td>Low threshold for central venous access/filling pressure monitoring</td>
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<tr>
<td></td>
<td></td>
<td>Maintain sinus rhythm and prevent tachycardia</td>
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<td></td>
<td></td>
<td>Increase in preload not well tolerated</td>
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<td></td>
<td>Address new-onset atrial fibrillation (rate control, consider cardioversion)</td>
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<td></td>
<td></td>
<td>Monitor closely for volume overload during first 24 hours after delivery</td>
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<tr>
<td></td>
<td>Valve area ≤ 1.5 cm², pulmonary hypertension</td>
<td>High-risk group</td>
<td>Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider percutaneous mitral valvuloplasty before labor/delivery</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Maintain sinus rhythm and prevent tachycardia</td>
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<td></td>
<td>Increase in preload not well tolerated</td>
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<td></td>
<td></td>
<td>Address new-onset atrial fibrillation (rate control, consider cardioversion)</td>
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<tr>
<td></td>
<td></td>
<td>Prevent/treat pain, hypoxemia, hypercarbia, and acidosis</td>
<td></td>
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<tr>
<td>Pulmonary stenosis</td>
<td>Mild-moderate</td>
<td>Pregnancy well tolerated</td>
<td>Low threshold for invasive blood pressure monitoring</td>
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<tr>
<td></td>
<td>Severe</td>
<td>High-risk group</td>
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<tr>
<td></td>
<td></td>
<td>Consider balloon valvuloplasty</td>
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<tr>
<td></td>
<td></td>
<td>Prevent tachycardia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mitigate increase in pulmonary artery resistance (e.g., hypoxemia, positive-pressure ventilation)</td>
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</tbody>
</table>

Continued
Administration of neuraxial analgesia/anesthesia for labor and vaginal delivery and emergency cesarean delivery has been described. Administration of neuraxial anesthesia, with meticulous attention to maintenance of normal intravascular preload, appears to be the preferred anesthetic technique for cesarean delivery. Use of neuraxial anesthesia avoids the adverse effects of myocardial depression and positive-pressure ventilation on the Fontan circulation, which lacks a functioning right ventricle (see Table 41.2).

Coarctation of the Aorta

Women with repaired coarctation of the aorta tolerate pregnancy well. Systemic arterial hypertension is often observed during labor. The coarctation may be associated with a bicuspid aortic valve in more than half the patients. Prepregnancy evaluation of the coarctation, including the residual degree of obstruction and associated anomalies (e.g., bicuspid aortic valve), is recommended. Vaginal delivery with neuraxial anesthesia is the preferred mode of delivery; cesarean delivery is reserved for obstetric indications. Epidural anesthesia has been successfully administered in a patient with an uncorrected coarctation. One report described the use of remifentanil to control blood pressure during administration of general anesthesia for cesarean delivery.

Fontan Repair

The Fontan repair is a surgical procedure that establishes blood flow from the venous system to the pulmonary artery by bypassing the right ventricle (Fig. 41.1). It can be performed for valvular defects such as tricuspid or pulmonic atresia, or other anomalies with a single ventricle. Because there is no functional right ventricle, blood flow from the periphery to the lungs occurs at very low pressure gradients. Owing to the presence of surgical scar tissue in the atrium, patients with a Fontan repair are prone to supraventricular and, less commonly, ventricular arrhythmias. The Fontan repair is associated with the highest prevalence of arrhythmias during pregnancy of any congenital heart condition. Deterioration in the NYHA functional status during pregnancy can occur.

Administration of neuraxial analgesia/anesthesia for labor and vaginal delivery and emergency cesarean delivery has been described. Administration of neuraxial anesthesia, with meticulous attention to maintenance of normal intravascular preload, appears to be the preferred anesthetic technique for cesarean delivery. Use of neuraxial anesthesia avoids the adverse effects of myocardial depression and positive-pressure ventilation on the Fontan circulation, which lacks a functioning right ventricle (see Table 41.2).

Transposition of the Great Arteries

Transposition of the great arteries comprises two distinct groups: complete transposition of the great arteries (d-transposition) and congenitally corrected transposition of the great arteries (l-transposition). In both conditions, the aorta originates from the right ventricle and the pulmonary artery originates from the left ventricle. Complete transposition of the great arteries manifests as neonatal cyanosis.

Pregnant women born with d-transposition of the great arteries have undergone surgical correction—traditionally an atrial switch procedure (Senning or Mustard) or the more contemporary arterial switch procedure (Jatene or Rastelli). In the atrial switch procedure, the right ventricle functions as the systemic ventricle. Atrial arrhythmias, right ventricular (systemic ventricle) dysfunction, tricuspid regurgitation (systemic atrioventricular valve), atrial baffle obstruction or leaks, and pulmonary hypertension are some of the long-term complications of the traditional atrial switch surgical repair of d-transposition of the great arteries. The advantage of the Jatene and Rastelli procedures is that the left ventricle functions as the systemic ventricle. However, myocardial ischemia

### TABLE 41.2 Anesthetic Considerations for Specific Cardiovascular Pathologic Processes—cont’d

<table>
<thead>
<tr>
<th>Disease</th>
<th>Modifier</th>
<th>Anesthetic Considerations</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Without LVOT obstruction</td>
<td>Pregnancy well tolerated</td>
<td>Low threshold for invasive blood pressure monitoring and central venous access/filling pressure monitoring</td>
</tr>
<tr>
<td></td>
<td>With LVOT obstruction</td>
<td>Maintain beta-adrenergic receptor antagonist therapy</td>
<td>Echocardiography helpful to follow outflow tract gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low preload and low afterload worsen outflow gradient</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Treat hypotension with phenylephrine</td>
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<td></td>
<td></td>
<td>Maintain sinus rhythm and prevent tachycardia</td>
<td></td>
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<td></td>
<td></td>
<td>Address new-onset atrial fibrillation (rate control, consider cardioversion)</td>
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<tr>
<td></td>
<td></td>
<td>Meticulous attention to preload</td>
<td>Invasive blood pressure monitoring</td>
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<tr>
<td></td>
<td></td>
<td>Maintain spontaneous ventilation</td>
<td>Central venous access/filling pressure monitoring</td>
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<tr>
<td></td>
<td></td>
<td>Positive-pressure ventilation is deleterious to preload</td>
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<tr>
<td></td>
<td></td>
<td>Volatile anesthetic agents depress ventricular function</td>
<td></td>
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<tr>
<td>Cardiac tamponade</td>
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</table>

All patients with cardiovascular disease should labor in the lateral position to decrease aortocaval compression. Central venous pressure monitoring should be performed above the diaphragm.

ASD, Atrial septal defect; LV, left ventricle; LVOT, left ventricular outflow tract; PAP, pulmonary artery pressure; RV, right ventricle; SVR, systemic vascular resistance; VSD, ventricular septal defect.
Ebstein’s Anomaly

In Ebstein’s anomaly, the tricuspid valve is displaced toward the apex of the right ventricle, which results in severe tricuspid regurgitation and right atrial enlargement (Figs. 41.2 and 41.3). It is commonly associated with an atrial septal defect and preexcitation syndromes. Accessory pathways result in arrhythmias in approximately 30% of patients; the most commonly observed arrhythmias include atrial tachycardia, atrial flutter, and atrial fibrillation. Pregnancy appears to be well tolerated in patients with Ebstein’s anomaly, especially in women with preserved ventricular function (see Table 41.2).68,95,96 Patients with a concomitant atrial septal defect and cyanosis have an increased risk for fetal loss and low infant birth weight.67

Tetralogy of Fallot

Unrepaired tetralogy of Fallot consists of a ventricular septal defect, an aorta that overrides the ventricular septal defect, and right ventricular outflow tract obstruction (infundibular, valvular, or both), with resulting right ventricular hypertrophy.67,68 Most women born with tetralogy of Fallot in the United States now present in pregnancy with surgically repaired tetralogy of Fallot. Unrepaired tetralogy of Fallot is rarely seen in developed countries; pregnancy is associated with significant risk in patients with unrepaired defects and is not recommended.67,68
During surgical repair, the ventricular septal defect is closed and the right ventricular outflow obstruction is repaired. After surgery, important considerations include residual pulmonic valve insufficiency and resulting right ventricular dilation and dysfunction. The preanesthesia evaluation of these patients should include detailed echocardiographic evaluation of cardiac structure and function. Preferably, preconception CMR imaging should be performed because it provides superior imaging of the right-sided chambers. Patients with repaired tetralogy of Fallot are at risk for atrial and ventricular arrhythmias. Sudden cardiac death has been observed late after repair.\textsuperscript{97}

Women with repaired tetralogy of Fallot and well-compensated hemodynamic function tolerate pregnancy well (see Table 41.2).\textsuperscript{98} However, the presence of pulmonary hypertension, right ventricular dysfunction, right ventricular dilation, and/or pulmonic regurgitation predisposes these patients to adverse peripartum complications such as arrhythmias and right-sided heart failure.\textsuperscript{68,98,99}

The safe management of neuraxial analgesia/anesthesia for labor and vaginal or cesarean delivery has been described in parturients with repaired tetralogy of Fallot and a wide range of residual pathologic processes.\textsuperscript{100} In patients with unrepaired tetralogy of Fallot or tetralogy of Fallot with residual pathology, the anesthesiologist should avoid a decrease in SVR, which worsens the severity of the right-to-left shunt. It is also important to maintain adequate intravascular volume and venous return. In the presence of right ventricular compromise, high filling pressures are needed to enhance right ventricular performance and ensure adequate pulmonary blood flow. Administration of neuraxial analgesia during early labor (low-dose local anesthetic–opioid epidural
analgesia or opioid-only intrathecal analgesia) may attenuate the surge of catecholamines and subsequent hemodynamic instability. It may be advisable to choose a titratable neuraxial technique for cesarean delivery (epidural or low-dose sequential spinal–epidural anesthesia; see Chapter 26) to avoid the abrupt decrease in SVR associated with single-shot spinal anesthesia.

**PULMONARY HYPERTENSION**

Box 41.4 outlines the current classification of pulmonary hypertension. Group 1 (pulmonary arterial hypertension or PAH) includes idiopathic pulmonary arterial hypertension. Other clinical conditions associated with Group 1 pulmonary hypertension include connective tissue disease, human immunodeficiency virus (HIV) infection, portal hypertension, drugs/toxins (e.g., selective serotonin reuptake inhibitors, anorectics, methamphetamine, cocaine). The 2013 updated classification lists pulmonary hypertension caused by congenital heart disease in Group 2. Pulmonary hypertension associated with chronic hemolytic anemia (e.g., sickle cell disease) is now listed as Group 5.

All of these conditions are associated with exceptionally high maternal mortality. Older studies reported maternal mortality rates as high as 56%; however, more contemporary studies have demonstrated some improvement in maternal mortality, with rates ranging from 16% to 33%. The contemporary Registry of Pregnancy and Cardiac Disease (ROPAC) reported the highest mortality associated with idiopathic PAH (43%) followed by left-heart disease PAH (2.7%) and congenital heart disease PAH (2.7%). Similarly, among 49 women with pulmonary hypertension who gave birth in one of four U.S. institutions between 2001 and 2015, the overall mortality rate was 16%; seven of eight deaths occurred in women with idiopathic PAH (mortality rate 23%). These differences in mortality rates underline the importance of PAH etiology on maternal outcomes. Of note, all deaths in both studies occurred in the postpartum period, most within the first postpartum week. Thus, pregnancy should be discouraged in women with pulmonary hypertension.

Normal mean (± SD) pulmonary artery pressure (PAP) at rest is 14 ± 3 mm Hg (upper limit of normal = 20 mm Hg). Pulmonary arterial hypertension is defined as a mean PAP greater than 25 mm Hg with a normal pulmonary artery occlusion pressure (PAOP) (less than or equal to 15 mm Hg) and pulmonary vascular resistance (PVR) greater than 3 Wood units. In contrast, in “postcapillary” pulmonary hypertension caused by left-sided heart failure (Group 2), PAOP is elevated (greater than 15 mm Hg). Increased PVR results in right ventricular overload, which is followed by right ventricular hypertrophy. Right ventricular hypertrophy progresses to dilation of the right-sided chambers, eventually leading to right ventricular failure and death.

A loud pulmonic heart sound (P2) can be heard on physical examination. The second heart sound is widely split owing to delayed closure of the pulmonic valve resulting from high right-sided pressures (pulmonary valve closes after the aortic valve). A right-sided holosystolic murmur of tricuspid regurgitation is frequently appreciated. Palpation of the precordium demonstrates the classic right ventricular heave. The most commonly encountered ECG findings in patients with pulmonary hypertension are right-axis deviation and right ventricular hypertrophy.

Echocardiography helps establish the diagnosis and prognosis of pulmonary hypertension because it demonstrates the degree of right ventricular hypertrophy and allows estimation of PAP by assessing the velocity of the tricuspid regurgitant jet (Fig. 41.4). Echocardiography also allows assessment of right ventricular function.

Echocardiographic assessment of right-sided pressures may be inaccurate; therefore, invasive right-sided—and frequently left-sided—heart catheterization is required for the definitive diagnosis of pulmonary arterial hypertension. Right-sided heart catheterization allows pressure measurements, thermodilution and Fick cardiac output determination, and vasoreactivity testing. Vasoreactivity testing is usually performed with inhaled nitric oxide or intravenous infusion of sodium nitroprusside, epoprostenol, or adenosine in the cardiac catheterization laboratory. Patients who achieve a decrease in mean PAP of 10 mm Hg or more and achieve a mean PAP of 40 mm Hg or less, without a decrease in cardiac output, are “positive acute responders.” Patients with a positive response have a better prognosis and may respond to oral therapy with a calcium entry–blocking agent.

**Eisenmenger Syndrome**

In patients with an anatomic shunt between the systemic and pulmonary circulations at the atrial, ventricular, or

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**Box 41.4 Classification of Pulmonary Hypertension**

1. Pulmonary arterial hypertension
2. Pulmonary hypertension due to left-sided heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvar disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung disease and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms


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*Wood unit, unit of measure of vascular resistance (mm Hg • min/L); multiply by 80 to convert to dyne • s • cm⁻².*
Pulmonary arterial hypertension due to congenital heart disease can be caused by a number of unrepaired congenital heart defects with a left-to-right shunt. Eisenmenger syndrome is associated with ventricular septal defect, atrial septal defect, patent ductus arteriosus, and atrioventricular septal defect (also referred to as endocardial cushion defect). More rarely encountered congenital heart defects (e.g., partial or total anomalous pulmonary venous return, transposition of the great arteries) may also lead to pulmonary arterial hypertension and Eisenmenger syndrome.105

Medical and Obstetric Management

Pregnant women with pulmonary hypertension should receive multidisciplinary care in a referral center. Diuretics are frequently needed to manage volume overload in patients with pulmonary arterial hypertension. Diuretics may be particularly helpful in the immediate postpartum period, when uterine contraction and autotransfusion cause an increase in ventricular preload. Dobutamine infusion may help improve right ventricular function. It is unclear whether all of these patients should receive thromboprophylaxis. Both hemorrhage and thromboembolism are causes of maternal mortality.105

Therapy for pulmonary arterial hypertension includes general supportive measures, assessment of vasoreactivity, and administration of vasoactive drugs.107 Inhaled nitric oxide selectively dilates the pulmonary vasculature. Case reports have described the successful use of nitric oxide for vaginal and cesarean deliveries in parturients with pulmonary arterial hypertension.108-110 Epoprostenol, treprostinil, and iloprost are prostacyclins used in the treatment of pulmonary hypertension. Successful pregnancy has been described in patients with pulmonary arterial hypertension treated with epoprostenol.111-114 Similarly, sildenafil, a phosphodiesterase type-5 inhibitor, has been successfully used in pregnant women with pulmonary arterial hypertension.115,116 Endothelin receptor antagonists (e.g., bosentan, ambrisentan) are likely teratogenic, and therefore their use is contraindicated during pregnancy.

The optimal mode of delivery in patients with pulmonary hypertension is unknown. In a systematic review that included reports from 1978 to 1996,104 operative delivery was an independent risk factor for maternal mortality. In contrast, the mode of delivery was not identified as a risk factor for maternal death in a systematic review that included more recent cases.105 In a contemporary study, the overall cesarean delivery rate was 54%. Cesarean delivery is associated with larger changes in intravascular volume, more bleeding complications and blood loss, and a greater risk for thromboembolism; therefore, it seems reasonable to reserve cesarean delivery for obstetric indications.

Anesthetic Management

The primary goals of anesthetic management are (1) maintenance of adequate SVR; (2) maintenance of intravascular volume and venous return; (3) avoidance of aortocaval compression; (4) prevention of pain, hypoxemia, hypercarbia,
and acidosis, which may increase PVR; and (5) avoidance of myocardial depression during general anesthesia (see Table 41.2).

Current evidence on choice of anesthetic technique for patients with pulmonary arterial hypertension is based on case reports and series from high-volume referral centers. The use of both general, epidural, and combined spinal-epidural anesthesia has been reported. Neuraxial (epidural and CSE) anesthesia with use of pulmonary vasodilators in highly specialized centers appears to be associated with favorable overall outcomes. In published case reports, cautious administration of epidural anesthesia did not affect the shunt flow in parturients with Eisenmenger syndrome. Slowly titrated epidural or combined spinal-epidural anesthesia eliminates the undesirable effects of myocardial depression and positive-pressure ventilation (with its associated decrease in preload) associated with general anesthesia.

Intravascular volume assessment in patients with pulmonary arterial hypertension is of utmost importance. It is likely best achieved with central venous pressure monitoring; pulmonary artery catheterization without the use of fluoroscopy is technically challenging owing to the frequent presence of tricuspid regurgitation and right-sided chamber enlargement in these patients. Pulmonary artery catheterization has not been shown to improve outcome. Both transthoracic and transesophageal echocardiography are very helpful, and invasive blood pressure monitoring is indispensable. Because patients with pulmonary arterial hypertension frequently require systemic anticoagulation, the choice of anesthesia in these patients is best determined by a multidisciplinary team.

Because of its ease of administration, nitric oxide can be readily administered in the urgent setting. Nitric oxide has been administered during epidural anesthesia for emergency cesarean delivery using a noninvasive ventilation device. Successful cesarean delivery with inhaled iloprost and slowly titrated epidural anesthesia has been reported.

Given the high rate of postpartum mortality, patients should be monitored in an intensive care setting for a number of days postpartum.

**INFECTIVE ENDOCARDITIS**

Endocarditis during pregnancy is rare. It is most frequently associated with intravenous drug use or preexisting structural heart and valve abnormalities (e.g., rheumatic valvular disease, congenital heart disease). Maternal and fetal mortality rates are both high (approximately 15% and 22% respectively).

**Antibiotic Prophylaxis**

Currently, the ACC, the AHA, and the American College of Obstetricians and Gynecologists (ACOG) do not recommend infective endocarditis antibiotic prophylaxis during vaginal or cesarean delivery in the absence of structural heart disease. In patients with congenital heart disease and the highest risk for adverse outcomes, it is reasonable to administer antibiotic prophylaxis against infective endocarditis before vaginal delivery at the time of membrane rupture. High-risk patients include those with one or more of the following: (1) a prosthetic cardiac valve or a valve repaired with prosthetic material, (2) unrepaired or palliated cyanotic congenital heart disease, and (3) surgically constructed palliative shunts and conduits (Box 41.5). In patients with one of these high-risk conditions who have an established infection (e.g., chorioamnionitis), the underlying infection should be treated. Additional antibiotics specific to endocarditis prophylaxis are not recommended. Mitral valve prolapse *is not* an indication for antibiotic prophylaxis. It is important to note that the level of evidence for these recommendations is B (data from a single randomized trial or nonrandomized trials). In young women of childbearing age, there is no difference in the rate of prosthetic valve endocarditis with mechanical or bioprosthetic valves.

**Diagnosis and Treatment**

The diagnosis of endocarditis rests on a very high index of suspicion, physical examination, laboratory findings, and cardiac imaging. The modified Duke criteria are the most widely accepted criteria for the diagnosis of endocarditis (Box 41.6). Patients with endocarditis may have negative blood cultures. Therefore, absence of bacterial growth in blood cultures does not automatically rule out endocarditis.

In addition to systemic antibiotic therapy, valve replacement may be required in pregnant women with endocarditis. Alternatively, successful treatment with aggressive antibiotic therapy has been described.

**Neuraxial Anesthesia in Patients with Systemic Infection**

anesthesia. Whether the neuraxial procedure contributed to the development of the infection if meningitis or epidural abscess should develop in a patient with endocarditis receiving neuraxial anesthesia. The majority of patients requiring temporary pacing have underlying congenital heart disease, it is critically important to understand the cardiac anatomy before placing the venous pacemaker to minimize complications such as perforation or valve injury.

**Implantable Cardioverter-Defibrillators**

Pacemaker and implantable cardioverter-defibrillator (ICD) implantation during pregnancy may be performed with echocardiographic guidance, thus reducing fetal radiation exposure. A wearable automatic defibrillator is an attractive alternative, but it is uncomfortable for prolonged use. Because the majority of patients requiring temporary pacing have underlying congenital heart disease, it is critically important to understand the cardiac anatomy before placing the venous pacemaker to minimize complications such as perforation or valve injury.

**Peripartum Management**

Pacemakers and ICDs should be interrogated before or during pregnancy, and before and after labor and vaginal or cesarean delivery (Fig. 41.5). The type of device, manufacturer, and model should be documented. The indication for the device, the patient’s underlying rhythm, and whether the patient is pacemaker dependent should be identified. Given the complexity of contemporary pacing and ICD devices, it is imperative to perform this evaluation in collaboration with an electrophysiologist or a cardiologist familiar with device management. It is helpful to obtain a 12-lead ECG before and after delivery, and before and after any change in device programming.

The response of the device to magnet placement and removal should be known. It is important to recognize that different devices may respond quite differently to magnet placement. Most pacemakers will pace in an asynchronous mode after application of an external magnet. For most ICDs, the magnet will disable tachycardia detection (i.e., the device will not deliver a shock for ventricular tachycardia or ventricular fibrillation), but the magnet will not alter the pacing mode and rate settings. Magnets do not change bradycardia pacing settings for ICDs.

**Implantable Cardiac Devices**

**Permanent and Temporary Pacemakers**

Permanent pacemakers implanted before pregnancy are generally well tolerated in these patients.

Advanced second-degree (two or more nonconducted P waves) or third-degree atrioventricular block is rare in pregnant women and is most commonly seen in patients with congenital heart disease. Recommendations are inconsistent as to whether temporary pacing is required for labor and delivery. Some of the principal indications for pacemaker placement (e.g., symptomatic bradycardia, periods of asystole greater than 3 seconds, escape rhythms below the atrioventricular node with rates less than 40 bpm) also appear to be appropriate indications for parturients; the decision to electively place either a temporary or permanent device should be made by a multidisciplinary team. Patients who develop hemodynamic instability caused by bradycardia should receive a temporary venous pacemaker. Transcutaneous pacing is an attractive alternative, but it is uncomfortable for prolonged use. Because the majority of patients requiring temporary pacing have underlying congenital heart disease, it is critically important to understand the cardiac anatomy before placing the venous pacemaker to minimize complications such as perforation or valve injury.

**Neurologic infectious complications after spinal or epidural anesthesia** are rare in large observational series; however, there is general agreement that patients with untreated systemic infection should not receive neuraxial anesthesia.

Published data and clinical experience suggest that spinal anesthesia may be safely administered in patients who have received antibiotic treatment and are responding to treatment at the time of dural puncture. Similarly, it is likely that epidural anesthesia may be safely administered to patients with treated systemic infection. In patients with endocarditis, bacteremia may seed the epidural space and cause epidural abscess in the absence of neuraxial anesthesia. Similarly, meningitis is a recognized neurologic complication of endocarditis. Therefore, it may be difficult to determine whether the neuraxial procedure contributed to the development of the infection if meningitis or epidural abscess should develop in a patient with endocarditis receiving neuraxial anesthesia.

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**BOX 41.6 Modified Duke Criteria for the Diagnosis of Bacterial Endocarditis**

**Major Criteria**
- Positive blood culture with typical infective endocarditis microorganism
- Evidence of endocardial involvement with positive echocardiogram

**Minor Criteria**
- Predisposing factor: known cardiac lesion, recreational drug injection
- Fever > 38°C
- Evidence of embolism: arterial emboli, pulmonary infarcts, Janeway lesions, conjunctival hemorrhage
- Immunologic problems: glomerulonephritis, Osler’s nodes
- Positive blood culture (with an atypical microorganism that does not meet a major criterion) or serologic evidence of infection with organism consistent with infective endocarditis but not satisfying a major criterion

**ADULT ARRHYTHMIAS**

The incidence of arrhythmias is increased during pregnancy in patients with and without structural heart disease. The mechanisms have been attributed to atrial and ventricular stretch caused by increased intravascular volume as well as the increase in resting heart rate. Additionally, autonomic and hormonal changes of pregnancy have been proposed as putative mechanisms.

Palpitations are frequent during pregnancy, and Holter monitoring often reveals premature atrial and ventricular contractions. The frequency of ectopy decreases after delivery. Interestingly, there is no correlation between symptomatic palpitations and frequency of underlying arrhythmias. Therefore, no treatment is needed in asymptomatic patients with premature atrial contractions or premature ventricular contractions. Substances such as caffeine, alcohol, and cocaine should be discontinued, and treatment with a beta-adrenergic receptor antagonist may be considered in symptomatic patients.

Women who have been diagnosed with an arrhythmia before pregnancy frequently develop an exacerbation of arrhythmia during pregnancy. Recurrence of a preexisting arrhythmia is associated with adverse fetal events.

**Supraventricular Arrhythmias**

Overall, supraventricular tachycardia (SVT) during pregnancy is rare, with an estimated 24 episodes/100,000 pregnancies. It is unclear whether pregnancy increases the risk for new-onset supraventricular tachycardia, although the first onset of paroxysmal supraventricular tachycardia during pregnancy is unusual. Symptoms of supraventricular tachycardia may be exacerbated during pregnancy.

Premature atrial contractions are frequently encountered during pregnancy. Their frequency generally decreases in the postpartum period. Premature atrial contractions are generally benign and rarely cause significant palpitations. Symptomatic patients can be treated with a low dose of a beta-adrenergic receptor antagonist.

Atrial fibrillation is encountered rarely during pregnancy. Rate and/or rhythm control along with prevention of thromboembolism are the mainstays of treatment of atrial fibrillation. The ventricular rate can be successfully controlled with digoxin, a beta-adrenergic receptor antagonist, or a nondihydropyridine calcium entry–blocking agent. Alternatively, quinidine, sotalol, flecainide, or amiodarone may be used to control rapid ventricular response. These drugs also allow for pharmacologic cardioversion of atrial fibrillation. Although restoration of sinus rhythm reduces the risk for thromboembolism and may provide considerable short-term hemodynamic advantages in certain patients, the impact of a rhythm–control treatment strategy on long-term outcome is unclear.

Because atrial fibrillation during pregnancy most frequently results from underlying structural heart disease (rheumatic mitral stenosis or congenital heart disease), systemic anticoagulation during pregnancy is recommended.
There is extensive published experience with the use of unfractionated heparin and warfarin during pregnancy; limited data are available with low-molecular-weight heparin (LMWH).

Use of CHADS2 and CHA2DS2-VASc scores facilitates risk stratification for predicting stroke and thromboembolism associated with atrial fibrillation. This risk stratification provides guidance for choice of anticoagulation. In the CHA2DS2-VASc score, points are assigned for Congestive heart failure, Hypertension, Age 75 years or older (doubled), Diabetes mellitus, prior Stroke or transient ischemic accident or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, and female Sex. The CHA2DS2-VASc score appears to have improved predictive ability in patients with low baseline CHADS2 scores. Nonpregnant patients at low risk for stroke generally receive aspirin, whereas those at high risk receive oral anticoagulation with warfarin or a newer (direct) oral anticoagulant (e.g., dabigatran, apixaban, rivaroxaban). There are case reports of unplanned pregnancy while women were receiving rivaroxaban anticoagulation for venous thromboembolism. These reports stress the need to educate women of childbearing age that direct-acting anticoagulants are contraindicated during pregnancy.

Atrial flutter is an organized macro-reentrant arrhythmia rarely seen during pregnancy. The atrial rate is usually 300 bpm; ventricular rate control may be difficult to achieve medically. Electric cardioversion is recommended for unstable patients, although pharmacologic cardioversion with ibutilide during pregnancy has been reported.

In a recent report from the ROPAC registry, atrial fibrillation and atrial flutter were found in 1.3% of pregnant patients with structural heart disease. The highest incidence was seen at the end of the second trimester. Both of these arrhythmias were associated with higher maternal mortality and low birth weight.

Atrial tachycardia most frequently results from increased automaticity of atrial cells. Incessant atrial tachycardia has been successfully ablated during pregnancy.

Ventricular preexcitation syndromes (e.g., Wolff-Parkinson-White syndrome) are rarely encountered in pregnancy; these patients are usually identified at a younger age and have undergone highly effective electrophysiologic treatment. A few case reports suggest that preexcitation syndromes may be associated with an increased rate of supraventricular arrhythmias during pregnancy.

Ventricular Arrhythmias

Ventricular arrhythmias are commonly associated with underlying structural heart disease. The diagnostic evaluation warrants a baseline ECG and echocardiography. During pregnancy, peripartum cardiomyopathy as cause of ventricular arrhythmias should be ruled out.

Idiopathic ventricular tachycardia is most commonly monomorphic, originating from the right ventricular outflow tract. New-onset idiopathic ventricular tachycardia during pregnancy has been reported in a very small series of patients. These reported arrhythmias were catecholamine sensitive and responsive to beta-adrenergic receptor antagonist therapy. Idiopathic ventricular tachycardia may also be sensitive to treatment with verapamil or isoproterenol. Polymorphic ventricular tachycardia and electrical storm with Brugada syndrome have also been reported during pregnancy.

Sudden cardiac death caused by idiopathic ventricular tachycardia has been described in pregnant women with hypertrophic cardiomyopathy. Sustained idiopathic ventricular tachycardia, successfully treated with lidocaine infusion, has been described in patients with repaired tetralogy of Fallot.

Congenital Long QT Syndrome

The congenital long QT syndrome is caused by mutations in cardiac ion channels resulting in prolongation of ventricular repolarization. The clinical spectrum ranges from a lack of symptoms to arrhythmia-associated syncope and sudden cardiac death. Risk for cardiac events (syncope, arrhythmias, or death) is decreased in pregnant women with long QT syndrome, owing at least in part to the increase in heart rate that occurs during pregnancy. Compared with the 40-week prepregnancy period, the 40-week postpartum period has been associated with an increased risk for ventricular tachycardia in women with long QT syndrome. Different long QT syndrome genotypes may have different risks associated with pregnancy. The LQT2 genotype is associated with a higher rate of cardiac events in the 9-month postpartum period than the LQT1 and LQT3 genotypes. Prophylactic treatment with a beta-adrenergic receptor antagonist is recommended during pregnancy and postpartum in patients with long QT syndrome.

Antiarrhythmic Drugs

The risk for adverse fetal effects of antiarrhythmic drugs should be assessed on an individual basis (see Chapter 14). Beta-adrenergic receptor antagonists, amiodarone, and sotalol are effective in preventing idiopathic ventricular tachycardia during pregnancy. Fetal exposure to amiodarone has been associated with hypothyroidism and, possibly, fetal growth restriction. Sotalol appears to be safe in pregnancy. Because sotalol is a beta-adrenergic receptor antagonist, its use may be associated with neonatal bradycardia and hypoglycemia.

Electric Cardioversion

Life-threatening or hemodynamically unstable arrhythmias should be terminated by electric cardioversion. Defibrillation refers to administration of electrical energy to terminate ventricular fibrillation. By contrast, synchronized cardioversion is delivery of an electric shock synchronized to the QRS complex. Synchronized cardioversion is administered for supraventricular rhythms (i.e., atrial fibrillation, atrial flutter, atrial tachycardia) as well as for monomorphic ventricular tachycardia with a pulse. Pulseless ventricular tachycardia and polymorphic ventricular tachycardia should be treated with unsynchronized cardioversion.
Electric cardioversion can be performed safely throughout pregnancy without apparent adverse effects on fetal hemodynamic function. Nonetheless, it is prudent to monitor the fetal heart rate (FHR) during cardioversion. Current guidelines recommend the use of a biphasic defibrillator. Ventricular fibrillation can be successfully terminated with biphasic devices that use lower energy than is required with monophasic devices. Biphasic automatic external defibrillators (AEDs) are more effective in terminating ventricular fibrillation with lower energy than older monophasic devices.

If hemodynamically significant or severely symptomatic arrhythmias develop during pregnancy, electrophysiologic interventional management may be performed. Successful radiofrequency catheter-based ablation has been reported in pregnant women with no or minimal ionizing radiation exposure.

Patients usually require anesthesia care for cardioversion. The risk for pulmonary aspiration of gastric contents associated with sedation (with an unprotected airway) should be weighed against the risks associated with general anesthesia and tracheal intubation. The judicious use of sedation rather than general anesthesia is usually preferred. A benzodiazepine or propofol can provide satisfactory sedation and amnesia. Regardless of whether sedation or general anesthesia is selected, a nonparticulate oral antacid should be administered; administration of a histamine-2 (H₂)-receptor antagonist to increase gastric pH should also be considered. The use of metoclopramide in these patients is controversial owing to its possible association with tachyarrhythmias.

**Maintenance of Sinus Rhythm**

Development of atrial fibrillation may cause significant hemodynamic compromise, particularly in pregnant women with stenotic valvular lesions (aortic stenosis or mitral stenosis) or hypertrophic cardiomyopathy with its associated diastolic dysfunction. Hemodynamic compromise results from the diminished diastolic filling time and loss of the atrial contraction contribution to ventricular filling. Maintenance of sinus rhythm and strict rate control have not been shown to be beneficial in older (nonpregnant) patients with paroxysmal or permanent atrial fibrillation. However, published studies are largely not applicable to pregnant women, and it seems reasonable to maintain sinus rhythm and control heart rate in this population. Rate control is particularly important in patients with stenotic valvular lesions and hypertrophic cardiomyopathy because the hemodynamic condition of these patients may quickly deteriorate in the presence of tachycardia.

**MYOCARDIAL INFARCTION**

The term myocardial infarction signifies myocardial cell death caused by ischemia. Myocardial infarction is diagnosed by clinical signs and symptoms, ECG patterns, elevation of biomarkers (CK-MB fraction, troponin), and various imaging modalities (echocardiography, radionuclide imaging, CMR imaging, CT). The current Universal Classification of Myocardial Infarction recognizes five types of myocardial infarction (Box 41.7). Myocardial infarction during pregnancy is rare; the estimated incidence is 6.2 to 6.5 per 100,000 deliveries. It occurs most commonly in the third trimester or the immediate postpartum period. Myocardial infarction during pregnancy is associated with maternal use of tobacco, dyslipidemia, family history of myocardial infarction, hypertension, African race, Hispanic ethnicity, and diabetes. Using data from the U.S. National Inpatient Sample for 2000 to 2002, James et al. estimated the maternal mortality rate from myocardial infarction during pregnancy at approximately 5%.

**Acute coronary syndrome** is an encompassing term used to describe unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Unstable angina is differentiated from NSTEMI by lack of elevation of cardiac biomarkers. Compared with unstable angina or NSTEMI, STEMI is an emergency and requires early reperfusion; a “door-to-balloon” interval of less than 90 minutes is optimal.

Only 40% of pregnant patients with myocardial infarction have evidence of coronary artery atherosclerosis (type I myocardial infarction); spontaneous coronary artery dissection (type II myocardial infarction) is observed in as many as 27% of patients. Angiographically normal coronary arteries are seen in 13% of patients; in these cases, myocardial infarction likely results from coronary artery spasm or embolism.

<table>
<thead>
<tr>
<th>BOX 41.7 Universal Classification of Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1—Spontaneous Myocardial Infarction</strong></td>
</tr>
<tr>
<td>Caused by atherosclerosis and plaque rupture/erosion resulting in intracoronary thrombus formation</td>
</tr>
<tr>
<td><strong>Type 2—Myocardial Infarction Caused by Ischemic Imbalance</strong></td>
</tr>
<tr>
<td>Caused by conditions other than atherosclerosis (e.g., supply-demand mismatch, coronary vasospasm, coronary embolism, coronary dissection, stress of noncardiac surgery)</td>
</tr>
<tr>
<td><strong>Type 3—Cardiac Death Caused by Myocardial Infarction</strong></td>
</tr>
<tr>
<td>Cardiac death highly suggestive of myocardial infarction without the availability of biomarker confirmation</td>
</tr>
<tr>
<td><strong>Type 4a—Myocardial Infarction Related to Percutaneous Coronary Intervention</strong></td>
</tr>
<tr>
<td>Caused by distal plaque embolization and side-branch occlusion; directly related to coronary intervention (e.g., stenting or balloon angioplasty)</td>
</tr>
<tr>
<td><strong>Type 4b—Myocardial Infarction Caused by Stent Thrombosis</strong></td>
</tr>
<tr>
<td>Detected by autopsy or angiography</td>
</tr>
<tr>
<td><strong>Type 5—Myocardial Infarction Caused by Coronary Artery Bypass Grafting (CABG)</strong></td>
</tr>
<tr>
<td>Cardiac biomarker elevation associated with surgical revascularization procedure</td>
</tr>
</tbody>
</table>

Spasm can be spontaneous, or it can be caused by cocaine or ergot alkaloids. Septic and metastatic neoplastic coronary embolism after abortion have been described. Atherosclerosis is more commonly the cause of myocardial infarction in the antepartum period than in the peripartum or postpartum period, whereas spontaneous coronary artery dissection is observed more frequently in the peripartum and postpartum periods. It has been hypothesized that the high rate of spontaneous coronary artery dissection is related to hormonal changes of pregnancy. The left anterior descending coronary artery is frequently the culprit vessel, and ST-elevations with reduced ejection fraction are often present. Recurrent spontaneous coronary dissection is common during follow-up.

Cesarean delivery is commonly associated with ischemic-appearing ST-segment depression. These changes have been attributed, at least in part, to oxytocin administration (see earlier discussion). ST-segment elevation is not a normal occurrence during labor and delivery or with any type of intrapartum anesthesia. Hence, ST-segment elevation should always be considered abnormal, and ST-segment depression should be carefully evaluated.

CK-MB fraction may be elevated during normal pregnancy and labor (see Fig. 46.1); thus, measurement of this enzyme is less useful for the diagnosis of myocardial infarction in pregnant women than in nonpregnant women. An elevated troponin level is much more specific, although troponin may be elevated in patients with gestational hypertension and preeclampsia/eclampsia. Both markers are quite sensitive for the diagnosis of myocardial infarction.

**Percutaneous Coronary Intervention**

STEMI during pregnancy should be treated with primary percutaneous coronary intervention. Although successfully used in anecdotal reports, use of thrombolytic therapy for STEMI in pregnant women should be reserved for rare instances. Radial arterial access for the percutaneous coronary intervention procedure is preferable because it has fewer bleeding complications and a lower mortality rate than femoral arterial access. Systemic anticoagulation with unfractionated heparin appears most reasonable owing to its short half-life, the availability of activated clotting time (ACT) monitoring, and the ability to rapidly reverse its anticoagulant effect. Importantly, larger doses of heparin are needed to achieve the desired level of anticoagulation in pregnant than in nonpregnant patients. Anticoagulation for percutaneous coronary intervention can be achieved with LMWH, although inability to rapidly assess its anticoagulant effect and its altered pharmacokinetics during pregnancy are disadvantages.

Percutaneous coronary interventions for treatment of myocardial infarction include conventional “plain old balloon angioplasty” and stent placement. An advantage of conventional balloon angioplasty is that it does not require dual antiplatelet therapy; however, placement of a stent is associated with a lower risk for abrupt vessel closure in the short term and a lower long-term risk for restenosis.

Dual antiplatelet therapy is mandatory after placement of a coronary artery stent to prevent stent thrombosis (Table 41.3). This therapy consists of both aspirin (81 to 325 mg daily) and clopidogrel. Clopidogrel can be substituted with a newer agent (e.g., prasugrel, ticagrelor) in specific nonpregnant patients. However, the safety and efficacy of these newer antiplatelet agents in pregnancy are unknown.

**Stent Type Choice**

In patients with a nonacute coronary syndrome (e.g., chronic stable angina), bare-metal stents require a minimum of 1 month of dual antiplatelet therapy, whereas drug-eluting stents require a minimum of 6 months. When either bare-metal stents or drug-eluting stents are placed in a patient with any acute coronary syndrome (e.g., unstable angina, NSTEMI, STEMI), 12 months of dual antiplatelet therapy is recommended. The advantage of drug-eluting stents is a decreased risk for in-stent restenosis than occurs with bare-metal stents. Drug-eluting stents elute an antiproliferative agent (e.g., everolimus, sirolimus, paclitaxel) into the arterial wall and reduce the neointimal proliferation that causes in-stent restenosis. However, the stent strut endothelialization process is slower with drug-eluting stents than with bare-metal stents; thus, a longer duration of dual antiplatelet therapy is required to prevent stent

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**TABLE 41.3 Dual Antiplatelet Therapy Recommendations**

<table>
<thead>
<tr>
<th></th>
<th>PERCUTANEOUS CORONARY INTERVENTION (PCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Balloon Angioplasty</td>
</tr>
<tr>
<td>Stable Coronary Artery Disease</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>Aspirin</td>
</tr>
<tr>
<td>High Bleeding Risk/Pregnancy</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

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*Given the fact that placement of drug-eluting stents requires prolonged dual antiplatelet therapy, drug-eluting stents are not recommended in pregnant women at high risk for bleeding. However, drug-eluting stent technology is advancing, and in the future, new generation drug-eluting stents may allow for shorter durations of dual antiplatelet therapy.

*Acute coronary syndrome includes unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction.
thrombosis. Overall rates of death and myocardial infarction are similar with drug-eluting and bare-metal stents. The risk for stent thrombosis may be lower with contemporary drug-eluting stents than with bare-metal stents. Polymer-free biolimus A9 drug-eluting stents allow for 1 month of dual antiplatelet therapy and will likely supplant the use bare-metal stents in patients with high bleeding risk. Polymer-free drug-eluting stents are approved for use outside the United States and are undergoing clinical trials in the United States.

**Dual Antiplatelet Therapy**

Bare-metal and polymer-free drug-eluting stents allow for discontinuation of dual antiplatelet therapy 1 month after percutaneous coronary intervention, if necessary, even in the setting of acute coronary syndrome (see Table 41.3). This may be advantageous in pregnant women who are at risk for intrapartum and postpartum hemorrhage. Therefore, although prospective clinical trials are not available, most interventional cardiologists will implant a bare-metal stent or a contemporary polymer-free drug-eluting stent in a pregnant woman with acute coronary syndrome. Although it appears reasonable to continue dual antiplatelet therapy as long as feasible in a pregnant woman with acute coronary syndrome, there are few data on the optimal duration of dual antiplatelet therapy in this unique clinical setting. Continuing research is being performed to determine the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention in the nonpregnant population.

It is not advisable to perform neuraxial anesthesia in patients receiving dual antiplatelet therapy. After clopidogrel is discontinued, aspirin should be continued indefinitely in patients with any type of stent. Both spinal and epidural anesthesia can be performed safely in patients receiving aspirin. Clopidogrel should be discontinued 7 days before performance of neuraxial anesthesia.

Aspirin crosses the placenta. A 2002 meta-analysis found no overall increase in the risk for congenital malformations when aspirin was administered in the first trimester; however, a twofold increase in the risk for gastroesophageal reflux was observed. Another meta-analysis that evaluated the use of aspirin for prevention of preterm birth found no evidence of increased risk for fetal growth restriction, pregnancy loss, or neonatal hemorrhage. Most evidence suggests that aspirin use is safe during pregnancy.

**Coronary Artery Anomalies**

Coronary artery anomalies occur in approximately 1% of the general population. Coronary artery anomalies are frequently associated with congenital heart disease such as d-transposition of the great arteries and tetralogy of Fallot.

There are numerous types of coronary anomalies, and most are benign. The two most common clinically significant anomalies are (1) a left main coronary artery that originates from the right coronary cusp and (2) a right coronary artery that originates from the left coronary cusp. External mechanical compression of those anomalous coronary vessels may cause myocardial ischemia and eventually lead to arrhythmias. The resulting ischemia and arrhythmias have been associated with sudden cardiac death. The effect of the physiologic changes of pregnancy in women with coronary artery anomalies has not been well studied.

**VALVULAR HEART DISEASE**

Pregnancy and its associated changes in cardiovascular physiology present a unique clinical challenge to women with underlying valvular heart disease. The general management principles for pregnant women with valvular heart disease are directed toward specific hemodynamic goals and the need for anticoagulation in patients with a mechanical valve.

**Aortic Stenosis**

The most common cause of aortic stenosis in pregnant women is a congenital bicuspid aortic valve. Less common causes/types of aortic stenosis include rheumatic, supravalvular, and subvalvular aortic stenosis. Rheumatic aortic stenosis is invariably associated with some degree of mitral valve involvement. The hemodynamic implications of the various causes of aortic stenosis are similar. Calcific aortic stenosis is an anatomically normal tricuspid aortic valve occurs much later in life and is unlikely to be encountered in women of childbearing age.

Bicuspid aortic valve, the most common congenital heart defect, occurs in 0.5% to 2% of the population; women are affected four times less commonly than men. It is heritable; therefore, first-degree relatives of patients with a bicuspid aortic valve should be screened. Bicuspid aortic valve is associated with accelerated and premature valve stenosis as well as aortic valve regurgitation. Symptoms of aortic stenosis (dyspnea on exertion, chest pain, syncope) generally present in the third and fourth decades of life. Importantly, patients with a bicuspid aortic valve have underlying aortic root pathology in the media that is associated with aortic root dilatation, thus predisposing to ascending root dissection.

The normal aortic valve area is 3.0 to 4.0 cm². There is no pressure gradient across a normal aortic valve with normal resting cardiac output. Patients generally develop symptoms when the valve area is less than 1.0 cm² and the pressure gradient across the valve is greater than 40 mm Hg. An aortic valve area less than 1.0 to 1.5 cm² and a mean valve gradient of 25 to 50 mm Hg generally define the group of patients with a high risk for cardiovascular complications caused by aortic stenosis.

Traditional criteria for aortic stenosis included patient symptoms, pressure gradients and flow velocity across the aortic valve, and calculated aortic valve area. The updated valvular aortic stenosis classification takes into account valve anatomy, valve hemodynamic characteristics, structural heart consequences of stenotic valve hemodynamics, and patient symptoms (Table 41.4). It should be noted that this new staging classification has not been evaluated in pregnant patients and will require further study in this particular population. Therefore, the traditional and new nomenclature are used interchangeably in this chapter.
TABLE 41.4 Stages of Valvular Aortic Stenosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk for AS</td>
<td>• Bicuspid aortic valve</td>
<td>Aortic $V_{\text{max}} &lt; 2 \text{ m/s}$</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Progressive AS</td>
<td>• Mild-moderate leaflet calcification • Rheumatic valve changes</td>
<td>Mild AS, $V_{\text{max}} 2.0$ to $2.9 \text{ m/s}$ or mean gradient $&lt; 20 \text{ mm Hg}$ Moderate AS, $V_{\text{max}} 3.0$ to $3.9 \text{ m/s}$ or mean gradient $20$ to $39 \text{ mm Hg}$</td>
<td>Normal LVEF</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe AS</td>
<td>• Severe leaflet calcification/ severely reduced leaflet opening</td>
<td>Aortic $V_{\text{max}} \geq 4 \text{ m/s}$ Mean gradient $\geq 40 \text{ mm Hg}$ Aortic valve area $\leq 1.0 \text{ cm}^2$</td>
<td>Mild LV hypertrophy Normal LVEF May have reduced LVEF $&lt; 50%$</td>
<td>May require exercise testing to confirm symptom status</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe high-gradient AS</td>
<td>• Severe leaflet calcification/ severely reduced leaflet opening</td>
<td>Aortic $V_{\text{max}} \geq 4 \text{ m/s}$ or mean gradient $\geq 40 \text{ mm Hg}$ Aortic valve area $\leq 1.0 \text{ cm}^2$</td>
<td>LV hypertrophy LV diastolic dysfunction Pulmonary hypertension may be present May have LVEF $&lt; 50%$</td>
<td>Dyspnea Decreased exercise tolerance Angina Syncope/presyncope Heart failure</td>
</tr>
</tbody>
</table>

AS, Aortic stenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; $V_{\text{max}}$, maximum aortic velocity.

Classically, the aortic valve area is estimated invasively in the cardiac catheterization laboratory using the Gorlin equation. Forward cardiac output is determined by thermodilution and/or Fick methods, and left ventricular and aortic pressures are simultaneously recorded. Doppler velocity measurements during echocardiography allow non-invasive estimation of aortic valve area using the continuity equation.

Using both methods, the estimated transvalvular gradient increases during pregnancy because of the physiologic increase in cardiac output. The calculated valve area remains unchanged, however, because both the Gorlin equation and the continuity equation take cardiac output into account. The echocardiographic dimensionless valve index is useful in pregnant women as well as other patients; it takes into account both left ventricular outflow velocity and the aortic velocity. Because both velocities are increased during pregnancy, the dimensionless index and estimated valve area remain unchanged during pregnancy.

The severity of aortic stenosis affects maternal risk during pregnancy. Mild and moderate aortic stenosis (corresponding to stages A and B) are associated with favorable pregnancy outcomes. Women with severe aortic stenosis (stages C and D) experience frequent cardiac complications during pregnancy (e.g., worsening NYHA functional class, pulmonary edema, congestive heart failure, arrhythmias, hospitalization). The reported rates of these complications during pregnancy vary widely (e.g., heart failure and pulmonary edema $4\%$ to $78\%$, arrhythmias $2\%$ to $33\%$, hospitalization rate as high as $78\%$). Additionally, women with severe disease are more likely to require a cardiac intervention (balloon valvuloplasty, valve replacement) during pregnancy or immediately postpartum. Percutaneous balloon valvuloplasty of the aortic valve is a palliative procedure that allows completion of pregnancy before definitive repair. Mortality is rare with contemporary care. Nonetheless, similarly to previously published data, severe aortic stenosis remains associated with significant risk for heart failure, hospitalizations, and low-birth-weight infants.

Successful transcatheter aortic valve replacement (TAVR) during pregnancy has been described in a single case report in a symptomatic patient with bicuspid aortic valve. This early successful experience offers an encouraging alternative for treatment of aortic stenosis during pregnancy beyond palliative balloon valvuloplasty.

Obstetric and Anesthetic Management

Labor and assisted vaginal delivery are preferred. Cesarean delivery is reserved for obstetric indications.

Whether general or neuraxial anesthesia is more appropriate for parturients with aortic stenosis has been a matter of debate. Historically, neuraxial anesthesia has been thought to be relatively contraindicated in patients with aortic stenosis; the simultaneous decrease in preload and afterload associated with neuraxial anesthesia may be particularly hazardous in these patients. However, case reports have documented successful administration of neuraxial anesthesia (spinal, continuous spinal, CSE, epidural) and
general anesthesia with favorable maternal and neonatal outcomes.

The choice between neuraxial and general anesthesia should not be made based on the aortic valve gradient or aortic valve area alone. The preanesthetic assessment should include physical examination, symptom evaluation, and comprehensive assessment of the right and left ventricular structure and function, as well as the structure and function of other cardiac valves. The presence or absence of pulmonary hypertension should also be determined.

Echocardiography offers indispensable information regarding left and right ventricular ejection fraction, left ventricular wall thickness, PAP, presence of aortic insufficiency, mitral valvular structure and function, and aortic root size. Serial assessment of the aortic valve area before and during pregnancy is very helpful in managing these patients. Patients with normal right and left ventricular function are more likely to tolerate fluid shifts and the depressant effects of general anesthetic agents. If left ventricular dysfunction develops in the presence of aortic stenosis, a condition referred to as low-output, low-gradient aortic stenosis may be present.

The presence of pulmonary hypertension, right ventricular dysfunction, or mitral regurgitation is associated with greater dependence on preload and may unfavorably affect the hemodynamic response to neuraxial anesthesia. Patients with a dilated aortic root will likely benefit from gradual blood pressure changes, because aortic root dilation has been associated with aortic dissection. Left ventricular hypertrophy, frequently present with aortic stenosis, is associated with significant diastolic dysfunction and may impede left ventricular filling. The presence of left ventricular hypertrophy will render these patients more sensitive to the adverse effects of decreased preload, tachycardia, and the development of congestive heart failure, especially in the setting of acute-onset atrial fibrillation. Aortic regurgitation is quite common in patients with a bicuspid aortic valve. The ventricles are exposed to both pressure and volume overload, further complicating hemodynamic management and response to anesthesia.

The goals of anesthetic management are (1) maintenance of a normal heart rate, sinus rhythm, and adequate systemic vascular resistance; (2) maintenance of intravascular volume and venous return; (3) avoidance of aortocaval compression; and (4) avoidance of myocardial depression during general anesthesia (see Table 41.2). In the absence of prospective randomized trials in this patient population, current clinical evidence suggests that either neuraxial analgesia/anesthesia or general anesthesia is safe for patients with mild or moderate aortic stenosis with normal right and left ventricular ejection fraction and the absence of other significant valvular lesions or pulmonary hypertension. Neuraxial anesthetic techniques that allow gradual titration of anesthesia seem advantageous in these patients.

In patients with severe aortic stenosis, general anesthesia remains the gold standard. Although published reports have described successful administration of neuraxial anesthesia for labor and vaginal and cesarean delivery in women with severe aortic stenosis, the influence of publication bias in these reports cannot be excluded. In contemporary obstetric anesthesiology practice, an opioid-based neuraxial labor analgesia technique, along with alternative forms of analgesia (e.g., pudendal nerve block, intravenous opioids) is well tolerated in parturients with severe aortic stenosis. A slowly dosed, low-concentration local anesthetic epidural technique, or a sequential CSE technique, with careful titration of a vasopressor to prevent the decrease in SVR, may be safely performed with vigilant blood pressure monitoring. The anesthesiologist may choose to avoid use of an epinephrine-containing local anesthetic solution because the unintentional intravenous injection of epinephrine can precipitate tachycardia; further, systemic absorption of epinephrine can diminish SVR and reduce venous return. General anesthesia may be the best choice for cesarean delivery in patients with severe aortic stenosis and other significant valvular lesions, pulmonary hypertension, and/or left ventricular dysfunction. Induction of anesthesia with a combination of etomidate and a moderate dose of a lipid-soluble opioid may be preferable to agents that cause myocardial depression and vasodilation (propofol, thiopental) and tachycardia (ketamine). Anesthesia can be maintained with an opioid and a low-dose volatile anesthetic technique.

Peripartum invasive arterial blood pressure monitoring is recommended for parturients with moderate and severe aortic stenosis. Pulmonary artery catheterization is unlikely to provide much clinical benefit in this patient population. Development of atrial fibrillation with rapid ventricular response is deleterious in these patients because it decreases diastolic filling time and eliminates the atrial component of left ventricular filling. If new-onset atrial fibrillation results in hypotension or pulmonary edema, sinus rhythm should be promptly restored.

**Aortic Regurgitation**

The most common etiology of chronic aortic regurgitation in pregnant women is a degenerated bicuspid aortic valve; rheumatic aortic regurgitation occurs less frequently. Dilation of the ascending aorta and the resulting aortic leaflet separation may also result in aortic regurgitation. Most commonly, aortic root dilation results from cystic medial necrosis associated with Marfan syndrome, or it occurs in association with a bicuspid aortic valve. Chronic aortic regurgitation is generally well tolerated during pregnancy, especially in patients with preserved left ventricular ejection fraction. The physiologic changes of pregnancy (increased heart rate resulting in a shorter duration of diastole, as well as reduced SVR) contribute to an overall reduction in regurgitant aortic flow.

Although patients with chronic aortic regurgitation can compensate for the hemodynamic stress over time, patients with acute aortic regurgitation are frequently very ill and may require surgery. Endocarditis is the most common etiology of acute aortic regurgitation during pregnancy. Ascending aortic dissection may also result in severe acute aortic regurgitation. Affected patients may require valve replacement during pregnancy.
Anesthetic Management

The goals of anesthetic management are (1) maintenance of a normal to slightly elevated heart rate, (2) prevention of an increase in SVR, (3) avoidance of aortocaval compression, and (4) avoidance of myocardial depression during general anesthesia (see Table 41.2). Antepartum echocardiography may guide decisions regarding the choice of anesthesia and monitoring. Patients with chronic, compensated aortic insufficiency and normal ejection fraction tolerate the hemodynamic changes of pregnancy well; however, patients with left ventricular dysfunction will likely require careful assessment of volume status and PAP during labor and delivery. Traditionally, a pulmonary artery catheter has been used for this purpose; in the future, transthoracic echocardiography will likely be used.

The degree of aortic insufficiency, concomitant involvement of the mitral valve, and the size of the aortic root help define hemodynamic goals. Patients with a bicuspid aortic valve may have simultaneous aortic stenosis and aortic regurgitation. Both neuraxial analgesia/anesthesia and general anesthesia can be safely performed in patients with aortic regurgitation and preserved left ventricular ejection fraction. Severe aortic insufficiency with left ventricular dysfunction is not a contraindication for neuraxial anesthesia. Initiation of neuraxial analgesia during early labor may mitigate pain-associated increases in SVR that can be deleterious in patients with aortic regurgitation. Intra-aortic balloon pump placement is contraindicated in patients with aortic regurgitation because its use increases regurgitant flow.

Mitral Stenosis

Mitral stenosis frequently becomes symptomatic during pregnancy owing to the increase in maternal blood volume and heart rate. Increased blood volume with decreased diastolic filling time can result in pulmonary edema. Additionally, mitral stenosis predisposes patients to development of atrial tachyarrhythmias (atrial fibrillation, atrial flutter) as well as thromboembolic complications, with or without atrial arrhythmias. The underlying hypercoagulable state of pregnancy also increases the risk for thromboembolic complications in patients with mitral stenosis. Therefore, systemic anticoagulation is recommended for the duration of pregnancy and postpartum.

The etiology of mitral stenosis is almost invariably rheumatic. Severe mitral stenosis (stages C and D) is defined as a valve area less than 1.5 cm² (Table 41.5). In addition to valve area, diastolic pressure half-time, presence of pulmonary hypertension, and symptoms define severe mitral stenosis stages. Transmitral valve gradients measured by echocardiography increase during pregnancy. Therefore, while transmitral gradients greater than 5 to 10 mm Hg are usually present in severe mitral stenosis, the dependence of this measure on underlying heart rate and forward flow may limit its usefulness during pregnancy. Similarly, diastolic pressure half-time is affected by the physiologic changes of pregnancy, and its use and interpretation can present a diagnostic challenge.

Poor functional status NYHA (e.g., III to IV) portends a greater risk for adverse outcomes. When possible, preconception treatment of symptomatic moderate or severe mitral stenosis is preferred. The procedure of choice is percutaneous balloon mitral valvuloplasty. Suitability for percutaneous balloon valvuloplasty is determined by an echocardiography-based scoring system, which takes into account valve calcification and mobility as well as valvular and subvalvular thickening.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk for MS</td>
<td>Mild valve doming during diastole</td>
<td>• Normal</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Progressive MS</td>
<td>Rheumatic valve changes</td>
<td>• Increased transmitral flow velocity</td>
<td>• Mild-moderate left atrial enlargement</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe MS</td>
<td>Rheumatic valve changes</td>
<td>• Mitral valve area &gt; 1.5 cm²</td>
<td>• Severe left atrial enlargement</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe MS</td>
<td>Rheumatic valve changes</td>
<td>• Mitral valve area ≤ 1.5 cm²</td>
<td>• Elevated pulmonary artery pressure ≥ 30 mm Hg</td>
<td>Dyspnea</td>
</tr>
</tbody>
</table>

TABLE 41.5 Stages of Mitral Stenosis

MS, Mitral stenosis.

For patients who require percutaneous valvuloplasty during pregnancy, the procedure is ideally performed after 12 to 14 weeks’ gestation to minimize fetal radiation exposure during the period of organogenesis. If the patient can be stabilized with medical management, delaying the procedure to 26 to 30 weeks’ gestation will reduce the risk for preterm delivery. Using data from 1990 to 1995, de Souza et al. found that open surgical mitral valve commissurotomy was associated with higher rates of fetal mortality than percutaneous valvuloplasty (38% versus 3%).

Standard medical therapy during pregnancy includes a reduction in activity level (e.g., bed rest), beta-adrenergic receptor antagonist and diuretic therapy, and anticoagulation.

**Obstetric and Anesthetic Management**

Cesarean delivery is typically reserved for obstetric indications. Vaginal delivery is usually assisted, because the Valsalva maneuver during the second stage of labor may result in a sudden increase in central venous pressure. Regardless of the method of delivery, patients are at risk for both intrapartum and postpartum hemodynamic compromise and pulmonary edema; therefore, these patients usually require postpartum intensive care. The important anesthetic goals are (1) maintenance of a low-normal heart rate and preservation of sinus rhythm; (2) aggressive treatment of atrial fibrillation, if present; (3) avoidance of aortocaval compression; (4) maintenance of venous return; (5) maintenance of adequate SVR; and (6) prevention of pain, hypoxemia, hypercarbia, and acidosis, which may increase PVR (see Table 41.2).

Intrapartum and postpartum invasive hemodynamic monitoring is often helpful, and close peripartum monitoring of filling pressures is important. Echocardiographic assessment of right-sided pressures appears to somewhat overestimate true pressures; therefore, in selected patients with severe mitral stenosis, a pulmonary artery catheter may help guide fluid management. The decision to place a pulmonary artery catheter should be guided by assessment of NYHA functional status, right ventricular function, PAP, and severity of symptoms related to mitral stenosis before pregnancy.

Neuraxial analgesia/anesthesia for labor and vaginal or cesarean delivery can be safely performed in patients with mitral stenosis. Adequate analgesia during the first stage of labor is essential. Intradiscal administration of a lipid-soluble opioid during the first stage of labor provides excellent analgesia without causing sympathetic blockade. Neuraxial administration of an opioid with a small dose of local anesthetic may provide satisfactory analgesia for the second stage of labor. Hypotension should be treated with a direct-acting vasoconstrictor (phenylephrine).

Neuraxial anesthesia for cesarean delivery is best administered with a titratable technique (epidural anesthesia, sequential CSE anesthesia), judicious intravenous fluid administration, and titration of phenylephrine to maintain hemodynamic stability. During induction and maintenance of general anesthesia, tachycardia should be prevented by administration of a beta-adrenergic receptor antagonist and/or an opioid. After delivery, care should be taken with the administration of the uterotonic agent 15-methyl prostaglandin-F2α, because it may increase PVR.

**Mitral Regurgitation**

Mitral regurgitation is generally well tolerated during pregnancy. Nonetheless, some evidence suggests that the volume overload associated with pregnancy may induce unfavorable structural alterations in women with mitral regurgitation. Both neuraxial and general anesthesia are well tolerated. Chronic mitral regurgitation may be associated with left ventricular dysfunction; thus, echocardiographic assessment of left ventricular function helps guide anesthetic and fluid management. The goals of anesthetic management in patients with mitral regurgitation include (1) prevention of an increase in SVR, (2) maintenance of a normal to slightly increased heart rate, (3) maintenance of sinus rhythm, (4) aggressive treatment of acute atrial fibrillation, (5) avoidance of aortocaval compression, (6) maintenance of venous return, (7) prevention of an increase in central venous volume, (8) avoidance of myocardial depression during general anesthesia, and (9) prevention of pain, hypoxemia, hypercarbia, and acidosis, which may increase PVR (see Table 41.2).

**Mitral Valve Prolapse Syndrome**

Historically, before the contemporary understanding of the complex three-dimensional echocardiographic anatomy of the mitral valve, mitral valve prolapse tended to be overdiagnosed. Currently, the term mitral valve prolapse should be restricted to conditions in which the free margin of the anterior, posterior, or both leaflets of the mitral valve is displaced superior to the annular plane of the mitral valve. With these diagnostic criteria, the prevalence of mitral valve prolapse in the general population is 2% to 3%, with no female preponderance. Mitral valve prolapse is a heterogeneous disorder with various causes and associations, including familial and degenerative or myxomatous disorders, Marfan syndrome, Ehlers-Danlos syndrome, a redundant papillary chordal apparatus, and many other diseases. Varying degrees of mitral regurgitation can be associated with this condition. Therefore, along with the history and physical examination, echocardiography plays a central role in the diagnosis, treatment, and ongoing assessment of these patients.

The overall clinical course in patients with mitral valve prolapse is excellent. Pregnancy and vaginal or cesarean delivery with either neuraxial or general anesthesia are well tolerated. Patients with moderate or severe mitral regurgitation and/or depressed left ventricular function are at increased risk for morbidity and mortality. The recommendations for anesthetic management of parturients with mitral regurgitation and/or left ventricular dysfunction also apply to patients with these conditions associated with mitral valve prolapse. Antibiotic endocarditis prophylaxis is not recommended.

**Tricuspid Stenosis and Regurgitation**

Rheumatic tricuspid stenosis is rarely encountered in pregnancy; most frequently, it accompanies rheumatic mitral...
stenosis. Clinically, it is associated with dyspnea, pulmonary hypertension, and congestive heart failure. Successful treatment with balloon valvuloplasty has been described.

**Tricuspid regurgitation** is rarely found in isolation during pregnancy. Functional tricuspid regurgitation is often observed in normal pregnancy with little clinical consequence. Severe tricuspid regurgitation is often associated with congenital heart disease such as Ebstein’s anomaly. Overall, pregnancy is well tolerated in the presence of tricuspid regurgitation; patients may be susceptible to hypotension with a decrease in preload.207

**Pulmonic Stenosis and Regurgitation**

Pregnancy is well tolerated in patients with pulmonic stenosis, and isolated pulmonic stenosis has not been found to affect maternal and fetal outcomes205 (see Table 41.2). In a small series of cases, affected patients had normal right ventricular function and only mild symptoms on initial presentation.205 Nonetheless, valvuloplasty is recommended in asymptomatic nonpregnant patients with pulmonic stenosis and a transpulmonic valve gradient greater than 40 mm Hg and in symptomatic nonpregnant patients with a gradient greater than 30 mm Hg.207

**Pulmonic regurgitation** occurs infrequently as an isolated valvular lesion; it is most commonly associated with congenital heart disease, such as repaired tetralogy of Fallot99 or repaired pulmonic stenosis. Physiologic pulmonic regurgitation is commonly seen during pregnancy.206 Overall, pregnancy and labor are well tolerated in the presence of mild or moderate pulmonic regurgitation; however, severe pulmonic regurgitation is highly associated with maternal cardiac events during pregnancy.207,208 Right-sided heart failure caused by pulmonic regurgitation occurs more commonly in patients with multiple gestation, pulmonary artery stenosis distal to the left and right pulmonary arteries, preexisting right ventricular systolic dysfunction, and/or right ventricular hypertrophy.208

**Prosthetic Heart Valves**

**Bioprosthetic Valves**

In a 2015 systematic review of 11 studies capturing 499 pregnancies (1995 to 2014), the estimated maternal mortality rate in women with prosthetic heart valves was 1.2/100 pregnancies (95% CI, 0.5 to 2.2).209 The study was too small to determine if the mortality rate differed between mechanical and bioprosthetic valves. The advantage of bioprosthetic valves is that long-term systemic anticoagulation is not required and the risk for thromboembolic events in pregnancy is lower than for mechanical valves.209 However, bioprosthetic valves incur a higher and earlier risk for valve deterioration requiring replacement.210 It is unclear whether pregnancy accelerates bioprosthetic valve structural degeneration; studies report inconsistent results. The 15-year incidence of bioprosthetic valve replacement is 50% for patients 20 years of age.210 Thus, although a bioprosthetic valve simplifies the required anticoagulant regimen during pregnancy, it may expose the mother to a high risk for reoperation and associated operative mortality. Current guidelines from the AHA/ACC suggest that a mechanical valve is a reasonable choice for patients less than 50 years of age unless anticoagulation is contraindicated or not desired (e.g., in women who desire childbirth).210 Thus, the choice of valve prosthesis type must balance the benefits and risks for individual patients.

**Anticoagulation for Patients with a Mechanical Valve**

All patients with a mechanical valve require systemic anticoagulation. Mechanical valves have a higher risk for thromboembolism than bioprosthetic valves. Valves in the mitral position have a higher risk for thromboembolism than valves in the aortic position. A higher risk for mechanical valve thromboembolic complications has been observed during pregnancy.211 No large prospective randomized trials have examined the use of various anticoagulation strategies for pregnant women with a mechanical valve. Additionally, newer prosthetic valve designs may have a lower risk for thromboembolism than older models. The current anticoagulation recommendations are based on expert consensus guidelines from three major professional organizations: the ACC/AHA,57 the American College of Chest Physicians (ACCP),178,212 and the European Society of Cardiology (ESC).36 Differences among these guidelines are summarized in Table 41.6.

**Warfarin.** In patients with a mechanical valve, anticoagulation with warfarin is associated with lower rates of thromboembolic complications and maternal death compared with unfractionated heparin or LMWH.213 However, warfarin crosses the placenta. The use of warfarin between 6 and 12 weeks’ gestation has been associated with embryopathy, and the use of warfarin at any time during pregnancy has been associated with fetal wasting, central nervous system abnormalities, and fetal hemorrhagic complications.178 Thus, there has been significant controversy about its use during pregnancy, particularly during the period of organogenesis, and previous guidelines have recommended substitution with unfractionated heparin or LMWH during this period. However, because of warfarin’s superior effectiveness in preventing thromboembolism compared with unfractionated heparin or LMWH, and a dose-dependent risk for embryopathy, the current guidelines state that after careful counseling about risks and benefits, women may continue warfarin during the first trimester if they can achieve a therapeutic international normalized ratio (INR) goal with daily doses less than 5 mg.36,57

Warfarin anticoagulation effect is monitored by periodic assessment of the INR. Low-dose aspirin may be safely administered in addition to warfarin in the second and third trimester. Warfarin should be discontinued before delivery; in patients with a mechanical heart valve, heparin must be substituted.

Warfarin anticoagulation should be stopped for 5 days and the INR measured immediately before administration of a neuraxial block (see Chapter 38).56 Concurrent administration of other anticoagulants or antiplatelet agents increases the risk for bleeding complications. After delivery, patients with a mechanical valve typically require bridging to warfarin;
### Major Professional Society Guidelines for Anticoagulation in Pregnant Patients with Mechanical Valve(s)

<table>
<thead>
<tr>
<th></th>
<th>American College of Cardiology/American Heart Association&lt;sup&gt;a&lt;/sup&gt;</th>
<th>European Society of Cardiology&lt;sup&gt;b&lt;/sup&gt;</th>
<th>American College of Chest Physicians&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td>Continuation of warfarin during first trimester (dose &lt; 5 mg daily) after discussion of risks and benefits with patient</td>
<td>May consider continuing low-dose warfarin (&lt; 5 mg daily) throughout pregnancy with informed patient consent</td>
<td>UFH or LMWH until 13 weeks’ gestation, then warfarin</td>
</tr>
<tr>
<td><strong>INR goal</strong></td>
<td>Aortic valve: 2.5 (range 2.0–3.0)</td>
<td>2.5–4.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Aortic valve: 2.5 (range, 2.0–3.0)</td>
</tr>
<tr>
<td></td>
<td>Mitral valve: 3.0 (range, 2.5–3.5)</td>
<td>2.5–4.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Mitral valve: 3.0 (range, 2.5–3.5)</td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td>Continuous infusion during first trimester if warfarin dose needed to achieve therapeutic INR &gt; 5 mg daily</td>
<td>In high-risk patients, continuous infusion</td>
<td>Subcutaneous administration twice daily</td>
</tr>
<tr>
<td><strong>aPTT goal</strong></td>
<td>aPTT twice control value</td>
<td>aPTT 4–6 h after subcutaneous injection: twice control value</td>
<td>Mid-interval aPTT (6 h after injection): twice control or anti–factor Xa level of 0.35–0.70 U/mL</td>
</tr>
<tr>
<td><strong>Low-molecular-weight heparin</strong></td>
<td>Subcutaneous administration at least twice daily during first trimester if warfarin dose needed to achieve therapeutic INR &gt; 5 mg daily</td>
<td>Subcutaneous administration twice daily</td>
<td>May give adjusted dose of LMWH throughout pregnancy, twice daily</td>
</tr>
<tr>
<td><strong>Anti–factor Xa level goal</strong></td>
<td>Maintain peak level 0.8–1.2 U/mL 4–6 h after administration</td>
<td>Maintain peak level 0.8–1.2 U/mL 4–6 h after administration</td>
<td>Maintain manufacturer’s recommended peak level (approximately 1.0 U/mL) 4 h after administration</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>Low-dose aspirin (75–100 mg daily) recommended in second and third trimesters in addition to warfarin or heparin (both bioprosthesis or mechanical prosthesis)</td>
<td>Not recommended</td>
<td>Low-dose aspirin (75–100 mg daily) added to thromboprophylactic regimen for patients with valves at high risk for thromboembolism</td>
</tr>
<tr>
<td><strong>Peripartum&lt;sup&gt;e&lt;/sup&gt;</strong></td>
<td>Discontinue warfarin before planned delivery, and start continuous intravenous UFH</td>
<td>Discontinue warfarin at 36 weeks’ gestation, and start dose-adjusted UFH or LMWH. Replace LMWH at least 36 h before planned delivery, and substitute with UFH. Discontinue UFH 4–6 h before planned delivery</td>
<td>Discontinue warfarin close to delivery; replace with UFH or LMWH</td>
</tr>
</tbody>
</table>

<sup>a</sup>A<sup>P</sup>TT, Activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.


<sup>e</sup>Specific goal dependent on patient risk factors and prosthesis thrombogenicity.

<sup>f</sup>For resumption of anticoagulation in the postoperative period, the 2018 American Society of Regional Anesthesia and Pain Medicine Practice Advisory<sup>g</sup> recommends the following: (1) Warfarin: The indwelling neuraxial catheter should be removed when the INR is less than 1.5, 12 to 24 hours after last warfarin administration. (2) UFH: The indwelling neuraxial catheter should be removed 4 to 6 hours after the last dose of UFH, after checking the patient’s coagulation status (aPTT). The next dose of UFH should not be given until at least 1 hour has elapsed after removal of the catheter. (3) LMWH: The first therapeutic dose should not be administered until 24 hours after the initiation of the neuraxial procedure. The U.S. Food and Drug Administration recommends waiting at least 4 hours after removal of a neuraxial catheter before administering a postprocedure dose of LMWH. (U.S. Food and Drug Administration. Drug Safety Communication—Updated Recommendations to Decrease Risk of Spinal Column Bleeding and Paralysis in Patients on Low Molecular Weight Heparins. November 6, 2013. [https://www.fda.gov/drugs/drugsafety/ucm373595.htm. Accessed January 2018.])
the type of anesthesia and timing of neuraxial catheter removal may significantly affect the timing of anticoagulation after delivery.\textsuperscript{46,47}

**Unfractionated heparin.** Unfractionated heparin does not cross the placenta and therefore may be safer for the fetus than warfarin. However, use of unfractionated heparin in the first trimester and close to term has been associated with an increased risk for valve thrombosis.\textsuperscript{57,213} Unfractionated heparin can be administered subcutaneously or preferably as a continuous intravenous infusion. Its therapeutic efficacy is monitored with the activated partial thromboplastin time (aPTT). Heparin requirements are higher during pregnancy caused by underlying physiologic changes (e.g., increased levels of heparin-binding proteins, factor VIII, fibrinogen). The incidence of heparin-induced thrombocytopenia is three times higher in women than in men.

Intravenous unfractionated heparin should be discontinued 4 to 6 hours before administration of a neuraxial anesthetic technique or anticipated delivery (see Table 38.3).\textsuperscript{46} The aPTT should be determined to verify normalization of coagulation function, and a platelet count should be checked to rule out heparin-induced thrombocytopenia. An indwelling neuraxial catheter can be removed 4 to 6 hours after the last dose of unfractionated heparin. Unfractionated heparin can be restarted 1 hour after removal of a neuraxial catheter.

**Low-molecular-weight heparin.** LMWH does not cross the placenta and is administered subcutaneously for most indications. The pharmacokinetics of LMWH are altered in pregnancy. Use of LMWH for thromboprophylaxis during pregnancy has been associated with mechanical valve thrombosis.\textsuperscript{214-217} The efficacy of LMWH can be monitored with anti–factor Xa levels. Peak anti–factor Xa levels should be checked 4 to 6 hours after LMWH administration in pregnant women with a mechanical valve. Importantly, in pregnant women with a mechanical valve, the required doses of LMWH are considered therapeutic and are therefore higher than those required for deep vein thrombosis prophylaxis. In the absence of anti–factor Xa monitoring, therapeutic use of LMWH in pregnant women with a mechanical valve is not advisable.\textsuperscript{36}

A neuraxial block should not be performed until at least 24 hours have elapsed after the last therapeutic dose of LMWH (see Table 38.3). Anti–factor Xa levels do not predict the risk for bleeding. Other anticoagulants or antiplatelet agents coadministered with LMWH increase the risk for bleeding complications. After delivery, therapeutic LMWH should not be administered until at least 24 hours have elapsed after performance of the neuraxial block procedure (see Chapter 38).\textsuperscript{46} After removal of a neuraxial catheter, at least 4 hours should elapse before administration of the next dose of LMWH.

**Newer anticoagulants.** The use of oral direct thrombin inhibitors (dabigatran) or oral anti–factor Xa inhibitors (apixaban, rivaroxaban) is contraindicated in patients with mechanical heart valves.

There are no published reports of the administration of bivalirudin during pregnancy; the use of argatroban during pregnancy has been described.\textsuperscript{218} The current ASRA guidelines recommend against neuraxial anesthesia administration in patients receiving bivalirudin or argatroban.\textsuperscript{46}

**Neuraxial anesthesia in patients with a mechanical valve.** No published observational or prospective randomized trials have investigated the use of neuraxial anesthetic techniques in patients with a mechanical heart valve who require systemic anticoagulation. Therefore, current clinical practice is guided by consensus guidelines.\textsuperscript{46,47,219,220} Systemic anticoagulation may affect the choice and timing of anesthesia, and the neuraxial anesthetic technique and timing of catheter removal may influence the choice and timing of resumption of systemic anticoagulation after vaginal or cesarean delivery. Therapeutic anticoagulation is usually not resumed for at least 12 hours after delivery. The choice and timing of the anesthetic technique should be developed in discussion with the patient, the cardiologist, and the obstetrician, with consideration of consensus guidelines (see Table 38.3).

**CARDIOMYOPATHIES**

**Heart Failure Nomenclature**

Accurate description of patients with heart failure is important for diagnostic, therapeutic, and prognostic purposes. It is helpful to broadly describe symptoms of heart failure as new-onset (acute) or chronic. Acute-on-chronic heart failure describes patients with worsening symptoms after an earlier diagnosis of heart failure.

Heart failure can be separated into left sided (predominantly pulmonary congestion and pulmonary edema) and right sided (predominantly peripheral edema). Biventricular heart failure describes symptoms that result from both right and left ventricular involvement.

Assessment of ventricular function allows for differentiation between systolic and diastolic heart dysfunction. Arbitrarily, left ventricular dysfunction is defined by a left ventricular ejection fraction less than 45% to 50%.

Left ventricular systolic or diastolic dysfunction are not synonymous with left- or right-sided heart failure. Therefore, heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are currently the preferred terms used to describe these clinical conditions.\textsuperscript{32}

The NYHA classification describes patients’ functional status (see Box 41.1), and the functional status can change over time. In contrast, the staging classification of heart failure recognizes that heart failure is a progressive condition and may manifest as variable symptoms over time.\textsuperscript{32,221} Both classifications remain highly useful in clinical practice.

**Peripartum Cardiomyopathy**

Peripartum cardiomyopathy is a unique cardiomyopathy of unknown cause that occurs during pregnancy or the postpartum period.\textsuperscript{222,223} The timing of development of heart failure is important to help exclude other causes of heart failure. To make the diagnosis of peripartum cardiomyopathy, the development of heart failure should occur in the last month
of pregnancy or within 5 months of delivery (Box 41.8). Other identifiable causes of heart failure should be excluded, and the absence of other recognizable cardiac disease before the last month of pregnancy should be verified. Echocardiographic diagnostic criteria include (1) left ventricular ejection fraction less than 45% (and/or M-mode fractional shortening less than 30%) and (2) end-diastolic left ventricular dimension greater than 27 mm/m² body surface area. Some women develop cardiomyopathy before the last month of pregnancy. This condition is referred to as pregnancy-associated cardiomyopathy. Its clinical signs, symptoms, and outcomes are similar to those for peripartum cardiomyopathy.

The incidence of peripartum cardiomyopathy varies around the world and has been reported to be as high as 1 in 300 live births in Haiti and 1 in 3000 to 4000 live births in the United States. The cause(s) for such regional variation are unclear. Risk factors for peripartum cardiomyopathy include African race, multiparity, multiple gestation, pre-eclampsia, gestational hypertension, use of tocolytic agents, cocaine abuse, and age older than 30 years. A possible genetic component has been identified, with overlap between genetic mutations linked to dilated cardiomyopathy and peripartum cardiomyopathy.

The etiology of this relatively rare condition remains unclear; several possible causes have been proposed, including underlying myocarditis, apoptosis, inflammation, pathologic maternal immune response to fetal antigens, effects of prolactin, viral triggers, and hereditary/familial factors.

Patients with peripartum cardiomyopathy have typical signs and symptoms of systolic heart failure. On clinical examination, the apical impulse is displaced laterally and an S3 gallop is appreciated. Because of left ventricular enlargement (Fig. 41.6) and changes in ventricular cavity geometry, functional mitral regurgitation is frequently seen. Peripartum cardiomyopathy is a diagnosis of exclusion, and the symptoms may be disguised as physiologic changes of pregnancy; thus, the use of echocardiography helps confirm the diagnosis. Right-sided heart pressures can almost always be assessed by echocardiography; hence, right-sided heart catheterization is rarely necessary. Left-sided heart catheterization may be necessary to assess the coronary arteries. However, given that the risk for ischemic cardiomyopathy in pregnancy is very low, and because coronary angiography results in fetal radiation exposure, left-sided heart catheterization is infrequently used to make the diagnosis. Ischemic cardiomyopathy is

**BOX 41.8 Diagnostic Criteria for Peripartum Cardiomyopathy**

**Traditional Criteria**
- Onset of heart failure during the last month of pregnancy or within 5 months of delivery
- No other identifiable cause of heart failure
- No known heart disease before pregnancy

**Echocardiographic Criteria**
- Left ventricular ejection fraction < 45%
- Fractional shortening < 30%
- Left ventricular end-diastolic dimension ≥ 27 mm/m²


![Fig. 41.6 Echocardiographic image of dilated cardiomyopathy. RV, right ventricle; LA, left atrium; LV, left ventricle; ALMV, anterior leaflet of the mitral valve; PLMV, posterior leaflet of the mitral valve; AO, aorta; DA, descending aorta. (Courtesy of Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)](image-url)
typically accompanied by regional wall motion abnormalities, whereas peripartum or nonischemic cardiomyopathy typically results in a global decrease in contractility.

Medical management of peripartum cardiomyopathy rests on basic treatment paradigms for congestive heart failure and dilated cardiomyopathy (see later discussion). The all-cause 5-year survival rate of peripartum cardiomyopathy in the United States is greater than 95%.227,228 African American women are almost three times more likely to die of peripartum cardiomyopathy than white women.228

The risk associated with subsequent pregnancy is substantially higher in women who do not recover normal left ventricular function.231 In a series of 44 women with peripartum cardiomyopathy, the maternal mortality rate in subsequent pregnancies was 19% in women with persistent left ventricular dysfunction compared with 0% in women without residual dysfunction.231 Therefore, subsequent pregnancy should be discouraged if left ventricular function has not recovered. Even in patients with normalized left ventricular function, careful counseling is advised owing to a significant risk for recurrence of left ventricular dysfunction in a subsequent pregnancy.36

Obstetric and Anesthetic Management
Obstetric management involves expedient delivery after stabilization of the mother; in most cases, cesarean delivery is reserved for obstetric indications. Continuous spinal anesthesia242 and CSE anesthesia233,234 have been safely administered in patients with severe peripartum cardiomyopathy. Given the intravascular fluid shifts associated with labor, delivery, and the immediate postpartum period, invasive blood pressure and central venous pressure monitoring are recommended. Neuraxial anesthesia appears ideally suited for these patients because it results in a beneficial decrease in both preload and afterload. Particular attention should be paid to the immediate postpartum period when autotransfusion combined with the regression of neuraxial anesthesia may cause worsening of heart failure.

Other Nonischemic Cardiomyopathies
Hypertrophic Cardiomyopathy
Hypertrophic cardiomyopathy is relatively common, with a prevalence estimated at 1 in 500. It is an autosomal dominant disorder associated with various forms of left ventricular hypertrophy; the risk that an affected patient will transmit the disease to offspring is 50%. Additionally, hypertrophic cardiomyopathy mutations are highly penetrant. Preconception genetic counseling is recommended.156

The complications that result from hypertrophic cardiomyopathy can be separated into two categories: mechanical and electrophysiologic. The mechanical consequences relate to left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, and development of heart failure. The electrophysiologic complications include atrial and ventricular arrhythmias and, most important, the risk for sudden cardiac death. The myocardial ischemia observed in patients with hypertrophic cardiomyopathy, often at ages younger than expected, is caused by supply-demand mismatch rather than coronary atherosclerosis. Hypertrophic cardiomyopathy is associated with disorganized myocardial architecture, myocardial disarray, and fibrosis (Fig. 41.7).

One of the hallmarks of hypertrophic cardiomyopathy is the dynamic left ventricular outflow tract obstruction. The obstruction gradient typically increases after a premature ventricular contraction. One-third of patients have left ventricular outflow tract obstruction at rest, one-third have a physiologically provable gradient, and one-third have no gradient (nonobstructive form of hypertrophic cardiomyopathy). A gradient of 30 mm Hg or more is clinically significant.235

Pregnant women with hypertrophic cardiomyopathy may have dyspnea, fatigue, angina, palpitations, and/or syncope. Symptoms of congestive heart failure are rarely seen in patients in sinus rhythm; these symptoms are more frequently encountered when atrial fibrillation is present.

On physical examination, the classic obstructive systolic murmur is heard at the apex (grade 3/6 to 4/6), and it radiates to the left sternal border. Although most patients will have a displaced and forceful left ventricular impulse, the presence of a murmur depends on the degree and type of obstruction. The intensity of a hypertrophic cardiomyopathy murmur increases with the Valsalva maneuver or standing (decreased preload or afterload causes more obstruction), and it decreases with squatting (increased afterload causes less obstruction). Invasive arterial pressure monitoring allows recognition of a bifid arterial pulse waveform.

The ECG is abnormal in the vast majority of patients and demonstrates an increase in voltage, T-wave inversions, and pathologic Q waves. ECG abnormalities correlate poorly with the severity of hypertrophic cardiomyopathy.157 Trans-thoracic echocardiography is indispensable for making the diagnosis, determining prognosis, and guiding management decisions.158 Diagnostic criteria include a septal thickness greater than 15 mm, although it should be emphasized that individuals may carry the genotype without evidence of increased wall thickness (so-called “subclinical hypertrophic cardiomyopathy”).156 Systolic anterior motion of the mitral valve has a specificity of 98% for hypertrophic cardiomyopathy. Left ventricular outflow tract obstruction is apparent during Doppler interrogation; the continuous wave tracing has a classic “dagger-shaped” contour (Fig. 41.8). In addition, echocardiography allows identification of various morphologic variants and assessment of the extent of hypertrophy. A wall thickness of 30 mm or greater is associated with a high risk for sudden cardiac death.236 Patients with a gradient of 50 mm Hg or greater are at highest risk for complications.156

Fortuitously, the increase in blood volume allows most patients with hypertrophic cardiomyopathy to tolerate pregnancy well.158 Both asymptomatic and symptomatic women with hypertrophic cardiomyopathy should continue taking a beta-adrenergic receptor antagonist throughout pregnancy and the peripartum period.156

Patients with hypertrophic cardiomyopathy are at increased risk for developing atrial fibrillation. Treatment
Fig. 41.7 Cardiac magnetic resonance image of hypertrophic cardiomyopathy with myocardial scar. Arrow shows scar with delayed enhancement with gadolinium in the hypertrophied myocardium. (Courtesy of Dr. Afshin Farzaneh-Far, University of Illinois at Chicago, Chicago, IL.)

Fig. 41.8 Dynamic left ventricular outflow obstruction in hypertrophic cardiomyopathy. Continuous wave Doppler tracing in left ventricular outflow tract displays typical late-peak (“dagger-shaped”) contour of dynamic outflow obstruction (arrows). (Courtesy of Dr. Mayank Kansal, University of Illinois at Chicago, Chicago, IL.)
of atrial fibrillation rests on rate and rhythm control as well as systemic anticoagulation to prevent thromboembolic stroke. Rate control can alleviate symptoms; beta-adrenergic receptor antagonists and nondihydropyridine calcium entry–blocking agents (e.g., verapamil, diltiazem) provide the best results. Digoxin is less effective in controlling rate and may be harmful in patients with hypertrophic cardiomyopathy in the absence of atrial fibrillation. Amiodarone can be successfully used for rate control in patients with hypertrophic cardiomyopathy. Rhythm control can be attempted pharmacologically with amiodarone and sotalol. In patients with a rapid ventricular response and significant hemodynamic compromise, electric cardioversion should be performed.

In the contemporary Registry of Pregnancy and Cardiac Disease (ROPAC), the rate of cesarean delivery was 60%, and pregnancy outcomes were similar between obstructive and nonobstructive hypertrophic cardiomyopathy.

**Obstetric and anesthetic management.** Traditionally, general anesthesia has been considered the anesthetic technique of choice for parturients with hypertrophic cardiomyopathy. It avoids a precipitous decrease in preload, and the negative inotropic effect of inhalation anesthetic agents may help reduce the degree of dynamic obstruction (see Table 41.2). No prospective controlled trials have compared general anesthesia with neuraxial anesthesia in parturients with hypertrophic cardiomyopathy; numerous case reports have described successful use of neuraxial anesthesia in these patients. Given that hypertrophic cardiomyopathy is a heterogeneous condition, and given the high likelihood of selection and publication bias in these case reports, it is difficult to make generalized recommendations for these patients. In deciding whether to administer general or neuraxial anesthesia, it is important to recognize the degree of left ventricular outflow tract obstruction. For cesarean delivery, it appears reasonable to recommend general anesthesia for patients with a gradient of 50 mm Hg or greater, or for those with symptoms of heart failure during pregnancy. In asymptomatic parturients with a lower gradient, slowly titrated neuraxial analgesia/anesthesia appears safe.

Because a decrease in preload is expected to increase the degree of left ventricular outflow tract obstruction, central venous pressure monitoring seems reasonable. Similarly, invasive arterial blood pressure monitoring may be helpful. Transthoracic echocardiography facilitates assessment of intravascular volume. Beta-adrenergic receptor antagonists decrease myocardial contractility and decrease the severity of left ventricular outflow tract obstruction. Phenylephrine is the drug of choice for the treatment of hypotension. Inotropic agents (e.g., dopamine, dobutamine) may be harmful in these patients. Rapid administration of intravenous oxytocin has been associated with hypotension; slow administration is therefore recommended.

**Stress-Induced Cardiomyopathy**

Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, broken heart syndrome, or apical ballooning syndrome, is a transient cardiomyopathy with typical left ventricular systolic dysfunction of the apical and mid-cavity segments. The basal ventricular segments are frequently hyperkinetic and may cause left ventricular outflow tract obstruction. Affected patients typically do not have underlying coronary artery disease. Stress-induced cardiomyopathy occurs predominantly in postmenopausal women in the seventh and eighth decades of life and is frequently associated with emotional and physical stressors. It has also been described during pregnancy in the setting of emotional and physical triggers, postpartum depression, and administration of pharmacologic triggers such as ergot alkaloids. It has been reported in the absence of apparent triggers during otherwise uncomplicated spinal anesthesia for cesarean delivery.

Clinically, patients have chest pain, dyspnea, and symptoms of left ventricular systolic dysfunction and heart failure. ECG abnormalities are frequently observed in the left precordial leads and may mimic STEMI because of plaque rupture. Coronary angiography is required to rule out STEMI; ventriculography or echocardiography allows recognition and characterization of wall motion abnormalities. The most critical differential diagnoses are STEMI and peripartum cardiomyopathy. When treating patients who develop shock, it is critically important to determine the degree of left ventricular outflow tract obstruction. Shock without left ventricular outflow tract obstruction can be treated in standard fashion with an inotropic agent. Patients with left ventricular outflow tract obstruction require optimization of intravascular volume and administration of a beta-adrenergic receptor antagonist; use of an intra-aortic balloon pump may be necessary to relieve the obstruction.

**Dilated and Other Cardiomyopathies**

In women with idiopathic or anthracycline-induced cardiomyopathy, pregnancy is associated with a high risk for adverse maternal, fetal, and neonatal outcomes. Pregnancy appears to unfavorably affect the short-term course of these cardiomyopathies. The NYHA functional status and ejection fraction may predict outcomes in this population. Other causes of cardiomyopathy during pregnancy include cocaine abuse and hemochromatosis; the latter results in an infiltrative cardiomyopathy.

Rapid atrial or ventricular rates caused by arrhythmia can cause tachycardia-induced cardiomyopathy. This cardiomyopathy is a potentially reversible condition that has been described in pregnancy and successfully treated with radiofrequency ablation. Differentiation from other forms of cardiomyopathy may be difficult, but it is important from a prognostic standpoint.

**Medical Management of Heart Failure**

Principles of heart failure management for pregnant patients are similar to those for nonpregnant patients with two notable exceptions: angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor–blocking agents and aldosterone antagonists (spironolactone, eplerenone) should not be used in pregnant women. A beta-adrenergic
receptor antagonist should be administered, and hydralazine can be substituted for ACE inhibitors/angiotensin receptor–blocking agents. Digoxin use is safe in pregnancy. Loop diuretics and sodium restriction are indicated to prevent or treat volume overload. In patients with decompensated heart failure, treatment with intravenous nitroglycerin and dopamine or dobutamine is indicated.

Observational studies have reported two distinct peaks of exacerbation of heart failure during pregnancy. The first one occurs between the second and third trimester and is more frequently seen in patients with pulmonary hypertension and mitral stenosis. The other peak occurs around the time of delivery with predominance of other cardiomyopathy etiologies.²⁵⁹

**Ventricular Assist Devices**

Anecdotal reports have described ventricular assist device use during pregnancy. A successful completion of pregnancy with cesarean delivery in a patient with a ventricular assist device has been reported.²⁶⁰ In another patient with myocardial infarction and subsequent severe left ventricular dysfunction, a ventricular assist device was placed, although pregnancy was not recognized at the time of placement; fetal death subsequently ensued.²⁶¹ The preconception presence of a ventricular assist device remains a contraindication to pregnancy.

**PERICARDIAL DISEASE**

**Pericardial Effusion**

Asymptomatic pericardial effusions are frequently found in otherwise healthy pregnant women (Fig. 41.9). A pericardial effusion may be seen in 15% to 20% of pregnancies in the first and second trimester; this rate increases to approximately 40% in the third trimester. The effusion is seen more often in nulliparous women than in parous women.²⁶² These effusions are transudative and disappear within 2 months after delivery. Treatment is rarely required. Physical signs of tamponade or pulsus paradoxus are rarely seen. Similarly, electrical alternans is not seen on the ECG.

**Acute Pericarditis**

Pericarditis remains a clinical diagnosis confirmed by ECG and echocardiography. Patients typically have precordial pain that improves with sitting and leaning forward. A pericardial friction rub may be appreciated on physical examination; this finding is frequently evanescent, and repeat examinations may be required. ECG findings consist of diffuse concave ST-segment elevations. Diffuse PR interval depression is frequently seen except in lead aVR, which demonstrates near-pathognomonic PR-interval elevation. Echocardiography may demonstrate various degrees of pericardial effusion. Importantly, the presence of a pericardial effusion is not
sive blood pressure monitoring is recommended. The etiology of acute pericarditis during pregnancy is most likely similar to that in the general population. A viral etiology is most common. Less common causes include tuberculosis, connective tissue disease (e.g., systemic lupus erythematosus), and neoplasm.

Treatment of pericarditis in the general population includes nonsteroidal anti-inflammatory drugs, glucocorticoids, colchicine, and, rarely, immunosuppressant drugs. During pregnancy, the maternal and fetal risks and benefits of these agents should be weighed carefully.

**Cardiac Tamponade**
Therapeutic and diagnostic pericardiocentesis or a surgical pericardial window can be safely performed during pregnancy. However, echocardiographic rather than fluoroscopic guidance is preferred because it avoids fetal radiation exposure.

**Constrictive Pericarditis**
Constrictive pericarditis is a condition in which a noncompliant pericardium prevents filling of the right- and left-sided heart chambers; specific hemodynamic features include equalization and elevation of both left and right ventricular diastolic pressures, preserved systolic function, and a “dip and plateau” pattern of the ventricular pressure tracing. Potential causes of constrictive pericarditis during pregnancy include previous irradiation, recurrent pericarditis caused by rheumatoid arthritis, tuberculosis, and neoplasm. Patients may be asymptomatic before pregnancy; the physiologic changes of pregnancy may exacerbate the condition.

**Anesthetic Management**
Constrictive physiology and cardiac tamponade share some common pathophysiologic features that are important for the conduct of anesthesia (see Table 41.2). Impaired filling of the right side of the heart results from either a noncompliant pericardium (constrictive physiology) or pericardial fluid (tamponade physiology). Cardiac output is reduced by any intervention that reduces preload (e.g., aortocaval compression, sympathectomy with neuraxial anesthesia, positive-pressure ventilation with general anesthesia). Therefore, maintenance of preload is critically important; this goal can be achieved with central venous pressure monitoring, slowly titrated neuraxial anesthesia, and avoidance of positive-pressure ventilation. Invasive blood pressure monitoring is recommended.

**CARDIOPULMONARY RESUSCITATION DURING PREGNANCY**
Cardiac arrest during pregnancy is rare; it occurs in 1 in 12,000 admissions for delivery. Older data suggested that overall survival rates were poorer than expected compared with other clinical arrest scenarios in nonpregnant patients, but newer data suggest that survival rates may be higher in pregnant women than in nonpregnant patients.253,263 The reversible causes of cardiac arrest during pregnancy are similar to those in nonpregnant patients. Additional causes specific to pregnancy include amniotic fluid embolism, eclampsia, placental abruption, and uterine atony (see Chapter 54).

Standard Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) principles apply to these patients. However, anatomic and physiologic changes of pregnancy require several specific modifications to the resuscitation protocol (Box 41.9; see also Box 54.5).264 Current scientific evidence does not support previous recommendations to place the hands performing chest compressions higher on the sternum. This recommendation was based on the belief that compressions would be less effective because of cephalad displacement of abdominal contents and the diaphragm during the third trimester of pregnancy. Intravenous access should be obtained above the diaphragm. In pregnant patients, aortocaval compression reduces the cardiac output that results from chest compressions. Although it was typically advised to tilt the patient leftward 15 to 30 degrees to facilitate left uterine displacement and optimize venous return and cardiac output, such a maneuver may impede the effectiveness of chest compressions. Therefore, current recommendations advocate manual left uterine displacement rather than the usual whole-body tilt (see Fig. 54.2). If this technique is not successful, a firm wedge may be placed under a resuscitation board to tilt the patient approximately 30 degrees. In the field, the responder may use his or her knees to tilt the patient.

If spontaneous circulation does not return within 4 minutes of cardiac arrest, hysterotomy or cesarean delivery should be performed (also referred to as postmortem cesarean delivery [PMCD]), with the goal of achieving delivery within 5 minutes of cardiac arrest. The primary purpose of cesarean

<table>
<thead>
<tr>
<th>Modifications of Cardiopulmonary Resuscitation in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual left uterine displacement from left or right side</td>
</tr>
<tr>
<td>Airway</td>
</tr>
<tr>
<td>• Consider airway edema associated with pregnancy</td>
</tr>
<tr>
<td>Breathing</td>
</tr>
<tr>
<td>• Be aware of the impact of decreased functional residual</td>
</tr>
<tr>
<td>capacity in pregnancy</td>
</tr>
<tr>
<td>Circulation</td>
</tr>
<tr>
<td>• Perform chest compressions on the sternum as in non-</td>
</tr>
<tr>
<td>pregnant patients</td>
</tr>
<tr>
<td>Defibrillation</td>
</tr>
<tr>
<td>• May use automated external defibrillator (AED)</td>
</tr>
<tr>
<td>• Apply same energies as in nonpregnant patients</td>
</tr>
<tr>
<td>• Do not delay defibrillation to remove fetal monitoring</td>
</tr>
<tr>
<td>probes and leads</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>• Drugs (and doses) are the same as those used in non-</td>
</tr>
<tr>
<td>pregnant patients</td>
</tr>
</tbody>
</table>

delivery is to improve the chance of maternal survival, but timely delivery also improves the chances of infant survival. PMCD should be performed at the site of cardiac arrest.265

Defibrillation should be performed based on current ACLS protocols. Transthoracic impedance is not changed during pregnancy, and the standard recommended electric energies should be used. Both cardioversion and defibrillation are considered safe at all stages of pregnancy. Although previous guidelines advised disconnecting fetal monitoring probes, it is unlikely that defibrillation is hazardous in the presence of external and internal fetal monitoring probes. The treatment delay and resulting risk to the mother outweighs any potential risks to the fetus; current guidelines have removed this recommendation.264

An intra-aortic balloon pump, a percutaneous left ventricular assist device, cardiopulmonary bypass, and extracorporeal membrane oxygenation have been successfully used in pregnant women with cardiac arrest; favorable outcomes have been reported. Therapeutic hypothermia has also been used after cardiac arrest during pregnancy, with successful delivery and favorable neonatal outcome.

**PREGNANCY AFTER HEART TRANSPLANTATION**

The first successful pregnancy in a heart transplant recipient was described in 1988. Subsequently, several reports have documented the feasibility and relative safety of pregnancy and delivery in female heart transplant recipients.266,267 Successful patient management requires an interdisciplinary team approach.

The transplanted heart is denervated, and the increase in cardiac output with pregnancy primarily results from an increase in stroke volume rather than heart rate. Because the risk for acute rejection is not increased in pregnant patients with a heart transplant, the immunosuppressant medications should be maintained at the lowest possible dose. The risk for infection is greater in patients receiving immunosuppression therapy. The AHA considers the presence of valvulopathy in heart transplant recipients a high-risk lesion for the development of bacterial endocarditis. Thus, given the unfavorable outcomes in heart transplant recipients who develop endocarditis, it appears reasonable to recommend antibiotic endocarditis prophylaxis at the time of membrane rupture for these parturients undergoing labor and vaginal delivery (see Box 41.5).128

Cardiac transplant vasculopathy is a disease specific to transplanted hearts; it consists of concentric and longitudinal intimal hyperplasia in the coronary arteries. In contrast, native coronary atherosclerosis manifests as focal, noncircumferential lesions. After malignancy, cardiac transplant vasculopathy constitutes the second most common cause of death 1 year after heart transplantation. Therefore, monitoring for ischemia appears prudent in these patients, especially because they may not present with classic anginal symptoms owing to denervation of the transplanted heart.

Baseline echocardiography allows assessment of ejection fraction and the presence of transplant valvulopathy. Most parturients with a heart transplant with a normal ejection fraction and normal right-sided pressures tolerate labor and delivery well; both neuraxial and general anesthesia are acceptable. Peripartum immunosuppression therapy should be managed by a multidisciplinary team.

**CARDIOPULMONARY BYPASS DURING PREGNANCY**

In the current era, maternal mortality associated with elective cardiopulmonary bypass during pregnancy is comparable to that for nonpregnant women.268 Fetal mortality remains high (14% in a single-center retrospective study of cases from 1976 to 2009), although some series report excellent fetal outcomes.269 The optimal timing of cardiopulmonary bypass appears to be the second trimester of pregnancy. Procedures performed immediately after delivery and on an emergency basis appear to confer added risk for maternal mortality. The degree of hypothermia is associated with poor fetal outcome. There is no evidence that anesthesia per se contributes to adverse maternal or fetal outcomes in this setting.268 The need for intraoperative FHR monitoring is universally accepted. Measures to lower fetal mortality include normothermic cardiopulmonary bypass with flow rates greater than 2.4 L/min/m^2^ while maintaining mean arterial blood pressure above 70 to 75 mm Hg. Left uterine displacement and maintenance of a hematocrit greater than 28% are recommended.

**KEY POINTS**

- Heart disease is the primary medical cause of nonobstetric maternal mortality.
- Congenital heart disease is the cause of 60% to 80% of cases of cardiac disorders in pregnant women in developed countries such as the United States.
- The management of most forms of congenital heart disease, including Eisenmenger syndrome, rarely requires pulmonary artery catheterization.
- Intrathecal administration of a lipophilic opioid is an excellent choice of intrapartum analgesia for women who may not tolerate decreased systemic vascular resistance and decreased venous return.
- Cardiac lesions do not represent an absolute contraindication to the use of neuraxial anesthesia, assuming that the induction of anesthesia proceeds slowly and the potentially adverse hemodynamic changes are prevented or corrected promptly. Single-shot spinal anesthesia can produce circulatory collapse in parturients with severe aortic stenosis, primary pulmonary hypertension, and Eisenmenger syndrome.
• The treatment of most arrhythmias during pregnancy is similar to that for nonpregnant women.
• When cardiopulmonary resuscitation is required during pregnancy, the standard advanced cardiac life support protocols should be used. Manual left uterine displacement should be employed to prevent aortocaval compression and a reduction in preload. Choice of drugs (and doses) as well as indications for defibrillation are the same as those for nonpregnant adult women. After 20 weeks' gestation, early hystereotomy and uterine evacuation may be necessary to facilitate resuscitation of the mother. Rescuers should be prepared to proceed with cesarean delivery if spontaneous circulation does not return within 4 minutes of cardiac arrest.
• Infective endocarditis prophylaxis is not recommended for vaginal or cesarean delivery except in patients with cardiac conditions at highest risk for endocarditis.

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CHAPTER 41 Cardiovascular Disease


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196. Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of


Chronic pain is common among young women. According to the 2016 Health, United States Report, 1 25% of women of childbearing age (18 to 44 years of age) report migraine headaches, 26% report low back pain, and 15% report neck pain. An increasing prevalence of chronic pain conditions in recent years has been attributed to a rise in risk factors, including obesity, sedentary lifestyle, and social and socioeconomic circumstances. The increasing prevalence of chronic pain is associated with an exponential increase in opioid use, which has contributed, in part, to the rapid rise in the incidence of neonatal opioid withdrawal syndrome in recent years (Fig. 42.1). This increase is not restricted to the United States. As far back as 2001, Blyth et al. 3 reported a 10% to 15% prevalence of chronic pain in women of childbearing age in Australia, with doubling predicted by 2050.

Any painful condition that occurs in young women can coexist with pregnancy, and pregnancy itself has variable impact on chronic pain conditions. Common chronic pain conditions in women include headache, fibromyalgia, pelvic pain, rheumatoid arthritis, and back pain. 4 Although migraine and autoimmune disease–mediated symptoms often improve or even resolve in pregnancy, back pain and pelvic girdle pain frequently worsen as a direct result of the pregnancy. 5,6

In a prospective study of 133 nulliparous women with uncomplicated singleton pregnancies recruited in the third trimester at a large perinatal center in Canada, 38% reported a chronic pain condition or pain before pregnancy, and 55% reported pain during the current pregnancy. 7 Forty-three percent of the cohort reported pain that persisted at 2 weeks postpartum and 25% at 3 months postpartum. Table 42.1 summarizes the characteristics of pain reported before pregnancy; migraine was the most common source of chronic pain, and lower back pain was the most common source of pain overall. 7 Pain during pregnancy was primarily described as mild or discomforting (Table 42.2); the average numerical rating scale (NRS; 11-point scale from 0 to 10) was 4. Lower back, hips, legs, and feet were the most common sites of pain. Table 42.3 summarizes pain characteristics at 3 months postpartum; lower back pain was the most common site of pain. Not surprisingly, prepregnancy and early postpartum pain was predictive of pain after delivery. Although pain before pregnancy is predictive of pain after delivery, pain during pregnancy and delivery can presage pain that persists during the postpartum period and beyond.

This chapter will identify factors that have been noted to be predictive of pain during pregnancy and persistence of pain during and after delivery. It will address the most common pain syndromes that complicate pregnancy and the pharmacological and nonpharmaceutical management approaches indicated for treatment of pregnant patients with chronic pain. Finally, the management of pain in women with chronic pain conditions during and after pregnancy will be discussed.

**PREDICTORS OF CHRONIC PAIN AFTER CHILDBIRTH**

A small number of patients will have new and persistent pain after cesarean and vaginal delivery. The estimated number of women with persistent pain has varied widely among studies, in part related to the study design and the population studied. Some studies with very high estimates used a retrospective cohort design that suffers from recall bias, and others with the...
TABLE 42.1 Prevalence of Chronic Pain Conditions and Pain before Pregnancy

<table>
<thead>
<tr>
<th>Pain Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain condition and/or pain before pregnancy</td>
<td>38%</td>
</tr>
<tr>
<td>Chronic pain condition</td>
<td>28%</td>
</tr>
<tr>
<td>Migraine</td>
<td>10%</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>6%</td>
</tr>
<tr>
<td>Back pain</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
</tr>
<tr>
<td>Pain before pregnancy</td>
<td>17%</td>
</tr>
<tr>
<td>Lower back</td>
<td>11%</td>
</tr>
<tr>
<td>Hips</td>
<td>5%</td>
</tr>
<tr>
<td>Genital/pelvic</td>
<td>5%</td>
</tr>
<tr>
<td>Legs</td>
<td>5%</td>
</tr>
<tr>
<td>Feet</td>
<td>6%</td>
</tr>
<tr>
<td>Head</td>
<td>3%</td>
</tr>
<tr>
<td>Other (wrists, knees, neck, shoulders)</td>
<td>7%</td>
</tr>
</tbody>
</table>

Prevalence of chronic pain conditions and pain before pregnancy in a cohort of women with subsequent uncomplicated singleton pregnancies.

"Pain before pregnancy was defined as pain more than once per week or more than five times per month.


TABLE 42.2 Characteristics and Prevalence of Pain during Pregnancy

<table>
<thead>
<tr>
<th>Pain Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of pain*</td>
<td>55%</td>
</tr>
<tr>
<td>Site of pain**</td>
<td></td>
</tr>
<tr>
<td>Lower back</td>
<td>41%</td>
</tr>
<tr>
<td>Hips</td>
<td>28%</td>
</tr>
<tr>
<td>Legs</td>
<td>19%</td>
</tr>
<tr>
<td>Feet</td>
<td>22%</td>
</tr>
<tr>
<td>Head</td>
<td>8%</td>
</tr>
<tr>
<td>Other (ribs, upper back)</td>
<td>23%</td>
</tr>
<tr>
<td>Present pain intensity</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>9%</td>
</tr>
<tr>
<td>Mild</td>
<td>13%</td>
</tr>
<tr>
<td>Discomforting</td>
<td>29%</td>
</tr>
<tr>
<td>Distressing</td>
<td>3%</td>
</tr>
<tr>
<td>Horrible</td>
<td>0.75%</td>
</tr>
<tr>
<td>Excruciating</td>
<td>0.75%</td>
</tr>
<tr>
<td>Pain severity</td>
<td>Median [IQR]</td>
</tr>
<tr>
<td>Average pain score during pregnancy*</td>
<td>4 [3–6]</td>
</tr>
<tr>
<td>Worst pain score during pregnancy*</td>
<td>6 [5–8]</td>
</tr>
<tr>
<td>Average unpleasantness score of pain during pregnancy*</td>
<td>6 [4–7]</td>
</tr>
</tbody>
</table>

Characteristics and frequency of pain during pregnancy in a cohort of women with uncomplicated singleton pregnancies.

*Pain during pregnancy was defined as pain more than once per week or more than five times over the past 4 weeks.

**Patients were allowed to select more than one site.

*11 point scale (0 to 10) with 0 = no pain and 10 = worst pain.

at 6 months. Eight percent of women described moderate pain, and 50% described mild pain. Among women who had chronic pain, 10% described severe pain, which was predictive of more severe pain, prolonged opioid use, and delayed functional recovery.

The interaction between pregnancy, pain, and emotional distress is complex and multidirectional. Preexisting chronic pain disorders are associated with absenteeism, depression, and disordered sleep during pregnancy. Maternal anxiety is associated with genetic variability in the catechol-O-methyltransferase gene (COMT) that encodes for regulation of response to catecholamines. The finding that a preoperative increase in blood pressure was predictive of longer use of opioid analgesics compared with vaginal delivery. Prenatal anxiety and poor physical function were also predictive of prolonged opioid use. The pain score reported on postpartum day 1 was predictive of overall postpartum pain burden and prolonged time to functional recovery. Poor breast-feeding on postpartum day 1 was also predictive of prolonged opioid use.

### Preexisting Chronic Pain and Postpartum Pain

The strongest predictor of postpartum pain is previous chronic pain. Additionally, in women without a history of chronic pain, severe pain in the early postpartum period is a predictor of persistent pain after childbirth. Possible reasons for this association include a more extreme response to the normal tissue trauma of delivery, inadequate response to normally prescribed analgesics, or a kindling response in which the experience of extreme pain makes one more sensitive to subsequent stimuli. It is unknown whether aggressive pain treatment in the early postpartum period is protective for the initiation of chronic pain.

### Patient Expectations

Patient expectations greatly impact the experience of pain. In a large, multicenter study of the association of maternal expectations with labor pain, the most satisfied mothers were those who expected more pain and had good pain relief from their analgesic treatment. Another study found that women’s preoperative expectation of pain was predictive of the severity of acute post–cesarean delivery pain at rest but not during activity. Simply asking women how much pain they expect and allowing them to choose a high- or low-dose pain regimen allows for better pain control and increased patient satisfaction. These results suggest that key factors predictive of post–cesarean delivery pain severity are the parturient’s expectation of pain and autonomy in its management.

### Anxiety and Depression

Anxiety is a complex state with both intrinsic and environmental contributions. The prevalence of generalized anxiety and pregnancy-related anxiety in early pregnancy is high. Maternal anxiety is associated with genetic variability in the catechol-O-methyltransferase gene (COMT) that encodes for regulation of response to catecholamines. The finding that a preoperative increase in blood pressure is strongly correlated with postpartum pain may be reflective of these genetic differences.

### Characteristics and Frequency of Postpartum Pain Conditions

<table>
<thead>
<tr>
<th>Pain Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of pain</td>
<td>25%</td>
</tr>
<tr>
<td>Site of pain</td>
<td></td>
</tr>
<tr>
<td>Lower back</td>
<td>13%</td>
</tr>
<tr>
<td>Hips</td>
<td>5%</td>
</tr>
<tr>
<td>Legs</td>
<td>5%</td>
</tr>
<tr>
<td>Feet</td>
<td>3%</td>
</tr>
<tr>
<td>Head</td>
<td>3%</td>
</tr>
<tr>
<td>Other (abdomen/incipition site, knee, mid-back, wrist)</td>
<td>11%</td>
</tr>
<tr>
<td>Present pain intensity</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>5%</td>
</tr>
<tr>
<td>Mild</td>
<td>9%</td>
</tr>
<tr>
<td>Discomforting</td>
<td>9%</td>
</tr>
<tr>
<td>Distressing</td>
<td>2%</td>
</tr>
<tr>
<td>Horrible</td>
<td>0%</td>
</tr>
<tr>
<td>Excruciating</td>
<td>0%</td>
</tr>
<tr>
<td>Pain severity</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Average pain score during the last month</td>
<td>4 [3–6]</td>
</tr>
<tr>
<td>Worst pain score during the past 2 weeks</td>
<td>6 [4–7]</td>
</tr>
<tr>
<td>Average unpleasantness score of pain during the past 2 weeks</td>
<td>5 [3–7]</td>
</tr>
</tbody>
</table>

Characteristics and frequency of pain conditions 3 months postpartum in a cohort of women with uncomplicated singleton pregnancies.

Pain at 3 months postpartum was defined as pain more than once per week for the past 2 weeks.

Patients were allowed to select more than one site.

11 point scale (0 to 10) with 0 = no pain and 10 = worst pain.


lowest estimates discontinued prospective follow-up of enrolled patients at the first report of no pain and thus may have missed those with episodic symptoms. Although most women have an uneventful recovery from peripartum pain and use opioids only briefly in the peripartum period, a systematic review and meta-analysis that included 15 studies suggested that 11% of women who deliver by cesarean report chronic pain at 12 months postpartum or later. Among women who had chronic pain, 10% described severe pain, 24% described moderate pain, and 50% described mild pain at 6 months.9

### Intrinsic Patient Factors

Many studies have proposed predictors of persistent pain, opioid use, and poor recovery after childbirth. A large prospective study followed women after planned vaginal delivery until resolution of pain, opioid use, and functional recovery (composite outcome). Factors predicting the longest resolution of the composite outcome were investigated. Even after correction for the effect of cesarean delivery, induction of labor was strongly predictive of more severe pain, prolonged opioid use, and delayed functional recovery. Cesarean delivery was predictive of longer use of opioid analgesics compared with vaginal delivery. Prenatal anxiety and poor physical function were also predictive of prolonged opioid use. The pain score reported on postpartum day 1 was predictive of overall postpartum pain burden and prolonged time to functional recovery. Poor breast-feeding on postpartum day 1 was also predictive of prolonged opioid use.

### Anxiety and Depression

The interaction between pregnancy, pain, and emotional distress is complex and multidirectional. Preexisting chronic pain disorders are associated with absenteeism, depression, and disordered sleep during pregnancy.
consumption within the first several days after cesarean delivery. Similarly, in a large French cohort, persistent pain 6 months after cesarean delivery was also associated with preoperative anxiety. Depression is also closely linked with chronic pain. Both prepregnancy anxiety and depression were predictive of physiosomatic symptoms (fatigue, back pain, muscle pain, dyspepsia, obstipation) during pregnancy and postpartum. In a large, prospectively followed cohort, women with severe acute postpartum pain had a threefold increased risk for postpartum depression compared with women who had mild postpartum pain.

### Genetic and Epigenetic Variability

In addition to COMT, the experience of postpartum pain and opioid use may also be associated with genetic variability in other genes, including the gene encoding the µ-opioid receptor (OPRM1). Data, however, are inconsistent. In one study, higher experimental pressure pain thresholds, but higher heat pain ratings, were observed in women who express the OPRM1 G118 allele. In a study in Asian women who received intrathecal morphine post–cesarean delivery analgesia, women with the G118 allele had higher pain scores and required a higher rescue dose of intravenous morphine. In another study in women of mixed ethnicity, no differences were observed in pain scores and rescue opioid requirements in women who received intrathecal morphine post–cesarean delivery analgesia. Possible explanations for these conflicting results include lack of control for other variables likely to influence pain after cesarean delivery, epigenetic influences on gene expression, the presence of linkage disequilibrium, differences in response to various pain stimuli, and differences in metabolic enzymes, transporters, and signal transduction pathway molecules, among other explanations.

There is also complex interplay between genetic variability in cytochrome P450 (CYP) enzymes required for opioid metabolism and pregnancy. For example, CYP2D6 is induced during pregnancy. After the administration of codeine, oxycodone, tramadol, and hydrocodone, increased expression of the metabolic enzyme, combined with intrinsic genetic variability in receptor affinity for opioid ligands, affects both production of the active opioid metabolites morphine, oxymorphone, O-desmethyltramadol, and hydromorphone, respectively, and their signal transduction. Little is known about epigenetic effects on gene expression and their possible link to pain in pregnancy. Epigenetic processes, including DNA methylation, histone modifications, and the activity of microRNAs, have been shown to alter the sensitivity to pain in nonpregnant individuals. The most commonly described epigenetic change, methylation, normally reduces gene transcription. Methylation of the gene for transient receptor potential ankyrin-1 (TRPA1) is inversely associated with the threshold for heat-induced pain and alters pressure-induced pain. Hypermethylation of the promoter for TRPA1 is associated with a low threshold for clinical pain. Decreased DNA methylation in genes related to the stress response and free radical clearance has been found in patients with fibromyalgia. The interaction between prepregnancy pain experiences and the hormonal and physiologic changes of pregnancy, and as well as effects on epigenetic modulation, is an important area for future research.

### Environmental Factors

#### Sleep deprivation

Acute to chronic pain9,37,38 associated with severe acute pain. Additionally, conversion from acute to chronic pain is associated with the presence of these factors. Patients may have an intrinsic tendency toward severe pain in response to injury. This tendency toward severe acute pain and its persistence may be genetically inherited or may be acquired through life experiences expressed through epigenetic changes. Measurement of these predictive factors with validated scales may be useful in identifying a subset of women for whom aggressive treatment of acute postsurgical pain with multimodal analgesia may prevent conversion of acute to chronic pain. Depression, anxiety, sleep deprivation, and disability, in addition to being risk factors for the development of chronic pain, are predictable consequences of severe acute pain, thus creating a positive reinforcing cycle. Interruption of this cycle by predicting and treating severe pain after delivery may be critical to preventing the development of acute severe and chronic pain. Identification and treatment of coexisting psychological distress and sleep disorders are key to effective...
postoperative pain management and may prevent conversion of acute to chronic pain.

**COMMON CHRONIC PAIN CONDITIONS IN PREGNANT WOMEN**

**Migraine**

Migraine and other headaches are common in women of reproductive age, with a peak prevalence of up to 25% per year in women between 30 and 40 years of age. A majority of women with migraine experience improved symptoms or even symptomatic remission during pregnancy, but migraine symptoms will worsen during pregnancy in 4% to 8% of women. Some women experience a first migraine in pregnancy, usually during the first trimester. In a cohort study of 3480 women who reported migraine during pregnancy, 73% reported using antimigraine drugs, including nonopioid analgesics (54%) and triptans (25%).

**Back Pain**

Preexisting chronic back pain is reported in 2% of women who become pregnant, but more than two-thirds of women complain of back pain over the course of pregnancy. Back pain persists postpartum in approximately 25% of women, and there is significant relapse in subsequent pregnancies. Proposed etiologies include weight gain, increased lumbar lordosis, and inefficient core muscle control (see Fig. 42.10). Thus, pregnancy is a significant life event that is associated with the onset of chronic back pain in many young women.

A 2015 meta-analysis provided moderate-quality evidence that an 8- to 12-week exercise program during pregnancy, whether land- or water-based, reduced the number of women who reported back pain and functional impairment (relative risk [RR] 0.66; 95% confidence interval [CI], 0.45 to 0.97) and sick leave (RR 0.76; 95% CI, 0.62 to 0.94). Pain and functional disability were also reduced by a multimodal intervention that included exercise, manual therapy, and education. One small study evaluated the efficacy of transcutaneous electrical nerve stimulation (TENS) and found that it was associated with reduced pain and functional disability without adverse effects. The same study also showed a small effect for acetaminophen (paracetamol). In spite of their common use, little evidence exists to support the use of rigid pelvic support belts for the treatment of back pain. There is broad consensus that the use of imaging, rest, opioids, spinal injections, and surgery are inappropriately high in the general population. Despite emphasis on these modalities in recent years, there has been an increase in reports of back pain and disability. Use of these modalities is even less desirable during pregnancy because of the possible fetal exposure to potentially dangerous medications and ionizing radiation. More favorable outcomes are achieved through promotion of activity and function, including work participation.

Basic early management of low back pain does not differ from management in nonpregnant individuals, and includes biopsychosocial management and nonpharmacologic treatmet (e.g., education supporting self-management, resumption of normal activities, and exercise). Psychological support programs and judicious pharmacologic intervention are indicated for those with persistent symptoms. Pharmacologic management of moderate to severe pain follows the World Health Organization (WHO) pain ladder; acetaminophen and other nonopioid drugs (see later discussion) are the foundation of treatment, with supplementation by opioid analgesics as the second and third steps on the ladder.

**Pelvic Pain**

Approximately 20% of women report pelvic pain during pregnancy. A long-term follow-up study found that 10% of women with pelvic girdle pain in pregnancy continued to suffer up to 10 years later. Thus, similar to other persistent pain conditions, pregnancy may be the condition that initiates long-term chronic pelvic pain. Pelvic pain can originate from various elements of the pelvic girdle, including the sacroiliac joints and pubic symphysis (Fig. 42.2). These joints are stabilized by thick ligaments that usually do not allow much motion. Increasing estrogen and progesterone in pregnancy cause softening of the ligaments, allowing important skeletal reconfiguration to support the enlarging pregnancy and future delivery. Systematic review and meta-analysis of studies assessing physical exercise and manipulation found no benefit to these therapies for reduction in pelvic pain.

Questions about the management of pelvic pain in pregnancy are common. Like low back pain, integration of a biopsychosocial model and identification of addressable risk factors, such as fears about delivery, are important.
Unlike back pain, there is no role for exercise therapy as the causes are largely ligamentous rather than muscular. Pain is relieved by rest. The FABER (flexion, abduction, and external rotation of the lower extremity) sign is commonly positive, and overextension during delivery, particularly in the setting of neuraxial analgesia (which can mask pain caused by maternal malpositioning) should be avoided. Pharmacologic treatment is similar to that for back pain, and follows the WHO ladder.51,58,59

**Fibromyalgia**

Fibromyalgia is a common pain syndrome in young women, and is associated with central nervous system sensitization to pain. Current criteria for diagnosis include myofascial pain in multiple body regions, fatigue, and cognitive symptoms.60 In a population-based study of more than 12 million pregnancies, mothers with fibromyalgia were more commonly older, obese, and users of alcohol, tobacco, and illicit drugs.61 Pregnancies among mothers with fibromyalgia are more likely to be complicated by fetal growth restriction, but not preterm birth, compared with the general population.62 Symptoms of fibromyalgia, especially pain in various parts of the body and generalized fatigue, may be difficult to differentiate from normal symptoms of pregnancy. In one study, 27% of otherwise healthy women had symptoms that technically meet criteria for fibromyalgia in term pregnancy.63 Therefore, fibromyalgia should not be diagnosed during pregnancy. Pain caused by fibromyalgia may increase during pregnancy; in a prospective case-controlled study, pain was associated with increasing depression scores.64 Lifestyle modification, including sleep hygiene and exercise, are mainstays for the treatment of fibromyalgia during and outside of pregnancy. Migraine headache is a frequent comorbidity with fibromyalgia, and if present, migraine management is helpful.65,66 The benefits and risks of pharmacologic management should be weighed for each individual as commonly used drugs, such as antidepressants, may have adverse fetal effects (see later discussion).67-69

**MANAGEMENT OF CHRONIC PAIN DURING PREGNANCY**

**Multimodal Approach**

Multimodal analgesia, also known as “balanced analgesia,” has been used effectively in treatment of cancer and chronic pain for many decades. The rationale behind its use is the optimization of additive and/or synergistic analgesic effects among different modes of analgesia or drug classes, while reducing doses and minimizing the side effects of each drug.70 Various combinations of opioids, nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, local anesthetics, and other drugs have been used with varying degrees of success in patients with chronic pain.71

A primary goal of multimodal analgesia for the pregnant patient is to provide adequate analgesia with minimum side effects to the mother balanced by minimal risk to the fetus/neonate. The use of nonpharmacologic interventions, including pain psychology and physiotherapy techniques, are particularly useful for the pregnant woman with chronic pain to reduce the amount of medication and support a positive pregnancy experience. Interventional techniques, including nerve blocks and radiofrequency techniques, are limited by the requirement to minimize radiation exposure from fluoroscopy. However, many of these procedures can now be accomplished with ultrasound guidance, and local anesthetic and low-dose steroid use are not contraindicated during pregnancy.72,73

Important postpartum concerns include minimizing transfer of drugs to breast milk and reducing maternal side effects that may interfere with breast-feeding or caring for the neonate. In general, medications for which infant plasma concentration is less than 10% of maternal plasma concentration are considered safe for the breast-feeding infant (Box 42.1).74 It is important that mothers not be expected to choose between severe pain and the benefits of breast-feeding. Although transferred into breast milk, the infant plasma concentration of anesthetic and analgesic drugs used for

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**Fig. 42.2** Common areas for pelvic pain in pregnancy related to changing body mechanics, shifting center of gravity, and hormonally induced changes in ligamentous attachments.
peripartum anesthesia and analgesia is almost always clinically insignificant and poses little or no risk to the nursing infant (see Chapter 14). There is no need to “pump and dump” after general anesthesia. Specifically, acetaminophen, low-dose aspirin, and NSAIDs are considered compatible with breast-feeding.

**Nonpharmacologic Interventions**

**Psychological Preparation and Support**

Psychological preparation has long been used to prepare for and manage labor pain. Several techniques, including mindfulness-based practices, have been associated with reduced opioid use in labor. Mindfulness-based therapies are established techniques for treating chronic pain and have efficacy in the treatment of acute pain. Indeed, a randomized controlled clinical trial suggested a medium-term impact on reducing the incidence of postpartum depressive symptoms in women assigned to mindfulness training compared with standard childbirth preparation.

**Physiotherapy**

Muscle-stabilizing exercises are useful in the management of chronic back pain but not chronic pelvic pain (see earlier discussion). There are limited studies regarding physiotherapy for pain syndromes other than back and pelvic pain. Postpartum physiotherapy may be useful to reverse and/or adapt to the musculoskeletal changes induced by pregnancy.

**Pharmacologic Treatments**

Pharmacologic intervention is used variably during pregnancy according to different perspectives on the risks and benefits of medication use. Chapter 42 shows the prevalence of pharmacologic treatments during pregnancy in four European countries. A general philosophy to guide the use of pharmacologic therapy in pregnancy, including the treatment of chronic pain, is to use the smallest amount of the safest drug for the shortest period. However, some chronic pain syndromes require continuing analgesic management throughout pregnancy. Important pharmacokinetic and pharmacodynamic changes occur during pregnancy (see Chapter 14). In general, drugs not indicated specifically for pregnancy are usually not studied during the drug development process because of perceived risk and a small market. Most information comes from drug registries, case-control studies, and national databases. These sources and reports are valuable as they provide important safety information, but they should be viewed through a lens that considers the limitations inherent to these types of studies and information sources. The impact of individual medications may vary depending on gestational age (early exposure may induce structural teratogenicity or embryonic loss; later exposure may induce preterm delivery or behavioral teratogenicity). Administration after childbirth requires consideration of the breast-fed infant. An important resource for information about the impact of individual drugs on breast-feeding can be found on LACTMED (/toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) (see Chapter 14).

**Nonsteroidal Antiinflammatory Drugs**

All NSAIDs have opioid-sparing activity. Ibuprofen is one of the most widely recognized and used NSAIDs; it is available without prescription. It nonselectively inhibits cyclooxygenase-1 and -2 enzymes (COX-1 and COX-2, respectively), which in turn reduces production of prostaglandins, leukotrienes, and other essential fatty acids and proinflammatory cytokines. NSAIDs are primarily classified as peripherally acting analgesics as they prevent peripheral release of substances that potentiate pain perception. They also have central antinociceptive activity. In addition to antiinflammatory, analgesic, and antipyretic properties, NSAIDs inhibit platelet adhesion and cause renal artery vasoconstriction and gastrointestinal irritation; therefore, use in patients at risk for hemorrhage and renal failure warrants caution. The American College of Obstetricians and Gynecologists (ACOG) has warned against their use in women recovering from preeclampsia with persistent postpartum hypertension; however, more recent data have called this recommendation into question.

**Use during pregnancy.** Despite a general recommendation to avoid the use of NSAIDs during pregnancy unless maternal benefit is deemed to significantly outweigh risk to the fetus, over-the-counter NSAID use is common during pregnancy. In one multicenter survey of more than 5000 parturients, 24% reported use of ibuprofen, 5% reported use of aspirin, and 4% reported use of naproxen.

NSAIDs should also be used sparingly and avoided when possible in the first trimester. Several large observational studies have suggested a small increase in the risk for congenital defects, generally small cardiac septal defects, but also possibly gastrochisis. Compared with neonates exposed to acetaminophen alone, neonates exposed to NSAIDs in the first trimester were found to have an increased risk for gastrochisis, hypospadias, cleft lip and palate, anencephaly, spina bifida, hypoplastic left heart syndrome, pulmonary valve stenosis, and tetralogy of Fallot (adjusted odds ratio [aOR] range, 1.2 to 1.6). Of course, association does not demonstrate causation, and it is possible that the

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**BOX 42.1 Drugs with Breast-fed Infant Plasma Concentrations Greater Than 10% of Maternal Plasma Concentrations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Lithium</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
</tr>
</tbody>
</table>

increased risk for congenital anomalies may be related to the indication for use rather than a pharmacologic effect of NSAIDs.

Older literature suggested that there may be an increase in the risk for spontaneous abortion associated with NSAID use in early pregnancy, but other studies suggested a protective effect. More up-to-date analyses have identified the association with abortion as a statistical aberration; there is likely no effect of NSAID use on early pregnancy loss.

Unless the maternal benefits significantly outweigh the risks, NSAIDs are generally contraindicated in the third trimester because of increased risk for premature closure of the ductus arteriosus as well as fetal renal dysfunction and oligohydramnios.

**Use immediately postpartum and during lactation.** NSAIDs are an important component in the multimodal management of postpartum pain in patients with chronic pain and opioid tolerance. NSAIDs are widely utilized and extremely effective for postdelivery pain. There is limited transfer of *ibuprofen* to breast milk, making it particularly useful for lactating mothers. Published data on other NSAIDs (e.g., etodolac, fenoprofen, meloxicam, oxaprozin, piroxicam, sulindac, and tolmetin) are limited, and U.S. Food and Drug Administration labeling discourages their use. Meloxicam concentrations in milk of lactating animals exceed maternal plasma concentrations, but the human implications of this finding are not known. Similar to other NSAIDs, its use is likely safe during lactation. Diflunisal has a long half-life and is not recommended because cataracts and fatality have been observed in neonatal animals. Mefenamic acid has a long half-life in preterm infants. Less than 1% of the maternal dose of *ketorolac* is excreted into human milk, and adverse events in nursing mothers have not been reported.

Low-dose *aspirin* is increasingly used beginning at 12 weeks’ gestation until delivery for preeclampsia prophylaxis...
in women at high risk for the disease. To date, no significant adverse fetal effects have been noted in the offspring of women allocated to aspirin compared with placebo therapy in these large clinical studies.\(^{94}\)

**Selective Cyclooxygenase-2 Inhibitors**

Like nonselective NSAIDs, COX-2 inhibitors are additive or synergistic with opioids and other analgesics. Selective inhibitors of the COX-2 isoenzyme inhibit the form of cyclooxygenase that is produced by inflamed tissue in preference to the form made constitutively that is important for gut integrity and other functions. Thus, compared with nonselective NSAIDs, COX-2 inhibitors have minimal effects on platelet adhesion and are less likely to contribute to suboptimal response to hemorrhage. However, concerns about potential increased risk for cardiovascular and thrombotic events, combined with the baseline elevated risk for these events during pregnancy and the postpartum period, have prevented COX-2 inhibitors from playing a major role in postpartum analgesia.\(^{97}\) In addition, use of celecoxib in late pregnancy has been associated with an increased risk for preterm delivery (aOR, 2.46; 95% CI, 1.28 to 4.72).\(^{36}\)

In a study in six lactating women, the breast milk content of celecoxib was sampled 48 hours after a 200-mg oral dose. The median milk-to-plasma (M/P) ratio was 0.23; thus the drug is considered safe during breast-feeding.\(^{87}\)

**Acetaminophen**

The mechanism of action of acetaminophen is still only partially understood. It has both antipyretic and mild analgesic properties.\(^{97}\) Central analgesia is thought to be mediated via activation of descending serotonergic pathways. In addition, acetaminophen may inhibit prostaglandin synthesis as well as interact with cannabinoid receptors. Peripherally, acetaminophen is thought to have nonselective inhibitory action at COX receptors.\(^{97}\)

**Use during pregnancy.** Acetaminophen is the first-line analgesic drug during pregnancy and a mainstay for multimodal therapy. It has few side effects at recommended doses and is additive or synergistic with other analgesic drugs.\(^{97}\) Large population studies have shown no association between acetaminophen use and congenital anomalies.\(^{99,98,99}\) Of note, although past evidence has found no adverse effects except in cases of maternal overdose, a small body of recent research has linked maternal acetaminophen use during pregnancy to neurobehavioral disorders such as attention deficit disorders and autism as well as asthma in children.\(^{100}\) These concerning associations remain to be confirmed.\(^{100}\) Despite increased clearance of acetaminophen in pregnancy, there is no evidence that changes in dose or frequency are required for therapeutic efficacy in pregnant women.

**Use immediately postpartum and during lactation.** Numerous studies in breast-feeding mothers have shown that infants solely ingesting breast milk from a mother who is taking acetaminophen receive no more than 3.6% of the maternal dose; thus, acetaminophen is safe for the breast-feeding infant.\(^{101,102}\)

**Gabapentin**

Gabapentin is a mainstay in the management of chronic pain. It is thought to provide analgesia by binding presynaptic voltage-gated calcium channels in the dorsal root ganglia of the spinal cord, thereby inhibiting the release of excitatory neurotransmitters.\(^{103}\) Although initially developed and still widely used as an antiepileptic drug, gabapentin is increasingly used for the management of chronic pain conditions.\(^{104}\) Perioperative gabapentin has been shown to decrease acute pain after a variety of surgical procedures,\(^{105}\) although data from healthy women undergoing elective cesarean delivery are conflicting (see Chapter 27).

**Use during pregnancy.** Gabapentin crosses the placenta. Studies on its use during pregnancy show a wide range of fetal-to-maternal (F/M) drug ratios, likely reflecting the timing of sampling after delivery. In a randomized controlled trial of gabapentin administered immediately before cesarean delivery, there was no difference in Apgar scores, interventions, or umbilical artery pH in neonates whose mothers were randomized to receive gabapentin compared with placebo.\(^{106}\)

In a study of six women with epilepsy who were treated with chronic daily gabapentin (900 to 2100 mg) during pregnancy, there were no observed adverse neonatal effects.\(^{107}\) The gabapentin F/M ratios in this study, reflecting steady-state concentrations, were much higher than the single-dose studies, ranging from 1.3 to 2.1. These ratios suggest active transplacental transport of gabapentin, possibly by the L-type amino acid transporter expressed in the placenta, resulting in fetal accumulation of gabapentin.\(^{107}\) The drug is rapidly metabolized by the newborn.\(^{107}\) Mean neonatal plasma concentrations were 27% of the umbilical artery plasma levels at 24 hours postpartum.

The Gabapentin Pregnancy Registry examined outcomes of 39 pregnancies in which mothers received gabapentin for epilepsy or chronic pain conditions.\(^{108}\) Thirty-six of these mothers received gabapentin continuously throughout pregnancy. The authors concluded that there was no evidence of increased risk for adverse maternal or fetal/neonatal effects compared with the general population.\(^{108}\) In a prospective cohort study, Fuji et al.\(^{109}\) compared 223 pregnancies with gabapentin exposure to 223 control pregnancies and found no increased risk for major malformations in the gabapentin group. Their results did suggest a possible association between gabapentin use and preterm birth as well as low birth weight (less than 2500 g); however, the analysis did not control for maternal indications for gabapentin, which included epilepsy and psychiatric disease, or concomitant drug therapy. The indications for gabapentin therapy were pain (n = 90), epilepsy (n = 71), and other (mostly psychiatric) reasons.\(^{109}\)

**Use immediately postpartum and during lactation.** The M/P ratio of gabapentin was assessed in five lactating mothers whose chronic gabapentin dose ranged from 600 to 2100 mg/day.\(^{107}\) The mean ratio was 1.0 (sampling ranged from 2 weeks to 3 months of neonatal age). The infant dose (mg/kg body
weight) of gabapentin was estimated to be 1.3% to 3.8% of the maternal dose. Finally, the infant plasma concentration in the breast-fed infant was as high as 12% of the maternal plasma concentration, but no adverse effects were observed in the five mother-infant dyads. Current data suggest that gabapentin use by lactating mothers is probably safe.

**Pregabalin**

Like gabapentin, pregabalin is structurally related to the inhibitory neurotransmitter γ-aminobutyric acid (GABA); its analgesic properties are attributed to binding to presynaptic calcium channels in the spinal cord and brain. The inhibition of these presynaptic voltage-dependent calcium channels reduces the influx of presynaptic calcium and the subsequent release of pronociceptive excitatory neurotransmitters. Gabapentin and pregabalin have similar indications and adverse reaction profiles. Pregabalin is not as well studied for the treatment of chronic pain in pregnancy.

**Use during pregnancy.** Though concerns were raised in a small 2016 study for a possible link between pregabalin use in the first trimester and increased risk for major fetal malformations, follow-up studies have proven more reassuring. A 2016 study included 116 pregnancies with first trimester exposure; 6% \(n = 7\) of offspring had malformations compared with 2% \(n = 2\) in the reference group. Four of the six fetal malformations in the pregabalin group were cerebral ventriculomegaly. By contrast, results from a subsequent, much larger, cohort study from the Medicaid Analytic eXtract database (477 infants exposed to pregabalin in the first trimester) were reassuring. After propensity score adjustment for indication, the relative risk for major fetal malformations in the pregabalin group was 1.16 (95% CI, 0.81 to 1.67). Additionally, none of the 477 pregabalin-exposed infants in this study carried a diagnosis of cerebral ventriculomegaly or other brain anomalies reported in the initial smaller study.

**Use postpartum and during lactation.** Pregabalin crosses into breast milk, as predicted by its low molecular weight and lack of plasma protein binding. In 10 lactating women receiving daily pregabalin 300 mg, the calculated amount of pregabalin present in 24-hour breast milk collection was 0.2% of the administered daily maternal dose. The calculated average daily infant dose was 0.31 mg/kg/day, or 7% of the maternal dose. No adverse effects were reported. Nipple latching does not appear to be affected by the use of pregabalin.

**Antidepressants**

Antidepressants are commonly used to treat chronic pain conditions ranging from migraine disorders to fibromyalgia and neuropathic pain conditions. Two classes of antidepressants have demonstrated efficacy in the management of chronic pain: tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The precise mechanism of action for the beneficial effects of these drugs on pain remains incompletely understood; however, both classes increase the synaptic concentrations of serotonin and norepinephrine. They are thought to increase inhibition of excitatory pain transmission in both the brain and spinal cord. Centrally, animal models demonstrate that increased norepinephrine levels act on the locus coeruleus to enhance the activity of the descending noradrenergic inhibitory system. In the spinal cord, norepinephrine directly inhibits neuropathic pain through α2-adrenergic receptors. Increased serotonin and dopamine levels may reinforce these effects.

**Tricyclic antidepressants.** TCAs used for chronic pain management include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and protriptyline. Among these drugs, amitriptyline and nortriptyline have the largest body of reassuring safety data in pregnancy and lactation. TCAs cross the placenta; the approximate F/M ratio is 0.6.

Although most epidemiologic studies show no association between maternal TCA use and the risk for major congenital malformation, the largest and most recent studies have yielded conflicting results. Using data from a research database from five U.S. health maintenance organizations, investigators identified 221 infants exposed to TCAs and compared them to almost 50,000 infants without exposure. No increased risk for major congenital malformations was identified (RR, 0.86; 95% CI, 0.57 to 1.3). Similarly, in a large 2013 study of 1608 women exposed to TCAs, 1875 women exposed to selective serotonin reuptake inhibitors (SSRIs), and 6617 women with no exposure to any antidepressants during pregnancy, no increased risk for congenital anomalies with TCA exposure was observed (RR, 0.9; 95% CI, 0.6 to 1.2). By contrast, a large Swedish registry study published in 2010 identified a possible link between in utero exposure to TCAs and an increased risk for congenital malformations. Almost 2500 women who took TCAs during pregnancy (early pregnancy, \(n = 1662\); later pregnancy, \(n = 782\)) were compared with over 1 million control patients in the same population. A small increase in the risk for severe malformations (aOR, 1.36; 95% CI, 1.07 to 1.72) as well as overall cardiac malformations (aOR, 1.63; 95% CI, 1.12 to 2.36) was identified after adjusting for maternal age, parity, smoking, and body mass index (but not psychiatric diagnoses or concurrent medication use). Among the TCAs, clomipramine was the most strongly implicated in increased risk, although in most studies, amitriptyline is the most commonly prescribed TCA. Overall rates of congenital malformations in this study were less than 5%, even in the TCA group. Many smaller studies have failed to show any link between maternal TCA use and increased risk for congenital anomalies.

There are some reports of neonatal symptoms possibly related to TCA withdrawal, including transient tachypnea, tachycardia, irritability, spasms, hypertonus, and clonus. A meta-analysis spanning studies from 1966 to 2010 found that TCAs, mostly clomipramine, were associated with transient poor neonatal adaptation, including an increased rate of respiratory distress, temperature instability, hypoglycemia,
and convulsions. Thus, close observation of the neonate in the immediate post-delivery period is likely warranted.

To date, maternal exposure to TCAs has not been linked to neuropsychiatric disorders in children. A 2017 meta-analysis included studies assessing the association between in utero antidepressant exposure and the risk for attention deficit disorder. After controlling for the presence of a maternal psychiatric disorder, the initial positive association disappeared (hazard ratio, 0.96; 95% CI, 0.76 to 1.2). Maternal TCA use has not been linked to differences in children's global IQ scores.

Tricyclic antidepressants have a long history of use in breast-feeding mothers, although most data on safety are from small case series. Nursing infants ingest approximately 1% of the maternal dose; the ingested drug undergoes significant first-pass metabolism; thus the nursing infant is exposed to a small proportion of the mother's total dose. However, the American Academy of Pediatrics (AAP) suggests that this class of medications should be “used with caution” in breast-feeding mothers, given that long-term neurodevelopmental outcomes with chronic exposure are unknown. Reassuringly, numerous small studies have failed to show significant effects on neonates.

**Serotonin-norepinephrine reuptake inhibitors.** Duloxetine and venlafaxine are the two most commonly used SNRIs for chronic pain conditions. Overall, these drugs are generally considered to be safe in pregnancy, with a much larger body of reassuring literature for venlafaxine than duloxetine. SSRIs, in contrast with mixed serotonin and norepinephrine reuptake inhibitors, are used primarily for the treatment of depression.

In 2010, Broy and Bérard reviewed the literature on rates of spontaneous abortion in women taking various antidepressants; venlafaxine was associated with an increased risk for spontaneous abortion (aOR, 2.1, 95% CI, 1.3 to 3.3). The only other antidepressant medication associated with increased risk for abortion was the SSRI paroxetine. A 2016 systematic review concluded that there was no associated risk for congenital malformations with venlafaxine or duloxetine based on data from 3186 infants exposed to venlafaxine and 668 infants exposed to duloxetine in the first trimester. These drugs have been linked with an increased risk for persistent pulmonary hypertension of the newborn, but further confirmatory study is required. Like the TCAs, neonates of mothers taking SNRIs at the end of pregnancy should be monitored for transient agitation and withdrawal symptoms; the risk is greater in drugs with shorter half-lives, such as venlafaxine.

Venlafaxine is excreted in the breast milk, with reported M/P ratios ranging from 1 to 4, depending on the study design. The calculated mean infant exposure has ranged from 2% to 8% of the maternal dose of both venlafaxine and its active metabolite desvenlafaxine. No adverse effects were reported among 7 breast-fed neonates in a 2002 study or among 13 neonates in a 2009 study. Very little data on use during breast-feeding are available for duloxetine. Based on two very small studies, infant exposure to duloxetine in breast milk is less than 1% of the maternal weight-adjusted dose; therefore, this drug may be safe for lactating mothers. In general, the AAP recommends using SNRIs with caution in lactating mothers because the long-term effects of chronic exposure on neurodevelopment are unknown.

**Opioids**

Although opioids are commonly prescribed in the United States to pregnant women, practitioners should bear in mind that there is no indication for long-term treatment with opioids for many common pain syndromes, including headache, fibromyalgia, and chronic back pain. The prevalence of opioid prescription is increasing in publicly insured populations in the United States. Opioids are prescribed for the treatment of acute and chronic pain as well as the management of opioid use disorder, or they may be taken illicitly. Within the United States, there is significant regional variation in prescription practice. Depending on the state of residence, between 10% and 42% of pregnant women with public insurance filled a prescription for an opioid between 2000 and 2007 (Fig. 42.4). Studies show that most patients who use opioids for chronic pain will continue their use during pregnancy.

**Use during pregnancy and lactation.** The mixed population of patients receiving opioids under medical care and those taking illicit opioids makes interpretation of epidemiologic data complex. Pregnant women who use illicit opioids or are prescribed opioid maintenance treatment for opioid use disorders often have concomitant chronic disease and life circumstances that may confound analyses of the effects of opioid use during pregnancy. These confounders include a higher incidence of tobacco use, frequent alcohol and/or polysubstance use disorder, and life stressors and experiences that may independently alter their pregnancy outcome. The indication for opioid prescription may also influence pregnancy outcome. Women prescribed opioids for opioid use disorder have longer gestations (median, 39 weeks), but a greater risk for low-for-gestational weight infants than mothers treated with opioids for chronic pain (median gestation, 36 weeks). The infants born to women who have been prescribed opioids for treatment of opioid use disorder have a greater risk for neonatal opioid withdrawal syndrome. The incidence of this syndrome has increased rapidly since 2000 (see Fig. 42.1).

A 2017 systematic review examined the effects of chronic maternal opioid use on the incidence of congenital malformations. The authors concluded that uncertainty remains regarding the teratogenicity of opioids because of variabilities in study design, poor-quality studies, and weaknesses in outcome and exposure measurement. The data were mixed, but some studies included in the systematic review identified statistically significant positive associations between maternal opioid use and oral clefts, atrial and ventricular septal defects, neural tube defects, and club feet in neonates exposed to opioids in utero compared with control populations. Two retrospective case-controlled studies showed an association between first-trimester opioid use and neural
opioids in opioid-naïve women, as the risk for overdose is lower with short-acting opioids. This recommendation is particularly relevant during the first 2 weeks of treatment when the hazard rate for overdose is elevated fivefold for long-acting compared with short-acting opioids in the general population.

**Methadone.** Two drugs commonly used for treating chronic pain and opioid use disorder, methadone and buprenorphine, have special considerations during pregnancy. Total daily methadone doses for chronic pain management are generally less than doses used for opioid replacement therapy. Methadone is a full opioid agonist with high affinity for the μ-opioid receptor, affinity for the N-methyl-D-aspartate (NMDA) receptor, and a long half-life. These properties make it an attractive drug for management of addiction as once-daily observed dosing is possible. However, pharmacokinetic changes in late pregnancy may make twice-daily maintenance dosing a more rational choice.

For the purposes of analgesia, short-acting opioids such as oxycodone and hydrocodone are preferred to long-acting opioids in opioid-naïve women, as the risk for overdose is lower with short-acting opioids. This recommendation is particularly relevant during the first 2 weeks of treatment when the hazard rate for overdose is elevated fivefold for long-acting compared with short-acting opioids in the general population.

**Fetal growth restriction may occur later in gestation. The neonate is at risk for neonatal opioid withdrawal syndrome if opioids are used by the mother in the third trimester.** In a meta-analysis of studies of neurobehavioral outcomes in infants and preschool children who were chronically exposed to opioids in utero, no significant impairment was identified compared with nonexposed peers. However, the subset of infants born to mothers with opioid use disorder may have risks that are not directly attributable to in utero opioid exposure. Behavioral issues have been identified in children raised by mothers with untreated opioid use disorder.

For the purposes of analgesia, short-acting opioids such as oxycodone and hydrocodone are preferred to long-acting opioids in opioid-naïve women, as the risk for overdose is lower with short-acting opioids. This recommendation is particularly relevant during the first 2 weeks of treatment when the hazard rate for overdose is elevated fivefold for long-acting compared with short-acting opioids in the general population.

**Fig. 42.4** The prevalence of opioid prescription during pregnancy, stratified by state, among U.S. Medicaid beneficiaries, 2000 to 2007. (From Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol. 2014;123:997–1002.)
of delivery. Approximately 50% of infants born to mothers treated with methadone for opioid use disorder require treatment for neonatal opioid withdrawal syndrome. However, opioid doses used in the treatment of chronic pain are often lower than those used for opioid replacement therapy. Lower rates of neonatal opioid withdrawal syndrome were observed with maternal doses less than 20 mg/day compared with higher doses; these low doses are more commonly used to treat chronic pain.

Many women treated for pain or opioid use disorder during pregnancy are exposed to multiple pharmaceutical agents as part of multimodal regimens intended to reduce the required amount of opioid or as part of treatment for comorbid psychiatric disease. In a large cohort study using 2000 to 2010 data from publicly insured patients in the United States, an increased risk for neonatal opioid withdrawal syndrome was identified in infants exposed in utero to gabapentin, antidepressants, and benzodiazepines in combination with opioid, when compared with opioid-only exposure. Although the finding of an association between polypharmacy and neonatal withdrawal syndrome suffers from the usual limitations of retrospective cohort studies, the authors did not identify an association between nonbenzodiazepine hypnotics or antipsychotics and neonatal withdrawal syndrome, suggesting a direct drug effect rather than other causes.

In a retrospective cohort study from Ireland, 618 mother-infant dyads treated with methadone during pregnancy were compared with the overall population of 61,000 singleton pregnancies. Methadone exposure was associated with preterm birth (aOR, 2.5; 95% CI, 1.4 to 4.3), small-for-gestational-age infants (aOR, 3.3; 95% CI, 2.5 to 4.3), admission to the neonatal intensive care unit (aOR, 9.1; 95% CI, 7.2 to 11.6), and a major birth anomaly (aOR, 1.9; 95% CI, 1.1 to 3.4). Of note, most of these women were receiving other drugs as well as methadone and/or were using illicit substances. Greater than 90% used tobacco during pregnancy. The authors did identify a dose-response relationship between methadone dose and neonatal opioid withdrawal syndrome.

Similarly, in a Danish study of pregnant women treated with buprenorphine and methadone for opioid use disorder, the risk for adverse pregnancy outcomes, including preterm birth, low birth weight, and small-for-gestational-age, was greater in exposed infants. Neonatal opioid withdrawal syndrome was more common in methadone- than buprenorphine-exposed infants.

In one of the few studies of methadone use for chronic pain, Sharpe and Kuschel retrospectively compared 19 pregnant women who received methadone for chronic pain to 24 women who received it to treat opioid use disorder. The women receiving methadone for chronic pain were also taking regular acetaminophen and amitriptyline, along with other medications for management of their pain. As anticipated, daily doses of methadone were lower in the chronic pain than in the opioid use disorder group. Only 11% of infants in the chronic pain methadone group required treatment for neonatal opioid withdrawal syndrome compared with 58% in the opioid use disorder group. However, the risk for preterm birth was greater in the pain group. Delivery was induced in many of these women because of pain exacerbation, emphasizing the importance of pain management during pregnancy.

The AAP considers methadone to be compatible with breast-feeding. Methadone is detected in very low levels in maternal breast milk, but M/P ratios vary significantly from 0.05 to 1.2 among different studies. Although the concentration of methadone in breast milk is probably insufficient to prevent neonatal opioid withdrawal syndrome, breast-feeding has been associated with reduced severity and duration of neonatal withdrawal.

Buprenorphine. Buprenorphine is used for treatment of both opioid use disorder and chronic pain; typically doses are lower when used to treat pain. It is a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor (see Chapter 13). This profile allows for a ceiling effect for respiratory depression and an improved side-effect profile compared with full µ-opioid agonists. Partial µ-opioid agonism reduces the overdose risk, and daily observed dosing for the treatment of opioid use disorder is less commonly required than for methadone. However, the strong binding affinity to the µ-opioid receptor, combined with its action as a partial agonist, has raised the concern that it may not be possible to overcome the ceiling effect, and adequate treatment of post–cesarean delivery pain may be difficult to achieve. It is not known whether this problem is specific to buprenorphine treatment or a consequence of opioid use disorder and the use of high doses of opioids in general. One study found that post–cesarean delivery opioid requirements were high but equivalent in women treated with either methadone or buprenorphine.

Buprenorphine is currently available in multiple formulations, including tablets, buccal films, transdermal patches, subcutaneous implants, and depo injections. Formulations that allow high doses (greater than 2 mg) may be combined with naloxone to prevent illicit injection. Some depo and implant forms of buprenorphine are very long lasting; strategies other than conversion to full-agonist opioid agonist therapy may need to be considered for peripartum pain management.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial compared the incidence of neonatal opioid withdrawal syndrome after maternal treatment with buprenorphine (n = 58) or methadone (n = 73) for maternal opioid use disorder. Treatment for withdrawal was required in 57% of neonates in the methadone group and 47% in the buprenorphine group, a nonsignificant difference (OR, 0.7; 95% CI, 0.2 to 1.8). However, the neonates in the buprenorphine group who did require treatment required significantly less morphine; duration of therapy and hospital stays were shorter than for neonates exposed to methadone. These results have led many clinicians to recommend buprenorphine over methadone for treatment of maternal opioid use disorder. It should be noted, however, that the maternal attrition rate was significantly greater in the buprenorphine group than in the methadone group.
The peripartum management of pregnant patients receiving buprenorphine may be challenging, especially if treatment doses are high. Possible reasons include the high \( \mu \)-opioid receptor affinity and partial agonist mechanism of buprenorphine, opioid tolerance, and/or opioid-induced hyperalgesia. Because buprenorphine can be administered in many forms and doses, the daily dose may not be immediately obvious (e.g., the extended-release subcutaneous formulation).  

Adequate pain control during labor, cesarean delivery, and the postpartum period requires planning and coordination among clinicians caring for the mother and infant, including the addiction medicine specialist. The decision to continue buprenorphine therapy throughout the peripartum period, transition to a full \( \mu \)-opioid agonist (with subsequent reinduction of buprenorphine in the postpartum period), or implement detoxification should consider the risk for opioid overdose and recidivism. Conversion from buprenorphine to a full \( \mu \)-opioid agonist should be supervised by a clinician with expertise, as partial agonism binding can last significantly longer than analgesic effects, and dose requirements for the full \( \mu \)-opioid agonist may decrease over the first few days of transition. Lower-dose buprenorphine regimens commonly used for management of chronic pain (less than 1 mg) usually do not result in full occupancy of available opioid receptors; thus, the partial agonism effect can be overcome by using higher doses of full \( \mu \)-opioid receptor agonists. 

The primary analgesic modality for managing labor and vaginal delivery analgesia for women receiving buprenorphine is regional analgesia/anesthesia. According to the ACOG, women on methadone or buprenorphine maintenance therapy should, at a minimum, continue their maintenance therapy without a change in dose through the peripartum period. For the treatment of short-term moderate pain, the buprenorphine dose can be increased to up to 32 mg/day. Buprenorphine can be administered up to 4 times per day when used for acute pain management. Opioid adjuvant medications with different mechanisms of action are useful to increase analgesic efficacy.  

Buprenorphine is found in the breast milk 2 hours after maternal dosing, but the overall concentration is low (approximately 1% of the maternal dose). As such, it is unlikely that buprenorphine in human milk has any negative effects on the neonate. Because studies have shown that breast-fed infants may have reduced severity of neonatal opioid withdrawal syndrome, women receiving buprenorphine therapy are encouraged to breast-feed in the absence of contraindications.  

### Drugs for Migraine Headache 

Migraine headache is common in women of childbearing age. Although its frequency and severity improve during pregnancy for many women, prophylaxis and treatment may be necessary during pregnancy in others. Acetaminophen is generally thought to be safe during pregnancy and lactation and is the first-line therapy for migraine headache. Magnesium, both oral and intravenous formulations, is also thought to be safe and often efficacious in both acute treatment and headache prophylaxis. Opioids have limited efficacy in migraine headache and create a risk for opioid use disorder and medication overuse headache. 

**Triptans.** Triptans are highly efficacious for the treatment of acute migraine headache. They act as serotonin 5HT 1B-, 1D-, and 1F-receptor agonists. These receptors are present in the umbilical artery and fetal brain. Of the seven triptans available worldwide, the longest clinical experience and greatest body of literature demonstrating safety in pregnancy and breast-feeding exist for sumatriptan.  

In a large study using the Swedish birth registry, 3286 women used ergot alkaloids or triptans in the first trimester, and 1394 women used these medications after the first trimester. No increased risk for congenital malformations was identified (OR, 0.86; 95% CI, 0.51 to 1.44). Most patients included in the analysis were taking sumatriptan; thus, the authors concluded that sumatriptan is likely safe for use in pregnancy, but data were lacking to assess the safety of other triptans and ergot alkaloid exposure. In a comprehensive 2015 review on management of migraine headache in pregnancy, the authors concluded that data on the use of triptans during pregnancy are reassuring, and that sporadic use of sumatriptan is probably safe during pregnancy. Given the limited data on other triptan medications, sumatriptan is the first choice among triptans. 

The AAP considers sumatriptan to be compatible with breast-feeding. In five women who received 6 mg of subcutaneous sumatriptan, breast milk was collected hourly for 8 hours; the mean M/P ratio was 4.9. The calculated infant dose of sumatriptan was 3.5% of the maternal dose. Oral bioavailability of sumatriptan is low (approximately 15%); thus the amount of sumatriptan that reaches the infant circulation is likely exceedingly low. 

**Eletriptan** may be even safer than sumatriptan for breast-feeding mothers because its high plasma protein binding results in even lower concentrations in breast milk (M/P ratio 0.25). Oral bioavailability is approximately 50%, and the estimated relative infant dose is 0.02% of the maternal dose. Because data regarding the safety of use other triptans during breast-feeding are lacking, sumatriptan and eletriptan should be selected for lactating mothers. 

**Ergot alkaloids.** Ergotamine and other ergot alkaloids that are used for migraine treatment are generally contraindicated during pregnancy because of known vasoconstrictive and uterotonic effects; the closely related drug, methylergometrine, is commonly used as a second-line agent for the treatment of uterine atony. No systematic evidence of increased risk for congenital malformations exists for ergot alkaloids, but there are case reports of sirenomelia (fusion of the lower limbs, lower spinal column defects, and malformations of the urogenital and gastrointestinal tracts), renal agenesis, and urethral atresia associated with methylergometrine use in the first weeks of pregnancy. The association has biological plausibility, as it is hypothesized that sirenomelia results from vascular...
insufficiency. One study of 77 neonates born to mothers who had received ergotamine during pregnancy found a significant increase in the risk for low-birth-weight infants (16.4% versus 4.7%) and preterm births (16.4% versus 9.2%) compared with nonexposed infants.\textsuperscript{161} The authors proposed that placental vasoconstriction caused by ergot alkaloids may have contributed to these unfavorable outcomes.\textsuperscript{161} Using data from 53 cases of maternal dihydroergotamine use for migraine treatment during pregnancy from the Quebec Pregnancy Registry, no increase in the risk for major congenital malformations, low birth weight, or spontaneous abortion was identified, but there was an increased risk for prematurity (OR, 4.2; 95% CI, 1.3 to 13.0).\textsuperscript{162} As such, mothers who use ergot alkaloids for migraine headache treatment in the first and second trimesters, usually because the pregnancy is not recognized, should be assessed carefully, and ergot alkaloid therapy should be avoided, if possible, once pregnancy is diagnosed.

Breast-feeding data for ergot alkaloids are limited. In a 1965 review article, Knowles\textsuperscript{163} cited a 1934 German study in which 90% of nursing infants of mothers using ergot alkaloids displayed vomiting, diarrhea, convulsions, and other symptoms of ergotism. As such, the AAP recommends that the drug be used with extreme caution in nursing mothers.\textsuperscript{87} However, methylergonovine is commonly used to treat uterine atony in the first 24 hours after delivery, and many mothers breast-feed during this interval. A small prospective controlled study found no differences in neonatal complication rate or growth or neurodevelopment outcomes in the infants whose mothers received short-term postpartum methylergonovine treatment compared with a control group without exposure.\textsuperscript{164}

**Beta-adrenergic blocking agents.** Beta-adrenergic blocking agents are frequently used in pregnancy for a variety of indications, including migraine headache prophylaxis. Their use is generally considered safe. The largest and most recent population-based studies show no overall increase in the risk for major congenital malformations.\textsuperscript{165} Metoprolol and propranolol at the lowest possible effective doses have been suggested as first-line medications for migraine prophylaxis in pregnancy. The increased volume of distribution and clearance during pregnancy require that metoprolol dose and dosing frequency be increased significantly to maintain efficacy.\textsuperscript{82} Transfer across the placenta to the fetus with subsequent risk for neonatal bradycardia and hypoglycemia have been observed when beta-adrenergic blocking agents are used in the peripartum period; however, these drugs have a long safety record when used to treat hypertension in women with preeclampsia.\textsuperscript{87}

Beta-adrenergic blocking agents are considered compatible with breast-feeding by the AAP.\textsuperscript{87} Although metoprolol concentrates in breast milk (approximate M/P ratio, 3), no adverse effects have been observed in nursing infants. The reported propranolol M/P ratio ranges widely from 0.2 to 1.5.\textsuperscript{87}

**Calcium entry–blocking agents.** Verapamil is generally considered to be safe in pregnancy. Retrospective and prospective studies have not identified increased risk for major malformations with first-trimester use.\textsuperscript{167} Data suggest a possible increase in preterm birth in patients taking verapamil; however, poor placental perfusion caused by hypertension, rather than a direct effect of hypertensive therapy, explains this finding.\textsuperscript{166} The AAP considers verapamil to be compatible with breast-feeding. The estimated relative infant dose is less than 0.01% of the maternal dose; no adverse effects have been reported.\textsuperscript{87} Verapamil has been recommended as the second-line prophylactic medication for migraine headache in women who are breast-feeding if beta-adrenergic blocking agents are contraindicated or ineffective.\textsuperscript{79} Data are lacking for safety in pregnancy and breastfeeding for the newer calcium entry–blocking agents, flunarizine and cinnarizine.

**Tricyclic antidepressants.** Amitriptyline has been used effectively for migraine prevention and has been suggested to be another second-line agent for migraine prevention in pregnancy.\textsuperscript{167} Although data are conflicting, the risk for teratogenicity from early gestational exposure is likely low (see earlier discussion).

**Anticonvulsants**

Valproic acid and topiramate are the two anticonvulsant medications with demonstrated efficacy in migraine prophylaxis that are considered teratogens and should not be used in pregnant women for migraine headache prophylaxis.\textsuperscript{42} Studies have shown an 11% risk for major congenital malformations, primarily an increased risk for cleft palate and neural tube defects, in infants with \textit{in utero} topiramate exposure.\textsuperscript{168} In addition, valproic acid use in late pregnancy has been associated with autism, lower cognitive function, and lower intelligence in offspring.\textsuperscript{168}

Valproic acid can be resumed for migraine prophylaxis in the postpartum period; the AAP believes the drug is compatible with breast-feeding.\textsuperscript{87} Valproic acid is almost completely bound to plasma proteins. In a study of six nursing mothers who were receiving valproate for epilepsy, milk concentrations were less than or equal to 15% of the maternal serum concentration.\textsuperscript{169} Infant serum levels of valproate were 0.9% to 2.3% of maternal values. However, one report described neonatal thrombocytopenia, anemia, and purpura that resolved after maternal discontinuation of valproate.\textsuperscript{170} Thus, nursing infants exposed to valproic acid who exhibit thrombocytopenia or jaundice should have serum valproate levels measured.\textsuperscript{79}

Topiramate is excreted into the breast milk.\textsuperscript{87} The estimated M/P ratio is 0.86, and the relative infant dose is 3% to 23% of the maternal dose.\textsuperscript{87} Breast-feeding mothers who are taking topiramate should be advised to watch for adverse effects in their infants, including decreased alertness, fatigue, anorexia, and weight loss. Although topiramate is considered safe for breast-feeding mothers, its use for migraine prophylaxis should be considered only if other medications are contraindicated or have been shown to be ineffective.
Interventional Treatments

Interventional treatments for pain syndromes in pregnancy are commonly deferred until the postpartum period, in part because many of these treatments, including nerve blocks, stimulators, and radiofrequency treatment, are done with the assistance of fluoroscopy. However, an increasing number of practitioners are forgoing fluoroscopy and using ultrasonography to facilitate a wide array of interventional pain procedures. The drugs used in most of these procedures, local anesthetics and low-dose corticosteroids, are commonly used in the antenatal period for other indications. Corticosteroids used as part of interventional pain procedures have been safely used in women with gestational diabetes. Therefore, wider availability and use of interventional pain procedures for pregnant women may be anticipated and prudent. Peripheral nerve blocks (e.g., greater occipital nerve blocks for the treatment of migraine headache) have been reported to be safe and efficacious in pregnancy. Similarly, local injection of a corticosteroid can be considered for severe radicular back pain and plantar fasciitis.

At the current time, advanced pain management treatment is increasingly being used for a broader array of indications in young people. For example, spinal cord stimulators may increasingly be implanted in young women who become pregnant. Although experience with these treatments in pregnancy is sparse, no evidence exists for concerns with continued use during pregnancy and the peripartum period. There are several reports of women with indwelling spinal cord stimulators who have had vaginal deliveries with successful epidural analgesia. In this setting, it is important to know the spinal level at which the stimulator leads have been placed, and to avoid them. They are seldom located in the lower lumbar spine. Whether antibiotic prophylaxis is indicated in patients with these devices is controversial.

Prophylaxis

Several studies have evaluated the incidence of the development of new chronic pain after childbirth. The highly variable results of these studies can likely be explained, in part, by study design differences, population differences, and the definition of chronic pain. In general, earlier retrospective questionnaire-based studies have reported higher incidences, thus raising the suspicion of recall bias, whereas later prospective studies have reported a lower incidence. In these studies, although patients were assessed at multiple time points after delivery, follow-up was terminated when the patient reported no pain. Thus, patients with intermittent pain received no further follow-up, and this may have contributed to the low reported incidence of persistent pain.

Several factors have been associated with an increased risk for developing chronic pain after delivery, including severe pain in the early postpartum period and preexisting chronic headache, back pain, and pelvic pain. Quantitative sensory testing, evaluating response to a pain stimulus, and simply asking patients how much pain they anticipate may contribute to better prediction of women at risk for severe acute postdelivery pain. Genetic factors may explain a small component of post–cesarean delivery pain (see earlier discussion).

The risk for progressing to chronic opioid use because of new persistent pain is likely small. However, given that cesarean delivery is the most common major surgical procedure in the world, with over 1 million women undergoing this procedure annually in the United States, an estimated 4000 women annually in the United States may become new chronic opioid users after delivery. This potential public health problem deserves further study.

It is unknown whether aggressive treatment of severe postdelivery acute pain will reduce the development of persistent pain or prevent initiation of chronic opioid use. Several approaches have been tried, but long-term follow-up is lacking. Wound infiltration with local anesthetics, diclofenac, and other NSAIDs improves pain and reduces opioid requirements in the short term but does not prevent the development of chronic pain. Similarly, abdominal wall nerve blocks, most commonly transversus abdominis plane blocks, are efficacious for acute pain, but do not improve analgesia when combined with long-acting neuraxial opioids in low-risk patients (see Chapter 27). Whether adjunctive therapy targeted toward patients at high risk for severe postpartum pain and the development of chronic pain will improve long-term pain outcomes remains to be studied (see later discussion).

MANAGEMENT OF INTRACTABLE PAIN AFTER DELIVERY

Most patients with chronic pain syndromes can be maintained on their usual pain medications, supplemented as needed after delivery. Patients who suffer from chronic pain syndromes may report more postdelivery pain than patients without chronic pain because of sensitization and tolerance to systemic opioids. In a study of patients on methadone maintenance therapy, higher post–cesarean delivery pain scores and 70% greater opioid analgesic use were reported compared with opioid-naive matched controls. Although most postpartum pain in healthy patients can be managed with a single dose of long-acting neuraxial opioid and oral analgesics (see Chapter 27), consideration should be given for continuous postoperative neuraxial analgesia in patients with a history of chronic pain and opioid use. Pain management in these patients may be particularly difficult if neuraxial analgesia is contraindicated. Meticulous planning with the care team, including assessment of the benefits and risks associated with available options, must be discussed with the multidisciplinary team and the patient.

Adjunctive therapies have not been found to be efficacious in healthy patients without chronic pain, likely caused by a floor effect. Most healthy patients have low pain scores and well-controlled pain using the normal multimodal approaches, making it difficult to identify incremental improvements with
additional therapy.34 However, this may not be true for patients with chronic pain. The best management for these patients, or patients at risk for the development of chronic pain, is not known. Severe acute pain after delivery is both a red flag for, and likely a precipitant to, the onset of chronic pain after delivery. It is likely that single-dose adjuvant regimens will not be effective in preventing progression to chronic pain in those at highest risk. Sustained, individualized treatment with adjuvant medications through the post-delivery period should be considered in this population. Future studies should evaluate longer-term treatment with analgesic adjuvants in patients at risk for chronic pain. Several classes of drugs, including NMDA antagonists and alpha2-adrenergic agonists, have potential to treat persistent pain after cesarean delivery and to prevent progression to chronic pain.

**NMDA Antagonists**

NMDA antagonists, including ketamine, are efficacious for the treatment of neuropathic pain and have been used in the treatment of chronic pain.149 NMDA antagonists have been used for treatment of acute postoperative pain and prevention or reversal of central sensitization in chronic pain.189,190 Ketamine is particularly useful for treatment of acute postoperative pain in opioid-tolerant patients. It is also used for intraoperative analgesia as an adjuvant to neuraxial anesthesia in cesarean deliveries; small intravenous doses provide significant analgesia with minimal respiratory depression.191 It is reasonable to consider using an NMDA antagonist in a patient with chronic pain or to prevent conversion to chronic pain after cesarean delivery. In one study, patients undergoing cesarean delivery with spinal anesthesia and multimodal postoperative analgesia that included spinal morphine were randomized to receive ketamine 10 mg or placebo after delivery.192 Women who received ketamine reported less pain at 2 weeks postpartum compared with women who received a placebo.

Perhaps the most commonly used NMDA antagonist in obstetric patients is magnesium, a medication commonly used for seizure prophylaxis in women with preeclampsia and fetal/neonatal neuroprotection for women at risk for preterm birth.193 Magnesium has been shown to reduce central sensitization and wound hyperalgesia.194 A systematic review concluded that magnesium has a positive effect on acute postoperative pain and may be particularly useful as an adjuvant in patients with opioid tolerance.195 Neuraxial magnesium has also been shown to be effective for postoperative analgesia; however, it has not been adequately evaluated for neurologic complications, and its use cannot be recommended at this time.

**Dextromethorphan** is another NMDA-blocking drug that has been studied for its effect on postoperative analgesia and chronic pain. A systematic review concluded that perioperative dextromethorphan therapy may contribute to a reduced need for opioid analgesia, although the clinical significance was unclear.196 In a single study, women undergoing cesarean delivery with multimodal analgesia that included intrathecal morphine were randomized to receive a single dose of dextromethorphan 60 mg197; efficacy was not demonstrated. However, the drug has not been studied in women with chronic pain. Memantine, a noncompetitive NMDA antagonist that does not have hallucinogenic side effects, is efficacious for neuropathic and postoperative pain149,198–200; it has not been evaluated for post–cesarean delivery analgesia.

**Alpha2-Adrenergic Receptor Agonists**

Alpha2-adrenergic agonists have been used for the treatment of acute and chronic pain in nonobstetric settings.201 Both neuraxial clonidine and dexmedetomidine have been used for post–cesarean delivery analgesia.202 Clonidine did not appear to add any benefit to intrathecal morphine in healthy women, but it may be useful in the setting of chronic pain.203 The epidural formulation of clonidine carries a black box warning from the U.S. Food and Drug Administration stating the following:

> Clonidine hydrochloride injection (epidural clonidine) is not recommended for obstetrical, postpartum or peripartum care. The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients. However, in a rare, obstetrical, postpartum or peripartum patient, potential benefits may outweigh the possible risks.204

This statement suggests that neuraxial clonidine may be beneficial in patients who are at risk for the development of neuropathic pain after cesarean delivery. The finding in one study that the combination of intrathecal clonidine (150 µg) and bupivacaine was associated with reduced wound hyperalgesia after cesarean delivery supports this hypothesis.205 Further study of the use of alpha2-adrenergic agonists in women with chronic pain is warranted.

**KEY POINTS**

- The prevalence of chronic headache, back pain, pelvic pain, and fibromyalgia is high in women of reproductive age. Thus, these syndromes commonly occur during pregnancy.
- Multimodal pain management, including medication, psychological support, and physical therapy, is key to the support of patients with chronic pain throughout pregnancy.
- Interventional pain injections may contribute to optimal control in the pregnant chronic pain patient and can be guided by ultrasonography to minimize fetal exposure to ionizing radiation.
- Knowledge of the pharmacokinetics and pharmacodynamics of medications used for management of chronic pain, as well as changes induced by pregnancy, are important to tailor management during pregnancy.
• Multidisciplinary management that includes the obstetric care providers and chronic pain physician should start as early as possible, optimally preconception.
• The prevalence of prescription opioid use during pregnancy is increasing and has significant regional variation.
• Management of patients with opioid use disorder throughout pregnancy and parturition can be challenging and requires a multispecialty team that includes an addiction specialist.
• Women who take chronic opioids during pregnancy are at risk for tolerance, and the neonate is at risk for opioid withdrawal syndrome.

REFERENCES


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DIABETES MELLITUS

Definition and Epidemiology
Diabetes mellitus (DM) is a common metabolic disorder with a prevalence of approximately 8% in the general adult population worldwide.1,2 DM results from either an absolute deficiency in insulin secretion (type 1) or a combination of resistance to insulin in target tissues and inadequate insulin secretion (type 2).3 Although a combination of genetic and environmental factors contributes to both types, type 1 DM is primarily an autoimmune disorder. Type 2 DM occurs primarily in obese individuals and accounts for 90% to 95% of cases of DM in the United States.3 Gestational DM refers to DM or glucose intolerance that is first diagnosed during pregnancy and occurs in approximately 5% to 20% of pregnancies in the United States, depending on the screening test strategies implemented.3,5

Pathophysiology
Insulin is a peptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas that binds to specific cell-surface receptors in insulin-responsive target tissues (e.g., liver, skeletal muscle, fat). The intracellular effects of insulin are mediated by tyrosine kinase in the beta-subunit of the receptor through a cascade of distal protein kinase–mediated phosphorylations.6,7 Normal hepatic glucose metabolism represents a balance between the effects of insulin and several “counterregulatory” hormones (e.g., glucagon, cortisol, epinephrine [adrenaline], growth hormone).5 This control system for glucose homeostasis permits rapid adjustments in glucose metabolism in the fed and fasted states. Insulin is also an important anabolic regulator of lipid and amino acid metabolism (Fig. 43.1). Insulin deficiency (absolute or relative) associated with DM results in abnormal metabolism of carbohydrates, lipids, and amino acids.

Acute and chronic complications occur in patients with DM (Box 43.1). The three major acute complications are diabetic ketoacidosis (DKA), hyperglycemic nonketotic state, and hypoglycemia. DKA occurs predominantly in patients with type 1 DM. It may develop with a new source of insulin resistance (e.g., infection, trauma, stress) and/or as a result of failure to administer usual insulin doses. DKA results from decreased uptake of glucose by insulin-responsive tissues and greater use of free fatty acids as a hepatic energy source. The lack of insulin favors lipolysis, beta-oxidation of free fatty acids in the liver, and hepatic formation of acetoacetate and beta-hydroxybutyrate from the excess acetyl-coenzyme A generated by fatty acid oxidation.5 These biochemical events result in metabolic acidosis, hyperglycemia, and dehydration secondary to osmotic diuresis. Signs and symptoms of DKA include nausea, vomiting, weakness, tachypnea, hypotension, tachycardia, stupor, and acetone on the breath. The diagnosis of DKA depends on the laboratory findings of hyperglycemia, ketosis, and acidosis.10
Hypoglycemia is a continuing health threat in diabetic patients, especially in patients receiving insulin therapy. Hypoglycemia results from an imbalance between insulin or oral hypoglycemic agents and available metabolic fuels. In hospitalized patients with DM, major risk factors for hypoglycemia include renal insufficiency and decreased caloric intake. Symptomatic awareness of hypoglycemia and counterregulatory responses may be inadequate in some diabetic patients with autonomic neuropathy. Problems with hypoglycemia awareness in patients receiving beta-adrenergic receptor antagonists can be minimized by using beta1-adrenergic receptor–selective antagonists. Factitious hypoglycemia results from a deliberate, inappropriate self-administration of insulin or an oral hypoglycemic agent.

In general, the rate of chronic complications increases with the duration of DM. The Diabetes Control and Complications Trial, a randomized multicenter study of patients with type 1 DM, demonstrated a positive relationship between tight glucose control and a lower incidence or rate of progression of retinopathy, nephropathy, and neuropathy. In a similar study of patients with type 2 DM—the UK Prospective Diabetes Study (UKPDS)—intensive glucose control lowered the incidence of microvascular complications but not of macrovascular complications or patient mortality. In contrast, antihypertensive therapy reduced the incidence of macrovascular complications and mortality in patients with both type 2 DM and chronic hypertension. DM may affect cardiovascular function as a result of coronary atherosclerosis, autonomic neuropathy, or development of a cardiomyopathy.

**Clinical Presentation and Diagnosis**

Box 43.2 lists the current diagnostic criteria for DM in non-pregnant patients.
Gestational DM is associated with (1) age greater than 35 years, (2) obesity, (3) family history of type 2 DM, (4) prior history of gestational DM, (5) history of polycystic ovarian syndrome, and (6) history of prior stillbirths or macrosomic babies. Several observational clinical studies, including the Hyperglycemia and Adverse Pregnancy Outcome study, have shown that adverse pregnancy outcomes are a continuous function of glucose intolerance in pregnancy. Box 43.3 lists the current recommendations of the American Diabetes Association (ADA) for screening and diagnosis of gestational DM, including one-step and two-step procedures. The choice between one-step and two-step screening strategies for gestational diabetes at 24 to 28 weeks’ gestation remains controversial. As diagnostic thresholds decrease for any disease process, the apparent prevalence in the population increases. The continuing debate over screening protocols for gestational DM centers on whether treatment of an expanded patient population is cost-effective and will improve outcomes.

Glycosylated hemoglobin measurements are used as time-integrated estimates of glycemic control, although both analytical and physiologic factors may affect this relationship. The normal range for hemoglobin A1c in nondiabetic pregnant women is 4.0% to 5.5%, compared with 4.8% to 6.5% in nondiabetic nonpregnant women.

**Interaction with Pregnancy**

**How Does Pregnancy Affect Diabetes Mellitus?**

Pregnancy is characterized by progressive peripheral resistance to insulin at the receptor and postreceptor levels in the second and third trimesters (Fig. 43.2). The presumed mechanism involves an increase in counterregulatory hormones (e.g., placental lactogen, placental growth hormone, cortisol, progesterone) during pregnancy. The change in placental lactogen is a plausible mechanism, given that (1) a graph of serum lactogen level during pregnancy is similar in shape to that of insulin requirement in pregnant women with type 1 DM and (2) placental lactogen has growth hormone–like activity. Also, maternal adipokines probably are important factors in insulin resistance of pregnancy; they facilitate the provision of maternal fuels for the fetus.

**Gestational DM** develops when a patient cannot mount a sufficient compensatory insulin response during pregnancy. In some patients, gestational DM can be viewed as a preclinical state of glucose intolerance that is not detectable before pregnancy. After delivery, most patients return to normal glucose tolerance but remain at increased risk for DM.

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**BOX 43.3 Screening and Diagnostic Strategies for Gestational Diabetes Mellitus**

A. One-step strategy

1. Perform a 75-gram oral glucose tolerance test, with plasma glucose measurements when the patient is fasting and at 1 hour and 2 hours, at 24 to 28 weeks’ gestation in women not previously diagnosed with overt DM.
2. The oral glucose tolerance test should be performed in the morning after an overnight fast of at least 8 hours.
3. The diagnosis of gestational DM is made when any of the following plasma glucose values are met or exceeded:
   - Fasting: 92 mg/dL (5.1 mmol/L)
   - 1 hour: 180 mg/dL (10.0 mmol/L)
   - 2 hours: 153 mg/dL (8.5 mmol/L)

B. Two-step strategy

1. Step 1:
   - Perform a nonfasting 50-gram oral glucose load test, with a plasma glucose measurement at 1 hour, at 24 to 28 weeks’ gestation in women not previously diagnosed with overt DM.
   - If the plasma glucose level 1 hour after the glucose load is ≥ 130 mg/dL (7.2 mmol/L), then proceed to a 100-gram oral glucose tolerance test (Step 2).
2. Step 2:
   - The 100-gram oral glucose tolerance test should be performed when the patient is fasting.
   - Four blood samples are collected: fasting, 1 hour, 2 hours, and 3 hours.
   - The diagnosis of gestational DM is made if at least two of the four plasma glucose samples exceed the following criteria (either Carpenter-Coustan or National Diabetes Data Group).

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**DM**, Diabetes mellitus.


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**Fig. 43.2** Insulin requirements in euglycemic women with type 1 diabetes mellitus during pregnancy. (From Crombach G, Siebolds M, Mies R. Insulin use in pregnancy: clinical pharmacokinetic considerations. *Clin Pharmacokinet.* 1993;24:89–100.)
(predominantly type 2) in later life. The recurrence rate for gestational DM in a subsequent pregnancy is 35% to 70%.

In patients with **pregestational DM**, insulin requirement progressively increases during pregnancy because of peripheral insulin resistance. At term, the daily insulin requirement is approximately 1.0 insulin unit/kg, compared with 0.7 unit/kg before pregnancy. Insulin requirement may be higher in pregnancies with multiple gestation. During late pregnancy in normal healthy patients, basal and glucose-stimulated plasma insulin levels are twice the postpartum measurements. These changes reflect pregnancy-related increases in pancreatic islet cell mass and glucose sensitivity, probably secondary to the net effect of competing progesterone and lactogenic hormone stimuli in the endocrine pancreas.

Near term, maternal overnight insulin requirements may decrease, presumably as a result of a “siphoning of maternal fuels” by the growing fetus during the overnight maternal fast.

Endogenous plasma insulin concentration during labor and delivery in nondiabetic parturients differs from exogenous insulin requirement in laboring diabetic women. In nondiabetic parturients, the plasma glucose concentration is only one of many factors that affect endogenous insulin secretion; glucose production and use are markedly higher during painful labor than postpartum. Plasma insulin concentration remains unchanged except for a brief increase during the third stage of labor and immediately postpartum. This finding suggests that glucose use during labor is largely independent of insulin. The pattern of plasma insulin concentrations is similar in nondiabetic patients with and without analgesia (e.g., nitrous oxide, meperidine [pethidine]).

In patients with type 1 DM, insulin requirement decreases with the onset of the first stage of labor. These patients may require no additional insulin during the first stage of labor, although insulin requirement is modified by (1) the level of metabolic control before labor, (2) the residual effect of prior doses of subcutaneous insulin, and (3) the glucose infusion rate. Insulin requirement increases during the second stage of labor via an unknown mechanism. The use of epidural analgesia or oxytocin does not affect exogenous insulin requirement during the first and second stages of labor. After delivery—either vaginal or cesarean—in insulin requirement in women with type 1 DM decreases markedly for at least several days, although there is significant variability among individuals (Fig. 43.3). Presumably, the decreased insulin requirement results from loss of counterregulatory hormones produced by the placenta. Pituitary growth hormone responsiveness to hypoglycemia is blunted in late pregnancy and may contribute to impaired counterregulatory responses during the postpartum period. Insulin requirement gradually returns to prepregnancy levels within several weeks of delivery in women with type 1 DM.

Before the discovery of insulin in 1921, pregnancies were rare in diabetic patients. Insulin therapy improved the rate of survival in women with severe DM, allowing these women to reach childbearing age and become pregnant. Maternal outcomes improved, but fetal and neonatal morbidity and mortality remained high.

In 1949, White proposed a classification system for DM during pregnancy based on 439 consecutive cases. Physicians caring for pregnant diabetic patients should be familiar with the White system, which has endured with some modifications (Table 43.1). The system emphasizes the relationship among the duration of type 1 DM, vascular complications of type 1 DM, and poor fetal outcome. In the 1950s, fetal survival rates were as follows: class A, 100%; class B, 67%; class C, 48%; class D, 32%, and class E, 3%. Diabetes. The incidence of DKA has decreased from 9% to between 0.5% and 3% of diabetic pregnancies, probably as a result of improvements in medical care and patient education. Similarly, the incidence of perinatal and maternal mortality from DKA during pregnancy has decreased in the past several decades. DKA during pregnancy occurs predominantly in patients with type 1 DM, but also in patients with type 2 DM or gestational DM. The higher risk for DKA during pregnancy reflects the metabolic adaptations of pregnancy, including peripheral insulin resistance.

During pregnancy, DKA occurs most commonly during the second and third trimesters. It is associated with (1) emesis, (2) infection, (3) poor compliance or noncompliance, (4) insulin pump failure, (5) use of beta-adrenergic receptor agonists, (6) use of corticosteroids, and (7) poor medical management. The infection rate in pregnant women with pregestational type 1 DM is 3.2 times higher than that in nondiabetic pregnant women. DKA may be the first clinical sign of type 1 DM during pregnancy. Beta-adrenergic receptor agonists, which are used to treat preterm labor, and corticosteroids, which are used to accelerate fetal lung maturity, both have counterregulatory pharmacologic effects that oppose insulin action. Beta-adrenergic receptor agonist tocolytic therapy, with or without concurrent corticosteroid therapy, and by any route of administration, can precipitate

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**Fig. 43.3** Insulin requirements in the postpartum period. (From Crombach G, Siebolds M, Mies R. Insulin use in pregnancy: clinical pharmacokinetic considerations. *Clin Pharmacokinet.* 1993;24:89–100.)
DKA during pregnancy. Beta-adrenergic receptor stimulation worsens glucose intolerance by stimulating glucagon secretion; beta-adrenergic receptor agonists may be well tolerated in pregnant women with DM if higher insulin requirements are anticipated and doses are adjusted in response to frequent blood glucose determinations.

Nonreassuring fetal heart rate patterns during episodes of maternal DKA have been described. After appropriate medical management of maternal DKA, preterm uterine contractions stopped and fetal heart rate patterns normalized. The mechanism of fetal compromise during DKA is unclear, but it may be related to changes in uterine blood flow. Blechner et al. demonstrated that uterine artery blood flow is reduced by acute maternal metabolic acidosis. A single case report demonstrated reversible redistribution of fetal blood flow during an episode of maternal DKA on the basis of Doppler pulsatility indices of the umbilical and middle cerebral arteries.

There are three case reports of HNS during pregnancy. No conclusion can be drawn about HNS and pregnancy, except that HNS rarely occurs during pregnancy.

Hypoglycemia. Hypoglycemia occurs in 33% to 71% of pregnant women with pregestational type 1 DM and is a significant health risk. This rate is 3 to 15 times higher than that in similar groups of nonpregnant patients with type 1 DM, 80% to 84% of severe hypoglycemia episodes occur before 20 weeks’ gestation. The risk for hypoglycemia during pregnancy in patients with type 1 DM increases with tight glucose control. This pattern mirrors the clinical experience in nonpregnant women with type 1 DM, in which a threefold rise in the occurrence of severe hypoglycemia results from tight insulin control. In both pregnant and nonpregnant patients with type 1 DM, counterregulatory hormone response to hypoglycemia is impaired after intensive insulin therapy. Two small series suggest that acute mild to moderate maternal hypoglycemia is not associated with acute alterations in fetal well-being in pregnant women with type 1 DM.

Other complications. The relationship between pregnancy and the development of macrovascular complications of DM is largely unknown. Patients with pregestational type 1 DM have higher systolic and diastolic blood pressure during pregnancy, and they are three times more likely than nondiabetic control subjects to have gestational hypertension. In women with pregestational type 1 DM, the risk for pre-eclampsia is increased with increased severity of diabetes (White classification), and proteinuria early in pregnancy is associated with an increased risk for adverse outcomes. Myocardial infarction is a rare complication. The effect of gestational hypertension on the progression of atherosclerotic disease in diabetic patients is unclear.

Pregnancy may accelerate the development of proliferative retinopathy, a microvascular complication of DM. Hyperglycemia and hypertension are also associated with the progression of retinopathy. In contrast to diabetic retinopathy, pregnancy does not accelerate the progression of diabetic nephropathy, provided that antihypertensive therapy is effective. It is unclear whether pregnancy accelerates the progression of somatic or autonomic neuropathy in diabetic women.

How Does Diabetes Mellitus Affect the Mother and Fetus?

Both pregestational and gestational DM are associated with higher rates of gestational hypertension, polyhydramnios, and cesarean delivery. The incidence of cesarean delivery is higher in women with pregestational DM than in women with gestational DM. Trial of labor after cesarean delivery (TOLAC) in patients with gestational DM is associated with rates of operative vaginal delivery and repeat cesarean delivery that are higher than those found in nondiabetic controls. Pregestational DM—but not gestational DM—is associated with a twofold to threefold increase in the incidence of preterm labor and delivery.

Box 43.4 lists the fetal complications of maternal DM during pregnancy. Fetal macrosomia is a well-recognized...
complication of maternal DM. Most studies suggest that both pregestational DM and gestational DM result in an increased incidence of fetal macrosomia.\textsuperscript{81–83} Depending on the definition of macrosomia (4000 g versus 4500 g), pregestational DM results in fetal macrosomia in 9% to 25% of women—a fourfold to sixfold higher rate than in nondiabetic controls.

Macrosomia results in an increased risk for shoulder dystocia and birth trauma with vaginal delivery.\textsuperscript{77,84,85} Moreover, when comparisons are made within birth weight categories above 4000 g, pregnancies in diabetic women have a higher risk for shoulder dystocia than nondiabetic women.\textsuperscript{86} The use of intensive insulin therapy may reduce the risk for birth trauma in women with pregestational DM.\textsuperscript{87} Several mechanisms have been suggested for the development of fetal macrosomia in diabetic pregnancy. Maternal hyperglycemia can result in fetal hyperglycemia, with reactive fetal hyperinsulinemia and an anabolic response in the fetus.\textsuperscript{88} Shoulder dystocia may reflect the excessive growth of the fetal trunk (relative to the fetal head) in response to fetal hyperinsulinemia.\textsuperscript{89}

Women with pregestational DM are at increased risk for fetal anomalies (see Box 43.4). The incidence of major anomalies, estimated to be 6% to 10%, is five times higher than in nondiabetic controls.\textsuperscript{77,90,91} Overall, cardiovascular anomalies are most common, followed by anomalies of the central nervous system (CNS). Caudal regression syndrome is uncommon, but it is 200 times more likely in diabetic than in nondiabetic pregnancies. The incidence of major congenital anomalies in infants of women with gestational DM is 3% to 8%, which is lower than in infants of women with pregestational DM.\textsuperscript{76}

Mechanisms that may be involved in the development of fetal structural malformations in diabetic pregnancies include embryonic apoptosis and yolk sac vasculopathy.\textsuperscript{92,93} Most fetal structural malformations that occur during diabetic pregnancies are likely to have a multifactorial etiology. However, hyperglycemia during the period of critical organogenesis before the seventh week after conception is probably the single strongest etiologic factor in diabetic women and may be associated with embryonic oxidative stress.\textsuperscript{91,92}

Studies have suggested that patient education and strict glycemic control during the preconception period may reduce the rate of major congenital anomalies from 10% to 1% in patients with pregestational DM.\textsuperscript{94} The latter figure is similar to the baseline risk for major structural malformations in the general population. Strict glycemic control initiated during the preconception period also increases the incidence of maternal hypoglycemic episodes. These studies suggest that hypoglycemia is not a significant factor in the etiology of human malformations, because the rate of anomalies decreased 10-fold despite hypoglycemic episodes.\textsuperscript{94} Similarly, strict glycemic control before conception also has been associated with a threefold decrease in the incidence of spontaneous abortion in women with pregestational DM.\textsuperscript{95} Dicker et al.\textsuperscript{96} observed normal induced ovulation, \textit{in vitro} fertilization, and early embryonic development in a small series of infertile patients with pregestational DM who attended a preconception diabetes clinic. However, only 36% of women with known pregestational DM receive appropriate medical care before conception.

During the 1950s to 1970s, the perinatal mortality rate in women with pregestational DM was 15% to 18%.\textsuperscript{76} Subsequent studies noted a decrease to 2%, a rate similar to that in nondiabetic controls.\textsuperscript{76} In contrast, one study noted a rate of 8%, three times greater than in nondiabetic controls.\textsuperscript{83} If the entire population is considered, the perinatal mortality rate likely remains higher in patients with pregestational DM than in nondiabetic controls. The rate in patients with gestational DM is intermediate between the rate in women with pregestational diabetes and the rate in nondiabetic controls.\textsuperscript{76,83}

Historically, \textit{intrauterine fetal death} was responsible for approximately 40% of the perinatal deaths in women with DM; 68% of the stillbirths occurred between 36 and 40 weeks’ gestation.\textsuperscript{45,81} In contemporary reports, the ratio of intrauterine deaths to neonatal deaths in diabetic pregnancies has varied from 0 to 1.0. Fetal macrosomia is a risk factor for intrauterine fetal demise in both diabetic and nondiabetic pregnancies. Recurrent episodes of intrauterine hypoxia can occur in diabetic pregnancies that end in stillbirth; episodes of hypoxia may reflect reduced uteroplacental blood flow and changes in fetal carbohydrate metabolism. \textit{Congenital anomalies} have now emerged as the leading cause of perinatal mortality in diabetic pregnancies.\textsuperscript{80} This change likely reflects better obstetric care during pregnancy, despite the lack of adequate glycemic control before conception.

\section*{BOX 43.4 Fetal Complications of Maternal Diabetes Mellitus}

\textbf{During Pregnancy and the Puerperium}

\textbf{Chronic}
\begin{itemize}
  \item Macrosomia
  \item Shoulder dystocia
  \item Birth injury or trauma
  \item Structural malformations
  \item Central nervous system: anencephaly, encephalocele, meningomyelocele, spina bifida, holoprosencephaly
  \item Cardiac: transposition of great vessels, ventricular septal defect, situs inversus, single ventricle, hypoplastic left ventricle
  \item Skeletal: caudal regression
  \item Renal: agenesis, multicystic dysplasia
  \item Gastrointestinal: anal or rectal atresia, small left colon
  \item Pulmonary: hypoplasia
\end{itemize}

\textbf{Acute}
\begin{itemize}
  \item Intrauterine or neonatal death
  \item Neonatal respiratory distress syndrome
  \item Neonatal hypoglycemia
  \item Neonatal hyperbilirubinemia
\end{itemize}

\textbf{After Pregnancy}
\begin{itemize}
  \item Glucose intolerance
  \item Possible impairment of cognitive development
\end{itemize}
Two series that involved women who delivered between 1950 and 1979 demonstrated an incidence of neonatal respiratory distress syndrome (RDS) in diabetic pregnancies that was 6 to 23 times that in nondiabetic controls.77,97 Respiratory distress is more common among newborns who are delivered preterm or who are surgically delivered without labor. Later studies of patients with both pregestational and gestational DM have not demonstrated a significant difference in the incidence of neonatal RDS between diabetic and nondiabetic pregnancies.76,96,99

The level of glycemic control during pregnancy affects the amniotic fluid phospholipid profile. In pregnancies of patients with poorly controlled diabetes, there may be a higher incidence of immature amniotic fluid fetal lung profiles at 34 to 38 weeks’ gestation.99–101

Neonatal hypoglycemia occurs in 5% to 12% of cases of pregestational and gestational DM.76 This represents a 6-fold to 16-fold higher risk for neonatal hypoglycemia than in nondiabetic controls. Neonatal hypoglycemia likely results from sustained fetal hyperinsulinemia in response to chronic intrauterine hyperglycemia. Clinical studies have demonstrated higher fetal insulin levels and exaggerated fetal insulin responses to acute maternal hyperglycemia in diabetic pregnancies.102,103 An acute increase in maternal glucose concentration, as might occur if a dextrose-containing solution is used for intravenous hydration during administration of neuraxial anesthesia, can lead to reactive neonatal hypoglycemia, even in nondiabetic women.104

There is a twofold to fivefold higher incidence of neonatal hyperbilirubinemia in women with pregestational and gestational DM than in nondiabetic controls.76 Other associated factors include the severity of gestational DM and excess maternal weight gain during pregnancy.105,106 Both the etiology and the clinical significance of neonatal hyperbilirubinemia are unknown, although one study noted the absence of long-term morbidity.76

Children of diabetic mothers are at increased risk for development of DM, likely from a combination of genetic and intrauterine environmental factors. Despite the well-known association of type 1 DM with human leukocyte antigen markers, studies of monozygotic human twins have suggested that genetic factors have a greater role in type 2 DM than in type 1 DM (100% versus 20% to 50% concordance, respectively).105 In addition, fathers with type 1 DM are five times more likely than mothers with the same disease to have a child with type 1 DM. The intrauterine environment also affects the development of glucose intolerance in offspring.31

Some investigators have suggested that cognitive development may be impaired in the children of diabetic mothers,107 but this issue remains controversial.

Obstetric Management

Glycemic Control

Early, strict glycemic control is the best way to prevent fetal structural malformations in women with pregestational DM.96,94 Determination of hemoglobin A1c concentrations may help the physician determine the adequacy of preconceptional glycemic control.

During pregnancy, the patient should frequently determine capillary blood glucose concentration using a reflectance meter. However, the ideal frequency of these measurements remains under investigation.108 Continuous glucose monitoring systems (e.g., transdermal, subcutaneous) have been used safely in pregnancy and enable remote monitoring.109 Glucose determinations guide adjustments in diet and insulin therapy. In general, insulin requirement increases progressively during the second and third trimesters. Both maternal and perinatal outcomes seem to improve when maternal glycemic control approaches that observed in normal pregnancies. Table 43.2 illustrates glycemic targets recommended by the American Diabetes Association for pregnant patients with either pregestational or gestational DM.4 Of course, strict glycemic control increases the risk for maternal hypoglycemia.

Therapeutic insulin is available in several forms. Initially, insulin was isolated as a natural product from domestic animals (e.g., cattle, pigs). In the past 30 years, synthetic human insulin has become commercially available and has largely replaced beef and pork insulin in human medicine.

The goal of insulin therapy is to provide plasma insulin concentrations that lead to tight glucose control without hypoglycemia. This goal is facilitated by the availability of several insulin preparations with different subcutaneous absorption rates (Table 43.3).110–112 Regular insulin can be administered by the intravenous or subcutaneous route. Regular insulin administered intravenously has a half-life of approximately 4 minutes.110 Administering a rapid-acting insulin by the subcutaneous route using a continuous programmable pump is an alternative to intermittent manual injections.113 It remains controversial whether the use of continuous subcutaneous insulin pumps will improve pregnancy outcomes in diabetic pregnancies.114,115

Human insulin therapy has fundamentally changed in recent years through the development of insulin analogs.110,111,116 These molecules have specific chemical substitutions in portions of the human insulin protein not involved

<table>
<thead>
<tr>
<th>TABLE 43.2 American Diabetes Association: Glycemic Targets in Pregnancy for Women with Diabetes Mellitus</th>
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<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
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<tr>
<td>One-hour postprandial plasma glucose</td>
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DM, Diabetes mellitus.

in receptor binding. Both short-acting and long-acting insulin analogues are in clinical use. Lispro, aspart, and glulisine are rapid-acting analogues, with a more physiologic onset and offset than regular insulin. Glargine, detemir, and degludec are long-acting insulin analogues with a sustained plateau of activity instead of a peak. Lispro, aspart, glargine and detemir have all been used safely during human pregnancy.

Because insulin requirement decreases abruptly at delivery, it is important to verify the times, doses, insulin preparations, and routes of administration in the 24 hours before delivery to avoid maternal postpartum hypoglycemia.

Management of DKA is similar in pregnant and nonpregnant women. It involves (1) intravenous hydration, (2) intravenous insulin, (3) treatment of the underlying cause of DKA, (4) careful monitoring of blood glucose and electrolyte levels, and (5) restriction of bicarbonate therapy to cases of extreme acidosis. In addition, left uterine displacement should be maintained, and supplemental oxygen should be administered. Initial management of the critically ill pregnant woman should focus on the effective management of DKA. Fetal compromise is likely to resolve with appropriate medical management.

Diet and exercise are the initial therapeutic approaches for glycemic control in women with gestational DM. Pharmacologic therapy with oral hypoglycemic agents and/or insulin is initiated if the lifestyle changes are not clinically effective. In current practice, many women with gestational DM are treated with metformin or the sulfonylureas glipizide or glibenclamide (glyburide). In the past, oral hypoglycemic agents were used sparingly during pregnancy because of concerns for fetal effects. These medications are in common use, although the concerns continue to be investigated. Concerns about the long-term health implications of gestational diabetes have resulted in national and international initiatives for postpartum metabolic surveillance. The goal is to identify and treat postpartum type 2 DM, with an emphasis on lifestyle interventions.

**Timing of Delivery**

Timing of delivery is important in the management of diabetic pregnancies. White noted, “Our problem must [be] … to prevent premature delivery of the infant of the diabetic mother prior to the period of its viability … and, secondly, the termination of the pregnancy at the point of viability and before the dreaded late intrauterine accident can occur.” Typically a nonstress test is performed twice weekly in patients with pregestational DM, beginning at 32 weeks’ gestation. A nonreactive nonstress test should prompt the performance of a fetal biophysical profile (see Chapter 6). Risk factors for abnormal fetal testing in diabetic pregnancies include maternal nephropathy, hypertension, and poor glycemic control. Patients with poorly controlled gestational DM should probably undergo antepartum fetal surveillance similar to that in patients with pregestational DM.

In the presence of reassuring fetal testing, delivery can be delayed until after 38 weeks’ gestation. If fetal testing is abnormal and amniotic fluid analysis indicates fetal pulmonary maturity, the fetus should be delivered as soon as possible. If fetal testing is abnormal but amniotic fluid analysis suggests that the fetal lungs are immature, decisions about the timing of delivery are more difficult.

The decision regarding the method of delivery requires consideration of estimated fetal weight, fetal condition, cervical dilation and effacement, and previous obstetric history. The obstetrician may choose elective cesarean delivery in the diabetic parturient with evidence of fetal macrosomia to decrease the risk for shoulder dystocia.

**Anesthetic Management**

There are few studies of the anesthetic management of pregnant women with DM. In general, neuraxial analgesia is the preferred technique for labor and cesarean delivery, but clinical decisions about these patients must be guided by logical extensions of studies of nonpregnant diabetic patients and nondiabetic pregnant patients.

Preanesthetic evaluation of the woman with DM should include a history and physical examination that focuses on the identification of the acute and chronic complications of DM (see Box 43.1). There are no published data on the relationship between the complications of DM and responses to anesthetic agents or on anesthetic outcomes in pregnant patients. In a study of nonpregnant diabetic patients, preoperative evidence of autonomic cardiovascular dysfunction was predictive of the need for a vasopressor during general anesthesia. Because of the potential for hypotension during neuraxial anesthesia, noninvasive testing of autonomic
function may be useful in obstetric patients with pregestational DM. For example, in nonpregnant diabetic patients, the corrected QT interval on an electrocardiogram correlates with the severity of autonomic neuropathy. Patients with evidence of autonomic dysfunction may benefit from more frequent blood pressure determinations and more vigorous intravenous hydration before and during the administration of neuraxial anesthesia. Gastroparesis is a manifestation of autonomic neuropathy in diabetic patients. In pregnant diabetic patients, autonomic neuropathy is associated with a decreased cough reflex threshold and a higher incidence of obstructive sleep apnea. Theoretical concerns have been expressed about local anesthetic toxicity in patients with diabetic polyneuropathy undergoing neuraxial or peripheral nerve blocks since diabetic nerves may be more susceptible to injury, but practically, neuraxial anesthesia is still the anesthetic of choice for the diabetic.

Several studies have examined the maternal, fetal, and neonatal effects of neuraxial anesthesia for cesarean delivery for women with pregestational DM. Datta and Brown observed that spinal anesthesia was associated with a slightly but significantly lower umbilical cord blood pH measurement at delivery in patients with pregestational DM than in similar patients who received general anesthesia for cesarean delivery. Subsequently, these investigators noted an association between fetal acidosis and peripartum maternal hypotension in patients with pregestational DM who received epidural anesthesia for cesarean delivery. In both studies, acute maternal hyperglycemia—secondary to intravenous hydration with 5% dextrose before administration of neuraxial anesthesia—was a potentially confounding factor.

Neonatal acidosis is not likely to occur during spinal or epidural anesthesia for cesarean delivery in diabetic parturients, provided that (1) maternal glycemic control is satisfactory, (2) the patient receives aggressive preanesthetic volume expansion with a non–dextrose-containing balanced salt solution, and (3) hypotension is treated promptly and aggressively.

Thalme and Engstrom demonstrated normal umbilical arterial blood pH measurements after the administration of general anesthesia in a small series of patients with pregestational DM.

After administration of epidural anesthesia for cesarean delivery, Ramanathan et al. observed an increased incidence of neonatal hypoglycemia in patients with pregestational DM compared with nondiabetic controls (35% versus 7%, respectively). In this study, maternal glycemic control was fair (mean fasting plasma glucose level was 127 mg/dL [7.1 mmol/L]), a non–dextrose-containing solution was used for intravenous hydration, and intravenous insulin therapy was adjusted on the basis of frequent blood glucose determinations. This study illustrates the neonate’s vulnerability to hypoglycemia after a diabetic pregnancy despite meticulous anesthesia care at the time of delivery.

A single case report describes a parturient who received combined spinal–epidural labor analgesia and subsequently became hypoglycemic. The authors hypothesized that the rapid decrease in catecholamine levels from the resultant analgesia led to hypoglycemia. In a retrospective study, epidural labor analgesia lowered cord blood glucose and improved the acid-base status in newborns after term vaginal delivery in mothers with well-controlled gestational diabetes. Maternal insulin requirements decrease with the onset of labor, increase again during the second stage of labor, and decrease markedly during the early postpartum period. Intravenous insulin therapy is the most flexible method of treatment during this period of rapid change. Absorption of subcutaneous insulin may be unpredictable and may increase the risk for maternal hypoglycemia, especially during the postpartum period. Moreover, strict glycemic control in pregnant women with type 1 DM increases the risk for maternal hypoglycemia as a result of impaired counterregulatory hormone responses (as discussed earlier).

Intravenous glucose and insulin infusions during the peripartum period should be titrated to maintain a maternal blood glucose concentration of 70 to 90 mg/dL (3.9 to 5 mmol/L). During active labor, the glucose requirement is 2.5 mg/kg/min or more. For cesarean delivery in patients using a subcutaneous insulin pump, a preoperative strategy should be formulated for perioperative insulin pump management. This plan should identify the individual(s), other than the patient, who are experienced and knowledgeable in adjusting her insulin pump if the patient is not able to adjust it herself during surgery. Some patients and obstetricians prefer discontinuing the subcutaneous insulin pump preoperatively in favor of an intravenous insulin infusion. The preanesthetic evaluation is an excellent opportunity to discuss with the patient the expected changes in insulin requirement at the time of delivery. The preprocedure and postprocedure “time-outs” are excellent opportunities to discuss the plan for perioperative pump management and other diabetic management concerns with all team members.

Many perioperative strategies have been proposed for metabolic control in nonpregnant patients with DM. No convincing evidence suggests that one clinical strategy for perioperative diabetic control is superior in terms of patient outcome. Frequent blood glucose measurements (e.g., at 30- to 60-minute intervals), followed by appropriate adjustment of glucose and insulin infusions, represent the cornerstone of optimal perioperative care in patients with DM.

There are no published data on the effects of DM on the pharmacokinetics and pharmacodynamics of anesthetic agents in pregnant women. In nonpregnant patients, DM may be associated with challenging neuromuscular monitoring because of diabetic polyneuropathy or alterations at the neuromuscular junction.

The diabetic stiff-joint syndrome has been associated with difficult direct laryngoscopy and tracheal intubation in patients with DM. This syndrome occurs in patients with long-standing DM type 1 and is associated with nonfamilial short stature, joint contractures, and tight skin. Limited movement of the atlanto-occipital joint may result in difficult direct laryngoscopy and tracheal intubation. During the preanesthesia evaluation of patients with DM, the anesthesia
THYROID DISORDERS

Thyroid Hormone Physiology

The follicular cells of the thyroid gland sequester iodine and synthesize thyroglobulin, an iodinated precursor protein. Thyroglobulin is secreted into the lumen of the microscopic thyroid follicles before it undergoes reuptake, proteolysis, and transfer to lysosomes, where it undergoes degradation. This process results in the systemic release of the thyroid hormones: thyroxine (T₄) and 3,5,3′-triiodothyronine (T₃). Reverse T₃ (3,3′,5′-triiodothyronine) is a structural variant with much less physiologic potency in most target organs.

Thyroid hormone synthesis and release are controlled primarily by thyroid-stimulating hormone (TSH)—a trophic hormone from the pituitary gland—and the supply of iodine. The thyroid hormones normally participate in a negative feedback loop that regulates TSH secretion and thyrotropin-releasing hormone production in the hypothalamus.

Thyroid hormones are highly bound to protein in the blood. In euthyroid nonpregnant humans, the normal total serum concentrations of T₄ and T₃ are 50 to 150 nmol/L and...
1.4 to 3.2 nmol/L, respectively. The unbound or free fractions of \( T_4 \) and \( T_3 \) are 0.03% and 0.3% of total circulating \( T_4 \) and \( T_3 \), respectively. Similar proportions of \( T_4 \) and \( T_3 \) are distributed among the three major plasma proteins that bind thyroid hormones, which are (1) thyroxine-binding globulin (70% to 80%), (2) thyroxine-binding prealbumin or transthyretin (10% to 20%), and (3) albumin (10% to 15%). The serum concentration of unbound or free \( T_4 \) is typically the major determinant of thyroid hormone activity in target tissues. Thyroid hormones are temporarily inert while bound to plasma proteins. Changes in the concentrations of thyroxine-binding proteins can occur during various physiologic states (e.g., pregnancy) and disease processes. Thyroid hormone action does not change with fluctuations in the total concentration of \( T_4 \) as long as the concentration of free \( T_4 \) remains constant.

Thyroid hormone is an endocrine regulator in many target organs (e.g., liver, kidneys, skeletal and cardiac muscles, brain, pituitary gland, placenta). The defined physiologic effects of thyroid hormones are mediated by regulation of specific gene products. These effects include (1) somatic and nervous system development, (2) calcitriogenesis, (3) augmented skeletal and cardiac muscle performance, (4) intermediary metabolism, and (5) feedback control. In target tissues, the molecular actions of \( T_4 \) begin with the enzymatic deiodination of \( T_4 \) to \( T_3 \). Iodothyronine deiodinase is widely distributed in the body and occurs in three molecular forms. Only 20% of the daily \( T_3 \) production is secreted by the thyroid gland; the rest is formed by peripheral deiodination. In the classic model of thyroid hormone action, \( T_3 \) enters the nuclei of target cells, binds to specific thyroid hormone receptors, and alters genomic transcription of specific proteins. Research has now characterized other mechanisms of action for thyroid hormones and their metabolites, including mitochondrial transcription and cytoplasmic or cell-surface nontranscriptional effects. The thyroid hormone receptor belongs to a family of structurally related, intracellular ligand-binding proteins. Variations in the number and types of thyroid hormone receptors, as well as receptor linkage to development- or tissue-specific genomic expressions, provide additional levels of physiologic control and vulnerability to disease processes.

Antithyroid medications may affect single or multiple steps in thyroid hormone synthesis and release, as well as concentrations of plasma-binding proteins, deiodinase activity, and peripheral uptake of thyroid hormones.

**Laboratory evaluation of thyroid function** consists of two measurements. First, the serum concentration of free \( T_4 \) can be directly measured or indirectly calculated. Second, the serum concentration of TSH is measured to assess the negative feedback loop that controls the thyroid gland. The TSH concentration is judged as appropriate or inappropriate in the context of the serum concentration of free \( T_4 \).

During normal human pregnancy, the serum concentration of thyroxine-binding globulin (TBG) steadily increases until it reaches a plateau at 20 weeks’ gestation, when it is 50% greater than the nonpregnant level. The greater concentration of TBG results from a prolonged half-life—not higher synthesis—during pregnancy. The normal pregnant woman is euthyroid because the serum concentrations of free \( T_4 \) and \( T_3 \) are in the normal or low-normal range for nonpregnant humans. However, the increased concentration of TBG means that total serum concentrations of \( T_4 \) and \( T_3 \) during pregnancy are at or above the upper limit of normal for nonpregnant women.

Human chorionic gonadotropin (hCG) is a placental protein that shares some structural features with TSH. The serum concentrations of TSH and hCG have an inverse relationship during normal human pregnancy, reflecting the mild TSH-like activity that results from increased plasma concentrations of hCG during early pregnancy.

Maternal iodine availability is decreased during pregnancy because of greater fetal uptake and increased maternal renal clearance. In geographic areas with marginal iodine supplies, the lower availability may predispose the mother to goiter unless she receives dietary iodine supplementation.

**Hyperthyroidism**

**Definition and Epidemiology**

Hyperthyroidism is defined as an abnormal increase in the serum concentration of unbound or free thyroid hormones. The prevalence of hyperthyroidism in the general population is 0.2% to 1.9%, with a female-to-male ratio of 10:1. The etiology of hyperthyroidism is shown in Box 43.5. Graves’ disease is responsible for 70% to 90% of cases; thyroiditis and the combined category of toxic adenoma and toxic multinodular goiter each account for approximately 5% of cases. There are multiple levels of interaction between the thyroid and reproductive endocrine systems in women, with specific implications for patients with hyperthyroidism and hypothyroidism.

**Pathophysiology**

Graves’ disease is an autoimmune thyroid disease. Its etiology is likely multifactorial and includes both...
environmental (e.g., stress, hormones) and genetic influences. Several autoantibodies against thyroid tissue have been described in patients with this disease. Autoantibodies known as thyroid receptor antibodies (TRAbs) directed against the TSH receptor in the thyroid gland may either augment or inhibit TSH action, depending on their binding specificities. The binding specificities of TRAbs in the blood of each patient with Graves’ disease affect the net thyroid-stimulating activity. Autoantibodies against thyroid peroxidase, the sodium-iodine cotransporter, and thyroglobulin also have been described in patients with Graves’ disease.

Clinical Presentation and Diagnosis

Hyperthyroidism presents as a physiologic state dominated by an increased metabolic rate. A hyperthyroid symptom scale has been developed on the basis of the following 10 clinical factors: nervousness, sweating, heat intolerance, hyperactivity, tremor, weakness, hyperdynamic precordium, diarrhea, appetite, and level of incapacitation.174 This symptom scale has been useful to follow the clinical course of patients with Graves’ disease. Exophthalmos or infiltrative ophthalmopathy is clinically apparent in most patients.174 Other physical signs may occur at low frequency, including pretibial myxedema or dermopathy (1% to 2%) and nail changes or acropachy (< 1%). The infiltrative ophthalmopathy in Graves’ disease is caused by enlargement of both the extraocular muscle bodies and intraorbital adipose tissue. The pathogenetic mechanism involves abnormal accumulation of hyaluronic acid and edema within these tissues; the orbital fibroblast appears to be the primary target cell of this autoimmune process.173

Hyperthyroidism stimulates the cardiovascular system in excess of the underlying increased metabolic rate, resulting in a hyperkinetic circulatory state.163,176 Myocardial contractility, heart rate, stroke volume, and ventricular size all increase, and peripheral vascular resistance decreases in skin and muscle. Thyroid hormones can affect the ratio of alpha- and beta-adrenergic receptors in the heart.176 Cardiomyopathy can be demonstrated during exercise in hyperthyroid patients, independent of beta-adrenergic receptors; it is reversible with normalization of thyroid function.177

The diagnosis of hyperthyroidism depends on increased serum concentrations of unbound or free T4. The more common forms of hyperthyroidism (e.g., Graves’ disease, toxic adenoma, toxic multinodular goiter) may be differentiated from the less common forms by a radiiodine uptake study. The identification of TSH receptor autoantibodies may have some role in distinguishing Graves’ disease from toxic adenoma or multinodular goiter.173

Interaction with Pregnancy

Normal human pregnancy is a euthyroid state, with normal serum concentrations of unbound or free T4 despite increased serum concentrations of TBG and total T4. During pregnancy, hyperthyroidism results from the same causes as in nonpregnant patients (see Box 43.5). Graves’ disease is the leading cause of hyperthyroidism during pregnancy, with a prevalence of 0.2%, which is lower than in the general population.178-180 The lower prevalence may reflect a beneficial effect of the immunotolerance of pregnancy on autoimmune disorders such as Graves’ disease.173 Human pregnancy is also associated with a change in the specificity of TSH receptor antibody activity from stimulatory to blocking activity.182

Gestational trophoblastic neoplasms are frequently associated with elevated serum hCG concentrations. High concentrations of hCG may possess significant thyroid-stimulating bioactivity because of the structural homology between hCG and TSH.165,182 Transient hyperthyroidism during pregnancy has been reported in association with hyperemesis gravidarum; hyperthyroidism and hyperemesis gravidarum may be parallel disease processes in pregnancy, with elevated hCG as a shared mechanism.183 Hyperthyroidism can, on rare occasions, result from two coincident disease processes (e.g., Graves’ disease, struma ovarii) in both pregnant and non-pregnant women.184

Thyroid nodules occur in 4% to 7% of adults. Pregnancy is associated with increases in the number and size of thyroid nodules.185 Pregnancy probably does not affect the development or recurrence of thyroid carcinoma, but may enhance the progression of active disease.186,187 Evaluation of a thyroid nodule that presents during pregnancy should include (1) measurement of serum TSH and free T4 concentrations, (2) ultrasonographic examination to determine whether the lesion is cystic or solid, and (3) fine-needle aspiration or percutaneous needle biopsy. Malignant lesions, depending on the level of cellular differentiation, can be resected in the second trimester or observed until after delivery.187 Radioactive iodine therapy should be delayed until the postpartum period.186

Medical and Surgical Management

Current therapies for Graves’ disease in nonpregnant patients include radioactive iodine, antithyroid medications, and surgery.170,175,188

Radioactive iodine is administered orally as iodine-131 (131I) in a dose range of 30 to 75 mCi.189 All forms of iodine are sequestered by the thyroid gland, and 131I exerts a therapeutic effect in Graves’ disease primarily through local emission of beta radiation. In most patients with Graves’ disease, hyperthyroidism develops after a therapeutic dose of radioactive iodine, necessitating careful follow-up and long-term thyroid hormone replacement therapy. In nonpregnant patients, the long-term health risks of radioactive iodine therapy are minimal.189 Radioactive iodine therapy is contraindicated in pregnancy, because all forms of iodine readily cross the placenta to the fetus. Currently recommended treatment is to delay pregnancy for 6 months to 1 year after radioactive iodine therapy,186 although 131I has a half-life of only 8 days.

Propylthiouracil and methimazole are the antithyroid medications used to treat Graves’ disease.175,188,190 These drugs interfere with the incorporation of iodine into thyroglobulin and with subsequent coupling reactions in the thyroid gland, and propylthiouracil inhibits iodothionine deiodinase in
periodic tissues. Typical oral doses are 5 to 15 mg two times daily for methimazole and 100 to 150 mg three times daily for propylthiouracil. The long-term clinical strategy is to adjust the dose downward as tolerated. Some patients with Graves' disease experience remission after the administration of an antithyroid medication. Asymptomatic agranulocytosis, with an incidence of 0.03% to 0.5%, is a rare complication of antithyroid medications; onset typically occurs within 3 months of initiating therapy. Another rare complication of propylthiouracil, fulminant hepatic necrosis, prompted an FDA safety alert in 2009.\(^{188}\) If treatment with antithyroid medications is unsatisfactory, nonpregnant patients may receive radioactive iodine.

**Surgical therapy** for Graves’ disease is typically reserved for patients unable or unwilling to undergo treatment with radioactive iodine or antithyroid medications.\(^{188,191}\) Controversy exists about the choice between subtotal and total thyroidectomy; the surgeon must weigh the risk for recurrent hyperthyroidism against that of permanent hypothyroidism requiring supplementation.\(^{191}\) Perioperative complications of thyroid surgery include (1) unilateral or bilateral vocal cord paralysis secondary to laryngeal nerve injury, (2) wound hematoma, (3) pneumothorax, (4) hypoparathyroidism, and (5) thyroid storm.\(^{194}\) Hypocalcemia secondary to acute hypoparathyroidism may manifest as laryngospasm during the postoperative period.\(^{192}\)

Adjunctive therapies for hyperthyroidism include iodine, radiocontrast agents, lithium, and glucocorticoids.\(^{163,170}\) Beta-adrenergic receptor antagonists also have been used to decrease cardiovascular responses to higher concentrations of thyroid hormones.

**Thyroid storm.** Thyroid storm, also known as thyroid crisis, is a life-threatening exacerbation or decompensation of a preexisting hyperthyroid state.\(^{193–196}\) It is a clinical diagnosis based on the following signs and symptoms: (1) fever, (2) mental and emotional disturbances, (3) tachycardia, (4) tachypnea, (5) diarrhea, (6) congestive heart failure, and (7) atrial fibrillation. Without treatment, thyroid storm may progress to coma, multiorgan system failure, and death. The mortality rate approached 100% in earlier series, but improved therapy has reduced the mortality rate to less than 20%.\(^{195}\)

In most cases, thyroid storm is associated with a precipitating event in a patient with untreated or incompletely treated hyperthyroidism (Box 43.6). Historically, the precipitating events reflect the common serious medical illnesses of a given era\(^{193–196}\); cases of thyroid storm were categorized as “surgical” or “medical” depending on whether the exacerbation occurred during the perioperative period. With improved perioperative management, the incidence of surgical thyroid storm has decreased markedly, and this terminology is rarely used in contemporary medical practice.

In the past, 2% to 7% of patients hospitalized for hyperthyroidism experienced thyroid storm.\(^{193,194,196}\) The current incidence of thyroid storm in hyperthyroid patients is difficult to determine but appears to be much lower. Akamizu et al.\(^{197}\) estimated that the incidence of thyroid storm in Japan was 0.2 per 100,000 hospitalized patients between 2004 and 2008.

The mechanism of the development of thyroid storm is unknown. On the basis of the clinical presentation and known precipitating events, one hypothesis is that it is caused by increases in thyroid hormone and catecholamine secretion. Limited data suggest that total serum concentrations of T\(_4\) and T\(_3\) do not increase during thyroid storm in hyperthyroid patients,\(^{198}\) although one case report suggests otherwise.\(^{199}\) Alternatively, the precipitating event in thyroid storm may augment thyroid hormone action by increasing the circulating free fraction of thyroid hormones. This hypothesis is supported by data that demonstrate higher serum concentrations of free T\(_4\) during thyroid storm as well as by observations of changes in thyroid hormone binding during fever or systemic illness.\(^{200}\)

Catecholamine secretion may also play a role in the development of thyroid storm. In hyperthyroid patients without thyroid storm, the endogenous secretion of epinephrine and norepinephrine is normal, as are the cardiovascular responses to exogenous epinephrine and isoproterenol.\(^{201,202}\) These parameters have not been measured during episodes of thyroid storm, but symptoms respond well to medications that block the synthesis or receptor binding of beta-adrenergic receptor agonists.\(^{194}\) The role of the sympathetic nervous system in thyroid storm is supported by historical observations that spinal anesthesia to the fourth thoracic dermatome level is therapeutic.\(^{203}\) It is unclear whether thyroid storm can develop with baseline catecholamine secretions; a surge of catecholamines may be necessary to trigger this condition.

**Box 43.6** outlines the treatment of thyroid storm. Several points merit discussion. Glucocorticoid supplementation is listed as a general supportive measure because endogenous glucocorticoid production is impaired in patients with hyperthyroidism.\(^{204}\) Glucocorticoids also inhibit both thyroid hormone production and the peripheral conversion of T\(_4\) to T\(_3\).\(^{171}\) Propylthiouracil and methimazole reduce thyroid hormone production, but only propylthiouracil inhibits the

<table>
<thead>
<tr>
<th>BOX 43.6 Events Associated with Precipitation of Thyroid Storm</th>
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<tbody>
<tr>
<td>- Surgery</td>
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<td>- Childbirth</td>
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<td>- Trauma</td>
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<td>- Iodinated contrast agents</td>
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<td>- Treatment with iodine-131</td>
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<tr>
<td>- Emotional stress</td>
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<td>- Pulmonary embolism</td>
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<td>- Stroke</td>
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<td>- Infection</td>
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<tr>
<td>- Diabetic ketoacidosis</td>
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<tr>
<td>- Hypoglycemia</td>
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<tr>
<td>- Congestive heart failure</td>
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<tr>
<td>- Bowel infarction</td>
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</table>

intraoperative hypermetabolic crisis that was initially diagnosed and treated as thyroid storm. The correct diagnosis of thyroid storm is an acute hypermetabolic state that precipitated the thyroid storm.

Diagnosis and Treatment of the Underlying Illness That Precipitated the Thyroid Storm

Thyroid storm is an acute hypermetabolic state that may be difficult to distinguish clinically from malignant hyperthermia; rhabdomyolysis is one of the few features of the latter disorder that has not also been reported in thyroid storm. Three cases of thyroid storm treated with dantrolene have been reported. Two patients survived, but the third succumbed to multiorgan system failure that antedated the dantrolene therapy. In another case, a patient with known Graves’ disease undergoing subtotal thyroidectomy had an intraoperative hypermetabolic crisis that was initially diagnosed and treated as thyroid storm. The correct diagnosis of thyroid storm was made on the basis of subsequent blood gas analysis, and the patient was successfully treated with dantrolene.

Treatment of Thyroid Storm

General Supportive Measures

- Cooling blanket and ice
- Chlorpromazine (25–50 mg IV) or meperidine (pethidine) (25–50 mg IV) to diminish shivering
- Intravenous hydration
- Glucose and electrolyte replacement
- Acetaminophen (paracetamol)
- Oxygen
- Glucocorticoids: dexamethasone (2–4 mg IV q8h) or hydrocortisone (100 mg IV q8h)
- B-complex multivitamins

Reduction of Synthesis and Secretion of Thyroid Hormones

- Antithyroid medications: propylthiouracil (200–400 mg orally q6–8h) or methimazole (20–25 mg orally q8h)
- Iodine: sodium iodide (1 g IV or Lugol’s solution 4–8 drops orally q6–8h) or supersaturated potassium iodide solution (5 drops orally q6h)
- Glucocorticoids

Reduction of Peripheral Conversion of Thyroxine (T4) to 3,5,3'-Triiodothyronine (T3)

- Propylthiouracil
- Glucocorticoids
- Radiographic contrast agents
- Propranolol

Decrease in the Metabolic Effects of Thyroid Hormones

- Beta-adrenergic receptor antagonists (propranolol, esmolol)

Other Therapeutic Maneuvers

- Plasma exchange

Preoperative preparation

The risk for thyroid storm during the perioperative period can be minimized by appropriate preoperative preparation of the hyperthyroid patient. Most cases of perioperative thyroid storm involve thyroid surgery. The preoperative therapeutic goals are to inhibit thyroid hormone synthesis and secretion in patients with preexisting hyperthyroidism and to decrease the vascularity of the thyroid gland. The four main therapies used in preoperative preparation are administration of (1) an antithyroid medication (primarily propylthiouracil), (2) a beta-adrenergic receptor antagonist, (3) a glucocorticoid, and (4) iodine. Iodine inhibits thyroid hormone secretion more effectively in hyperthyroid patients than in euthyroid patients because the latter are capable of mounting a compensatory TSH response as serum T4 levels decrease.

In some patients, beta-adrenergic receptor blockade may be sufficient to prevent perioperative thyroid storm, although thyroid storm has been reported after preoperative preparation with propranolol alone. In some of these cases, patients probably did not receive effective beta-adrenergic receptor blockade. A 25% reduction in exercise-induced heart rate is a better indication of adequate beta-adrenergic receptor blockade than a change in the resting heart rate. One advantage of beta-adrenergic receptor antagonists over antithyroid medications is the shorter time typically required for preoperative preparation (2 weeks versus 6 to 8 weeks, respectively). Several investigators have recommended preoperative preparation with a beta-adrenergic receptor antagonist, with the addition of iodine beginning 10 days before surgery. The use of beta-adrenergic receptor antagonists entails a risk for hypoglycemia in hyperthyroid patients, because they have reduced hepatic glucose reserves and nonspecific beta-adrenergic receptor blockade results in a pharmacologic blunting of counterregulatory sympathetic responses.

No prospective randomized studies have compared the efficacy of various methods for preoperative preparation of hyperthyroid patients. A reasonable clinical approach would include the use of multiple therapeutic agents (e.g., a beta-adrenergic receptor antagonist, iodine, glucocorticoid), with the doses titrated to the clinical response of each patient. The clinical parameters may include exercise-induced heart rate, fine tremor, weight gain, and recovery of muscle strength.

Elective surgery should not proceed without adequate preoperative preparation of hyperthyroid patients. In cases of emergency surgery, physicians should use the therapies discussed for the treatment of thyroid storm (as discussed earlier) (see Box 43.7).
Medical and surgical management during pregnancy.

All of the therapeutic options used in nonpregnant hyperthyroid patients should be efficacious in pregnant women. However, the potential effects on the fetus dictate modifications in the options for treatment of hyperthyroidism during pregnancy.

Radioactive iodine is contraindicated during pregnancy because iodine readily crosses the placenta to the fetus. Fetal effects of inadvertent maternal administration of \( 131 \text{I} \) vary with gestational age.\(^{188}\) Before 10 weeks’ gestation, the risk to the fetus is less well defined and likely approximates that of a low-level dose of radiation during early development;\(^{189}\) after 10 weeks’ gestation, however, the fetal thyroid gland can sequester iodine, and \( 131 \text{I} \) may destroy or significantly damage the gland.

The mainstays of therapy for hyperthyroidism during pregnancy are the antithyroid medications propylthiouracil and methimazole,\(^ {179,180,220,221}\) which cross the placenta much more easily than the maternal thyroid hormones, potentially inducing fetal hypothyroidism and goiter. Although these agents are similar in efficacy for treatment of hyperthyroidism during pregnancy,\(^ {179,190}\) propylthiouracil has been used more frequently than methimazole. Propylthiouracil is favored in the first trimester of pregnancy, owing to rare congenital anomalies reported with methimazole (e.g., scalp defects, choanal atresia, tracheoesophageal fistula).\(^ {179,190,220}\) After the first trimester, therapy can be switched to methimazole if there are concerns for hepatotoxicity with propylthiouracil.

Surgical therapy (e.g., subtotal thyroidectomy) is generally reserved for pregnant women in whom medical therapy has failed.\(^ {191,220}\) The pregnant woman should receive preoperative preparation with a beta-adrenergic receptor antagonist, a glucocorticoid, and iodine to minimize the risk for thyroid storm. Clinical data suggest that treating maternal Graves’ disease with iodine does not result in fetal hypothyroidism,\(^ {222}\) implying that short-term preoperative maternal treatment with iodine should be safe for the fetus.

One national database study of pregnant women undergoing thyroid or parathyroid surgery demonstrated a threefold increase in general complications compared with age-matched nonpregnant controls.\(^ {225}\) In pregnant patients with Graves’ disease, surgical thyroidectomy may lead to fetal hyperthyroidism through a combination of autoimmune and medication effects.\(^ {224}\)

During pregnancy, thyroid storm is a rare hypermetabolic event. Prior reports of a 2% to 4% incidence among pregnant patients are probably overestimates of the true incidence.\(^ {197}\) Most contemporary cases of thyroid storm during pregnancy occur in patients with undiagnosed or undertreated preexisting hyperthyroidism.\(^ {225-227}\) Precipitating events for thyroid storm during pregnancy include infection, thyroid cancer, normal labor, hemorrhage, cesarean delivery, and eclampsia.\(^ {225-228}\)

Treatment of thyroid storm is identical for both pregnant and nonpregnant patients (as discussed earlier) (see Box 43.7). Despite an association with fetal growth restriction (formerly called intrauterine growth restriction) or preterm labor,\(^ {229}\) beta-adrenergic receptor antagonists are commonly prescribed during pregnancy.

Several case reports have described the use of the beta-adrenergic receptor antagonist esmolol for treatment of hyperthyroidism in both pregnant and nonpregnant patients,\(^ {207,208}\) although laboratory and clinical observations suggest that maternal administration of esmolol may result in fetal bradycardia and acidosis.\(^ {230,231}\) Esmolol may be considered when longer-acting beta-adrenergic receptor antagonists are contraindicated or the patient’s hemodynamic status requires the use of a short-acting beta-adrenergic receptor antagonist. Esmolol is preferred for patients with a relative contraindication to nonspecific beta-adrenergic receptor blockade (e.g., asthma). Patients with significant cardiomyopathy from hyperthyroidism, who may be very sensitive to beta-adrenergic receptor blockade,\(^ {177,232,233}\) may benefit from esmolol because the dose can easily be titrated to the desired effect.\(^ {234}\) Hyperthyroid cardiomyopathy during pregnancy or the puerperium may require invasive monitoring and the use of multiple medications that require titration.\(^ {225,239,236}\) Esmolol’s short half-life allows a rapid reversal of effect if needed. Untreated hyperthyroidism is associated with secondary pulmonary hypertension.\(^ {237}\)

In general, maternal and fetal interests are best served by optimal maternal therapy. When the physician opts for maternal therapy that could, in theory, adversely affect fetal well-being, the rationale should be documented in the medical record.

Obstetric Management

Poorly controlled hyperthyroidism during pregnancy increases the risk for severe preeclampsia in the mother and for low birth weight in the newborn.\(^ {238}\) Pregnant patients with treated hyperthyroidism have perinatal outcomes similar to those for euthyroid parturients.\(^ {239}\) The presence of hyperthyroidism does not affect the obstetric management of preeclampsia. In a retrospective study, Davis et al.\(^ {225}\) suggested that early diagnosis and treatment of hyperthyroidism during pregnancy is associated with better maternal and fetal outcomes.

The use of a nonselective beta-adrenergic receptor antagonist may precipitate or aggravate preterm labor. In women with Graves’ disease, the placental transfer of antithyroid medications or thyroid-stimulating antibodies may result in the development of fetal goiter,\(^ {240}\) which can interfere with vaginal delivery or lead to airway obstruction in the newborn. Fetal goiter can be diagnosed with ultrasonography; fetal hypothyroidism can be diagnosed with percutaneous umbilical cord blood sampling and can be treated with intraamniotic injections of thyroxine.\(^ {241}\) In pregnant women with Graves’ disease, maternal serum concentrations of TRAbs during the third trimester may predict neonatal thyroid function.\(^ {242}\)

Normal somatic and intellectual development have been reported in the children of hyperthyroid mothers treated with antithyroid medications;\(^ {243}\) such treatment does not contraindicate breast-feeding.\(^ {190}\)
**Anesthetic Management**

No prospective randomized studies have evaluated the efficacy or safety of various anesthetic techniques in patients with hyperthyroidism. The following features of hyperthyroidism may affect anesthetic management: (1) the hyperdynamic cardiovascular system and the possibility of cardiomyopathy, (2) partial airway obstruction secondary to an enlarged thyroid gland, (3) respiratory muscle weakness, and (4) electrolyte abnormalities.243,244

Halpern243 described two patients with uncontrolled hyperthyroidism who required anesthesia for cesarean delivery and suggested that either neuraxial or general anesthesia can be safely administered in these parturients. On the basis of theoretical concerns, he suggested the omission of epinephrine from the epidural solution of local anesthetic agent and the use of an alpha-adrenergic receptor agonist (e.g., phenylephrine) for the treatment of hypotension. Earlier clinical studies in nonpregnant subjects with spontaneous hyperthyroidism, however, have shown normal hemodynamic responses to exogenous epinephrine, norepinephrine (noradrenaline), phenylephrine, and clonidine.245,246 It therefore appears safe to use epinephrine to minimize local anesthetic uptake and toxicity during the administration of epidural anesthesia in both euthyroid and hyperthyroid patients. One case report described a successful low-dose combined spinal-epidural anesthetic for an urgent cesarean delivery in a patient with uncontrolled hyperthyroidism, thyrotoxic heart disease, and severe preeclampsia.247

Hyperthyroid women should receive glucocorticoid supplementation because they have a relative deficiency of glucocorticoid reserves.204 It seems prudent to avoid medications associated with tachycardia (e.g., ketamine, atropine).163,244 Patients with Graves’ disease may have exophthalmos and therefore may require additional care to prevent corneal abrasions during general anesthesia.244 Some investigators have emphasized the efficacy of deep preoperative sedation in nonpregnant hyperthyroid patients.163,203 The routine use of this technique in pregnant patients is not recommended because of the risks for maternal aspiration and neonatal depression.

Adequate preoperative preparation minimizes the risk for perioperative thyroid storm; when time permits, the goal is to make the patient euthyroid. In an emergency, the hyperthyroid patient can be prepared for surgery with oral propylthiouracil, an intravenous glucocorticoid, sodium iodide, and a beta-adrenergic receptor antagonist. The anesthesia provider should be prepared to treat perioperative thyroid storm (see Box 43.7).

**Hypothyroidism**

**Definition and Epidemiology**

Hypothyroidism is defined as an abnormal decrease in the serum concentration of unbound or free thyroid hormones. The prevalence of hypothyroidism in the general population is 0.1% to 2%, which is similar to that of hyperthyroidism.248 Hypothyroidism is more common in women and the elderly. Screening tests for hypothyroidism in asymptomatic nonpregnant adults are not recommended by the American Academy of Family Physicians.249 When clinically indicated, the preferred screening test is a sensitive assay for serum TSH.

**Pathophysiology**

The etiology of hypothyroidism can be divided into primary and secondary categories (Box 43.8); primary hypothyroidism is more common than secondary hypothyroidism. The clinical manifestations of hypothyroidism result from withdrawal of thyroid hormone from its many target organs and tissues.

**Clinical Presentation and Diagnosis**

The clinical presentation of hypothyroidism is dominated by constitutional signs and symptoms such as dry skin, decreased sweating, hoarseness, paresthesia, periorbital edema, and delayed reflexes.250 A diagnosis of hypothyroidism may be suggested by detection of the following factors during the preanesthetic history and physical examination: (1) a history of neck irradiation or radioiodine therapy; (2) the use of lithium, iodine, amiodarone, antithyroid medications, or thyroid replacement medications; and (3) a history of thyroid

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**BOX 43.8 Causes of Hypothyroidism**

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<thead>
<tr>
<th>Primary Autoimmune</th>
<th>Iatrogenic</th>
<th>Pharmacologic</th>
<th>Congenital</th>
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<tbody>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Radioiodine therapy for hyperthyroidism</td>
<td>Iodine deficiency or excess</td>
<td>Dyshormonogenesis</td>
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<tr>
<td>Atrophic hypothyroidism</td>
<td>Subtotal thyroidectomy</td>
<td>Lithium</td>
<td>Thyroid gland dysgenesis or agenesis</td>
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<tr>
<td>Iatrogenic</td>
<td>Pharmacologic</td>
<td>Congenital</td>
<td>Secondary Pituitary Dysfunction</td>
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<tr>
<td>Radioiodine therapy for hyperthyroidism</td>
<td>Dyshormonogenesis</td>
<td>Thyroid gland dysgenesis or agenesis</td>
<td>Irradiation</td>
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<td>Hypothalamic Dysfunction</td>
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<td>Irradiation</td>
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<td>Granulomatous disease</td>
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<td>Neoplasm</td>
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surgery or the presence of a surgical scar overlying the site of the thyroid gland.

By definition, hypothyroidism is diagnosed by measuring a decreased serum concentration of unbound or free T₄. In the presence of an intact feedback loop, the serum concentration of TSH should be increased in patients with primary hypothyroidism. The serum TSH concentration is a more sensitive indicator of primary hypothyroidism than the serum T₄ concentration and is therefore the best initial laboratory test in a patient with suspected hypothyroidism. 248,249

Interaction with Pregnancy
The prevalence of hypothyroidism during pregnancy is 0.3% to 0.5%.251 This estimate is based on laboratory screening of all obstetric patients in a given geographic area. Pregnant women likely exhibit overt or symptomatic hypothyroidism at a much lower rate than nonpregnant women. Hypothyroid women have a lower fertility rate than euthyroid women; this difference reflects neuroendocrine and ovarian dysfunction.172,252 The immunosuppressive effects of pregnancy may lead to a temporary improvement of Hashimoto’s thyroiditis during pregnancy.

Medical Management
Hypothyroidism is treated by replacement therapy with oral thyroid hormones. The medication most commonly used in replacement therapy is levothyroxine,253 which has a half-life of 7 days. Numerous studies have shown that the required replacement dose of thyroid hormone in hypothyroid women often increases during pregnancy.178,180,220 Ideally, the increased dose of thyroid hormone replacement will begin as soon as pregnancy is recognized, and it will be titrated to serum TSH levels at 4-week intervals during the first half of pregnancy.220,254,255

Obstetric Management
Hypothyroidism is associated with an increased incidence of the following obstetric complications: anemia, preeclampsia, fetal growth restriction, gestational diabetes, preterm delivery, placental abruption, and postpartum hemorrhage.178,220,256–258 However, several reports have emphasized successful pregnancy outcomes in some untreated hypothyroid patients.239,259 Early diagnosis and treatment of hypothyroidism appear to be associated with improved maternal and fetal well-being.

In most instances of maternal hypothyroidism, neonatal thyroid function is normal because fetal thyroid development is typically independent of maternal thyroid function. The fetus, however, depends on maternal thyroxine until the fetal thyroid system is fully functional at approximately 20 weeks’ gestation. Therefore, maternal hypothyroidism in the first half of pregnancy may affect fetal brain development. In addition, fetal hypothyroidism during the second half of pregnancy may also affect normal maturation of the CNS.260 With universal screening of neonates for hypothyroidism, these neonates should be readily identified. Published data suggest that cognitive development is relatively normal in hypothyroid infants who receive timely and appropriate thyroid hormone replacement with an initial dose of 10 to 15 µg/kg/day.262 Controversy continues on the issue of screening pregnant women for hypothyroidism with serum TSH levels. It is unclear whether screening should be universally applied to all pregnant women or restricted to a high-risk subgroup identified by medical history.180,220,263–267

Anesthetic Management
The clinical manifestations of hypothyroidism that may affect anesthetic management include the following:268–278

• Reversible myocardial dysfunction
• Coronary artery disease
• Reversible defects in hypoxic and hypercapnic ventilatory drives
• Obstructive sleep apnea
• Paresthesias
• Prolonged somatosensory-evoked potential central conduction time
• Abnormal peripheral nerve conduction
• Increased peripheral nociceptive thresholds
• Hyponatremia
• Decreased glucocorticoid reserves
• Anemia
• Abnormal coagulation factors and platelets

Hypothyroid patients may have an abnormal response to peripheral nerve stimulation that decreases the clinical utility of a nerve stimulator during neuromuscular blockade.279 Clinical studies of vasopressors in nonpregnant hypothyroid patients show normal responses to exogenous epinephrine and diminished responses to phenylephrine.280,281

Whether elective surgery should or should not be delayed to treat hypothyroidism adequately is controversial.282 Patient safety issues may justify such a delay. For emergency procedures, anesthesia care should include glucocorticoid supplementation. Myxedema (hypothyroid) coma is likely the only circumstance in which acute intravenous thyroid hormone replacement is indicated.195 In most hypothyroid patients, acute intravenous replacement therapy entails a significant risk for myocardial ischemia.270

No prospective randomized studies have compared the safety or efficacy of different anesthetic techniques in pregnant or nonpregnant hypothyroid patients. Hypothyroidism is associated with qualitative platelet dysfunction and is a rare cause of acquired von Willebrand’s disease.278,283,284 The anesthesia provider should use findings from the history and physical examination as well as laboratory testing to verify the presence of normal coagulation before administering neuraxial anesthesia to the patient with severe untreated hypothyroidism. Although epidural hematoma represents a theoretical risk in such patients, there are no published reports of this complication in this patient population.

PHEOCHROMOCYTOMA

Definition and Epidemiology
Pheochromocytomas belong to a heterogeneous group of tumors called paragangliomas that develop from neural
crested chromaffin cells and arise in the adrenal medulla (90%) or in the adjacent sympathetic nervous system tissues.285,286 Extra-adrenal paragangliomas may develop from sympathetic or parasympathetic tissues and include such diverse neoplasms as glomus tumors, chemodectomas, carotid body tumors, and jugulotympanic tumors.287 Pheochromocytomas occur bilaterally (e.g., in the medulla of both adrenal glands) in 5% to 10% of cases.288 Approximately 10% of pheochromocytomas are malignant.289,290 Histopathologic features are not reliable predictors of malignancy;290 however, large tumor size, extra-adrenal location, and certain tumor susceptibility gene mutations (e.g., succinate dehydrogenase subunit B) are associated with malignant pheochromocytomas.285

Pheochromocytomas occur in 0.1% to 0.2% of hypertensive adults.287 Men and women are affected relatively equally, and the peak incidence varies between the third and seventh decades of life.

Pheochromocytoma is one of the tumors found in two of the multiple endocrine neoplasia (MEN) syndromes, MEN 2A (e.g., medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma) and MEN 2B (e.g., medullary thyroid carcinoma, mucocutaneous neuromas, pheochromocytoma).291 Other disease processes associated with pheochromocytoma include von Recklinghausen’s disease, von Hippel–Lindau disease, Sturge-Weber syndrome, and tuberous sclerosis. At least 10 distinct genetic mutations have been identified in patients with paragangliomas; the estimated rate of the familial form of pheochromocytoma is 30%.285,287 There is an evolving concept of combined genotype/biochemical phenotype classifications to predict the clinical behavior of pheochromocytomas, and to guide therapy in individual patients.292

Pathophysiology

The pathophysiology of pheochromocytoma is related almost entirely to the systemic effects of its endocrine secretory products, typically norepinephrine and epinephrine. Some pheochromocytomas may, however, secrete other catecholamines (e.g., dopamine, dihydroxyphenylalanine [DOPA]) or peptide hormones. In an individual patient, the clinical manifestations of pheochromocytoma represent the net systemic effects of the tumor’s secretory products.

Clinical Presentation and Diagnosis

Patients with pheochromocytoma can have a variety of common or uncommon symptoms.285–291 Patients typically have paroxysmal symptoms because of the episodic nature of hormone secretion by the tumor (Table 43.4). The most common symptoms are sweating, tachycardia, and headaches; one study suggested that the diagnosis of pheochromocytoma can be excluded with 99.9% certainty if a patient does not have these symptoms.283 The attacks may remain the same, or the symptoms may evolve over time.289 Pallor is common and flushing is uncommon in patients with pheochromocytoma. Paroxysmal symptoms may be triggered by a wide variety of physical activities that patients learn to avoid.289 Typically, these activities directly or indirectly increase the pressure around the tumor. As the tumor grows, the attacks may last longer and occur more frequently.289

The ability of pheochromocytomas to mimic other diseases has frustrated and confused many generations of physicians. In one series of patients with pheochromocytoma, 76% of the tumors were not diagnosed before autopsy.289 Reports include numerous examples of pheochromocytomas that were initially confused with other medical or psychiatric disorders.294–296 In addition to their systemic endocrine effects, pheochromocytomas can occasionally cause local abdominal symptoms.297

Hypertension is a common but not universal finding, occurring in 77% to 98% of patients with pheochromocytoma.289 Although most patients have paroxysmal episodes of hypertension, one-half may also experience sustained hypertension.287 Orthostatic hypotension occurs in 70% of patients.289,291 The presumed mechanisms for orthostatic hypotension are chronic vasoconstriction with intravascular volume depletion and impaired reflex responses secondary to receptor down-regulation or synaptic effects of circulating catecholamines.289,291

The current approach to the diagnosis of pheochromocytoma involves the following four steps: (1) biochemical testing for increased catecholamine secretion, (2) anatomic imaging, (3) functional imaging, and (4) genetic testing.286,287,292 Catecholamine secretion is evaluated by measuring norepinephrine and epinephrine or concentrations of their metabolites (normetanephrine, metanephrine, or vanillylmandelic acid) in plasma or urine samples. Although the relative merits of these laboratory tests have been debated for years, a consensus has emerged in favor of measuring free metanephrines in plasma or urine.286,287,288

| TABLE 43.4 Symptoms of Pheochromocytoma during Paroxysmal Attacks |
|-------------------------|-------------------------|-------------------------|
| Symptom                 | Patients Affected in Previous Series (%) | Patients Affected in Ross and Griffith Series (%) |
| Headache                | 59.9  43–80              | 57                      |
| Sweating                | 52.2  37–71              | 61                      |
| Palpitations            | 49.2  44–71              | 63                      |
| Pallor                  | 42.9  42–44              | 43                      |
| Nausea                  | 34.5  10–42              | 33                      |
| Tremor                  | 33.5  30–38              | 13                      |
| Anxiety                 | 28.9  15–72              | 30                      |
| Abdominal pain          | 25.8  5–62               | 14                      |
| Chest pain              | 25.0  19–50              | 0                       |
| Weakness                | 19.4  8–58               | 25                      |
| Dyspnea                 | 17.0  15–39              | 23                      |
| Weight loss             | 16.5  14–23              | 7                       |
| Flushing                | 14.8  10–19              | 4                       |
| Visual disturbances     | 12.4  11–22              | 19                      |

plasma or urinary fractionated metanephrines as the initial laboratory test.\textsuperscript{286,298–300}

Conversion of norepinephrine and epinephrine to the respective metanephrines by catecholamine-\textit{O}-methyl transferase occurs to a large extent within the pheochromocytoma before secretion.\textsuperscript{298} Several medical conditions may confound the diagnosis of pheochromocytoma by altering the plasma and urinary concentrations of catecholamine metabolites. These conditions include congestive heart failure, acute myocardial infarction, stroke, cocaine abuse, sleep apnea, and ethanol or clonidine withdrawal.\textsuperscript{301} Medications that alter normal catecholamine secretion and metabolism include tricyclic antidepressants, acetaminophen (paracetamol), hydralazine, and beta-adrenergic receptor antagonists.\textsuperscript{302}

Chromogranin-A is a protein found with catecholamines inside secretory vesicles within pheochromocytoma and normal adrenal medullary cells. Originally, chromogranin-A was thought to be a packaging protein in secretory vesicles, but it is now recognized as a prohormone for several peptide hormones, including vasostatin.\textsuperscript{303} The measurement of plasma concentrations of chromogranin-A has been used as a confirmatory biochemical test for pheochromocytoma.\textsuperscript{304,305}

For patients in whom initial laboratory findings are equivocal, a clonidine suppression test can be performed.\textsuperscript{309} The basis of the test is that clonidine fails to suppress catecholamine secretion by pheochromocytoma cells.

After the laboratory diagnosis is confirmed, the pheochromocytoma is localized with anatomic and functional imaging.\textsuperscript{306} The major anatomic imaging modalities are computed tomography (CT) and magnetic resonance imaging (MRI). Functional imaging relies on labeled compounds with a high affinity for pheochromocytoma cells. Meta-iodobenzylguanidine (MIBG) is an analogue of norepinephrine, and \textsuperscript{123}I-MIBG is commonly used for scintigraphic localization. Positron emission tomography (PET) with either fluorine-18 (\textsuperscript{18}F)–fluoro-2-deoxy-D-glucose (\textsuperscript{18}F-FDG) or \textsuperscript{18}F-fluoro-L-3,4-dihydroxyphenylalanine (\textsuperscript{18}F-DOPA) can be used to localize pheochromocytomas.\textsuperscript{306}

**Interaction with Pregnancy**

Pheochromocytoma is rare during pregnancy, with an overall incidence estimated to be less than 0.2 per 10,000 pregnancies.\textsuperscript{307,308} Although pregnancy may accelerate the growth of some tumors, no data suggest that it does so for pheochromocytoma. Both sporadic and familial types of pheochromocytoma, as well as benign and malignant forms, may occur during pregnancy. Case reports have demonstrated specific tumor susceptibility gene mutations in pregnant patients who have familial cases of pheochromocytoma.\textsuperscript{309–312}

Clinical signs and symptoms of pheochromocytoma are similar in pregnant and nonpregnant patients.\textsuperscript{307,308,313} Noninvasive hemodynamic measurements demonstrated intense vasoconstriction and decreased cardiac output during episodes of hypertension in two pregnant patients with pheochromocytoma.\textsuperscript{314,315} The clinical recognition of pheochromocytoma during pregnancy is especially difficult because of its rarity and its similarity to preeclampsia, a common obstetric disease.\textsuperscript{316,317} The diagnosis of pheochromocytoma before labor and delivery may reduce maternal mortality from 35% to near zero.\textsuperscript{307} Easterling et al.\textsuperscript{315} demonstrated that either an inverse relationship between blood pressure and heart rate or an increasing hematocrit during treatment with a beta-adrenergic receptor antagonist in a patient with suspected preeclampsia suggests the presence of pheochromocytoma. Pheochromocytoma may also manifest in the early postpartum period after an unremarkable vaginal delivery.\textsuperscript{318,319}

Plasma concentrations of epinephrine, norepinephrine, and dopamine in normal pregnant women do not differ significantly from those in nonpregnant controls.\textsuperscript{320} These data suggest that the same threshold levels can be used to interpret most laboratory test results (except urinary norepinephrine and normetanephrine) for the diagnosis of pheochromocytoma in pregnant and nonpregnant patients. During pregnancy, ultrasonography or MRI is most commonly used for anatomic imaging of pheochromocytomas.\textsuperscript{307,308} One case report described functional PET/CT imaging of a pheochromocytoma during pregnancy using \textsuperscript{18}F-FDG.\textsuperscript{321} However, this imaging was delayed until 21 weeks’ gestation to minimize the fetal radiation effects.

**Medical and Surgical Management**

Definitive therapy for pheochromocytoma is surgical resection of the tumor.\textsuperscript{286,287,300} The greatest challenge in perioperative management is to prevent or effectively treat wide swings in hemodynamic parameters. The patient is at risk for severe hypertension during induction of anesthesia and surgical manipulation of the tumor; severe hypotension frequently occurs after excision of the tumor because of an abrupt decline in circulating concentrations of catecholamines.

**Preoperative Preparation**

The preoperative preparation of a patient with pheochromocytoma relies on pharmacologic therapy to return the patient to a near-normal physiologic state. Patients with a norepinephrine-dominant pheochromocytoma have intense peripheral vasoconstriction and severe intravascular volume depletion. In these patients, preoperative preparation includes alpha-adrenergic receptor blockade and intravascular volume repletion.\textsuperscript{286,287,322} The most commonly used alpha-adrenergic receptor antagonist is phenoxycbenzamine, at an initial dose of 10 mg orally twice a day, titrated upward to 40 to 50 mg twice a day. Doxazosin, prazosin, and phentolamine are other alpha-adrenergic receptor antagonists that have been used successfully.\textsuperscript{323–325} Beta-adrenergic receptor antagonists may be added to treat arrhythmias, but their use must be preceded by effective alpha-adrenergic receptor blockade to prevent a paradoxical hypertensive response.\textsuperscript{323,324} Beta-adrenergic receptor blockade must be individualized because patients with pheochromocytoma are at risk for catecholamine-induced cardiomyopathy.\textsuperscript{326}

The administration of nicardipine, a calcium entry–blocking agent, is an alternative approach in the preoperative preparation of these patients.\textsuperscript{324,327} Metyrosine is another
therapeutic option that interferes with catecholamine synthesis; it has been used as an adjunct to preoperative alpha-adrenergic receptor blockade at a dose of 250 to 1000 mg orally twice a day. Patients whose symptoms or early responses to alpha-adrenergic receptor blockade suggest an epinephrine-dominant pheochromocytoma may need beta-adrenergic receptor blockade as primary preoperative therapy.

Alpha-adrenergic receptor blockade with phenoxybenzamine is the most commonly used technique for preoperative preparation of the patient with pheochromocytoma. Administration of a long-acting alpha-adrenergic receptor antagonist (e.g., phenoxybenzamine) may be desirable before tumor excision but can contribute to hypotension after tumor removal. Prospective randomized studies comparing different methods of patient preparation have not been performed. A retrospective review of patients with pheochromocytoma who were treated preoperatively with phenoxybenzamine, prazosin, or doxazosin suggests that all of these agents are effective and safe. Regardless of the method chosen, the patient must be prepared adequately for surgery. Adequate preparation could be the major reason for the decline in operative mortality over the past several decades in patients with pheochromocytoma. Hull stated, “Emergency surgery to remove a pheochromocytoma from an unprepared patient should never be contemplated.” However, recent authors have suggested that “perioperative management may actually be more critical for achieving good clinical outcomes than administration of preoperative hypotensive drugs.” It is likely that meticulous preoperative and perioperative medical care both contribute substantially to patient safety with pheochromocytomas. Fleischer and Mythen have described four widely accepted criteria for adequate preoperative alpha-adrenergic receptor blockade in patients with pheochromocytoma (Box 43.9). Most patients require 7 to 14 days of treatment to meet these criteria. Individual reports of rapid preoperative patient preparation techniques for pheochromocytoma resection (e.g., intravenous urapidil plus magnesium) will need additional confirmation before they become mainstream clinical practices.

Intraoperative Management

Intraoperative management includes the treatment of episodic hypertension and tachycardia before excision and treatment of profound hypotension after excision. Many medications have been used successfully to manage intraoperative hypertension and tachycardia, including calcium entry–blocking agents, nitroprusside, nitroglycerin, esmolol, magnesium sulfate, dexametomidine, and adenosine. Because of the episodic nature of catecholamine secretion and the change in cardiovascular status that occurs after tumor excision, the use of agents with a short duration of action may be advantageous. The successful use of various regimens implies that the intraoperative treatment of hypertension and tachycardia depends more on the vigilance and skill of the anesthesia provider than on the specific medication used.

Intraoperative monitoring of a patient with pheochromocytoma should include the use of standard monitors, an intra-arterial catheter, and a urinary catheter. Ongoing assessments of cardiac contractility and cardiac filling pressures and volumes facilitate the successful treatment of catecholamine-induced cardiomyopathy or postexcision hypotension. This information may be acquired via a pulmonary artery catheter or transesophageal echocardiography. Laparoscopic resection of pheochromocytomas has almost completely replaced open surgical approaches, except for very large or malignant tumors. Laparoscopic resection is associated with a shorter hospitalization and greater patient satisfaction. In a small study, patients undergoing laparoscopic resection of a pheochromocytoma were randomized to receive one of two different intra-abdominal pressures during the carboperitoneum (either 8 to 10 or 15 mm Hg). Patients with lower intra-abdominal pressure had less perioperative catecholamine release and fewer hemodynamic fluctuations than patients with higher intra-abdominal pressure. A retrospective review of 143 patients who underwent predominantly open resection of pheochromocytoma or paraganglioma at the Mayo Clinic from 1983 to 1996 showed a 25% incidence of sustained intraoperative hypertension but very few serious perioperative complications. Hypoglycemia may also be a serious problem after the resection of a pheochromocytoma. Insulin secretion is inhibited by alpha-adrenergic receptor stimulation, and removal of the tumor may result in a rebound of insulin release. Blood glucose concentration should be measured frequently after pheochromocytoma excision.

Medical therapy for pheochromocytoma is used only as a temporizing measure during pregnancy or in patients with inoperable or metastatic disease. Pheochromocytoma recurs in 6.5% of patients who have undergone complete surgical resection.

Management during Pregnancy

When pheochromocytoma presents during pregnancy, surgical resection of the tumor is the preferred therapy. A

### Box 43.9 Criteria for Adequate Preoperative Alpha-Adrenergic Receptor Blockade in Patients with Pheochromocytoma

1. No in-hospital blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours before surgery.
2. Orthostatic hypotension is acceptable, as long as arterial blood pressure on standing is not less than 80/45 mm Hg.
3. The electrocardiogram should be free of ST-segment/T-wave changes that are not permanent.
4. No more than one premature ventricular contraction should occur every 5 minutes.

variety of clinical strategies have been associated with successful obstetric and surgical outcomes. They include (1) open or laparoscopic tumor resection at 16 to 23 weeks’ gestation followed by vaginal or cesarean delivery at term,348–352 (2) cesarean delivery with concurrent open tumor resection,353 (3) cesarean delivery with open or laparoscopic tumor resection 2 to 8 weeks later,313,354,355 and (4) vaginal delivery with laparoscopic tumor resection 6 weeks later.349 A number of case reports have described successful laparoscopic resection of abdominal pheochromocytoma during pregnancy between 12 and 23 weeks’ gestation with good maternal and fetal outcomes.350–352 These reports included one robotic case and one set of twins. Before 24 weeks’ gestation, surgery should proceed as soon as the patient is adequately prepared with adrenergic blockade.322,356 After 24 weeks’ gestation, the gravid uterus represents a mechanical obstruction to surgery for most abdominal pheochromocytomas. Women with pregnancy at this gestational age should receive adrenergic receptor blockade for the remainder of the pregnancy, or until the tumor is removed.322

Phenoxybenzamine, the most widely used medication for preoperative preparation of the pregnant woman with pheochromocytoma, easily crosses the placenta.356 A case series suggested that neonates should be monitored closely in an intensive care nursery after intrauterine exposure to phenoxybenzamine.357 Other alpha-adrenergic receptor antagonists have been used successfully in pregnant patients with pheochromocytoma, including phentolamine, prazosin, and doxazosin. Beta-adrenergic receptor blockade may be added if needed to control tachycardia or arrhythmias or to treat an epinephrine-dominant pheochromocytoma. Beta-adrenergic receptor antagonists that have been used successfully in pregnant patients with a pheochromocytoma include propranolol, atenolol, and metoprolol.307,336,358 Clinical experience with metyrosine during pregnancy is very limited. Pending further assessment of safety during pregnancy, the use of metyrosine in pregnant women with pheochromocytoma should be restricted to those whose tumors are resistant to adrenergic receptor blockade.

Medications that have been used successfully to control intraoperative hypertension and tachycardia in pregnant patients with pheochromocytoma include phentolamine, nitroprusside, nitroglycerin, magnesium sulfate, propranolol, remifentanil, esmolol, and hydralazine.313,358–360 Esmolol, however, may not be an ideal medication during pregnancy (as discussed earlier).230,231 The safety of maternal administration of nitroprusside has also been questioned because of possible fetal cyanide toxicity.361 Adverse effects were noted in fetal lambs when high doses of nitroprusside were administered in pregnant ewes in which tachyphylaxis had developed.361

Clinical case reports suggest that a low-dose maternal infusion of nitroprusside (approximately 1 µg/kg/min) should be safe during the peripartum period.362,363 If maternal tachyphylaxis develops, nitroprusside should be discontinued and a different vasodilator used. Nitroprusside reduces uteroplacental vascular resistance in hypertensive sheep, and it antagonizes norepinephrine-induced uterine artery vasoconstriction in humans and guinea pigs.364,366 These data suggest theoretical advantages for the perioperative use of nitroprusside in pregnant women with pheochromocytoma.

In summary, early diagnosis of pheochromocytoma during pregnancy and adequate adrenergic receptor blockade are essential to optimize maternal and fetal safety. Phenoxybenzamine is used for preoperative preparation of the pregnant patient. If beta-adrenergic receptor blockade is necessary, metoprolol can be used unless specifically contraindicated. During surgery, short-acting, titratable cardiovascular medications are preferred. Monitoring and therapy should be directed toward optimization of preload, afterload, and cardiac contractility for a patient with rapid changes in circulating concentrations of catecholamines. Attention to detail is likely more important than the choice of specific medications.

Obstetric Management

Pheochromocytoma during pregnancy is associated with an increased incidence of fetal death and fetal growth restriction. The presumed mechanism is decreased uterine blood flow secondary to catecholamine secretion by the tumor; the metabolic activity of the placenta is an effective barrier to the transplacental passage of maternal catecholamines.367 When pheochromocytoma is diagnosed and effective maternal alpha-adrenergic receptor blockade is instituted before delivery, the fetal death rate declines from 50% to near zero.307,308

Placental abruption has been reported in patients with pheochromocytoma.368 From a hemodynamic standpoint, this process may be analogous to the occurrence of placental abruption in patients with acute cocaine intoxication.369 Pheochromocytoma and preeclampsia may have overlapping clinical presentations; proteinuria, for example, occasionally occurs in patients with pheochromocytoma.370

To avoid the increased abdominal pressure on the tumor that can occur during active labor, cesarean delivery is preferred in patients with an unresected pheochromocytoma.307,308

Anesthetic Management

Preoperative preparation and intraoperative monitoring and management have already been discussed. A variety of general anesthetic agents as well as spinal and epidural anesthesia have been successfully used in nonpregnant patients with pheochromocytoma.324,329 Box 43.10 lists perioperative medications that should be avoided to minimize hormone secretion by a pheochromocytoma. A case series of nonpregnant patients suggested that exogenous glucocorticoids can unpredictably trigger a pheochromocytoma crisis,371 but this observation requires further confirmation. There are two published cases of nonpregnant patients with pheochromocytoma who were incorrectly diagnosed intraoperatively with malignant hyperthermia.372,373 Manipulation of a pheochromocytoma during resection may result in a small increase in end-tidal carbon dioxide374; it is unlikely, however, that the modest magnitude of this effect would be confused with malignant hyperthermia.

In pregnant women with pheochromocytoma, analgesia during labor is not usually a concern because cesarean
Perioperative Medications to Avoid in Patients with Pheochromocytoma

- Atracurium
- Droperidol
- Glucocorticoids
- Metoclopramide
- Morphine
- Pancuronium
- Pentazocine
- Succinylcholine
- Vancomycin

These medications may, either directly or indirectly, increase the release of catecholamines by the tumor.


KEY POINTS

- Pregnancy is characterized by a progressive increase in peripheral insulin resistance.
- Insulin requirement decreases during the first stage of labor, increases during the second stage, and decreases again after delivery.
- Maternal diabetes mellitus is associated with a higher incidence of polyhydramnios, preterm labor, preeclampsia, fetal macrosomia, neonatal hypoglycemia, and cesarean delivery.
- Fetal structural malformations are the leading cause of perinatal mortality in diabetic parturients; strict glycemic control before conception reduces the risk.
- Normal pregnancy is a euthyroid state because serum concentrations of unbound or free thyroid hormones are within the normal nonpregnant range.
- Thyroid storm is a rare but life-threatening disorder during pregnancy. It is best prevented by effective treatment of preexisting hyperthyroidism and adequate preparation of the patient for surgery.
- The required dose of thyroid hormone replacement medication increases during pregnancy; neonatal thyroid function is normal in most cases of maternal hypothyroidism.
- Maternal and fetal safety is enhanced by early diagnosis of pheochromocytoma and effective adrenergic receptor blockade before resection.
- At the time of pheochromocytoma resection, the anesthesiologist should anticipate the potential for (1) episodic hypertension and tachycardia during manipulation of the tumor and (2) severe hypotension after tumor resection.
- For women with an unresected pheochromocytoma, cesarean delivery is preferred.

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Hematologic and Coagulation Disorders

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**ANEMIA**

**Normal Hemoglobin Morphology**

Normal adult hemoglobin consists of four polypeptides (two alpha and two beta chains) and an iron-containing prosthetic group (heme or ferriprotoporphyrin IX). In the early embryo, theta (θ) and zeta (ζ) chains are present instead of the alpha (α) chains, and epsilon (ε) chains are present instead of the beta (β) chains. After early embryogenesis, pairs of alpha chains are linked with pairs of either beta, gamma (γ), or delta (δ) chains to form adult hemoglobin (Hgb A = αβ2), fetal hemoglobin (Hgb F = αγ2), or hemoglobin A2 (Hgb A2 = αδ2). By term gestation, the ratio of hemoglobin F to hemoglobin A is approximately 1:1. By 1 year of age, hemoglobin A2 is present; it constitutes less than 2.5% of total adult hemoglobin.

The sequence of amino acids (141 amino acids for alpha chains and 146 for beta chains) defines the primary structure; the three-dimensional shape of each chain defines the secondary structure; the relationship between the four chains and the heme prosthetic group defines the tertiary structure; and the binding of the ligands 2,3-diphosphoglycerate (2,3-DPG) and oxygen defines the quaternary structure of the hemoglobin molecule. The physiology of oxygen transport in the fetus is described in Chapter 5.

**Anemia in Pregnancy**

During normal pregnancy, plasma volume increases by approximately 50%, but red blood cell (RBC) mass increases by only 30%; this differential increase results in the physiologic anemia of pregnancy (see Chapter 2). If the hemoglobin concentration decreases below 10.5 g/dL, the physician should consider other causes of anemia.1,2 Iron deficiency is the most common cause of anemia in pregnancy. It becomes more prevalent as pregnancy advances; in a population-based sample of women in the United States, the prevalence increased from 7% in the first trimester to 14% in the second trimester and 30% in the third trimester of pregnancy.3 The global incidence is estimated at 19.2%.4 In addition to reduced hematocrit, iron-deficiency anemia is characterized by low mean corpuscular volume (MCV) and low total serum iron, ferritin, and transferrin saturation.

Iron-deficiency anemia during the first trimester of pregnancy increases the risk for preterm delivery and low birth weight, but evidence is inconclusive for any association
between anemia in the second and third trimester and adverse perinatal outcomes. In the United States, the risk for iron deficiency is increased by advanced parity, short interpregnancy interval, Mexican-American ethnicity, and African race. Daily oral iron treatment in pregnancy reduces the risk for maternal anemia, but likely only improves birth outcomes in populations with high rates of anemia and preterm birth. A 2013 meta-analysis of randomized controlled trials identified a dose-response relationship between total daily dose of iron (up to 66 mg/day) and birth weight, but found insufficient evidence of any benefit on the incidence of preterm birth or small-for-gestational age infants. Doses of oral iron also correlate directly with side effects, including nausea, vomiting, constipation, and abdominal cramps. Antepartum anemia is a leading risk factor for postpartum blood transfusion; however, no study has evaluated the impact of antepartum iron supplementation on the risk for postpartum maternal blood transfusion.

Parenteral (intramuscular or intravenous) iron enhances hematologic response compared with oral iron, but formulations that contain dextran may increase risk for venous thrombosis and allergic reactions. An elevated hemoglobin concentration (greater than or equal to 14.5 g/dL) has been associated with adverse pregnancy outcomes, including preterm delivery, small-for-gestational-age infants, and stillbirth. In the third trimester of pregnancy, iron overload, as demonstrated by high serum ferritin and low soluble transferrin receptor concentrations, is associated with smaller birth size; consequently, the association between polycythemia and decreased fetal growth can be explained partially, but not exclusively, by inadequate plasma expansion.

**Thalassemias**

The thalassemias are a group of microcytic, hemolytic anemias that result from the reduced synthesis or dysfunction of one or more of the polypeptide globin chains. This reduced synthesis leads to (1) an imbalance in globin chain ratios, (2) defective hemoglobin, and (3) erythrocyte damage resulting from excess globin subunits. In α-thalassemia, alpha-chain production is reduced, and in β-thalassemia, beta-chain production is reduced. Clinically, thalassemia is divided between transfusion-dependent thalassemia and non-transfusion-dependent thalassemia. Patients with transfusion-dependent thalassemia require ongoing transfusion therapy for survival, but even patients with non-transfusion-dependent thalassemia may require blood transfusions during periods of stress such as infection or pregnancy.

**α-Thalassemia**

There are two alpha-chain loci on each chromosome 16; therefore, there are four genes that can produce alpha chains. Because deletions or mutations can affect any or all of these genes, four types of α-thalassemia exist: (1) silent carrier (three functioning genes), (2) α-thalassemia trait (two functioning genes), (3) hemoglobin H disease (one functioning gene), and (4) α-thalassemia or Bart’s hydrops (no functioning genes). As the number of functioning genes decreases from three to zero, the ratio of alpha to beta chains decreases from 0.8:1 to 0.6:1 to 0.3:1 to 0:1. More than 120 specific genetic mutations have been identified in cases of α-thalassemia, including deletional and nondeletional mutations of the α-globin genes, and mutations in regulatory genes that enhance genetic transcription (e.g., MCS-R2). As beta (or beta-like) chains accumulate, they can form tetramers in utero (hemoglobin Bart’s = γ) or after delivery (hemoglobin H = βγ) and appear as Heinz bodies on the peripheral blood smear.

In the United States, 25% to 30% of black women are silent carriers and have slightly smaller (78 to 85 fl) mean corpuscular volume (MCV) than women without thalassemia. A chromosome lacking one alpha gene is common in Africa, the Mediterranean basin, the Middle East, India, Southeast Asia, and Indonesia, and the South Pacific Islands. Silent carriers are not at increased risk for adverse outcome during pregnancy or surgery.

The α-thalassemia trait affects 2% to 3% of black women in the United States and is almost exclusively due to homozygous α+-thalassemia, in which one functional α-globin gene is preserved on each chromosome (α+/α−). These women have an MCV of 70 to 75 fl and mild anemia. They typically are asymptomatic and, beyond the effects of mild anemia, experience no additional risk for adverse outcomes during pregnancy or surgery. Heterozygous α-thalassemia trait (−/αα) is common among individuals of Southeast Asian descent. It is phenotypically indistinguishable from homozygous α+-thalassemia trait but introduces the risk for bearing an offspring with hemoglobin H disease or Bart’s hydrops.

Patients with hemoglobin H disease experience moderately severe microcytic anemia, splenomegaly, fatigue, and generalized discomfort. Hemoglobin H (βγ) constitutes 2% to 15% of the total hemoglobin in these patients. Affected patients generally do not have a decreased life span, and hospitalization for the treatment of their anemia rarely is required. However, disease severity and prognosis vary, depending on the specific mutations present; some patients have transfusion-dependent thalassemia and require lifelong transfusion and chelation therapy.

Hemoglobin Bart’s, or α-thalassemia, is generally incompatible with life. The disease is found predominantly in Southeast Asia, China, and the Philippines. Affected individuals die in utero or shortly after birth of hydrops fetalis; mothers carrying these fetuses are prone to develop hypertension or peripartum hemorrhage, or both. Intact neonatal survival has been reported with intrauterine transfusion therapy and postnatal hematopoietic stem cell transplantation. Antenatal screening for the disease is possible (see later discussion).

**β-Thalassemias**

In β-thalassemia, the production of beta chains is reduced. There are more than 250 genetic causes for ineffective
beta-chain production, including gene deletion, transcription mutations, RNA-processing mutations, and mutations that affect protein stability.\(^\text{12}\) Unlike the alpha chains, which have four genes (two on each chromosome 16), beta chains have only one gene on each chromosome 11. Severity depends on the combination of mutations present. \(\beta^+\)-thalassemia, also called \(\beta\)-thalassemia major or Cooley’s anemia, is a transfusion-dependent thalassemia characterized by a complete absence of beta-chain formation. With \(\beta^-\)-thalassemia, beta-chain production exists, but either production or function is impaired. For example, Hemoglobin E is a variant of \(\beta^-\)-thalassemia in which a point mutation on the \(\beta\)-globin gene both decreases mRNA transcription and decreases affinity between the resulting \(\alpha\) - and \(\beta\)-globin proteins. Individuals who receive \(\beta\)-thalassemia genes from both parents but with mutations of different types often develop \(\beta\)-thalassemia, a condition that is not transfusion dependent.

\(\beta\)-thalassemia is found most often in persons from the Mediterranean basin, the Middle East, India, Pakistan, and Southeast Asia and less often among persons from Tajikistan, Turkmenistan, Kyrgyzstan, and China.\(^\text{21}\)

Individuals with \(\beta\)-thalassemia have a relative excess of alpha chains that cumulate in RBC precursors. Excess alpha chains undergo auto-oxidation and precipitate to form inclusion bodies called \(\alpha\)-hemocromes. Oxidized ferric iron and reactive oxidative species in the \(\alpha\)-hemocromes trigger a cascade of events leading to ineffective erythropoiesis and splenic hemolysis.\(^\text{21}\) In the fetus, the gamma chain is unaffected; therefore, anemia only develops as gamma-chain production ceases during the first year of life.\(^\text{21}\) In some patients, gamma-chain production continues to a variable extent. Thus, the ongoing production of hemoglobin F (even in adults) may minimize the effects of decreased beta-chain production.\(^\text{12}\)

**\(\beta\)-thalassemia major.** In patients with \(\beta\)-thalassemia major, progressively severe anemia develops beginning in the first few months of extrauterine life.\(^\text{21}\) Untreated anemia results in tissue hypoxia, increased intestinal absorption of iron, and increased erythropoietin production. The resulting expansion of marrow cavities causes skeletal abnormalities, extramedullary hemato poiesis, leg ulcerations, osteopenia, and pathologic fractures. Splenomegaly leads to thrombocytopenia and leukopenia. Ineffective erythropoiesis and chronic hemolysis increase the risk for thrombotic complications including venous thrombosis and pulmonary hypertension, with risk particularly elevated among those who have undergone splenectomy.\(^\text{22,23}\) Similar pathology may develop in individuals with thalassemia intermedia, particularly in cases of compound hemoglobin E/\(\beta^+\)-thalassemia.\(^\text{13}\)

RBC transfusions can restore normal childhood development, but the resulting iron load leads to iron accumulation, first in Kupffer’s cells (noncirculating macrophages found in the liver), then in liver parenchymal cells, and finally in endocrine and myocardial cells. Clinical effects of iron overload typically present by the end of the first decade of life. Deposition of iron in endocrine tissues may result in short stature, diabetes mellitus, adrenal insufficiency, hypothyroidism, hypoparathyroidism, and infertility.\(^\text{24}\) Pulmonary fibrosis with restrictive disease, and renal dysfunction have been attributed to iron deposition.\(^\text{23}\) Myocardial accumulation of iron can lead to conduction abnormalities and intractable heart failure, which are exacerbated by anemia-induced tachycardia. Heart failure and infection are the most common causes of death.

Patients with \(\beta\)-thalassemia major who present when younger than 2 years of age often have hepatomegaly and a hemoglobin concentration as low as 2 g/dL. Patients who present later in life (2 to 12 years of age) typically have a hemoglobin concentration between 4 and 10 g/dL, with marked aniso- and poikilocytosis and numerous target cells, nucleated RBCs, and inclusion bodies. Levels of hemoglobin F range from 10% to 90% of the total hemoglobin, and hemoglobin A\(_1\) constitutes the remainder of the hemoglobin present.

Treatment includes (1) lifelong transfusion of leukocyte-poor RBCs every 2 to 3 weeks to maintain a hemoglobin concentration greater than 10 g/dL, thus preventing endogenous erythropoiesis; (2) splenectomy; and (3) iron chelation therapy to prevent hemosiderosis. Deferoxamine was the first available chelation agent; it has a long record of successful use, but it requires continuous subcutaneous infusion or intermittent intramuscular injection.\(^\text{22}\) Deferiprone and deferasirox are oral chelation drugs. Deferiprone may reduce cardiac iron levels more quickly than other chelation agents, but no studies have demonstrated improved clinical cardiac outcomes.\(^\text{25,26}\) Hematopoietic stem cell transplantation may be curative if a human leukocyte antigen (HLA)-matched family donor without \(\beta\)-thalassemia major is found.\(^\text{22}\) Research exploring the potential of gene therapy is underway.\(^\text{22,27,28}\)

It is unusual for patients with \(\beta\)-thalassemia major to become pregnant; nonetheless, transfusion and chelation regimens improve fertility, and assisted reproductive technologies facilitate conception in women with hemosiderosis-related infertility.\(^\text{29}\) The metabolic demands of pregnancy increase transfusion requirements. Mordel et al.\(^\text{30}\) reviewed reports of these patients and suggested that up to 8 L of transfused RBCs may be required over the course of pregnancy to maintain the hemoglobin concentration above 10 g/dL.\(^\text{30}\) Usually chelation agents are discontinued in pregnancy, given evidence of teratogenicity in animal models and fetal iron depletion described in case reports;\(^\text{31}\) nevertheless, successful pregnancies have been described despite inadvertent use during the first trimester,\(^\text{32}\) and some experts suggest resuming chelation therapy in the second and third trimesters among women who develop cardiac symptoms or rapid increase in ferritin.\(^\text{13,34}\)

Historically, these patients had an increased incidence of spontaneous abortion, intrauterine fetal death, and fetal growth restriction (also known as intrauterine growth
Hypertension may be identified using echocardiography. A systematic review of case reports and case series identified more than 400 pregnancies complicated by transfusion-dependent β-thalassemia; among women with normal cardiovascular function, careful transfusion therapy and multidisciplinary care appears to facilitate uneventful pregnancy. Although severe skeletal defects and short stature increase the risk for cesarean delivery, trial of labor is usually appropriate, and operative delivery should be reserved for obstetric indications.

In preparation for delivery, careful history and physical examination for the cardiac, pulmonary, hepatic, skeletal, renal, and endocrine manifestations of the disease and complications of iron overload are indicated. Maternal cardiac iron deposition may be quantified using modified magnetic resonance imaging (MRI). Telometry may be indicated for dysrhythmia surveillance. Heart failure and pulmonary hypertension may be identified using echocardiography. Chronic transfusions increase the risk for alloimmunization, which prolongs the time required to identify compatible allogeneic blood products in the event of peripartum hemorrhage. Intraoperative blood salvage has been safely performed during cesarean delivery in a parturient with thalassemia. Postpartum pharmacologic thromboprophylaxis is indicated.

Craniofacial abnormalities (e.g., maxillary hypertrophy, high arched palate) that increase the risk for difficult airway management may be evident on airway examination. Extra-medullary hematopoiesis can result in vertebral cortical weakening, pathologic fractures, and, rarely, paraplegia. However, in the absence of a major pathologic process of the spine, neuraxial anesthesia can be safely administered. Patients with splenomegaly may develop thrombocytopenia; therefore, anesthesia providers should exclude a history of spontaneous hemorrhage and determine the platelet count before initiating a neuraxial procedure.

**β-thalassemia intermedia and minor.** The clinical course is usually benign in patients with β-thalassemia minor and with β-thalassemia intermedia when it is not transfusion dependent. The anemia is typically mild (hemoglobin concentration of 9 to 11 g/dL) and is characterized by microcytosis and hypochromatosis. Levels of hemoglobin F range from 1% to 3%, and levels of hemoglobin A2 range from 3.5% to 7%.

Moderate anemia develops only during periods of stress, such as pregnancy and severe infection. Most patients with non–transfusion-dependent β-thalassemia tolerate pregnancy well, although the incidence of oligohydramnios and fetal growth restriction are greater than in nonthalassemic women. Because of an increased rate of RBC turnover and an increased risk for neural tube defects, high-dose folate supplementation is recommended in the first trimester. Transfusions are reserved for patients with hemorrhage or a hemoglobin concentration below 8 g/dL. Infection, which can cause bone marrow suppression, must be treated promptly. Non–transfusion-dependent β-thalassemia typically does not affect anesthetic management during labor or cesarean delivery.

**Antenatal Thalassemia Screening**

Among populations at risk for α- or β-thalassemia, antenatal screening can identify couples at increased risk for offspring with a serious hemoglobinopathy. Low maternal and paternal MCV (≤ 80 fl) or mean corpuscular hemoglobin (MCH ≤ 27 pg/cell) with normal serum iron and ferritin should prompt peripheral smear analysis for inclusion bodies, or hemoglobin electrophoresis, or both. The latter test may reveal elevated hemoglobin A2 or hemoglobin F, suggesting β-thalassemia or another hemoglobinopathy (sickle cell trait [AS], sickle cell anemia [SS], or hemoglobin C trait [SC]). Decreased hemoglobin A2 suggests hemoglobin H disease; however, α-thalassemia cannot be detected by electrophoresis alone. Focused genetic testing targets known mutations in the population, but rare variants require genome scanning techniques. For β-thalassemia, cell-free fetal DNA obtained from maternal plasma can be used to screen for a paternally inherited mutation that would indicate a 50% risk for fetal disease. Counseling for fetal genetic testing should be offered if both parents carry at least one abnormal hemoglobin gene.

Prenatal diagnosis can be accomplished with the use of fetal cells obtained by means of chorionic villus sampling or amniocentesis and subjected to DNA analysis. In the future, cell-free fetal DNA obtained from maternal plasma may provide an alternative source of material for fetal genetic analysis.

**Sickle Cell Disorders**

A **sickle cell disorder** refers to a state in which erythrocytes undergo sickling when they are deoxygenated. Normal erythrocytes have a biconcave shape, whereas sickle cells are elongated and crescent shaped, with two pointed ends. Sickling is attributed to polymorphisms in the β-chains of the hemoglobin molecule. In hemoglobin S, valine is substituted for glutamic acid as the sixth amino acid in the hemoglobin molecule. The β-chains of the hemoglobin molecule to aggregate when the hemoglobin is in the deoxygenated state. This substitution results in a propensity for hemoglobin molecules to aggregate when the hemoglobin is in the deoxygenated state. The hemoglobin molecules stack on top of one another and form microtubules. Hemoglobin C, D, and E are other hemoglobin variants, all characterized by point mutations in the genes that encode the β-chains, and all less prone to sickling than hemoglobin S.

**Sickle cell disease** refers to disorders in which sickling results in clinical signs and symptoms; it includes hemoglobin SS disease (i.e., sickle cell anemia) and several heterozygous hemoglobinopathies (e.g., sickle cell β-thalassemia, hemoglobin SC disease). Sickle cell disease variants are discussed in the following sections.

**Sickle Cell Anemia**

**Epidemiology.** Table 44.1 lists the prevalence of sickle cell anemia and the other common hemoglobinopathies in the adult black population in the United States. Sickle cell disease is less commonly identified among Hispanic, Middle Eastern, or Asian Indian ethnic groups. The current number of individuals with sickle cell disease in the United States may...
The formation of hemoglobin S aggregates is time dependent; the proportion of sickled hemoglobin increases with the length of exposure to hypoxia. Hemoglobin S begins to aggregate at a P50 of less than 50 mm Hg (6.7 kPa), and all of the hemoglobin S is aggregated at a P50 of approximately 23 mm Hg (3.1 kPa). The formation of hemoglobin S aggregates is time dependent; the proportion of sickled hemoglobin increases with decreasing cardiac output and prolonged venous transit time. If an erythrocyte sickles, it can return to its normal shape once the hemoglobin becomes oxygenated. However, repeated sickling cycles produce erythrocyte metabolic abnormalities and membrane damage, eventually leading to irreversible sickling regardless of oxygen tension. Sickled cells are cleared rapidly from the circulation by the reticulo-endothelial system; as a result, the erythrocyte life span is reduced to approximately 12 days.

Sickled cells can form aggregates and lead to vaso-occlusive crises and end-organ injury. Repeated cycles of sickling, vaso-occlusion, reperfusion injury, and acute inflammation can lead to chronic inflammation and inflammatory vascular disease. Elevated levels of cell-free hemoglobin deplete nitric oxide, activate the endothelium, and further exacerbate inflammation. The reduced erythrocyte life span results in anemia, jaundice, cholecystitis, and a hyperdynamic hemodynamic state.

Marked ventricular hypertrophy can occur in pregnant women with sickle cell disease secondary to increased cardiac output. This may lead to a decrease in ventricular compliance and a deterioration in ventricular diastolic function. Anemia also leads to erythroblastic hyperplasia, expansion of medullary spaces, and a loss of cortex in long bones, vertebral bodies, and the skull. Vaso-occlusive events can give rise to infarctive crises (which most often occur in the chest, abdomen, back, and long bones), cerebrovascular accidents, and rarely peripheral neuropathy. Aggregate formation in the spleen can result in microinfarcts.

Functional asplenia and abnormal neutrophil responses both contribute to susceptibility to infection. Consequently, the incidence of pneumonia and pyelonephritis is higher in pregnant patients with sickle cell disease than in healthy pregnant patients. Aplastic crises can occur from depression of erythropoiesis secondary to infection (especially parvovirus) or from marrow failure secondary to folate deficiency during pregnancy. During an aplastic crisis, the hemoglobin concentration can decrease rapidly, leading to high-output cardiac failure and death. Sequestration crises can result from the massive pooling of erythrocytes, especially in the spleen. This event occurs more frequently in patients with hemoglobin SC disease or sickle cell β-thalassemia than in patients with other forms of sickle cell disease. In general, a major sequestration crisis is one in which the hemoglobin concentration is less than 6 g/dL and has decreased more than 3 g/dL from the baseline measurement.

The long-term clinical course of sickle cell disease is highly variable. Higher fetal hemoglobin expression and coincident α-thalassemia were among the first genetic modulators described. Subsequent work has identified a complex network of single nucleotide polymorphisms associated with specific complications of sickle cell disease, most prominently the transforming growth factor-beta (TGF-β) family of membrane-bound receptors. These receptors play a role in fibrosis, cell proliferation, hematopoiesis, osteogenesis, angiogenesis, nephropathy, wound healing, and immune response.

### Diagnosis
In the adult, sickle cell anemia is characterized by (1) a hemoglobin concentration of 6 to 8 g/dL, (2) an elevated reticulocyte count, and (3) the presence of sickle cells on a peripheral blood smear. The diagnosis is confirmed by electrophoresis, thin-layer isoelectric focusing, or high-pressure liquid chromatography. Because most hemoglobinopathies are inherited as autosomal recessive conditions, prenatal screening for abnormal hemoglobin is recommended in couples at high risk for sickle cell disease. In utero, the diagnosis can be made through the use of restriction endonucleases specific for the sickle mutation applied to fetal cells obtained during amniocentesis or chorionic villus sampling.

### Interaction with pregnancy
Pregnancy typically exacerbates the complications of sickle cell anemia. Maternal

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**TABLE 44.1 Prevalence of Hemoglobinopathies in the United States in Persons of African Descent**

<table>
<thead>
<tr>
<th>Type</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traits</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin AS</td>
<td>1:12.5</td>
</tr>
<tr>
<td>Hemoglobin AC</td>
<td>1:33</td>
</tr>
<tr>
<td>β-Thalassemia minor</td>
<td>1:67</td>
</tr>
<tr>
<td>Persistent hemoglobin F</td>
<td>1:1000</td>
</tr>
<tr>
<td><strong>Sickling Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin SS</td>
<td>1:625</td>
</tr>
<tr>
<td>Hemoglobin SC</td>
<td>1:833</td>
</tr>
<tr>
<td>Hemoglobin S–β-thalassemia</td>
<td>1:1667</td>
</tr>
<tr>
<td>Hemoglobin S–persistent hemoglobin F</td>
<td>1:25,000</td>
</tr>
<tr>
<td>Hemoglobin CC</td>
<td>1:4444</td>
</tr>
<tr>
<td>β-Thalassemia major</td>
<td>1:17,778</td>
</tr>
<tr>
<td>Hemoglobin C–β-thalassemia</td>
<td>1:4444</td>
</tr>
</tbody>
</table>

mortality from sickle cell disease composes as many as 1% of all maternal deaths in the United States.40 Thromboembolic complications, infection, cardiomyopathy, and pulmonary hypertension are the most serious maternal medical complications.49,50 Patients with sickle cell anemia have an increased incidence of preterm labor, placental abruption, fetal growth restriction, preeclampsia, and eclampsia.49,50 Intensive fetal surveillance may reduce the risk for intrauterine fetal death.49

**Medical management.** Sickle cell anemia is a chronic anemia; blood transfusions are given only when they are specifically indicated (e.g., acute anemia, aplastic crisis, acute chest syndrome, pneumonia with hypoxemia, before or during surgery).42,43 The goals of transfusion are to achieve a hemoglobin concentration greater than 8 g/dL and to ensure that hemoglobin A represents more than 40% of the total hemoglobin present. Systematic review of cohort studies suggests that prophylactic blood transfusions during pregnancy decrease perinatal and maternal mortality, preterm birth, and maternal vaso-occlusive pain episodes, pulmonary complications, and pulmonary embolism;51 randomized trials confirm a decrease in the frequency of maternal pain crises, but more evidence is needed to evaluate the other outcomes.52,53 If the patient’s baseline hemoglobin concentration is less than 6 to 7 g/dL, simple transfusions with buffy-coat–poor, hemoglobin S–free, washed RBCs should be adequate to meet treatment goals. Otherwise, partial exchange transfusions57 may be necessary.

Hemoglobin F does not form aggregates with hemoglobin S. Hydroxyurea enhances the production of hemoglobin F, and reduces vaso-occlusive crises and other complications of sickle cell anemia.41 It is unclear whether hydroxyurea is safe in pregnancy; the drug is known to be carcinogenic, mutagenic, and teratogenic in animals.55 However, among a small series of pregnancies conceived at the time of maternal or paternal hydroxyurea administration, there was no evidence of abnormal pregnancy outcomes or teratogenicity among surviving offspring.55 L-glutamine powder was approved by the U.S. Food and Drug Administration in 2017 to reduce acute complications of sickle cell disease, on the basis of a trial that demonstrated decreased rates of vaso-occlusive crisis.56 Bone marrow transplantation is a potentially curative therapy for individuals with complicated sickle cell disease, although HLA-matched donors can be difficult to locate and the procedure is associated with significant morbidity and mortality.57,58

**Obstetric management.** During prenatal visits, the obstetrician should monitor maternal weight gain, blood pressure, urine protein content, and uterine and fetal growth. Antenatal aspirin therapy reduces the risk for preeclampsia (see Chapter 35).59 Maternal surveillance for the complications of sickle cell disease continues throughout pregnancy,54 and antepartum fetal surveillance begins at the time of extraterine viability. Finally, pharmacologic thromboprophylaxis is indicated.54

**Anesthetic management.** Principles of anesthetic management include (1) close surveillance for the complications of sickle cell disease, (2) use of crystalloid to maintain intravascular volume, (3) transfusion of RBCs to maintain oxygen-carrying capacity, (4) administration of supplemental oxygen, (5) maintenance of normothermia, (6) prevention of peripheral venous stasis, and (7) provision of appropriate venous thromboembolism prophylaxis.41,60 Preoperative evaluation should focus on recent sickle cell disease exacerbations, the degree of anemia, and chronic end-organ injury.41,54 Pulmonary hypertension and high-output heart failure should be excluded with echocardiography. Preoperative blood transfusion to achieve a hemoglobin concentration of 10 g/dL improves perioperative outcomes for nonobstetric sickle cell patients undergoing medium-risk surgery with general anesthesia, but no trial has evaluated prophylactic blood transfusion before cesarean delivery. Early preparation of cross-matched blood products should be considered because alloimmunization, and the antigen cross-matching procedures recommended to prevent its development, can prolong cross-matching procedures.41 Pain control during labor is essential; continuous neuraxial analgesia is recommended.53 Although general anesthesia for cesarean delivery has been associated with postoperative sickling complications, either neuraxial or general anesthesia is acceptable, and the choice of anesthetic technique ultimately depends on the time available to induce anesthesia and the patient’s preference and physical status.60

**Sickle Cell Disease Variants**

If a patient carries one hemoglobin S gene and another gene for a hemoglobin that has a propensity to sickle, that patient is considered to have sickle cell disease. Patients with hemoglobin SD disease tend to have the mildest form, and patients with SC disease or sickle cell β-thalassemia tend to have more severe disease.62

As with the hemoglobin S gene, hemoglobin C is most prevalent among persons of West African descent, whereas hemoglobin D is distributed among persons of African, northern European, and Indian descent, and hemoglobin E is most prevalent among persons of Southeast Asian descent.62 Patients with hemoglobin SC and hemoglobin SD disease tend to be asymptomatic during childhood with only mild anemia. Typically, these individuals do not develop symptoms until the second half of pregnancy. During late pregnancy, they may have severe anemia (secondary to splenic sequestration) and splenomegaly. Patients with hemoglobin SC disease also have a tendency to develop bone marrow necrosis, which predisposes to fat emboli. The other clinical manifestations are similar to those observed in patients with sickle cell anemia.62

Blood transfusion is recommended only when the hemoglobin concentration is less than 7 to 8 g/dL. Obstetric and anesthetic management are similar to the management of patients with sickle cell anemia.

Patients who are homozygous for hemoglobin C, D, or E typically have mild anemia. Target cells often are observed, and splenomegaly is common. The diagnosis is confirmed with electrophoresis, thin-layer isoelectric focusing, or high-pressure liquid chromatography.62 Pregnancy typically is well
tolerated, and no specific change in obstetric or anesthetic management is required.

**Sickle Cell Trait**
Sickle cell trait (i.e., hemoglobin SA) occurs in approximately 8% of African-American women in the United States. The RBCs of patients with sickle cell trait do not sickle until the \( P_{O_2} \) decreases below 15 mm Hg (2.0 kPa); therefore, RBC life span is normal.63 Patients with sickle cell trait are not at increased risk for adverse outcome during surgery or the peripartum period.64 Nevertheless, sickle cell trait is associated with higher rates of thromboembolic complications,65 and may contribute to long-term adverse outcomes among African Americans, including renal failure and diabetes.

Likewise, patients who are heterozygous for other hemoglobin variants (i.e., one gene for hemoglobin C, D, or E and one hemoglobin A) are asymptomatic. The heterozygous state for both the thalassemias and the structural hemoglobinopathies appears to protect against malaria, which may explain their geographic distribution and continued presence in the gene pool.31

**Autoimmune Hemolytic Anemia**
Patients with autoimmune hemolytic anemia produce antibodies to their own RBCs, resulting in hemolysis and varying degrees of anemia. The annual incidence of new cases of autoimmune hemolytic anemia is approximately 1 in 80,000 persons, but the prevalence approaches 1 in 5000.66 Warm antibodies react with RBCs at a temperature of 35° to 40° C, whereas cold antibodies react optimally at a temperature lower than 30° C. Table 44.2 lists the characteristics of the four main types of autoimmune hemolytic anemia. Approximately one-half of cases are idiopathic, with the remainder attributed to malignancies, autoimmune diseases, infections, or drugs.67

Patients with **warm-reacting antibodies** typically respond to treatment with corticosteroids; splenectomy and the anti-CD20 antibody rituximab are second-line therapies.66 After splenectomy, relapses and blood transfusions may lead to the continued requirement for intermittent or continuous corticosteroid therapy. The presence of the antibody and the requirement for extended phenotyping may delay matched blood product availability. In acute hemorrhage, the rapid transfusion of body-temperature, ABO-compatible and Rh-negative blood can be lifesaving, with the expectation that the half-life of transfused red blood cells will be shortened; this practice will allow time to procure compatible blood products.66

In patients with **cold-reacting antibodies**, the anemia typically is mild, and maintenance of normal body and ambient temperatures typically is all that is required to prevent hemolysis.

**COAGULATION**

**Thrombotic and Thrombolytic Pathways**
Hemostasis depends on the normal function of vascular tissue, platelets, and coagulation factors. During the initial response to loss of vessel integrity, platelets adhere to exposed collagen, facilitated by the von Willebrand factor (vWF) (primary hemostasis). Platelet activation results in the release of substances that constrict the injured vessels and cause other platelets to adhere and form a hemostatic plug. The platelet plug is not stable, and initiation of the coagulation cascade, followed by deposition and stabilization of fibrin, is

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**TABLE 44.2 Characteristics of Autoimmune Hemolytic Anemias**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Immunoglobulin (lg)</th>
<th>Complement Involved</th>
<th>Site of Red Blood Cell Destruction</th>
<th>Treatment</th>
<th>Transfusion Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete warm autoantibodies</td>
<td>Typically IgG</td>
<td>No</td>
<td>Spleen</td>
<td>Corticosteroids, splenectomy, immune globulin</td>
<td>Rarely needed; if given, combined with corticosteroids</td>
</tr>
<tr>
<td>Complete warm autoantibodies</td>
<td>Rarely IgA</td>
<td>No</td>
<td>Spleen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Rarely IgM</td>
<td>C4b and C3b</td>
<td>Liver</td>
<td>Corticosteroids, splenectomy</td>
<td>Rarely needed</td>
</tr>
<tr>
<td>Type 2</td>
<td>IgM</td>
<td>C1–C9</td>
<td>Intracellular</td>
<td>Plasma exchange, corticosteroids</td>
<td>Frequently needed</td>
</tr>
<tr>
<td>Cold autoagglutinins and hemolysins</td>
<td>IgM</td>
<td>No</td>
<td>Intracellular</td>
<td>Corticosteroids, keeping patient warm</td>
<td>Very rarely needed</td>
</tr>
<tr>
<td>Biphasic hemolysins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>IgG</td>
<td>Yes</td>
<td>Intracellular agglutination</td>
<td>Treatment of underlying infection</td>
<td>Occasionally needed</td>
</tr>
<tr>
<td>Chronic</td>
<td>IgG</td>
<td>Yes</td>
<td>Intracellular hemolysis</td>
<td>Plasmapheresis, chlorambucil</td>
<td>Frequently needed</td>
</tr>
</tbody>
</table>

*lgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.*

necessary for definitive hemostasis (secondary hemostasis). Most coagulation factors circulate in the blood as zymogens, which are converted to active enzymes that in turn convert other zymogens to active enzymes. For example, factor X (a zymogen) is converted to factor Xa (an enzyme), which converts prothrombin (factor II) to thrombin (factor IIa).

In its original conception, the coagulation cascade (Fig. 44.1) was believed to propagate within plasma. Subsequent work has located the enzymatic reactions of the extrinsic system primarily to the surface of subendothelial cells and currently, a widely used model divides the coagulation cascade into three phases: (1) an initiation phase (classical extrinsic pathway), in which small amounts of active coagulation factors are generated; (2) an amplification phase, in which the level of active coagulation factors is boosted; and (3) a propagation phase, in which coagulation factors bind to the membrane of activated platelets, leading to the formation of fibrin clots.

In the classic extrinsic pathway, tissue damage activates tissue factor (TF) (also known as factor III or thromboplastin) on the surface of extravascular cells (e.g., fibroblasts, smooth muscle cells), which are exposed to the bloodstream after tissue damage. TF has also been identified on the surfaces of syncytiotrophoblasts, adhered leukocytes, circulating monocytes, and circulating microparticle membrane vesicles released by inflammatory and tumor cells. TF binds factor VII and promotes proteolysis and activation to factor VIIa. On the membrane surface, the TF/VIIa complex converts factor X to Xa and small amounts of factor IX to IXa. Factor Xa amplifies conversion of factor VII to VIIa in the first of many positive feedback loops, and factor Xa forms a complex with factor Va. The membrane-bound prothrombinase complex (i.e., Xa/Va) converts small amounts of soluble prothrombin to thrombin. This thrombin diffuses to the activated platelet surface, where it amplifies the intrinsic coagulation pathway.

In the intrinsic pathway, factor XII binds to a negatively charged substrate (e.g., collagen, platelet phosphatidylserine) and may undergo autolysis to form factor XIIa, or it may be converted to XIIa by trace amounts of XIIa. In addition to activating its own zymogen, factor XIIa converts prekallikrein to kallikrein and factor XI to XIa. High-molecular-weight kininogen can bind factor XI and facilitate its conversion to XIa by XIIa. Kallikrein and high-molecular-weight kininogen also can convert factor XII to XIIa. Factor XIa converts factor IX to IXa, which, with factor VIIIa, converts factor X to Xa.

Factor Xa promotes platelet aggregation, and it converts factors V and VIII to factors Va and VIIIa, respectively. Factor Xa, combined with factor Va, converts factor II (prothrombin) to factor IIa (thrombin), a process termed the thrombin burst. Activated platelets provide the primary surface for conversion of factor X to Xa and prothrombin to thrombin. Thrombin converts factors I (fibrinogen), V, VIII, and XIII to factors Ia (fibrin), Va, VIIIa, and XIIIa, respectively. Thrombin also causes platelet activation. Factor XIIIa is required to cross-link fibrin strands, which helps form a stable clot.

Clot formation is limited by the natural anticoagulants antithrombin III, proteins C and S, and tissue factor pathway inhibitor (TFPI). Antithrombin III, whose activity is enhanced by heparin, inhibits factor IXa, factor Xa, and thrombin. Protein C is activated by a thrombin-thrombomodulin complex. With protein S as a co-factor, protein C breaks down factors Va and VIIIa. TFPI is produced by endothelial cells and inhibits coagulation by simultaneously binding factor Xa and the TF/factor VIIa complex.

**Fig. 44.1** Components of the extrinsic, intrinsic, and common pathways and the fibrinolytic system. The term cascade is a misnomer that stems from the presence of positive and negative feedback loops in both the coagulation and fibrinolytic systems. PF3, Platelet factor 3; t-PA, tissue plasminogen activator.
The final component of the coagulation system is the fibrinolytic system, in which plasmin breaks down fibrin. Tissue-type plasminogen activator (t-PA) circulates as an active protease; however, its activity increases dramatically when it binds to fibrin, at which time it converts plasminogen to plasmin. Urokinase-like plasminogen activator (u-PA) is secreted as the relatively inactive pro-urokinase; it is converted to the active form (single-chain urokinase) by plasmin. Single-chain urokinase is converted to its most active form (double-chain urokinase) by kallikrein, which is released during activation of the coagulation cascade.

Plasmin-mediated fibrinolysis is confined to the clot by the local availability of fibrin and by plasminogen activator inhibitor-1 (PAI-1), which is secreted by many cells, and by plasminogen activator inhibitor-2 (PAI-2), which is secreted primarily by the placenta. Thrombin-activatable fibrinolysis inhibitor (TAFI) is synthesized in the liver, is activated by the thrombin-thrombomodulin complex, and inhibits fibrinolysis by eliminating the binding sites on fibrin for plasminogen and t-PA. The antifibrinolytic drugs tranexamic acid and aminocaproic acid inhibit fibrinolysis by binding to plasminogen and plasmin and preventing their binding to fibrin.

Changes in the concentrations of coagulation factors during pregnancy are outlined in Chapter 2 (see Box 2.2). The levels of most procoagulants increase during pregnancy, while anticoagulant levels remain stable or decrease.90 Although t-PA levels decrease and antifibrinolytic proteins (i.e., PAI-1, PAI-2, TAFI) increase, plasminogen and fibrin degradation product levels increase, suggesting that fibrinolysis continues unabated during pregnancy.

Placental syncytiotrophoblasts promote coagulation by presenting tissue factor and phospholipids to maternal blood coursing through the intervillous space.91 The concentrations of the thrombin-antithrombin complex and fibrin degradation products are elevated in blood from the uterine vein compared with peripheral blood, suggesting that many of the hemostatic changes of pregnancy originate in the placental bed.90

Deficiencies in procoagulant factors or an increase in fibrinolytic factors cause hemorrhagic disorders. Deficiencies in antithrombin III, protein C or S, or the fibrinolytic system cause thromboembolic disorders.

Assessment of Coagulation

Routine Hematology

The increase in the concentration of most coagulation factors is associated with a shortening of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) during normal pregnancy. Similarly, fibrinogen and fibrin degradation products are increased. These changes may mask the early diagnosis of disseminated intravascular coagulation (DIC), so serial laboratory parameters are indicated if the diagnosis is suspected.92 Thrombocytopenia is a sensitive, but not specific, indicator of DIC. For women with severe pre-eclampsia, a platelet count is a clinically useful screening test; a result below 100,000/µL suggests the possibility of impairment of other coagulation parameters.91,92 In the healthy parturient with no history or clinical signs of bleeding, the routine laboratory assessment of hemostasis parameters, including platelet count, is not indicated.91

Whole-Blood Viscoelastic Testing

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) measure whole-blood coagulation and provide information about the adequacy of platelet function and other coagulation factors. In both technologies, a pin connected to a strain gauge and suspended in a cup of blood records the clot kinetics and strength over time. In the case of TEG, a cup of blood oscillates around the torsion pin, and as clot strength increases, the pin records greater torque. In the case of ROTEM, the cup is still, and a pin connected to the strain gauge spins within the blood. Torque is translated to a graphic representation of clot strength (Fig. 44.2) in which specific parameters are interrelated and reflect activities of coagulation proteins, platelets, and their interaction.93 Commonly used thromboelastography and thromboelastometry parameters are defined in Table 44.3. Activators added to the whole blood can be used to accelerate clotting and to isolate specific components of coagulation (Table 44.4).

Investigations using viscoelastic monitoring confirm that pregnancy is a hypercoagulable state.92,94 Reference ranges for normal values likely vary over the course of pregnancy and into the postpartum period.94 TEG and ROTEM have been proposed to assess coagulation status in normal and high-risk pregnant women94 to assess hemostasis before the initiation of neuraxial anesthesia in high-risk patients,96 and to monitor the efficacy of venous thromboembolism prophylaxis.97 Whether viscoelastic monitoring improves clinical outcomes in these contexts is unknown.

Observational data suggest that viscoelastic monitoring may reduce consumption of blood products when used to guide resuscitation for postpartum hemorrhage98 (see Chapter 37). In general, deficits in clotting factor amplification, and fibrin cross-linkage may be corrected with plasma. Deficits in clot strength reflect the need for platelets or fibrinogen (either cryoprecipitate or fibrinogen concentrate). The FIBTEM and functional fibrinogen assays add a platelet inhibitor (cytchalasin D or abciximab) to isolate the need for fibrinogen. For example, a FIBTEM A5 value less than 10 mm corresponds to a fibrinogen concentration below 200 mg/dL. Evidence of clot lysis (LY30 > 3% or ML > 15%) supports the need for antifibrinolytic therapy.

Platelet Function Analyzer

The PFA-100® (Siemens Healthcare Diagnostics, Deerfield, IL) measures platelet function in vitro, especially platelet activation and aggregation. This simple test evaluates the capacity of a sodium-citrated whole-blood sample to form a platelet plug at the aperture situated on a collagen/adenosine phosphate or collagen/epinephrine surface under high-shear conditions. The time required for full occlusion of the aperture by the platelet plug is designated as the closure time. PFA-100 measurements do not correlate with platelet counts.
Fig. 44.2 Normal thromboelastomeric tracing using the ROTEM EXTEM assay. A, current amplitude; Alpha, \(\alpha\)-angle; A5, A10, and A15, amplitude at specific minute interval; CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness. (From Katz D, Beilin Y. Disorders of coagulation in pregnancy. Br J Anaesth. 2015;115(Suppl 2):ii75–ii88.)

### TABLE 44.3 Commonly Used Thromboelastography and Thromboelastometry Parameters

<table>
<thead>
<tr>
<th>Coagulation Process</th>
<th>Key Components Tested</th>
<th>TEG</th>
<th>ROTEM</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factor activation</td>
<td>Soluble coagulation factors, tissue factor</td>
<td>R (reaction time, minutes)</td>
<td>CT (clotting time, minutes)</td>
<td>Time to amplitude of 2 mm</td>
</tr>
<tr>
<td>Factor amplification and fibrin cross-linkage</td>
<td></td>
<td>K (kinetics time, minutes)</td>
<td>CFT (clot formation time, minutes)</td>
<td>Time for amplitude to increase from 2 to 20 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha)-angle (degrees)</td>
<td>(\alpha)-angle (degrees)</td>
<td>Angle between the line in the middle of the graph and the tangential line of the body of the graph</td>
</tr>
<tr>
<td>Clot strength</td>
<td>Fibrinogen, platelets, Factor XIII</td>
<td>A5, A10, A15 (mm)</td>
<td>A5, A10, A15 (mm)</td>
<td>Amplitude measured at specific time points after CT or R (e.g., A5 is at 5 minutes)</td>
</tr>
<tr>
<td>Clot lysis</td>
<td>Fibrinolytic enzymes, fibrinolysis inhibitors, Factor XIII</td>
<td>MA (maximum amplitude, mm)</td>
<td>MCF (maximum clot firmness, mm)</td>
<td>Maximum amplitude reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LY30 (lysis)</td>
<td>LI30 (lysis index)</td>
<td>% of decrease in MA or MCF 30 minutes after MA or MCF has been reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPL (estimated percent lysis)</td>
<td>ML (maximum lysis, %)</td>
<td>Maximal reduction in clot firmness after MA or MCF</td>
</tr>
</tbody>
</table>


in healthy parturients, but they may demonstrate impairment in platelet function with severe preeclampsia.

### THROMBOCYTOPENIC COAGULOPATHIES

Thrombocytopenia is defined as a platelet count less than 150,000/µL, and affects 5% to 10% of the pregnant population, becoming more frequent as pregnancy advances. Gestational thrombocytopenia (also known as essential thrombocytopenia) is the most common cause of thrombocytopenia in the second half of pregnancy (Table 44.5). Platelet count rarely decreases below 80,000/µL, and no changes in clinical management are indicated. When platelet count decreases below 100,000/µL, pathologic thrombocytopenic conditions should be considered, including: (1) autoimmune thrombocytopenic purpura, (2) preeclampsia, (3) DIC, (4)
thrombotic thrombocytopenic purpura, (5) acute fatty liver of pregnancy, (6) drug-induced thrombocytopenia, (7) post-transfusion purpura (in individuals who have received a blood transfusion in the previous 1 to 2 weeks), and (8) inherited platelet disorders (e.g., Bernard-Soulier syndrome).  

Pseudothrombocytopenia is a laboratory artifact in which chelation of calcium ions by ethylene-diamine-tetraacetic acid (EDTA) exposes antigenic sites that react with antibodies, causing clumping that artificially lowers the platelet count. In these cases, the automated platelet count is normal if citrate anticoagulant is used.

### Autoimmune Thrombocytopenic Purpura

Although autoimmune thrombocytopenic purpura (ATP) (previously called immune thrombocytopenic purpura and idiopathic thrombocytopenic purpura) is rare, with an incidence of between 0.01% and 0.1%, it composes the majority of cases of thrombocytopenia in the first trimester of pregnancy, and a sizable percentage of cases with profound thrombocytopenia later in pregnancy (see Table 44.5). In this condition, immunoglobulin G (IgG) antibodies directed against platelet antigens are produced primarily in the spleen, where phagocytosis by macrophages occurs. The liver and bone marrow are secondary sites of antibody production and phagocytosis. The binding of complement to platelets can facilitate their clearance, and antibody binding to megakaryocytes can result in ineffective production of platelets. In ATP, the blood smear often reveals the presence of higher platelet volume and greater platelet diameter, and a bone marrow biopsy identifies normal or increased numbers of megakaryocytes.

### TABLE 44.4 Additives Used in Common Viscoelastic Assays to Isolate Components of the Coagulation System

<table>
<thead>
<tr>
<th>TEG-Based Tests</th>
<th>Activators</th>
<th>ROTEM-Based Tests</th>
<th>Test</th>
<th>Activator</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaolin-activated TEG</td>
<td>Kaolin</td>
<td>INTEM</td>
<td>Ellagic acid</td>
<td>Reveals defects in intrinsic pathway</td>
<td></td>
</tr>
<tr>
<td>Rapid TEG</td>
<td>Kaolin + tissue factor</td>
<td>EXTEM</td>
<td>Tissue factor</td>
<td>Reveals defects in intrinsic and extrinsic pathways; tissue factor accelerates results</td>
<td></td>
</tr>
<tr>
<td>Functional Fibrinogen Test</td>
<td>Tissue factor + abciximab</td>
<td>FIBTEM</td>
<td>Tissue factor + cytochalasin D</td>
<td>Reveals defects in intrinsic pathway; reveals platelet deficiency when compared with FIBTEM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>APTEM</td>
<td>Tissue factor + aprotinin</td>
<td>Addition of a platelet inhibitor reveals fibrin-based clot defects—fibrinogen deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aprotinin blocks fibrinolysis; comparison with EXTEM confirms fibrinolysis</td>
<td></td>
</tr>
</tbody>
</table>


### TABLE 44.5 Leading Thrombocytopenia Diagnoses Based on Trimester of Presentation and Platelet Count

<table>
<thead>
<tr>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (per µL)</td>
<td>&gt; 100,000</td>
<td>&lt; 100,000</td>
<td>&gt; 100,000</td>
<td>&lt; 50,000</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>ATP</td>
<td>GT</td>
<td>ATP</td>
<td>GT</td>
</tr>
<tr>
<td></td>
<td>HT</td>
<td>Preeclampsia</td>
<td>Preeclampsia</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>ATP</td>
<td>IPD</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>TTP</td>
<td>Other</td>
<td>GT</td>
<td>ATP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPD</td>
<td>TTP</td>
<td>IDP</td>
</tr>
</tbody>
</table>

Diagnoses are listed from most common to least common within each category. “Other” includes infection, DIC, type 2B von Willebrand disease, and immune and nonimmune drug-induced thrombocytopenia, and so on.

ATP, autoimmune thrombocytopenic purpura; GT gestational thrombocytopenia; IPD inherited platelet disorders; TTP thrombotic thrombocytopenic purpura.

Although maternal IgG can cross the placenta and affect fetal platelets, ATP should not be confused with neonatal alloimmune thrombocytopenia, in which maternal antibodies specific to a fetal platelet antigen cause perinatal thrombocytopenia.

**Interaction with Pregnancy**

Conservative management is typically sufficient if ATP is diagnosed during pregnancy, but risk for postpartum hemorrhage appears to correlate with the degree of platelet deficit.90 Symptoms (e.g., gingival bleeding, hematuria, gastrointestinal bleeding) suggest profound thrombocytopenia;86,88; corticosteroids are indicated if the platelet count is less than 20,000 to 30,000/µL before the onset of labor or less than 50,000/µL at the time of delivery.85,89 High-dose intravenous immune globulin (IVIG) produces a rapid but transient increase in the platelet count and is administered if there is no response to corticosteroid therapy.85,99 In some women with preexisting ATP who become pregnant, thrombocytopenia becomes sufficiently severe that administration of high-dose corticosteroids and immune globulin is inadequate. Rituximab, thrombopoietin receptor agents, and recombinant human thrombopoietin (not currently available in the United States) are alternative second-line treatments; however, pharmacokinetics, dosing, and safety in pregnancy have not been established.82 Splenectomy is another second-line treatment; women who have undergone splenectomy are at increased risk for infection with encapsulated organisms.83

**Obstetric Management**

Maternal IgG can cross the placenta and cause fetal thrombocytopenia, which increases the risk for neonatal hemorrhage.88,89 Although there is a correlation between maternal platelet-associated IgG and fetal thrombocytopenia,90,91 it is not possible to predict the degree of fetal thrombocytopenia based on maternal platelet count or serology.83,93 No study has demonstrated a correlation between the fetal platelet count and intrapartum fetal risk. Neonatal intracranial hemorrhage is rare and is not related to the method of delivery.94 Thus, current guidelines recommend that cesarean delivery should be reserved for obstetric indications.83,94 Current guidelines do not recommend attempts to measure the fetal platelet count before delivery.95 Both periumbilical blood sampling and fetal scalp blood sampling introduce additional risks, and the measured platelet counts are not always accurate.

Operative wounds, including episiotomies, increase risk for peripartum bleeding. Bleeding occurs less often from the placental implantation site, where contraction of the uterus represents the primary mechanism for postpartum hemostasis.90 After delivery, the platelet count often returns to normal in these patients.91

**Thrombotic Thrombocytopenic Purpura**

The classic pentad that defines the syndrome of thrombotic thrombocytopenic purpura (TTP) includes (1) thrombocytopenia (platelet count as low as 20,000/µL); (2) microangiopathic hemolytic anemia; (3) fever; (4) neurologic signs such as photophobia, headache, and seizures; and (5) renal failure. Only the first two elements are essential for diagnosis.95 Disseminated platelet aggregation is a hallmark of TTP.95,96 Neurologic and renal changes result from the deposition of platelet emboli and may be of variable intensity in the acute presentation and during recurrences. Diseases that share some of the clinical findings of TTP include DIC, preeclampsia, and hemolytic-uremic syndrome.

TTP is associated with either a congenital or acquired deficiency of the enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). ADAMTS13 is responsible for cleaving vWF multimers. These multimers promote systemic platelet aggregates and microemboli.95 Decreased levels of the large multimeric forms of vWF are seen in the acute phase of TTP97 but return to normal during remission. In contrast, in hemolytic-uremic syndrome the large multimeric forms of vWF are present in normal amounts.98 The affinity of vWF for platelet membrane glycoprotein Ib/Iiia is also increased in TTP.96 The presence of vWF (but not fibrinogen) in platelet aggregates helps differentiate TTP from DIC.99 (In patients with DIC, fibrinogen but not vWF is found in platelet aggregates.)

Approximately 40% of patients who achieve remission have at least one recurrence, but relapse is rare in patients without severe ADAMTS13 deficiency.100 Pregnancy appears to be a precipitating event for both initial and recurrent episodes of TTP, particularly among women with congenital ADAMTS13 deficiency, also known as Upshaw-Schulman syndrome.100,101 ADAMTS13 activity declines progressively through normal pregnancy, while vWF levels increase.102

Prompt diagnosis and effective treatment for TTP appear to improve both maternal and fetal survival,89,103,104 although perinatal loss remains significant if the disease develops in the first and second trimesters.103 Diagnosis of TTP may be delayed because of a misdiagnosis with the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; concurrent diagnoses have been reported.103 Clinical signs that suggest TTP include microangiopathic anemia with thrombocytopenia in the first half of pregnancy, concomitant fever or neurologic signs, and a high ratio of lactate dehydrogenase to aspartate aminotransferase.103

Plasma exchange is the mainstay of therapy for treating symptomatic TTP, with an exchange volume of 1.0 to 1.5 times the predicted plasma volume of the patient.95,103,105 For congenital ADAMTS13 deficiency, low-dose aspirin combined with regular plasma infusions may limit disease recurrence, and should be resumed in subsequent pregnancies.104 Human plasma–derived factor VIII concentrate, which contains vWF, is an alternative to plasma infusion. Acquired TTP frequently requires immunosuppressant therapy (e.g., with corticosteroids, IVIG, rituximab, or azathioprine) to reduce antibodies to ADAMTS13.104,106 Platelet transfusions are usually avoided but may be safe if administered immediately before or after plasma exchange therapy begins.106 Because of the coagulopathy present in patients with TTP, neuraxial anesthesia is not recommended. One case report described...
spinal anesthesia administered for cesarean delivery in a woman with familial ADAMTS13 deficiency treated with fresh frozen plasma.107

**Inherited Platelet Disorders**

A large number of inherited platelet disorders impact either platelet quantity or function or both, and can increase the risk for both peripartum and perioperative bleeding.108

**Bernard-Soulier syndrome** is a rare autosomal recessive disorder characterized by (1) thrombocytopenia, (2) large platelets on the peripheral blood smear, and (3) defects of the platelet membrane glycoprotein Ib-IX-V complex.109 Laboratory diagnosis includes prolonged bleeding time and prolonged closure time on PFA-100. Treatment during labor and delivery may require tranexamic acid, desmopressin, human leukocyte antigen (HLA), and platelet antigen–matched platelet transfusion, if available, or unmatched platelet transfusion, if necessary.109,110

Patients with **Glanzmann thrombasthenia** have a deficiency in platelet surface glycoprotein Ib/IIa receptors, the major receptor for fibrinogen; this deficiency results in abnormal platelet aggregation.111 These patients have a normal platelet count, but bleeding time and closure time on PFA-100 are prolonged. The treatment for Glanzmann thrombasthenia during labor and delivery is similar to that for Bernard-Soulier syndrome.108,111

**Drug-Induced Platelet Disorders**

Drugs can accelerate platelet destruction through immunologic mechanisms.112,113 Drugs used in obstetric patients that are known to trigger antibodies against platelet receptors include antibiotics (e.g., beta-lactam drugs, trimethoprim-sulfamethoxazole, vancomycin), nonsteroidal anti-inflammatory drugs, and abciximab.113 Most penicillins and some cephalosporins also impair platelet activity directly.114 Likewise, heparin impairs platelet function via immunologic and nonimmunologic mechanisms. Nonimmunologic mechanisms are expected; heparin reduces thrombin production, and thereby prevents thrombin from amplifying platelet activation during the thrombin burst. Heparin-induced thrombocytopenia refers to an immunologic reaction that causes both profound platelet destruction, and a prothrombotic state, usually within 5 to 10 days of starting heparin therapy.115,116 In postoperative patients, the risk for heparin-induced thrombocytopenia (HIT) is lower with low-molecular-weight heparin (LMWH) than unfractionated heparin.117

Drugs that *impair* platelet function are often used in obstetric patients. Aspirin irreversibly inactivates cyclooxygenase, and *in vitro* platelet function tests can remain abnormal for as long as 1 week.118 However, low-dose aspirin (i.e., 60 to 80 mg) does not significantly prolong the bleeding time in pregnant women.119 Moreover, a large number of women receiving low-dose aspirin therapy for the prevention or treatment of preeclampsia have received neuraxial analgesia for labor and delivery without complications.120 Therefore, in the absence of a co-administered anticoagulant (e.g., LMWH) or preexisting hemostatic defect (e.g., von Willebrand’s disease, hemophilia A, uremia) in which aspirin’s effect is more pronounced,120,121 recent ingestion of aspirin does not contraindicate the administration of neuraxial anesthesia.

Other nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, indomethacin, naproxen) reversibly inhibit cyclooxygenase.122 These drugs have only a transient effect on the bleeding time123,124 and have been given to patients with hemostatic diseases (e.g., hemophilia A) without deleterious effect.125 Maternal ingestion of these drugs is not a contraindication for neuraxial blockade, and should not affect anesthetic management for delivery.

Drugs that increase platelet cyclic adenosine monophosphate (cAMP) levels decrease platelet responsiveness.122 This increase in cAMP levels can occur after the administration of prostaglandin E, or prostacyclin (which stimulates adenyl cyclase)126 or after the administration of drugs that decrease the destruction of cAMP (e.g., caffeine, theophylline).

Dextran, which is absorbed onto platelet membranes, can reduce platelet aggregation, secretion, and procoagulant activity.122 Because platelet membranes are a substrate for steps in the coagulation system, clot formation may also be impaired by dextran. Hydroxyethyl starch also appears to worsen platelet function.122 A diet rich in omega-3 fatty acids or fish oil can reduce the platelet concentration of arachidonic acid and prolong bleeding time.122

The use of herbal medications such as garlic, ginkgo, or ginseng alone may not increase the risk for spinal anesthesia; however, concurrent use of an oral anticoagulant or heparin may increase the risk for bleeding complications in these patients.127

### CONGENITAL COAGULOPATHIES

#### von Willebrand’s Disease

The hemostatic disorder, von Willebrand’s disease, was named for Erich von Willebrand, who first described it in 1926.128 vWF is synthesized by endothelial cells and megakaryocytes.129 The vWF subunit is 260 to 275 kDa. A dimer is formed by a combination of two subunits, and variable numbers of the dimers are combined to form multimers that range from 500 to 200,000 kDa. vWF plays two primary roles in coagulation: (1) it forms a complex with factor VIII, which decreases the excretion of factor VIII; and (2) it mediates platelet adhesion by binding to collagen and platelets (a reaction enhanced by ristocetin).129,130

von Willebrand’s disease can be divided into several subtypes based on quantitative and qualitative defects in vWF (Table 44.6).131,132 **Type 1 von Willebrand’s disease** is the most common congenital bleeding disorder, which typically is inherited as an autosomal dominant trait that affects up to 1% of the population, and is diagnosed more frequently in women than in men.129,133 In this subtype, vWF functions normally but its levels are reduced. Both vWF and factor VIII increase in normal pregnancy, so antenatal bleeding is rare in women with type 1 disease.129 **Type 2 von Willebrand’s disease** is less common and includes a family of disorders...
is repeated every 12 to 24 hours. For patients who are administered intravenously as labor begins, and the dose-arginine vasopressin ([DDAVP]) is
administered, the usual dose is 40 to 60 IU/kg. For acute bleeding, fresh frozen plasma (FFP) or cryoprecipitate (500 to 1500 units of factor VIII activity) may be administered. During labor, factor VIII and vWF ristocetin co-factor levels should each be maintained at greater than 50 IU/dL. When considering anesthetic and analgesic options, the balance between risks and benefits of a neuraxial procedure should be evaluated for each patient. In women with untreated type 1 von Willebrand’s disease, factor VIII and vWF levels measured in the third trimester of pregnancy reflect intrapartum levels; for example, vWF activity peaks at 2.5 times the baseline values within the first 4 hours after delivery, and falls rapidly in the first postpartum week. Postpartum hemorrhage rates are increased for up to 1 month after delivery. The factor VIII level should be checked daily during the postpartum period, and treatment should be initiated if the factor VIII level decreases below 50% of normal levels or if significant bleeding occurs.

### Other Coagulation Factor Deficiencies

In males, the two most common coagulation factor deficiencies are factor VIII (hemophilia A) and factor IX (hemophilia B). Both occur as X-linked traits. It is possible for a female to have hemophilia if her father is a hemophiliac and her mother is a carrier for hemophilia and passes the abnormal X chromosome to her daughter. A female can also have hemophilia if she is a carrier (i.e., she received one abnormal gene from a carrier mother or an affected father) and she has either a new mutation of the other gene for factor VIII or IX, or another X-chromosome abnormality.

In early embryogenesis, half of the X chromosomes are inactivated. Of the gene population, half of the abnormal genes and half of the normal genes are inactivated in females who are heterozygous for hemophilia A or B. On average, these women have half of the normal concentration of factor VIII or IX, which typically is adequate for coagulation. Because the chromosome inactivation is random, more abnormal genes are inactivated in a certain percentage of carriers, and these women have a normal concentration of factor VIII or IX. However, if most of the normal genes are inactivated, the individual can have severely depressed levels of factor VIII or IX. If such a patient becomes pregnant, factor supplementation with pooled human plasma concentrate (antihemophilic factor/vWF concentrate [hemophilia A] or prothrombin complex concentrate [PCC] [hemophilia B]) may be necessary before or during delivery.

On average, one-half of the male children of heterozygous carriers for hemophilia A or B will have hemophilia. These infants have an increased incidence of excessive bleeding after circumcision, and cephalohematoma with instrumental vaginal birth. Cesarean birth reduces, but does not eliminate the risk for cephalohematoma, when compared with spontaneous vaginal birth; decisions about mode of delivery should be individualized to optimally balance maternal and perinatal risk. During any trial of labor and vaginal delivery, the following procedures should be avoided: (1) placement of a fetal scalp electrode, (2) fetal scalp blood pH determination, and (3) instrumental vaginal delivery. One report has described the administration of epidural analgesia during labor in a patient with severe hemophilia A after factor replacement.

Acquired hemophilia is an autoimmune disease resulting from antibodies to factor VIII and is associated with

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**TABLE 44.6 Classification of von Willebrand’s Disease**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of vWF</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative vWF defects</td>
</tr>
<tr>
<td>2A</td>
<td>Decreased vWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight vWF multimers</td>
</tr>
<tr>
<td>2B</td>
<td>Increased affinity for platelet glycoprotein Ib</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased vWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight vWF multimers</td>
</tr>
<tr>
<td>2N</td>
<td>Markedly decreased binding affinity for factor VIII</td>
</tr>
<tr>
<td>3</td>
<td>Virtually complete deficiency of vWF</td>
</tr>
</tbody>
</table>

vWF, von Willebrand factor.

pregnancy and the postpartum period. Both recombinant factor VIIa (rFVIIa) and factor eight inhibitor bypassing activity (FEIBA) have been used to treat bleeding in patients with acquired hemophilia, but both agents are associated with thromboembolism. Immunosuppression is necessary to treat the underlying cause of the disease.

Other congenital factor deficiencies occur as autosomal recessive traits and cause symptoms only in the homozygous state. Table 44.7 lists the plasma concentrations of coagulation factors that are required for hemostasis. The patient whose liver disease or vitamin K deficiency is responsible for the coagulopathy may benefit from intramuscular administration of vitamin K. In an emergency, factors may be rapidly replaced by administration of the appropriate pooled human plasma product or FFP (10 to 15 mL/kg).

**ACQUIRED COAGULOPATHIES**

Coagulopathies associated with hypertensive disorders of pregnancy and obstetric hemorrhage are discussed in Chapters 35 and 37, respectively. Pharmacologic anticoagulation to prevent and treat venous thromboembolism is discussed in Chapter 38.

**Disseminated Intravascular Coagulation**

DIC results from an abnormal activation of the coagulation system, which leads to (1) formation of large amounts of thrombin, (2) activation of the fibrinolytic system, (3) depletions of coagulation factors, and (4) hemorrhage. In severe cases, diffuse microvascular thrombosis can lead to end-organ injury. In the obstetric population, the most frequent causes of DIC are preeclampsia, placental abruption, sepsis, retained dead fetus syndrome, postpartum hemorrhage, ac|ute fatty liver of pregnancy, and amniotic fluid embolism (Fig. 44.3).69

Laboratory findings consistent with DIC include (1) decreased platelet count, (2) decreased fibrinogen concentration, (3) variable increases in PT and aPTT, and (4) increased concentrations of D-dimer, fibrin monomer, and fibrin degradation products.69 Viscoelastic monitoring confirms delayed clot activation, decreased clot strength, and evidence of fibrinolysis.73

There is no gold standard for diagnosing DIC. A scoring system that incorporates standard laboratory measures has been established by the International Society on Thrombosis and Haemostasis (ISTH) (Table 44.8), and has been shown to predict adverse outcomes in nonpregnant women. Physiologic changes in the hemostatic system in pregnancy decrease the sensitivity of this scoring system to detect DIC. To improve accuracy in pregnant populations, some experts recommend serial laboratory assessment, and to follow trends in the ISTH score.69 Erez143 analyzed laboratory values from 87 women who developed DIC, and compared them against 24,693 control patients to modify the cut-points of the ISTH. Preliminary validation of the modified ISTH scoring system (see Table 44.8) among the 684 women with abruption in the original sample demonstrated superior sensitivity and specificity to detect clinically significant DIC compared with the standard ISTH scoring system.

Therapeutic goals for these patients are to (1) treat or remove the precipitating cause, (2) replace depleted coagulation factors, (3) stop ongoing proteolytic activity (i.e., both the coagulation and fibrinolytic pathways), and (4) provide multisystem support as required.144 In obstetric patients, evacuation of the uterine contents often results in removal of the precipitating cause (see Fig. 44.3).155 Vaginal delivery can be attempted if the mother is stable and delivery can be

**TABLE 44.7 Minimum Coagulation Factor Levels**

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Plasma Concentration Required for Hemostasis (U/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10–25</td>
</tr>
<tr>
<td>II</td>
<td>40</td>
</tr>
<tr>
<td>V</td>
<td>10–15</td>
</tr>
<tr>
<td>VII</td>
<td>5–10</td>
</tr>
<tr>
<td>VIII</td>
<td>10–40</td>
</tr>
<tr>
<td>IX</td>
<td>10–40</td>
</tr>
<tr>
<td>X</td>
<td>10–15</td>
</tr>
<tr>
<td>XI</td>
<td>20–30</td>
</tr>
<tr>
<td>XIII</td>
<td>1–5</td>
</tr>
</tbody>
</table>

*The difference between the result of the patient and that of the laboratory normal control.

DIC, Disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis.


**TABLE 44.8 Scoring Systems to Detect Disseminated Intravascular Coagulation during Pregnancy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ISTH Score</th>
<th>Modified ISTH Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, 100,000/µL</td>
<td>&gt; 100 = 0</td>
<td>&gt; 185 = 0</td>
</tr>
<tr>
<td>&lt; 100 = 1</td>
<td>101–185 = 1</td>
<td></td>
</tr>
<tr>
<td>= 50 = 2</td>
<td>51–100 = 2</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>No increase = 0</td>
<td>Moderate increase = 2</td>
</tr>
<tr>
<td>= Strong increase = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged prothrombin time*</td>
<td>&lt; 3 s = 0</td>
<td>&lt; 0.5 s = 0</td>
</tr>
<tr>
<td>= 3–6 s = 1</td>
<td>0.5–1.0 s = 5</td>
<td></td>
</tr>
<tr>
<td>= 6 s = 2</td>
<td>1.1–1.5 s = 12</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.5 s = 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td>&gt; 1.0 g/L = 0</td>
<td>&gt; 4.5 g/L = 0</td>
</tr>
<tr>
<td>&lt; 1.0 g/L = 1</td>
<td>4.0–4.5 g/L = 1</td>
<td></td>
</tr>
<tr>
<td>= 3.0–3.9 g/L = 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.0 g/L = 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated score</td>
<td>&gt; 5 compatible with overt DIC</td>
<td>&gt; 26 high probability for DIC</td>
</tr>
</tbody>
</table>
Patients with DIC often have multiorgan system failure and require mechanical ventilatory support and care in the intensive care unit (see Chapter 54). DIC almost always mandates administration of general anesthesia in patients who require cesarean delivery. Given the increased risk for venous thromboembolism among patients with DIC, thromboprophylaxis with unfractionated heparin or LMWH (as soon as active bleeding is controlled), mechanical methods, or a combination of multiple methods is indicated.144,147

**NEURAXIAL ANESTHESIA IN THE PATIENT WITH COAGULOPATHY**

Concern exists that an epidural hematoma may develop after the administration of neuraxial anesthesia in patients with coagulopathy (see Chapter 31). There are few published case reports of epidural or spinal subdural hematoma after the administration of neuraxial anesthesia in pregnant patients. Similarly, multicenter survey studies have not reported this complication in obstetric patients.149,150 However, in view of
the serious consequences of an epidural hematoma, the risks and benefits of performing neuraxial anesthesia should be carefully assessed in a patient with either clinical or laboratory evidence of coagulopathy.

Frank coagulopathy represents an absolute contraindication to the administration of neuraxial anesthesia. For patients receiving pharmacologic anticoagulation, professional societies have developed evidence-based guidelines to optimize the safety of neuraxial blockade \(^{127,151}\) (see Chapter 38). For nonbleeding patients with diagnoses that increase the risk for coagulopathy (see Fig. 44.3), the anesthesia provider can use standard laboratory testing (i.e., the platelet count, PT/INR, aPTT, and fibrinogen) or viscoelastic testing, or both to exclude hemostatic derangements before neuraxial blockade. If use of a neuraxial anesthetic technique is considered in a patient with a congenital coagulopathy, results of relevant factor assays should be within the normal range before neuraxial needle placement. \(^{153,141,152}\)

Thrombocytopenia develops in 5% to 10% of healthy women by the end of pregnancy, normally with little clinical consequence, particularly when thrombocytopenia is mild (100,000 to 149,000/µL). \(^{82}\) However, the combination of both quantitative and qualitative platelet deficits presents a more serious risk for epidural hematoma and may develop in the context of severe preeclampsia (see Chapter 35), ATP, and congenital platelet disorders. A number of groups have reported the safe administration of epidural anesthesia—without any neurologic complications—in healthy pregnant women with thrombocytopenia, preeclampsia, and ATP. \(^{153,154}\)

A retrospective cohort study from the Multicenter Perioperative Outcomes Group identified no cases of epidural hematoma requiring surgical decompression among 573 parturients with a platelet count less than 100,000/µL. \(^{154}\) Combined with an additional 951 parturients identified by systematic review, the authors calculated an upper bound of the 95% confidence interval for risk of epidural hematoma to be 11% for a platelet count less than 49,000/µL, 3% for 50,000 to 69,000/µL, and 0.2% for 70,000 to 100,000/µL. \(^{154}\)

Although there is no widespread consensus about the minimum platelet count needed to ensure safe neuraxial procedures, several experts have reviewed the available evidence and concluded that a minimum platelet count of 80,000/µL is usually sufficient for the safe initiation of neuraxial analgesia/anesthesia and removal of a neuraxial catheter. \(^{153,155}\)

Under selected circumstances, neuraxial procedures may be appropriate in a well-counseled patient with a platelet count between 50,000 and 80,000/µL. \(^{155}\) When determining whether neuraxial anesthesia is safe in a thrombocytopenic patient, the anesthesia provider should consider the following factors: (1) clinical evidence of bleeding; (2) time interval since the platelet count was measured; (3) any recent change in the platelet count (e.g., downward trending); (4) quality of platelet function; (5) adequacy of coagulation factor level and function; and, perhaps most importantly, (6) the risk versus benefit of performing neuraxial anesthesia. The bleeding time measurement is not helpful in determining the risk for epidural hematoma. Although viscoelastic monitoring shows some promise, its usefulness in predicting the risk for epidural hematoma is unproven. The use of single-shot spinal anesthesia may be associated with a lower risk for epidural vein trauma than epidural catheter insertion and removal.

Clinical judgment represents the most important means of assessing the risk for epidural hematoma in an individual patient. Clearly, the anesthesia provider would not want to perform neuraxial anesthesia in a patient with clinical evidence of coagulopathy (e.g., bleeding from nasal or oral mucosae or venipuncture sites, presence of petechiae or ecchymoses). In contrast, a surgical patient with severe preeclampsia, severe upper airway edema, a platelet count of 70,000/µL, and no clinical evidence of coagulopathy may be an appropriate candidate for spinal anesthesia. The risk for airway complications with general anesthesia is greater than the risk for an epidural hematoma in such a patient. \(^{156}\)

Neuraxial analgesia may be offered to such a patient after a thorough discussion of the risks and benefits. However, some anesthesia providers advocate a more conservative approach in such cases and recommend alternative methods of analgesia during labor, followed by awake laryngoscopy and tracheal intubation if cesarean delivery should become necessary.

Several modifications of the neuraxial technique may decrease the risk for venous injury during the administration of epidural analgesia: (1) administration of epidural analgesia early in labor before the platelet count or platelet function declines, (2) needle and catheter placement with the patient in the lateral rather than sitting position, (3) the use of a wire-embedded polyurethane rather than polyamide epidural catheter, (4) limiting catheter insertion length to 6 cm or less, and (5) administration of saline through the needle to distend the epidural space before insertion of the catheter. \(^{157}\) The epidural catheter may be sited several hours before the patient requires analgesia. This interval allows the anesthesia provider to observe for symptoms and signs of epidural hematoma formation (e.g., back pain, radicular pain, leg weakness) before the administration of an analgesic or anesthetic solution. This last recommendation is impractical in most circumstances. Furthermore, it is unclear that any of these recommendations reduces the likelihood of epidural hematoma in patients with platelet dysfunction or coagulopathy.

During the administration of epidural analgesia, the anesthesia provider can minimize motor blockade, which might confuse the diagnosis of epidural hematoma, by administering a dilute solution of local anesthetic with an opioid. Lower-extremity motor function should be verified at 1- to 2-hour intervals, and the epidural solution adjusted as needed to maintain lower-extremity strength. In addition, all clinical staff should be aware of the signs and symptoms of epidural hematoma, including (1) severe, unrelenting backache; (2) neurologic deficit, including bowel or bladder dysfunction or radiculopathy; (3) tenderness over the spinous or paraspinal area; and (4) unexplained fever. \(^{158}\) If clinical findings raise concern for epidural hematoma, immediate steps should be taken to obtain appropriate diagnostic imaging and to consult a neurosurgeon (see Chapter 31).
In some cases, severe thrombocytopenia and coagulopathy may develop after the placement of an epidural catheter. Epidural hematomas have been reported after epidural catheter removal in obstetric patients with coagulopathy. It is possible that movement or removal of the catheter may dislodge a clot, resulting in fresh bleeding and an epidural hematoma. As such, recommended hemostatic conditions for epidural catheter removal parallel those recommended for neuraxial block administration.

**HYPERCOAGULABLE STATES**

Effective hemostasis is maintained by an appropriate balance of procoagulant and anticoagulant activity. A congenital deficiency in anticoagulant activity occurs in more than 50% of women with pregnancy-related venous thrombosis. Factor V Leiden mutation, prothrombin mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency are the most common thrombophilias diagnosed in pregnancy. Venous thromboses are more common than arterial thromboses; the incidence increases with surgery, pregnancy, oral contraceptive use, and immobilization. Although the results of small case-control studies have suggested that patients with thrombophilias may have an increased incidence of fetal growth restriction, intrauterine fetal death, preeclampsia, and placental abruption, these associations have not been replicated in large prospective cohorts. There is insufficient evidence that screening for thrombophilias improves birth outcomes for women with a history of pregnancy complications.

The American College of Obstetricians and Gynecologists (ACOG) and the American College of Chest Physicians (ACCP) have recommended thromboprophylaxis for pregnancies complicated by inherited thrombophilias (see Chapter 38). Commonly used anticoagulation regimens during pregnancy are listed in Table 38.2.

**Factor V Leiden Mutation**

Factor V Leiden is a genetic disorder attributable to genetic mutation resulting in a single amino acid substitution in the factor V protein. The mutant protein persists longer in the circulation owing to its slower degradation by activated protein C, leading to a hypercoagulable state. Although heterozygous factor V Leiden affects less than 15% of the childbearing population, these women experience as many as 40% of all obstetric thromboembolic events. Among women with factor V Leiden heterozygosity, a personal history of a venous thromboembolism increases the risk from 1% among those without previous thrombosis to 10% for those with previous thrombosis. A homozygous state is found in 1 in 1600 individuals; these patients have at least a 25-fold higher risk for thrombosis.

**Prothrombin Gene Mutation**

The prothrombin G20210A gene mutation results in elevated circulating prothrombin levels. This gene mutation is present in 2% to 3% of the general population and accounts for up to 17% of cases of venous thromboembolism in pregnancy. For women who are heterozygous for the prothrombin mutation, a personal or family history of venous thrombosis increases the risk for a subsequent venous thromboembolism in pregnancy from less than 0.5% to approximately 10%. Further, the combination of factor V Leiden and prothrombin mutations has synergistic hypercoagulable effects.

**Antithrombin III Deficiency**

Antithrombin III is synthesized in the liver and endothelial cells. It inactivates thrombin and factors IXa, Xa, XIa, and XIIa, its activity is potentiated by heparin. Deficiency of antithrombin III occurs in 0.02% to 0.4% of the general population; the risk for thrombosis in pregnancy is increased up to fivefold. The risk for thrombosis during pregnancy increases from 3% to 7% among those with antithrombin III deficiency and no prior thromboembolism to more than 40% among those with a prior venous thromboembolism. Quantitative (type I) and qualitative (type II) deficiencies exist; thus, both immunologic and functional assays are required to detect abnormalities.

Heparin acts by potentiating the activity of antithrombin III. If antithrombin III levels are decreased, heparin may not ensure effective thromboprophylaxis. Antithrombin III replacement, with or without co-administration of heparin, has been proposed for perioperative or peripartum therapy for patients with antithrombin III deficiency and a history of venous thromboembolism. Although long-term antithrombin III replacement is expensive, its use may be indicated for women who experience venous thrombosis despite thromboprophylaxis with LMWH. Warfarin is an alternative option for women in the second or third trimester of pregnancy, remote from delivery.

**Protein C Deficiency**

Protein C is produced in the liver and acts by inhibiting activated factors V and VIII. Deficiency is defined by an activity level less than 50%. The incidence of protein C deficiency is approximately 0.3% in the general population; the risk for thrombosis in pregnancy is increased up to fivefold. Protein C levels normally increase by 35% during pregnancy, but this increase is attenuated in patients with protein C deficiency. Among women with protein C deficiency, the risk for venous thromboembolism during pregnancy increases from less than 1% among those without previous thrombosis to between 2% and 17% for those with a previous thrombosis.

Protein C is a vitamin K–dependent protein with a short half-life (8 hours). If warfarin is administered without prior heparin anticoagulation, protein C levels decrease before the levels of factors II, VII, IX, and X decrease. Thrombosis with skin necrosis can result.

**Protein S Deficiency**

Protein S acts as a co-factor for protein C. In contrast to protein C, the plasma levels of protein S normally decrease
during pregnancy. The prevalence of protein S deficiency is less than 0.2% in the general population; the risk for venous thromboembolism during pregnancy is increased up to 2- to 4-fold. Protein S is also produced in the liver and depends on vitamin K for its synthesis. Circulating protein S binds to C4b-binding protein (a protein of the complement system), but it is the free fraction of protein S that acts as a co-factor for protein C. Immunologic assays measure total protein S concentration; therefore, a diagnosis of protein S deficiency is made either by using a functional assay (less than 50% activity) or by calculating the percent of protein S bound to C4b-binding protein. The risk for antepartum and postpartum venous thromboembolism is low in patients with protein C or protein S deficiency; hence thromboprophylaxis is not indicated unless the patient has a history of venous thromboembolism or additional risk factors are present.

**Lupus Anticoagulant**

The term lupus anticoagulant is a misnomer. Patients with lupus anticoagulant do not have a coagulopathy; rather, they are at risk for thromboembolic events. The hypercoagulable state associated with lupus anticoagulant is discussed in Chapter 40.

### KEY POINTS

- Blood product preparation is frequently delayed for patients with hemoglobinopathies because of high rates of alloimmunization and extended cross-matching procedures to limit future alloimmunization.
- Lifelong transfusion dependence increases the risk for hemosiderosis, causing primarily cardiac, pulmonary, and hepatic toxicity.
- Neuraxial anesthetic techniques can be used safely during labor and delivery in patients with a hemoglobinopathy.
- Routine laboratory assessment of the platelet count and coagulation status is not indicated before the initiation of neuraxial procedures in healthy parturients.
- The first goal in the treatment of disseminated intravascular coagulation is to treat or remove the precipitating cause. In pregnant patients, evacuation of the uterine contents often results in removal of the precipitating cause.
- Uncorrected, frank coagulopathy represents an absolute contraindication to the administration of neuraxial anesthesia.
- In a patient with an isolated laboratory abnormality and no clinical evidence of coagulopathy, the anesthesia provider should assess the risks and benefits of performing neuraxial anesthesia.

### REFERENCES


Liver Diseases Incidental to Pregnancy

Various hepatobiliary diseases are not unique to pregnancy but may affect pregnant patients. Some of these diseases may have been preexisting before pregnancy, while others may be provoked by pregnancy and may have different clinical courses during pregnancy compared with nonpregnant patients. They can lead to acute or chronic liver failure and have important implications for obstetric and anesthetic management as discussed in the following sections.

Viral Hepatitis

The presentation of viral hepatitis ranges from mild, non-clinical illness to fulminant hepatic necrosis. Viral hepatitis is the most common cause of jaundice and most frequent reason for gastroenterology consultation during pregnancy. Six types—hepatitis A, B, C, D, E, and G—have been identified and are associated with specific viruses. Types A, B, and C are the most common. Infrequently, hepatitis can also be caused by herpes simplex virus (HSV), yellow fever virus, rubella virus, Epstein-Barr virus (EBV), or cytomegalovirus (CMV).

Hepatitis A (HAV) and hepatitis E (HEV) are viral infections of hepatocytes that typically spread by oral ingestion of food or water contaminated with feces from infected individuals. Although endemic in other countries, the current all-time low incidence of HAV of 0.4 per 100,000 in the United States is attributed to good sanitation. Despite its prevalence, it has been infrequently reported among pregnant women. In a study from Ireland, there was only one case of HAV in 13,181 consecutive deliveries. The incidence of HAV infection has also been reduced by vaccination for preexposure prophylaxis; immune globulin is available for postexposure prophylaxis to prevent or attenuate infection. Clinically, a preicteric phase typically occurs with nonspecific viral symptoms, followed by an icteric phase with jaundice and acholic stools. Acute treatment is supportive. Increased risk for preterm labor, premature rupture of membranes, and placental abruption have been associated with HAV during pregnancy, and vertical transmission to the fetus has been reported. Chronic HAV infection does not occur, but a prolonged or relapsing course occurs in up to 20% of patients. HEV infection may be largely asymptomatic. In symptomatic patients, the disease is usually self-limited. Pregnant women and patients already infected with another hepatitis virus, however, have more severe presentations. A mortality rate of 27% has been reported in pregnant women with HEV, a consequence of fulminant hepatic failure. Pregnancy complications such as premature rupture of membranes, placenta previa, retained placenta,
and preterm delivery are also more common. Chronic HEV infection may occur in immunosuppressed patients, and vertical transmission can occur.\textsuperscript{6} Pegylated interferon and/or ribavirin treatment for chronic HEV infection has shown moderate success, and HEV vaccines are under development.\textsuperscript{7}

**Hepatitis B (HBV) and hepatitis D (HDV)** are usually transmitted via percutaneous or permucostral exposure to infected body fluids. In high-prevalence areas, HBV infection is most commonly acquired perinatally or in early childhood. In low-prevalence areas, infection is primarily acquired in adulthood through sexual contact or intravenous drug abuse. The incidence is decreasing after implementation of widespread vaccination and safety precautions in health care settings. Postexposure prophylaxis with HBV vaccination alone or a combination of vaccination with hepatitis B immune globulin (HBIG) is highly effective in preventing HBV transmission in adults as well as in infants of HBV-infected mothers and may prevent perinatal transmission in 90% of cases. The majority of acute infections are asymptomatic, with only 30% of adults developing typical symptoms of hepatitis, and less than 0.5% developing fulminant hepatitis. Most cases can be managed with supportive treatment, although nucleoside analogue therapy may improve prognosis in severe cases. Chronic HBV develops in less than 5% of adults but in more than 20% of children, and exacerbations of chronic HBV may occur in the postpartum period. The 5-year cumulative incidence of cirrhosis in those with chronic HBV may be as high as 20%, and once cirrhosis has developed the annual risk for hepatocellular carcinoma may be as high as 5%.\textsuperscript{8} Therefore, treatment of chronic HBV is aimed at clearance of virus to prevent the development of cirrhosis and cancer. Vertical transmission to the fetus from hepatitis Be antigen (HBeAg)-positive mothers can be as high as 90% without attempts to prevent transmission.\textsuperscript{9} For patients with active disease or high viral loads, oral antiviral therapies (lamivudine, telbivudine, or tenofovir) reduce transmission with apparent increased risk for adverse maternal or fetal outcomes, as does cesarean delivery.\textsuperscript{10} Interferon therapy has a finite course of treatment and an increased chance of viral clearance and significantly reduces the risk for cirrhosis and liver cancer; however, it has more side effects and is contraindicated during pregnancy.\textsuperscript{11} Current recommendations are to administer HBV vaccination to all neonates, and to administer HBIG to all offspring of infected mothers.\textsuperscript{12}

HDV is dependent on HBV co-infection to replicate. Acute co-infection with both viruses can be more severe than acute HBV infection alone and may result in acute liver failure. HDV superinfection in the setting of chronic HBV results in chronic HDV infection in most patients, and these patients have more rapid progression to cirrhosis.\textsuperscript{13}

**Hepatitis C (HCV)** transmission most commonly occurs from transfusion of infected blood products or injection of contaminated drugs (both illicit and iatrogenic). Maternal-fetal and sexual transmission are less common routes of transmission. Initial infection is generally asymptomatic, but up to 30% of patients develop acute hepatitis. In patients with acute HCV infection that has not cleared spontaneously within 12 weeks, treatment with pegylated interferon may be used to prevent chronic infection, with treatment success in up to 98% of patients. In most asymptomatic and untreated cases, infection persists for over 6 months and leads to chronic infection with progression to cirrhosis in up to 30% of patients within 30 years. Thus, HCV is the leading cause of chronic hepatitis, cirrhosis, and liver cancer (which develops in up to 3% of patients per year) and a primary indication for liver transplantation in the developed world. Depending on the severity of liver fibrosis, therapy may be warranted to prevent these complications. Combination treatment with pegylated interferon, ribavirin, and a protease inhibitor can result in a sustained virologic response in up to 80% of patients, but is contraindicated during pregnancy.\textsuperscript{14,15} Various second-generation antiviral drugs have been introduced for single-agent or combination regimens to clear HCV infection, but there are insufficient data to endorse their use during pregnancy.\textsuperscript{16}

**Hepatitis G (HGV)** is transmitted parenterally, sexually, or vertically. In the United States, nearly 20% of all blood preparations are infected with HGV. Although there have been reports of acute, fulminant, and chronic hepatitis and hepatic fibrosis, HGV replicates predominantly in the hematopoietic system rather than in hepatocytes. Clinical significance is mostly for those co-infected with HCV or human immunodeficiency virus (HIV) or for individuals with hematologic cancers.\textsuperscript{17}

**Cholecystitis**

Pregnancy may promote gallstone formation. Cholelithiasis is present in up to 3% of pregnant women, although acute cholecystitis occurs in only 0.1% of pregnancies. Patients may have right upper-quadrant pain, fever, and leukocytosis, and diagnosis is generally made by ultrasonography. Serious complications include cholangitis, pancreatitis, gangrenous cholecystitis, and perforation. To avoid surgery, conservative treatment may be considered in mild cases and includes intravenous hydration, antibiotics, opioid analgesia, bowel rest, and possibly percutaneous cholecystostomy. Although a conservative approach does not seem to be associated with poorer fetal outcomes, treatment failure or disease recurrence during pregnancy are common, so many conservatively managed patients ultimately require surgical treatment.\textsuperscript{18} Both open and laparoscopic cholecystectomy (preferably in the second trimester) can be considered, though laparoscopic techniques offer maternal recovery advantages similar to those in the nonpregnant patient and may have slightly lower fetal complication rates. With either technique, the incidence of miscarriage or preterm labor/delivery is over 25%.\textsuperscript{18,19}

**Liver Abscess**

Liver abscess can develop from infection by a range of organisms with various sites of entry. Organisms with a predilection for the liver include parasites such as *Entamoeba, Echinococcus, Clonorchis*, and *Ascaris*. Direct inoculation during medical instrumentation or hematogenous spread from intravenous drug abuse or endocarditis can occur.
Appendicitis, diverticulitis, or other intra-abdominal infections may spread to the liver. **Fungal infections** are also possible in immunocompromised patients. Management of liver abscess includes antimicrobial agents, percutaneous or open drainage, and possibly surgical resection.20 The condition is rare during pregnancy, but treatment modalities are similar to those described for the nonpregnant patient.21

**Autoimmune Diseases**

Autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis are conditions that may overlap and may also be associated with other extrahepatic autoimmune disorders.22,23 All may lead to end-stage liver disease, and treatment with corticosteroids, other immunosuppressants, and/or ursodeoxycholic acid is aimed at preventing this progression. For advanced and intractable disease, liver transplantation may be necessary. Pregnancy is associated with a 33% incidence of disease flares (mostly in the postpartum period), one-third of which result in maternal hepatic decompensation, liver transplantation, or death. Risks for preterm birth, gestational diabetes, and low birth weight are also significantly increased.24 Immunosuppressive therapy during pregnancy is reportedly safe and effective in reducing disease flares.23

**Vascular Syndromes**

Budd-Chiari syndrome involves thrombosis of the hepatic vein or suprahepatic inferior vena cava and may be associated with pregnancy (comprising nearly one-half of all cases) or other hypercoagulable states. Hepatic venous congestion can also result from right-sided heart failure or other cardiopulmonary diseases that increase central venous pressure or from mechanical compression or compartment syndrome that impedes hepatic venous outflow. This congestive hepatopathy can ultimately lead to fibrosis, portal hypertension, and liver failure. **Portal vein thrombosis** may also occur and cause portal hypertension without cirrhosis. Initial therapy is anticoagulation with low-molecular-weight heparin, and endoscopic screening/treatment and beta-adrenergic receptor blockade (propranolol or nadolol) for prophyaxis of variceal bleeding are also recommended. Liver transplantation may ultimately be required in chronic cases. “**Shock liver**” syndrome can occur in the setting of perioperative hypotension, critical illness with septic shock or cardiac arrest, pulmonary embolus, heart failure, or heatstroke caused by disruption of hepatic arterial and/or portal venous inflow, resulting in acute ischemic/hypoxic hepatitis, especially in the setting of other co-existing liver disease.23–27

**Metabolic Diseases**

Wilson disease is a condition of reduced copper excretion. Gradual copper accumulation in the liver can lead to cirrhosis, while rapid accumulation may result in acute liver failure. Patients may also develop neurologic, ophthalmologic, and renal dysfunction. Fertility is generally reduced in women, but treatment with copper-chelating agents during pregnancy can result in positive outcomes for both the mother and fetus.28 **Hemochromatosis** is a condition of iron accumulation that results in arthropathy, skin pigmentation, diabetes, hypopituitarism, hypogonadism, heart failure, and liver cirrhosis. Phlebotomy (with or without a chelating agent) to deplete iron stores markedly improves survival and prevents most of the complications.29 **α1-Antitrypsin deficiency** results in uncontrolled tissue degradation, with effects predominantly in the lungs and liver. This leads to emphysematous changes in the lung as well as liver cirrhosis.30 Pregnancy can be complicated by fetal growth restriction, preterm labor, and pneumothorax or other respiratory decompensation.21

**Hepatotoxicity**

Hepatotoxicity can result from a variety of exposures. **Acetaminophen (paracetamol),** involved in 20% of drug overdoses during pregnancy, is metabolized by the liver into highly reactive oxides. If their formation exceeds the binding capacity of glutathione, maternal and fetal hepatic injury occurs. Treatment with N-acetylcysteine within 16 hours of acetaminophen ingestion may bind toxic metabolites in both the mother and the fetus and improve outcomes.31 **Alcoholic hepatitis** can result from the acute ingestion of large amounts of alcohol, and chronic alcohol ingestion may lead to cirrhosis.32 Other agents that have potential to cause hepatotoxicity during pregnancy are **antiretroviral drugs** for HIV infection, **propylthiouracil** for hyperthyroidism, **alpha-methyldopa** and **labetalol** for hypertension, **sevoflurane** (given for status asthmaticus), **isoniazid** for tuberculosis, **statins** for antiphospholipid syndrome or hyperlipidemia, **mushrooms** and **herbal supplements,** and **industrial agents.**33–38 In one report, liver transplantation was successfully accomplished during pregnancy to treat acquired propylthiouracil-induced hepatotoxicity.29

**Liver Diseases Specific to Pregnancy**

Liver diseases specific to pregnancy are summarized in Table 45.1.

**Hyperemesis Gravidarum**

Hyperemesis gravidarum occurs in 0.3% to 3% of pregnancies and is characterized by a severe and persistent form of nausea and vomiting that can lead to dehydration and electrolyte imbalances, as well as elevated liver transaminases, mild jaundice, and transient hyperthyroidism (see Chapter 16). The possible etiologies include hormonal, infectious (e.g., *Helicobacter pylori*), mechanical (e.g., gastroesophageal reflux), genetic, and psychogenic causes. Treatment with **ginger,** vitamin supplementation (pyridoxine) and antiemetics (e.g., doxylamine, metoclopramide, promethazine, ondansetron) is beneficial. Severe cases may require corticosteroids, rehydration, and enteral or parenteral nutrition. Adverse pregnancy outcomes are rare but may occur in women who fail to gain adequate weight during pregnancy.40

**Intrahepatic Cholestasis of Pregnancy**

Intrahepatic cholestasis of pregnancy occurs with an incidence ranging from less than 2% in Europe up to 25% in
some populations of South America, with the large variation possibly related to population genetics. Other risk factors include multiple gestation, advanced age, and hepatitis C infection. Proposed causes include genetic canalicular transporter mutations that alter phospholipid or bile salt transport across hepatocyte membranes, as well as abnormal steroid hormone profiles, resulting in pruritus and elevated serum bile acid levels during the second or third trimester. Pruritus, primarily on the palms and soles, is more severe at night, and may lead to excoriations resulting from scratching, though jaundice is unusual.}

Intrahepatic cholestasis of pregnancy has minimal impact on maternal health during gestation. By some reports, vitamin K malabsorption may lead to coagulopathy (incidence of abnormal coagulation tests up to 20%) and an increased incidence of postpartum hemorrhage, while others have found no increased risk for obstetric bleeding or neuraxial hematoma. While maternal outcome is generally good, the fetus may be at increased risk for prematurity and fetal compromise, with reported incidence of such fetal complications ranging from 19% to 64%.

Acute fatty liver of pregnancy (AFLP), or reversible peripartum liver failure, occurs in up to 1 in 7000 pregnancies. It is more common in twin gestations and has been associated with preeclampsia and HELLP syndrome. The disease is characterized

**TABLE 45.1 Liver Diseases Specific to Pregnancy**

<table>
<thead>
<tr>
<th>Incidence/Presentation</th>
<th>Hyperemesis Gravidarum</th>
<th>Intrahepatic Cholestasis of Pregnancy</th>
<th>Preeclampsia/Eclampsia</th>
<th>HELLP Syndrome</th>
<th>AFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence/Presentation</td>
<td>&lt; 0.3%–3%</td>
<td>0.3%–6%</td>
<td>2%–8%</td>
<td>0.1%–0.6%</td>
<td>&lt; 0.01%</td>
</tr>
<tr>
<td>Presentation</td>
<td>First trimester</td>
<td>Second or third trimester</td>
<td>Second or third trimester, or after delivery</td>
<td>Second or third trimester, or after delivery</td>
<td>Third trimester</td>
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<tr>
<td>Symptoms, Signs, and Complications</td>
<td>Nausea/vomiting</td>
<td>Pruritus</td>
<td>Hypertension</td>
<td>Abdominal pain</td>
<td>Nausea/vomiting</td>
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<td>Ketonis</td>
<td>Jaundice</td>
<td>Proteinuria</td>
<td>Renal dysfunction</td>
<td>Abdominal pain</td>
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<td>Seizures</td>
<td>Hepatic hemorhoma/rupture</td>
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<td>Renal failure</td>
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<td>Pulmonary edema</td>
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<td>Laboratory Findings</td>
<td>Elevated aminotransferase levels</td>
<td>Increased serum bile acid levels</td>
<td>Low platelet count</td>
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<td>Hyperbilirubinemia</td>
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<td>Mild abnormalities of liver function tests</td>
<td>Increased uric acid level</td>
<td>Markedly elevated aminotransferase levels</td>
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<td>Treatment</td>
<td>Supportive management</td>
<td>Delivery at fetal maturity</td>
<td>Blood pressure control</td>
<td>Prompt delivery</td>
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<td>Ursodeoxycholic acid</td>
<td>Seizure control</td>
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<td>Delivery</td>
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<tr>
<td>Outcome</td>
<td>Benign for mother and fetus</td>
<td>No increase in maternal death rate</td>
<td>Increased risk for maternal morbidity and mortality</td>
<td>Maternal death rate 1%–4%</td>
<td>Maternal death rate up to 10%</td>
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<tr>
<td></td>
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<td>Increased risk for preterm delivery and fetal loss</td>
<td>Increased risk for perinatal morbidity</td>
<td>Fetal death rate 1%–30%</td>
<td>Fetal death rate up to 20%</td>
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<td>May recur with subsequent pregnancies</td>
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<td>Increased risk for subsequent liver and biliary tract disease</td>
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by microvesicular fatty infiltration of the liver (and possibly kidney) believed to be caused by defective beta oxidation of fat, usually in the third trimester. In AFLP, genetic enzymatic defects in the fetus (e.g., fetal long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency) and placenta are thought to cause toxic free fatty acid metabolites to build up in maternal hepatocytes. Early symptoms are nonspecific and include anorexia, nausea, emesis, malaise, fatigue, and headache. Jaundice, edema, hypertension, hypoglycemia, diabetes insipidus, and encephalopathy may develop. Progression to fulminant hepatic and renal failure, disseminated intravascular coagulation (DIC), and acute respiratory distress syndrome (ARDS) can be rapid. AFLP is commonly misdiagnosed as preeclampsia or HELLP syndrome because of a similar constellation of presenting symptoms. After additional laboratory tests (e.g., renal function), the definitive diagnosis can be made. Rarely, percutaneous or transjugular liver biopsy to identify microvesicular fatty infiltration of hepatocytes may be needed for diagnosis in indeterminate cases. Similarities between AFLP and preeclampsia or eclampsia are intriguing. Both disorders primarily occur near term and are associated with nulliparity and multiple gestation. AFLP is a medical emergency that demands rapid evaluation and treatment. Hepatic failure and fetal death may occur within days. Once the diagnosis is made, immediate delivery of the fetus or termination of the pregnancy is recommended. Additional supportive care may include transfusion, mechanical ventilation, dialysis, plasmapheresis, antibiotics, and N-acetylcysteine. Mode of delivery is not as critical as is doing so expeditiously. Liver transplantation may be indicated in severe cases. The anesthesia provider should anticipate postpartum hemorrhage, establish adequate intravenous access, and ensure that cross-matched blood is immediately available for any parturient with AFLP. The use of neuraxial anesthesia may be limited by coagulopathy, encephalopathy, and ascites, respiratory compromise, or other contraindications. Evisceration is avoided if possible, and abdominal delivery may be complicated by wound dehiscence related to coagulopathy; delayed wound closure may be indicated.

Improvements in diagnosis and management have reduced maternal mortality rates (once as high as 85%) to less than 10% worldwide. Recovery typically occurs within 1 to 3 weeks, though it is unclear if there are significant long-term maternal sequelae. Fetal mortality may be as high as 20% as a result of the maternal milieu as well as preterm delivery.

**Spontaneous Hepatic Rupture of Pregnancy**

From 2000 to 2010, only 93 cases of hepatic rupture in pregnancy had been published. Hepatic rupture may complicate preeclampsia, eclampsia, HELLP syndrome, and AFLP, or it may be an isolated event. By definition, spontaneous hepatic rupture of pregnancy occurs in the absence of antecedent trauma. Instead, rupture is preceded by an intraparenchymal hepatic hematoma. The strong association with preeclampsia suggests that perportal hemorrhagic necrosis, hypertension, and coagulopathy may lead to hematoma formation. With expansion of the hematoma, the hepatic capsule is progressively distended and dissected from the parenchyma, leading to rupture. Primary hepatic pregnancy with embryonic implantation on the liver is another rare condition that can result in liver hemorrhage and shock. In the early postpartum period, growth of hepatic hemangiomas, adenomas, or other potentially hemorrhagic masses may occur.

Diagnostic ultrasonography, computed tomography, magnetic resonance imaging, angiography, technetium scintigraphy, and exploratory laparotomy may demonstrate the expanding hematoma before rupture. Hematomas that are contained within the liver may be conservatively managed with intravenous fluids and blood products. More aggressive treatment options include open laparotomy, hepatic artery ligation or embolization, and compression of bleeding points with hepatic packing. Recombinant factor VIIa may be considered in the presence of intractable hemorrhage (although it is controversial), and liver transplantation can be considered as a last resort. Maternal and fetal mortality rates with current therapy are 17% and 38%, respectively.

**LIVER FUNCTION AND DYSFUNCTION**

Regardless of the disease state and whether it is incidental or unique to pregnancy, the signs and symptoms of acute and chronic liver diseases are similar.

**Markers of Liver Dysfunction**

The liver performs a variety of physiologic functions, derangements of which are characteristic of liver diseases (Box 45.1). Amino acid metabolism in the liver uses enzymes that include alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Levels of these enzymes are generally normal in pregnancy, but hepatocyte injury leads to their release (commonly called “transaminits”) into the blood, where abnormal serum levels can be detected. The liver also removes bilirubin produced from heme metabolism in the blood. Thus, liver dysfunction can lead to accumulation of bilirubin that becomes symptomatic as jaundice. Gluconeogenesis can be impaired by liver dysfunction leading to hypoglycemia and accumulation of lactate. Synthetic functions of the liver include production of albumin and coagulation factors. Although albumin concentration normally decreases during pregnancy secondary to increased maternal plasma volume, prothrombin time (PT) is unchanged during normal pregnancy; therefore, an increase in PT is an indicator of possible liver disease. Decreased thrombopoietin production in the liver, along with hypersplenism from portal hypertension, may lead to thrombocytopenia. Alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) are found in biliary tract cells. ALP is normally increased during pregnancy because of fetal and placental production, but an elevated level of GGT is suggestive of biliary disease. Detoxification functions of the liver are responsible for clearance of many toxic metabolites and drugs. Failure of conversion of ammonia to urea in the liver results in accumulation of ammonia and consequent encephalopathy. Decreased clearance of estrogen and progesterone with liver disease may
cause hyperventilation, and other signs of a hyperestrogenic state such as telangiectases and palmar erythema, although this may occur even in normal pregnancies because of increased production by the placenta. Various antigens and antibodies also show characteristic patterns of abnormalities in autoimmune and infectious forms of hepatitis and can be used for diagnosis and treatment monitoring.26,55

**Acute Liver Failure**

Acute (or fulminant) hepatic failure is an extreme complication of liver disease specific or incidental to pregnancy. Because the liver is responsible for many physiologic processes, liver failure manifests in profound ways that may be life-threatening. A patient’s condition can deteriorate in an unpredictable and rapid manner, and the patient may require management in a critical care setting. Treatment is mostly supportive, except in cases with specific anecdotal or proven therapies (e.g., immediate delivery for pregnancy-related causes,56 N-acetylcysteine therapy for acetaminophen toxicity, lamivudine for acute HBV infection, penicillin therapy in *Amanita phalloides* intoxication, chelating agents in Wilson disease, steroid therapy for autoimmune hepatitis). Despite advances in care, maternal mortality in women with acute liver failure still remains as high as 55%.57

**Encephalopathy** results from reduced hepatic ammonia metabolism that leads to astrocytic glutamine accumulation and cerebral edema. Subtle mental status changes are followed by somnolence and disorientation, then by incoherence, and finally by coma. Use of invasive intracranial pressure (ICP) monitoring to determine cerebral perfusion pressure (CPP) is controversial because of questionable usefulness and concerns about intracranial bleeding from the procedure. If monitored, ICP should be maintained below 25 mm Hg, and CPP should be maintained above 50 mm Hg. Jugular bulb oxygen saturation can provide information about cerebral oxygen use, with levels below 55% indicative of cerebral hypoperfusion and levels above 85% suggestive of cerebral hyperemia or inadequate neuronal metabolism.58

Patients should be kept in a quiet room with the head of the bed elevated more than 30 degrees. N-acetylcysteine given early may decrease cerebral edema and improve survival. Mannitol or hypertonic saline infusion may be used to manage intracranial hypertension. Indications for tracheal intubation include (1) progressive encephalopathy; (2) acute respiratory distress syndrome (ARDS); (3) pulmonary aspiration prevention; (4) sedation for agitation, which can contribute to increased ICP; and (5) hyperventilation for refractory intracranial hypertension. High tidal volumes and levels of positive end-expiratory pressure (PEEP), hypercarbia, and frequent suctioning should be avoided. Hyperthermia should be actively treated, but deliberate hypothermia has not proven beneficial. Phenytoin or propofol can effectively decrease the risk for seizure activity. For patients whose ICP and CPP have been refractory to therapy, a technetium-99m albumin scan can document the absence of cerebral blood flow so that these patients can be removed from the liver transplant waiting list.

**Immune dysfunction** is related to loss of Kupffer and other immune cell function, and complications of bacterial or fungal infections are a leading cause of mortality. Infection and sepsis have been associated with progression to high-grade encephalopathy and poorer outcomes, though prophylactic antimicrobial therapy does not appear to improve survival compared with surveillance and treatment only as needed.59

**Coagulopathy** results from impaired synthesis of coagulation factors, most of which are produced in the liver, and from thrombocytopenia, which may be caused by reduced hepatic thrombopoietin production, acute portal hypertension with splenic sequestration, and reduced marrow production. DIC may also develop. Mucocutaneous, gastrointestinal, and iatrogenic bleeding can all occur in this setting. Cholestasis leads to malabsorption of vitamin K, an important cofactor required for the synthesis of factors II, VII, IX, and X. A therapeutic trial of vitamin K may be attempted if malabsorption is the primary defect, but women with impaired hepatic synthesis do not respond. Routine use of fresh frozen plasma or platelet transfusion is not recommended except when there is evidence of active bleeding or an invasive procedure is planned. Proton-pump inhibitors may help prevent

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**Box 45.1 Signs and Symptoms of Liver Disease**

**Laboratory Findings**

- Increased
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Gamma glutamyl transferase (GGT)
  - Bilirubin
  - Lactate
  - Prothrombin time/international normalized ratio (PT/INR)
  - Ammonia
  - Thrombocytopenia
  - Hypoglycemia
  - Hypoalbuminemia
  - Metabolic acidosis
  - Respiratory alkalosis
  - Immune dysfunction
  - Renal dysfunction
  - Decreased systemic vascular resistance
  - Portal hypertension and varices
  - Pulmonary hypertension

**Symptoms and Physical Findings**

- Jaundice
- Pruritus
- Abdominal pain
- Decreased appetite
- Telangiectases
- Palmar erythema
- Easy bruising
- Gastrointestinal bleeding
- Ascites
- Encephalopathy
gastric stress ulcers and bleeding. Although liver failure is generally thought to be a hypocoagulable state, it can also be a hypercoagulable state, with clinical manifestations that are difficult to predict and cannot be effectively prevented by prophylactic treatment with blood product transfusions.60

Circulatory dysfunction is common because of low systemic vascular resistance, and subclinical myocardial injury is common. Fluid resuscitation is the initial treatment for hypotension, but fluid overload can increase the risk for cerebral edema and acute lung injury. Norepinephrine and vasopressin are preferred agents for maintaining CPP. Corticosteroids may be considered for patients unresponsive to vasopressors with suspected relative adrenal insufficiency.

Increased production and reduced hepatic uptake of lactate results in metabolic acidosis. In addition, renal function is impaired in up to 40% of patients. Renal failure, acidemia, electrolyte disturbances, or volume overload necessitate renal replacement therapy with continuous venovenous hemofiltration with dialysis. Decreased gluconeogenesis can lead to hypoglycemia, whereas hyperglycemia may worsen neurologic outcome. Enteral feeding is preferred to parenteral nutrition, although parenteral nutrition with hypocaloric, low-glutamine, and normal protein formula appears to be safe.

For patients who are not expected to recover liver function necessary for survival, liver transplantation may be planned. In patients with toxicity from massive liver necrosis, total hepatectomy and temporary portocaval shunting can be performed in the interim, while awaiting a donor organ. Auxiliary partial orthotopic liver transplantation has also been performed, where only one-half of the native liver is resected and transplanted, allowing the native liver time to recover/regenerate and eventually allowing the donor liver to be rejected, avoiding lifelong immunosuppression. Artificial and bioartificial liver-support devices are also under development.62,65-68

Cirrhosis and Chronic Liver Failure

Any chronic liver disease can progress to cirrhosis, which is characterized by diffuse hepatic fibrosis. Cirrhosis may be asymptomatic until up to 90% of the hepatic parenchyma is destroyed or until a comorbidity causes decompensation. Many manifestations are similar to those of acute liver failure, although gradual in onset and of lesser severity, whereas others are unique to cirrhosis. Pregnancy is rare in patients with cirrhosis (approximately 1 in 6000 pregnancies) because cirrhosis is uncommon in women of reproductive age and because hormonal changes can cause anovulation and infertility in those who are cirrhotic during childbearing age. Risks for preeclampsia, preterm delivery, low birth weight, small for gestational age, and neonatal death appear to be increased in cirrhotic parturients.64

Hepatic fibrosis causes increased resistance to portal blood flow, resulting in portal hypertension that promotes blood flow through portosystemic anastomoses such as esophageal, hemorrhoidal, and other intra-abdominal veins. Congestion and dilation of these collateral vessels increases the risk for spontaneous or iatrogenic bleeding. In addition, coagulopathy of cirrhosis resulting from decreased clotting factor production and thrombocytopenia can exacerbate bleeding from many causes. Esophageal variceal bleeding has been reported in up to 32% of pregnant women with cirrhosis, 50% of those with known portal hypertension, and 78% of those with pre-existing varices, with a mortality rate up to 50%. It most commonly occurs later in pregnancy when maternal blood volume is expanded and fetal growth causes compression of collateral vessels. Bleeding risk theoretically increases during labor because of the repetitive intra-abdominal pressure increases, especially from pushing during the second stage, though few cases of variceal bleeding at the time of delivery have been reported. Elective cesarean delivery for women with known varices has been suggested to avoid Valsalva-related pressure and variceal bleeding, but surgical delivery also carries the risk for bleeding from abdominal wall collateral vessels. Therefore, an attempt at vaginal delivery (possibly with forceps to shorten the second stage of labor) may be considered before cesarean delivery.65 Screening for varices and prophylaxis against bleeding should be considered early in the pregnancy. Nonselective beta-adrenergic receptor antagonists can decrease the risk for variceal bleeding by reducing portal pressure through reduction of cardiac output and splanchnic vasoconstriction, but have been associated with fetal bradycardia, growth restriction, and hypoglycemia. Prophylactic endoscopic band ligation or surgical portocaval shunting may also be considered in high-risk parturients. For acute esophageal variceal hemorrhage, endoscopic band ligation (after tracheal intubation for airway protection) is the first-line management. Octreotide infusion may also be considered, although its safety has not been proven in pregnant patients. Transjugular intrahepatic portosystemic shunting may be considered for refractory variceal bleeding (see later discussion).66 Surgical shunt procedures may also be considered in extreme cases.

Splenic artery aneurysms may also develop in cirrhotic parturients, and rupture in late pregnancy carries high maternal and fetal mortality rates.67 Management options include splenectomy, transcatheter embolization, and stent-graft placement. Postpartum uterine hemorrhage, a consequence of coagulopathy, is another potential source of maternal morbidity and mortality, occurring in up to 10% of pregnancies in patients with cirrhosis.

Encephalopathy secondary to ammonia accumulation may occur in cirrhotic patients and may be precipitated or exacerbated by sedative medications, infection, hypoglycemia, gastrointestinal hemorrhage, hypotension, or hypoxemia. Management includes correction of precipitating factors and reducing the nitrogenous load from gastrointestinal tract with oral, nonabsorbed antimicrobial agents such as lactulose and neomycin. Flumazenil may also improve mental status transiently, and bromocriptine may improve extrapyramidal symptoms, although these have not been studied extensively in cirrhotic parturients.

Massive ascites appears to be uncommon in pregnancy, possibly because the increased intra-abdominal pressure
been reported worldwide. Successful pregnancy outcome has been rare during pregnancy.\textsuperscript{68–74} Vasodilation and shunting resulting in hypoxemia appears to be a common complication in cirrhotic parturients. Similarly, renal dysfunction secondary to splanchnic and systemic vasodilation of cirrhosis, does not appear to be caused by intrapulmonary vascular resistance caused by arteriolar medial hyperplasia, thrombosis, or fibrosis, and eventually right-sided heart failure, has been reported as a complication during pregnancy, resulting in postpartum maternal death.\textsuperscript{68} \textbf{Hepatorenal syndrome}, renal dysfunction secondary to splanchnic and systemic vasodilation of cirrhosis, does not appear to be a common complication in cirrhotic parturients. Similarly, \textbf{hepatopulmonary syndrome} caused by intrapulmonary vasodilation and shunting resulting in hypoxemia appears to be rare during pregnancy.\textsuperscript{68–74}

\section*{Liver Surgery}

\subsection*{Liver Transplantation during Pregnancy}

Fulminant hepatic failure during pregnancy may necessitate liver transplantation if supportive measures prove inadequate and maternal death is likely without transplantation. In second-trimester pregnancies, pregnancy following transplantation has been continued with good maternal and fetal outcomes possible. In third-trimester pregnancies, combined cesarean delivery and liver transplantation have also resulted in positive maternal and fetal outcomes.\textsuperscript{75} In some cases, liver failure first develops or worsens postpartum after spontaneous labor and delivery and necessitates transplantation. A cadaveric organ can be used for transplantation or, if unavailable in the required timeframe, a living donor graft can be utilized. Auxiliary grafts may be implanted in parallel with the native liver left \textit{in situ} when the donor graft is too small to work independently, or when eventual native liver recovery is anticipated, after which the graft can be explanted and immunosuppression discontinued.\textsuperscript{48,75–81} In patients for whom a matching organ cannot be found, artificial liver systems have been used temporarily while awaiting an organ or spontaneous recovery of the native liver.\textsuperscript{82,85}

The literature is insufficient to make evidence-based recommendation about specific anesthetic and surgical techniques (e.g., venovenous bypass versus piggyback/caval preservation) for liver transplantation during pregnancy.

\subsection*{Pregnancy after Liver Transplantation}

In 1978, the first pregnancy in a liver transplant recipient was reported.\textsuperscript{86} Subsequently, hundreds of such pregnancies have been reported worldwide. Successful pregnancy outcome has even been achieved after triple organ transplantation (small intestine, liver, and pancreas).\textsuperscript{85}

Approximately 8% of liver transplant recipients are females of reproductive age, and the hormonal changes of chronic liver disease that disrupt menstruation are usually corrected by transplantation, with 74% of women recovering regular menstrual cycles within 1 year. Still, it is recommended that pregnancy be delayed for 1 to 2 years after transplantation until such time as graft function has stabilized on a low-dose immunosuppression regimen with low teratogenic potential.\textsuperscript{86}

Pregnancy after liver transplantation carries an increased risk for preterm birth, fetal growth restriction, and maternal graft dysfunction. Cesarean delivery is commonly necessary for obstetric indications. Posttransplant thrombocytopenia is of particular concern since it is has implications for neuraxial anesthesia during labor and delivery as well as blood loss during cesarean delivery.

\subsection*{Liver Resection}

Benign and malignant liver tumors may occur during pregnancy in patients with or without chronic underlying liver disease. Hepatic ectopic pregnancy may also occur. Surgical resection, where feasible, is the definitive treatment.\textsuperscript{87} Partial hepatectomy has been reported during pregnancy with favorable maternal outcomes. Management of the pregnancy has ranged from termination\textsuperscript{88} to simultaneous cesarean delivery,\textsuperscript{89} to later spontaneous vaginal delivery.\textsuperscript{90} There are inadequate data to make specific recommendations about the intraoperative management of liver resection during pregnancy compared with nonpregnant patients, including the role of vascular clamping and maintenance of low central venous pressure to reduce blood loss.\textsuperscript{91}

\subsection*{Transjugular Intrahepatic Portosystemic Shunt}

Indications for a transjugular intrahepatic portosystemic shunt include variceal bleeding and massive ascites refractory to other therapies. Contraindications include right-sided heart failure, polycystic liver disease, severe hepatic failure, systemic infection, hepatic encephalopathy, hepatic tumors, and portal vein thrombosis. The procedure involves accessing a jugular vein, fluoroscopically guiding an endovascular needle into a hepatic vein, and then perforating the liver parenchyma until the needle tip reaches an intrahepatic portal vein. An endovascular stent is then placed across the liver parenchyma to maintain the shunt. The communication created between the portal and systemic venous systems decompresses the portal system, thereby decreasing the pressure that was causing bleeding and formation of ascites.\textsuperscript{92} This procedure has been successfully performed during pregnancy and can be done with radiation-limiting techniques that minimize exposure to the fetus and allow the pregnancy to continue.\textsuperscript{56,93}

\section*{Anesthetic Considerations}

Anesthetic management is influenced by the extent of hepatic impairment. If hepatic synthetic and metabolic functions are
The liver’s numerous metabolic functions include clearance of drugs as well as synthesis of plasma proteins that bind drugs. Liver disease, therefore, can alter the normal pharmacokinetics of anesthetics and other drugs. Drug clearance may be decreased by hepatocyte dysfunction or reductions in liver blood flow. Impaired hepatic synthesis of plasma proteins can lead to decreased drug binding and increased free fraction of drugs. This makes more drug available for clearance by the liver, but at the same time increases tissue availability and effective volume of distribution, which can alter drug effects and clearance. Overall, severe liver disease can decrease clearance of various agents, and repeated or continuous administration can lead to drug accumulation and adverse effects. Additionally, compared with their effects in healthy individuals, anesthetic agents at any concentration may cause increased sedation or decompensation in patients already compromised by hepatic encephalopathy.

Clearance of some opioids, including morphine, meperidine, and alfentanil may be decreased in patients with advanced liver disease. Other opioids, including fentanyl and sufentanil, do not appear to have significantly impaired clearance, although repeated or continuous dosing may be problematic. Remifentanil undergoes breakdown by plasma and tissue esterases, and so its pharmacokinetics are not significantly changed. Methadone also appears to have nearly normal disposition. Codeine, which requires hepatic conversion to morphine for analgesia and clearance, may not be safe or effective, and similar uncertainty exists regarding tramadol. Prolonged effects can also be seen with etomidate and benzodiazepines including midazolam and diazepam, whereas propofol, methohexital, and thiopental clearances are unchanged after anesthesia induction doses. Neuromuscular blocking agents normally cleared by the liver...
Neuraxial Anesthesia

Neuraxial analgesia/anesthesia is the preferred technique for labor, vaginal delivery, and cesarean delivery and can be offered to patients with liver disease in the absence of significant intravascular volume depletion or a coagulopathy. Before administration of a neuraxial technique, a full coagulation profile and platelet count should be obtained and intravascular volume assessed. Epidural techniques in particular may have added risk in patients with portal hypertension because the epidural venous plexus is engorged even beyond that of normal pregnancy and could predispose to intravascular needle/catheter placement or epidural hematoma. The potential for impaired clearance of local anesthetics and opioids described earlier should also be considered, especially when repeated boluses or continuous infusions are used. There are no data indicating that one local anesthetic is clearly superior to another for epidural analgesia, and we use our standard epidural infusion of bupivacaine with fentanyl for labor analgesia. Single-shot spinal techniques with small-gauge needles may minimize the issues of drug metabolism and bleeding, although with possibly increased risk for acute hypotension and reduced liver blood flow.

General Anesthesia

Coagulopathy, obstetric hemorrhage, altered mental status, and severe fetal compromise may necessitate the use of general anesthesia for cesarean delivery. Intravascular volume should be evaluated before induction. Invasive blood pressure monitoring and pulmonary artery catheterization may be useful in the patient with cardiovascular compromise or portopulmonary hypertension. Large-bore intravenous access should be established, and blood products should be available. Gastric acid neutralization should precede rapid-sequence induction and tracheal intubation. All standard induction agents are safe, and the dose should not be altered. Liver disease and reduced pseudocholinesterase concentrations may delay the metabolism of succinylcholine, but the delay is of negligible clinical importance. Succinylcholine thus remains the muscle relaxant of choice during rapid-sequence induction of general anesthesia, and it should be administered in the same dose as for healthy parturients. For patients with contraindications to succinylcholine, rocuronium may be used. Sugammadex may be considered for emergent or routine reversal of rocuronium, but this agent has not been studied in patients with liver dysfunction and may worsen coagulopathy in this setting. Careful gastric tube placement may be considered, even in the presence of esophageal varices.

For maintenance of anesthesia, agents that do not undergo significant hepatic metabolism (e.g., isoflurane, desflurane, atracurium, cisatracurium, remifentanil, and nitrous oxide) may be preferable to other inhalational agents that further reduce liver blood flow or intravenous agents that may accumulate before clearance. Reversal of neuromuscular blockade must be ensured before tracheal extubation. To this end, sugammadex pharmacodynamics in cirrhotic patients appear to be similar to controls.

Postoperative Care

Although clearance is delayed in patients with severe liver disease, intravenous opioids may be administered judiciously to provide postoperative analgesia. Neuraxial opioids, especially a single dose of morphine, may obviate any accumulation issues. Advanced liver disease can lead to hepatic encephalopathy. Neurologic deterioration in the postoperative period may result from the residual effects of anesthetic agents, acute liver decompensation, or an intracranial process. Other postoperative complications to be anticipated include paracentesis-induced circulatory dysfunction, decompensation of preexisting liver disease, cirrhotic cardiomyopathy, hepatoportal syndrome, and hepatopulmonary syndromes. Perioperative strategies to avoid these (e.g., administration of albumin, terlipressin, norepinephrine, midodrine, octreotide, N-acetylcysteine) may be considered.

KEY POINTS

- Liver disease can be either incidental or unique to pregnancy and complicates as many as 3% of all pregnancies.
- Viral hepatitides are the most common cause of jaundice during pregnancy.
- All pregnant women should be screened for hepatitis B virus, and all neonates should be vaccinated against it.
- Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy that demands rapid evaluation and prompt delivery.
- AFLP is commonly misdiagnosed as preeclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome because of a similar constellation of presenting symptoms.
- Hepatic rupture may complicate preeclampsia/eclampsia, HELLP syndrome, or AFLP, and the mortality rate can be greater than 60%.
- Encephalopathy may result from reduced hepatic ammonia metabolism.
• Coagulopathy may result from impaired synthesis of coagulation factors and from thrombocytopenia. paradoxically, in some cases, liver failure may result in hypercoagulability.
• Renal failure and cardiovascular, renal, pulmonary, and immune dysfunction may accompany liver failure.
• Women with portal hypertension may develop esophageal varices that are prone to bleed during the third trimester of pregnancy, and this risk increases during labor.
• Successful pregnancy is common after liver transplantation, and pregnancy does not affect the long-term survival of hepatic allografts, though pregnancy complications are more common.
• Liver disease can alter the normal pharmacokinetics of anesthetics and other drugs.
• Both neuraxial and general anesthesia can be administered safely to the parturient with liver disease, with close attention to hemodynamics to preserve hepatic blood flow.
• Neuraxial analgesia/anesthesia is the preferred technique for labor, vaginal delivery, and cesarean delivery and can be offered to patients with liver disease provided significant intravascular volume depletion and coagulopathy have been excluded.
• Hepatic, neurologic, cardiovascular, renal, and pulmonary complications should be anticipated in the postpartum period in patients with significant liver disease.

REFERENCES


Malignant Hyperthermia

M. Joanne Douglas, MD, FRCPC

CHAPTER OUTLINE

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Malignant hyperthermia (MH) is an inherited disorder of skeletal muscle. On exposure to triggering agents (e.g., succinylcholine, volatile halogenated anesthetic agents), affected individuals demonstrate a hypermetabolic syndrome characterized by hypercapnia, acidosis, muscle rigidity, arrhythmias, and hyperthermia. MH was first described in 1960 by Denborough and Lovell, but may have been responsible for some of the earlier deaths attributed to ether and chloroform anesthesia.

EPIDEMIOLOGY

Ordning, reviewing the incidence of MH in Denmark, noted that the incidence of the fulminant syndrome (e.g., muscle rigidity, acidosis, hyperkalemia, arrhythmias, hyperthermia, increased creatine kinase [CK] levels, myoglobinuria) was 1 in 220,000 patients who received general anesthesia and 1 in 62,000 patients in whom succinylcholine was combined with a volatile halogenated agent. MH (either mild or fulminant) was suspected in 1 in 16,000 patients who received anesthesia of any type. The male-to-female ratio was 1.4:1. MH appears in all ethnic groups and throughout the world.

There are few reports of development of MH during pregnancy and parturition. The infrequent occurrence during pregnancy probably reflects both the low frequency of this disorder in the general population and the widespread use of local and neuraxial anesthetic techniques in obstetric patients.

PATHOPHYSIOLOGY

MH is the result of a disorder in the regulation of intracellular calcium in skeletal muscle. The precise mechanism by which volatile anesthetics and depolarizing muscle relaxants cause an MH crisis is still unknown. In muscle, the sarcoplasmic reticulum is responsible for controlling calcium release and reuptake during muscle contraction. During skeletal muscle excitation-contraction coupling, calcium is released from the terminal sarcoplasmic reticulum via the ryanodine receptor (RYR1). Dihydropyridine receptors (DHPR) in the T-tubule membrane also participate in the excitation-contraction coupling. In humans, mutations in both the dihydropyridine and ryanodine receptor genes can result in clinical MH. Dantrolene inhibits excitation-contraction coupling, and succinylcholine, caffeine, and volatile halogenated agents increase it.

GENETICS

MH is a heterogeneous disorder, meaning that more than one gene defect is responsible for expression of the clinical syndrome. It is inherited in an autosomal dominant fashion with variable penetrance, although this pattern has been questioned in some families. Porcine MH is transmitted as a recessive gene. The defective gene in MH-susceptible pigs has been localized to a single point mutation in the ryanodine receptor gene (RYR1).
Investigators have found the corresponding point mutation in the human RYR1 in some families with MH (chromosome 19q12.1–13.2; locus MHS-1), and other mutations in RYR1 have been linked to MH susceptibility. Other point mutations in RYR1 are found in patients with central core disease, a myopathy associated with MH. As of 2015, more than 400 RYR1 variants had been identified, and as of 2017, 36 of these variants were determined to be causal for MH. Mutations responsible for MH in some families are located on chromosomes 5p, 17, 7q, 3q, and 1q. Some 50% to 70% of human MH cases are linked to mutations in RYR1, and approximately 1% are linked to the gene encoding the main subunit of the DHPR, the calcium voltage-gated channel subunit alpha-1 S gene (CACNA1S). Some cases of MH may not be genetically linked, or the causal genetic mutations have not yet been identified.

Some myopathies may be characterized by a hyperthermic state with muscle damage and metabolic derangements similar to those seen in MH, but their chromosomal abnormality has not been mapped to the same area. A potential association between exertional rhabdomyolysis, exercise-induced rhabdomyolysis (EIR), exertional heat illness, heat stroke, and MH has been identified, with the presence of MH-causative mutations in some of these patients.

**TRIGGERS**

Known triggers of MH include depolarizing muscle relaxants (e.g., succinylcholine) and all the volatile halogenated anesthetic agents (i.e., sevoflurane, desflurane, isoflurane, halothane) (Box 46.1). The dose and duration of exposure to the triggering agent may influence the onset and severity of a reaction. The combination of a volatile agent and succinylcholine worsens the severity of the MH response. Previous uneventful administration of general anesthesia with triggering anesthetic agents does not rule out the diagnosis of MH.

In contrast to the porcine model, reports of stress-induced MH in humans are rare. In one report, two cases of fatal, stress-induced MH occurred in unrelated families; both children had a known RYR1 mutation, and one had a second mutation, possibly suggesting an additive effect. The sympathetic nervous system is active during an episode of acute MH, but there is insufficient evidence to implicate increased sympathetic activity as a cause in humans. Although muscle biopsy contracture testing may help distinguish MH from EIR, exertional heat stroke, and other myopathies, there is some evidence of a link between some cases of heat stroke and EIR and MH susceptibility.

Investigators have explored other possible triggers of MH both in the porcine model and in humans. No evidence suggests that exogenous calcium, digoxin, hypercarbia, potassium, or norepinephrine triggers MH. Exercise and environmental temperature may intensify an existing reaction or modify a developing reaction. Sodium thiopental and pancuronium delay the onset of MH in susceptible pigs and may modify the reaction in humans. Postulated that hypomagnesemia may increase the probability and severity of an MH event in MH-susceptible humans.

There are case reports of the occurrence of MH during regional anesthesia and during general anesthesia with non-triggering agents. The cases that occurred during regional anesthesia appeared mild and responded readily to treatment. In some cases, however, the diagnosis was not confirmed with muscle biopsy or appropriate laboratory investigation at the time of the event.

**CLINICAL PRESENTATION**

Individuals who are MH-susceptible may demonstrate the fulminant syndrome when anesthetized with a triggering agent. During an acute episode, the diagnosis is based on the finding of an elevated end-tidal CO2 concentration, muscle rigidity (generalized and/or masseter), respiratory and metabolic acidosis, rhabdomyolysis, hyperkalemia, elevated CK concentration, and myoglobinuria (Box 46.2). A dramatic increase in temperature may occur early, but often it is a late sign. Hypoxemia, unstable blood pressure, and evidence of sympathetic hyperactivity (e.g., tachycardia, hypertension, arrhythmias) are other signs. Perioperative rhabdomyolysis, without any of the previously mentioned clinical signs, also may indicate MH susceptibility.

With the advent of routine end-tidal CO2 monitoring, MH may be detected early, often before the development of rhabdomyolysis and hyperthermia. This situation may lead to...
uncertainty about the clinical diagnosis of MH, given that many of the confirmatory signs and laboratory abnormalities may be absent during the early phase of MH. Thus, early treatment of possible MH could present a dilemma as to whether the patient should undergo diagnostic muscle biopsy or should be assumed to be MH susceptible.

Masseter Muscle Rigidity
Masseter muscle rigidity is one of the early signs of MH. The masseter muscles are sensitive to the action of succinylcholine and respond with increased tension in normal individuals. Often this tension is imperceptible, but in some patients it is impossible to open the mouth for laryngoscopy and tracheal intubation. The duration of rigidity parallels the duration of action of succinylcholine. Typically there is no difficulty with mask ventilation. Patients with myopathies and other neuromuscular disorders also may have masseter muscle rigidity after the administration of succinylcholine.

If masseter muscle rigidity is accompanied by generalized rigidity, anesthesia should be discontinued, dantrolene should be administered, and the patient should be monitored closely. However, there is controversy regarding the management of isolated masseter muscle rigidity. Options include (1) discontinuation of the anesthetic agents and administration of dantrolene; (2) continuation of anesthesia with nontriggering, “safe” agents and close attention to the end-tidal CO₂ concentration; and (3) continuation of anesthesia with triggering agents and careful monitoring. In our judgment, the anesthesia provider should either discontinue anesthesia altogether or continue anesthesia with nontriggering agents. If anesthesia is continued, the minute ventilation, end-tidal CO₂ concentration, electrocardiogram (ECG), temperature, and arterial blood gas measurements should be monitored. The anesthesia provider also should look for evidence of rhabdomyolysis by monitoring CK levels and looking for myoglobinuria, and should recommend that the patient undergo muscle biopsy and caffeine-halothane contracture testing (see later discussion).

DIAGNOSIS
Investigators have correlated clinical presentation (i.e., evidence of metabolic and muscle derangements) with abnormal contracture on the caffeine-halothane contracture test. The greater the number of clinical signs or abnormal laboratory findings, the greater the risk for MH (Table 46.1). The mortality rate for MH is as high as 80% without dantrolene therapy. Early administration of dantrolene lowers the mortality rate to 4%.

An international group of experts has developed a clinical grading scale to predict MH susceptibility. This scale consists of six processes (rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, family history) and their clinical indicators. Points are assigned for each indicator present in a patient, and the total represents a raw score. A rank is subsequently assigned to this score, which indicates the likelihood of development of MH in the patient.

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms/Signs</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulminant/classic</td>
<td>Metabolic acidosis</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Muscle rigidity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperthermia (&gt; 38.5°C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myoglobinuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased creatine kinase level</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Inconclusive signs of MH involving metabolic and muscle abnormalities, with MH the probable diagnosis</td>
<td>0.88</td>
</tr>
<tr>
<td>Mild</td>
<td>Signs of metabolic derangement (pH &gt; 7.3, body core temperature &lt; 38.5°C)</td>
<td>0.14</td>
</tr>
<tr>
<td>Masseter spasm with rhabdomyolysis</td>
<td>Creatine kinase level &gt; 1500 U/L, myoglobinuria</td>
<td>0.76</td>
</tr>
<tr>
<td>Masseter spasm with signs of metabolic disturbance</td>
<td>Arrhythmias, rising core temperature</td>
<td>0.57</td>
</tr>
<tr>
<td>Masseter spasm only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained perioperative death or cardiac arrest</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Other</td>
<td>Postoperative pyrexia or rhabdomyolysis</td>
<td>0.07</td>
</tr>
</tbody>
</table>

MH, Malignant hyperthermia.

TESTING
Susceptibility to MH is determined by a positive caffeine-halothane contracture test result. During this test, fresh muscle is exposed to halothane and caffeine, and the extent of contraction is measured. The caffeine-halothane contracture test has been standardized in MH testing centers throughout North America (the North American protocol) and Europe (the European protocol is called the in vitro contracture test). This test is the “gold standard” for the diagnosis of MH. The sensitivity and specificity of the North American protocol are 97% and 78%, respectively. Patients with a negative caffeine-halothane contracture test result subsequently have received anesthesia with triggering agents without incident.

Testing for the known genetic mutations associated with MH is now available. However, because all the genetic mutations responsible for MH have yet to be identified, genetic testing is still not sensitive enough to use for routine screening. In the future, MH may be detected in most MH-susceptible patients with genetic analysis without the need for an invasive muscle biopsy.
studying other relatively noninvasive tests (e.g., assessment of metabolism in B-lymphocytes).\textsuperscript{64} In the absence of muscle biopsy results, a parturient with a positive family history should be treated as if she were MH susceptible.

**PREGNANCY AND MALIGNANT HYPERThERMIA**

In 1972, Crawford\textsuperscript{65} wondered “whether or not there was a record of a pregnant or newly born patient or animal having developed hyperpyrexia and ... whether hyperpyrexia has been encountered in a patient undergoing an operation under regional block anesthesia.” Subsequently there have been few reports of MH during parturition and fewer reports of maternal mortality attributable to MH. Wadhwa\textsuperscript{5} reported the death of a woman with a known family history of MH in whom muscle rigidity developed during twilight sleep for parturition. Douglas et al.\textsuperscript{9} reported one fatal case of MH in a parturient undergoing general anesthesia for cesarean delivery.

There are three published reports\textsuperscript{7–9} of nonfatal MH during cesarean delivery and one report of MH after cesarean hysterectomy performed because of postpartum hemorrhage.\textsuperscript{12} The triggering agents were succinylcholine and halothane,\textsuperscript{7} succinylcholine and isoflurane,\textsuperscript{12} cyclopropane,\textsuperscript{8} and succinylcholine alone (without a volatile halogenated agent).\textsuperscript{9} There are several reports of the successful administration of epidural and spinal anesthesia during labor and cesarean delivery in MH-susceptible parturients.\textsuperscript{5,12,66–73}

Although it is unclear whether pregnancy alters susceptibility to MH, the rarity of MH events during pregnancy suggests that pregnancy protects against the occurrence of MH. However, it also may reflect the widespread use of neuraxial anesthesia for labor, vaginal delivery, and cesarean delivery.

**Maternal Physiology**

Basal metabolic rate, oxygen consumption, and minute ventilation increase during pregnancy (see Chapter 2). Serum bicarbonate, buffer base, and base excess decrease to maintain normal pH. Thus, the pregnant patient typically has a compensated respiratory alkalosis. The reduced buffering capacity could adversely affect the pregnant woman during an episode of MH.

Oxygen consumption and minute ventilation increase further during labor. Maternal lactate and pyruvate concentrations increase steadily during labor, indicating an increase in both aerobic and anaerobic metabolism. Hyperventilation during contractions may result in periods of hypoventilation between contractions, which may adversely affect the PaO\textsubscript{2} of both the mother and fetus. These metabolic and physiologic responses to pain are similar to the metabolic and physiologic changes that are observed during acute MH. Effective epidural analgesia decreases oxygen consumption and minute ventilation. If tachycardia and hyperventilation occur despite effective analgesia, they are more likely to signal an episode of MH.

Aortocaval compression from the pregnant uterus results in decreased cardiac output, hypotension, and reduced uteroplacental perfusion. Thus, aortocaval compression may accelerate the occurrence of acidosis during an episode of MH. Aortocaval compression hinders resuscitative efforts during cardiac arrest, and evacuation of the uterus (i.e., delivery of the fetus) facilitates maternal resuscitation (see Chapters 41 and 54).\textsuperscript{7} The obstetrician may need to deliver the fetus to facilitate maternal resuscitation during a fulminant case of MH.

CK concentrations are not diagnostic of MH. During pregnancy, there is a slight decrease in CK levels during the first trimester. CK levels remain stable until term, when they increase by approximately 50%. At delivery, there is an abrupt rise in the CK concentration, followed by a return to normal by 6 weeks postpartum (Fig. 46.1).\textsuperscript{7} The increased CK concentration results from increases in both the CK-M fraction (skeletal muscle) and the CK-B fraction (myometrium, placenta, and fetal blood). Postpartum CK levels are higher in nulliparous women regardless of differences in duration of labor.\textsuperscript{7} Mean plasma CK activity is approximately 50% higher in African Americans than in Caucasians or Asians.\textsuperscript{79}

Acute cocaine toxicity may mimic MH. Although cocaine does not induce contractures in MH-susceptible muscle,\textsuperscript{77} elevated CK concentrations and myoglobinemia can occur secondary to rhabdomyolysis and renal failure from cocaine intoxication.\textsuperscript{78} Umbilical cord blood CK and myoglobin levels are elevated when cocaine metabolites are present in maternal urine.\textsuperscript{79}

**Effects on the Fetus and Newborn**

MH usually is inherited as an autosomal dominant gene. Thus, there is a 50% chance that the infant of an MH-susceptible parent will also be MH susceptible. All anesthetic agents cross the placenta. Small quantities of succinylcholine also cross the placenta. This knowledge should prompt the anesthesia provider to question the choice of anesthetic agents for an MH-negative mother whose fetus has an MH-susceptible
father. In this situation, the anesthesia provider should avoid the use of triggering agents until after delivery.\textsuperscript{80}

There is only one published report of suspected MH in a newborn.\textsuperscript{81} The condition is rare in infancy, and some reports of infant MH may represent undiagnosed myopathy.\textsuperscript{51,82,83}

**MANAGEMENT OF THE MALIGNANT HYPERTERMIA–SUSCEPTIBLE PARTURIENT**

Ideally, an anesthesiologist will evaluate every MH-susceptible pregnant patient before she is hospitalized for labor and delivery. Clearly, the obstetrician should consult an anesthesia provider immediately after the admission of each MH-susceptible patient. All hospitals and birthing facilities should be prepared to provide care for MH-susceptible patients. Adequate supplies of dantrolene (at least 36 vials of Dantrium or Revonto, or 3 vials of Ryanodex\textsuperscript{84}), sterile water, and sodium bicarbonate should be immediately available.\textsuperscript{85}

**Analgesia for Labor**

Soon after admission, a large-gauge intravenous catheter should be placed in each MH-susceptible patient. Maternal temperature, heart rate, and blood pressure should be monitored throughout labor. During early labor, it may be acceptable to monitor temperature and heart rate intermittently to facilitate maternal ambulation, if desired. Once active labor is established, frequent monitoring of the maternal heart rate and temperature should be initiated. Continuous ECG and axillary temperature monitoring are ideal once the parturient is confined to bed. (Measurement of axillary temperature allows placement of a temperature probe in close proximity to large muscle groups.) Of course, aortocaval compression should be avoided throughout labor and delivery.

Most agents used for intrapartum analgesia are considered safe in the MH-susceptible parturient (Table 46.2). Both the obstetrician and the anesthesia provider should encourage the early administration of neuraxial analgesia. Relief of pain reduces maternal stress (as reflected by decreased catecholamine,\textsuperscript{86} cortisol,\textsuperscript{87} and adrenocorticotropic hormone [ACTH] concentrations) and decreases maternal metabolism and oxygen consumption.\textsuperscript{88} Although experts continue to debate the role of stress in human MH,\textsuperscript{89} it is best to diminish stress when possible. Further, the anesthesia provider may extend epidural analgesia for vaginal or cesarean

### Table 46.2 Common Anesthetic Drugs and Their Safety in Malignant Hypertermia–Susceptible Women

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Use</th>
<th>Safe in MHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Anesthetic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Neuraxial</td>
<td>Analgesia/anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Neuraxial</td>
<td>Analgesia/anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Neuraxial</td>
<td>Analgesia/anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Neuraxial</td>
<td>Analgesia/anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl, sufentanil, alfentanil, remifentanil</td>
<td>Neuraxial, intravenous</td>
<td>Analgesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Neuraxial</td>
<td>Analgesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Morphine</td>
<td>Neuraxial</td>
<td>Analgesia</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Sedative-Hypnotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Intravenous</td>
<td>Induction of anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Sodium thiopental</td>
<td>Intravenous</td>
<td>Induction of anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Intravenous</td>
<td>Induction of anesthesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Intravenous</td>
<td>Induction of anesthesia, analgesia</td>
<td>Yes</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Intravenous</td>
<td>Amnesia, anxiolysis</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Neuromuscular Blocking Agents</strong></td>
<td>Intravenous</td>
<td>Muscle relaxation</td>
<td>No</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td></td>
<td>Muscle relaxation</td>
<td>No</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Intravenous</td>
<td>Muscle relaxation</td>
<td>Yes</td>
</tr>
<tr>
<td>Cis-atracurium</td>
<td>Intravenous</td>
<td>Muscle relaxation</td>
<td>Yes</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Intravenous</td>
<td>Muscle relaxation</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>General Anesthetic Agents</strong></td>
<td>Inhalation</td>
<td>Anesthesia, uterine relaxation</td>
<td>No</td>
</tr>
<tr>
<td>Sevoflurane, desflurane, isoflurane, halothane</td>
<td>inhalation</td>
<td>Analgesia/anesthesia</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MHS, Malignant hyperthermia–susceptible.
delivery if necessary, thus avoiding administration of general anesthesia.

All local anesthetic agents appear safe for MH-susceptible patients. Epinephrine can be safely added to the local anesthetic agent to improve the quality and duration of analgesia, if clinically appropriate.

**Anesthesia for Cesarean Delivery**

General anesthesia should be avoided for operative delivery if possible. Spinal or epidural anesthesia using either amide or ester local anesthetic agents can be given safely. Phenylephrine is probably the preferred agent for the treatment of hypotension. Ephedrine may exacerbate the catecholamine response during an acute episode of MH. In doses greater than those used clinically, ephedrine exacerbates halothane-induced muscle contractures in vitro.90

Rarely, the mother may refuse neuraxial anesthesia. In other cases, neuraxial anesthesia may be contraindicated (e.g., maternal hemorrhage, coagulopathy, prolonged fetal bradycardia). When the anesthesia provider encounters an MH-susceptible parturient, the anesthesia machine and delivery circuit should be flushed of volatile agents. Preparation consists of replacing the carbon dioxide absorbent and the delivery tubing, disabling the vaporizers, and purging the machine of residual anesthetic agent with a 10 L/min flow of oxygen through the circuit (including the ventilator).91 The time required to purge the anesthesia machine is dependent on the specific machine; new-model anesthesia machines with plastic components require longer flushing times.94 Activated charcoal filters appear to be an effective alternative to the prolonged flushing required to reduce the volatile anesthetic concentration in these new machines.92

Nontriggerring agents should be administered for induction and maintenance of general anesthesia (Box 46.3; see Table 46.2). Unless difficult tracheal intubation is expected, rapid-sequence induction should be performed with a sedative-hypnotic drug and a nondepolarizing neuromuscular blocking agent. All commonly used induction agents (e.g., propofol, thiopental, ketamine, etomidate) are safe in MH-susceptible patients. Succinylcholine and the volatile halogenated agents (sevoflurane, desflurane, isoflurane, halothane) are contraindicated. For intubation, rapid onset (approximately 60 to 90 seconds) of muscle relaxation can be achieved with rocuronium (0.6 to 0.9 mg/kg, which is two to three times the dose causing 95% twitch depression [ED95]) or vecuronium (0.25 mg/kg). Nitrous oxide (delivered via a prepared anesthesia machine), opioids, and propofol are safe agents for the maintenance of anesthesia. Midazolam administered after delivery provides amnesia. It is safe to reverse neuromuscular blockade with glycopyrrolate and neostigmine or edrophonium. Atropine may cause an increase in temperature, which could cause a diagnostic dilemma.

At delivery, determination of maternal and umbilical cord blood gas and pH measurements may provide information about an impending reaction in either the mother or the neonate. As well, if the MH-susceptible mother has a known genetic mutation, umbilical cord blood may be used to assess MH susceptibility in the neonate.95 If uterine relaxation (tocolyis) is required to assist with delivery of the infant or to facilitate the removal of a retained placenta, we prefer to give 100-µg bolus doses of nitroglycerin intravenously96; the action of this agent is brief and easily reversed with oxytocin. Clearly, a volatile halogenated agent should never be given to effect uterine relaxation in an MH-susceptible patient.

Concern has been raised about administering triggering agents to a non–MH-susceptible mother who is carrying a fetus whose father is MH susceptible.97 In this situation, the Malignant Hyperthermia Association of the United States recommends that the mother be treated as if she were MH susceptible to avoid a possible MH reaction in the neonate.40

**Obstetric Drugs in Malignant Hyperthermia–Susceptible Parturients**

Information on use of obstetric drugs in MH-susceptible patients is scant (Table 46.3). The beta-sympathomimetic tocolytic agents (e.g., terbutaline) produce anxiety and tachycardia in normal parturients. Such side effects may be confused with MH, although these agents are safe in the MH-susceptible parturient.

Magnesium sulfate attenuates but does not prevent MH in MH-susceptible swine.98 There is one report of a fatal adverse interaction between dantrolene and the calcium entry-blocking agent diltiazem,99 and hyperkalemia has been described after the co-administration of dantrolene and...
verapamil. Administration of calcium entry–blocking agents should be avoided during an episode of MH. These agents do not prevent the development of MH.

Oxytocin is safe. Some of the commercial preparations of oxytocin contain a preservative (chlorbutol) that has been shown to reverse the development of MH in susceptible pigs in vitro. The ergot alkaloids cause vasoconstriction, which may lead to decreased muscle perfusion and a greater tendency toward lactic acidosis. The prostaglandins may be associated with changes in blood pressure and maternal oxygen desaturation. Prostaglandin E2, prostaglandin F2α, and misoprostol may cause pyrexia, which may lead to confusion in the diagnosis of an MH episode. In one study, fever greater than 38°C occurred in 30.4% of women randomized to receive misoprostol compared with 6.3% in a placebo group. The routine postpartum administration of ergot alkaloids, prostaglandins, or misoprostol probably should not be performed in MH-susceptible patients. However, persistent uterine atony and postpartum hemorrhage may warrant the administration of these agents.
Differential Diagnosis of Tachycardia during Parturition

- Pain
- Fever
- Anxiety
- Blood loss
- Hypotension
- Drug reactions: cocaine, atropine, beta-adrenergic tocolytic agents
- Malignant hyperthermia

Tachycardia and tachypnea are normal responses to pain, anxiety, and fever. Fever may be a sign of dehydration and infection. Pain and infection (e.g., chorioamnionitis, urinary tract infection) are much more common during parturition than MH. Some healthy parturients may have a gradual increase in temperature during epidural analgesia (see Chapter 23). The fever may be accompanied by corresponding increases in maternal and fetal heart rates.

The butyrophenones, phenothiazines, thioxanthenes, and other miscellaneous antipsychotic agents may produce tachycardia, fever, and rigidity (i.e., neuroleptic malignant syndrome). There is one published report of neuroleptic malignant syndrome in a pregnant woman. Drugs capable of increasing serotonin in the central nervous system (i.e., selective serotonin reuptake inhibitors) also can produce a hypermetabolic reaction. Cocaine intoxication causes severe vasoconstriction, fever, and rhabdomyolysis.

Management of Malignant Hyperthermia Crisis

1. Call for help, and obtain dantrolene.
2. Notify the surgeon to finish surgery as quickly as possible.
3. Discontinue all triggering agents.
4. Hyperventilate with 100% oxygen at high gas flows (≥10 L/min). If available, insert charcoal filters into the breathing circuit.
5. Administer dantrolene 2.5 mg/kg intravenously. Repeat until signs and symptoms resolve.
6. Perform serial blood gas measurements. Treat acidosis with sodium bicarbonate 1 to 2 mEq/kg.
7. Treat hyperkalemia with sodium bicarbonate, glucose, insulin, and calcium.
8. Treat arrhythmias with antiarrhythmics, but avoid calcium entry-blocking agents.
9. If temperature greater than 39°C or rising rapidly, cool patient (administration of cold intravenous solutions, removal of covers, cooling of room temperature, surface cooling with ice and/or cooling blanket, peritoneal lavage with iced saline, use of new cooling devices).
10. Maintain urine output with fluids, mannitol, and/or furosemide.
11. Call the Malignant Hyperthermia Hotline for assistance (1-800-MH-HYPER).
12. Postoperatively, monitor patient in intensive care unit for 24 to 48 hours. Administer maintenance dantrolene for 24 hours or longer. Discontinue when metabolically stable.
13. Counsel patient and family, and refer for caffeine-halothane contracture test.

The anesthesia provider must initiate treatment of acidosis, hyperkalemia, arrhythmias, and hyperthermia. Metabolic acidosis (base excess greater than –8 mEq/L) is treated by administering sodium bicarbonate in 1- to 2-mEq/kg increments, as guided by blood gas and pH measurements. Hyperkalemia (K+ greater than 5.9 mEq/L) is treated by administration of calcium chloride (10 mg/kg) or calcium gluconate (30 mg/kg intravenously), sodium bicarbonate (1 to 2 mEq/kg intravenously), and glucose and insulin (10 units regular insulin intravenously; 50 mL of 50% glucose intravenously). Glucose levels should be monitored.

Early administration of dantrolene often prevents or successfully treats arrhythmias. If arrhythmias persist, one should follow standard advanced cardiac life support (ACLS) protocols. Amiodarone, lidocaine, procainamide, and adenosine may be used safely. Calcium entry–blocking agents should be avoided because simultaneous administration of dantrolene and a calcium entry–blocking agent may precipitate cardiovascular collapse.

The operating room care team should actively cool the patient if the core temperature is greater than 39°C (or less, if rising rapidly). Options for doing so include (1) intravenous administration of cold saline; (2) removing blankets and cooling the room temperature; (3) surface cooling with ice and/or a hypothermia blanket; (3) peritoneal lavage with iced saline; and (4) new devices specifically developed for rapid cooling. Cooling should stop when core temperature reaches 38°C.

Myoglobin is excreted in the urine. Thus, diuresis should be maintained by giving adequate volumes of crystalloid and furosemide 1 mg/kg and/or mannitol 0.25 g/kg. Mannitol is present in dantrolene, and separate administration of a diuretic agent may not be required. Ryanodex contains significantly less mannitol than the older formulations of dantrolene. Sedation should be administered as necessary.

After an acute episode of MH, postoperative administration of dantrolene (1 mg/kg or more intravenously every 4 to 6 hours for 24 to 48 hours) is recommended. In addition, the patient should be monitored closely in an intensive care unit for at least 24 to 48 hours. In a retrospective analysis of data from the North American Malignant Hyperthermia Registry, 20% of patients had recrudescence of MH after the initial MH episode. Recrudescence was associated with increased muscle mass and a longer interval between anesthesia induction and intraoperative reaction. Counseling and diagnostic muscle biopsy should be performed after recovery from the acute episode. The Malignant Hyperthermia Association of the United States provides a registry and an informative newsletter for MH-susceptible patients. An MH hotline (800-MH-HYPER [800-644-9737] or, outside the United States, +1-209-417-3722) is available 24 hours a day to assist physicians with questions on treatment, diagnosis, and follow-up.

**DANTROLENE IN PREGNANCY**

Dantrolene is the drug of choice for the treatment of MH crisis. Dantrolene works by blocking the release of calcium from the sarcoplasmic reticulum of skeletal muscle cells. It crosses the placenta and can be detected in the fetus after maternal administration. Clinical doses do not adversely affect maternal or fetal cardiovascular and acid-base measurements in gravid ewes. Morison reported a fetal-to-maternal serum dantrolene concentration ratio of approximately 0.4 after prophylactic oral administration of dantrolene. In one study in which oral dantrolene was administered prophylactically, there were no adverse effects on the fetus or newborn, but theoretically, dantrolene may cause neonatal hypotonia if administered before delivery.

There is one published report of postpartum uterine atony after the administration of dantrolene. Laboratory testing of the effects of dantrolene sodium on pregnant uterine muscle suggests that the relaxant effect is secondary to the mannitol.

There is no benefit to dantrolene prophylaxis in the MH-susceptible patient when triggering agents are avoided. However, the anesthesia provider should give dantrolene promptly when an MH crisis is suspected.

Fricker et al. reported serial measurements of dantrolene concentrations in breast milk after administration of dantrolene in a patient with suspected MH during cesarean delivery (Fig. 46.2). The authors estimated that the half-life of dantrolene in breast milk is approximately 9 hours. They concluded that “breast-feeding can be expected to be safe for the newborn 2 days after discontinuation of intravenous dantrolene administration in the mother.”

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![Fig. 46.2 Estimation of the half-life of dantrolene in breast milk by log-linear fitting of the terminal elimination phase (dantrolene measured in breast milk by high-pressure liquid chromatography, reverse-phase high-pressure liquid chromatographic column, by in-line ultraviolet absorption spectrometer; detection limit, 0.02 µg/mL).](image-url)
KEY POINTS

- Malignant hyperthermia is a heterogeneous disorder of skeletal muscle with variable clinical penetrance.
- Affected individuals develop a hypermetabolic syndrome on exposure to triggering agents (succinylcholine, volatile halogenated agents).
- The current diagnostic test is the caffeine-halothane contracture test.
- Current genetic testing has low sensitivity.
- It is unclear whether pregnancy alters susceptibility to MH.
- Both the obstetrician and the anesthesia provider should encourage early administration of neuraxial analgesia during labor in MH-susceptible patients.
- The anesthesia provider may convert epidural analgesia to epidural anesthesia for emergency cesarean delivery and thus avoid administration of general anesthesia.
- All local anesthetic agents are safe in MH-susceptible patients.
- If general anesthesia is indicated, the anesthesia provider should avoid succinylcholine and volatile halogenated agents in MH-susceptible patients.
- Intravenous administration of dantrolene is lifesaving treatment for MH crisis.
- Dantrolene crosses the placenta and may result in neonatal hypotonia if administered before delivery.
- Dantrolene may cause uterine atony.
- The anesthesia provider need not administer dantrolene prophylactically to MH-susceptible parturients.

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26. Britt BA. Combined anesthetic- and stress-induced malignant hyperthermia in two offspring of malignant


Pregnancy commonly results in musculoskeletal complaints. Although these complaints typically are benign and self-limited, symptoms may be disabling in some women. In addition, preexisting musculoskeletal disorders interact with pregnancy to a variable extent. These interactions range from an ameliorating effect of pregnancy on the course of the disease (e.g., rheumatoid arthritis) to the potential for significant and possibly life-threatening deterioration in maternal condition (e.g., uncorrected severe thoracic scoliosis). The purpose of this chapter is to discuss the most common musculoskeletal disorders encountered in pregnant women and their implications for obstetric and anesthesia providers.

**LUMBOPELVIC PAIN OF PREGNANCY**

*Lumbopelvic pain* is the most common musculoskeletal complaint during pregnancy; it comprises two distinct areas of discomfort: (1) the lumbar spine area (low back pain) and (2) the posterior pelvic girdle area (from the sacroiliac joints radiating down into the posterior thighs), which has been termed *pelvic girdle pain.*\(^1\) Pregnancy-related lumbopelvic pain occurs at some time during gestation in more than 50% of pregnant women and impairs at least one normal activity of daily life, including sleep; the prevalence ranges from 25% to 70%. It is the most common reason for sick leave during pregnancy. Women who complain primarily of pelvic girdle pain report more disability during pregnancy than those with isolated lumbar pain.\(^1\)\(^2\) Severe pelvic girdle pain is seen in less than 0.5% of women; however, differentiation between pelvic girdle pain and low back pain is important because the management differs and the disability of pelvic girdle pain is more likely to extend into the postpartum period for up to 1 to 2 years. There are indices developed specifically for the pregnant woman to assist in diagnosis and determining the degree of disability; the Pregnancy Mobility Index and Overall Complaints Index are examples.\(^3\) Risk factors for pregnancy-related lumbopelvic pain include a history of low back pain, young age, hypermobile joints, low socioeconomic class, multiparity, and spondylolisthesis; the strongest factors are prior history of lumbopelvic pain, previous non-pregnancy-related low back pain, and strenuous work.\(^4\) In addition, there are psychological determinants affecting the
development of lumbopelvic pain. Women who score high on the stress and fear domains are more likely to have significant lumbopelvic pain. Women who have high pain scores on pain threshold testing are also more likely to develop lumbopelvic pain.3,5

The etiology includes hormonal and mechanical factors. The corpus luteum synthesizes and releases relaxin, and maternal blood concentrations of this peptide hormone increase 10-fold during gestation. Relaxin induces ligamentous softening and peripheral and pelvic joint laxity, which cause instability of the symphysis pubis and sacroiliac joints; the extent of instability and disability may be related to the maternal concentration of relaxin. There is a correlation between serum levels of relaxin and the occurrence of back pain during pregnancy; women with incapacitating symptoms have the greatest serum concentrations of relaxin.6

Mechanical changes have a later onset than hormonal changes. Women with pelvic girdle pain have increased pelvic joint motion, which increases sheer forces across the joints and likely results in pain. In all pregnant women, uterine enlargement results in a forward rotation of the sacrum and an increase in the lumbar lordotic curve, which tends to close the lumbar interlaminar space (see Fig. 2.10). This change exaggerates the mechanical load borne by both the facet joints and the posterior aspect of the intervertebral discs. These mechanical changes also may compromise nerve root foramina. Sciatica occurs in 1% of pregnant women, and most cases occur late in pregnancy. Sciatica is distinguished from pelvic girdle pain by its extension to the ankle or involvement of the foot, and it may be associated with neurologic changes. Disc herniation and sacral stress fractures are rare in pregnancy but do occur.7,9 Incapacitating pain that radiates below the knee, typically accompanied by progressive neurologic deficits or bowel and bladder dysfunction, distinguishes disc herniation from the more common and benign pregnancy-related lumbopelvic pain.7

In summary, hormonal changes cause sacroiliac joint dysfunction, which is responsible for the lumbopelvic pain that occurs early in pregnancy. Mechanical changes are primarily responsible for the pain that manifests during late gestation, although symphysis pubis and sacroiliac joint instability may also continue to cause pain. Disc herniation is uncommon and is characterized by the presence of neurologic findings.

Obstetric Management
Treatment is conservative in the absence of neurologic compromise. The many studies now published on various treatment modalities for lumbopelvic pain have discordant results. Moderate quality evidence from single studies supports the use of structured exercise programs, acetaminophen administration, osteomaneipulative therapy, pelvic belts, and acupuncture in the treatment of lumbopelvic pain.8 However, a 2015 systematic review revealed overall low-quality evidence supporting exercise therapy for low back pain and no effect on pelvic girdle pain.10 If nonrandomized controlled studies are included in the analysis, the evidence suggests combining modalities is the most effective strategy.9 Patients with severe neurologic signs or symptoms of disc herniation should be assessed by a consultant neurosurgeon or neurologist who can provide recommendations for intrapartum and postpartum care. In a woman with severe symptoms, the obstetrician may choose to perform elective assisted vaginal delivery to decrease maternal work and back stress during the second stage of labor; however, this strategy does not protect against having postpartum pelvic girdle pain.2 Because the disability associated with lumbopelvic pain, especially pelvic girdle pain, can impair the woman’s ability to function postpartum, it is important to diagnose pregnancy-related lumbopelvic pain and treat it appropriately.

Anesthetic Management
No evidence suggests that epidural or spinal anesthesia is contraindicated in patients with pregnancy-related lumbopelvic pain. The anesthesia provider may administer neuraxial anesthesia, even to patients with sciatica. However, neurologic signs and symptoms should be first identified, delineated, and recorded. It seems prudent to administer a dilute solution of local anesthetic, with or without an opioid, to minimize motor block associated with epidural analgesia during labor to reduce any further stress on relaxed sacroiliac joints. Women with lumbopelvic pain may be reluctant to have neuraxial anesthesia because of concern that it may aggravate symptoms. The literature does not support this fear, and reassurance may be required.

Careful attention to the positioning of the patient with back complaints is critical. The patient must not be placed in a position that she could not tolerate before the administration of neuraxial anesthesia. The lithotomy position puts significant stress on the lower back and should be avoided whenever possible. If it is used, care must be taken to raise and lower both legs simultaneously to prevent injury to the lumbar spine and to avoid extremes when positioning the legs. Finally, caregivers should avoid rotational movements of the spine during transfer of the patient between the bed and the operating table.1

CHRONIC LOW BACK PAIN
Approximately 50% of pregnant women with a previous history of back pain or those with chronic low back pain experience a recurrence or exacerbation of their symptoms during pregnancy.1 Neuroaxial anesthesia may be more likely to fail in patients with chronic low back pain and in those who have had back surgery,12,13,14 although newer data are conflicting.15 Benzon et al.12 reported a delayed onset of epidural anesthesia in patients with back pain or sciatica; the affected roots were blocked 10 to 70 minutes later than the contralateral roots at the same level. The delay in block onset most likely results from the inability of the local anesthetic agent to diffuse into the area of the injured root. Luyendijk and van Voorthuisen16 evaluated 600 epidurograms and confirmed that contrast material failed to reach the nerve root in
33% of patients with uncomplicated disc prolapse and did not move beyond the affected disc space in 5% of cases. This may be caused by epidural space scarring and adhesions that may develop during healing after disc injury. Prolapse of an intervertebral disc may result in relative or total obstruction of the flow of local anesthetic agent within the epidural space.

Sharrock et al.\textsuperscript{13} reported a 91.2% success rate of epidural anesthesia in nonobstetric patients with a history of limited spine surgery, as compared with a 98.7% success rate in patients without back surgery. The greater failure rate was postulated to be secondary to the distortion of surface anatomy and the tethering of the dura to the ligamentum flavum by scar formation, which renders the epidural space discontinuous or obliterated. Support for this hypothesis is provided by LaRocca and Macnab’s\textsuperscript{17} description of the postlaminectomy membrane. They noted the postlaminectomy formation of organized fibrous tissue surrounding the dura and, at times, binding of the nerves to the posterior aspect of the disc and adjacent vertebral body. The fibrous response was proportional to the extent of surgical trauma and was more marked with greater operative exposures. Postlaminectomy spinal stenosis also may lead to attenuation or obliteration of the epidural space, and the most common site of obstructive stenosis is immediately above the fusion mass.\textsuperscript{18}

In contrast, Bauchat et al.,\textsuperscript{15} in a prospective observational, case-controlled study of 42 women with a history of discectomy and 42 matched control women studied between 2007 and 2010, found no difference in the total bupivacaine consumption (primary outcome), duration of the neuraxial procedure, or need for epidural catheter replacement between the postlaminectomy parturients and the control parturients after combined spinal-epidural (CSE) or epidural labor analgesia. The only difference between groups was the need to attempt more than one interspace more often in the postlaminectomy group. A possible explanation for the difference in the Bauchat et al. study\textsuperscript{15} to former studies\textsuperscript{13} is that surgical techniques have changed in the past half century, and newer techniques may cause less trauma and scarring in the epidural space.

**Obstetric Management**

It is not uncommon for obstetricians to offer pregnant women who have had persistent chronic low back pain the option of cesarean delivery to decrease the potential for further back injury during labor. There are no data to either encourage or discourage this option.

**Anesthetic Management**

The anesthesia provider may offer epidural or spinal anesthesia to patients with previous lumbar spine pathology or surgery after an appropriate history and screening examination to identify any neurologic deficits. A decreased incidence of successful epidural anesthesia is possible, especially in patients who have had extensive surgery. Nonetheless, the experienced anesthesia provider will likely administer epidural anesthesia successfully in most patients. Subarachnoid anesthesia is likely to be more reliable than epidural anesthesia in this patient population.

**POSTPARTUM BACKACHE**

Postpartum backache is a common complaint worldwide, occurring in at least 25% of women, with 5% to 7% of women seeking medical help. Evidence emerged in the early 1990s implicating epidural labor analgesia as the cause for postpartum backache.\textsuperscript{19,20} These original investigations were based on postal surveys, notably provided to women up to 9 years after childbirth.\textsuperscript{19} These studies were followed by several prospective studies to eliminate the potential for reporting bias that may confound retrospective surveys.

Macarthur et al.\textsuperscript{21} prospectively studied the association between epidural analgesia and early, new-onset postpartum backache in 329 women. In patients who labored without epidural analgesia, the incidence of postpartum backache was 43% at 1 day, 23% at 7 days, and 7% at 6 weeks. The incidence of symptoms in patients who had received epidural analgesia was greater on the first postpartum day (53%), but this increase did not persist. At 1 year postpartum, 12% of the patients had back pain (9.9% in the epidural group and 13.8% in the control group). Howell et al.\textsuperscript{22} performed a randomized controlled trial comparing epidural with nonepidural labor analgesia in 369 nulliparous women. There was no difference in the incidence or characteristics of postpartum backache at 3 and 12 months postpartum. In a follow-up study, there was no difference between the two groups in the incidence of back pain, disability, or movement restriction more than 2 years after delivery.\textsuperscript{23}

Both transient and persistent postpartum backaches are common, but there is little evidence that they are related to the provision of epidural analgesia during labor. Similarly, no evidence suggests that denying a parturient epidural analgesia results in a lower incidence of back problems during the postpartum period. Factors associated with persistent postpartum backache include the presence of back pain before pregnancy, the presence of pregnancy-related lumbopelvic pain, cesarean delivery, and performance of physically demanding work.\textsuperscript{1} Some evidence supports the use of osteopathic manipulation to help relieve postpartum backache.\textsuperscript{24,25}

**SCOLIOSIS**

Scoliosis is a lateral deviation in the vertical axis of the spine. The severity of scoliosis is determined by measurement of the angle of the spinal curve, the Cobb angle, which is expressed in degrees (Fig. 47.1). The prevalence of minor curves is 4 per 1000 in the North American population; larger curves occur less frequently, predominantly in females. Severe scoliosis is relatively rare in pregnant women, occurring in 0.03% to 0.07% of pregnancies.\textsuperscript{26} Although women with moderate to severe scoliosis constitute a small population of obstetric patients, pregnancy in this population is common.\textsuperscript{27} Most cases of scoliosis are idiopathic, although some are associated with other conditions, most commonly neuromuscular disorders (Box 47.1).

Scoliotic curves can be divided into structural and non-structural varieties. Nonstructural curves are those seen with
postural scoliosis, sciatica, and leg-length discrepancies. They do not affect the mobility of the spine and are nonprogressive. **Structural curves** are seen in patients with idiopathic scoliosis and with scoliosis resulting from the conditions listed in Box 47.1. Structural curves lead to reduced spinal mobility, and affected patients typically have a fixed prominence (rib hump) on the convex side of the curve. A rotary component is associated with the structural scoliotic curve. The axial rotation of the vertebral body is such that the spinous processes rotate away from the convexity of the curve toward the midline of the patient (Figs. 47.2 and 47.3). Deformation of the vertebral bodies results in shorter, thinner pedicles and laminae, and a more narrow vertebral canal on the concave side. Vertebral deformation is unusual in patients with a Cobb angle less than 40 degrees. Scoliosis interferes with the formation, growth, and development of the lungs; the occurrence of scoliosis before lung maturity may reduce the number of alveoli that ultimately form. The pulmonary vasculature develops in parallel with

**BOX 47.1 Conditions Associated with Scoliosis**

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**Fig. 47.1** Schematic representation of the Cobb angle. A line is drawn parallel to the superior cortical plate of the proximal end vertebrae and another line parallel to the inferior cortical plate of the distal end vertebrae. A perpendicular line is drawn to each of these lines. The angle of intersection is the Cobb angle of the curve.

**Fig. 47.2** Spinal rotation with scoliosis. Left, View of the lumbar spine in a patient with a scoliotic curve to the left demonstrating surface landmark palpation. Right, Skeletal anatomy at the same level in the same patient. There is a reduction in the dimensions of the interlaminar space on the concave side of the curve (to the right) and an expansion on the convex side. These changes are enhanced with greater severity of the curve. As the curve increases, the spinous processes rotate into the concavity of the curve, further altering the local anatomy. Surface landmark palpation from the view at left superimposed on the skeleton reveals how the palpated midline (*indicated by the white X*) is to the right of the true axial midline. (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
pressure exceeding 25 mm Hg) occurs in many patients with severe deformity long before the onset of right-sided heart failure and is largely attributable to increases in vascular resistance resulting from chronic alveolar hypoxia, hypoxic pulmonary vasoconstriction, and anatomic changes in the vascular bed. Fixed pulmonary hypertension carries a grave prognosis in pregnancy and may prompt a recommendation to avoid or terminate pregnancy (see Chapter 41).

Scoliosis Associated with Neuromuscular Disease

When scoliosis develops secondary to a neurologic or myopathic disorder, abnormal respiratory function results not only from the skeletal deformity but also from abnormalities in the central control of respiration and the supraspinal innervation of the respiratory muscles, as well as from the loss of muscle function caused by the underlying disorder. Respiratory function may be further compromised by (1) impairment of the defense mechanisms of the airways caused by loss of control of the pharynx and the larynx, (2) an ineffective cough mechanism, and (3) infrequent or reduced large breaths. Recurrent aspiration pneumonitis may result from compromised protective airway reflexes. In general, the prognosis of scoliosis caused by neuromuscular disease is poorer than that of idiopathic scoliosis and is determined predominantly by progression of the primary disorder. Affected patients typically develop irreversible respiratory failure at a younger age, and pulmonary hypertension is common; pregnancy is uncommon in this population.

Interaction with Pregnancy

Pregnancy may exacerbate both the severity of the spinal curvature and cardiopulmonary abnormalities in women with uncorrected scoliosis. Progression of a curve, defined as an increase in the Cobb angle of 5 degrees or more over subsequent assessments, is more likely during periods of rapid growth and in patients with larger curves at the time of diagnosis. Curves that are less than 25 degrees or curves that have been stable before pregnancy typically do not progress during pregnancy. In contrast, more severe curves and those that have not stabilized may worsen. Some investigators have described a correlation between the severity of the curve and maternal morbidity and mortality. However, it is likely that the severity of functional cardiopulmonary impairment before pregnancy is a better predictor of maternal outcome than the severity of the curve. Patients with a severe curve (i.e., Cobb angle greater than 60 degrees) but good cardiopulmonary function tolerate pregnancy well, whereas in those with significant cardiopulmonary compromise, and especially in those with pulmonary hypertension, maternal mortality is high.

The physiologic changes of pregnancy include decreases in both functional residual and closing capacities and increases in minute ventilation and oxygen demand. The thoracic cage normally increases in circumference during pregnancy as a result of increases in both anteroposterior and transverse diameters. If the chest cage is relatively fixed by scoliosis, the alveoli; early-onset scoliosis and severe scoliosis may result in greater pulmonary vascular resistance and eventually lead to pulmonary hypertension. Musculoskeletal deformities also affect the mechanical function of the lungs; anatomic findings in scoliosis that are most commonly associated with respiratory compromise include the presence of a thoracic curve, thoracic lordosis, and a rib cage deformity. The most common pulmonary function abnormality is a restrictive pattern with decreases in vital capacity, total lung capacity, and lung compliance. This pattern occurs in all patients with a thoracic curve greater than 65 degrees. The functional residual capacity is reduced, and airways may close during normal tidal breathing. If the functional residual capacity is reduced to the extent that it falls below the closing capacity, atelectasis may occur in basal alveoli. The most common blood gas abnormality is an increased alveolar-to-arterial oxygen gradient, with reduced PaO₂ and a normal PaCO₂. It results from both venoarterial shunting and altered regional perfusion. Venous admixture may lead to arterial hypoxemia.

The natural history of severe, progressive scoliosis includes early death from cardiopulmonary failure. Permanent changes of the pulmonary vasculature are common in patients with a curve greater than 65 degrees. Pulmonary hypertension (a resting mean pulmonary artery
diaphragm is responsible for all increments in minute ventilation. As the enlarging uterus causes elevation of the diaphragm, diaphragmatic activity is restricted and further decreases in residual and closing capacities may occur, which may result in both greater ventilation-perfusion mismatch and decreased arterial oxygen content. The antepartum onset of new symptoms of respiratory compromise or the exacerbation of preexisting symptomatology is associated with higher maternal morbidity and a greater likelihood that assisted ventilation will be required after cesarean delivery. In a retrospective review from Canada of 12 women (15 pregnancies) with restrictive lung disease (defined as forced vital capacity less than 70%), Lapinsky et al. found 20% had deterioration in pulmonary function during the pregnancy. Seven women had an initial forced vital capacity of less than 1 L; four of these women had underlying kyphoscoliosis.

Dyspnea on exertion is uncommon in patients with scoliosis who have curves less than 70 degrees, but it becomes more common as the deformity exceeds 100 degrees. In younger patients with a curve less than 70 degrees, exercise capacity is more likely to be impaired because of the lack of regular aerobic exercise and subsequent deconditioning rather than intrinsic ventilatory impairment. Dyspnea is common in many pregnant women; two features help distinguish physiologic from pathologic dyspnea. Physiologic dyspnea tends to occur earlier in pregnancy and often plateaus or even improves as term approaches. The pathologic dyspnea of cardiopulmonary decompensation more often begins in the second half of pregnancy and is progressive, often becoming most severe as gestation advances and the physiologic loading is maximal. Second, physiologic dyspnea is rarely extreme, and patients can maintain most daily activities. Dyspnea that is extreme or has a limiting effect on normal activity may signal maternal cardiorespiratory decompensation. Dyspnea at rest is also rare in the absence of cardiopulmonary dysfunction, as is dyspnea that is acute in onset or progressive and intractable.

Minute ventilation typically increases by 45% during pregnancy. Minute ventilation of the unmedicated parturient increases by a further 70% to 140% in the first stage of labor and by 120% to 200% in the second stage. Oxygen consumption increases above prelabor values by 40% in the first stage and 75% in the second stage (see Chapter 2). These levels may be unattainable by the scoliotic parturient with restrictive lung disease, and respiratory failure and hypoxemia may result during labor.

Pregnant women with pulmonary hypertension have a limited ability to increase cardiac output. During normal pregnancy, cardiac output increases 40% to 50% above nonpregnant measurements; during labor and delivery, even greater increases are observed. These increases are achieved with both larger stroke volume and a higher heart rate. These demands may put an excessive burden on the cardiovascular system in parturients who had marginal cardiac reserve before pregnancy. If the right ventricle fails in the presence of pulmonary hypertension, left ventricular filling will decrease and low-output failure and sudden death may occur.

**Surgical Management**

During spinal fusion and instrumentation, the spinal musculature is reflected off the vertebrae over the course of the curve and the spinous processes and interspinous ligaments are removed. The spine is subsequently extended, correcting the curve. The vertebrae are decorticated throughout the extent of the planned fusion, instrumentation is placed, and bone graft material from the ileum is placed over the decorticated vertebrae. A number of techniques for fusion have been described, but all involve both spinal instrumentation and extensive bone grafting in the axial spine.

**Obstetric Management**

Pregnant women with corrected scoliosis tolerate pregnancy, labor, and delivery well. In the absence of major lumbo-sacral deformity, there is little alteration of the pelvic cavity, and malpresentation is not more common than in women without scoliosis. Uterine function is normal, and labor is not prolonged. Spontaneous vaginal delivery is anticipated, and cesarean delivery should be reserved for obstetric indications.

The literature is conflicting as to whether the cesarean delivery rate is greater in women with scoliosis with or without surgery. In a retrospective study from Israel, 98 women with idiopathic scoliosis out of a cohort of more than 220,000 were reviewed for birth outcomes. Women with scoliosis (corrected or uncorrected) were not found to have an increased risk for cesarean delivery. Conversely, Chopra et al. reviewed pregnancy outcomes in 22 women with kyphoscoliosis (59% idiopathic) with a total of 34 pregnancies. In this study, 60% of women had severe restrictive lung disease, only one had surgical correction, and the cesarean delivery rate was greater than 75%. The difference in outcomes may be influenced by the severity and etiology of the scoliosis in the populations reviewed or differences in the local practice patterns for managing these patients.

Pelvic abnormalities are more common when scoliosis is associated with neuromuscular disorders and in patients with a severe, uncorrected curve. In addition, abdominal and pelvic muscle weakness predisposes parturients to problems with expulsion of the infant during the second stage of labor and may necessitate instrumental vaginal delivery. The need for instrumental or cesarean delivery is likely related to the severity of skeletal deformity, the resulting maternal compromise, and cephalopelvic disproportion.

In the second stage of labor, the diaphragm has a nonrespiratory function. With expulsive efforts, maximal isometric contractions may be sustained for 20 seconds or more, and diaphragmatic fatigue has been demonstrated even in normal, laboring women. In parturients whose diaphragmatic function is compromised by neuromuscular disease or severe scoliosis, the potential for fatigue and failure is greater; expulsive forces are decreased, the second stage may be prolonged, and a trial of labor may fail, necessitating instrumental or cesarean delivery. In addition, women with severe cardiopulmonary disease (especially those with gestational decompensation)
may require urgent or emergency cesarean delivery because of maternal compromise or nonreassuring fetal status.

**Anesthetic Management**

Pregnant women who have thoracolumbar scoliosis with a Cobb angle greater than 30 degrees or who have undergone spinal instrumentation and fusion for scoliosis should be referred to an anesthesia provider for antepartum consultation. The anesthesia provider should (1) determine the etiology of the scoliosis, as well as the severity and stability of the curve; (2) obtain a history of maternal musculoskeletal and cardiopulmonary symptoms; and (3) review prior obstetric and anesthetic experiences. For patients with scoliosis secondary to neuromuscular disorders, the anesthesia provider should also become familiar with anesthetic considerations specific to the underlying disorders.

Women with suspected or evident pulmonary compromise should undergo evaluation by a pulmonologist, and pulmonary function studies and arterial blood gas measurements should be obtained. These patients must be reevaluated periodically to ensure that they are tolerating the increasing physiologic demands of pregnancy. Echocardiography is useful to assess right-sided heart function in patients with one or more of the following: (1) a curve of 60 degrees or more, (2) hypoxemia on arterial blood gas measurement, (3) moderate or greater reductions in predicted lung volumes or flows, (4) pulmonary hypertension, and/or (5) evidence of decompensating cardiopulmonary status. Radiographic studies performed before pregnancy and operative notes describing spinal surgical procedures should be reviewed before neuraxial anesthesia is initiated in any patient with significant scoliosis or previous spinal surgery. The anesthesia provider should also examine the spine and note the surface landmarks and interspaces that are least affected by the deformity. Modes of analgesia and anesthesia for labor and delivery can be discussed during antepartum consultation.

Invasive hemodynamic monitoring is rarely indicated during labor and delivery. Pulmonary function studies that suggest significant respiratory compromise or clinical evidence of impending respiratory failure warrant placement of an arterial catheter and serial assessment of blood gas measurements. Echocardiographic demonstration of significant right-sided heart dysfunction may warrant invasive or noninvasive cardiac function monitoring.

The anesthesia provider may offer neuraxial analgesia for labor and delivery to patients with severe thoracolumbar scoliosis. Identification of the epidural space is more difficult in such patients, and the anesthesia provider should anticipate a greater incidence of complications. It is useful to remember the presence of the vertebral rotation during the performance of neuraxial anesthesia in a patient with a significant lumbar curve, which results in the spinous processes (which often may be structurally deformed) rotating into the concavity of the curve. Therefore, the midline of the epidural space is deviated toward the convexity of the curve relative to the spinous process palpable at the skin level (see Figs. 47.2 and 47.4). The extent of lateral deviation is determined largely by the severity of the deformity. One method of placing an epidural or spinal needle is to direct the needle from a palpated spinous process toward the convexity of the curve, often at a significant angle. The experienced anesthesia provider can track the resistance of both the interspinous ligament and the ligamentum flavum to maintain the correct course into the epidural space. The extent of the local anatomic distortion is the limiting factor, and the selection of spaces that are least involved with the curve is advised. Huang suggested a modified paramedian approach based on work by Boon et al. in cadavers. The needle is placed lateral to the spinous process on the convex side of the curve (taking advantage of the wider interlaminar spaces on that side) and aimed directly perpendicular to the skin. The intent is to find lamina with the needle tip and then “walk up or down” the lamina to enter the epidural space (Fig. 47.4).

![Fig. 47.4 Image of the lumbosacral vertebrae affected by a scoliotic curve to the left. Note the axial and lateral rotation of the vertebral bodies, and the rotation of the affected spinous processes (blue dots) into the concavity of the curve; these spinous processes are frequently anatomically abnormal. The apparent midline (trajectory A) suggested by palpated surface landmarks is to the right of the true axial midline. The figure demonstrates two approaches to enter the epidural/subarachnoid space: one where the needle is directed along the line of a spinous process toward the convexity of the curve (trajectory B), and the other a modified paramedian approach where needle entry starts on the convex side of the curve and is directed perpendicular to the skin (trajectory C). (Illustration by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine, Chicago, IL.)
Ultrasonography is a useful technique to facilitate administration of neuraxial anesthesia in parturients with challenging spinal anatomy, including those with scoliosis. Asymmetry of the spine is not difficult to appreciate; learning how to use the information and determine the optimal space and needle direction requires more experience. The paramedian view may provide the best information with respect to the widest interlaminar space, and the transverse view shows presence of rotation and asymmetry. There are a few studies on the use of preprocedural ultrasonography to identify the best space and angle of approach in parturients with difficult surface anatomy. Ekinci et al. and Creaney et al. in two separate studies, randomized patients with poor palpable surface landmarks into ultrasonography-facilitated and landmark palpation-only groups. Both studies found fewer needle passes in the ultrasonography group with no increase in procedural time. Chin et al. described a simplified technique for facilitating neuraxial anesthesia in patients with difficult anatomy, including scoliosis. Using a transverse view, the anesthesia provider can visualize the rotation of the spinous process and use this information to perform a more precise version of the paramedian technique described by Huang (Fig. 47.5).

Local anesthetic dose requirements for epidural and spinal anesthesia in the patient with scoliosis are variable. Moreover, during administration of spinal anesthesia in a patient with a severe scoliotic curve, hyperbaric local anesthetic solution may pool in dependent portions of the spine, resulting in an inadequate block. Thus, it may be preferable to use a continuous technique in women with severe scoliosis so that the dose of local anesthetic agent can be titrated to the desired segmental level of anesthesia.

Fig. 47.5 Ultrasonography-assisted paramedian approach to neuraxial blockade in patients with difficult anatomy. An illustration of needle trajectory in the paraspinous approach in (A) the axial view, (B) the anterior-posterior view, and (C) the lateral view of the spine. The white rectangle in (B) shows the transverse ultrasound probe position used to establish the position of the neuraxial midline and spinous processes (white dotted lines). Ultrasonography (D) and computed tomography (E) axial images of spine rotation in a patient with lumbar scoliosis. When the ultrasound probe is placed perpendicular to the patient’s back (F), the rotation is evident from the angulation of the acoustic shadow of the spinous process. Paraspinous needle insertion should be performed 1 cm lateral to the midline (defined by the tip of the spinous process), but without medial angulation. (Reprinted with permission from Chin KJ, Perlas A, Chan V. The ultrasound-assisted paraspinous approach to lumbar neuraxial blockade: a simplified technique in patients with difficult anatomy. Acta Anaesthesiol Scand. 2015;59:668-673.)
When offering neuraxial anesthesia to patients with a history of corrective spine surgery, the anesthesia provider must consider the following potential problems:

- Persistent back pain occurs in many patients with corrected scoliosis and correlates with both the extent of fusion and the time since surgery. 47
- Degenerative changes occur in the spine below the area of fusion, and there is a higher incidence of both retrolisthesis and spondylolisthesis. 43
- Twenty percent of patients undergo fusion to the lowest lumbar levels, limiting the potential for neuraxial anesthesia. 41,48,49
- Insertion of an epidural needle in the fused area may not be possible because of the presence of instrumentation, scar tissue, and bone graft material.
- Intraoperative trauma to the ligamentum flavum may result in adhesions in or obliteration of the epidural space, and these changes may interfere with the spread of injected local anesthetic. 17
- Obliteration of the epidural space may increase the incidence of unintentional dural puncture.
- These patients often manifest a high level of anxiety about their backs and may be reluctant to have neuraxial anesthesia.

In 2009, Ko and Leffert 50 published a qualitative literature review on neuraxial anesthesia in the parturient with scoliosis. The review describes 117 attempted neuraxial procedures, the majority (93) in surgically corrected patients. Overall, 71% had a successful neuraxial block; however, the corrected patients proved to be more challenging, with a 69% success rate versus 79% for the uncorrected group. The challenges in corrected patients included (1) inability to place the needle (22%), (2) multiple attempts (13%), (3) patchy analgesia (10%), (4) excessive local anesthetic dose requirements (9%), (5) unintentional dural puncture (4%), and (6) inadequate analgesia (4%). In the uncorrected group, the issues included (1) patchy, asymmetric, or unilateral blocks (8% of each) and (2) multiple attempts or failed placement (4% of each). There were also two cases of persistent low back pain of unknown etiology. Complications occurred more frequently in patients with fusion that extended to the lower lumbar and lumbosacral interspaces than in those with fusions that ended in the upper lumbar spine. These findings were corroborated by Bauchat et al. 41 in a prospective case-matched study in which 41 women with previous corrective surgery were compared with 41 healthy matched controls. The rate of neuraxial analgesia failure was higher (12% versus 0%) and the mean time to placement longer (by 41%) in the surgical correction group; however, there was no difference in local anesthetic requirements to maintain analgesia.

Thus, in patients with severe or corrected scoliosis, both the anesthesia provider and the patient should anticipate the possibility that neuraxial analgesia may fail with or without ultrasonography. Alternative modes of intrapartum analgesia include administration of single-shot technique spinal analgesia (may be repeated), caudal analgesia, patient-controlled intravenous opioid analgesia, and inhalation analgesia especially with nitrous oxide. 50 Continuous spinal analgesia or anesthesia is a reasonable alternative to epidural analgesia or anesthesia for labor or cesarean delivery in parturients who have undergone major spinal surgery with instrumentation. The dural-puncture epidural (DPE) technique may also be considered as the presence of cerebrospinal fluid (CSF) confirms the epidural needle tip location and may enhance spread of epidural local anesthetic (see Chapter 12). 50,51

**CHRONIC INFLAMMATORY ARTHRITIDES**

This group of diseases includes rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and undifferentiated arthritis. Of these, rheumatoid arthritis is most affected by pregnancy and has been studied most extensively with respect to the immunologic relationship between mother and fetus. The most common arthritides seen in pregnancy are rheumatoid arthritis and ankylosing spondylitis.

**Rheumatoid Arthritis**

Rheumatoid arthritis is a chronic systemic disorder characterized by synovial proliferation that leads to joint destruction and subsequent deformity. It is becoming increasingly a disease of older people. From 1985 to 2005, the overall prevalence in the United States fell from 1.07% to 0.6%; the greatest decline in prevalence occurred among people younger than 55 years of age. 52 The disease occurs approximately two times more frequently in women than in men. 52

The lumbosacral spine is affected in only 5% of patients with rheumatoid arthritis. In contrast, the cervical spine is commonly involved, and atlantoaxial subluxation occurs in 30% to 45% of patients with rheumatoid arthritis. 53,54 Although atlantoaxial subluxation may occur early in the course of the disease, it most often occurs in patients with a history of 5 years or more of highly active and erosive disease. 55 Atlantoaxial subluxation occurs as a result of an attenuation or disruption of the transverse ligament, which allows anterior movement of C1 on C2 during neck flexion. Radiographically, atlantoaxial subluxation is marked by an increase in the atlas-dens interval, which is best demonstrated on the lateral cervical spine radiograph with the neck flexed (Fig. 47.6).

Vertical subluxation of the odontoid process is associated with a scoliotic deformity of the trachea and larynx. 56 The deformity is complex, involving both rotation and deviation of the larynx from the midline, and it may make laryngoscopy and tracheal intubation difficult. However, vertical subluxations occur primarily in older patients with severe, longstanding disease and are unlikely to be seen in women of childbearing age. Other airway issues such as cricoarytenoiditis and temporomandibular joint (TMJ) dysfunction may occur earlier in the disease and may complicate airway management of the parturient. 57

Extra-articular features are common in patients with rheumatoid arthritis. Anesthesia providers have a special interest in abnormalities that affect the airway and the cardiovascular and respiratory systems (Box 47.2). Although
these complications occur more typically in patients with long-standing disease, it is prudent to inquire about those with more significant anesthetic implications. Cardiovascular mortality is especially high in patients with rheumatoid arthritis. Similar to patients with type 2 diabetes mellitus, cardiovascular disease often presents atypically.57

Interaction with Pregnancy
Rheumatoid arthritis is associated with a higher incidence of preterm birth, small-for-gestational-age infants, preeclampsia, and elective cesarean delivery compared with reference populations of women in North America and Europe.58 In the absence of vasculitis, fetal outcome is good, although as a group, the chronic inflammatory arthritides are associated with higher perinatal morbidity.58 Although earlier evidence consistently showed that pregnancy has a beneficial, ameliorating effect on the activity of rheumatoid arthritis, more recent prospective studies using objective and validated disease scoring systems have shown less benefit. Remission occurs in only 16% to 39% of patients, and improvement in symptoms in 39% to 65% of patients, rather than the previously quoted 75%.59 The improvements in disease activity (pain, swelling, stiffness) occur despite the discontinuation of effective but teratogenic disease-modifying antirheumatic drugs and a substantial reduction in the dose of safe drugs (e.g., corticosteroids). Relapse occurs postpartum in approximately 35% to 75% of women, beginning as early as the second week after delivery. It appears that most women return to a disease status comparable to their prepregnant state. Current emphasis is on continuing appropriate medications during pregnancy, as a substantial number of women will have moderate to high disease activity.

Medical Management
Drug therapy for rheumatoid arthritis is divided into (1) symptom-modifying drugs, (2) disease-modifying antirheumatic drugs, and (3) biologic drugs.

**Symptom-modifying therapies** include nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors and glucocorticoids. NSAIDs and glucocorticoids have been the mainstay of therapy in rheumatoid arthritis during pregnancy for many years.60 A small study of COX-2 inhibitors revealed an increase in congenital anomalies; hence, they are best avoided in pregnancy.61 In a population-based cohort study, NSAID use in early pregnancy, especially around the time of conception, was associated with an increased incidence of early pregnancy loss.62 When used later in pregnancy, NSAIDs are associated with premature closure of the ductus arteriosus and increased risk for neonatal bleeding. Although a large multicenter epidemiologic study did not find an association between NSAID consumption during pregnancy and pulmonary hypertension of the newborn,63 the current recommendation is that all NSAIDs except low-dose aspirin be discontinued at 32 weeks’ gestation.

Nonfluorinated glucocorticoids (prednisone, prednisolone) are considered safe in pregnancy after the first trimester,
but early use is associated with a small increase in the incidence of cleft palate.\(^6\) High doses and use later in pregnancy increase the risk for gestational diabetes, gestational hypertension, and premature rupture of the membranes.

**Disease-modifying antirheumatic drugs** reduce flares, prevent joint erosions, and have proven efficacy in decreasing morbidity and mortality from rheumatoid arthritis. This drug category includes sulfasalazine, azathioprine, methotrexate, leflunomide, gold salts, and antimalarial agents. **Methotrexate** is considered a first-line treatment for rheumatoid arthritis and is typically started at diagnosis, but unfortunately it and **leflunomide** are highly teratogenic and must be stopped several months before conception.\(^6\) **Sulfasalazine** inhibits folate synthesis, and therefore additional folate supplementation is required during pregnancy. **Azathioprine** may be used during pregnancy at doses less than 2 mg/kg/day; although other options are preferable.

The **biologic drugs**, which are proving as effective as methotrexate in preventing erosions and reducing long-term disability, include **the anti–tumor necrosis factor therapy**s (anti-TNF) (e.g., etanercept, certolizumab). Experience with these drugs has grown considerably as they are also used in inflammatory bowel disease; overall they appear safe in pregnancy.\(^5\!8,64,65\) A 2016 analysis of data from health registries in Denmark and Sweden identified 683 women who had received TNF inhibitor therapy in early pregnancy; the odds ratio for any birth defect was not significantly greater than in women with chronic inflammatory disease who were not treated with anti-TNF therapy.\(^46\) In contrast, there is little collective evidence on the use of other biologic drugs (e.g., **abatacept**, **rituximab**, **tocilizumab**) in pregnancy, or they have been associated with adverse fetal effects. Thus, the recommendation is to discontinue these drugs before conception.\(^6\) There is insufficient information on the newest class of drug, the **JAK-1 inhibitors**, to make any recommendations.\(^6\)

Avoiding disease flares by optimal medical management with acceptable therapies is becoming the standard, rather than the preconception discontinuation of successful anti-rheumatic drugs that have been shown to be safe for use in pregnancy.

**Obstetric Management**

Vaginal delivery is preferred for parturients with rheumatoid arthritis, and cesarean delivery should be reserved for obstetric indications. A major concern is maternal positioning during labor. Rheumatoid joints are unstable because of ligamentous and cartilage swelling. It is important to determine the permissible range of motion and activity for affected joints. Special emphasis should be given to the hips, knees, and neck. Physicians and nurses should be aware of the potential risks associated with forcing motion beyond the disease-imposed limits.

**Anesthetic Management**

The preanesthetic evaluation should include a careful evaluation of the airway. Patients with rheumatoid arthritis may have a small mandible, TMJ dysfunction, cricoarytenoid arthritis, and laryngeal deviation, all of which may complicate direct laryngoscopy.\(^5\) In particular, these findings may be present in parturients with juvenile rheumatoid arthritis. Cervical spine involvement is not common in young patients but may occur in patients with disease of long duration and in those with severe, deforming disease—typically, patients with juvenile rheumatoid arthritis. Although there is no guideline or consensus on the need to obtain cervical spine radiographs in patients with rheumatoid arthritis, it would be reasonable even in the pregnant woman if her rheumatoid arthritis includes severe erosive disease, neck symptoms, or a history of disease of 10 or more years’ duration.\(^5\!7\) The cardiac and pulmonary features of rheumatoid arthritis are not common in young patients, but signs and symptoms of pleural and pericardial effusions and pulmonary parenchymal involvement should be sought.

No evidence contraindicates the administration of spinal or epidural anesthesia in patients with rheumatoid arthritis. However, evidence in the nonpregnant population has indicated that spinal blocks rise higher than expected in patients with rheumatoid arthritis, independent of body mass index.\(^6\!7,68\) Care should be taken to avoid excessive manipulation of the neck during administration of general anesthesia. Finally, joints should be padded and protected appropriately during labor and delivery.

**Ankylosing Spondylitis**

Ankylosing spondylitis is a chronic inflammatory arthropathy characterized by infiltration of granulation tissue into the bony insertions of ligaments and joint capsules, with subsequent fibrosis, ossification, and ankylosis. The disease is a major subtype of an interrelated group of rheumatic diseases called the spondylarthritides, which are linked by the major histocompatibility complex (MHC) Class 1 tissue antigen HLA B27.\(^6\!9\) Ankylosing spondylitis primarily affects the sacroiliac, facet, and costovertebral joints; sacroilitis is pathognomonic. There is progressive flexion and fusion of the spine and fixation of the rib cage; however, the clinical spectrum is wide, and only a small proportion of patients progress to total spinal ankylosis.

The global prevalence of ankylosing spondylitis is estimated to be 0.86%.\(^6\!5\) Onset is common during the second and third decades of life, a period of peak childbearing potential. The disease is milder in women than in men, but women are more likely to have peripheral arthritis and involvement of the cervical spine and symphysis pubis.\(^7\!0\) Although clinically significant lesions of the cervical spine may occur early in the course of the disease, they are far more common in patients with long-standing ankylosing spondylitis (Fig. 47.7).\(^5\!6,7\!1\) Ultimately, 21% of patients with ankylosing spondylitis develop clinically significant atlantoaxial subluxation. TMJ involvement causes limited mouth opening in 10% of patients early in the disease, increasing to 30% to 40% as the disease progresses.\(^7\!2\) A slower development of radiologic changes of the dorsolumbar spine occurs in women, and spinal rigidity or deformity and extra-articular manifestations are rare in
Turkey and Sweden reported that the mean maternal age was higher in women with ankylosing spondylitis than in healthy counterparts. Jakobsson et al., in the largest study assessing ankylosing spondylitis and pregnancy to date, compared 388 women with ankylosing spondylitis with 1082 healthy women. After adjustment for confounding factors, women with ankylosing spondylitis were more likely to deliver prematurely and by elective cesarean. The overall incidence of preeclampsia was not increased.

Care should be taken when positioning women with ankylosing spondylitis, as the biomechanics of the spine are altered by decoupling of bone formation and resorption that occurs as part of the disease. Holding a flexed trunk for prolonged periods while pushing may result in vertebral fractures, as demonstrated in a case report in which a 33-year-old woman with a 5-year history of ankylosing spondylitis suffered a T12 to L1 fracture dislocation with subsequent neurologic compromise during attempted vaginal birth.

**Interaction with Pregnancy**

In contrast to rheumatoid arthritis, pregnancy does not seem to reduce the symptoms or slow the progression of disease in patients with ankylosing spondylitis, and many patients experience an aggravation of morning stiffness and back pain. However, a retrospective review of 35 case-control matched pregnancies identified improvement in pain and stiffness in 51% of women in early pregnancy, although unfortunately there was some return of pain as pregnancy progressed. Pregnancy may ameliorate the extra-articular features of this disease (e.g., psoriasis, inflammatory bowel disease, small joint arthritis), but it appears that women with ankylosing spondylitis are more likely than women with rheumatoid arthritis to enter pregnancy with active disease and, hence, to have higher levels of pain at the beginning of pregnancy. Two retrospective case-control studies from

**Anesthetic Management**

An anesthesia provider should review the patient’s history with respect to the duration of the disease, the presence of extra-articular features, and the recent use of analgesics. TMJ disorders, cervical spine involvement, and cardiopulmonary complications are rare early in the disease course; however, difficult tracheal intubation has been reported in parturients. Severity of back symptoms is often out of proportion
to the radiographic appearance of the spine, and calcification of the spinal ligaments is typically not advanced in young patients. Neuraxial anesthesia is acceptable in parturients with ankylosing spondylitis; however, even in young patients it may be technically challenging. Calcification of the inter-spinous ligaments and osteophyte formation may limit the parturient’s ability to flex forward, making midline needle placement difficult. A paramedian approach can be considered in this instance. Additionally, the epidural space becomes narrowed in patients with ankylosing spondylitis, and there have been reports of unexpectedly high blocks, as well as failed blocks despite confidence that the catheter was in the epidural space. After multiple failed attempts to provide epidural analgesia in a parturient with advanced ankylosing spondylitis, Hoffman et al. suggested that a highly calcified posterior longitudinal ligament may limit rostral spread of local anesthetic in the epidural space. Preprocedural ultrasonography may be helpful, either to identify the best interlaminar space, or to indicate that administration of neuraxial anesthesia may be impossible.

**SPINAL DYSRAPHISM**

The term *dysraphism* refers to a neural tube closure defect; however, use of the term has expanded to include all congenital dorsal midline spinal disorders. The old and confusing terms of *spinal bifida occulta* and *spina bifida cystica* were based on clinical findings and plain films. With vastly improved neuroradiologic imaging available, a mixed clinical–neuroradiologic classification system of spinal dysraphism has been proposed that discourages use of the term *occult spinal dysraphism* for the reasons described in the following sections.

Spinal dysraphisms fall into two main categories: open spinal dysraphism and closed spinal dysraphism (Box 47.4). Open spinal dysraphisms are neural tube defects that are open to the environment and contain malformed spinal cord. Closed spinal dysraphisms include all midline neural tissue abnormalities that are covered by skin; they are not necessarily occult as their presence is usually suspected by cutaneous stigmata such as hairy nevus, hairy tufts, dimples, discolored patches, capillary hemangioma, and subcutaneous masses. Finally, the finding of an isolated failed fusion of the bony neural arch, found typically at L5 or S1 (80%), is common enough (occurring in 5% to 36% of the population) that it can be considered a normal variant. Overall, spinal dysraphism is one of the most common birth defects, with a prevalence of 0.2 to 10 per 1000 births; the incidence is higher in regions that do not advocate for folate supplementation during pregnancy.

Open spinal dysraphisms are relatively uncommon, occurring in 3.7 per 10,000 births in the United States, typically at the lumbosacral level. Early and aggressive surgical treatment of open spinal dysraphisms has improved survival from 45% in the early 1970s to 70% to 90% by the mid-1980s. Obstetric and anesthesia providers can expect to encounter a growing number of pregnant women with surgically-closed open spinal dysraphisms.

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**BOX 47.4 Clinical-neuroradiologic Classification of Spinal Dysraphism**

**Open Spinal Dysraphism**
- Myelomeningocele
- Myelocele
- Hemimyelocele
- Hemimyelocele

**Closed Spinal Dysraphism**
- With a subcutaneous mass
- Without a subcutaneous mass
- Simple dysraphic states
  - Posterior spina bifida
  - Intradural and intramedullary lipoma
  - Filum terminale lipoma
  - Tight filum terminale
  - Abnormally long spinal cord
  - Persistent terminal vertebra
- Complex dysraphic states
  - Dorsal enteric states
  - Neurenteric cysts
  - Split cord malformations
  - Dermal sinus
  - Caudal regression syndrome
  - Segmental spinal dysgenesis


Neurologic deficits involving the lower extremities and sphincters occur in almost all patients with open lesions, although the deficits vary in severity. Many patients have significant residual neurologic impairment and ongoing orthopedic and genitourinary complications. Hydrocephalus is present in many patients, and shunting of the ventricular system is common, with revisions often required during childhood. By puberty, as many as 50% of patients who have received shunts no longer require them. Kyphoscoliosis, which is common in patients with a thoracic lesion, occurs in 20% of patients with a lumbosacral defect. Paralytic scoliosis is the most common type and results from an imbalance of paravertebral muscle tone.

Closed spinal dysraphisms are further divided into those with or without a subcutaneous mass. The lesions are usually in the lumbosacral region, and the skin covering these defects is frequently abnormal. Meningoceles are herniated sacs of CSF lined by dura and arachnoid; the sacs do not contain parts of the spinal cord, although nerve roots may pass through the sac. Closed spinal dysraphisms without a subcutaneous mass comprise an intermediate group of conditions in which the bony defect is associated with one or more anomalies of the spinal cord, some simple and others complex. Complex closed spinal dysraphisms usually have cutaneous markers. Dermal sinus tracts should not to be confused with pilonidal cysts; dermal cysts are frequently connected to the intradural space and therefore pose a risk for developing meningitis.
Affected patients may have no neurologic symptoms or may have minor sensory, motor, and functional deficits of the lower limbs, bowel, and bladder. They also may have orthopedic issues such as scoliosis, limb pain, and lower extremity abnormalities. Fifty percent of patients with spinal cord abnormalities have cutaneous stigmata, and 70% have a tethered spinal cord, which has implications for neuraxial anesthesia. The malformations may not be clinically evident at birth and present later in life with tethered cord syndrome. Magnetic resonance imaging (MRI) is the preferred imaging method to diagnose these lesions.

Tethered Cord Syndrome and Arnold-Chiari Malformation

Tethered cord syndrome is characterized by neurologic deterioration secondary to traction on the conus medullaris, which typically, but not invariably, is low lying (L2 to L4). Congenital abnormalities of the spinal cord such as lipoma, tight filum terminale, dermal sinus, and split cord malformations are found in more than 50% of patients with adult-onset tethered cord syndrome.

A new classification of tethered cord syndrome in adults has been proposed to differentiate tethered cord occurring secondary to open spinal dysraphism from the adult-onset neurologic syndrome associated with closed spinal dysraphism. MRI studies suggest that tethering is present in virtually all patients with open spinal dysraphism. Although many patients with closed spinal dysraphism do not have obvious neurologic impairment secondary to the tethering, adults with tethered cord syndrome often have a long history of minor neurologic or orthopedic issues. Others present with acute symptoms after a precipitating event that stretched the spinal cord, such as heavy lifting or placement in the lithotomy position. Of note, more than 50% of adults with tethered cord syndrome present only with a history of low back and leg pain before a precipitating event that leads to the diagnosis. The common isolated finding of a defective laminar arch (spina bifida) is not associated with a low-lying or tethered cord.

Low-lying spinal cords and the possibility of undiagnosed tethered cord syndrome have come to the attention of obstetric anesthesia providers with the publication of several case reports of neurologic injury after spinal or epidural anesthesia in women subsequently diagnosed with closed spinal dysraphism, in whom typically there was no obvious history or cutaneous stigmata. An important feature of adult tethered cord syndrome is that the low-lying cord is located more posteriorly than a normal cord, increasing the likelihood of direct needle trauma during administration of spinal or epidural anesthesia (Fig. 47.8). Open spinal dysraphism is usually associated with Arnold-Chiari malformation, which is characterized by cerebellar herniation through the foramen magnum and descent of thepons and medulla. Tethered cord from a tight filum terminale has also been deemed causal in the development of syringomyelia and subsequent Arnold-Chiari syndrome. Symptoms are more common if the cerebellar herniation exceeds 12 mm or if syringomyelia is present.

Obstetric Management

Recurrent urinary tract infection is the most common antenatal complication in patients with open spinal dysraphism and is associated with preterm labor. Intestinal and urinary tract obstruction, as well as problems related to ileal conduits and stomas, are common during pregnancy, as are pressure sores resulting from greater immobility. The enlarging uterus may compromise pulmonary function, especially in patients with kyphoscoliosis.

Cesarean delivery is reserved for obstetric indications, and its incidence is increased and proportionate to the severity of the underlying defect and its consequences. Vaginal delivery is more common in women who are independently mobile and is less common in wheelchair-dependent patients. Sterling et al. found a 60% cesarean delivery rate in a series of 32 women with spinal cord injury—69% secondary to spinal dysraphism. Pelvic and lower limb anomalies and contractures may obstruct the pelvic outlet and warrant cesarean delivery. Cesarean delivery is complicated by the presence of stomas and conduits; postoperative complications and prolonged hospital stays are common. Women with known tethered cord syndrome should avoid both the squatting position and a prolonged lithotomy position for delivery.

Anesthetic Management

Administration of epidural or spinal anesthesia may be considered in women with various forms of spinal dysraphism and stable neurologic function. Imaging studies provide valuable information on neural anatomy and facilitate anesthetic management. A neurologic examination, as well as a full
discussion with the patient of the risks and benefits of neuraxial anesthesia, including risk for inadequate block, should be performed and documented before the administration of neuraxial anesthesia.

An isolated laminar arch defect rarely causes issues for administration of neuraxial anesthesia. First, the lesion typically occurs at the L5 to S1 segments, below the level at which most epidural and spinal anesthetics are administered. Second, the most common anomaly is a simple midline split in the lamina, and this defect rarely seems to interfere with either the performance or the development of spinal or epidural anesthesia. The epidural space may be incomplete or discontinuous across the level of an isolated laminar arch defect because of the variable formation of the ligamentum flavum at this site. An attempt to identify the epidural space at the site of this lesion may result in unintentional dural puncture, although successful epidural analgesia has been reported with the catheter placed within the zone of the lesion.

In patients with surgically corrected open spinal dysraphism, the anesthesia provider should be aware that the terminal portion of the spinal cord typically lies at a vertebral level lower than normal; detethering surgery in the patient with open spinal dysraphism does not usually result in the conus ascending to a normal position.\textsuperscript{93} Closed spinal dysraphism without a subcutaneous mass is of concern because of the possibility of a low-lying, posteriorly located, and tethered spinal cord, potentially with no cutaneous stigmata. A neurologic history should be taken and a screening neurologic and lower limb examination should be performed in all women with a known defective laminar arch, preferably antenatally, to determine whether MRI for spinal dysraphism is necessary.\textsuperscript{89,100} The presence of skin dimpling (greater than 2.5 cm from the anal margin), hair tufts, pseudotails and midline lumbosacral hemangiomas should raise suspicion that an underlying cord abnormality exists.\textsuperscript{82} In our judgment, in women with a known low-lying cord, epidural anesthesia performed by an experienced anesthesia provider is safer than spinal anesthesia. If spinal dysraphism is suspected but no imaging studies are available, it may be prudent to avoid neuraxial anesthesia.

In the patient with an open spinal dysraphism lesion, the anesthesia provider should determine the level of the lesion and whether the patient has residual spinal cord function below it. Patients with a complete lesion at or above T11 are likely to experience painless labor. However, the risk for autonomic hyperreflexia should be evaluated in patients with thoracic lesions, and neuraxial anesthesia should be provided if the patient is deemed to be at risk; this issue is especially important if the lesion is between T5 and T8 (see Chapter 48). If the patient has undergone ventricular shunt placement, the current status of the shunt should be determined. Neurosurgical consultation should be obtained if questions remain about the requirement for, or function of, the shunt. Baseline renal function should be assessed as well as pulmonary function, especially in patients with scoliosis.

There are published reports of the use of epidural and spinal anesthesia in patients with open spinal dysraphism.\textsuperscript{101–103} However, experience is limited, and most published series of pregnant women with open spinal dysraphism report neither the type of anesthesia nor complications. Tidmarsh and May\textsuperscript{102} reported the management of intrapartum analgesia in 16 patients with spinal dysraphism, 8 of whom had myelomeningocele. Five of the eight patients with open spinal dysraphism received epidural analgesia for labor and delivery. Three patients had a “normal” block, one patient had a sensory level that was higher than expected (T3 after the administration of 10 mL of 0.25% bupivacaine), and one patient had poor sacral analgesia. In the UK Registry of High-Risk Obstetric Anesthesia, the period from 1997 to 2002 included 23 cases of parturients with spinal dysraphisms among 102 cases of neurologic conditions.\textsuperscript{104} Of those, the extent of the lesion was defined further in only 10 cases, and 8 had only a bony arch defect. Neuraxial anesthesia was provided in 8 cases. Only epidural anesthesia was used owing to concern about a low-lying or tethered cord; only 5 patients had MRI performed before delivery. Murphy et al.\textsuperscript{82} authored a comprehensive review of spinal dysraphism in the parturient, including a summary of reported obstetric anesthesia care. Of the published 139 cases (some only abstracts), epidural anesthesia was used in 52 cases, and spinal or CSE anesthesia was used in 15 cases. There were numerous complications ranging from difficult block placement; rapid onset of anesthesia; and asymmetric, high, and failed blocks, certainly at a rate far higher than in typical obstetric patients. However, no patient had neurologic sequelae.

Asakura et al.\textsuperscript{105} demonstrated the use of ultrasonography to detect a bony arch defect. Ultrasoundographic imaging of the terminal portion of the cord is difficult, however, and although it has been shown to be feasible in children, it is unlikely to be helpful in determining the safety of neuraxial anesthesia in adults.\textsuperscript{106} Spinal anesthesia should be performed below the known level of the conus medullaris or avoided in favor of epidural anesthesia. If possible, epidural anesthesia should also be initiated below the level of cord termination in case of unintentional dural puncture. It should be noted that the epidural space is often abnormal, which increases the likelihood of inadequate epidural anesthesia. In our judgment, spinal anesthesia is not contraindicated in women with negligible function of the lower extremities and sphincters, given that the concern for direct neural trauma to a low-lying spinal cord is not clinically relevant.

Limited data exist on the obstetric anesthesia experience in parturients with Arnold-Chiari malformation. Chantigian et al.\textsuperscript{107} described their experience with 12 parturients who delivered a total of 30 infants. Nine deliveries were accomplished with neuraxial anesthesia, including six vaginal deliveries with epidural analgesia, two cesarean deliveries performed with single-shot spinal anesthesia, and one cesarean delivery performed with a spinal catheter. No patient experienced postprocedural neurologic sequelae related to the use of neuraxial anesthesia.
ACHONDROPLASIA

Achondroplasia, an inherited disorder of bone metabolism, is the most common cause of disproportionate dwarfism, with a prevalence of 1 in 26,000 live births. Although it is inherited in an autosomal dominant mode, most cases arise from spontaneous mutations.107 The range of cervical motion may be decreased, lumbar lordosis and thoracic kyphosis are increased, and thoracic kyphoscoliosis occurs.108 The vertebral pedicles are short, and reduced length of the neural arch leads to shortened anteroposterior and transverse diameters of the vertebral canal, resulting in foramen magnum and spinal stenosis.109 Although it may occur earlier, symptomatic spinal stenosis often does not present until the fourth or fifth decade, when kyphosis, scoliosis, osteophytes, and herniated discs typically cause further narrowing of the spinal canal. There is considerable interindividual variation in the clinical and radiographic characteristics, and skeletal abnormalities often show more variation than consistency.109,110

Obstetric Management

The uterus is an abdominal organ in the achondroplastic patient.111 With advancing pregnancy it may encroach on the small thoracic cage and lead to decreases in the functional residual and closing capacities; severe dyspnea may occur with advancing gestational age. Back discomfort is common during pregnancy, and the reported incidence of sciatica is greater than in healthy pregnant women,112 most likely owing to the underlying spinal abnormalities. Typically, an inadequate maternal pelvis combined with a normal-sized (nonachondroplastic) fetus results in cephalopelvic disproportion. Imaging techniques may be used to confirm this situation, and the obstetrician should anticipate the need to deliver most patients with achondroplasia by cesarean delivery.108,109

Anesthetic Management

The short, obese limbs of the patient with achondroplasia may make it difficult to obtain measurements of blood pressure with a noninvasive cuff, and an intra-arterial catheter may be necessary. Prominent paraspinal muscles and marked lumbar lordosis may complicate attempts to palpate landmarks during the administration of spinal or epidural anesthesia; the use of ultrasonography may help identify landmarks.108,113 Scoliosis of the spine also may cause technical difficulties with neuraxial anesthesia attempts. The small stature and spinal stenosis reduce the dose of local anesthetic required for major neuraxial anesthesia.108,110,111,114 It is difficult to estimate the appropriate dose of local anesthetic for single-shot spinal anesthesia. Continuous epidural anesthesia or CSE anesthesia is preferable because it allows the anesthesia provider to titrate the dose of local anesthetic to the desired level of anesthesia. Local anesthetic dose requirements are typically smaller than those in parturients of normal stature; this is not always the case, however, supporting the use of a neuraxial anesthetic technique that may be titrated to the desired effect.112,113,115

OSTEOSTENOSIS IMPERFECTA

Osteogenesis imperfecta is an inherited condition that occurs with an incidence between 1 in 10,000 and 1 in 25,000.118,119 The genetic defect is within the genome that encodes for type I collagen, the major collagen in tissues that require structural strength. The disease is a generalized connective tissue disorder, and expression ranges from mild osteoporosis to the classical clinical stigmata characterized by multiple bone fractures and skeletal deformities, blue sclera, and middle ear deafness (otosclerosis). There are now eight types classified by genetic mutations, although clinical features are still the primary differentiation.119 Type I is the prototype disease. It is inherited as an autosomal dominant trait and is the most common and mildest form of this disease. It typically manifests in childhood as multiple fractures after minor trauma. Types II and III are inherited as autosomal dominant traits and are characterized by extreme bone fragility. Type II is uniformly lethal, and stillbirth or early neonatal death is common; death in utero is caused by skeletal collapse, and early neonatal death typically results from chest wall failure and respiratory insufficiency. Infants with type III disease may have fractures at birth and may have progressive skeletal deformities during the first two decades of life; it is the most severe form of osteogenesis imperfecta that survives beyond the newborn period. Type IV, also autosomal dominant, is much less common and the most clinically diverse. Types V to VIII are recent additions, and do not result from genetic mutations of collagen I, nor do they exhibit the typical findings of osteogenesis imperfecta such as blue sclerae and hearing loss. Type V formerly was a subset of Type IV and is characterized by the tendency to develop hypertrophic calluses following surgery or trauma. Type VI varies from moderate to severe deformities secondary to a mineralization defect; it is inherited as an autosomal recessive disease. Types VII and VIII represent less than 10% of all cases of osteogenesis imperfecta, and clinically present with moderate to severe deformities and fragility (VII) or severe growth abnormalities (VIII).119

The majority of pregnant women with osteogenesis imperfecta have type I disease, although pregnancy has been reported in more severe forms of the disease.120,121 There is considerable variability among affected patients in age at
onset and frequency of fractures. Dwarfism is typical, and kyphoscoliosis is common, as are other chest wall abnormalities. These chest and spinal abnormalities result in restrictive lung disorders (Fig. 47.9). Other abnormalities include a decrease in the range of motion of the shortened cervical spine, micrognathia, and malformed, brittle teeth.\textsuperscript{121} The abnormal bleeding and early bruising seen in patients with osteogenesis imperfecta is multifactorial; platelet dysfunction, vessel wall fragility, and reduced factor VIII are all potential contributors. Hyperthyroidism occurs in 40\% of patients; an elevated concentration of thyroxine leads to increases in both oxygen consumption and heat production.\textsuperscript{121} Although there is one published case of a patient with osteogenesis imperfecta who developed malignant hyperthermia, there is no known association between the two diseases.\textsuperscript{122} Intraoperative hyperthermia has often been reported; however, a retrospective cohort study of 49 patients with osteogenesis imperfecta undergoing noncardiac surgery revealed no difference in intraoperative temperature changes compared with matched controls.\textsuperscript{123} This information should allay ongoing concerns about risk for developing malignant hyperthermia.

Obstetric Management

Pregnancy results in transfer of calcium from the mother to the fetus, which in the patient with osteogenesis imperfecta can lead to increased maternal fracture risk.\textsuperscript{124} Platelet dysfunction and vessel fragility in osteogenesis imperfecta as well as abnormal uterine function result in a higher incidence of uterine atony and postpartum hemorrhage.\textsuperscript{125} Additionally, the incidence of cesarean delivery and pregnancy complications, including preterm birth, preeclampsia, bleeding, bone fractures, and other musculoskeletal issues, are greater in patients with osteogenesis imperfecta.\textsuperscript{125} A retrospective cohort study using a U.S. database containing more than 7 million births found 295 births to women with osteogenesis imperfecta.\textsuperscript{124} Compared with women without osteogenesis imperfecta, parturients with the disease were more likely to have antepartum hemorrhage (odds ratio [OR], 2.01; 95\% confidence interval [CI], 1.04 to 3.91) and placental abruption (OR, 2.50; 95\% CI, 1.24 to 5.03), and less likely to have a spontaneous vaginal birth (OR, 0.19; 95\% CI, 0.15 to 0.25).\textsuperscript{124} In addition, there was an increased risk for preterm birth, blood transfusion, and venous thromboembolism.\textsuperscript{124} Finally, it is important to recognize the increased incidence of chronic pain, and the risk for developing acute musculoskeletal pain during pregnancy in these women.\textsuperscript{125}

Anesthetic Management

The anesthesia provider must be aware of the fragility of the bones, the potential for difficult tracheal intubation, and the presence and severity of restrictive lung disease. Transfers, positioning, and any invasive intervention must be accomplished with extreme care. Blood pressure cuffs and tourniquets to facilitate placement of intravenous catheters should be applied gently to prevent fractures. Alternatives to direct laryngoscopy, such as video laryngoscopy, may be considered to reduce the applied forces necessary for direct laryngoscopy. Authors of a case report raised the theoretical concern that fasciculations following succinylcholine administration may be harmful.\textsuperscript{126}

Before administration of neuraxial anesthesia, the anesthesia provider should consider the technical difficulties inherent in performing neuraxial anesthesia in patients with spinal deformities and consider using preprocedural ultrasonography to facilitate needle placement. The possibility of platelet dysfunction is best evaluated by obtaining a thorough bleeding history. In the setting of a reassuring history, neuraxial anesthesia need not be withheld. Small stature and spinal abnormalities reduce the local anesthetic dose requirements and increase the risk for both misplaced injection and local anesthetic systemic toxicity. It may be difficult to estimate the appropriate dose for single-shot spinal anesthesia in these patients. Thus, continuous epidural, continuous spinal, or CSE anesthesia is the neuraxial anesthetic technique of choice, barring other contraindications.\textsuperscript{127} Yeo and Paech\textsuperscript{128} reported the successful use of both epidural and subarachnoid blocks for cesarean delivery on five occasions over 9 years in a single patient with type I osteogenesis imperfecta. Dinges et al.\textsuperscript{129} described twin sisters with type III osteogenesis imperfecta, one who received a general anesthetic because of severe corrected kyphoscoliosis and predicted difficult airway, for cesarean delivery at 32 weeks’ gestation for increasing respiratory compromise. The second twin, who had only mild scoliosis and a reassuring airway, developed respiratory compromise and was delivered urgently by cesarean with CSE anesthesia at 28 weeks’ gestation for a nonreassuring fetal heart rate tracing.

Fig. 47.9 A chest radiograph of a 30-year-old woman with osteogenesis imperfecta type I. Generalized osteoporosis, corrected thoracic kyphoscoliosis, a restricted thoracic cage, and multiple old fractures are demonstrated. (General anesthesia was provided for cesarean delivery and tubal ligation.)
KEY POINTS

- Lumbopelvic pain is the most common musculoskeletal complaint during pregnancy. It results from both hormonal and mechanical factors.
- Low back pain does not contraindicate the administration of spinal or epidural anesthesia.
- Corrected idiopathic thoracolumbar scoliosis is the most common major musculoskeletal disorder seen in pregnant women. Prepregnancy pulmonary function is a better predictor of maternal outcome than the severity of the curve.
- Neuraxial anesthesia is technically challenging in patients with scoliosis, and the anesthesia provider should anticipate a greater incidence of complications and inadequate anesthesia.
- Preprocedural ultrasonography is a useful tool to facilitate neuraxial needle placement in patients with difficult surface anatomy and challenging spinal anatomy.
- Maternal rheumatoid arthritis is associated with preterm delivery and low birth weight, but ankylosing spondylitis does not adversely affect the outcome of pregnancy.
- Pregnancy may mitigate the symptoms of rheumatoid arthritis; however, many women require medical therapy during pregnancy and may require medical management of disease flares.
- *Spinal dysraphism* is the overall term for neural tube defects, encompassing the older terms of *spina bifida occulta* and *spina bifida cystica*.
- An isolated posterior spinal bony defect does not contraindicate the administration of spinal or epidural anesthesia.
- Adult tethered cord syndrome secondary to spinal dysraphism is important to diagnose, as it may preclude the use of spinal anesthesia.
- Cephalopelvic disproportion often mandates cesarean delivery in parturients with achondroplasia or osteogenesis imperfecta.

REFERENCES


The choice of anesthetic technique for pregnant women with neurologic disease requires knowledge of the pathophysiology of the disorder and an understanding of controversies involved in the diagnosis and management of the disease. If a patient’s neurologic condition deteriorates postpartum, the cause may be unclear and the anesthetic technique may be blamed unfairly. There are limited published data on specific neurologic and neuromuscular disorders in pregnant women. However, few of these disorders contraindicate the use of neuraxial anesthesia. In most cases, the obstetrician should obtain early antepartum consultation from an anesthesia provider. Early consultation allows accurate antepartum documentation of the extent and pattern of the neurologic deficit as well as discussion and formulation of the anesthetic plan with the patient, her obstetrician, and a neurologist or neurosurgeon.

Because patients with a wide variety of neurologic disorders will present for preoperative evaluation, the following thought process will assist the clinician with completing a proper evaluation and formulating an anesthetic plan.

**CHAPTER OUTLINE**

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What is the basic pathophysiology of the neurologic disorder? Neurologic disorders may be stable, progressive, or relapsing/recurrent. It is important to understand the common disease patterns. The potential for progression of the disease after delivery will depend on the pattern of progression and underlying pathophysiology, and on the effect of pregnancy on disease progression.

What is the patient’s history and current findings after neurologic examination? A history should include the onset date and current course of the disorder. Symptoms related to neurologic issues should be documented (e.g., seizure type and frequency, deficits after cerebrovascular events, cognitive deficits). A basic physical examination should be conducted to document existing deficit patterns, including cognitive dysfunction (e.g., ability to understand and cooperate), deficits involving vision, hearing, speech, and swallowing; respiratory symptoms; and weakness and sensory deficits in the head and neck, trunk, and extremities. Motor and sensory deficits are classified as mild, moderate, or severe, with a description of the affected area. Special attention should be directed to limitations in ambulatory ability (e.g., bed-bound, wheelchair, walking with assistance) or positioning.

What are the current treatments, and what testing results are available? Documentation of medical and nonmedical therapies is essential. For some disorders (e.g., myasthenia gravis), documentation of the timing of treatment is also critical. In most cases, specific laboratory testing will not influence anesthetic management and outcome. However, pulmonary function testing should be considered in patients with neurologic disorders that result in significant respiratory compromise; the findings may assist the anesthesia provider in making recommendations about anesthetic management.

What is the impact of the neurologic disorder on other organ systems (e.g., cardiac, respiratory, airway)? The patient’s neurologic disease may affect organ systems that are relevant to the anesthetic plan. For example, central core disease is associated with a risk for malignant hyperthermia. In addition, progressive neurologic disorders may significantly compromise the patient’s respiratory status, thereby increasing the risks associated with neuraxial and general anesthesia.

What are the potential impacts, risks, and benefits of anesthetic options based on the disease’s pathophysiology, symptoms, and treatment? Can treatment be initiated antepartum or before delivery that will improve outcome? For most rare neurologic disorders, there is limited evidence on which to base decisions about anesthetic management. In these cases, the anesthesia provider should consider the disease’s basic pathophysiology and its possible direct and indirect interactions with specific anesthetic techniques. Encouraging the obstetrician to send these patients for early antepartum consultation will enable the anesthesia provider to obtain formal input from a neurologist or other consultant if necessary. A multidisciplinary discussion that includes the patient and her family may be necessary to weigh the risks and benefits of specific obstetric and anesthesia plans. A team approach to peripartum care in patients with complex neurologic disorders is essential.

What are the plans for postpartum management of the patient’s disease? Will the intrapartum anesthetic management or postpartum analgesia management influence outcomes? Some conditions, such as multiple sclerosis, can have significant implications for the postpartum period. The anticipated progress of the disease and planned postpartum management should be discussed with the patient in the antenatal period.

In all cases, accurate documentation of the responses to the previous questions will greatly assist the team providing peripartum care for these patients. Some of the more common neurologic conditions are addressed in this chapter, and the existing literature is surveyed relative to the peripartum management of these patients. This knowledge allows the anesthesia provider an opportunity to formulate a safe and rational anesthetic plan as well as enable an appropriate discussion with the patient regarding the risks and benefits of anesthetic options.

### MULTIPLE SCLEROSIS

Multiple sclerosis is a major cause of neurologic disability in young adults, and it is at least two to three times more common in females than in males. First-time symptoms typically manifest in the second or third decade of life; therefore, the disease typically presents in females in their reproductive years. The prevalence of the disorder varies with the population, and may be as high as 300 per 100,000 in some parts of North America, although the accuracy of epidemiologic estimates have been limited by heterogeneous methods for identifying people with disease and by different data analytic strategies.

The disease is characterized by variable neurologic disabilities with two general patterns of presentation: (1) exacerbating remitting, which accounts for 85% of cases, in which attacks appear abruptly and resolve over several months; and (2) chronic progressive, in which continued deterioration occurs over time. The relapse rate varies significantly among patients, averaging approximately 0.4 attacks per year; this rate reflects the large proportion of patients with relapsing/remitting disease. The deficits tend to become more progressive and debilitating over time. Environmental factors (e.g., stress, infection, increased body temperature) may provoke a relapse. Most relapses reproduce previously experienced neurologic deficits, which can manifest as pyramidal, cerebellar, or brainstem symptoms. It is estimated that about one-half of affected individuals with exacerbating remitting disease will eventually convert to chronic progressive.

The etiology remains unclear, although it is widely believed to be autoimmune in nature. There is a clinically significant heritable component, and alleles in the HLA locus have been identified as risk factors for multiple sclerosis. Pathologic findings include local inflammation, demyelination, gliotic scarring, and axonal loss; on magnetic resonance imaging (MRI), the formation of gray and white matter plaques is
seen. It is possible that the disease results from a yet undetermined combination of genetic predisposition and exposure to specific environmental factors. The more common symptoms include motor weakness, impaired vision, ataxia, bladder and bowel dysfunction, and emotional lability.

Although there is no cure, over the last two decades relapsing/remitting multiple sclerosis has become a treatable disease as a result of advancements in disease-modifying therapies. Immunosuppressive therapies may hasten recovery from a relapse, but no evidence suggests that these agents influence the progressive course of the disease. Administration of interferon-beta may significantly reduce the relapse rate and retard disability; however, an increased risk for fetal loss and low birth weight (LBW) has been observed with the use of this therapy during the first trimester of pregnancy. In contrast, administration of intravenous immunoglobulin or plasmapheresis for severe relapses has no known adverse effects on pregnancy outcome. Acute relapses during pregnancy are treated with short courses of high-dose corticosteroids, although longer-term use may be associated with maternal glucose intolerance, neonatal adrenal suppression, cleft palate if used in the first trimester, and an increased risk for premature rupture of membranes.

**Interaction with Pregnancy**

The effects of multiple sclerosis and long-term use of disease-modifying therapies on fertility are poorly studied. Findings from a prospective study in Finland suggest that multiple sclerosis is associated with increased requirement for assisted reproductive techniques. A large Danish national cohort study found that multiple sclerosis was associated with having no or fewer children; however, it is not known whether this finding is explained by the disease itself or if it is caused by altered reproductive behaviors among diseased individuals. In one study of women with multiple sclerosis undergoing assisted reproductive techniques, failed assisted reproductive attempts were associated with increased annual relapse rates. These findings may be explained by the stress of infertility, temporary interruption in disease-modifying therapy, and increases in inflammatory cytokines associated with hormonal therapies.

Pregnancy and obstetric outcomes in women with multiple sclerosis are likely no different from individuals without disease. One cohort study compared 198 affected women with 1584 healthy women; the number of maternal complications was not higher in women with multiple sclerosis. However, infants delivered of women with multiple sclerosis were at greater risk for meconium aspiration. This finding may reflect an intratranine environment in patients with multiple sclerosis that is more susceptible to acute hypoxic events. A subsequent cohort study of 649 pregnancies in women with multiple sclerosis concluded that infants of these women were more likely to be small for gestational age, attributed to a suboptimal intratranine environment. Moreover, this study found that mothers with multiple sclerosis were more likely to undergo induction of labor and operative delivery, possibly as a result of neuromuscular weakness and spasticity. These findings have not been reproduced in other studies. A 2017 United Kingdom case-controlled study of 181 pregnancies in 98 mothers with multiple sclerosis and 244,573 pregnancies in 124,830 mothers without multiple sclerosis did not find any associations with neonatal birth weight, gestational age at birth, mode of delivery, stillbirth, or neonatal death. A 2011 meta-analysis did not find significant associations between multiple sclerosis and adverse obstetric and neonatal outcomes. The relapse rate was lower during pregnancy than before or after pregnancy.

Data from prospective studies suggest that the rate of relapse increases during the first 3 months postpartum in comparison with the year before pregnancy. Relapses during this period were more likely in women who had higher relapse rates in the year before pregnancy or during pregnancy. Stress, exhaustion, infection, the loss of antenatal immunosuppression, and the postpartum decline in concentrations of reproductive hormones may account for the higher postpartum relapse rate. Treatment with immunologically active agents (e.g., interferon-beta) may result in a decreased postpartum relapse rate, but data are limited. Pregnancy does not negatively affect the long-term outcome of multiple sclerosis. Rather, at least one study has suggested that parturition may have a slightly favorable effect on long-term disease activity.

Data are conflicting as to whether exclusive breast-feeding is associated with a lower risk for relapse than partial or no breast-feeding. A 2015 prospective study in 201 German women found a modestly protective effect against relapses among women with multiple sclerosis who exclusively breast-fed for at least 2 months (first postpartum relapse adjusted hazard ratio, 1.70; 95% confidence interval [CI], 1.02 to 2.85; P = .04).

**Anesthetic Management**

The anesthesia provider should assess the patient’s level of compromise, document the pattern of deficits, and give special attention to respiratory involvement, in particular the ability to cough, clear secretions, and take vital capacity breaths. Historically, the optimal mode of anesthesia in patients with multiple sclerosis has been controversial. Most anesthesia providers have considered general anesthesia to be safe. Many anesthesia providers have been reluctant to administer neuraxial anesthesia because the effect of local anesthetic drugs on the course of the disease is unclear. Some anesthesia providers have expressed concern that neuraxial anesthesia may expose demyelinated areas of the spinal cord to potentially neurotoxic effects of local anesthetic agents. Several animal studies have investigated the histologic effects of local anesthetic agents on the normal spinal cord. In one study, subarachnoid injection of small doses of a local anesthetic agent produced no histologic changes in the spinal cord or meninges. Injection of very large doses caused reversible inflammatory and degenerative changes, but all changes resolved within 14 days of injection. Diagnostic lumbar puncture is not associated with a higher rate of relapse. Two small reports have implicated spinal anesthesia in the exacerbation of multiple sclerosis.
Bamford et al.\(^\text{19}\) described one case of relapse after the administration of spinal anesthesia in 9 patients, and Stenuit and Marchand\(^\text{20}\) identified two cases of relapse after the administration of spinal anesthesia in 19 patients. The relationship of these relapses to spinal anesthesia or other postoperative conditions (e.g., stress, infection, hyperpyrexia) known to exacerbate multiple sclerosis is unclear.

There are few published data on the use of epidural anesthesia in patients with multiple sclerosis. Warren et al.\(^\text{21}\) reported minor exacerbations after the administration of epidural anesthesia for two separate vaginal deliveries in one patient. Crawford et al.\(^\text{22}\) reported one postoperative relapse in 50 nonobstetric and 7 obstetric patients who received epidural analgesia. Confavreux et al.\(^\text{23}\) reported a study of 269 pregnancies in 254 women with multiple sclerosis, of whom 42 received epidural analgesia; epidural analgesia did not have an adverse effect on the rate of relapse or on the progression of disability in these patients. Bader et al.\(^\text{24}\) retrospectively evaluated 32 pregnancies in women with multiple sclerosis; they observed that women who received epidural anesthesia for vaginal delivery did not have a higher incidence of relapse than those who received only local infiltration anesthesia. The Pregnancy in Multiple Sclerosis (PRIMS) study followed 227 women who had multiple sclerosis for at least 1 year before conception, of whom 42 received epidural analgesia during labor; no adverse effect of epidural analgesia on the rate of postpartum relapse or the progression of disability was identified.\(^\text{13}\) Similarly, a 2012 prospective study followed 349 patients for 5 years postpartum and did not find an increased risk for relapse associated with labor epidural analgesia.\(^\text{25}\) A 2013 record linkage study comparing 431 deliveries in women with multiple sclerosis who received peripartum neuraxial analgesia or anesthesia to 2959 deliveries in women from the general population in British Columbia did not find an association between the use of neuraxial techniques and increased disability.\(^\text{26}\)

Bader et al.\(^\text{24}\) observed that all of the women who experienced a relapse after epidural anesthesia had received a concentration of bupivacaine greater than 0.25%. The concentration of local anesthetic in the CSF progressively increases during prolonged administration of epidural anesthesia, and the authors suggested that the higher concentration may overwhelm the protective effect of dilution within the CSF. An alternative explanation is that women who require a higher concentration of neuraxial local anesthetic may have more stressful labor. However, these observations suggest that anesthesia providers should use a dilute solution of local anesthetic for epidural analgesia during labor, when possible.

The administration of neuraxial anesthesia for cesarean delivery is considered safe. Because the operation is of limited duration, multiple doses of local anesthetic are typically not needed, so a progressive increase in CSF concentration of local anesthetic over time is less likely. The 2013 record linkage study from British Columbia compared spinal anesthesia use in cesarean deliveries in 128 women with multiple sclerosis and 846 women in the general population, and did not find a link between spinal anesthesia and increased disability.\(^\text{26}\)

Although there are limited data on spinal and general anesthesia for cesarean delivery in patients with multiple sclerosis, they are both considered safe, and prior concerns over these techniques are attributable to recall bias associated with postpartum relapses after regional anesthesia.\(^\text{3}\) No data suggest harmful effects of neuraxial opioids in women with multiple sclerosis. In light of the significant benefits of neuraxial techniques for intraoperative anesthesia and postoperative analgesia, either spinal or epidural anesthesia is the principal anesthetic technique used for cesarean delivery in patients with multiple sclerosis in many institutions, including our own.

In summary, published data do not contraindicate the use of neuraxial anesthetic techniques for labor analgesia or operative anesthesia. The patient should be aware that there is a higher incidence of relapse during the postpartum period, even without the use of neuraxial analgesia or anesthesia. In addition, when anesthetic techniques are used, the type of anesthesia selected does not appear to influence the relapse rate. Neither pregnancy nor anesthesia appear to have a negative influence on the long-term course of the disease. The willingness of anesthesia providers to use neuraxial techniques in pregnant patients with multiple sclerosis is reflected in a survey of obstetric anesthesia providers published in 2006.\(^\text{27}\) The majority (91%) of respondents had seen fewer than 10 cases of multiple sclerosis in the past 10 years; 79% and 98% of anesthesia providers indicated they would perform a neuraxial anesthetic technique for labor and elective cesarean delivery, respectively.

### HEADACHE DURING PREGNANCY

Headaches are among the most frequently observed neurologic symptoms during pregnancy (Table 48.1). Tension headaches, migraine headaches, and headaches associated with hypertensive disorders of pregnancy are commonly observed during pregnancy. De novo primary headaches (e.g., tension and migraine) are very common during pregnancy, particularly in the first few months of pregnancy; however, new headaches in the third trimester and puerperium should prompt closer evaluation for secondary causes.\(^\text{28}\) A pregnant patient with a history of chronic headaches who reports new or different symptoms should be closely evaluated to exclude serious causes such as preeclampsia, tumor, or intracranial vascular malformation. Symptoms of concern include sudden onset, intense severity, altered mental status, meningeal signs, fever, vomiting, changes in vision, pulsatile tinnitus, headache in a woman with prior malignancy or HIV infection, and any localizing or lateralizing abnormality. All imaging modalities may be used to assist in the diagnosis of secondary headaches in pregnancy, although measures should be taken to minimize maternal and fetal exposure to ionizing radiation.\(^\text{28}\)

#### Tension Headache

Tension or muscle contraction headaches are the most common type of headache observed during pregnancy. The
symptoms typically consist of dull, persistent pain that extends over the entire head. The onset is usually gradual, but the symptoms may persist for long periods. Although the etiology is unknown, this type of headache is believed to be associated with stress rather than hormonal changes. These headaches are more common in women, are frequently associated with anxiety, and may be a symptom of postpartum depression.29

Treatment
Acetaminophen should be used as a first-line analgesic in the pregnant patient. Caffeine and butalbital may be contained in combination analgesic products (e.g., Fioricet, Fiorinal). The American College of Obstetricians and Gynecologists (ACOG) has concluded that there is no clear evidence that caffeine exposure increases the risk for fetal growth restriction.30 Because a definitive conclusion regarding high caffeine intake and the risk for miscarriage cannot be made, the ACOG recommends caffeine be limited to moderate consumption (less than 200 mg/day) during pregnancy. Butalbital is sometimes prescribed for treatment of migraine and tension headaches, but its appropriateness has been questioned given increased risks for abuse, overdose headache, and withdrawal. Emerging data from the National Birth Defects Prevention Study, an ongoing case-control study, suggest that butalbital exposure in pregnancy is associated with an increased risk for congenital heart abnormalities, including tetralogy of Fallot, pulmonic stenosis, and atrial septal defect.31 Butalbital use, however, was rare; only 73 case mothers and 15 control mothers reported periconceptional use.32

Ergot alkaloids (e.g., ergotamine) are contraindicated during pregnancy; these agents may cause marked increases in uterine tone, which may compromise placental perfusion and fetal oxygenation.32 Use of nonsteroidal antiinflammatory drugs (NSAIDs) should be limited during the third trimester because of risk for premature closure of the fetal ductus arteriosus, oligohydramnios, and prolongation of pregnancy. Although a 2013 review did not find evidence that first-trimester exposure to benzodiazepines is associated with an increased risk for congenital malformations,33 these drugs are not usually used to treat headache during pregnancy. Opioids have a long record of safe use during pregnancy, but because of escalated use and abuse, and their association with neonatal opioid withdrawal syndrome with long-term maternal exposure, their prescription during pregnancy and the puerperium is undergoing increased scrutiny.34 Tricyclic antidepressants similarly have a record of safe use during pregnancy. Although earlier studies reported links between tricyclic antidepressant use during pregnancy and congenital malformations, most subsequent larger studies have been negative.35 Findings from one study suggest that tricyclic antidepressants do not have detrimental effects on the neurodevelopment of children exposed in utero.36

Obstetric and Anesthetic Management
Pregnancy is not likely to reduce the frequency or severity of tension headaches because they are not hormonally mediated. Obstetric and anesthetic management are rarely affected by the presence of tension headaches, although a history of chronic tension headaches has been associated with an increased risk for placental abruption (adjusted odds ratio [OR], 1.60).37 The frequency and severity of tension headaches should be assessed and documented in the preanesthetic assessment to better differentiate preexisting symptoms from new or changing symptoms in the postpartum period.
**Migraine Headache**

Migraine headaches are classically described as unilateral, throbbing headaches sometimes accompanied by nausea and vomiting. The duration varies from hours to days. Visual disturbances (e.g., scotomata) typically precede the onset of these headaches, and focal neurologic symptoms (e.g., aphasia, hemiplegia) may also occur. Most investigators favor neurovascular vasospasm, followed by cerebral vasodilation, as a cause of these headaches; a primary vascular disorder or a disturbance in the noradrenergic nervous system also may be involved. Patients appear to be more susceptible to symptoms when serotonin levels are low.

The 1-year period prevalence of migraine headache in the United States is 3.9% for men and 5.1% for women. Prevalence is higher in middle life, between 30 and 59 years of age. Hormonal influences have a strong association with these headaches; estrogen withdrawal is associated with an exacerbation of symptoms. After delivery, the reduction in hormonal concentrations coincides with an increase in migraine symptoms.

**Treatment**

In nonpregnant patients, therapy centers around prevention, abortive treatments, and rescue treatments. Preventive medications are typically avoided during pregnancy; beta-adrenergic receptor antagonists (e.g., propranolol) may be used for prophylaxis, however, owing to their ability to cross the placenta, these agents should be used only when a patient’s symptoms are severe. Antidepressants such as selective serotonin reuptake inhibitors can be used off-label for migraine prevention, although fetal exposure to some antidepressants has been controversially linked to congenital anomalies and adverse neonatal outcomes (see Chapter 50). Abortive treatments often involve triptans or ergotamine tartrate, typically in combination with caffeine (e.g., Cafergot, Migergot). However, ergot alkaloids are contraindicated during pregnancy because of associated uterotonic effects and possible (but unproven) teratogenic effects. The use of sumatriptan or other selective serotonin receptor agonists is controversial. A higher incidence of congenital anomalies was observed after administration of high doses of sumatriptan in animals; however, in a review of human studies, no evidence of any specific adverse effect of sumatriptan on pregnancy outcome was found. A prospective study also showed no relationship between triptan use for migraine and teratogenicity.

Rescue treatments are given when abortive therapies fail and include acetaminophen, antiemetics, and NSAIDs. In general, acetaminophen is considered the first-line treatment during pregnancy. Combination therapy with agents containing caffeine and/or butalbital should be used with caution, as should therapy with NSAIDs (see earlier discussion). Occasionally, calcium entry–blocking agents are used.

**Obstetric and Anesthetic Management**

Women with a lifetime history of migraine have been reported to have a twofold higher risk for placental abruption. Pregnant women with migraines are at four times higher risk for developing preeclampsia, as well as at higher risk for stroke during pregnancy and the puerperium.

Cerebral ischemia has been reported after the administration of terbutaline in pregnant patients with migraine. Rosene et al. recommended that physicians avoid the administration of terbutaline in pregnant women with a history of vascular headache.

Although there are no published data on the relationship between intrapartum anesthesia and postpartum migraine headaches, one cohort study suggested that patients with a prior history of migraine may be more likely to present with atypical symptoms of post–dural-puncture headache, including nonpostural headache; cervical, thoracic, or lumbar vertebral stiffness and pain; and vertigo.

**SPINAL CORD INJURY**

Worldwide, there are large geographic differences in the incidence, prevalence, and lethality of spinal cord injuries. In the United States, traumatic spinal cord injuries occur with an incidence of 23.7 to 77.0 per million population per year; the prevalence per million inhabitants is 473 to 1800. Improved handling and stabilization of victims at the site of an accident and the availability of extensive rehabilitation services have resulted in more women who present for obstetric care after spinal cord injury than in the past.

Patient disability and residual function depend on the anatomic location of the injury. Cord injuries below S2 involve mainly bladder, bowel, and sexual functions. Affected patients have relaxed perineal muscles, and women with such injuries experience labor pain. Women with a lesion above T10 do not experience labor pain. Patients with a lesion above T6 have varying levels of respiratory compromise and are at risk for autonomic hyperreflexia (see later discussion).

**Spinal shock,** defined as immediate and temporary areflexia/hyporeflexia and transient sensorimotor dysfunction resolving within 24 to 48 hours after injury, may develop in about one-half of spinal cord–injured patients. Patients with injuries at or above the T6 level are at risk for neurogenic shock caused by loss of signals from the sympathetic nervous system. It is characterized by hemodynamic and sensorimotor abnormalities, and flaccid paralysis with loss of tendon and autonomic reflexes. Patients experience loss of vasomotor tone, temperature regulation, sweating, and piloerection in the parts of the body below the lesion. Pulmonary edema, hemodynamic instability, and circulatory collapse can develop in the absence of brainstem regulation of vasomotor tone. Patients are at risk for aspiration, infection, and other pulmonary complications. Paraplegic patients may have a compensatory tachycardia, whereas quadriplegic patients may have bradycardia caused by unopposed vagal tone.

After a variable period, the spinal cord-injured patient progresses to a chronic stage in which reflex activity is regained. In most cases, this return of reflex activity occurs within 1 to 6 weeks after the injury; rarely, return of reflex activity may take several months. This stage is characterized...
The mass reflex is a phenomenon in which a stimulus that normally would cause the contraction of a few muscle units leads to the widespread spasm of entire muscle groups. It results from the absence of central inhibitory mechanisms. The mass reflex can occur with any level of spinal cord injury. It may occur with autonomic hyperreflexia in a patient with a lesion above T6.

Approximately 85% of patients with chronic spinal cord injuries at or above T6 experience the syndrome of autonomic hyperreflexia. This is a life-threatening complication that results from the absence of central inhibition on the sympathetic neurons in the cord below the injury. Noxious stimuli, including bladder or bowel distention and ureteric contractions, result in afferent transmission by means of the dorsal spinal root (Fig. 48.1). These afferent neurons synapse with sympathetic neurons, and the impulse is propagated both cephalad and caudad in the sympathetic chain, without central inhibition. The propagation results in extreme sympathetic hyperactivity and severe systemic hypertension secondary to vasoconstriction below the level of the lesion. In response, the reflex arcs involving the baroreceptors of the aortic and carotid bodies lead to bradycardia and vasodilatation above the level of the lesion. In patients with lesions at T6 and above, these compensatory mechanisms are insufficient to compensate for the severe hypertension. Intracranial hemorrhage, arrhythmias, and myocardial infarction occur in some cases. A variety of agents have been used for control of the hypertension of autonomic hyperreflexia (Fig. 48.2).

**Obstetric Management**

Approximately 2000 women in the United States with spinal cord injury become pregnant each year. Pregnancy may aggravate many of the medical complications of spinal cord injury (Box 48.1). The loss of both functional residual capacity and expiratory reserve volume during pregnancy may increase the likelihood of respiratory compromise associated with spinal cord injury, with worsening of respiratory function occurring as early as 20 weeks’ gestational age. Patients may require tracheal intubation and mechanical ventilatory support, and cesarean delivery may be indicated to avert the fetal risks associated with maternal hypercapnia and to improve maternal respiratory mechanics.

Pregnancy increases the risks for thromboembolic phenomena and urinary tract infection. Loss of sympathetic tone below the level of the lesion renders pregnant patients with spinal cord injury particularly prone to orthostatic hypotension, which may result in reduced uteroplacental perfusion. In pregnant women, autonomic hyperreflexia occurs most commonly during labor; uterine contractions, vaginal and cervical examinations, speculum insertion, and urethral catheterization may trigger autonomic hyperreflexia. Autonomic hyperreflexia may affect uteroplacental blood flow, necessitating careful monitoring of the fetal heart rate (FHR).
Symptoms of autonomic hyperreflexia are also common in the immediate postpartum period, possibly triggered by postpartum pain, urethral catheterization, and uterine contractions. Women with a lesion above T11 may be at higher risk for preterm labor. Because these women do not experience labor pain, obstetric management includes weekly cervical examinations during the third trimester, and patients are instructed on uterine palpation techniques to detect contractions at home. Although vaginal delivery is preferred, the development of autonomic hyperreflexia in the second stage of labor may necessitate expedited instrumental delivery. Assisted vaginal delivery may also be necessary because of the inability of the mothers to push during the second stage. In a study of 52 pregnancies in spinal cord–injured women, 9 of 12 patients with lesions above T5 had symptoms of autonomic hyperreflexia. The cesarean delivery rate was 47% for women with lesions above T5 and 26% for women with lesions at T5 or below. Preterm delivery occurred in 19% of patients.

**Anesthetic Management**

The ACOG recommends continuous hemodynamic monitoring during labor for all patients at risk for autonomic hyperreflexia. This syndrome can be distinguished from other causes of intrapartum hypertension by the occurrence of...
of cyclic hypertension (i.e., blood pressure increases during contractions and decreases between contractions).

Early neuraxial anesthesia is preferred for the prevention or treatment of autonomic hyperreflexia during labor and delivery. Although neuraxial labor analgesia may attenuate the risk and symptoms of autonomic hyperreflexia, it may not ablate the phenomenon entirely, particularly when low doses of local anesthetics are used. Spinal anesthesia has effectively controlled blood pressure in paraplegic patients undergoing general surgical procedures. Although some anesthesia providers contend that distortion of the vertebral column in paraplegic patients makes it more difficult to predict and control the level of spinal anesthesia, published data do not lend support to this assumption. If spinal anesthesia is chosen, insertion of an intrathecal catheter and use of a continuous technique may be appropriate; this approach may allow careful titration of the resulting neuroblockade. Assessment of level of blockade in an insensate patient may be accomplished by assessing for loss of lower extremity deep tendon reflexes and meticulous monitoring for acute hypertension and bradycardia.

Most obstetric anesthesia providers prefer the use of epidural analgesia for the prevention or treatment of autonomic hyperreflexia during labor and vaginal delivery. Consideration also should be given to providing epidural analgesia after vaginal delivery to minimize the possibility of autonomic hyperreflexia, which has been reported to occur in response to pain as late as 5 days after delivery.

Case reports have described the successful epidural administration of 0.25% or 0.5% bupivacaine, or the administration of combined spinal-epidural (CSE) anesthesia for the mitigation of autonomic hyperreflexia. Baraka reported the successful use of epidural meperidine, an opioid with local anesthetic qualities, in avoiding the signs of autonomic hyperreflexia. Abouleish et al. observed that epidural fentanyl alone did not effectively treat the hypertension of autonomic hyperreflexia, but the addition of 0.25% bupivacaine led to a decrease in blood pressure to baseline levels. Maehama et al. described the successful use of magnesium sulfate for management of autonomic hyperreflexia during labor.

Patients with spinal cord injury often have a low baseline blood pressure and some hemodynamic instability. Placement of an intra-arterial catheter before induction of anesthesia allows the continuous assessment of blood pressure. In patients with a history of autonomic hyperreflexia, continuous hemodynamic monitoring with an intra-arterial catheter will permit early detection and treatment of symptoms. Pulse oximetry is particularly useful in patients with respiratory compromise, and the anesthesia provider should always be available to provide ventilatory assistance if necessary.

Positioning for neuraxial block may be difficult; the anesthesia provider should consider performing the block with the patient in a lateral position because the sitting position may cause hypotension from venous pooling in the lower body. Therapeutic doses of a local anesthetic agent should be administered cautiously with the understanding that the cephalad level of the sensory block can be fully assessed only if it is higher than the level of the spinal cord lesion. As a result, the typical epidural test dose may not identify unintentional subarachnoid injection in a patient with spinal cord injury. Neuraxial blockade can be partially assessed by evaluating segmental reflexes below the level of the lesion. For example, the anesthesia provider can lightly stroke each side of the abdomen above and below the umbilicus, looking for contraction of the abdominal muscles and deviation of the umbilicus toward the stimulus. Reflexes are absent below the level of the block. In some patients with spastic paresis at baseline, the level of anesthesia may be confirmed by the conversion of spastic paresis to flaccid paresis. A decline in blood pressure may also herald the onset of neuraxial blockade.

Alternative means of treating autonomic hyperreflexia should be available at the bedside if neuraxial analgesia or anesthesia is inadequate or not successful. Antihypertensive medications such as magnesium sulfate or arteriolar vasodilators may be effective, recognizing that hypotension can result in decreased uterine blood flow. Careful titration of sodium nitroprusside, noting the potential for fetal/neonatal cyanide intoxication, or beta-adrenergic receptor blockade, may also be useful. The anesthesia provider should recognize that increased vagal activity during autonomic hyperreflexia can result in electrocardiographic changes including first- and second-degree atrioventricular block and sinus arrest.

If cesarean delivery is necessary, epidural or spinal anesthesia can be administered. Spinal anesthesia is generally associated with more rapid onset and greater need to treat hypotension. The effect of neuraxial blockade on respiratory function may be less severe with epidural anesthesia than with spinal anesthesia.

Severe respiratory insufficiency or technical difficulties with neuraxial anesthesia may necessitate the use of general anesthesia. If general anesthesia is required, a depolarizing muscle relaxant such as succinylcholine should not be given during the period of denervation injury. By a conservative definition, this period begins 24 hours after the injury and lasts for 1 year. The use of succinylcholine during this period of denervation injury may cause severe hyperkalemia; therefore, a nondepolarizing muscle relaxant should be used to facilitate laryngoscopy and tracheal intubation.

### MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder characterized by episodes of skeletal muscle weakness that are made worse by activity. Its prevalence is 150 to 250 per million. Women are twice as likely to have the disease as men, and the onset is earlier. Subgroups are defined based on autoimmune and antibody disease mechanisms, skeletal muscle target molecules, thymic status, genetic characteristics, response to therapy, and disease phenotype.

Myasthenia gravis results from an abnormality in autoimmune regulation, which leads to the production of antibodies against the nicotinic acetylcholine receptor or to
functionally related molecules on the neuromuscular end plate of skeletal muscle. The result is receptor destruction as well as antibody-induced blockade of the remaining acetylcholine receptors.\textsuperscript{68} Smooth muscle and cardiac muscle are not affected. The diagnosis is based on characteristic symptoms and positive antibody tests, and in the absence of antibodies, on neurophysiologic tests or response to therapy. Thymic hyperplasia is common, and thymic tumors occur in approximately 10\% of patients. Weakness is confined to the ocular muscles in 15\% of patients. There is an association between myasthenia gravis and other autoimmune disorders, such as rheumatoid arthritis and polymyositis. In general, an early age at onset and an extended duration of purely ocular myasthenia are good prognostic signs.

### Medical Management

Anticholinesterase drugs, which inhibit the breakdown of acetylcholine, are the mainstay of therapy for all subtypes of the disease. Pyridostigmine, a quaternary ammonium compound that does not cross the blood-brain barrier, is the preferred maintenance drug because it has less severe muscarinic side effects than other anticholinesterase drugs.\textsuperscript{68} The treatment goal is full or nearly full remission; most patients will also require immunosuppressive therapy to meet this goal. Prednisone or prednisolone combined with azathioprine are the usual first-line immunosuppressants. Mycophenolate mofetil may also be added; other drugs include rituximab, methotrexate, cyclosporine, tacrolimus, and cyclophosphamide. Monotherapy with glucocorticoids may prevent progression of ocular myasthenia gravis to generalized disease. Thymectomy is performed in all patients with thymomas; however, there is also a benefit of total thymectomy for patients with early-onset symptoms without thymoma.\textsuperscript{68}

Myasthenia gravis can manifest in two types of crises. A cholinergic crisis is rare, especially if the daily dose of pyridostigmine is less than 960 mg.\textsuperscript{69} It results from an excess of the muscarinic effects of anticholinesterase medications combined with a poor response to anticholinesterase therapy. In contrast, a myasthenic crisis results from a worsening of the disease; its symptoms include worsening muscle weakness, especially muscles of respiration. Admission to an intensive care unit, ventilatory support, and rapid therapies such as plasma exchange and intravenous immune globulin are indicated.\textsuperscript{68,69}

Many drugs can cause a worsening of myasthenic symptoms. These patients are extremely sensitive to drugs that potentiate muscle weakness. These agents include neuromuscular blocking agents, quinidine, propranolol, aminoglycoside antibiotics, and tocolytic agents such as magnesium sulfate\textsuperscript{70} and terbutaline. One case report noted worsened symptoms after the maternal administration of betamethasone.\textsuperscript{71}

### Obstetric Management

The course of myasthenia gravis during pregnancy varies. In general, approximately 30\% of cases improve, 30\% worsen, and 30\% show no change.\textsuperscript{72} Retrospective data are inconsistent, suggesting that the course of the disease during pregnancy is highly variable. The baseline clinical state does not predict the course of the disease during pregnancy, and the course during one pregnancy does not predict the course in a subsequent pregnancy. Because disease exacerbations occur more frequently in the first year after diagnosis of myasthenia gravis, women should be counseled to delay pregnancy for 1 to 2 years after the initial disease diagnosis.\textsuperscript{73} The is no consistent evidence that myasthenia gravis has adverse effects on pregnancy, although complications of pregnancy and their treatment (e.g., preeclampsia) may contribute to worsening myasthenia gravis symptoms.\textsuperscript{72} For example, magnesium therapy has been reported to precipitate a myasthenic crisis.\textsuperscript{70,72}

The maternal physiologic changes of pregnancy, including alterations in drug absorption, increases in blood volume, and changes in renal clearance, may require adjustments in the doses of anticholinesterase drugs. Each patient should be monitored carefully for progressive respiratory compromise secondary to diaphragmatic elevation during pregnancy. Vital capacity can be measured to monitor fatigue during labor. The treatment of the myasthenic patient with preeclampsia or preterm labor is problematic because the use of magnesium sulfate for maternal seizure prophylaxis or fetal neuroprotection reduces acetylcholine release and may be associated with a significant increase in maternal and fetal muscle weakness, and even maternal death.\textsuperscript{74} In those cases, seizure prophylaxis with anticonvulsants has been described.\textsuperscript{75}

The uterus consists of smooth muscle; therefore, myasthenia gravis should not affect the first stage of labor. However, the second stage of labor often requires the use of striated muscle, and consequently an assisted (e.g., vacuum or forceps) vaginal delivery may be required.

Maternal IgG antibodies to the acetylcholine receptor are transferred across the placenta. Transient neonatal myasthenia gravis occurs in approximately 10\% to 20\% of infants of mothers with myasthenia gravis.\textsuperscript{72} Notably, the risk and severity of neonatal myasthenia is not related to the severity of maternal disease; therefore, all neonates of mothers with myasthenia gravis must be closely monitored. The symptoms, including poor sucking, generalized hypotonia, difficulty feeding, feeble cry, ptosis, and respiratory distress, usually develop within the first 12 to 48 hours after birth and abate as the antibodies are metabolized, with resolution typically occurring within 2 to 4 weeks. Arthrogryposis multiplex congenita is a rare and severe disease, occurring in about 6.2 per 100,000 live births. In this condition, infants have multiple joint contractures from reduced movement in utero; the condition is associated with stillbirth, spontaneous abortion, and neonatal death.

### Anesthetic Management

Myasthenia gravis patients should undergo early antepartum consultation with an anesthesia provider. This evaluation should assess the extent of bulbar and respiratory involvement and overall baseline muscle strength. Pulmonary function testing should be performed in patients with evidence of respiratory compromise. In a study of surgical patients, the...
presence of bulbar symptoms, a preoperative serum level of anticholinesterase receptor antibody greater than 100 nmol/L, and intraoperative blood loss greater than 1000 mL were risk factors for having a postoperative myasthenic crisis.76

Patients with respiratory compromise may be more susceptible to opioid-induced respiratory depression, and consideration should be given to minimizing or avoiding opioids when possible. Neuraxial techniques are the preferred method for labor analgesia in patients with myasthenia gravis, and early labor neuraxial analgesia is recommended to attenuate stress and preserve maternal strength and reserve for the second stage of labor.1 The use of anticholinesterase drugs may prolong the half-life of ester local anesthetic agents.

Neuraxial anesthetic techniques are preferred for cesarean delivery unless the patient has significant bulbar involvement or respiratory compromise. The use of bilevel positive airway pressure for ventilatory support in patients with moderate respiratory compromise may improve the safety of neuraxial anesthesia.27

In the patient with severe bulbar involvement or respiratory compromise, it may be prudent to secure the airway before surgery. Depolarizing muscle relaxants (e.g., succinylcholine) have an unpredictable effect in these patients, with affected and unaffected muscles being more sensitive and resistant to these agents, respectively.27 However, the commonly administered dose of succinylcholine (1 to 1.5 mg/kg), which is three to five times the dose required to depress neuromuscular function by 95%, will most likely provide adequate relaxation even for resistant muscles. Anticholinesterase agents and plasmapheresis cause decreases in the activity of plasma cholinesterase and may cause delays in succinylcholine hydrolysis.

Myasthenic patients are extremely sensitive to nondepolarizing muscle relaxants. If a nondepolarizing muscle relaxant must be given, the anesthesia provider should administer a small amount of an agent with a short half-life (e.g., rocuronium, atracurium, vecuronium).78 Mivacurium is metabolized via plasma pseudocholinesterase, which may be inhibited by pyridostigmine. In general, greater disease severity corresponds with enhanced sensitivity to nondepolarizing muscle relaxants, necessitating the use of clinical judgment and neuromuscular monitoring to determine the amount and timing of drug doses. Myasthenia may prevent a full-strength contraction with nerve stimulation; therefore, a control train-of-four stimulus test should be performed before paralysis for later comparison. For nondepolarizing agents, approximately 50% of the standard dose may be adequate, and a prolonged recovery should be anticipated. Sugammadex, a cycloextrin that works by encapsulating nondepolarizing neuromuscular blocking agents, may be preferred for neuromuscular blockade reversal in patients with myasthenia gravis. The limited available data on its use in pregnancy suggest that it is safe.29,30

After delivery, fluid shifts and decreased maternal alphafetoprotein concentrations may necessitate an adjustment of anticholinesterase drug doses. Some patients who receive general anesthesia require postoperative ventilation. The following factors are predictive of an increased risk for postoperative ventilation: (1) female gender; (2) FEF25%–75% (forced expiratory flow during the middle half of the forced vital capacity) less than 3.3 L/sec and less than 85% of that predicted; (3) FVC (forced vital capacity) less than 2.6 L/sec and less than 78% of that predicted; and (4) MEF50% (maximal expiratory flow at 50% of expired vital capacity) less than 3.9 L/sec and less than 80% of that predicted.31

EPILEPSY

Epilepsy is a condition characterized by recurrent seizure activity in the absence of metabolic disorders or acute brain disease. The classification scheme for epilepsy52 and seizure types83 was updated in 2017 by the International League Against Epilepsy. The first level of classification is one of three seizure types: focal onset, generalized onset, and unknown onset.53 The second level of classification is epilepsy type; these are generalized, focal, combined generalized-focal, and unknown.54 In focal seizures, the excess neuronal discharge is limited to one hemisphere of the brain; in generalized seizures, the discharge occurs bilaterally and involves the entire cortex.

Medical Management

A variety of antiepileptic agents are used for seizure therapy, depending on the type of seizure and clinical response (Table 48.2).84–86 A variety of adverse effects have been reported with these agents, including early-onset events (e.g., somnolence, dizziness, hypersensitivity, rash, gastrointestinal symptoms) and late-onset events (e.g., depression, leukopenia, aplastic anemia, thrombocytopenia, megaloblastic anemia, hyponatremia).55

Prognosis for medical control of seizures is good for patients with generalized seizure disorders; as many as 20% to 40% of newly diagnosed epilepsy patients become seizure-free without or with minimal antiepileptic drug therapy.87 Two in three newly treated epilepsy patients will eventually enter long-term remission (5 years or more without a seizure).87 However, about one-third of patients will have an intermittent pattern (early remission with late recurrence or late remission). Finally, the standard mortality ratio for patients with epilepsy (observed number of deaths in the study compared with the general population) is consistently increased in the first several years after the diagnosis of epilepsy.

Interaction with Pregnancy

Epilepsy is common in pregnancy, affecting about 1 in 200 parturients.88 Maternal mortality is greater in women with epilepsy.89 Pregnancy may increase the frequency of seizures in 1 in 3 epileptics; this may be secondary to increases in plasma volume and higher drug clearance, which reduces serum levels of antiepileptic drugs.90 Women who are free of seizures for at least 9 months to 1 year before pregnancy have a probability of 84% to 92% of remaining seizure-free during pregnancy.91
Increased stress and anxiety also have been suggested as mechanisms. In addition, anticonvulsant drug levels can decrease during pregnancy, often despite the administration of a larger dose; this may be partially explained by the decreased plasma protein binding and greater drug clearance observed during pregnancy. The American Academy of Neurology and American Epilepsy Society concluded that monitoring of lamotrigine, carbamazepine, and phenytoin levels should be considered during pregnancy. Monitoring of levetiracetam and oxcarbazepine (and its active metabolite, monohydroxy derivative) may be considered, and monitoring of other antiepileptic agents should not be discouraged despite limited data regarding their pharmacokinetic behavior during pregnancy.

Maternal seizures can have devastating consequences. Hypoxia and acidosis that occur during a generalized seizure can result in fetal compromise or intrauterine fetal death. Placental abruption may occur during a seizure. During the past three decades, the overall risk for obstetric complications in epileptic women has declined. Although some studies have suggested an increased risk for hypertension in pregnancy (including preeclampsia), bleeding, and preterm birth, a systematic review concluded that evidence is inconclusive.

A variety of causes have been proposed for the increase in seizure frequency observed in some pregnant women (Table 48.3). Higher estrogen concentrations in pregnancy lower the seizure threshold. Greater sodium and water retention, alkalosis secondary to hyperventilation, sleep deprivation, and increased stress and anxiety also have been suggested as mechanisms. In addition, anticonvulsant drug levels can decrease during pregnancy, often despite the administration of a larger dose; this may be partially explained by the decreased plasma protein binding and greater drug clearance observed during pregnancy. The American Academy of Neurology and American Epilepsy Society concluded that monitoring of lamotrigine, carbamazepine, and phenytoin levels should be considered during pregnancy. Monitoring of levetiracetam and oxcarbazepine (and its active metabolite, monohydroxy derivative) may be considered, and monitoring of other antiepileptic agents should not be discouraged despite limited data regarding their pharmacokinetic behavior during pregnancy.

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However, women with epilepsy may have a moderately increased risk for cesarean delivery.

Fetuses and neonates of women with epilepsy are approximately twice as likely to have adverse pregnancy outcomes, including intrauterine fetal death, cesarean delivery, 1-minute

### Table 48.2 Epilepsy Drugs

<table>
<thead>
<tr>
<th>Antiepilepsy Drug</th>
<th>Enzyme Inducer</th>
<th>Enzyme Inhibitor</th>
<th>Target Dose (mg/day)</th>
<th>Target Plasma Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>No</td>
<td>600–1200 bid or tid</td>
<td>3–12</td>
</tr>
<tr>
<td>Clobazam</td>
<td>No</td>
<td>No</td>
<td>10–20 bid</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Yes</td>
<td>No</td>
<td>500 qd</td>
<td>40–100</td>
</tr>
<tr>
<td>Felbamate</td>
<td>No</td>
<td>No</td>
<td>2400–3600 bid or tid</td>
<td>20–45</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No</td>
<td>No</td>
<td>900–2400 bid or tid</td>
<td>2–20</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>Yes</td>
<td>100–400 qd or bid</td>
<td>2–15</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No</td>
<td>No</td>
<td>1000–3000 bid</td>
<td>12–46</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>No</td>
<td>800–1800 bid or tid</td>
<td>7.5–20 (MHD)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Yes</td>
<td>No</td>
<td>50–200 qd or bid</td>
<td>10–40</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>No</td>
<td>200–300 bid or tid</td>
<td>5–25</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>No</td>
<td>No</td>
<td>150–600 bid or tid</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Yes</td>
<td>No</td>
<td>500–750 tid</td>
<td>10–40 (PHB)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>No</td>
<td>No</td>
<td>36–60 tid</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>No</td>
<td>100–400 bid</td>
<td>5–20</td>
</tr>
<tr>
<td>Valproate</td>
<td>No</td>
<td>Yes</td>
<td>600–1500 bid (slow release) or tid</td>
<td>40–120</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>No</td>
<td>No</td>
<td>500–3000 bid</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>No</td>
<td>No</td>
<td>300</td>
<td>10–40</td>
</tr>
</tbody>
</table>

*bid*, twice daily; *MHD*, monohydroxy derivative; *PHB*, phenobarbital; *qd*, daily; *tid*, three times daily.

*Enzyme inducer of the CYP cytochrome P450 system.

*Enzyme inhibitor of the CYP cytochrome P450 and uridine diphosphate glucuronyl transferase systems.

*Dash (−) indicates not relevant.

*Dose should be reduced in patients with renal dysfunction.

*For doses > 200 mg/day.


### Table 48.3 Possible Causes of Increased Seizure Frequency during Pregnancy

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td>Changes in levels of estrogen (proconvulsant) and progesterone (anticonvulsant)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Increased water and sodium retention</td>
</tr>
<tr>
<td>Psychologic</td>
<td>Stress, sleep deprivation</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Increase in liver metabolism, renal clearance, or volume of distribution</td>
</tr>
<tr>
<td>Physiologic</td>
<td>Decreased gastrointestinal absorption</td>
</tr>
</tbody>
</table>

**Optimizing antiepileptic therapy before and during pregnancy is critical to maintain prepregnancy serum antiepileptic drug levels. Because of the teratogenic aspects of many antiepileptic agents, some physicians consider withdrawal of these drugs after 2 years without seizures and recommend waiting at least 6 additional months after withdrawal before attempting to conceive. Substituting new antiepileptic agents after conception is not recommended because of increased risk for teratogenicity associated with polytherapy.**

**A variety of causes have been proposed for the increase in seizure frequency observed in some pregnant women (Table 48.3). Higher estrogen concentrations in pregnancy lower the seizure threshold. Greater sodium and water retention, alkalosis secondary to hyperventilation, sleep deprivation, and increased stress and anxiety also have been suggested as mechanisms.** In addition, anticonvulsant drug levels can decrease during pregnancy, often despite the administration of a larger dose; this may be partially explained by the decreased plasma protein binding and greater drug clearance observed during pregnancy. The American Academy of Neurology and American Epilepsy Society concluded that monitoring of lamotrigine, carbamazepine, and phenytoin levels should be considered during pregnancy. Monitoring of levetiracetam and oxcarbazepine (and its active metabolite, monohydroxy derivative) may be considered, and monitoring of other antiepileptic agents should not be discouraged despite limited data regarding their pharmacokinetic behavior during pregnancy.

**Maternal seizures can have devastating consequences. Hypoxia and acidosis that occur during a generalized seizure can result in fetal compromise or intrauterine fetal death. Placental abruption may occur during a seizure. During the past three decades, the overall risk for obstetric complications in epileptic women has declined. Although some studies have suggested an increased risk for hypertension in pregnancy (including preeclampsia), bleeding, and preterm birth, a systematic review concluded that evidence is inconclusive.** However, women with epilepsy may have a moderately increased risk for cesarean delivery.

**Fetuses and neonates of women with epilepsy are approximately twice as likely to have adverse pregnancy outcomes, including intrauterine fetal death, cesarean delivery, 1-minute**
Apgar score less than 7, neonatal and perinatal death, LBW, and abnormal development. Antiepilepsy drugs taken in the first trimester of pregnancy are associated with an increased risk for major congenital malformations. Data are insufficient to judge whether intrauterine exposure to antiepileptic agents in general increases the risk for cognitive impairment in the offspring of women with epilepsy, although there is some evidence that the risk may be increased for specific drugs. Specifically, intrauterine exposure to valproate has been associated with maladaptive childhood behavior and autism.

The risk for congenital malformations in women with epilepsy receiving antiepileptic drug monotherapy is 4% to 6%. Malformations have been associated with all currently used therapeutic modalities; those most often observed are cleft lip and palate, and cardiac, neural tube, and urogenital defects (hypospadias).

Certain drugs have been associated with a higher relative risk for congenital defects than others. Data from prospective studies indicate that valproate in particular is associated with significantly higher rates of major malformations. Newer agents (e.g., lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, pregabalin) have fewer teratogenic effects. A systematic review and meta-analysis of 31 studies on antiepileptic drug therapies in pregnant women concluded that lamotrigine and levetiracetam carried the lowest overall risk for malformation, although data on specific malformations were insufficient. Several studies suggest that maternal folate acid supplementation before conception may decrease the risk for major congenital abnormalities in the offspring of women with epilepsy who are receiving antiepileptic therapy.

Tomson and Battino reviewed data from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and made the following suggestions: (1) before conception select the most appropriate agent for the woman’s type of epilepsy; (2) select the drug with the lowest teratogenic potential; (3) aim for monotherapy with the lowest effective dose; (4) whenever possible, avoid valproate; and (5) if possible, avoid valproate at doses of 700 mg/day and higher.

Neonates of mothers undergoing long-term antiepileptic therapy may be at risk for deficiencies in vitamin K–dependent clotting factors or other coagulation defects, despite the absence of clinically evident maternal coagulation abnormalities. Enzyme-inducing antiepileptic agents (e.g., phenytoin, phenobarbital, carbamazepine) can cross the placenta and may increase the rate of oxidative degradation of vitamin K in the fetus. Affected infants are at risk for neonatal hemorrhage and respond to typical vitamin K doses (1 mg) given intramuscularly at birth. The administration of prenatal vitamin K to epileptic women with long-term exposure to these antiepileptic agents has not been conclusively shown to reduce the risk for neonatal hemorrhage.

Anesthetic Management
There are significant interactions between antiepileptic drugs and anesthetic agents. Carbamazepine, phenytoin, phenobarbital, and primidone are potent inducers of the cytochrome P450 enzymes in hepatic metabolism (see Table 48.2), which may result in decreased plasma concentrations of many medications, including neuromuscular blockers, beta-adrenergic receptor antagonists, and calcium entry–blocking agents.

Serum levels of antiepileptic drugs should be checked if therapeutic levels are known (see Table 48.2). Drug doses should not be missed during the peripartum period. If the patient experiences a seizure during labor, airway protection and support of ventilation are essential. Small doses of a benzodiazepine or propofol arrest most seizures. Fetal bradycardia may necessitate immediate delivery.

Oral antiepileptic therapies should be continued whenever possible throughout the peripartum period. Unfortunately, many of the agents are not available in parenteral forms. If oral agents cannot be taken, conversion to a parenteral agent such as phenytoin may be required. In general, antiepileptic agents have sedating properties.

The presence of epilepsy is not a contraindication to the administration of neuraxial analgesia or anesthesia. Although antiepileptic drugs have been associated with adverse effects on the coagulation system, Manohar et al. observed no abnormal clotting parameters or platelet counts preoperatively in a series of patients with epilepsy undergoing surgery.

If general anesthesia is necessary, it seems prudent to avoid opioids, particularly meperidine, as these drugs have been associated with seizures, even after low to moderate doses. Sevoflurane has stronger epileptogenic properties than isoflurane, but limiting the concentration to less than 1.5 minimum alveolar concentration minimizes risk, and co-administration of nitrous oxide and hyperventilation both counteract this effect. The highest incidence of seizure activity with induction of anesthesia is believed to occur with etomidate. Ketamine may also facilitate seizures at low doses, but at high doses each of these induction agents acts as an anticonvulsant. One study noted that some patients who receive phenytoin are resistant to vecuronium but not to atracurium.

**MYOTONIA AND MYOTONIC DYSTROPHY**

Myotonia is the general term used to describe a prolonged contraction of certain muscles after stimulation, which is followed by a delay in relaxation. Myotonic dystrophies are a genetically and phenotypically heterogeneous group of neuromuscular disorders caused by expansion defects in nucleotide sequences, principally on chromosome 19. Based on clinical ascertainment, the estimated prevalence of myotonic dystrophy is about 1 in 8000; however, prevalence estimates vary widely. As the most common form of myotonic disorders, myotonic dystrophies manifest in two distinct forms with different nucleotide sequences, DM1 and DM2. Both DM1 and DM2 are multisystem disorders characterized by skeletal muscle weakness and myotonia, cardiac conduction abnormalities, cataracts, hypogammaglobulinemia, and insulin resistance. DM1, also known as Steinert disease, is generally more severe and exists in congenital, juvenile, and adult forms, whereas only an adult form has been identified for DM2.
Myotonias can involve specific muscles, typically the hand, facial, masseter, and pretibial muscles, which become dystrophic or wasted. The disorder is slowly progressive with continual deterioration and gradual involvement of pharyngeal and laryngeal muscles, proximal limb muscles, and the diaphragm. Uterine smooth muscle is affected, and cardiac conduction abnormalities are often present. Patients typically succumb to either pulmonary or cardiac failure.

**Congenital myotonic dystrophy** is a severe form of myotonic dystrophy (DM1) that manifests early in infancy and usually predicts a poor outcome. DM1 is characterized by myotonia of the skeletal muscles; multisystem involvement does not occur. Unlike myotonic dystrophy, cardiac abnormalities are not present, and smooth muscles are not affected. In some cases, muscle hypertrophy rather than wasting occurs. This disorder can be compatible with long life. It is distinguished from DM1 and DM2 by characteristic clinical features and an absence of significant histopathology in the muscle biopsy specimen. Myotonia congenita is characterized by dysfunction of the chloride channel.

**Central core disease** is a rare disorder in which muscle biopsies demonstrate the absence of oxidative enzyme activity in the longitudinal axis of the muscle fiber (i.e., the “central core”). Affected individuals have proximal muscle weakness and often scoliosis. This disease is caused by mutations in the skeletal muscle ryanodine receptor gene (RYR1) on chromosome 19q13.1, which has been associated with malignant hyperthermia. Many patients with central core disease test positive for the malignant hyperthermia susceptibility trait (see Chapter 46); these patients should be considered at risk for malignant hyperthermia and should not be exposed to triggering agents (i.e., succinylcholine, volatile halogenated agents). Some patients with multi-minicore and nemaline rod myopathy may also be at risk for malignant hyperthermia.

Drugs such as quinine and mexiletine are most commonly used to relieve myotonic symptoms. Corticosteroids, phenytoin, and tocainide also have been prescribed.

**Obstetric Management**

In patients with myotonic dystrophy, symptoms of weakness and myotonia usually remain unchanged during pregnancy; however, in a minority of women, symptoms worsen during pregnancy but generally resolve after delivery. Antepartum evaluation should include pulmonary function testing, to assess the severity of restrictive lung disease caused by muscle wasting, and an electrocardiogram, which may reveal conduction abnormalities.

There may be a higher risk for preterm labor in patients with myotonic dystrophy. Other complications of pregnancy include polyhydramnios (secondary to reduced fetal swallowing) and an increased risk for placenta previa and accreta. Magnesium sulfate has been reported to cause respiratory compromise. Poor uterine contractions may result in prolonged labor, uterine atony, and an increased risk for postpartum hemorrhage. Skeletal muscle weakness increases the risk for prolonged second stage of labor and operative delivery. The neonate also may have respiratory distress if affected by congenital myotonic dystrophy.

There are reports of patients with myotonia congenita who experience temporary worsening of symptoms during pregnancy. Obstetric problems have not been described, most likely because this disease involves skeletal muscle only; uterine smooth muscle is not affected in these patients.

**Anesthetic Management**

Many reports of anesthetic management of patients with myotonic dystrophies were published before the distinction between DM1 and DM2 was appreciated, and before the era of modern anesthesia management; therefore, generalization from these reports may not be valid. Reports suggest that patients with myotonic disorders may be especially sensitive to the respiratory depressant effects of opioid analgesic and general anesthetic agents. Sedative-hypnotic agents should be used with caution; in some cases, opioids or sedatives may precipitate apnea. Thus, neuraxial anesthesia is preferred for labor and vaginal or cesarean delivery. Both spinal and epidural anesthesia have been used successfully in patients with myotonic dystrophy.

Although the clinical characteristics of myotonic dystrophy DM2 are generally more benign than DM1, anesthesia providers should be aware that both may be associated with dysphagia, cardiomyopathy, and cardiac conduction abnormalities. Two case reports described atrial flutter and fibrillation resulting in shock after tracheal intubation in myotonic dystrophy patients receiving general anesthesia for cesarean delivery.

The prolonged contractions witnessed in patients with myotonia are caused by an intrinsic muscle disorder that is not relieved by spinal or epidural anesthesia; however, infiltration with a local anesthetic agent may partially release contractions. Cold external temperatures and shivering are known triggers of myotonia, so the patient should be kept warm. Patients with myotonic dystrophy have a high incidence of pulmonary complications after general anesthesia.

If general anesthesia is required, it may be prudent to limit the use of opioids and carefully titrate muscle relaxants to mitigate the risk for postoperative pulmonary complications. Depolarizing agents such as succinylcholine should be avoided because fasciculations trigger myotonia, thereby making ventilation and tracheal intubation difficult. In contrast, patients with myotonic dystrophy appear to have a normal response to nondepolarizing muscle relaxants. Regardless, careful neuromuscular monitoring is essential, particularly in those with significant baseline muscle weakness. Reversal of neuromuscular blockade with sugammadex has been described. In a review of dystrophic myotonias and their possible association with malignant hyperthermia, Parness et al. concluded that susceptibility to malignant...
hyperthermia in this group of patients is similar to that of the general population. Patients with central core disease should be assumed to be susceptible to malignant hyperthermia.107

MUSCULAR DYSTROPHY

Muscular dystrophy is a group of disorders characterized by a progressive degeneration of skeletal muscle with intact innervation.126 Research on the subsarcolemmal muscle fiber protein dystrophin has led to a reclassification of these disorders. Analysis of dystrophin quality and quantity can be used diagnostically before and during pregnancy, and can identify carriers in some cases.

Duchenne and Becker muscular dystrophies are transmitted as X-linked recessive disorders and occur almost exclusively in males. However, female carriers may have electrocardiographic and/or echocardiographic abnormalities. The most common muscular dystrophies affecting females are fascioscapulohumeral dystrophy and limb-girdle dystrophies. Fascioscapulohumeral dystrophy is an autosomal dominant, slowly progressive disorder that primarily involves the muscles of the shoulders and face.126 Over time, the pelvic and pretibial muscles may be affected. Tachycardia and arrhythmias have been infrequently reported. Limb-girdle dystrophies involve slow degeneration of the shoulder and pelvic muscles; exacerbations are common during pregnancy, and risk for cesarean delivery is increased because of weakness in the trunk and pelvic muscles.126 The inheritance pattern and severity of these diseases are variable. Cardiac conduction disorders and cardiomyopathies occur in some affected patients.

Obstetric Management

The presentations of dystrophinopathies are variable, and the overall management is guided by the presence and severity of symptoms. If significant weakness is present, pulmonary function testing should be obtained to assess the extent of restrictive disease. An antepartum electrocardiogram and echocardiogram should be considered. Pregnant women with muscular dystrophies may have an increased incidence of operative delivery; the presence of severe pelvic wasting may necessitate instrumental vaginal or cesarean delivery.127 A study of the course of pregnancy in women with hereditary neuromuscular disorders reported a high rate (27%) of abnormal fetal presentation in women with limb-girdle muscular dystrophy, especially in chair-bound patients. Muscle weakness worsened during and after pregnancy in one-half of patients with limb-girdle dystrophy.109

Anesthetic Management

Limb-girdle muscular dystrophy is associated with various cardiac abnormalities, including cardiomyopathies and conduction abnormalities. Reduced lung function and respiratory compromise can be exacerbated by the physiologic changes of pregnancy; one report of a parturient with limb-girdle muscular dystrophy noted the requirement of noninvasive positive-pressure ventilation for progression of severe restrictive pulmonary disease during the third trimester of pregnancy.128 Neuraxial techniques are preferred for labor analgesia and cesarean delivery anesthesia. Severe disease may result in both airway abnormalities and spinal deformities, which may complicate the administration of either general or neuraxial anesthesia.

Whereas most females are asymptomatic carriers of the abnormal gene for muscular dystrophies, approximately 2.5% of female carriers have mild symptoms of the disease.129 Cardiac manifestations may be significant; one report described a female carrier of Becker’s muscular dystrophy who had peripartum cardiomyopathy; general anesthesia was associated with intraoperative respiratory insufficiency, hemodynamic instability, and cardiac arrest.130 There are reported cases of muscular dystrophy associated with “malignant hyperthermia–like” reactions. In a systematic review, Gurnaney et al.131 summarized reported cases of patients with muscular dystrophy who developed hyperthermia, tachycardia, rhabdomyolysis, and hyperkalemia after exposure to succinylcholine and/or volatile anesthetic agents. However, none of these patients had other classic signs of malignant hyperthermia or evidence of hypermetabolism. The mechanism for this response may be related to the ability of these agents to exacerbate instability and permeability of dystrophin-deficient muscle membranes.131 Although muscular dystrophy does not increase risk for malignant hyperthermia, volatile anesthetic agents should be used cautiously because of the risk for severe rhabdomyolysis. Succinylcholine may lead to life-threatening hyperkalemia because of upregulation of extrajunctional acetylcholine receptors or because of rhabdomyolysis. Thus, succinylcholine should not be administered to patients with known muscular dystrophy. In general, these patients have a normal response to nondepolarizing muscle relaxants, but careful neuromuscular monitoring is needed, especially in patients with severe muscle wasting.

THE PHAKOMATOSES (NEUROCUTANEOUS SYNDROMES)

The phakomatoses are congenital disorders that manifest as CNS and cutaneous abnormalities. Structures of ectodermal origin such as skin, nervous system, and eyes are commonly affected.132 The diseases are classified into three main groups: neurofibromatoses, tuberous sclerosis, and angiomatoses with CNS abnormalities (Box 48.2).133 The most common phakomatoses are neurofibromatosis types 1 and 2, tuberous sclerosis, Sturge-Weber disease, and von Hippel-Lindau disease. Abnormalities of the brain and spinal cord can have significant implications for anesthetic management.

Neurofibromatosis

Neurofibromatosis occurs as a result of excessive proliferation of neural crest elements such as Schwann cells, melanocytes, and fibroblasts. Clinical manifestations include hyperpigmented lesions (café-au-lait spots) accompanied by a variety of cutaneous and subcutaneous tumors. This disorder is now believed to exist in two distinct forms with gene abnormalities
on two different chromosomes. Neurofibromatosis type 1, the “classic” form, has an incidence of approximately 1 in 3000. The severity and progression of the disease are variable, with the neurologic symptoms depending on the location of the tumors. Intracranial tumors and paraspinal neurofibromas are a cause of concern and may require surgical excision. The risk for pheochromocytoma is greater in these patients. Neurofibromatosis type 2 is a less common form of the disease with fewer cutaneous lesions. Acoustic neuromas as well as other cranial or spinal neurofibromas, meningiomas, and gliomas may be present.

**Obstetric Management**

Pregnancy may exacerbate the disease by increasing tumor growth. Regression occurs after delivery in some women. A population-based cohort study of 1553 pregnancies associated with neurofibromatosis type 1 found increased risks for gestational hypertension, preeclampsia, fetal growth restriction, cerebrovascular disease, and cesarean delivery. Pelvic neurofibromas may necessitate cesarean delivery. Risk for thromboembolic events, stillbirth, cardiac events, or maternal death were not elevated compared with the general population. The presence of intracranial masses may be problematic during labor and vaginal delivery, particularly with the increased intracranial pressure (ICP) that occurs with the Valsalva maneuver during the second stage of labor.

**Anesthetic Management**

Anesthesia providers should thoroughly assess the patient’s current symptoms and known lesions, particularly if they involve neck and laryngeal tumors; these tumors are common, particularly in patients with neurofibromatosis type 1.

Antenatal evaluation for concomitant pheochromocytoma and potential neuretal, intracranial, and peripheral nerve tumors should be considered.

Neuraxial anesthetic techniques can be used for labor analgesia and operative anesthesia in most patients with the disorder. However, severe kyphoscoliosis owing to the presence of paraspinal tumors may complicate the administration of neuraxial anesthesia. The presence of asymptomatic paraspinal and intracranial tumors has prompted some anesthesia providers to suggest that neuraxial anesthesia should be administered only after careful clinical and radiographic evaluations.

The use of muscle relaxants in these patients is controversial, because both increased and decreased sensitivity to succinylcholine has been reported; increased sensitivity to nondepolarizing agents has been reported as well. However, a number of investigators observed only minimal alterations in dose response to both depolarizing and nondepolarizing muscle relaxants in these patients and have recommended no alterations in the dose of drug.

**Tuberous Sclerosis**

Tuberous sclerosis is a phakomatosis characterized by epilepsy, mental retardation, and adenoma sebaceum. The brain shows abnormal growth of glial cells in hamartomas called tubers. Hamartomatous tumors can occur in multiple organs, including the heart, kidneys, liver, and lungs. The inheritance pattern is autosomal dominant with a variable expression, and the disease is slowly progressive.

**Obstetric and Anesthetic Management**

A retrospective cohort study using the Nationwide Inpatient Sample from 1998 to 2008 found that tuberous sclerosis may be associated with increased rates of preterm labor (adjusted OR, 2.1) and preeclampsia (adjusted OR, 2.8). The obstetrician and anesthesia provider should know the locations of lesions in an individual patient. Hemorrhage into the tumors, renal failure, and hypertension may complicate pregnancy. Renal involvement appears to represent an important prognostic factor during pregnancy, and spontaneous rupture of a renal angiomyolipoma has been reported. Factors that could potentially impact anesthetic management of these patients include the presence of cardiac and renal tumors (angiomyolipomas), spinal and intracranial tubers, epilepsy, pharyngeal tumors, and pulmonary involvement. Cardiac rhabdomyosarcomas have been reported to occur in over 60% of children with this disorder. These tumors generally regress with age, but arrhythmias and cardiac failure from ventricular obstruction may occur. In the presence of known elevated ICP from cerebral lesions, some anesthesia providers believe that neuraxial anesthesia is contraindicated. Imaging should be considered before administration of neuraxial blockade if intracranial or spinal lesions are suspected. In addition, the airway should be assessed closely for the presence of oral tubers, which have been described in approximately 15% of these patients.

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**BOX 48.2 The Congenital Neuroectodermoses**

**True Phakomatoses**
- Tuberous sclerosis
- Neurofibromatosis
  - Type 1 (classical)
  - Type 2 (acoustic)
- Familial schwannomatosis

**Cutaneous Angiomatosis with Abnormalities of the Central Nervous System**
- Sturge-Weber syndrome (meningofacial or encephalofacial angiomatosis with cerebral calcification)
- Dermatomal hemangiomas and spinal vascular malformations
- Epidermal nevus (linear sebaceous nevus) syndrome
- Osler-Rendu-Weber disease (hereditary hemorrhagic telangiectasia)
- von Hippel-Lindau disease
- Ataxia-telangiectasia (Louis-Bar disease)
- Fabry disease

Cutaneous Angiomatosis with Central Nervous System Abnormalities

One group of phakomatoses consists of disorders in which a cutaneous vascular anomaly is accompanied by CNS abnormalities (see Box 48.2). There are few reports of pregnancy in patients with these disorders. Patients may have neurologic problems related to hemangiomas of the CNS. Epidural and spinal anesthesia have been reported in only a few patients with spinal hemangiomas; epidural anesthesia may be preferable to spinal anesthesia as von Hippel-Lindau hemangioblastomas are not present in the epidural space. The presence of widespread varicosities in these disorders may result in a chronically low ventricular preload; if a significant increase in preload occurs during the peripartum period, cardiac overload and peripartum cardiomyopathy may occur.

ACUTE IDIOPATHIC POLYNEURITIS

(AUGUIN-BARÈ SYNDROME)

Acute idiopathic polyneuritis, also known as Guillain-Barré syndrome, is an inflammatory demyelinating illness with a reported incidence of approximately 1 case per 100,000 persons per year. In 60% of patients, a viral illness precedes neurologic symptoms by 1 to 3 weeks. Zika virus is a newly identified antecedent infection. Cases also have occurred after the administration of antirabies and influenza vaccines.

Patients with this disorder initially have weakness in the limbs, followed by the trunk, neck, and facial muscles. Loss of reflexes, total motor paralysis, and respiratory failure can occur. Symptoms peak at 2 to 3 weeks. The majority of patients recover completely; approximately 10% of patients have severe residual disability, and in 3% the syndrome is fatal. Autonomic nervous system involvement and dysfunc-
tion may occur.

Treatment is largely supportive and may include mechanical ventilatory support. Plasmapheresis reduces the duration of illness when instituted during the evolution phase and has been used safely during pregnancy.

Obstetric Management

The incidence of this syndrome appears unchanged in pregnant women, but increases in the first 3 months postpartum. There is no evidence that pregnancy affects the natural history of the disease, and termination of pregnancy does not appear to improve its course.

Anesthetic Management

Anesthetic management depends on patient status at the time of delivery; epidural and spinal techniques have been described in patients with Guillain-Barré syndrome. However, some anesthesia providers have expressed concern regarding the use of neuraxial techniques in these patients, citing the theoretical potential for adverse neurologic effects as a result of anesthetic toxicity or immunologic modulation. Steiner et al. implicated epidural anesthesia as a trigger of Guillain-Barré syndrome in four patients; Wiertlewski et al. reported the immediate worsening of neurologic status after delivery in a pregnant patient with Guillain-Barré syndrome who had received epidural anesthesia. These authors did not establish a causal relationship between the disease and neuraxial anesthetic techniques, nor did they properly acknowledge the increased frequency of Guillain-Barré syndrome in the postpartum period.

If general anesthesia is necessary, succinylcholine should be avoided because of the risk for hyperkalemia in patients with acute muscle wasting. Careful titration of nondepolarizing muscle relaxants is also necessary.

The parturient with a history of remote Guillain-Barré syndrome may have persistent diminished respiratory reserve, even in the absence of obvious residual disability. Pulmonary evaluation should be considered before the administration of anesthesia. Approximately 5% of patients experience a relapse, with a small number of cases progressing to a chronic disorder.

POLIOMYELITIS

Poliomyelitis is a disease caused by a picornavirus that is transmitted by the fecal-oral route. Most cases are asymptomatic or are accompanied by mild systemic symptoms. More severe symptoms and nervous system involvement occur in approximately 1% of patients. Motor neurons in the cerebral cortex, brainstem, and spinal cord are affected. Asymmetric flaccid paralysis develops over several days. Bulbar paralysis is more common in young adults. The CSF findings are consistent with viral meningitis. Recovery occurs 3 to 4 months after onset, most likely from motor axon terminal sprouting that reinnervates the previously denervated muscle fibers; however, residual deficits often persist. A slowly progressive syndrome called postpoliomyelitis muscular atrophy (postpolio syndrome) may develop as many as 40 years after the acute illness as a result of death or dysfunction of the enlarged, surviving motor neurons.

Obstetric Management

Although the poliovirus vaccine has been available since the 1950s, the last phase of poliomyelitis eradication has been difficult; in 2014, the World Health Organization declared the worldwide transmission of polio virus to formerly polio-free countries to be a public health emergency. The oral form of the vaccination does not appear to have harmful effects on fetal development and can be used if vaccination is required during pregnancy. A history of poliomyelitis may increase the risk for preeclampsia, maternal renal dysfunction, LBW infants, perinatal death, and cesarean delivery in poliomyelitis survivors. Some of these adverse outcomes may be related to chronic pulmonary issues or mechanical obstruction during labor.

Anesthetic Management

A complete preanesthetic evaluation should be performed for the presence of respiratory impairment, sleep apnea, swallowing difficulties, and other neurologic and motor deficits in
all parturients with a history of poliomyelitis. Some anesthesiologists have feared that administration of neuraxial anesthesia in patients with a history of poliomyelitis might cause reactivation of the virus or postpolio syndrome. However, there is no evidence that neuraxial anesthesia worsens symptoms in these patients. Rezende et al.\textsuperscript{158} reported a series of 123 patients with a history of poliomyelitis undergoing 162 surgical procedures and observed postoperatively for 22 months; neuraxial blockade was used in 64% of cases, with no patients exhibiting worsening of neurologic symptoms. Anesthetic considerations in these patients should include assessment for pulmonary restrictive disease as well as anatomic issues that may make neuraxial techniques difficult.\textsuperscript{159} For the patient with postpolio syndrome in whom general anesthesia is needed, some anesthesia providers have suggested the use of a decreased dose of a short-acting nondepolarizing muscle relaxant in lieu of succinylcholine, which may provoke severe acute hyperkalemia.\textsuperscript{160}

**BRAIN NEOPLASMS**

Intracranial neoplasms vary in incidence, histology, clinical presentation, and prognosis (Table 48.4).\textsuperscript{161} Brain neoplasms in pregnant women appear to occur with the same relative frequency as in nonpregnant women; however, the physiologic alterations that occur during pregnancy can have profound implications for symptomatology and management.

**Gliomas** are the most common intracranial neoplasms, accounting for approximately 39% of all primary intracranial tumors.\textsuperscript{162} These tumors, which result from anaplasia of astrocytes, exhibit diversity in invasive potential and include glioblastoma multiforme, astrocytomas, ependymomas, and oligodendrogliomas. Glioblastoma multiforme is the most lethal, whereas oligodendrogliomas have a better prognosis.

**Pituitary adenomas** account for 7% of diagnosed primary brain neoplasms.\textsuperscript{162} Only a small fraction of these tumors cause symptoms (e.g., visual field deficits). These tumors may secrete prolactin, growth hormone, or adrenocorticotropic hormone. Tumor growth is physically limited by the sella turcica of the sphenoid bone and the hypothalamus. The resulting compression of the hypothalamus or pituitary gland may cause decreases in the production or release of vasopressin, leading to diabetes insipidus. The pituitary gland normally enlarges during pregnancy, and this additional growth may cause symptoms in a woman who was previously asymptomatic.\textsuperscript{162} Women with known microadenomas should be carefully monitored during pregnancy to detect symptoms of pituitary compression.\textsuperscript{162} Growth of pituitary tumors can be triggered by breast-feeding.

Bromocriptine often provides effective medical therapy for prolactin-secreting adenomas and has a track record of use during pregnancy; its continued use during breast-feeding must be balanced against its suppressive effect on lactation. Surgery is indicated for tumors that do not respond to medical management.

**Schwannomas**, also called **neurinomas**, account for 7% of all brain tumors.\textsuperscript{162} These lesions originate in the Schwann cells surrounding the nerve. Clinical presentation depends on the location of the tumor. Acoustic neuromas result when the eighth cranial nerve is involved; these lesions are often seen in patients with neurofibromatosis. The treatment is surgical excision.

**Metastatic carcinomas** account for a significant number of brain neoplasms.\textsuperscript{162} Common primary cancers include those of the lung, breast, and colon. Prognosis and therapy depend on the tumor of origin.

Brain tumors share several pathophysiologic features. Neurologic deficits can result from a mass effect or increased ICP, even if the tumor is benign. Brain edema, which may result from a combination of vasogenic and cytotoxic mechanisms, is a prominent feature of cerebral neoplasms.

The potential for herniation must be considered in any patient with a mass lesion. The brain is divided into three basic compartments. The falx cerebri separates the cerebrum into right and left halves, and the tentorium isolates the cerebellum. High pressure from a mass can cause shifts from one compartment to another with devastating effects.

**Obstetric Management**

The incidence of primary brain tumors first manifesting in pregnancy does not appear to be greater than that in age-matched, nonpregnant women.\textsuperscript{162} However, pregnancy may affect existing tumor biology in one case series, 44% of pregnant women with an existing history of grade II or III gliomas experienced tumor progression during pregnancy or within 8 weeks postpartum.\textsuperscript{164} Approximately 9% of patients...
with choriocarcinoma have brain metastases at the time of
diagnosis. In one epidemiologic study, patients with
primary brain tumors had a higher incidence of spontaneous
abortion, possibly because of hormonal factors. A 2012
study using a retrospective cohort from the National Inpa-
tient Sample reported an increased rate of maternal mortality,
cesarean delivery, and preterm labor in patients with mali-
gnant brain tumors, and an increased rate of preterm labor
and cesarean delivery in patients with benign brain tumors. Pregnancy complications were significantly more likely to
occur in patients having a neurosurgical procedure during
their admission.

Although pregnancy does not affect the incidence of brain
tumors, some of these lesions appear to grow faster during
pregnancy. Visual field defects from pituitary adenomas worsen as a result of tumor enlargement during pregnancy,
and symptoms have been observed to improve during the
postpartum period. Edema and the increased blood volume
may account for some of these symptoms. Pregnancy-induced hormonal changes also may play a role because estrogen and
progesterone receptors are present in meningiomas and some gliomas.

Diagnosis during pregnancy requires intracranial imaging.
In general, MRI is preferred because it avoids the use of ion-
izing radiation. MRI may require the use of gadolinium-based
contrast agents. Gadolinium has the advantage compared
with other contrast agents of not containing iodine, and
studies demonstrating adverse fetal effects are lacking in
humans. However, gadolinium appears rapidly in the fetal
bladder and amniotic fluid, from where it may be swallowed
by the fetus and absorbed from the gastrointestinal tract. Its
default-life is unknown. The American College of Radiol-
gy has stated that in pregnant patients, gadolinium-based
contrast agents “…should only be used if their usage is con-
sidered critical and the potential benefits justify the potential
unknown risk to the fetus.”

Management during pregnancy depends on the nature of
the tumor. Surgery for benign tumors (e.g., meningiomas)
with mild symptoms can often be delayed until after delivery.
Women with more aggressive, malignant tumors or with
tumors causing seizures or severe visual impairment may
require urgent surgery during pregnancy to avoid acute neu-
rologic deterioration. Delivery also may be recommended as
soon as reasonable fetal survival can be expected, sometimes
by cesarean delivery immediately before neurosurgery. For
women with pregnancies far from fetal viability, radiation
therapy or stereotactic radiosurgery can be considered.
Cranial radiation therapy is generally administered as a first
therapeutic procedure to reduce the size of the mass in cases
of aggressive neoplasm. However, radiation therapy, and
particularly systemic chemotherapy, can pose significant
hazards to the fetus, especially when administered during the
first trimester. Some women may opt for surgery after an
elective abortion.

In the healthy parturient, CSF pressure may increase sig-
nificantly with painful uterine contractions. In patients
with an intracranial mass lesion, this situation could result in
an increased risk for herniation. Increased ICP from Valsalva
maneuvers can further exacerbate herniation risk. The loca-
tion and size of the tumor should be assessed in the individual
patient so that an appropriate delivery plan can be developed
with multidisciplinary input. In general, either a pain-free
second stage (with instrumental vaginal delivery to avoid
pushing) or cesarean delivery may be appropriate.

Anesthetic Management

The optimal anesthetic technique for labor analgesia and
cesarean delivery anesthesia in the patient with an intracranial
tumor is controversial. Epidural analgesia prevents the
increase in ICP that can result with pushing during the second
stage of labor. Several published reports have described the
successful use of labor epidural analgesia in women with
intracranial neoplasms, in addition, the use of spinal
anesthesia for an emergency cesarean delivery in a patient
with a glioblastoma has been described. However, in preg-
nant women with increased ICP, an unintentional dural
puncture associated with an attempted epidural catheter
placement can result in a fatal brain herniation. As a conse-
quency, many anesthesiology providers favor general anesthesia
for cesarean delivery in the patient with a brain neoplasm; however,
potential disadvantages of general anesthesia include (1) the loss of verbal and motor responses that facil-
tate neurologic assessment, and (2) the risks of increased ICP
with tracheal intubation and extubation. Leffert and
Schwamm proposed a decision tree for risk stratifying
patients with intracranial space-occupying lesions for whom
neuraxial anesthesia is being considered.

Wang and Paech have reviewed specific elements in the
anesthetic management of the pregnant patient undergoing
neurosurgery, many of which are also relevant to the patient
with an intracranial tumor undergoing cesarean delivery. The
induction of general anesthesia may consist of the adminis-
tration of an induction dose of propofol or thiopental and
either a depolarizing or a rapid-acting nondepolarizing
neuromuscular-blocking agent. Some anesthesia providers
avoid succinylcholine because it may cause a transient
increase in ICP, but others consider this effect to be clinically
insignificant. A combination of a volatile halogenated agent
(sevoflurane or isoflurane), nitrous oxide, and an opioid is
commonly used for maintenance of anesthesia. When appro-
priate, accommodations for monitoring the FHR during
intracranial surgery should be made.

To preserve cerebral and uteroplacental perfusion, hemo-
dynamic stability should be maintained through appropriate
fluid administration, avoidance of aortocaval compression,
the prophylactic or early use of vasopressor drugs, and intra-
arterial blood pressure monitoring instituted before induc-
tion of anesthesia. In general, blood pressure should be
kept close to baseline measurements; in the setting of an
emergency neurosurgical procedure in a patient with
increased ICP, a drop in blood pressure may compromise
cerebral perfusion. Fluid management for intracranial surgery
should involve administration of isonatremic, isotonic, and
glucose-free intravenous solutions to reduce the risk for
cerebral edema and hyperglycemia.\textsuperscript{179} Mannitol administered to a pregnant woman slowly accumulates in the fetus, leading to fetal hyperosmolality and the subsequent physiologic changes of reduced fetal lung fluid production, decreased fetal urine production, and increased fetal plasma sodium concentration;\textsuperscript{179} however, mannitol in doses of 0.25 to 0.5 mg/kg has been reported in individual cases and appears to be associated with favorable maternal and fetal outcomes.\textsuperscript{179} Furosemide is an alternative diuretic that also should be administered cautiously.

There may be some conflict between maternal and fetal interests in the patient with increased ICP. Moderate mechanical hyperventilation may be used to reduce the increased ICP that occurs in nonpregnant patients with a brain tumor or brain injury. Minute ventilation increases during normal pregnancy, resulting in a maternal PaCO\textsubscript{2} of 28 to 32 mm Hg; additional hyperventilation and hypocapnia may cause uterine artery vasoconstriction and a leftward shift in the maternal oxyhemoglobin dissociation curve (see Chapter 2). For pregnant women with an acute increase in ICP, Wang and Paech\textsuperscript{179} have suggested a target PaCO\textsubscript{2} range of 25 to 30 mm Hg; however, data are currently insufficient to support evidence-based recommendations specific to pregnant women undergoing intracranial surgery. In pregnant patients with increased ICP, we recommend maintenance of maternal PaCO\textsubscript{2} in the middle or at the lower end of the normal range for pregnancy. Management should be individualized according to the clinical setting.

When the decision is made to perform a cesarean delivery and brain tumor resection sequentially during a single anesthetic, hypotension should be avoided during induction and endotracheal intubation. Some authors have used combinations of high-dose fentanyl or remifentanil, labetalol, and propofol or thiopental with succinylcholine.\textsuperscript{179,180} Postoperatively, measures to minimize risk for respiratory depression are indicated as hypoventilation can exacerbate ICP.

Often, pregnant women with intracranial neoplasms undergo definitive tumor resection with continuation of the pregnancy. In these women, neuraxial techniques may be considered for delivery if ICP is normal.

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**Fig. 48.3** Decision tree summarizing the critical elements for assessing the risk for neurologic deterioration from neuraxial anesthesia in patients with intracranial space–occupying lesions. CSF, cerebrospinal fluid. (Redrawn from Leffert LR, Schwamm LH. Neuraxial anesthesia in parturients with intracranial pathology: a comprehensive review and reassessment of risk. Anesthesiology. 2013;119:703–718.)
IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension, previously referred to as pseudotumor cerebri or benign intracranial hypertension, is defined as an increase in ICP with a normal CSF composition in the absence of hydrocephalus or a mass lesion. The disorder most often occurs in obese women of childbearing age, suggesting that hormonal factors may play a role in the pathophysiology. The majority of patients have a headache and vision symptoms, with vision loss reported in 1 in 4 affected cases. The condition may be chronic or episodic, and there is a small risk for recurrence.

Therapies include serial lumbar punctures and the administration of carbonic anhydrase inhibitors and/or corticosteroids. Lumboperitoneal shunting may be required in severe cases with visual symptoms. Weight loss appears to improve the condition.

Interaction with Pregnancy

Pregnancy in patients with idiopathic intracranial hypertension does not increase the risk for relapse or worsen the prognosis of idiopathic intracranial hypertension. In the presence of severe maternal symptoms, the placement of an intracranial shunt can result in clinical improvement and normal perinatal outcomes. Overall, this disorder does not adversely affect maternal and perinatal outcomes.

Anesthetic Management

Deliberate lumbar puncture represents a common form of treatment for idiopathic intracranial hypertension. Cerebellar tonsillar herniation does not occur because of the uniform, global increase in ICP. Paruchuri et al. noted that there are only two published cases of cerebellar tonsillar herniation after diagnostic lumbar puncture in patients with this disorder. Both patients had severe headache, neck pain exacerbated by movement, and focal neurologic deficits. In the absence of these signs and symptoms, the anesthesia provider can provide neuraxial analgesia or anesthesia.

Some anesthesia providers recommend the administration of general anesthesia for cesarean delivery in patients with lumboperitoneal shunt. They contend that local anesthetic agents that reach the subarachnoid space may escape into the peritoneum, making it difficult to achieve adequate anesthesia. Moreover, the performance of neuraxial anesthesia may result in trauma to the shunt catheter. However, successful use of neuraxial anesthesia in patients with lumboperitoneal shunts has been reported. Preoperative radiographic examination may help the anesthesia provider avoid needle placement near the catheter. Both increased and decreased local anesthetic effects have been reported in patients receiving neuraxial anesthesia with shunts. Neuraxial anesthesia with an intrathecal catheter has been performed for both vaginal and cesarean delivery in these patients. In one case, the intrathecal catheter provided a route to both administer labor analgesia and drain CSF to treat worsening symptoms caused by elevated ICP. Questions regarding the functional status of an in situ subarachnoid shunt or the possible (very rare) use of the shunt for the administration of spinal anesthesia should be discussed with neurology or neurosurgery consultants.

MATERNAL HYDROCEPHALUS WITH SHUNT

Hydrocephalus results from a variety of conditions. The most common are intracranial hemorrhage in preterm infants, fetal and neonatal infections, the Arnold-Chiari malformation, aqueductal stenosis, and the Dandy-Walker syndrome. The Arnold-Chiari malformation consists of extension of a portion of cerebellar tissue into the cervical canal, with progressive hydrocephalus. The Dandy-Walker syndrome occurs with failure of development of the midline of the cerebellum, with resultant hydrocephalus of the fourth ventricle.

Ventriculostomy or ventriculoperitoneal shunt catheters are placed for the treatment of many of these disorders. Because of advances in neonatal and neurosurgical care, women with hydrocephalus and CSF shunt catheters are reaching childbearing age in increasing numbers.

Anesthetic Management

Anesthetic management of the patient with hydrocephalus depends on the condition and function of the shunt. Both epidural and spinal anesthesia have been used in patients with lumboperitoneal, ventriculostomy, and ventriculoperitoneal shunts (as discussed earlier). A review of 24 studies encompassing 130 pregnancies of parturients with cerebrospinal fluid shunts found that shunt malfunctions were common in pregnancy, that epidural analgesia is safe in women with functional shunts, and that labor anesthetic management varies in response to shunt function and clinical status. A basic thought process for evaluating use of neuraxial anesthesia in patients with hydrocephalus is shown in Fig. 48.3.

INTRACEREBRAL HEMORRHAGE

Cerebrovascular disease during pregnancy can result from three major mechanisms—hemorrhage, arterial infarction, and venous thrombosis. Intracerebral hemorrhage during pregnancy is most commonly associated with an arteriovenous malformation or aneurysm. Using data from the National Inpatient Sample (1995 to 2008), the prevalence of subarachnoid hemorrhage was 5.8 per 100,000 deliveries in women 15 to 44 years of age. The ratio of hemorrhage from
an arteriovenous malformation to that from an aneurysm was significantly higher in pregnant than in nonpregnant patients. The mortality rate was 10.6%; subarachnoid hemorrhage was associated with 4.1% of all pregnancy-related deaths.

Data are conflicting as to whether the aneurysm bleeding rate is higher during pregnancy. Some authors have reported a progressive increase in the incidence of aneurysm bleeding throughout gestation and up to 6 weeks postpartum, while others find no link between pregnancy or the puerperium and increased risk for aneurysmal hemorrhage. In general, asymptomatic and unruptured aneurysms in pregnancy can be managed conservatively with close monitoring and noninvasive imaging. The treatment of ruptured aneurysms during pregnancy should mimic treatment of aneurysms in nonpregnant patients. The American Heart Association (AHA) guidelines for the management of aneurysmal subarachnoid hemorrhage include monitoring and controlling blood pressure (balancing the risk for stroke, rebleeding, and maintenance of cerebral perfusion pressure) and early surgical clipping or endovascular coiling. Controversy exists as to whether endovascular coiling results in better outcomes than clipping. Although the AHA has suggested that “endovascular coiling should be considered” in patients with ruptured aneurysms judged to be technically amenable to both surgical clipping and coiling, some experts argue that several factors may alter the risk-benefit ratio in pregnancy. These factors include (1) the need for exposure to ionizing radiation for coil placement, (2) the possible need for anticoagulation or use of antifibrinolytic agents, and (3) the increased rate of incomplete aneurysm occlusion associated with coiling compared with clipping. Endovascular coiling has not been specifically studied in the pregnant population, although several cases of successful endovascular treatment of ruptured intracranial aneurysms in pregnant women have been reported.

Bleeding from arteriovenous malformations has been reported to occur with equal or greater frequency with advancing gestational age. The risk for hemorrhage from an arteriovenous malformation in pregnant women does not appear to differ from that in the general population, although the risk for bleeding appears greater during the second half of pregnancy and the first 6 weeks postpartum, corresponding to the period of high cardiac output. The management of arteriovenous malformations in pregnancy does not differ from standard care of the nonpregnant patient. As with aneurysms, a multidisciplinary decision-making process allows planning based on the location of the lesion, the duration of pregnancy, and the relative risks associated with interventional and noninterventional methods of management. Management of arteriovascular malformations, including those that present during pregnancy, has increasingly shifted over the past decade from a surgical to an endovascular approach.

Obstetric Management
If the lesion has been treated surgically, the patient requires no special care during labor and delivery. For an untreated aneurysm or arteriovenous malformation, the hemodynamic stress occurring during labor and delivery should be minimized. Current data do not demonstrate a definite advantage of cesarean delivery over assisted vaginal delivery. The decision about the method of delivery should be based on the individual patient and her pregnancy history. For labor and vaginal delivery, neuraxial analgesia and low outlet forceps or vacuum assistance may be used to shorten the second stage of labor and attenuate fluctuations in blood pressure.

Anesthetic Management
If the parturient has undergone surgical repair of either an aneurysm or arteriovenous malformation, anesthetic management need not differ from that for other obstetric patients. Hypertension should be avoided in the parturient with an untreated lesion. If vaginal delivery is planned, epidural or CSE analgesia should be considered. For cesarean delivery, epidural, spinal, or CSE anesthesia can be used. Interdisciplinary planning is important.

In some cases, the neurosurgeon may ligate or excise the vascular lesion during pregnancy, before delivery. The anesthesia provider should consider the general principles of anesthetic management for pregnant women undergoing nonobstetric surgery (see Chapter 17) as well as the special considerations for pregnant women undergoing neurosurgery (as discussed earlier). The risks for hypertension and intracranial bleeding, as well as the risk for pulmonary aspiration should be considered during induction of anesthesia. It is critical to maintain stable blood pressure during induction of anesthesia, laryngoscopy, tracheal intubation, and extubation. The patient should receive adequate sedation before and after arrival in the operating room. Placement of an intra-arterial catheter is mandatory. The anesthesia provider may attenuate the hypertensive response to laryngoscopy and tracheal intubation by intravenous administration of esmolol, lidocaine, nitroglycerin, nitroprusside, and/or an opioid (e.g., remifentanil). Succinylcholine can be used for tracheal intubation. Regardless of the choice of muscle relaxant, it is critical that laryngoscopy and tracheal intubation not be performed until the patient is anesthetized adequately.

The anesthesia provider may maintain anesthesia with nitrous oxide and modest doses of isoflurane and an opioid. Aggressive maternal hyperventilation may result in decreased uterine blood flow. However, the anesthesia provider may use modest hyperventilation (e.g., PaCO₂ of 28 to 30 mm Hg) as needed to reduce maternal ICP. The anesthesia provider should maintain left uterine displacement in patients beyond 20 weeks’ gestation. Intraoperative FHR monitoring allows assessment of the fetal response to maternal general anesthesia, hemodynamic changes, and hyperventilation, but a clear plan in case of fetal compromise that is not responding to intrauterine resuscitation efforts during surgery must be discussed with the patient, anesthesia provider, neurosurgeon, and obstetrician. At many institutions, including our own, intraoperative FHR monitoring is used beginning at 24 weeks’ gestation, which corresponds to the onset of extraterine neonatal viability. Typically, an obstetric nurse monitors the FHR tracing during surgery and requests
obstetric consultation if needed. An adverse change in the FHR tracing should prompt the anesthesia provider to ensure adequate maternal oxygenation, ventilation, and perfusion. There is no consensus regarding an acceptable or safe level of hypotension in these patients, and deliberate hypotension in current neuroanesthesia practice has generally fallen out of favor. Endovascular treatment with general anesthesia avoids the need for craniotomy and deliberate hypotension.

In some cases, the obstetrician and neurosurgeon may perform a combined procedure (e.g., a cesarean delivery followed by ligation or excision of the neurovascular lesion). Principles of anesthetic management are similar to those described earlier for intracranial neurovascular surgery during pregnancy.178,179

CEREBRAL VEIN THROMBOSIS

Thrombosis of the cerebral veins and sinuses most often affects young adults and children; approximately 75% of the adult patients are women.202 Thromboses commonly involve the cavernous sinus, lateral sinus, sagittal sinus, or cortical veins. Thrombosis of the cerebral veins causes venous obstruction with local effects, whereas thrombosis of the major sinuses causes intracranial hypertension. A prothrombotic risk factor or a direct cause can be identified in approximately 85% of patients. Pregnancy may be a precipitating factor for sinus thrombosis in a person with a genetically increased risk.201

Primary cerebral cortical vein thrombosis is the type of thrombosis most often seen in pregnancy. The estimated incidence of cerebral vein thrombosis during pregnancy is 12 cases per 100,000 deliveries in developed countries.202 Cerebral vein thrombosis occurs more frequently during the last trimester of pregnancy and in the second and third postpartum weeks.202 Although the etiology is unclear, pregnancy may predispose patients to this condition because of at least two factors. First, traumatic damage to the endothelial lining of vessels may occur during the second stage of labor. Second, pregnancy is a hypercoagulable state (see Chapters 2 and 38). Mechanical causes of sinus thrombosis may include head injury and lumbar puncture.203 It has been postulated that low CSF pressure after a lumbar puncture causes the brain to shift downward, resulting in traction on the cortical veins and sinuses.

Patients with cerebral vein thrombosis may have headache, nausea and vomiting, and blurred vision. In more severe cases, lateralizing neurologic signs, lethargy, and seizures may occur. In severe cases, transtentorial herniation caused by a focal mass effect can occur. A 2017 systematic review of cerebral vein thrombosis in pregnancy linked headache alone with favorable prognosis, while coma and obtundation predicted poor outcomes.204

Care should be taken to differentiate cerebral vein thrombosis from post–dural puncture headache (PDPH). In general, the headache associated with cerebral vein thrombosis is more diffuse in location. Earlier teaching suggested that the headache does not vary with position, but a 2007 review concluded that the nature of the headache may change over time and often manifests “as a positional headache that overlaps the usual timing…and treatment of PDPH in the parturient.”203

Diagnosis can be confirmed by magnetic resonance (MR) venography. The American Heart Association/American Stroke Association published a set of management guidelines in 2011; the guidelines recommend full anticoagulation with unfractionated heparin (titrated to an activated partial thromboplastin time two times normal) or weight-adjusted low-molecular-weight heparin, continued for a minimum of 6 months’ duration.202 Intra-arterial thrombolysis and thrombectomy during pregnancy and the puerperium have been described; some data suggest improved outcomes when both thrombolyis and thrombectomy are performed.204 Lumbar puncture and drainage of a large volume of CSF may be needed to treat acute elevations in ICP that stem from reduced venous drainage; the procedure must be timed with pharmacologic anticoagulation.

**Obstetric and Anesthetic Management**

Cerebral vein thrombosis rarely occurs before delivery, although such an occurrence may prompt an urgent delivery if associated with maternal neurologic instability and fetal deterioration. Maternal anticoagulation contraindicates the administration of neuraxial anesthesia. The anesthesia provider should avoid systemic hypotension, which may reduce cerebral perfusion pressure and blood flow to injured areas already subjected to marginal perfusion. If the patient has an asymmetric cerebral hematoma with mass effect, dural puncture may precipitate herniation of the brainstem. Thus, it seems preferable to administer general anesthesia for cesarean delivery, with special attention to the treatment of increased ICP. Cerebral venous thrombosis is a rare, but reported, complication after spinal and epidural anesthesia, presumably caused by intracranial hypotension.203

**MOTOR NEURON DISORDERS**

Motor neuron diseases are a group of disorders characterized by progressive muscular weakness and atrophy. These disorders may affect motor function alone or in conjunction with sensory deficits. There are few data on the course of these disorders in pregnant women. This discussion focuses on three of these disorders, amyotrophic lateral sclerosis and primary spinal muscular atrophy, which are pure motor neuron disorders, and peroneal muscular atrophy, which involves both motor and sensory degeneration. Currently there is no cure for any of these degenerative disorders.

**Amyotrophic Lateral Sclerosis**

Amyotrophic lateral sclerosis involves progressive degeneration of anterior horn cells with progressive atrophic weakness and hyperreflexia. Patients typically succumb to respiratory failure within 6 years of diagnosis.

This disease is seen more often in patients older than 50 years of age, but there are several reports of this disorder
in pregnant women. Physicians should assess and frequently monitor the patient’s respiratory compromise throughout the peripartum period. Epidural analgesia and anesthesia have been used in these patients without evidence of worsened neurologic function postoperatively. Patients with amyotrophic lateral sclerosis may be sensitive to the effects of nondepolarizing muscle relaxants. The physiologic changes during the late stages of pregnancy may worsen marginal respiratory status in these patients, and early cesarean delivery may be warranted.

**Spinal Muscular Atrophy**

Like amyotrophic lateral sclerosis, primary spinal muscular atrophy involves degeneration of anterior horn cells. However, affected patients tend to be younger, and this disorder progresses more slowly. Some types are hereditary. Spinal muscular atrophy mainly involves the spinal cord, without involvement of the corticospinal tract. Marked kyphoscoliosis combined with truncal and limb weakness, especially involving the proximal musculature, can occur and result in significant ventilatory limitations.

Spinal muscular atrophy may be associated with an increased incidence of preterm labor and worsened muscle weakness that persists after delivery. Epidural and spinal analgesia and anesthesia have been used successfully in patients with this disorder. In children with this rare disorder, both general and regional anesthesia have been successfully used; special attention should be paid to postoperative respiratory function.

**Peroneal Muscular Atrophy**

Peroneal muscular atrophy, also known as Charcot-Marie-Tooth disease, includes several inherited peripheral motor and sensory neuropathies; it is one of the most common inherited neuromuscular diseases. It involves a progressive sensory and motor degeneration of peripheral nerves and roots. The peroneal nerve is affected early. Restrictive pulmonary impairment, phrenic nerve dysfunction, diaphragmatic dysfunction, thoracic cage abnormalities, and sleep apnea have been described in association with peroneal muscular atrophy. Vocal cord dysfunction, possibly caused by laryngeal nerve involvement, can also be present. Assessment of peripartum respiratory function is essential. Approximately 30% of patients with this disorder report deterioration in overall function during pregnancy.

A review of 108 deliveries found that women with this disorder have higher rates of abnormal fetal presentation, emergency operative delivery, and postpartum bleeding. Both neuraxial and general anesthesia have been used for delivery.

**ISOLATED MONONEUROPATHIES DURING PREGNANCY**

Pregnancy is associated with an increased incidence of several specific mononeuropathies: Bell’s palsy, carpal tunnel syndrome, and meralgia paresthetica.
Patients with myasthenia gravis require close surveillance. Continuous neuraxial anesthesia is the method of choice. Multiple sclerosis does not contraindicate the use of neuraxial analgesia or anesthesia. Continuous neuraxial anesthesia is the method of choice for the prevention or treatment of autonomic hyperreflexia during labor and delivery in patients with spinal cord injury. Patients with myasthenia gravis require close surveillance during labor. Increasing muscle weakness may require an adjustment in the dosage of the anticholinesterase drug. Severe respiratory involvement may preclude the use of neuraxial anesthesia for cesarean delivery.

Symptoms of multiple sclerosis may worsen postpartum, regardless of the anesthetic technique used during delivery. However, the long-term prognosis of this disease is most likely unaffected by pregnancy.

Multiple sclerosis does not contraindicate the use of neuraxial analgesia or anesthesia. Symptoms of multiple sclerosis may worsen postpartum, regardless of the anesthetic technique used during delivery. Increasing muscle weakness may require an adjustment in the dosage of the anticholinesterase drug. Severe respiratory involvement may preclude the use of neuraxial anesthesia for cesarean delivery.

The anesthesia provider should avoid succinylcholine in patients with myotonic dystrophy because fasciculations can trigger myotonia.

Neuraxial analgesia or anesthesia does not appear to precipitate the onset of postpoliomyelitis muscular atrophy (postpolio syndrome).

Hemodynamic stability should be maintained in the parturient with an untreated intracranial aneurysm or arteriovenous malformation. Neuraxial anesthesia should be considered during labor and delivery.

Bell’s palsy, carpal tunnel syndrome, and meralgia paresthetica occur at higher rates during pregnancy. Symptoms typically resolve postpartum.

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18. Bell’s palsy, carpal tunnel syndrome, and meralgia paresthetica occur at higher rates during pregnancy. Symptoms typically resolve postpartum.


89. Kinney MO, Craig JJ. Pregnancy and epilepsy; meeting the challenges over the last 25 years: the rise of the pregnancy registries. Seizure. 2017;44:162–168.


Obesity is a worldwide health problem, with the prevalence in the general population growing at an alarming rate. Data from the National Health and Nutrition Examination Survey show that in 2015 to 2016, 36.5% of women of reproductive age (20 to 39 years of age) were obese, compared with a prevalence of 28.3% in 1999 to 2000. Although no definition of obesity specific to pregnancy exists, a pregnant woman is generally considered overweight when her body mass index (BMI) is 25.0 to 29.9 kg/m², and obese when her BMI is 30 kg/m² or greater. The World Health Organization defines three grades of obesity: class I (BMI 30.0 to 34.9 kg/m²), class II (BMI 35.0 to 39.9 kg/m²), and class III (BMI 40 kg/m² or greater). The prevalence of class III obesity among women of reproductive age has significantly increased in recent years, with a prevalence of 10% in 2013 to 2014, compared with 5% in 1999 to 2000. To allow for the weight gain of pregnancy, some groups have suggested adding 5 kg/m² to the World Health Organization classes to define pregnancy thresholds.

Obesity is associated with an increased risk for maternal morbidity and mortality. The care of obese parturients poses significant challenges to the anesthesia provider as a result of common comorbidities, an increased cesarean delivery rate, and technical difficulties associated with both neuraxial and general anesthesia. Understanding the pathophysiologic changes and comorbidities associated with obesity and pregnancy is crucial for the safe conduct of anesthesia in these high-risk patients.

PHYSIOLOGIC CHANGES OF OBESITY

Cardiopulmonary Changes

Obesity increases the demands on the cardiopulmonary system. The effects of obesity and pregnancy on the respiratory and cardiovascular systems are summarized in Table 49.1 and Table 49.2. As energy expenditure increases proportionate to the increase in body mass, oxygen consumption and carbon dioxide (CO₂) production also increase proportionate to the increase in work performed. Minute ventilation is increased owing to the elevated respiratory demand, except in the 5% to 10% of obese patients with Pickwickian syndrome, who display a reduced sensitivity to CO₂. Obesity affects the body's ability to meet these demands by changing pulmonary mechanics, altering lung volumes, and impairing oxygen consumption.

Obesity increases the weight of the chest wall; thus, greater energy expenditure is required during ventilation to move this mass. Morbidly obese patients in comparison with lean controls expend a disproportionately high percentage of total oxygen consumption on respiratory work, even during quiet breathing. The weight gain during pregnancy further increases the work of breathing. In obese individuals, frequent shallow respirations may represent a more efficient breathing pattern than large tidal volumes. This pattern of frequent shallow respirations contrasts to the increased tidal volumes that typically accompany pregnancy.
and lung compliance decrease, but airway resistance increases as a result of reduction in lung volumes.14

Pulmonary diffusion typically remains normal in most women with morbid obesity. Decreased chest wall compliance and greater abdominal weight promote airway closure in the dependent portion of the lung.13 Ventilation preferentially occurs in the more compliant, nondependent portion of the lung. In contrast, pulmonary blood flow preferentially occurs in the dependent portion of the lung, resulting in ventilation-perfusion mismatch and hypoxemia.13 Consistent with the positional deterioration of lung volumes, oxygenation worsens in obese individuals in the supine and Trendelenburg positions.

Blood volume and cardiac output are increased, the latter owing to increases in both stroke volume and heart rate. Both preload and left ventricular afterload are increased; these changes result in both eccentric and concentric left ventricular hypertrophy. Among morbidly obese pregnant women, left atrial size, left ventricular thickness, interventricular septal thickness, and left ventricular mass are increased compared with nonobese pregnant women.14 The increase in heart rate limits the time for diastolic filling, thus diastolic relaxation is impaired. Pulmonary blood volume increases in proportion to increases in cardiac output and total blood volume. Pulmonary hypertension can occur and may be position dependent. A BMI of 30 kg/m² or more is associated with a threefold higher incidence of hypertension during pregnancy than a BMI less than 30 kg/m².2 Aortocaval compression of the great vessels in the supine position may be greater in obese parturients, particularly those with a large fat panniculus.

**Gastrointestinal Changes**

It is unclear whether obesity in pregnancy is associated with an increase in gastric volume and a decrease in gastric pH. Roberts and Shirley15 reported that gastric volumes aspirated from obese laboring women undergoing cesarean delivery were significantly higher than those obtained from lean controls. Studies in the general surgical population, however, reported conflicting results; some confirmed these findings16 and others reported no difference in gastric volume and pH in obese compared with lean patients.17

Similarly, data regarding gastric emptying in the obese population are conflicting; studies have reported delayed, unchanged, or more rapid rates of gastric emptying in obese subjects compared with lean subjects.18 In a nonobstetric obese population, Maltby et al.19 reported that drinking 300 mL of clear fluid 2 hours before surgery had no effect on gastric fluid volume and pH compared with fasting after midnight. Similarly, Wong et al.20 found that gastric emptying in obese, nonlaboring term pregnant volunteers was not delayed after ingestion of 300 mL of water compared with ingestion of 50 mL of water. The gastric volume returned to baseline 60 minutes after ingestion of water.

Both gastroesophageal reflux and hiatal hernia are more common in obese than in nonobese patients.21 Obesity is also associated with a higher risk for difficult airway management,

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**TABLE 49.1 Physiologic Changes in the Respiratory System Induced by Pregnancy and Obesity**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Pregnancy</th>
<th>Obesity</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>↑</td>
<td>↔ or ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Minute volume</td>
<td>↑</td>
<td>↓ or ↔</td>
<td>↑</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Residual volume</td>
<td>↓</td>
<td>↓ or ↔</td>
<td>↓</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁</td>
<td>↔</td>
<td>↓ or ↔</td>
<td>↔</td>
</tr>
<tr>
<td>FEV₁/VC</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Compliance</td>
<td>↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Work of breathing</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>PaO₂</td>
<td>↑</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

↑, Increase; ↓, decrease; ↔, no change; more than one arrow represents the degree of intensity; FEV₁, forced expiratory volume in 1 sec; VC, vital capacity; V/Q, ventilation/perfusion. Modified from Saravanakumar K, Rao SG, Cooper GM. Obesity and obstetric anaesthesia. Anaesthesia. 2006;61:36-48.

**TABLE 49.2 Physiologic Changes in the Cardiovascular System Induced by Pregnancy and Obesity**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Pregnancy</th>
<th>Obesity</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>↓ or ↔</td>
<td>↑↑</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Systolic function</td>
<td>↔ or ↓</td>
<td>↓</td>
<td>or ↓</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>↔</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>↔</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Occlusion pressure</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

↑, Increase; ↓, decrease; ↔, no change; more than one arrow represents the degree of intensity. Modified from Saravanakumar K, Rao SG, Cooper GM. Obesity and obstetric anaesthesia. Anaesthesia. 2006;61:36-48.

Greater abdominal weight restricts diaphragm movement, especially in the supine or Trendelenburg position, thus encouraging smaller tidal volumes. Functional residual capacity (FRC) decreases at the expense of expiratory reserve volume and may be less than closing capacity. Both chest wall...
which is a known risk factor for aspiration. Therefore, it seems likely that morbidly obese patients are at higher risk for pulmonary aspiration of gastric contents.

Coagulation Changes

Obesity is associated with a higher risk for thromboembolic complications. Venous thromboembolism is a leading cause of direct maternal mortality. In the United Kingdom, 54% of women who died from thromboembolic complications in 2009 to 2013 were overweight or obese.

Obesity is associated with changes in coagulation, venous stasis, and endothelial injury that contribute to the pathogenesis of venous thromboembolism. For instance, adipose tissue secretes the following: (1) adipokines such as plasminogen activator inhibitor-1 (PAI-1), which results in impaired fibrinolysis; (2) leptin, which promotes platelet aggregation; and (3) interleukin-6, which stimulates the liver to produce coagulation factors. C-reactive protein levels are also elevated in obese women, leading to platelet activation. Venous stasis is compounded in obese women by increased intra-abdominal pressure, which leads to increased iliofemoral venous pressure. Obesity was shown to be associated with endothelial dysfunction in the nonpregnant population. Therefore, all risk factors that contribute to the pathogenesis of thromboembolic complications are likely to be exacerbated by obesity. The risk is further increased by reduced mobility, comorbidities such as preeclampsia, and an increased frequency of operative delivery.

Endocrine Changes

Gestational diabetes and diabetes mellitus occur more frequently in obese patients. The pathologic process is attributed to the following: (1) peripheral insulin resistance as a result of augmentation of free fatty acids by visceral obesity; (2) increased proinflammatory cytokine levels; (3) relative gonadotropin resistance, and (4) a low sex hormone–binding globulin concentration, which leads to hyperandrogenism and decreased insulin sensitivity. The concentration of adiponectin, an adipokine with insulin-sensitizing properties, is also decreased in obesity, which leads to decreased insulin sensitivity.

COMORBIDITIES ASSOCIATED WITH OBESITY

Sleep Apnea

Obesity is a significant risk factor for obstructive sleep apnea (OSA), which is characterized by repeated episodes of complete or partial upper airway collapse, leading to hypoxemia and hypercarbia. Those repeated periods of hypoxemia and reoxygenation lead to significant endocrine and metabolic disturbances, which result in an increased risk for hypertension, myocardial infarction, stroke, diabetes, and metabolic syndrome. It is estimated that 15% to 20% of obese pregnant women have OSA.

The changes of pregnancy may both worsen and protect against OSA. For instance, weight gain and estrogen-induced hyperemia and edema of nasal mucosa might promote OSA, whereas sleeping in the lateral position, reduced rapid eye movement (REM) sleep, and the progesterone-induced increase in minute ventilation might protect against it.

OSA may adversely affect maternal and neonatal outcomes. A large inpatient database study showed that pregnant women with OSA are at increased risk for preeclampsia, eclampsia, cardiomyopathy, and pulmonary embolism, and are five times more likely to die in the hospital during a pregnancy or delivery admission than women without OSA. These differences were unchanged after controlling for obesity, but the associations with preeclampsia and severe cardiovascular complications were stronger in obese women. The association between OSA and increased risks for preeclampsia and gestational diabetes were confirmed in a large prospective study involving 3705 women.

Some studies have examined the impact of maternal OSA on perinatal outcomes. A 2014 meta-analysis reported an association between sleep-disordered breathing and low birth weight, neonatal intensive care unit admission, fetal growth restriction, and a 1-minute Apgar score less than 7.

Other Comorbidities

Obesity is associated with an increased risk for a number of disease states compared with lean controls (Table 49.3). These comorbidities complicate the care of obese parturients.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>12.41</td>
<td>9.03, 17.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.42</td>
<td>1.95, 3.67</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.10</td>
<td>2.81, 3.43</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.78</td>
<td>1.07, 2.95</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3.51</td>
<td>2.61, 4.73</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.49</td>
<td>1.27, 1.74</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.78</td>
<td>1.36, 2.32</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>2.32</td>
<td>1.17, 4.57</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.96</td>
<td>1.88, 2.04</td>
</tr>
<tr>
<td>Chronic back pain</td>
<td>2.81</td>
<td>2.27, 3.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>1.55</td>
<td>1.22, 1.98</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1.89</td>
<td>1.70, 2.09</td>
</tr>
</tbody>
</table>

CI, confidence interval.


**IMPACT OF OBESITY ON PREGNANCY**

**Maternal and Fetal Complications**

Obesity results in greater use of health care resources. Chu et al.\(^4\) reported that obese pregnant women receive significantly more prenatal tests, ultrasonographic examinations, medications, and prenatal visits with a physician, and they are at greater risk for having a high-risk pregnancy, cesarean delivery, and prolonged hospitalization than pregnant women of normal weight.

Obesity is associated with a significantly increased incidence of maternal, fetal, and neonatal complications. These include a higher risk for spontaneous abortion (miscarriage), thromboembolic complications, gestational diabetes, hypertensive disorders of pregnancy, dysfunctional labor, shoulder dystocia, operative vaginal delivery, cesarean delivery, postpartum hemorrhage, wound infection, fetal macrosomia, fetal congenital anomalies, stillbirth, and neonatal death (Table 49.4).\(^6,42,43\)

Most importantly, obesity increases the risk for death during pregnancy. The report of Confidential Enquiries into Maternal Deaths in the United Kingdom for 2012 to 2014 showed that 51% of women who died were overweight or obese, a trend that has been consistent for the last several reports.\(^7\) The increased risk for death associated with obesity has been attributed to the associated comorbidities such as hypertensive disorders of pregnancy. The impact of obesity on maternal mortality is particularly evident in women who die of thromboembolism or cardiac disease.\(^44\)

Obesity has also been identified as a risk factor for anesthesia-related maternal mortality. Six of the 13 direct maternal deaths attributed to anesthesia in the United Kingdom between 2003 and 2008 occurred in obese parturients.\(^44,45\) In the United States, Mhyre et al.\(^46\) reported that six of eight pregnant women who died of anesthesia-related deaths in Michigan between 1985 and 2003 were obese. Because of the increased risk for complications, guidelines published both in the United Kingdom\(^47\) and by the American College of Obstetricians and Gynecologists (ACOG)\(^48\) recommend a multidisciplinary approach to the care and treatment of obese pregnant women, including referral for antepartum consultation with an anesthesia provider.

**Progress of Labor and Method of Delivery**

The progress of labor appears to be affected by BMI. A large multicenter study involving 118,978 patients whose labor management reflected current practice in the United States found that labor progressed more slowly with increasing BMI for both nulliparous and parous women.\(^49\) The median time to progress from 4 to 10 cm cervical dilation increased from 5.4 hours to 7.7 hours for lean and morbidly obese nulliparous women, respectively, and from 4.6 hours to 5.4 hours for lean and morbidly obese parous women, respectively. These findings were independent of gestational age and induction of labor. Entry into the active phase of labor was also delayed in parous women as a function of BMI. Possible explanations include increased fetal size, higher labor induction rates, and/or decreased responsiveness to oxytocin.\(^49\)

Poor uterine contractility has also been demonstrated in obese parturients. Myometrium obtained from obese women at cesarean delivery contracted with less force and frequency and had less calcium flux than that from normal-weight women.\(^50\) This observation may be attributable to the inhibitory effect of cholesterol\(^50\) and/or adipokines (e.g., leptin, ghrelin, apelin), which inhibit human uterine contractility in vitro.\(^51\) Inadequate myometrial contractility has also been implicated in a higher rate of uterine atony and postpartum hemorrhage, after both vaginal and operative deliveries, in obese women. In a large retrospective study involving 30,298 pregnancies over an 8-year period,\(^52\) the risk for postpartum hemorrhage was significantly higher with increasing BMI (odds ratio [OR], 2.7; 95% confidence interval [CI], 2.2 to 3.4 for obesity class III compared with nonobese).

Obesity is also associated with a higher risk for failed medical induction of labor. In a secondary analysis of data from a large labor induction trial involving 1273 patients, the duration of labor, oxytocin requirements, and cesarean delivery rates were significantly higher in women with a greater BMI.\(^53\) In a large series from Sweden involving 233,887 deliveries, Cedergren\(^54\) found a fourfold increase in the risk for cesarean delivery in parturients with a BMI greater than 40 kg/m\(^2\) compared with parturients of normal weight, primarily because of failed or obstructed labor. Operative vaginal delivery, with its associated maternal and fetal morbidity, is also more likely in the obese parturient.\(^6\)

Risk for fetal macrosomia is higher with obesity, which increases the risk for shoulder dystocia and its associated birth trauma, and predisposes to perineal lacerations, newborn infant injury, and postpartum hemorrhage.\(^6,55\) One study examining maternal anthropometric parameters associated with shoulder dystocia reported a 2.7-fold increase in

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**TABLE 49.4 Obstetric Complications in Obese and Morbidly Obese Women**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obese versus Control</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2.6 (2.1, 3.4)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>2.5 (2.1, 3.0)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.6 (1.1, 2.3)</td>
</tr>
<tr>
<td>Birth weight &gt; 4500 g</td>
<td>2.0 (1.4, 3.0)</td>
</tr>
<tr>
<td>Birth weight &gt; 4000 g</td>
<td>1.7 (1.4, 2.0)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.1 (0.9, 1.5)</td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>1.0 (0.8, 1.3)</td>
</tr>
<tr>
<td>Cesarean delivery(^a)</td>
<td>1.7 (1.4, 2.2)</td>
</tr>
</tbody>
</table>

\(^a\)Nulliparous women.

risk for shoulder dystocia in obese compared with lean parturients, even after adjustment for potential confounders such as macrosomia and diabetes. Higher BMI, increased prepregnancy weight, and excessive maternal weight gain increase the risk for both elective and emergency cesarean delivery. This risk is further increased by obesity-related pregnancy complications such as macrosomia, fetal growth restriction, diabetes mellitus, and hypertensive disorders of pregnancy. In a meta-analysis of 33 trials, the unadjusted odds ratios (95% CI) of cesarean delivery were 1.46 (1.34 to 1.60), 2.05 (1.86 to 2.27), and 2.89 (2.28 to 3.79) among overweight, obese, and morbidly obese women, respectively, compared with normal-weight pregnant women.

**ANESTHETIC MANAGEMENT**

The high incidence of comorbid conditions among obese pregnant women necessitates early, careful preanesthetic assessment. A number of technical matters should be considered when caring for an obese parturient.

An appropriate-sized blood pressure cuff must be used for noninvasive blood pressure measurements. Unless the length of the sphygmomanometer cuff exceeds the circumference of the arm by 20%, systolic and diastolic blood pressure measurements may overestimate true maternal blood pressure. Forearm blood pressure measurement is sometimes used if an appropriate-sized blood pressure cuff is not available or if the upper arm cuff continues to slide from its position owing to the shape of the obese patient’s upper arm. There is a good correlation between upper arm and forearm noninvasive measurements, but forearm pressures exceed upper arm pressures by 10 ± 10 mm Hg (mean ± SD), which is often compromised by excessive lumbar adiposity. There is poor agreement between invasive blood pressure readings and those obtained with the currently available cylindrical blood pressure cuffs placed in various locations on the upper arm or forearm. A study comparing invasive blood pressure readings with a conical blood pressure cuff specifically developed for forearm use showed good agreement with invasive blood pressure readings in obese patients. In selected cases, invasive monitoring of blood pressure with an intra-arterial catheter may be desirable.

Intravenous access may be difficult in obese patients. Ultrasonographic guidance may be useful; however, if peripheral intravenous access is unsuccessful, central venous cannulation may be necessary. Appropriately sized labor beds, transportation gurneys, and operating tables, and sufficient personnel to assist with patient transport, are imperative. Although standard operating tables are generally rated for persons weighing up to 500 pounds (227 kg), this rating may be insufficient for morbidly obese patients, especially when the table is articulated. Regardless of the weight rating of the table, it is critical that the obese patient be centered over the operating table pedestal at all times. Special equipment for moving and positioning the patient, such as motorized lifts, and longer spinal/epidural needles, may be needed (see later discussion).

**Labor and Vaginal Delivery**

Many of the options for labor analgesia have limitations in the obese parturient. For example, obese parturients with OSA may be more susceptible to the respiratory depressant effect of systemic opioids, leading to episodes of apnea and oxyhemoglobin desaturation. Pudendal nerve block may be technically difficult in obese patients. Inhalation analgesia is useful in some patients; however, nitrous oxide has limited effectiveness and is not available in many birthing rooms. Further, inhalation analgesia may lead to a reduced level of consciousness, which can be very dangerous in an obese woman with a difficult airway.

Neuraxial analgesia represents the best option for pain relief and is particularly desirable in the obese parturient. Given the greater risks for fetal macrosomia and shoulder dystocia in obese patients, adequate analgesia is often needed to facilitate an atraumatic vaginal delivery. The use of epidural analgesia during labor allows the anesthesia provider to extend epidural analgesia to surgical anesthesia for cesarean delivery and thus avoid the need for general anesthesia with its associated risks. Given the increased likelihood for cesarean delivery and the greater risk for general anesthesia in the obese parturient, the early administration of neuraxial labor analgesia is recommended in the obese parturient.

When performing a neuraxial anesthetic technique in the obese parturient, technical difficulties may include (1) inability to palpate the spinous processes or identify the midline; (2) greater depth of the epidural space, which may exaggerate minor needle directional errors and increase the likelihood of identifying a lateral portion of the epidural space; and (3) the presence of fat pockets as well as hormonal softening of the ligaments, which may result in a false loss of resistance and/or higher risk for unintentional dural puncture. In most obese parturients, however, the epidural space can be identified with a standard-length epidural needle. Therefore, it seems prudent to use a standard-length needle first, which allows the provider better control, before switching to a longer needle.

Observing the prominence of the seventh cervical vertebra and the gluteal cleft can facilitate identification of the midline. Asking the parturient about the perceived location of the needle during block placement (relative to the midline) can also facilitate identification of the midline. Marroquin et al. reported that 77% of morbidly obese parturients who were questioned about the position of the needle during a difficult labor epidural needle placement provided useful feedback to the anesthesia provider. Probing the subcutaneous tissue with a needle can also help identify the spinous processes and help identify a lumbar interspace. More objectively, ultrasonographic guidance can be used to identify the midline, image the epidural space, and measure the distance from the skin to the epidural space (see Chapter 12). Sahin et al. reported fewer attempts needed to establish spinal anesthesia in obese parturients undergoing cesarean delivery when preprocedure ultrasonography was performed. Ultrasound image quality, which is often compromised by excessive lumbar adiposity...
in obese patients, may be improved with the paramedian sagittal oblique plane compared with the transverse plane. Balki et al. found a strong correlation between the skin-to-epidural space distance measured by ultrasonography and that measured by the epidural needle in obese parturients. However, soft tissue compression with the ultrasound probe resulted in underestimation of the depth of the epidural space in obese women.

Placing the patient in the sitting position facilitates identification of the midline and is preferred by many anesthesia providers when initiating a neuraxial anesthetic procedure in obese parturients. In the lateral position, gravity may cause lateral fat to sag downward and obscure the midline. Further, the distance from the skin to the epidural space is minimized when the patient is in the sitting-flexed position.

Care is needed to avoid dislodgement of the epidural catheter after insertion. Movement of the epidural catheter relative to the skin is most striking in obese patients. Hamilton et al. demonstrated that patient movement from the sitting-flexed to the lateral decubitus position causes redistribution of the soft tissue of the back. The distance from the skin to the epidural space increases, and an unsecured catheter will appear to be drawn inward by as much as 1.0 to 2.5 cm. An epidural catheter secured with tape to the back of a patient in the sitting flexed position can be unintentionally dislodged from the epidural space when the patient moves from the sitting to the lateral decubitus position. Therefore, these investigators recommended that the patients assume the lateral position before the epidural catheter is secured to the skin. Alternatively, when placing the block in the sitting-flexed position, the patient should be asked to sit upright before taping the catheter to the skin.

Many authors have documented technical difficulties with neuraxial techniques in obese parturients. In 1993, Hood and Dewan reported that 94% of patients who weighed more than 300 lb (136.4 kg) experienced adequate analgesia for delivery, compared with 98% of controls. More attempts were required to identify the epidural space in obese women, there was a significantly higher initial failure rate (42% versus 6%), and placement of a second or third epidural catheter was more often required. A more recent study by Tonidandel et al. from the same center reported that the failure rate in morbidly obese parturients was lower than their previous study (17%), but this rate was still significantly higher than the 3% failure rate reported in the lean control group. Similarly, Dresner et al. reported an increased risk for failed labor epidural analgesia and need for catheter replacement with increasing BMI (2.4% for BMI less than 25 kg/m² versus 6.6% for BMI greater than 40 kg/m²). Perlow and Morgan reported that 74.4% of morbidly obese parturients needed more than one attempt and 14% needed more than three attempts for successful epidural catheter placement. In contrast, Bamgade et al. reported a significantly higher number of attempts to perform neuraxial anesthesia in obese parturients, but they observed no difference in the rate of failure of neuraxial anesthetic techniques for cesarean delivery in obese parturients. Kula et al. reported increased rates of difficult and failed labor epidural analgesia by 2.5- and 2.1-fold, respectively, in obese compared with nonobese parturients. Although some investigators have reported a higher incidence of unintentional dural puncture in morbidly obese parturients than in lean parturients, others have not confirmed this finding.

It is not clear if epidural local anesthetic dose requirements are altered in morbidly obese parturients. In 1980, Hodgkinson and Husain administered 20 mL of 0.75% epidural bupivacaine in the L3 to L4 interspace to women undergoing elective or emergency cesarean delivery. The patients remained supine for 40 minutes after drug injection. Twenty-seven percent of the patients with a BMI less than 28 kg/m² needed supplementation of the block at 30 minutes, whereas none of the patients whose BMI exceeded 28 kg/m² required additional local anesthetic to achieve surgical anesthesia. The cephalad extent of neuroblockade was associated with patient BMI and weight but not with height. Similarly, using an up-down sequential allocation study design to estimate the median effective epidural bupivacaine dose (administered in a volume of 20 mL), Panni and Columb found that obese women required significantly less epidural bupivacaine for initiation of labor analgesia than lean parturients. In contrast, Milligan et al. observed that neither patient position nor obesity affected the extent of sensory blockade when 12 mL of 0.25% bupivacaine was administered for epidural labor analgesia. Duggan et al. found that obesity had only a weak effect in enhancing the spread of epidural local anesthetics; this effect was only observed with the largest volume and concentration used in the study (15 mL of bupivacaine 0.75%), but not with a lower volume (10 mL) and concentration (0.5%) of bupivacaine.

The goals of epidural labor analgesia should be the provision of excellent pain relief with minimal motor block. Epidural administration of a dilute solution of local anesthetic with a lipophilic opioid provides analgesia for labor while minimizing adverse effects such as hypotension and motor blockade. The neuroblockade provided to obese parturients in labor should be bilateral and near perfect. Otherwise, the epidural catheter should be removed and replaced because an inadequate block with a frequent need for top-up doses may lead to failure of extending the block for cesarean delivery. Regular evaluation of the parturient’s neuraxial block is essential. In a study of morbidly obese parturients published in 1993, the initial administration of local anesthetic through the epidural catheter resulted in failure of analgesia/anesthesia for cesarean deliveries attempted with epidural anesthesia by 2.5- and 2.1-fold, respectively, in obese compared with nonobese parturients. Although some investigators have reported a higher incidence of unintentional dural puncture in morbidly obese parturients than in lean parturients, others have not confirmed this finding.

The combined spinal-epidural (CSE) technique provides a rapid onset of excellent pain relief. In the past, some providers were concerned that an epidural catheter sited as part of a CSE technique remains untested until the spinal block has regressed. Thus, recognition of a malpositioned catheter might
be delayed and result in failed epidural anesthesia should the need for emergency cesarean delivery arise. Several studies have refuted these concerns and reported a higher success rate for epidural catheters sited using a CSE technique compared with those sited using a standard epidural technique. Presumably, the higher success rate can be attributed to observing backflow of cerebrospinal fluid (CSF) through the spinal needle, thus indirectly confirming correct epidural needle position. Further, Booth et al. found that catheter failure was more often recognized within the first 30 minutes of placement in catheters sited as part of a CSE technique compared with those sited with an epidural technique.

The dural puncture epidural technique (DPE, see Chapter 12) is a modification of the CSE technique in which a spinal needle is used to puncture the dura, but no intrathecal drug is injected. Some investigators have noted improved quality of analgesia compared with an epidural technique, and fewer adverse effects compared with a CSE technique. DPE analgesia may be a useful technique to consider in obese parturients with anticipated difficulty in identifying the epidural space. The backflow of CSF through the spinal needle confirms that the tip of the epidural needle is located in the posterior epidural space, decreasing the risk for block failure. However, the DPE technique has not been specifically studied in this patient population.

In cases of unintentional dural puncture, continuous spinal analgesia can be used to provide labor analgesia. In addition to providing reliable labor analgesia, continuous spinal analgesia may be converted to spinal anesthesia for emergency cesarean delivery. It is crucial, however, that the catheter be clearly labeled and all personnel are made aware of its intrathecal location. Unintentional administration of an epidural dose of local anesthetic through the spinal catheter markedly increases the risk for high spinal block and subsequent respiratory arrest.

Some have suggested that the risk for post–dural puncture headache may be lower in the obese parturient, perhaps secondary to reduced CSF leak through the dural puncture site caused by the higher intra-abdominal pressure that results from a large abdominal panniculus. However, data are conflicting. In a retrospective study of 516 women with unintentional dural puncture with a 17-gauge Tuohy needle, Peralta et al. reported a significantly lower incidence of post–dural puncture headache in women with BMI greater than or equal to 31.5 kg/m² compared with those with BMI less than 31.5 kg/m² (39% versus 56%), even after controlling for pushing during the second stage of labor. Conversely, two other retrospective studies found no difference in the risk for post–dural puncture headache between obese and nonobese parturients. A study found no reduction in the risk for post–dural puncture headache in obese parturients compared with lean parturients except in those with a BMI greater than or equal to 50 kg/m².

Cesarean Delivery

A thorough preanesthetic evaluation is critical to the safe care of the obese parturient. Of particular importance is a thorough airway assessment. Large breasts, the greater anteroposterior diameter of the chest, airway edema, and reduced chin-to-chest distance increase the likelihood of difficult laryngoscopy and failed tracheal intubation in obstetric patients. Obesity exaggerates many of the anatomic changes of pregnancy. Increased fat in the neck and shoulders increases the difficulty of positioning the patient for laryngoscopy and tracheal intubation. Excess fat deposition may also cause distorted anatomy, such as an enlarged tongue and redundant pharyngeal and palatal soft tissue. Further, the fat pads on the back of the shoulders often restrict the range of motion of the neck, exacerbating the difficulty of mask ventilation, laryngoscopy, and tracheal intubation.

All morbidly obese parturients undergoing cesarean delivery should be placed in a ramped position with left uterine displacement, regardless of the planned anesthetic technique. This position was shown to improve laryngoscopic view compared with the traditional sniffing position in morbidly obese patients undergoing elective bariatric surgery. Folded blankets or a padded ramp designed for this purpose are placed under the chest and head to achieve horizontal alignment between the external auditory meatus and the sternal notch. This position aligns the oral, pharyngeal, and tracheal axes to facilitate tracheal intubation and has been shown to improve hemodynamic and respiratory parameters during laparoscopic gastric bypass surgery. Modern surgical tables can also be flexed at a number of angles, and this feature can be used to optimize the patient position for laryngoscopy and tracheal intubation.

It may be difficult to position the obese patient appropriately and safely. The protuberant abdomen may shift markedly with left uterine displacement. The patient must be secured to the operating table before the table is tilted leftward; however, it is important to initiate left uterine displacement as soon as possible.

The anesthesia provider should confirm that the patient’s weight does not exceed the weight limits of the operating table, consider use of lateral table extenders, and use appropriate pads to ensure that the shoulders and arms are positioned in a horizontal plane. Correct arm position will maximize patient comfort, improve stability, and avoid neurologic injury to the upper extremity.

The anesthesia care team may be asked to participate in cephalad retraction of the large panniculus by tethering retractors to an object such as the ether screen or the head of the table. Both the obstetrician and the anesthesia provider must remain cognizant of the risks for hypotension, difficulty with ventilation, and fetal compromise during cephalad retraction of the panniculus in morbidly obese patients. Hodgkinson and Husain reported an intraoperative fetal death in a morbidly obese patient who had received epidural anesthesia for cesarean delivery. The death was attributed to prolonged hypotension associated with cephalad retraction of a large panniculus. A vertical and cephalad suspension of the panniculus has been suggested to avoid maternal hypotension and hypoxemia. Commercially available retraction devices can also be used to retract the panniculus, but there
Obesity within 5 minutes. The anesthesia provider must be aware that the patient remains at risk for aspiration at the end of surgery; the efficacy of sodium citrate wanes 45 to 60 minutes after administration. Administration of a histamine-2 (H2)-receptor antagonist and metoclopramide provide additional protection (see Chapter 28).

Antibiotic Prophylaxis

Obesity is an independent predictor for surgical site infection. The Clinical Practice Guidelines for Antibiotic Prophylaxis in Surgery recommend a dose of 3 g of cefazolin before cesarean delivery in women weighing over 120 kg; however, the data supporting this recommendation are inconsistent. Pevzner et al. found that a 2-g dose of cefazolin administered 30 to 60 minutes before cesarean delivery in obese and morbidly obese patients failed to achieve targeted minimum inhibitory concentrations (MICs) in 20% and 33% of patients, respectively, at the time of skin incision, and in 20% and 40% of patients, respectively, at the time of incision closure. Stitely et al. randomized 20 obese patients undergoing cesarean delivery to receive 2 g or 4 g of cefazolin. The 4-g dose was associated with higher blood and tissue levels, but all collected subcutaneous and myometrial tissue samples had antibiotic concentrations above the MIC. Swank et al. reported that the administration of cefazolin 2 g resulted in the target MIC in all normal and overweight women, but only 20% of parturients with a BMI between 30 and 40 kg/m² and none of those with a BMI greater than 40 kg/m² reached the target MIC. Conversely, after cefazolin 3 g, the MIC target was achieved in all women with a BMI between 30 and 40 kg/m² and in 71% of women with a BMI greater than 40 kg/m². Maggio et al. did not find higher adipose tissue concentrations after cefazolin 3 g compared with 2 g, and there was no difference in surgical site infections between the two regimens. Similarly, two retrospective studies compared surgical site infections in morbidly obese women undergoing cesarean delivery and found no difference in surgical site infections between 2-g and 3-g regimens.

Valent et al. explored another strategy; obese women undergoing cesarean delivery were randomized to receive oral cephalexin 500 mg plus metronidazole 500 mg or placebo every 8 hours for 48 hours after delivery. All patients received a single 2-g intravenous dose of cefazolin before surgical incision. The rate of surgical site infection was significantly lower with the cephalexin/metronidazole regimen (6.4% versus 15.4%), yielding a number needed to treat of 12 (95% CI, 6.7 to 33.8).

Neuraxial Techniques

Neuraxial anesthesia is the anesthetic technique of choice in the obese parturient. Single-shot spinal anesthesia provides reliable, fast onset and dense neuroblockade, and it is a common anesthetic technique in nonobese parturients undergoing planned cesarean delivery. However, concerns about the use of single-shot spinal anesthesia in obese patients include technical difficulties, appropriate dosing, and insufficient duration of anesthesia.
Spinal anesthesia is technically feasible in morbidly obese pregnant women, although a longer spinal needle may be required. The distribution of adipose tissue varies among obese patients. Spinal needle placement can be uneventful in women who do not have excessive adipose tissue over the midline of the back. However, in others with excessive adipose tissue at the needle placement site, identification of the epidural space with a small-gauge spinal needle can be very challenging. Identification of the epidural space with a large-gauge epidural needle is often technically easier, and a needle-through-needle CSE technique may be easier to perform than a single-shot spinal technique in the morbidly obese parturient. Ross et al. reported fewer attempts to establish the neuraxial block with a CSE technique compared with a single-shot spinal technique in morbidly obese parturients undergoing elective cesarean delivery.

The duration of surgery is often prolonged in the obese parturient; therefore, single-shot spinal anesthesia may not have sufficient duration. Because intraoperative induction of general anesthesia is undesirable and potentially hazardous in morbidly obese pregnant women, a continuous neuraxial technique such as a CSE or epidural technique that allows the maintenance of neuraxial anesthesia with the epidural catheter is preferable to a single-shot spinal technique. Epidural anesthesia is preferred if the patient has a well-functioning epidural catheter in situ. Otherwise, a CSE technique may be preferable because it combines the reliability of the spinal block and the flexibility of epidural anesthesia. It also gives the option of initiating the block with a low dose of intrathecal local anesthetic, with the ability to increase the cephalad neuroblockade by administering additional local anesthetic via the epidural catheter if needed (i.e., sequential CSE anesthesia). Continuous spinal anesthesia with a spinal catheter is also an option. Some anesthesia providers have suggested that this technique should be considered in the setting of emergency cesarean delivery for obese parturients because it may be technically easier to rapidly identify the spinal space with a large-gauge epidural needle than with a spinal needle. The use of a double-catheter technique has been described if a high vertical suprapubic incision is planned; a lumbar spinal catheter or CSE technique is used for intraoperative anesthesia and a thoracic epidural catheter is used for postoperative analgesia to achieve adequate anesthesia for the upper end of the incision if needed.

Local anesthetic dosing for neuraxial techniques. The choice of local anesthetic dose in morbidly obese parturients is controversial. It has been a long-held belief that neuraxial local anesthetic doses should be reduced in obese patients because of fear of an unpredictable and exaggerated spread of local anesthetic, resulting in a high block. Magnetic resonance imaging (MRI) has confirmed that obese patients have a reduced lumbar CSF volume. Engorgement of the epidural veins secondary to compression of the inferior vena cava by the gravid uterus and abdominal panniculus, as well as inward movement of soft tissue through the intervertebral foramina as a result of increased abdominal pressure, may be responsible for the reduced CSF volume in these patients.

A separate study using magnetic resonance imaging (MRI) demonstrated an inverse correlation between the cephalad extent of neuroblockade and lumbar CSF volume; this finding suggests that reduced CSF volume in obese patients increases the risk for a high spinal block.

Multiple studies, however, do not support the concern of exaggerated cephalad spread of spinal anesthesia in morbidly obese women undergoing cesarean delivery. In an up-down sequential allocation dose-finding study, Lee et al. reported that the estimated ED95 (effective dose in 95% of patients) for hyperbaric bupivacaine was similar in obese and nonobese patients; no patient had an excessively high cephalad block with bupivacaine doses up to 12 mg. In another study, Carvalho et al. estimated the ED50 (median effective dose) and ED95 for hyperbaric spinal bupivacaine for cesarean delivery in 42 morbidly obese parturients who were randomized to receive doses that ranged from 5 to 11 mg as part of a CSE technique. They reported that the ED50 and ED95 in these morbidly obese parturients were similar to those in nonobese parturients enrolled in a previous study performed by the same authors using similar methodology. Although it was common to obtain a satisfactory initial sensory level, even with the lowest doses, few of the low-dose blocks were adequate for surgery, and many required supplementation via the epidural catheter. Thus, the findings of these studies suggest that reducing the dose of intrathecal bupivacaine is not justified in morbidly obese patients and might increase the risk for inadequate anesthesia.

Superobese parturients with a BMI greater than 50 kg/m² are rarely included in these studies. Ngaka et al. reported a higher block level by a median of 2 dermatomes but no significant differences in vasopressor requirements, hand grip strength, and peak expiratory flow rate in 25 morbidly obese parturients with a mean BMI of 51 kg/m² compared with nonobese parturients after receiving hyperbaric bupivacaine 10 mg. Another retrospective study compared the incidence of high spinal anesthesia (defined as need to convert to general anesthesia within 20 minutes of initiation of spinal anesthesia) because of high neuroblockade or a cephalad extent of anesthesia higher than T2) in nonobese, obesity class I, II, III, and superobese (BMI greater than 50 kg/m²) women. Anesthesia was induced with hyperbaric bupivacaine (predominant dose 12 mg). The incidence of high spinal anesthesia was increased in superobese women (2.5%) compared with all other groups (0.71% or less). Vasopressor requirements were also higher in this group; unscheduled cesarean delivery was a risk factor for high spinal anesthesia. In summary, these studies suggest that intrathecal dose reduction may be warranted in parturients with a BMI greater than 50 kg/m², ideally as part of a CSE technique, but not in obese women with a BMI less than 50 kg/m². In our practice, we use a dose of hyperbaric bupivacaine 9 mg to 10.5 mg as part of a needle-through-needle CSE technique in superobese parturients.

Results of studies of epidural local anesthetic dosing in morbidly obese parturients are also inconsistent (see earlier discussion). Unlike single-shot spinal anesthesia in which titration of the dose is not possible, careful titration of...
epidural anesthesia is recommended to achieve the desired dermatomal level of neuroblockade.

**General Anesthesia**

Difficult mask ventilation and tracheal intubation are associated with more rapid oxyhemoglobin desaturation during apnea in obese patients than in lean individuals. The association between obesity and a short neck can make tracheal intubation difficult in this population. In a series of patients who received general anesthesia for cesarean delivery, the incidence of difficult tracheal intubation was 33% among women who weighed more than 300 lb (136.4 kg). This study was performed at a time when video laryngoscopes were not available in routine practice. Quinn et al. conducted a 2-year survey of failed tracheal intubation in obstetric patients in the United Kingdom and reported that BMI was an independent predictor of failed intubation; the odds increase by 7% for each 1-kg/m² increase in BMI.

**Airway management.** The potential for failed tracheal intubation and difficult mask ventilation in the obese patient underscores the need for an experienced assistant during induction of general anesthesia. The primary anesthesia provider may fatigue rapidly with attempted mask ventilation of an obese patient. Further, the jaw-thrust maneuver may require the use of both hands, and additional personnel will be required to provide positive-pressure ventilation and cricoid pressure. A short-handled laryngoscope, assorted laryngoscope blades, various sizes of endotracheal tubes, endotracheal tube guides, supraglottic airway devices, a video laryngoscope, a fiberoptic intubation device, and equipment suitable for emergency surgical airway (e.g., cricothyrotomy) should be readily available. A failed tracheal intubation algorithm should be initiated and help should be called immediately in the event of failed tracheal intubation (see Chapter 29). Supraglottic airway devices may be lifesaving in these situations. Some experts have suggested that a video laryngoscope should be the first-line device used in obstetric patients; this recommendation may be particularly relevant in the obese parturient.

Awake tracheal intubation using video laryngoscopy or direct fiberoptic laryngoscopy is an alternative method of securing the anticipated difficult airway. However, women requiring urgent cesarean delivery may not be ideal candidates for awake tracheal intubation because of the lack of adequate time to optimally prepare the airway.

When preanesthetic assessment suggests that tracheal intubation will not be difficult, a rapid-sequence induction is indicated. The administration of general anesthesia begins with effective denitrogenation (so-called preoxygenation). During apnea, pregnant women become hypoxic more rapidly than nonpregnant women, and obese patients become hypoxic more rapidly than nonobese patients. Therefore, adequate denitrogenation is essential before the induction of general anesthesia in obese pregnant women. A nasal cannula insufflating oxygen 5 L/min during the period of apnea and tracheal intubation increases the time to desaturation and should be strongly considered in the obese parturient.

The technique of denitrogenation is important. One study demonstrated that four maximal inspirations of 100% oxygen within 30 seconds (4-deep breaths (DB)) provide benefit similar to that provided by 3 minutes of tidal-volume breathing of 100% oxygen before rapid-sequence induction of general anesthesia for cesarean delivery. However, another study reported a more rapid onset of hypoxemia in patients who used 4-DB than patients who used 3 minutes of tidal-volume breathing of 100% oxygen. Goldberg et al. evaluated the use of both techniques in morbidly obese nonpregnant patients undergoing gastric bypass surgery. The techniques provided similar increases in PaO₂, but patients who used the 3-minute technique showed evidence of slight retention of CO₂. The investigators speculated that a blunted ventilatory response to CO₂ contributed to the increase in PaCO₂. Later data from a study in 20 pregnant volunteers (at 36 to 38 weeks’ gestation) compared 3 minutes of tidal-volume breathing with 4-DB or eight deep breaths in 1 minute (8-DB) of 100% oxygen by measuring end-tidal fractional oxygen concentration (FETO₂) after preoxygenation. An FETO₂ value of 90% or greater was achieved in 76% of women after either the 3-minute or the 8-DB method, compared with only 18% of women after the 4-DB method of preoxygenation. The investigators concluded that for emergency cesarean delivery using general anesthesia, the 8-DB method was as effective as the 3-minute tidal volume method of preoxygenation and was more quickly performed.

It is wise to apply a tight-fitting face mask and administer 100% oxygen as soon as the patient enters the operating room; this maneuver helps achieve denitrogenation while the patient is moved to the operating table and other preparations are being made. It then seems reasonable to let circumstances dictate the selected method of denitrogenation. When the 3-minute tidal volume breathing technique is selected, the anesthesia provider should encourage the patient to take several deep breaths. In urgent situations, such as emergency cesarean delivery for maternal hemorrhage, the patient should be instructed to take eight deep breaths (the 8-DB method) to extend the safe interval before oxyhemoglobin desaturation occurs. When time allows, the 8-DB method is preferred over the 4-DB method.

**Induction and maintenance of anesthesia.** The dose of intravenous induction agents should be based on lean body weight rather than total body weight. This practice will avoid excessive doses of drug with subsequent adverse effects. Propofol 2 to 2.8 mg/kg, thiopental 4 to 5 mg/kg, or other induction agents can be used according to availability, clinical circumstances, and anesthesia provider preference. All these agents will cross the placenta and can affect the neonate.

Succinylcholine in doses of 1.0 to 1.5 mg/kg is commonly used for rapid-sequence induction and tracheal intubation in obese parturients. Lemmens and Brodsky compared the efficacy of succinylcholine in dosing regimens of 1 mg/kg based on ideal body weight, lean body weight, and total body weight in morbidly obese nonpregnant patients. The third regimen (1 mg/kg total body weight) was superior for providing complete neuromuscular paralysis and predictable effects.
laryngoscopic conditions in almost every patient, whereas intubating conditions were poor in one-third of the patients dosed according to ideal body weight. The investigators also noted that “none of these dosing regimens will provide…a safe (short) duration of apnea.”

Rocuronium at a dose of 1 to 1.2 mg/kg provides equivalent intubating conditions to succinylcholine 1 mg/kg. However, this dose range is associated with a significantly prolonged duration of neuromuscular blockade. In obese patients, the dose of rocuronium should be based on ideal body weight. Sugammadex will effectively reverse high-dose rocuronium (1.2 mg/kg) in 2 minutes. Sugammadex has been used successfully in obstetric patients with no major adverse maternal or neonatal effects. The optimal dosing regimen in obese patients is not clear; two studies in nonpregnant obese patients suggested that sugammadex dosing can be based on ideal body weight plus 40% or on corrected body weight: ideal body weight + 0.4(total body weight – ideal body weight). However, its use has not been specifically studied in obese parturients, and its safety in this patient population remains to be confirmed. Inadequate reversal of neuromuscular blockade in an obese parturient and recu-
larization in another obese patient undergoing bariatric surgery have been reported following administration of sugammadex for reversal of rocuronium-induced neuromuscular blockade, highlighting the importance of appropriate dosing and vigilance in ensuring adequate recovery in this patient population.

Maintenance of anesthesia is usually achieved with a volatile halogenated agent with or without nitrous oxide. No evidence suggests that obesity alters the minimum alveolar concentration (MAC) of volatile halogenated anesthetic agents in pregnant women. In theory, the body fat reservoir could increase the threat of biotransformation of volatile halogenated agents, which would increase the risk for organ toxicity. Isoflurane is an appropriate choice for morbidly obese parturients owing to its limited biotransformation. Desflurane and sevoflurane are associated with a shorter time to extubation than isoflurane in obese patients, although the difference may not be clinically relevant.

Morbidly obese patients may require administration of a higher inspired oxygen concentration and may not tolerate usual concentrations of nitrous oxide. Moreover, general anesthesia reduces FRC. The supine and Trendelenburg positions further decrease FRC, thus increasing the risk for intraoperative hypoxemia. The following strategies have been recommended to reduce the risk for small airway closure, atelectasis, and hypoxemia in obese patients: (1) use of inspired oxygen concentration of less than 0.8, (2) ventilation with tidal volumes ranging from 6 to 10 mL/kg ideal body weight, (3) increasing the respiratory rate to maintain physiologic PaCO₂, (4) use of manual or automated periodic lung inflation (i.e., a recruitment maneuver), and (5) application of positive end-expiratory pressure (approximately 10 cm H₂O).

Emergence from general anesthesia is a critical period. Indeed, maternal deaths from hypoventilation and airway obstruction have been reported during emergence and recovery from general anesthesia. It is imperative that the patient is fully awake with complete reversal of neuromuscular blockade before tracheal extubation, which preferably should be performed in the semi-upright position to minimize diaphragmatic compression by abdominal viscera. Trained personnel should provide postoperative care before the discharge of the patient to the ward.

**POSTOPERATIVE COMPLICATIONS**

Obesity increases the risk for postoperative complications such as endometritis, urinary tract infection, wound infection, wound dehiscence, peripheral nerve injury, hemorrhage, deep vein thrombosis, pulmonary thromboembolism, atelectasis, pneumonia, respiratory depression, hypoxemia, tracheal reintubation, myocardial infarction, cardiac arrest, and maternal death.

The combination of obesity, OSA, general anesthesia, and opioid administration may increase the risk for opioid-induced respiratory depression. In a report on maternal mortality in Michigan, Mhyre et al. found that all anesthesia-related maternal deaths from airway obstruction or hypoventilation occurred during emergence and recovery, with obesity identified as a significant risk factor for these complications. The American Society of Anesthesiologists has issued Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea, which include recommendations for the preoperative, intraoperative, and postoperative management of these patients (Box 49.1). These recommendations are not intended specifically for pregnant women, but they do provide some guidance for the care of the obese parturient with OSA undergoing cesarean delivery.

**POSTOPERATIVE CARE**

**Postoperative Analgesia**

Adequate postoperative analgesia is crucial to facilitate early mobilization, thereby reducing the risk for thromboembolic and pulmonary complications. However, the ideal analgesic regimen in the obese parturient remains unclear. Neuraxial morphine has been shown to provide superior analgesia to that provided by parenteral and oral opioids after cesarean delivery, at the expense of increased opioid-related side effects such as pruritus and nausea. There is a concern, however, that obese patients might be at greater risk for respiratory depression after neuraxial opioid administration, although there are few data. In a series of 856 patients who received intrathecal morphine 0.2 mg combined with hyperbaric bupivacaine for cesarean delivery, respiratory depression (defined as an SaO₂ of 85% or less and/or a respiratory rate of 10 breaths per minute or less) occurred in 8 patients, all of whom were obese. Conversely, a large retrospective study including 5036 parturients who received neuraxial morphine, 63% of whom were obese, did not identify any instances of respiratory depression, defined as need for naloxone or rapid response team calls for respiratory complications. The risk for sedation and respiratory depression might be greater...
BOX 49.1 American Society of Anesthesiologists Practice Guidelines for Perioperative Management of Patients with Obstructive Sleep Apnea

Preoperative
- Preoperative initiation of continuous positive airway pressure (CPAP) should be considered, particularly if obstructive sleep apnea (OSA) is severe.
- Patients with known or suspected OSA may have a difficult airway and therefore should be managed according to the ASA Practice Guidelines for Management of the Difficult Airway* or other similar airway management guidelines.

Intraoperative
- The potential for postoperative respiratory compromise should be considered.
- Neuraxial anesthesia (spinal/epidural/combined spinal-epidural) should be considered.
- Patients at increased perioperative risk from OSA should be extubated while awake.
- Full reversal of neuromuscular blockade should be verified before tracheal extubation.
- When possible, extubation and recovery should be carried out in the lateral, semi-upright position, or other non supine position.

Postoperative
- Postoperative analgesia: regional analgesic techniques should be considered to reduce or eliminate the requirement for systemic opioids in patients at increased perioperative risk from OSA.
- If neuraxial analgesia is planned, the anesthesia provider should weigh the benefits (improved analgesia, decreased need for systemic opioids) and risks (respiratory depression from rostral spread) of using an opioid or opioid–local anesthetic mixture compared with a local anesthetic alone.
- If a patient-controlled systemic opioid analgesic technique is used, a continuous background infusion should be used with extreme caution or avoided entirely.
- Nonsteroidal antiinflammatory agents and other modalities should be considered if appropriate to reduce opioid requirements.
- Concurrent administration of sedative agents increases the risk for respiratory depression and airway obstruction.
- Supplemental oxygen should be administered continuously to all patients who are at increased perioperative risk from OSA until they are able to maintain their baseline oxygen saturation while breathing room air.
- Hospitalized patients at increased risk for respiratory compromise from OSA should be monitored with continuous pulse oximetry after discharge from the post–anesthesia care unit.


with systemic opioids compared with neuraxial opioids, although there are no data comparing the risk for respiratory depression between the two routes of opioid administration in this patient population. In patients who have not received neuraxial opioid analgesia, systemic opioids are best administered using an intravenous patient-controlled analgesia (PCA) system. With all routes of opioid administration, vigilance and appropriate postoperative monitoring are essential in the obese patient who may have undiagnosed OSA and be at a greater risk for opioid-induced respiratory depression. The use of sedative agents or magnesium sulfate in the postoperative period may also increase the risk for respiratory depression.

A multimodal analgesic regimen including regular administration of a nonsteroidal antiinflammatory drug and acetaminophen may contribute to opioid sparing and improve postoperative analgesia (see Chapter 27). A systematic review of randomized controlled trials found that local anesthetic wound infiltration was associated with a reduction in opioid consumption and pain scores in women undergoing cesarean delivery, but did not reduce the incidence of opioid-related side effects. There are limited data on the use of this technique in women receiving neuraxial morphine, but the review suggested that opioid sparing was only achieved in women who did not receive neuraxial morphine. Analgesia was better with catheter placement below compared with above the fascia.

Similarly, transversus abdominis plane (TAP) block was found to produce opioid sparing and reduce pain scores and opioid-related adverse effects in women who did not receive neuraxial morphine as part of their neuraxial anesthetic technique. However, performance of TAP block may be technically challenging in the obese parturient with a large abdominal panniculus. Recently, quadratus lumborum block was reported to be effective for postcesarean analgesia; one study found greater opioid sparing with this technique compared with TAP blocks. Some approaches to the quadratus lumborum block may be technically easier than the TAP block in obese parturients. Patient-controlled epidural analgesia (PCEA) may be another option. Investigators found that PCEA with ropivacaine provides analgesia comparable to that provided by epidural morphine, but with more motor block, thus delaying patient mobilization. PCEA techniques have not been specifically studied in obese parturients.

Thromboprophylaxis
The American College of Chest Physicians (ACCP) published guidelines for antithrombotic therapy in the parturient. They used major and minor risk factors to identify women at increased risk for venous thromboembolism after cesarean delivery; obesity (BMI greater than 30 kg/m²) was classified as a minor risk factor. Thromboprophylaxis was recommended in the presence of one major risk factor (risk for thromboembolism greater than 3%) or two minor risk factors (combined risk greater than 3%) (see Box 38.1). In the setting of emergency cesarean delivery (a minor risk factor), an additional minor risk factor (e.g., obesity) results in a risk greater than...
3%, and, therefore, mechanical or pharmacologic thromboprophylaxis is recommended.

The ACOG thromboembolism guidelines do not specifically address the obese parturient. Instead, they recommend perioperative mechanical thromboprophylaxis for all women, with the addition of low-molecular-weight heparin (LMWH) in selected high-risk parturients, without specifying obese women. In the United Kingdom, the Royal College of Obstetricians and Gynaecologists’ (RCOG) guidelines recommend thromboprophylaxis for at least 10 days with LMWH for all women with the addition of low-molecular-weight heparin (LMWH) perioperative mechanical thromboprophylaxis for all women, without specifying obese women.

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Psychiatric disorders occur commonly during pregnancy and can have significant effects on the mother, child, and family, and important economic costs to society. Suicide is a major cause of maternal mortality. Women have higher rates than men of many psychiatric disorders, such as anxiety, feeding and eating disorders, and depression; the reproductive years coincide with the greatest period of risk. Management can be difficult and may be complicated by variable presentation of symptoms, social stigmas, confusion with normal symptoms of pregnancy, and inconsistent published treatment recommendations. Further, pregnant women with psychiatric disorders may resist drug treatment because of their desire to avoid fetal harm. Psychiatric disorders during pregnancy may be associated with other aspects of poor maternal health and deficient prenatal care, which may affect anesthesia care. Women with a history of previous psychiatric hospitalization or an identified mental illness are at increased risk for cesarean delivery.

CLASSIFICATION

Internationally, psychiatric disorders are most commonly classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) produced by the World Health Organization. In the United States, a clinical modification of ICD is used (ICD-10-CM). Although in the United States ICD is the official diagnostic system for mental disorders, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association (APA), is widely used. These classification systems provide standardized language and criteria for diagnosis and classification of mental disorders; however, definitions may not have precise boundaries and there may be considerable overlap between “mental” and “physical” disorders.

EPIDEMIOLOGY

It has been estimated that more than 500,000 pregnancies each year in the United States involve women who have a psychiatric illness that either predates or emerges during pregnancy. Psychiatric illness occurs in approximately 15% of pregnant women, and 10% to 13% of fetuses are exposed...
to psychotropic drugs. The World Health Organization has reclassified maternal suicide as a direct cause of maternal death, and the Confidential Enquiries into Maternal Deaths in the United Kingdom has identified suicide as an important cause of maternal mortality and the leading cause of direct maternal deaths occurring within 1 year after the end of pregnancy.

Pregnancy is widely considered a time of increased vulnerability to psychiatric disorders. However, studies suggest that the prevalence is similar between pregnant and nonpregnant women. A conspicuous exception is the risk for major depressive disorder, which is increased during the postpartum period. Identified risk factors for developing psychiatric disorders during pregnancy include younger age, unmarried status, exposure to traumatic or stressful life events, pregnancy complications, and poor overall health. Treatment rates among pregnant women with psychiatric disorders are often low.

**MOOD DISORDERS**

Mood disorders include depressive disorders and bipolar disorders ("manic-depressive disorders").

**Major Depressive Disorder**

The DSM-5 has defined criteria for major depressive disorder that are based on the presence, within the same 2-week period, of specific symptoms that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; these symptoms should not be the result of the physiologic effects of a substance. Although depression is recognized as being relatively common during pregnancy, many of its symptoms (e.g., weight gain, appetite changes, sleep disturbances, fatigue) must be differentiated from symptoms that may occur during normal pregnancy. Risk factors for depression during pregnancy include a history of depression or bipolar disorder, childhood mistreatment, being a single mother or having more than three children, marital problems, unwanted pregnancy, smoking, low income, age younger than 20 years, poor social support, and domestic violence. The risk for major depressive illness is increased in women who have a miscarriage (i.e., early pregnancy loss); this most frequently occurs in the first month after miscarriage and is more likely to occur in women who are childless or who have a prior history of major depressive disorder. Depression during pregnancy is associated with an increased risk for poor obstetric outcomes such as miscarriage, preterm birth, and low birth weight.

**Bipolar (Manic-Depressive) Disorder**

Patients with bipolar disorder (BPD) have episodes of major depression with other distinct periods of mania or hypomania. A strong familial association exists. DSM-5 diagnostic criteria for mania specify a distinct period when there is abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy, which lasts at least 1 week and is present most of nearly every day or requires hospitalization. Specific symptoms are listed, which should be severe enough to cause marked impairment in occupational functioning, social activities, and interpersonal relationships and necessitate hospitalization or have psychotic features; symptoms should not meet criteria for a mixed episode and should not be caused by substance abuse or general medical conditions (e.g., hyperthyroidism). BPD in pregnancy is particularly important because there is a strong link between discontinuation of medication and relapse of BPD and a relatively high suicide rate among patients. Treatment of BPD typically consists of mood stabilizer and antipsychotic medication, with psychotherapy as an adjunct. Electroconvulsive therapy (ECT) is very effective for patients with BPD and severe depression.

**Postpartum Depression**

Postpartum depression describes a major depressive episode that occurs in the first 4 to 6 weeks after birth. Symptoms do not differ from those of depression occurring at other times. There may be accompanying psychotic features, which are thought to be more common in nulliparous women, and there is a high risk for recurrence in subsequent pregnancies. It is important to differentiate postpartum depression from the "baby blues," which affects up to 70% of women in the first 10 days after delivery and is transient without functional impairment. It is also important to differentiate postpartum depression from delirium that arises from physical causes. In a systematic review, Robertson et al showed that the strongest predictors of postpartum depression were (1) depression, anxiety, or stressful life events occurring during pregnancy or the early puerperium; (2) low levels of social support; and (3) previous history of depression. Biologic effects such as hormonal changes and psychological and social role changes that occur with childbirth may increase the risk for postpartum depression. In a retrospective study, Ding et al showed an association between use of labor epidural analgesia and a decreased risk for postpartum depression; further research is required to confirm these findings.

**Postpartum Psychosis**

Postpartum psychosis occurs within 2 weeks of approximately 1 to 2 per 1000 live births; a relatively high risk continues for the first 3 months postpartum. The risk is higher in patients with a history of BPD or a history of previous postpartum psychosis, as well as in women with major depression and schizophrenia. Typical features include prominence of cognitive symptoms such as disorganization, confusion, impaired sensorium, disorientation, and distractibility. Infanticide is rare and may be associated with command hallucinations to kill the infant or delusions that the infant is possessed.

**ANXIETY DISORDERS**

Anxiety disorders affect women twice as often as men and are the most common psychiatric disorders during pregnancy and the postpartum period. There is a wide range of anxiety
disorders, including panic disorder, separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder. Closely related to anxiety disorders are trauma- and stressor-related disorders, which includes posttraumatic stress disorder and obsessive-compulsive disorder. Clinical features of anxiety disorders in pregnant women are similar to those in nonpregnant women, but concern about the pregnancy and the fetus may be the predominant feature.

Panic Disorder
Panic disorder is characterized by the occurrence of recurrent, unexpected panic attacks. Affected women experience discrete episodes of intense fear or discomfort in the absence of a true danger; these episodes are accompanied by somatic or cognitive symptoms such as palpitations, sweating, shaking, dyspnea, choking, chest pain, nausea, paresthesias, chills, and/or flushes. Typically there is a rapid onset and peak of symptoms that may be accompanied by an urge to escape. It is important to be aware of the possibility that panic attacks may occur during preparation of a patient for cesarean delivery. Panic attacks with hyperventilation may mimic local anesthetic systemic toxicity. Patients with panic disorder often have comorbid major depression.

Posttraumatic Stress Disorder
Posttraumatic stress disorder (PTSD) occurs after the experience of a traumatic event that evokes intense fear or helplessness and has been estimated to occur in 4% to 6% of women in pregnancy or postpartum. PTSD may arise during the perinatal period, or preexisting PTSD can be exacerbated during pregnancy. Symptoms of PTSD are more common after emergency cesarean delivery than after other modes of delivery, and PTSD has resulted from (1) awareness during general anesthesia, (2) inadequate neuraxial anesthesia for cesarean delivery, and (3) inadequate pain control during vaginal delivery. The risk for PTSD may be increased if the pregnancy has resulted from rape or if memories of sexual trauma are triggered. It has been suggested that the childbirth experience itself can precipitate PTSD with a resulting fear of cesarean delivery.

Obsessive-Compulsive Disorder
Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions (intrusive thoughts or images) and compulsions (repetitive or ritualistic behaviors or thought patterns). OCD is more common in pregnant and postpartum women than in the general population. Obsessions most frequently center around contamination or aggression toward the child and may lead to compulsive cleaning, checking, or avoidance of the child. Care should be taken to identify infanticidal ideation.

FEEDING AND EATING DISORDERS
There are conflicting data on the effect of pregnancy in patients with feeding and eating disorders, which include anorexia nervosa and bulimia nervosa as well as pica, rumination disorder, avoidant/restrictive food intake disorder, binge-eating disorder, other specified feeding or eating disorder, and unspecified feeding or eating disorder. Improvement in symptoms during pregnancy has been described, but conversely, pregnancy may result in body image preoccupations and unfavorable eating habits that may develop into a frank eating disorder. Although fertility is reduced in patients with anorexia nervosa, patients may still conceive. Patients with eating disorders have a higher risk for psychiatric comorbidity, including anxiety and postpartum depression, and are at greater risk for fetal growth restriction and cesarean delivery.

SCHIZOPHRENIA SPECTRUM AND OTHER PSYCHOTIC DISORDERS
These disorders include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. Defining features include abnormalities in one or more of the following areas: hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. In schizophrenia, the disorder lasts for at least 6 months, with at least one month of active symptoms.

OTHER DISORDERS

Personality Disorders
Personality disorders have high prevalence rates of approximately 10% in the general population and up to 40% among psychiatric patients. The DSM-5 lists 10 specific personality disorders that are grouped into three clusters based on descriptive similarities. Patients in cluster A (paranoid, schizoid, schizotypal) appear odd or eccentric; patients in cluster B (antisocial, borderline, histrionic, narcissistic) appear dramatic, emotional, or erratic; and patients in cluster C (avoidant, dependent, obsessive-compulsive) appear anxious and fearful. There is also one further category, personality disorder not otherwise specified. The DSM-5 also provides an alternative dimensional model for personality disorders based on both personality functioning and pathologic personality traits that takes the perspective that personality disorders represent maladaptive variants of personality.
traits that merge into normality and into one another. This accounts for the observation that patients who meet criteria for a specific personality disorder frequently also meet criteria for other personality disorders.

**Pseudocyesis**

*Pseudocyesis* is a clinical syndrome in which a woman firmly believes that she is pregnant in the absence of a true gestation. Patients may develop convincing signs and symptoms suggestive of pregnancy, including abdominal enlargement and menstrual disturbance. Diagnosis can be made using a pregnancy test and ultrasonography. Physical diagnoses should be excluded. For example, tumors such as bronchogenic carcinoma or ovarian carcinoma may produce hormones (e.g., human chorionic gonadotrophin [hCG]) that can cause secondary amenorrhea, which may be confused with pregnancy.

**Denial of Pregnancy**

In contrast to pseudocyesis, denial of pregnancy is more common, with an estimated incidence of 1 in 400 to 516 pregnancies. It may be associated with adverse outcomes, including psychological stress, unassisted delivery, and infanticide. Patients who are identified should be referred for psychiatric assessment.

**Substance Abuse**

Substance abuse during pregnancy is discussed in Chapter 53.

**MANAGEMENT OF PSYCHIATRIC DISORDERS IN PREGNANCY**

**General Considerations**

Guidelines for the management of pregnant women with psychiatric disorders have been published by the American College of Obstetricians and Gynecologists (ACOG) and the APA, and guidelines are also available from the United Kingdom and Australia.

Screening for anxiety and depression in pregnancy and in the postpartum period is effective for diagnosing perinatal mental health problems. This can be achieved through face-to-face screening and online. Pregnant women should also be screened for substance abuse and domestic violence.

Treatment options for different psychiatric disorders overlap and include nonpharmacologic and pharmacologic therapies. Data are limited on pregnancy-specific efficacy of treatments, but in general, response in pregnant patients is thought to be similar to that in nonpregnant patients. A family-centered approach is recommended, and cultural and social context should be taken into account. Nonpharmacologic therapies are especially important because of maternal preferences and concerns about potential effects of drugs on the fetus and infant. Although there is often concern about potential harmful effects of psychotropic drugs given during pregnancy and lactation, it appears that most psychotropic drugs are relatively safe, and there is a significant risk for exacerbation of illness and serious harm associated with cessation or withholding of psychotropic drugs.

Because diabetes, obesity, smoking, and substance abuse are more common in people with psychiatric disorders, it can be difficult to separate the effects of psychiatric drugs on the fetus from the effects of these other factors. Further, some of the risks associated with psychiatric drugs may be attributable to the fact that women who take medication for psychiatric disorders are likely to have more severe disease than women not on medication (i.e., confounding by indication).

General recommendations for the management of women with psychiatric disorders include the following: (1) a psychiatric history should be identified prenatally and, even if affected patients are well, they should be frequently monitored and supported during pregnancy and the first few weeks postpartum; (2) psychiatric services should have priority-care pathways for pregnant and postpartum women; and (3) care by multiple psychiatric teams should be avoided. Conversely, care should be taken to avoid misattribution of physical symptoms to psychological causes in patients with no psychiatric history and other concurrent disease. All patients with psychiatric disorders, particularly those with acute or postpartum psychosis, should be carefully screened for thoughts of harm to themselves and/or their infants.

A multidisciplinary approach is essential in the management of pregnant patients with psychiatric disorders, especially because many anesthesia providers may not be familiar with management of these patients. Patients who are noncooperative or violent may be challenging and require patience, compassion, and emotional support. Flexibility in management is important. For example, general anesthesia may sometimes be required if neuraxial anesthesia is considered impractical or unsafe.

**Psychological and Psychosocial Therapies**

Psychological and psychosocial interventions include cognitive behavioral therapy, interpersonal therapy, nondirective counseling, and peer support; these strategies are particularly effective for management of anxiety disorders and depression. Promising interventions for postpartum depression include professionally-based postpartum home visits, lay- or peer-based postpartum telephone support, and interpersonal psychotherapy.

**Psychotropic Drugs**

There is often concern about potential harmful fetal/neonatal effects of psychotropic drugs given during pregnancy and lactation. However, because of the difficulties of performing experimental studies in this area, much of the available evidence is based on observational studies that are unable to differentiate association and causation. The decision to initiate or continue a pregnant woman on psychotropic medication requires the physician and patient to weigh carefully the possible risks associated with medications versus the serious potential consequences of inadequately treated disease. Psychiatric medications should generally be continued in pregnant women presenting for anesthesia and surgery.

Box 50.1 outlines principles for the use of psychiatric medications during pregnancy. The use of nonanesthetic
As a mainstay therapy for depression and anxiety, these drugs were replaced by serotonin reuptake inhibitors (SRIs), which are newer agents. Tricyclic antidepressants have largely fallen out of favor owing to their numerous side effects and potential dangers, including seizures, delirium, hyperthermia, and arrhythmias, and were commonly used and have generally been avoided in pregnancy. Previously, psychiatric medications during pregnancy and lactation is discussed in Chapter 14. Data from American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 87. Use of psychotropic medications during pregnancy and lactation. Obstet Gynecol. 2008;111:1001–1020; Levey L, Ragan K, Hower-Hartley A, et al. Psychiatric disorders in pregnancy. Neurol Clin. 2004;22:863–893; Howard LM, Meginn-Viggs O, Symington I, Pilling S. Antenatal and postnatal mental health: summary of updated NICE guidance. BMJ. 2014;349:g7394.

BOX 50.1 General Principles Related to the Use of Psychiatric Drugs in Pregnancy

- Use nonpharmacologic therapy when possible, but do not assume that it is always better to avoid psychotropic drugs.
- Be aware that discontinuing medication exchanges the fetal and neonatal risks of drug exposure for the risks of untreated maternal illness.
- Be aware that all psychotropic drugs cross the placenta and pass into breast milk, and that the major risk for teratogenesis occurs during embryogenesis (i.e., 3 to 8 weeks’ gestation).
- Use drugs with largest up-to-date evidence of safety for the mother and fetus.
- Prescribe the smallest number of drugs possible, preferring monotherapy to multiple medications.
- Use the lowest effective doses, and minimize changing drug regimens.
- Prefer medications with fewer metabolites, higher protein binding, and fewer drug interactions.
- Monitor mental state and adjust doses as pregnancy progresses because of alteration in pharmacokinetics.
- Involve the mother and partner/family in decisions, and document decisions.

Antidepressants are the most common psychotropic drugs prescribed in pregnancy. Previously, tricyclic antidepressants were commonly used and have generally been considered safe to use in pregnancy. These drugs may have anticholinergic side effects, including dilated pupils, agitation, seizures, delirium, hyperthermia, and arrhythmias, and they have a greater fatality risk after overdose compared with newer agents. Tricyclic antidepressants have been largely replaced by serotonin reuptake inhibitors (SRIs), which are a mainstay therapy for depression and anxiety. These drugs include selective serotonin reuptake inhibitors (SSRIs) such as sertraline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), and citalopram (Celexa), and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as desvenlafaxine (Pristi/Khedezla), duloxetine (Cymbalta), levomilnacipran (Fetzima) and venlafaxine (Effexor XR). Much research has investigated the possible association between the use of SRIs in pregnancy and an increased risk for congenital abnormalities including cardiovascular defects, persistent pulmonary hypertension, and postnatal adaptation syndrome; although the overall risk is considered to be small, the subject remains controversial.35 Reassuring results from a recent large retrospective study from Sweden showed that, after accounting for confounding variables, first-trimester exposure to SRIs was associated with a small increased risk for preterm birth but no increased risk for a small for gestational age infant at delivery, autism spectrum disorder, or attention-deficit/hyperactivity disorder.36 Serotonin syndrome (i.e., agitation, restlessness, hallucinations, increased body temperature, vomiting) may occur with an overdose or a combination of serotonergic drugs.37

Routine prescription of benzodiazepines for pregnant women is typically avoided, except for short-term treatment of extreme anxiety and agitation, because of concerns for risks including oral clefts, floppy baby syndrome, and neonatal withdrawal syndrome.13

Lithium is a foundation therapy for management of BPD. Early studies reported that use of lithium in early pregnancy was associated with an increased risk for congenital malformations, with particular concern for cardiac abnormalities, especially Ebstein’s anomaly. Although the risk now appears to be less than initially thought, it has been recommended that women who are exposed to lithium in the first trimester undergo fetal echocardiography. Exposure in later gestation has been associated with fetal and neonatal diabetes insipidus, polycythaemia (thought to occur from fetal diabetes insipidus), thyroid dysfunction, cardiac arrhythmias, hypoglycemia, preterm delivery, and floppy baby syndrome.13 Renal clearance of lithium is increased in pregnancy; therefore, serum levels should be closely monitored in pregnant women who are taking lithium. Discontinuation of lithium is associated with a high risk for recurrent illness, particularly in the postpartum period.

Anticonvulsant drugs are often used as mood stabilizers in patients with BPD. Valproate use in pregnancy is associated with a dose-related risk for many congenital anomalies (e.g., craniofacial, limb, cardiovascular abnormalities) and a variable risk for cognitive impairment.1 Fetal valproate syndrome, which includes fetal growth restriction, facial dysmorphism, and limb and heart defects, has been described.13 Carbamazepine has also been associated with congenital abnormalities, although with less frequency or severity compared with valproate.1 Fetal carbamazepine syndrome, which includes facial dysmorphism and fingernail hypoplasia, has been described.13 Lamotrigine appears to be associated with less fetal risk than occurs with valproate and carbamazepine.10,13 Folate supplementation should be offered to patients taking anticonvulsants to reduce the risk for neural tube defects.

Typical antipsychotic drugs (e.g., haloperidol, thioridazine, fluphenazine, perphenazine, chlorpromazine, trifluoperazine) have a long history of use in pregnant patients and generally have minimal teratogenic effects.13 The phenothiazines are also used for their antiemetic effects. Fetal and neonatal toxicity after maternal exposure can include dyskinesia, extrapyramidal side effects, neonatal jaundice, and postnatal intestinal obstruction. The neuroleptic malignant syndrome is of particular interest to anesthesia providers because of its similarity to malignant hyperthermia. Features
include hyperthermia, rigidity, mental status alteration, creatine kinase elevation, sympathetic nervous system lability, tachycardia, and tachypnea. Treatment is largely supportive and includes discontinuation of triggering agents, antipyretics, cooling, rehydration, and management of autonomic instability. Use of dantrolene, bromocriptine, and amantadine has been described.

Atypical antipsychotic drugs (e.g., clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole) are now commonly used for schizophrenia and also for BPD, OCD, and resistant depression. Although these drugs are well tolerated, fewer data about reproductive safety are available, when compared with older drugs.

Drug Interactions

A number of drug interactions involving psychiatric drugs are relevant to anesthesia providers. The most important of these involve monoamine oxidase inhibitors (MAOIs), which include older irreversible drugs (e.g., phenelzine, tranylcypromine) and newer reversible drugs (e.g., selegiline, moclobemide). Potential interactions include (1) hypertension after administration of an indirect-acting vasopressor (e.g., ephedrine, metaraminol), which results from increased norepinephrine concentration in sympathetic nerve endings; and (2) excitatory interactions associated with serotonin toxicity. The latter are characterized by clonus, hyperreflexia, hyperthermia, and agitation, and may be precipitated by co-administration of an MAOI and an SRI. Of note, phenylpiperidine opioids, especially meperidine (pethidine), but also tramadol, methadone, and dextromethorphan, are weak serotonin reuptake inhibitors and have been implicated in toxic reactions associated with MAOIs, including hyperpyrexia coma. Irreversible MAOIs should be stopped 2 weeks before administration of anesthesia to allow regeneration of MAO and restoration of normal monoamine metabolism, and reversible MAOIs should be stopped for 24 hours before administration of anesthesia.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is considered an important treatment option in the pregnant patient with psychiatric disease, especially when balancing the risk for morbidity from psychiatric illness and the potential adverse effects of psychiatric drugs. Indications include major unipolar or bipolar depressive episodes, mania, and certain acute schizophrenic exacerbations. Acute suicide risk, poor response to medications, and patient preference may also affect the decision to use ECT. Contraindications include anticipated intolerance of associated physiologic changes that result from autonomic activation during ECT (e.g., increased intracranial pressure). Relative contraindications include hypertensive disease and impaired uteroplacental perfusion.

There is a paucity of controlled data evaluating the use of ECT in pregnancy, with most information coming from case series. The APA has endorsed the use of ECT in all three trimesters of pregnancy. The use of ECT in pregnancy has been considered effective with low risk to the mother and fetus. However, a recent systematic review reported that adverse events such as decreased fetal heart rate, uterine contractions, and preterm labor occurred in 29% of cases. ECT for pregnant patients should be administered in a facility that can handle fetal emergencies. Anesthetic agents that have been used include thiopental, methohexital, propofol, succinylcholine, and anticholinergics. Suggested guidelines for ECT during pregnancy are summarized in Box 50.2. Denitrogenation (preoxygenation), left uterine displacement, and fetal heart rate and uterine contraction monitoring should be used. Pharmacologic aspiration prophylaxis and tracheal intubation should be considered in patients with symptoms of gastroesophageal reflux. Some anesthesia providers contend that tracheal intubation should be performed after 20 weeks’ gestation, when the enlarging uterus has arisen out of the pelvis.

KEY POINTS

- Psychiatric disorders occur commonly during pregnancy, but their prevalence is often underestimated and underappreciated.
- Anxiety disorders are the most common psychiatric disorders in pregnant women.
- The risk for major depressive disorder is increased during the postpartum period.
- Suicide is an important cause of maternal mortality.
- Psychological and psychosocial interventions are effective for many psychiatric diseases in pregnancy.
- When managing pregnant patients with psychiatric disorders, the risks of withholding psychiatric drugs because of concerns for harmful fetal effects must be balanced against the potential consequences of untreated disease.
• Patients with a previous psychiatric history should be identified prenatally and frequently monitored and supported during pregnancy and the first few weeks postpartum. Psychiatric services should have priority-care pathways for pregnant and postpartum women, and care by multiple psychiatric teams should be avoided.
• A multidisciplinary approach is essential in the management of pregnant patients with psychiatric disorders, and the partner and family should be involved with decisions.

REFERENCES

“Children of women with renal disease used to be born dangerously or not at all—not at all if their doctors had their own way.” This statement describes early experiences with maternal renal disease and pregnancy outcome. It remains true that renal disease, either preexisting or occurring during gestation, may impair maternal and fetal health. Experience and investigations during the past three decades have significantly improved both maternal and neonatal outcomes in pregnant women with renal disease.

PHYSIOLOGIC CHANGES IN PREGNANCY

A review of the renal physiologic changes that occur during normal pregnancy is helpful to understand and evaluate coexisting renal disorders (see Chapter 2). Early in gestation, increased intravascular volume leads to renal enlargement. Hormonal changes result in dilation of the renal pelvis and ureters; dilation often is accompanied by decreased ureteral peristalsis. Dilated uterine and ovarian veins, and the gravid uterus, may obstruct ureter drainage at the pelvic brim. Together, these changes predispose pregnant women to vesicoureteric reflux and ascending infection. Alterations in glomerular hemodynamics and tubular function also occur. Increased cardiac output and decreased intrarenal vascular resistance cause an 80% increase in renal blood flow and a 50% increase in glomerular filtration rate (GFR) during pregnancy. These changes are somewhat less pronounced near term. Because of the increased GFR, a serum creatinine concentration greater than 0.6 to 0.8 mg/dL and a blood urea nitrogen (BUN) concentration greater than 8 to 9 mg/dL (upper limit of normal for the pregnant patient) suggest renal insufficiency in the pregnant woman. Tubular sodium reabsorption and osmoregulation are reset, allowing a “physiologic hypervolemia” during gestation. Modest proteinuria, up to 300 mg in 24 hours, also occurs during pregnancy.

Urinary tract infections (see Chapter 36) and renal dysfunction associated with hypertensive disorders of pregnancy (see Chapter 35) are discussed elsewhere in this text.

RENAL PARENCHYMAL DISEASE

Definition and Pathophysiology

Renal parenchymal disease consists of two general groups of disorders, glomerulopathies and tubulointerstitial disease. Glomerulopathies are further subdivided into disorders that involve inflammatory or necrotizing lesions—the nephritic syndromes—and disorders that involve abnormal
permeability to protein and other macromolecules—the nephrotic syndromes. More than 20 specific glomerulopathies exist. The nomenclature for these glomerulopathies is complex, and specific diseases are not discussed in detail here. Tubulointerstitial diseases are disorders characterized by abnormal tubular function. They result in abnormal urine composition and concentration but are not characterized by decreased GFR until late in the disease course. The disorders in this category include interstitial nephritis, acute tubular necrosis, multiple myeloma of the kidney, and functional tubular defects such as renal tubular acidosis.

Patients with renal parenchymal disorders may remain asymptomatic for years, and they may exhibit only proteinuria and microscopic hematuria, with little if any evidence of reduced renal function. Spontaneous recovery or improvement with treatment occurs with many glomerulopathies. However, other patients exhibit progressive nephropathy, hypertension, and renal insufficiency. The incidence of kidney disease in pregnancy is approximately 0.12%. In two-thirds of these patients, the disorder results from glomerulopathy, and in one-third, from tubulointerstitial disease.

Diagnosis

Women with preexisting disease may choose to become pregnant without the counsel of their nephrologist. When such patients become pregnant, the obstetrician and nephrologist seek to define the extent of renal involvement. Serial blood pressure measurements are obtained to define the severity of hypertension and the efficacy of current antihypertensive therapy. Creatinine clearance and the level of proteinuria should be determined. Urinalysis yields information about the presence of renal casts and bacteriuria. The determination of serum creatinine and BUN concentrations defines the extent of renal insufficiency. A serum creatinine concentration greater than 0.8 mg/dL, which may be normal in the nonpregnant woman, may represent significant renal insufficiency during pregnancy. Alternatively, the obstetrician may first detect renal dysfunction through routine prenatal screening tests since patients may otherwise be asymptomatic, as symptoms rarely develop until GFR decreases by 25%. If proteinuria, hematuria, or azotemia is detected, a complete biochemical evaluation should be performed.

Both preeclampsia and renal disease may manifest as hypertension, proteinuria, and edema. The distinction between the two disorders is often unclear, especially after 20 weeks’ gestation. Fisher et al. evaluated 176 renal biopsy specimens obtained from hypertensive women immediately postpartum, most of whom had a clinical diagnosis of preeclampsia. The clinicopathologic correlation was poor. Histologic evidence of preeclampsia (e.g., glomerular endotheliosis without hypercellularity) was present in only 65% of these hypertensive women. Primary renal disease was present in 20%, and hypertensive nephrosclerosis occurred in 11%. Nulliparous women (84%) were more likely to have a correct diagnosis of preeclampsia than parous women (38%), further demonstrating the difficulty in making the diagnosis in different patient populations.

Renal tissue biopsy is often used to establish a diagnosis in nonpregnant patients. The decision to perform a kidney biopsy in the parturient is complex, as the value of the clinical information obtained that may guide therapy must be balanced against the risks associated with the procedure. Studies reporting the safety of biopsies are small and heterogeneous. A recent meta-analysis by Piccoli et al. compared complication rates from 243 renal biopsies performed during pregnancy with 1236 performed in the postpartum period. Significant complications occurred in 7% of biopsies performed before delivery compared with 1% in the postpartum period. Most complications were minor and included groin pain as well as hematuria. The authors did report, however, that more serious complications (e.g., bleeding and loin pain) occurred the further along in pregnancy the biopsy was performed and seemed to peak around 25 weeks’ gestation. It should be noted that in 23 of the studies in the meta-analysis, kidney biopsies were performed as a means to characterize morphologies in preeclampsia, a practice that is no longer recommended and may have influenced the subject pool substantially. Given the apparent increase in risk associated with biopsy during pregnancy, it should only be performed in patients with a high likelihood of severe glomerular disease and when definitive diagnosis is critical to guide appropriate and immediate treatment.

Emerging research in the area of biomarkers may further guide treatment and management in this population as well as preclude the need for biopsy. When diagnosis is obtained through antineutrophil cytoplasmic antibodies or through double-stranded DNA antibodies, empiric treatment may begin with steroids, azathioprine, or calcineurin inhibitors in lieu of a kidney biopsy in a variety of the disorders, including lupus nephritis and glomerulonephritis. Novel biomarkers such as soluble urokinase plasminogen activator receptor (suPAR) for focal segmental glomerulosclerosis, M-type phospholipase A2 receptor (PLA2R) in membranous nephropathy, and others have been described in case reports and once further developed may change diagnosis and management.

Effect of Pregnancy on Preexisting Kidney Disease

The extent to which pregnancy affects preexisting renal disease depends on the level of renal insufficiency before pregnancy. Among women with mild antenatal renal insufficiency, pregnancy does not substantially alter the natural course of renal disease. Jungers et al. evaluated the effect of pregnancy on renal function among 360 women with primary glomerulonephritis. During the study period, 171 (48%) women became pregnant. All study subjects had normal renal function at the time of entry into the study, and all patients who became pregnant had normal renal function at conception. In the case-control analysis of the study, pregnancy was not identified as a risk factor for progression to end-stage renal failure. Limardo et al. evaluated 223 women with biopsy-documented IgA nephropathy who had a serum creatinine level greater than 1.2 mg/dL, 136 of whom became
pregnant. Women were observed for a minimum of 5 years (median, 10 years), and pregnancy did not seem to affect long-term outcome of kidney disease or the onset of proteinuria or hypertension.

In contrast, Jones and Hayslett\textsuperscript{14} analyzed the outcome of 82 pregnancies in 67 women with preexisting moderate or severe renal insufficiency (i.e., serum creatinine level greater than 1.4 mg/dL before pregnancy or at the first antepartum visit). The mean ± standard deviation serum creatinine concentration increased from 1.9 ± 0.8 mg/dL in early pregnancy to 2.5 ± 1.3 mg/dL in the third trimester. The prevalence of hypertension rose from 28\% at baseline to 48\% during late pregnancy. Pregnancy-related deterioration of maternal renal function occurred in 43\% of cases. Purdy et al.\textsuperscript{15} also found that greater than 40\% of women with moderate to severe kidney disease had deterioration in renal function caused by pregnancy. Women with a serum creatinine concentration greater than 2.0 mg/dL who became pregnant had a one in three chance of developing dialysis-dependent end-stage renal disease during or shortly after pregnancy.\textsuperscript{16} In summary, the preponderance of evidence seems to demonstrate that while pregnancy exacerbates renal disease, it appears to have a greater effect on those who present with moderate to severe levels of renal dysfunction before pregnancy.

The pathophysiology by which pregnancy exacerbates renal disease is unknown. One hypothesis is that increased glomerular perfusion, which normally accompanies pregnancy, paradoxically causes further injury to the kidneys in patients with preexisting impairment of function. However, this hypothesis is unsupported by published data, which demonstrate no evidence of hyperfiltration (i.e., an initial decline in serum creatinine concentration) during early pregnancy in patients with renal disease. An alternative hypothesis is that preexisting renal disease may induce a cascade of platelet aggregation, microvascular fibrin thrombus formation, and endothelial dysfunction that leads to microvascular injury in the already tenuous kidneys.\textsuperscript{16} In addition to general changes to renal mechanics discussed earlier, exacerbation or improvement of the initial disease process during pregnancy could also alter the long-term course of renal dysfunction.

**Effect on the Mother and Fetus**

Pregnant women with chronic kidney disease (CKD) are at an increased risk for maternal and fetal complications. Nevis et al.\textsuperscript{18} systematically reviewed all published observational studies of women with CKD that included a control group for comparison, excluding retrospective studies. They identified 13 studies between 1966 and 2010 that included at least five women. Maternal complications included gestational hypertension, preeclampsia/eclampsia, and maternal mortality. Adverse fetal outcomes included preterm births, fetal growth restriction (also known as intrauterine growth restriction), small-for-gestational-age infants, neonatal mortality, stillbirths, and low birth weight. Adverse maternal outcomes were found in 12 studies, and when examined in aggregate, their incidence was five times greater than in women without kidney disease. Adverse fetal outcomes were identified in nine studies, and when examined in aggregate, the incidence was two times greater than in the otherwise healthy women. There was no analysis of the variance of magnitude of the effect by specific outcome.

The incidence of obstetric complications is proportional to the extent of preexisting maternal renal disease and preexisting hypertension.\textsuperscript{19} Bar et al.\textsuperscript{20} evaluated maternal and neonatal outcomes in 38 women (46 pregnancies) with primary renal disease. They did not have a control group of women without renal disease. They observed that most women (98\%) had a successful pregnancy, but many had complications including superimposed preeclampsia (22\%), preterm delivery (22\%), fetal growth restriction (13\%), and cesarean delivery (24\%) (Fig. 51.1). In a logistic regression model, only preexisting hypertension and an elevated preconception serum uric acid level were independent predictors of poor outcome. Other factors (e.g., degree of preexisting renal impairment) were not found to be significant predictors, but because 90\% of the cohort had mild disease the study may have been underpowered to detect an association. In a study of women with moderate to severe renal disease, Jones and Hayslett found the complication rate was much higher.\textsuperscript{14} The incidence of preterm birth was 59\%, the incidence of fetal growth restriction was 37\%, and the cesarean delivery rate was 59\%. The largest literature review on the topic by Lindheimer and Davison\textsuperscript{21} supports the results of prior studies, demonstrating good outcomes for patients with mild renal disease (serum creatinine less than or equal to 1.4 mg/dL) in which over 95\% of patients had live births (75\% were size appropriate for gestational age). Outcomes worsened substantially as renal dysfunction increased, with patients suffering from severe dysfunction (serum creatinine greater than or equal to 2.0 mg/dL) having a successful obstetric outcome only 78\% of the time and with 40\% of patients developing end-stage renal failure within 1 year postpartum.
Medical and Obstetric Management

During pregnancy, the nephrologist and the obstetrician monitor maternal renal function, blood pressure, and fetal development at frequent intervals. Monthly determination of serum creatinine concentration, creatinine clearance, and proteinuria allows the recognition of renal deterioration and establishes a baseline for the patient, which may be useful in diagnosing superimposed preeclampsia if it occurs. An antepartum consultation with the anesthesia provider should also be considered to address issues such as peripartum medication and fluid management, and to perform an overall risk assessment to discuss and develop potential plans for anesthetic technique and monitoring.

Some glomerulopathies respond to corticosteroids, and corticosteroid therapy should be continued during pregnancy. Rapid deterioration of renal function that occurs before 28 weeks’ gestation may require renal biopsy to exclude rapidly progressive glomerulopathies that require treatment, as discussed earlier. Antihypertensive therapy should be instituted as needed (see Chapter 35). As in patients with iron deficiency anemia or patients who refuse blood products, recombinant human erythropoietin has been used successfully to improve maternal anemia in patients with CKD.23 Because of its large molecular weight, recombinant erythropoietin does not appear to cross the placenta or have an adverse impact on the fetus.23 In the non-CKD population, doses of 4000 units subcutaneously 3 times per week for 4 weeks in the third trimester for the treatment of iron deficiency anemia caused a gain of 1.9 ± 1.0 g/dL of hemoglobin at delivery, although the optimal dose range and timing in pregnancy are unknown.24 Data in the CKD population are limited to case reports and small case series. In patients who are treated with erythropoietin, a decreased response to the current dose may actually be the first sign that the patient is pregnant.25 As in the non-CKD population, no optimal regimen is known; however, it should be noted that doses may need to be changed during varying stages of the pregnancy to keep the hemoglobin target within the range of 11 to 12 g/dL, as recommended by the National Kidney Foundation for the pregnant patient. Efficacy has been shown in pregnant patients with CKD and end-stage renal disease on hemodialysis, as well as renal transplant recipients; however, the efficacy and doses are highly variable, and the number of cases reported is very small.22,23,26 Protein restriction places the fetus at risk for growth restriction and is not used. Deterioration of maternal renal function, the onset of preeclampsia, or evidence of fetal compromise may necessitate urgent delivery.

Hemodialysis and Long-Term Ambulatory Peritoneal Dialysis

When renal disease has progressed to end-stage renal failure (i.e., GFR less than 5 mL/min), fertility is suppressed and conception and pregnancy are rare. Less than 10% of premenopausal patients undergoing dialysis have regular menses. Luteinizing hormone and follicle-stimulating hormone concentrations assume an anovulatory pattern, which causes 40% of affected women to be amenorrheic. One-half of all female patients undergoing dialysis exhibit hyperprolactinemia because of reduced clearance and hypothalamic disturbances.27 Toma et al.28 surveyed 2504 dialysis units in Japan and reported only 172 pregnancies among 38,889 women who were undergoing dialysis.

When pregnancy does occur, there are several important management considerations necessary to maximize the probability of a successful outcome. There are two modalities of dialysis: extracorporeal hemodialysis and intracorporeal peritoneal dialysis. Hemodialysis necessitates vascular access and the need for anticoagulation of the extracorporeal circuit and may be complicated by cardiovascular instability, large fluid and electrolyte shifts, and the risk for hepatitis. Hypotension may compromise uteroplacental perfusion and cause fetal compromise. Even when hypotension and major fluid shifts are avoided, Doppler ultrasonographic examination of uterine and umbilical artery flow during hemodialysis suggests the occurrence of a redistribution of arterial flow away from the uteroplacental vascular bed.29 Fetal heart rate monitoring is recommended during dialysis.30 Rapid removal of maternal solutes and reduced oncotic pressure with attendant free-water diffusion into the amniotic cavity may lead to polyhydramnios. Hemodynamic consequences are minimized by more frequent but shorter dialysis runs. Long-term ambulatory peritoneal dialysis allows less hemodynamic trespass, a more stable fetal environment, and the freedom to undergo dialysis at home. However, peritoneal dialysis may not be associated with greater fetal survival. Complications of this modality include peritonitis and catheter difficulties.31 Rates of successful pregnancy in women undergoing dialysis vary by study but range between 50% and 70%.30,32 A meta-analysis and systematic review by Piccoli et al.33 reviewed almost 550 pregnancies in patients undergoing both hemodialysis and peritoneal dialysis and reported a low maternal/perinatal mortality rate (0.4%), with a malformation rate of approximately 2%, which is in line with the risk in the general population. Fetal complications are most often seen in the form of respiratory distress, sepsis, and retinopathy and are likely a result of the higher incidence of preterm birth rather than related specifically to dialysis. The optimal dialysis schedule is an area of active research, with a trend toward more favorable outcomes with longer and more frequent dialysis sessions. BUN levels should be kept below 50 mg/dL before dialysis and below 30 mg/dL after dialysis.31 At birth, azotemia in the newborn is similar to that in the mother, but this quickly corrects because the newborn has normal kidney function. The long-term effects of intrauterine azotemia on newborn cognitive development are unknown; however, it appears that if the neonate survives the complications from preterm delivery, further development may be normal.34

Patients undergoing hemodialysis have a high rate of viral hepatitis, a greater frequency of active tuberculosis, and a higher rate of infection with vancomycin-resistant enterococci, human immunodeficiency virus (HIV), and methicillin-resistant Staphylococcus aureus. The risk for hepatitis C virus (HCV) infection is particularly of concern, with
reported rates as high as 36%. However, with improvement in aseptic technique and more attention to handwashing, the decline in the reuse of dialysis equipment, and the use of dedicated isolated dialysis machines for HCV-seropositive patients, the rates of infection and seroconversion can be markedly reduced.35,36

Anesthetic Management
Anesthetic management is influenced by the extent of renal dysfunction and hypertension. The parturient with stable renal disease, mild to moderate renal insufficiency, well-controlled hypertension, and euvo lemia requires minimal special consideration. In contrast, the dialysis patient with end-stage renal failure presents many anesthetic challenges because renal disease may affect almost every organ system (Box 51.1). Poorly controlled hypertension leads to left ventricular hypertrophy and dysfunction. Symptoms of cardiovascular compromise should prompt a cardiac workup including echocardiography to evaluate ventricular function. An intra-arterial catheter also may aid the management of the parturient with poorly controlled hypertension, especially when multiple agents are required to control blood pressure or when the continuous infusion of antihypertensive agents is required. Uremic pericarditis, cardiomyopathy, and accelerated atherosclerosis are rarely seen until advanced uremia has been present for several years.

Normochromic, normocytic anemia secondary to impaired erythropoietin production, chronic gastrointestinal bleeding, and vitamin deficiency are common findings. Typically, the anemia is well tolerated and does not require transfusion unless excessive surgical bleeding occurs. Uremic toxins may cause functional platelet defects; these abnormalities are reversed by dialysis. Thrombocytopenia may also occur as a result of increased peripheral destruction of platelets. Generalized coagulopathy may result from the anticoagulation used during the dialysis process.37 A full coagulation profile and careful bleeding history should be performed, especially before the initiation of neuraxial anesthesia. Hemodialysis fistulas should be padded carefully to prevent thrombosis. Blood pressure cuffs should not be placed on these extremities.

Neuraxial Anesthesia
Neuraxial anesthesia is the preferred technique for both labor analgesia and cesarean delivery, but there are some unique considerations in the parturient with renal disease. Uremic patients may be hypervolemic or hypovolemic, depending on the time elapsed since their last dialysis session. Hypovolemia and autonomic neuropathy may lead to profound hypertension during the initiation of sympathetic blockade. Intravascular volume should be assessed before induction of anesthesia. Assessment of clinical signs (e.g., current body weight relative to dry body weight, skin turgor, mucous membranes, tachycardia) is generally sufficient. Transthoracic echocardiography may be useful when the volume status remains unclear. Although there are no studies in the CKD patient, a role for intravenous prehydration to prevent hypotension is unlikely because this modality is not efficacious in the healthy parturient.38 There is insufficient evidence to recommend spinal versus epidural techniques for the patient with renal disease. Frequent monitoring of blood pressure and immediate treatment of hypotension is suggested.39 Preexisting peripheral neuropathy should be documented before the administration of neuraxial anesthesia. Local anesthetic systemic toxicity (LAST) after bupivacaine brachial plexus blockade has been reported in patients with chronic renal failure.40 Whether LAST is related to toxic

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<td>Restless legs syndrome</td>
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<td>Seizure disorder</td>
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<td>Hepatitis (viral or drug-induced)</td>
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<td>Malnutrition</td>
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<td>Peripheral neuropathy</td>
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<td>Cerebrovascular insufficiency</td>
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levels of local anesthetic unique to the renal failure patient is unclear. Rice et al. found no significant difference in the pharmacokinetic profile of bupivacaine after brachial plexus blockade in a group of uremic patients and in patients with normal renal function. There are no published data on the pharmacokinetics of epidurally administered local anesthetic agents in patients with chronic renal failure.

Orko et al. administered spinal anesthesia with plain bupivacaine 22.5 mg to 20 nonpregnant patients with chronic renal failure and 20 control patients. Maximal segmental anesthesia occurred more rapidly in the patients with renal disease (21 minutes versus 35 minutes), but the duration was reduced. Further, the extent of sensory blockade was two segments higher in the patients with renal disease. There were no untoward effects in any of the patients. Potential mechanisms proposed for these findings included a difference in blood pH and potassium concentration, as well as the existence of underlying neuropathy increasing susceptibility to blockade. An alternative hypothesis suggested that the hyperdynamic state of uremia causes further distension of epidural veins, hastening onset and decreasing duration through a washout phenomenon.

**General Anesthesia**

Patients with chronic uremia exhibit delayed gastric emptying and hyperacidity, which may increase the risk for aspiration pneumonia. In addition to sodium citrate, when time allows, the anesthesia provider also should consider administering a histamine-2 (H2-) receptor antagonist and metoclopramide. Recommended single doses for patients with renal failure are ranitidine 50 mg and metoclopramide 10 mg given intravenously, which do not differ from patients without renal failure.

All the standard induction agents are safe in patients with renal failure. Etorphidate may have an advantage if the volume status is unknown or if there is left ventricular dysfunction. Propofol exhibits normal volume of distribution and elimination in patients with renal failure and is also commonly used. Protein binding of propofol is unaffected by renal failure. Uremia increases blood–brain barrier permeability to many drugs. These changes may warrant a small reduction in the dose of propofol or thiopental for induction. The serum potassium concentration should be determined before induction of anesthesia. If the potassium concentration is greater than 5.5 mEq/L, dialysis should be performed before an elective procedure. Succinylcholine will cause a 0.5 to 0.7 mEq/L increase in potassium concentration, which is similar to the increment that occurs in patients without renal disease. If the patient is already hyperkalemic, this mild elevation may be sufficient to precipitate cardiac dysrhythmias. Plasma cholinesterase concentrations are normal, even after dialysis, and the duration of action of succinylcholine is not prolonged.

Neuromuscular blockade should be maintained with an agent that does not rely on renal elimination. Cisatracurium undergoes Hofmann degradation, and therefore the duration of action is not prolonged in patients with renal failure. Hypermagnesemia, commonly found in patients with kidney disease, may potentiate neuromuscular blockade. Although anticholinesterase agents undergo renal elimination and have a prolonged duration in patients with renal insufficiency, the volume of distribution remains the same, and standard doses are used for the reversal of neuromuscular blockade.

**Postoperative Analgesia**

The principles of postoperative analgesia for the woman with renal disease are the same as for healthy women, with some important considerations because drug clearance can be altered for opioids and their metabolites (see Chapter 27). Morphine is generally safe as a single dose, but with longer-term use its metabolite, morphine-6-glucuronide, may accumulate. Meperidine is of particular concern because its active metabolite, normeperidine, is neurotoxic and is renally excreted. Hydromorphone and oxycodone, and their metabolites hydromorphine-3-glucuronide and α- and β-oxycodol, respectively, are also renally excreted and may accumulate with prolonged use. Fentanyl and sufentanil are only minimally excreted in the urine, and they may be particularly useful because they are short-acting drugs. Remifentanil is metabolized by blood and tissue esterases and is not dependent on the kidney for excretion, making it safe for use in patients with renal failure. The safest approach may be to use neuraxial opioids because small doses are administered. Alternative techniques that avoid opioids such as transversus abdominis plane (TAP) block may also be considered, especially when neuraxial opioids are not administered (see Chapter 27). Nonsteroidal antiinflammatory drugs (NSAIDs), although effective, are best avoided as they may worsen renal function and can interact with several renal medications including loop diuretics.

**ACUTE KIDNEY INJURY**

**Definition and Epidemiology**

Acute kidney injury (AKI) is a serious potential complication that can develop in pregnancy. The inciting disorders vary throughout the world. In developing countries, septic abortion is the leading cause of pregnancy-related AKI (PR-AKI). In developed countries, severe preeclampsia/ eclampsia, acute pyelonephritis of pregnancy, and bilateral renal cortical necrosis are the most common underlying disorders. Rapid deterioration of renal function leads to an accumulation of fluid and nitrogenous waste products with impaired electrolyte regulation. Definitions for renal dysfunction in the general population vary and have changed over time. What used to be called acute renal failure (ARF) is now included among a greater spectrum of disorders including varying levels of kidney dysfunction, and is now termed AKI. Recent guidelines and recommendations (including definitions) have been maintained by the Kidney Disease: Improving Global Outcomes (KDIGO) consortium of the International Society of Nephrologists (Table 51.1). These definitions and recommendations are based on the RIFLE (risk, injury, failure, loss, and end-stage renal failure) and
Once the risk for death and renal replacement therapy is subdivided according to underlying cause (i.e., prerenal, intrarenal, and postrenal) (Box 51.2).

### Prerenal Causes

The most common prerenal causes of PR-AKI—hyperemesis gravidarum and obstetric hemorrhage—lead to hypovolemia and inadequate renal perfusion. Urinary indices show urine osmolality greater than 500 mOsm/kg, urine sodium less than 20 mEq/L, fractional sodium excretion less than 1%, and a urinary-to-plasma creatinine ratio greater than 40. Conceived hemorrhage from placental abruption may remain unrecognized until hypotension and renal failure ensue. Women with preeclampsia may be more likely to develop AKI after hemorrhage because of preexisting intravascular con- traction and widespread maternal endothelial dysfunction. Women who developed preeclampsia during pregnancy, with or without renal failure, are more likely to develop renal failure later in life.

### Intrarenal Causes

An intrarenal cause is diagnosed once prerenal and postrenal causes of AKI have been excluded. In general, oliguric intrarenal AKI is not easily reversed and must run its course. Causes include acute tubular necrosis, interstitial nephritis, and acute glomerulonephritis as well as a few causes unique to pregnancy. The latter include renal cortical necrosis, acute pyelonephritis, severe preeclampsia/eclampsia, acute fatty liver of pregnancy, and idiopathic postpartum renal failure. A thorough history, review of medications, and urinalysis typically help determine the specific initiating factor.

**Acute tubular necrosis** may result from nephrotoxic drugs, amniotic fluid embolism, rhabdomyolysis, intrauterine fetal death, and prolonged renal ischemia secondary to hemorrhage or septic shock. Urinalysis demonstrates dirty brown epithelial cell casts and coarse granular casts. Urinary indices show urine osmolality less than 350 mOsm/kg, urine sodium concentration greater than 40 mEq/L, fractional sodium excretion greater than 1%, and a urinary-to-plasma creatinine ratio less than 20.

### TABLE 51.1 KDIGO Staging of Acute Kidney Injury

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<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
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<tr>
<td>1</td>
<td>1.5–1.9 times baseline or increase in serum creatinine to ≥ 0.3 mg/dL (≥ 26.5 μmol/L)</td>
<td>&lt; 0.5 mL/kg/h for 6–12 h</td>
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<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt; 0.5 mL/kg/h for ≥ 12 h</td>
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<tr>
<td>3</td>
<td>3 times baseline or increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 μmol/L) or initiation of renal replacement therapy, or in patients &lt; 18 years, decrease in eGFR to &lt; 35 mL/min/1.73 m²</td>
<td>&lt; 0.3 mL/kg/h for ≥ 24 h or anuria ≥ 12 h</td>
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**KDIGO, Kidney Disease: Improving Global Outcomes; eGFR, estimated glomerular filtration rate.**


### BOX 51.2 Causes of Acute Kidney Injury during Pregnancy

- Hyperemesis gravidarum
- Uterine hemorrhage
- Heart failure
- Acute tubular necrosis
- Septic abortion
- Amniotic fluid embolism
- Drug-induced acute interstitial nephritis
- Acute glomerulonephritis
- Bilateral renal cortical necrosis
- Acute pyelonephritis
- Preeclampsia/eclampsia
- Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
- Acute fatty liver of pregnancy
- Idiopathic postpartum renal failure
- Ureteral obstruction by the gravid uterus

Acute Kidney Injury Network criteria, which have been applied to the pregnant population because no similar guidance exists for pregnant patients. Fortunately, during the past five decades, the incidence of PR-AKI has decreased worldwide from 1 in 3,000 to 1 in 15,000. This progress has resulted from improved obstetric care and fewer septic abortions. Although the overall incidence of PR-AKI is declining worldwide, it has been increasing in incidence in the United States and Canada. Mehrabadi et al. reported that the incidence of PR-AKI rose from 2.4 per 10,000 deliveries between 1991 to 2001 to 6.6 per 10,000 deliveries between 2010 to 2011. It should be noted that the overall severity of AKI decreased, which is likely because of an increase in vigilance and a change in diagnostic thresholds. However, AKI associated with the need for dialysis and AKI associated with maternal death increased from 0.27 to 0.36 and 0.13 to 0.23 per 10,000 deliveries, respectively. The increase in the need for dialysis was abolished by controlling for chronic hypertension and chronic kidney disease, demonstrating an increase in the incidence of these conditions between the two cohorts.

### Pathophysiology and Diagnosis

AKI is defined by one of the following criteria: increase in serum creatinine by greater than or equal to 0.5 times baseline within the last 7 days, or urine volume less than or equal to 0.5 mL/kg/h for 6 hours. Once the diagnosis is made, it is recommended to stage the level of severity of AKI. This is an important component of management because the risk for death and renal replacement therapy increases significantly with each stage (see Table 51.1). AKI is subdivided according to underlying cause (i.e., prerenal, intrarenal, and postrenal) (Box 51.2).
Acute interstitial nephritis is caused by NSAIDs and various antibiotics. Patients typically exhibit fever, rash, eosinophilia, and urine eosinophils.

Acute glomerulonephritis is rare during pregnancy. It is suggested by hematuria, red cell casts, and proteinuria. Urinary indices of acute glomerulonephritis are similar to those of prerenal AKI.

Bilateral renal cortical necrosis, which is rarely observed in the nonobstetric patient, is responsible for 10% to 38% of cases of PR-AKI. It may occur during early or late pregnancy. Hemorrhage is the most common precipitating event. The pathogenesis of this disorder is unclear but may involve renal hyperperfusion or endothelial damage by endotoxins imposed on the normal hypercoagulable state of pregnancy. A single dose of endotoxin may precipitate bilateral renal cortical necrosis in pregnant animals and has led some investigators to view this disorder as a clinical analogue of the experimental Sanarelli-Shwartzman reaction. Extensive microthrombi are found within the glomeruli and renal arterioles. Diagnosis is made by selective renal arteriography, which reveals absence or patchiness of blood flow in the cortex. Renal biopsy may also be performed in the absence of active coagulopathy.

Acute pyelonephritis is one of the most common infectious complications of pregnancy (see Chapter 36). Although acute pyelonephritis rarely leads to AKI in the nongravid patient, it accounts for 5% of cases of PR-AKI. The reason for this greater susceptibility is unclear. Whalley et al. noted that acute pyelonephritis causes a marked reduction of GFR in pregnant women. In contrast, pyelonephritis causes little reduction in GFR in nonpregnant patients. The kidney may be more sensitive to bacterial endotoxins during pregnancy.

Severe preeclampsia/eclampsia may be responsible for, or contributes to, 40% to 60% of cases of PR-AKI. Renal failure is generally associated with severe preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, where the incidence ranges from 3% to 15%. However, many cases of renal dysfunction and failure may only mimic preeclampsia and may actually result from other factors. Other causes of AKI should be considered before preeclampsia is determined to be the basis of renal failure.

Gul et al. analyzed the maternal and fetal outcomes of 132 patients with HELLP syndrome. Despite the high rate of major complications in these patients, even when examining those with the most severe levels of renal failure (creatinine greater than 2.0 mg/dL), of whom 50% required dialysis, no patient was discharged with renal impairment, and there was no maternal mortality. Perinatal mortality, however, was high, at 26.1% when serum creatinine was greater than 1.2 mg/dL and increased to 37.5% when greater than 2.0 mg/dL.

Renal histology in a woman with HELLP syndrome and renal failure demonstrated thrombotic microangiopathy and acute tubular necrosis, suggesting a possible pathogenesis of acute renal failure associated with HELLP syndrome. Of interest, Flynn et al. reported the successful use of cadaveric kidneys procured from a parturient who died after HELLP syndrome and AKI. Both recipients had acceptable graft function 2 years after transplantation.

Acute fatty liver of pregnancy, a rare but life-threatening disorder of pregnancy, is associated with a 60% to 100% incidence of AKI. Specific clinical features of acute fatty liver of pregnancy are discussed in Chapter 45.

The syndrome of idiopathic postpartum renal failure was initially described in 1968 by Robson et al. Subsequently, approximately 200 cases have been reported. This syndrome is characterized by AKI, microangiopathic hemolytic anemia, and thrombocytopenia occurring 2 days to 10 weeks after an uncomplicated delivery. It appears closely related to the hemolytic-uremic syndrome. Idiopathic postpartum renal failure is typically preceded by a viral upper respiratory tract or gastrointestinal syndrome that rapidly progresses to AKI. The use of ethynyl estradiol as a contraceptive may also be causally related to this syndrome. Spontaneous bleeding, congestive heart failure, hypertension, and seizures have been reported. Some investigators believe that this syndrome represents a clinical analogue to the generalized Shwartzman reaction, a condition induced in laboratory animals by two successive injections of endotoxin, which results in factor XII activation, thrombin generation, and fibrin deposition. Others consider the platelet deposition to be the primary event that leads to microvascular thrombi.

Management involves plasma exchange transfusion, dialysis, and antiplatelet therapy. The role of heparin therapy in idiopathic postpartum renal failure is controversial. The morbidity and mortality among affected patients vary by study. Reports from 1979 and 1988 suggested a mortality rate of approximately 50%. Although survival has improved with prompt diagnosis and aggressive treatment, morbidity is still high. Shrivastava et al. reported three patients who had postpartum hemolytic-uremic syndrome and had initial recovery with immediate exchange transfusion; long-term follow-up was not reported. Dashe et al. reported 10 patients with peripartum or postpartum hemolytic-uremic syndrome and followed their course for a mean of 9 years. Although all 10 initially survived, one subsequently died and all had major morbidity, including recurrence of renal failure, hypertension, and seizures.

Postnatal Causes

The postnatal causes of PR-AKI include nephrolithiasis and ureteral obstruction by the gravid uterus. The latter complication is more likely in pregnant women with polyhydramnios or multiple gestation. Preexisting ureteral dilation and impaired peristalsis increase the risk for obstructive uropathy during pregnancy. Flank pain and decreased urine output during late gestation should alert the clinician to this possibility. Courban et al. reported an unusual case of multiple uterine leiomyomas that caused obstructive uropathy that resulted in PR-AKI.

Effect on the Mother and Fetus

Although maternal prognosis has improved significantly in developed countries, mortality ranges between 20% and 30%
in developing countries, likely because of the lack of availability of renal replacement therapy. Although mortality in developed countries is very low, up to one-third of mothers do not have complete recovery and suffer long-term sequelae from their AKI episode. The prognosis for the fetus is poorer than that for the mother, with fetal mortality as high as 65% depending on onset and severity of disease.

Medical and Obstetric Management

Management is directed toward rapid recognition of the underlying abnormality. Reversible disorders such as hypovolemia, concealed uterine hemorrhage, urinary tract infection, ureteral obstruction, and drug-induced AKI must be excluded. Urine osmolality (greater than 500 mOsm/kg) is a useful laboratory test to identify reversible prerenal causes. Intravascular volume should be optimized. Electrolyte and acid-base status should be monitored carefully. Hypertension and preeclampsia must be managed aggressively. Many obstetric causes of AKI also may cause disseminated intravascular coagulation; therefore, coagulation abnormalities should be excluded in pregnant women with AKI.

Because urea and other metabolic products cross the placenta, hemodialysis or peritoneal dialysis should be directed toward maintaining the postdialysis BUN concentration at or below 30 mg/dL. Fluid shifts during hemodialysis should be minimized by short but frequent periods of dialysis. If the fetus is mature, delivery should be accomplished when the maternal condition is stabilized. The pediatrician must be alerted to the presence of high fetal BUN levels, which may lead to an osmotic diuresis and neonatal dehydration. Ertürk et al. reported the first known delivery of a healthy infant during a hemodialysis session. All nephrotoxic drugs should be discontinued and avoided if possible. Renal dosing of medications (e.g., muscle relaxants, antibiotics, magnesium) should be considered in these patients.

Anesthetic Management

A multidisciplinary approach involving anesthesia providers, obstetricians, and nephrologists should be employed to optimize the maternal condition before delivery in a woman with AKI. The level of azotemia, electrolyte balance, and hematologic status should be assessed. If the BUN level is greater than 80 mg/dL or if the serum potassium concentration is greater than 5.5 mEq/L, dialysis should be performed before vaginal or cesarean delivery. Neuraxial anesthesia may be administered in the absence of coagulopathy, thrombocytopenia, and severe hypovolemia. Volume status may be difficult to assess. In the past, it was common to place a central line or pulmonary artery catheter to assess volume status, but this is now rarely done given the advent of transthoracic echocardiography.

Both spinal and epidural analgesia/anesthesia are safe and preferred to general anesthesia. As the sympathetic blockade dissipates, the mother should be monitored for evidence of volume overload and pulmonary edema. General anesthesia may be required for urgent cesarean delivery or in patients with coagulopathy or hemorrhage.

RENAL TRANSPLANTATION

Although pregnancy is uncommon in women undergoing long-term dialysis, fertility is improved within months of transplantation. In a review of female renal transplant patients in the United States, a pregnancy rate of 20 per 1000 was estimated in transplanted patients in the year 2000 compared with 100 per 1000 in the general population.

Although a successful obstetric outcome can be anticipated in more than 95% of kidney transplant recipients, they are at greater risk for both maternal and fetal complications than healthy women. In a systematic review of articles published between 2000 and 2010, Deshpande et al. reported pregnancy-related outcome data in kidney transplant recipients. Fifty studies representing 4706 pregnancies in 3570 recipients met inclusion criteria. The incidences of preeclampsia (27%), gestational diabetes (8%), cesarean delivery (56.9%), and preterm delivery (45.6%) were greater than in the general population. Smaller more recent cohort studies have found similar increases in complication rates, including one study from Norway that demonstrated an increased incidence rate ratio for developing preeclampsia of 6.06 (95% CI, 3.118 to 11.55). In a separate cohort study examining renal transplant patients in the United Kingdom, potential predictive factors for poorer outcomes were described, including: greater than one prior kidney transplant, first-trimester serum creatinine greater than 125 µmol/L, and a diastolic blood pressure greater than 90 mm Hg in both the second and third trimesters.

Effect of Pregnancy on the Renal Allograft

When a kidney is removed from a donor and transplanted into an anephric recipient, it undergoes a process of hyperfiltration. This is a maladaptive response that, in the short term, attempts to bring the GFR toward the rate of a binephric system. In the long term, this hyperfiltration may lead to glomerular sclerosis and loss of renal function if it is associated with increased glomerular or capillary pressure. In normal pregnancy, the GFR increases by 30% to 50% during the first and second trimesters and subsequently decreases somewhat during the third trimester. Theoretically, this additional hyperfiltration of pregnancy predisposes the patient to a loss of renal function.

Baylis and Reckelhoff allayed many of these concerns by demonstrating that gestational hyperfiltration is not associated with increased glomerular pressure because of matching afferent and efferent arteriolar vasodilation. They produced hyperfiltration in rodent kidneys by performing uninephrectomy, maintaining the animals on a high-protein diet, and subjecting them to five consecutive pregnancies. The investigators observed no functional impairment or renal histologic changes in this animal model. In addition, they demonstrated that glomerular pressure is lower in female rats than in male rats 10 months after uninephrectomy. Similar sex advantage has been seen in humans after uninephrectomy.

There have been a number of studies assessing graft function after pregnancy. Most studies suggest that there is no adverse
TABLE 51.2  Effect of Pregnancy on Long-Term Function of Renal Allografts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant Group (n = 18)</th>
<th>Nonpregnant Control Group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>1.26 ± 0.83 (19% increase)</td>
<td>1.44 ± 0.59 (8% increase)</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min)</td>
<td>58 ± 29 (18% decrease)</td>
<td>56 ± 32 (7% decrease)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>96 ± 12 (1% decrease)</td>
<td>101 ± 9 (5% increase)</td>
</tr>
<tr>
<td>Graft loss or chronic rejection</td>
<td>2 (11%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

*Percentage increase or decrease represents change from initial assessment to end of follow-up. No statistically significant differences were noted. Continuous variables are shown as mean ± standard deviation. From Sturgiss SN, Davison JM. Effect of pregnancy on long-term function of renal allografts. Am J Kidney Dis. 1992;19:167–172.

The Parturient with Systemic Disease

...effect provided renal function is normal before conception and there is no evidence of hypertension.104–107 Levidiotis et al.104 analyzed 40 years of outcome data from the Australian and New Zealand Dialysis and Transplant Registry and did not find any impact of pregnancy on 20-year graft or patient survival.

Rahamimov et al.105 compared long-term graft survival, kidney function, and patient survival between women who became pregnant after renal transplantation (n = 39; 55 births) and those who did not (n = 117). Each pregnant woman was matched with three nonpregnant women for 12 factors that may affect graft survival. Graft survival (61.6%) and patient survival (84.8%) in the pregnant women did not differ from the matched nonpregnant group (68.7% graft and 78.8% patient survival) during the 15-year follow-up study.

Sturgiss and Davison106 performed a case-control study of 36 renal transplant recipients, of whom 18 became pregnant and 18 did not. Groups were matched according to age, early rejection episodes, primary renal function, interval since transplantation, and extent of histocompatibility. The investigators noted no significant difference between the two groups in plasma creatinine concentration, GFR, mean arterial blood pressure, or the number who suffered graft loss or chronic rejection over a mean follow-up period of 12 years (Table 51.2).

Kashanizadeh et al.107 also compared graft survival, allograft function, and patient survival between transplant recipients who conceived (n = 86) and those who did not (n = 125). They, too, did not find a difference in 5-year graft or patient survival between groups. Interestingly, they noted a smaller increase in creatinine levels in women who had conceived, suggesting that pregnancy might exert a protective effect, but this finding has not been confirmed by others.108

Effect on the Fetus

Although pregnancy seems to have minimal effect on maternal health or allograft survival in renal transplant recipients, fetal outcome is less favorable. In the Norwegian cohort study mentioned earlier, the adjusted incidence rate ratio of patients with preterm delivery was 4.45 (95% CI, 2.13 to 9.30).98 Likewise, the incidence of delivering an infant below the 10th percentile in birth weight was double that of the control cohort, and the risk for stillbirth or perinatal death within the first 24 hours was tenfold greater. Despite the increases in relative risk, absolute outcomes are reassuring. For example, in a large systematic review, Deshpande et al.97 found a 73.5% live birth rate in renal transplant patients.

Most posttransplantation protocols consist of a primary immunosuppressant (cyclosporine or tacrolimus) and one or two adjunctive agents (azathioprine, mycophenolate mofetil, sirolimus, and/or corticosteroids).109 Despite transplacental exposure to immunosuppressant drugs, congenital anomalies and other adverse effects are not greater than in the general population, but none of the studies included patients who were receiving mycophenolate mofetil.109,110 There have been reports of congenital defects with mycophenolate mofetil, including cleft lip and palate, microtia, absence of auditory canals, brachydactyly of the fifth finger, and hypoplastic toenails; therefore, its use has to be weighed against the risk for allograft rejection.112

Intrauterine exposure to cyclosporine impairs development and function of T, B, and NK lymphocytes in neonates. This effect, as well as depressed levels of serum immunoglobulin, persists during the first year of life.113 These factors place the infant at risk for a suboptimal immunologic response after administration of classic vaccines and for adverse effects after administration of live, attenuated vaccines.

Transplant recipients may become infected with cytomegalovirus (CMV) at the time of transplantation, or they may experience reactivation secondary to immunosuppression. Active CMV infection during pregnancy is associated with congenital anomalies (e.g., cerebral cysts, microcephaly, mental retardation). In addition, active neonatal CMV infection may lead to serious illness or death.

After renal transplantation, residual impairment of renal function may lead to false-positive results of biochemical screening for trisomy 21. Karidas et al.114 demonstrated a significant correlation between free β-subunit human chorionic gonadotropin and BUN and creatinine concentrations. Similar alterations in alpha-fetoprotein levels were not observed. In this setting, the double-marker biochemical test may be interpreted inaccurately. In patients with altered BUN and creatinine concentrations, first-trimester nuchal translucency measurement—in combination with second-trimester ultrasonography—may be a more useful screening regimen (see Chapter 6).

Medical and Obstetric Management

Discontinuation of immunosuppressant therapy, even years after transplantation, may lead to acute rejection. Thus, the renal transplant recipient’s immunosuppressant regimen must be continued during pregnancy unless toxicity results, although some practitioners discontinue mycophenolate mofetil. Cyclosporine requirements increase during pregnancy, most likely because of enhanced metabolism.115 The
pregnant patient must be intensively monitored for any evidence of acute or chronic allograft rejection, infection, ureteral and renal artery obstruction, impaired renal function, hypertension, fluid volume disturbances, anemia, or any combination of these symptoms. As noted earlier, recombinant human erythropoietin (darbepoetin) has been successfully used to treat anemia during pregnancy. There are reports in the posttransplant patient as well, although the degree of success and dosage regimens are highly variable.\(^\text{26,116}\)

Initial laboratory studies in pregnant renal transplant patients include (1) complete blood cell count, (2) renal function tests, (3) serum electrolyte and glucose concentrations, and (4) viral serologic testing for CMV, hepatitis B virus, HCV, and HIV. Serial ultrasonographic assessments allow the recognition of fetal anomalies and the evaluation of fetal growth.

Cultures of the lower genital tract should be obtained in women with lesions suggestive of herpes simplex virus infection. A patient who presents in labor and with evidence of active genital herpes simplex virus infection should undergo cesarean delivery (see Chapter 36).

Vaginal examinations are minimized and always performed in a strict aseptic manner. The renal allograft is typically implanted in the extraperitoneal iliac fossa and does not impair vaginal delivery. Prophylactic antibiotics and stress-dose corticosteroids are indicated in patients who undergo cesarean delivery.

**Anesthetic Management**

In the absence of renal dysfunction and hypertension, anesthetic management of the parturient with a renal transplant is similar to that of the healthy parturient. Strict aseptic technique is maintained during the placement of intravascular catheters and the performance of neuraxial anesthetic techniques. Sowter et al.\(^\text{117}\) reported an epidural abscess that occurred 23 days after epidural anesthesia in a nonpregnant patient receiving corticosteroid therapy for rheumatoid arthritis. Fortunately, this complication is exceedingly rare. In the absence of systemic infection, immunosuppression itself should not be considered a contraindication to administration of epidural or spinal anesthesia.

**UROLITHIASIS**

**Definition and Epidemiology**

Urolithiasis is characterized by the abnormal formation of calculi within the renal calyces or pelvis. Calculi may lodge within the ureters or bladder. The disorder affects 1% to 5% of the general U.S. population, but it is more common in the southeastern “stone belt” and mountainous regions. Symptomatic urolithiasis occurs during 1 in 188 to 1 in 4600 pregnancies and is more common among whites than African Americans, and more common in multiparous women in the second and third trimesters.\(^\text{118,119}\) This incidence approximates that observed among nonpregnant young women, suggesting that pregnancy does not affect the rate of urolithiasis.

**Pathophysiology**

The presence of urolithiasis presumes an underlying physiologic abnormality that leads to persistent supersaturation of the particular minerals involved. During pregnancy, an elevated plasma 1,25-dihydroxyvitamin D level causes greater intestinal absorption of calcium, net mobilization of calcium from bone, and a state of absorptive hypercalciuria.\(^\text{120}\) Ultimately, these changes provide calcium for the fetal skeleton. Because pregnant women do not develop urolithiasis at a rate greater than that in the general population, it would appear that the occurrence of other physiologic changes during pregnancy offsets these factors that might promote the formation of stones. Calcium stone inhibitors such as citrate, magnesium, and glycoprotein are excreted in the urine to a greater extent during pregnancy.\(^\text{121}\) As expected, calcium stones account for the majority of stones in both the general population (80%) as well as in pregnancy (74%). However, whereas calcium oxalate stones are more prominent in the general population, calcium phosphate stones are more common in pregnancy.\(^\text{122,123}\) This difference is thought to be caused by both the renal physiologic changes of pregnancy as well as a higher pH of urine in the parturient.

**Diagnosis**

As mentioned earlier, urolithiasis most commonly manifests during the second or third trimester. Only 20% of affected pregnant women recount a prior history of renal calculi. More than 80% of cases of gestational urolithiasis are diagnosed in parous women, possibly reflecting the higher incidence of this disease with advanced age.\(^\text{124}\) Similar to that seen in nonpregnant women, stones occur with equal frequency on the right and left sides.\(^\text{125}\) The signs and symptoms of urolithiasis during pregnancy are often nonspecific and may include flank pain, hematuria, nausea, vomiting, and fever; these must be differentiated from those occurring from ectopic pregnancy, preterm labor, appendicitis, pylonephritis, and benign hematuria of pregnancy. A history of previous urolithiasis, recurrent urinary tract infections, or urologic surgery is suggestive. Examination may reveal costovertebral tenderness, abdominal tenderness, pyuria, and hematuria. Urolithiasis must be considered in patients with pylonephritis who remain febrile or have continued bacteriuria despite 48 hours of parenteral antibiotics.

The initial imaging modality for the evaluation of urolithiasis during pregnancy is transabdominal ultrasonography. Transabdominal ultrasonography is diagnostic in about 60% of cases and does not expose the mother or fetus to radiation.\(^\text{126}\) Color Doppler ultrasonography allows the identification of ureteral jets; the asymmetry or absence of these jets indicates the presence of urinary calculi. Transvaginal ultrasonography may augment suboptimal transabdominal ultrasonographic images.\(^\text{127}\) Combining ultrasound evaluation with assessment of the intrarenal artery resistive index increases the accuracy of ultrasonography to greater than 70%.\(^\text{128}\)

If urinary calculi are not successfully visualized with ultrasonography and clinical suspicion for urolithiasis remains...
high, magnetic resonance (MR) urography should be considered because it does not use ionizing radiation or iodinated contrast media (see Chapter 17). If the diagnosis is still unclear and the patient has persistent flank pain after both these tests, some experts recommend low-dose computed tomography, whereas others recommend intravenous pyelography.

**Effect of Pregnancy on Urolithiasis**

In an effort to determine any effect of pregnancy on the natural history of urolithiasis, Coe et al. reviewed the records of 58 pregnancies in women with the preexisting diagnosis of urolithiasis. The stone recurrence rate in this group was 0.49 stone per patient-year, which was not significantly different from the rate of 0.44 stone per patient-year in the general population. The authors concluded that pregnancy does not alter the activity or severity of stone disease.

**Effect on the Mother and Fetus**

In a retrospective cohort study, Swartz et al. compared pregnant women with nephrolithiasis (n = 2339) with randomly selected women without nephrolithiasis (n = 6729). The investigators found that women with nephrolithiasis had an almost twofold higher rate of preterm delivery. However, these women were not at increased risk for other adverse pregnancy outcomes, including premature rupture of the membranes, low birth weight, and infant death. The etiology of preterm labor and perhaps delivery is unclear but may be related to urinary tract infections that occur with a greater frequency in those with urolithiasis. Honoré suggested that there is a higher incidence of renal stones among women who have a spontaneous abortion. He hypothesized that abnormalities of calcium hemostasis may lead to myometrial hyperirritability or abnormal hormonal secretion by the corpus luteum, the placenta, or both. Rare cases of ureteral rupture and obstructed labor caused by a bladder calculus have been reported.

**Urologic and Obstetric Management**

Women with a history of urolithiasis should increase their intake of fluids. Calcium supplementation through prenatal vitamins should be avoided in women with recurrent urolithiasis. During pregnancy, 70% of calculi pass spontaneously with conservative management (e.g., hydration, antibiotics if the patient is febrile, bed rest, analgesia). More aggressive therapy will be required if conservative management is not successful. The decision to move beyond conservative therapy should be taken on a case-by-case basis. Infected hydronephrosis, especially with impaired renal function or urosepsis, is an indication for more aggressive therapy.

Medical management, commonly used for treatment of urolithiasis, is limited during pregnancy by fetal concerns. Medical expulsive therapy with alpha-adrenergic receptor blocking agents has been used successfully to increase the rate of stone passage and decrease pain associated with expulsion by relaxing ureteral smooth muscle. There are no randomized studies examining safety or efficacy in the pregnant population; however, a survey study reported that 44.3% of respondent urologists endorsed its use in the pregnant population. Other medical treatments that are used to treat urolithiasis, including thiazide diuretics, xanthine oxidase inhibitors, and β-penicillamine, are contraindicated during pregnancy owing to possible effects on the fetus.

Urologic intervention is indicated in the patient with persistent pyelonephritis, deterioration of renal function, massive hydronephrosis, persistent pain, or sepsis. Ureteral stent placement with ureteroscopy and ultrasonographic guidance, or percutaneous nephrostomy, should be considered because either one can be performed without the need for anesthesia or radiation exposure. Holmium:yttrium-aluminum-garnet (YAG) laser lithotripsy, using state-of-the-art ureteroscopes, is an emerging technique for stone management in pregnancy. Extracorporeal lithotripsy should be avoided during pregnancy because the shockwaves may be harmful to the fetus.

The following conditions may raise suspicion of the presence of primary hyperparathyroidism in a pregnant woman: (1) urolithiasis with or without pancreatitis, (2) hyperemesis beyond the first trimester, (3) a history of recurrent spontaneous abortion or intrauterine fetal death, (4) neonatal hypocalcemia or tetany, and (5) a total serum calcium concentration greater than 10.1 mg/dL during the second trimester or greater than 8.8 mg/dL during the third trimester.

**Anesthetic Management**

Anesthesia providers are occasionally asked to provide analgesia for patients with renal or ureteral stones. The ureters receive sensory innervation through the renal, ovarian, and hypogastric plexuses (T11 to L1 spinal segments). During conservative management of urolithiasis, epidural analgesia provides the patient with significant pain relief and facilitates the passage of the calculus, possibly through decreased ureteral spasm. Ready and Johnson reported the use of epidural analgesia in a patient with severe renal colic at 23 weeks’ gestation. Analgesia that was maintained for 16 hours allowed the passage of the stone. Neuraxial analgesia avoids the use of systemic opioids, which impair normal peristalsis in ureteric smooth muscle. Improved maternal pain control may also decrease endogenous catecholamine release and improve uteroplacental blood flow.

**KEY POINTS**

- Pregnant women with moderate or severe renal insufficiency are at increased risk for deterioration of renal function, exacerbation of hypertension, and other obstetric complications, including fetal growth restriction and preterm delivery.
• Patients requiring renal dialysis have decreased fertility, and pregnancy is rare.
• Pregnancy does not affect the long-term survival of a renal allograft.
• Both preeclampsia and renal disease may manifest as hypertension, proteinuria, and edema; the distinction between the two disorders is often unclear, especially after 20 weeks’ gestation.
• Renal disease affects almost every organ system, so a thorough history before initiation of anesthesia, with emphasis on the cardiac and respiratory system, is critical.
• Anesthetic management is influenced by the extent of renal dysfunction and hypertension.

• Neuraxial anesthetic techniques are safe and are the preferred methods for labor analgesia and cesarean delivery anesthesia.
• Renal transplantation improves fertility rates within a few months of transplantation. Immunosuppressive therapy must be continued during pregnancy in renal transplant patients. The anesthesia provider should maintain strict aseptic technique during the placement of intravascular catheters and the performance of neuraxial anesthetic techniques.
• Epidural analgesia may facilitate the spontaneous passage of renal calculi.

REFERENCES


Respiratory Disease

Karen S. Lindeman, MD

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ASTHMA

Definition
Asthma is defined by the presence of the following three characteristic findings: (1) reversible airway obstruction, (2) airway inflammation, and (3) airway hyperresponsiveness. Airway obstruction produces the clinical manifestations of wheezing, cough, and dyspnea. Airway inflammation modulates the course of asthma by independently producing airway obstruction and enhancing airway hyperresponsiveness. Airway hyperresponsiveness is marked by exaggerated responses to a wide variety of bronchoconstrictor stimuli, including histamine, methacholine, prostaglandin F₂α, hypo-osmotic solutions, and cold air.

Epidemiology
Asthma is an increasingly common problem among young, otherwise healthy women of childbearing age. From 2001 to 2010, the prevalence of asthma in the United States increased from 7.3% to 8.4%. The prevalence of asthma in women of childbearing age also continues to rise. The rate was approximately 3% in the 1990s and has increased to approximately 8.8% in the early 2000s.

Pathophysiology
Asthma is believed to occur under a variety of environmental influences in the presence of genetic susceptibility. The underlying defect that produces the clinical syndrome of asthma is unknown. The most important potential mechanisms are (1) an enhancement of contractility or an impairment of relaxation of airway smooth muscle, (2) a neural imbalance, (3) airway inflammation, and (4) changes in the function of the airway epithelium.

Airway Smooth Muscle
Contraction of airway smooth muscle is believed to be the most important factor in producing acute airway obstruction. For many years, an enhancement of airway smooth muscle responsiveness to contractile agonists was assumed to be a major mechanism of asthma. To test this hypothesis, investigators attempted to correlate airway responsiveness in vivo and in vitro in humans and in the basenji-greyhound dog model of asthma. These studies did not demonstrate a significant correlation between the airway response to histamine or cholinergic agonists in vivo and airway smooth muscle contraction in vitro. Some studies actually demonstrated a negative correlation between the in vivo and in vitro responses,
sugesting that diminished responsiveness may represent a chronic adaptive response of airway smooth muscle.

Instead of an enhancement in responsiveness to contractile stimuli, a reduction in responsiveness to relaxant stimuli may contribute to airway obstruction. One study demonstrated impaired relaxant responses to isoproterenol in airway smooth muscle from human asthmatic subjects in comparison with the responsiveness of airway smooth muscle from controls.11 Other evidence substantiates the presence of impaired airway relaxation in asthmatic subjects in vivo.12 Although the mechanism for this effect is poorly understood, a reduction in airway sensitivity to beta-adrenergic agonists could contribute to airway hyperresponsiveness by altering the balance between constricting and dilating influences.

**Neural Components**

A balance between constricting and dilating influences also exists with respect to the autonomic nervous system. A shift in this balance, with an increase in constricting influences, may be a mechanism of asthma.

The parasympathetic nervous system provides the dominant constrictor input to the airways (Fig. 52.1). Efferent cholinergic fibers travel in the vagus nerve to synapse in ganglia within the airway wall.13 Postganglionic fibers release acetylcholine to activate muscarinic receptors and stimulate airway smooth muscle contraction. A negative feedback system limits release of acetylcholine from nerve terminals. Muscarinic autoreceptors, or receptors on the nerve ending,14 also are activated by acetylcholine and inhibit further release of acetylcholine from the nerve terminal.

The importance of exaggerated cholinergic efferent activity in the pathogenesis of airway hyperreactivity has been debated extensively. The relatively limited efficacy of anticholinergic agents in relieving clinical bronchospasm, as well as growing evidence supporting other mechanisms, suggests that this pathway has a limited role in the pathophysiology of asthma. However, this mechanism appears to be very important in the perioperative management of asthmatic subjects. Reflex stimulation of airway smooth muscle by placement of a tracheal tube represents one of the most important causes of bronchospasm in the perioperative period.

An alternative mechanism by which the parasympathetic nervous system may contribute to airway hyperresponsiveness is through dysfunction of the muscarinic autoreceptors. Dysfunction of these receptors allows increased postganglionic release of acetylcholine after reflex stimulation.15 This mechanism is well established in a guinea pig model of viral infection16 and may explain the airway hyperresponsiveness that occurs for several weeks after an upper respiratory tract infection, although additional autoreceptor-independent mechanisms may also be present.17 The role of this mechanism in the pathophysiology of clinical asthma is unclear.

The sympathetic nervous system primarily acts to decrease airway tone. In contrast to the parasympathetic nervous system, sympathetic innervation of airway smooth muscle in human subjects is either sparse or absent.18 Circulating catecholamines activate beta-adrenergic receptors in airway smooth muscle and provide the primary sympathetic efferent input to human airways. Because airways of normal human subjects do not become hyperresponsive after beta-adrenergic blockade,19 it is unlikely that impaired catecholamine secretion contributes significantly to the pathogenesis of asthma.

The alpha-adrenergic system is thought to play a relatively minor role in determining the state of airway responsiveness. Although alpha-adrenergic receptors are present in human airways,20 the protective effects of alpha-adrenergic antagonists have been disappointing and can be attributed to other properties, such as antihistamine activity.

In addition to cholinergic and adrenergic input, a third neural system, the nonadrenergic noncholinergic (NANC) system, provides efferent nerves to the airways. Both constricting and dilating pathways have been identified.21 Nitric oxide serves as the inhibitory NANC neurotransmitter in human airways.22 Potentially, a relative increase in constricting influences or a decrease in dilating influences in the NANC system could contribute to asthma. However, asthmatic subjects demonstrated no deficit in NANC inhibitory pathways,23 and inhibition of NANC excitatory neurotransmission did not improve airway hyperresponsiveness.24 Thus, current evidence does not support imbalance of the NANC system as a major mechanism of asthma.

**Airway Inflammation**

Airway inflammation appears to serve primarily as a modulating influence in asthma. Inflammation is certainly present in some but not all asthmatic subjects.25 The process of inflammation involves the occurrence of airway wall edema and infiltration of the mucosa by a variety of inflammatory cells, including neutrophils, mast cells, helper T lymphocytes, macrophages, and eosinophils. These cells produce and release mediators of inflammation, such as histamine, leukotrienes, platelet-activating factor, prostaglandins, thromboxanes,
Airway hyperresponsiveness is correlated with increased base addition, airway inflammation can reduce airway diameter. Cells, modifying neural control of the airways, increasing muscle contraction, directing migration of inflammatory late airway responsiveness by stimulating airway smooth mucosal permeability, or disrupting airway epithelium. In addition, airway inflammation can reduce airway diameter. Airway hyperresponsiveness is correlated with increased baseline airway tone. The overall importance of inflammation in asthma has been debated. Although inflammation appears to modulate the course of asthma, other factors certainly contribute to the pathogenesis.

Airway Epithelium
The epithelium provides a barrier to protect the subepithelial layers against stimuli that could provoke bronchospasm. Airways of asthmatic subjects demonstrate areas of epithelial destruction, and the clinical significance of this finding has been demonstrated.

The epithelium not only serves as a barrier but also plays an active role in the maintenance of airway tone. The epithelium produces constricting and dilating factors. An alteration in the balance between these factors could alter airway responsiveness. The relative importance of alterations in epithelial function in the pathogenesis of asthma is unknown.

Diagnosis
Medical History
The classic symptoms of asthma include wheezing, cough, dyspnea, and chest tightness. A patient’s medical history also should include information about the pattern and severity of the symptoms, precipitating and aggravating factors, and the duration and course of these symptoms.

Physical Examination
Physical examination is directed to the respiratory tract. Auscultation of the chest may reveal wheezing and a prolonged phase of expiration.

Laboratory Studies
Laboratory studies that aid in the diagnosis of asthma depend on findings from the medical history and physical examination. In general, pulmonary function tests are useful to document the severity and establish the reversibility of obstruction (Box 52.1). In the absence of additional findings, other tests are not as useful in establishing the diagnosis of asthma. Bronchoprovocation tests (with agents such as methacholine or histamine) are used when the history and physical examination strongly suggest the presence of asthma but spirometry does not show airway obstruction.

Interaction with Pregnancy
Effects of Pregnancy on Asthma
The overall course of asthma has been reported to improve, worsen, or remain the same during pregnancy. Although earlier evidence suggested that patients with more severe asthma are more likely to experience deterioration during pregnancy, other studies indicate that asthma severity during pregnancy is similar to severity during the year before pregnancy, provided that patients continue to use their prescribed medication during pregnancy. Even mild asthma can become significantly more severe if women discontinue their prescribed medication during pregnancy. A likely reason for the variation in the results of published studies is the difference in methods of assessing the severity of asthma. Most studies have used either clinical symptoms or requirements for pharmacologic therapy as indicators of the course of the disease. These measures do not correlate with objective measures of airway obstruction. Juniper et al. measured methacholine sensitivity before, during, and after pregnancy. Measurements of sensitivity to methacholine made during the second and third trimesters were lower than preconception or postpartum measurements (Fig. 52.2). Although these findings suggest a reduction in airway hyperresponsiveness during pregnancy, the limited study population (16 subjects) makes extrapolation of the data to the general population unclear. Conversely, a small (n = 20) prospective study showed temporary declines in pulmonary function between 21 and 28 weeks’ gestation that returned to baseline later in the pregnancy. Exacerbations of asthma during labor and delivery occur in as many as 20% of subjects.

A number of mechanisms may be responsible for the changes in the clinical course of asthma during pregnancy (Box 52.2). An increase in the progesterone level is thought to be one mechanism that improves asthma during pregnancy. Progesterone relaxes uterine and gastrointestinal smooth muscle and may or may not have similar effects on airway smooth muscle. However, Juniper et al. did not demonstrate a strong association between methacholine responsiveness and progesterone levels during pregnancy, suggesting that progesterone does not play a central role in attenuating airway hyperresponsiveness. In contrast, progesterone may actually worsen asthma by enhancing inflammation. Thus, effects of pregnancy on asthma appear to involve a number of factors other than direct effects of hormones on airway smooth muscle.

Effects of Asthma on the Parturient and Fetus
Many investigators have questioned whether maternal asthma adversely affects perinatal outcome. Differences in study design (e.g., retrospective, prospective) and differences in severity and treatment of asthma may account for different

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**BOX 52.1 Pulmonary Function Tests in Patients with Asthma**

**Forced Vital Capacity (FVC)**
- The volume of gas exhaled after maximal inspiration
- May be reduced in asthma

**Forced Expiratory Volume in 1 Second (FEV₁)**
- The volume exhaled in the first second after maximal inspiration
- May be reduced in asthma

**FEV₁/FVC < 0.75 in Asthma**
controlled studies have documented better perinatal outcome with aggressive asthma treatment. Potential mechanisms of increased perinatal morbidity and mortality in patients with uncontrolled asthma include hypoxemia and hypocapnia, inflammation, and altered placental function from asthma-associated mediator release. Siddiqui et al. have documented an association between preeclampsia and airway hyperresponsiveness and have proposed that the mechanism involves an interaction between mast cells and smooth muscle. A large prospective study is needed to confirm this association.

**Medical Management**

Pharmacologic therapy for asthma during pregnancy is directed toward avoiding acute exacerbations and episodes of status asthmaticus. Ideally, management should begin before conception. Although general principles typically dictate that unnecessary medication should be avoided during pregnancy, studies investigating the effects of asthma on perinatal outcome suggest that the risks for uncontrolled asthma are significantly higher than medication-associated risks. Medications that are currently used to treat asthma fall into two general categories: bronchodilators and antiinflammatory agents. These agents generally are safe for the fetus. The prophylactic use of antibiotics is unnecessary.

**Bronchodilators**

Beta-adrenergic agonists exert beneficial effects in asthmatic patients by activation of β₂-adrenergic receptors, which mediate a number of processes (Box 52.3). Short-acting beta-adrenergic agonists represent the most effective therapy for acute exacerbations of asthma. Daily use of long-acting beta-adrenergic agonist therapy is associated with a significant increase in the risk for death, but controlled studies have not confirmed a cause-and-effect relationship. Certain genetic polymorphisms affect responses to short-acting but not long-acting beta-adrenergic agonists, leading to hopes that a personalized approach to therapy would improve clinical efficacy. Although regular use of beta-adrenergic agonists in asthma may be beneficial in conjunction with other forms of therapy, these agents do not appear to provide optimal control when used alone. Conversely, no compelling evidence requires that beta-adrenergic agonists be discontinued after conception or that their use be reserved for treatment of an acute exacerbation.

These agents may be administered as aerosols, orally, or parenterally. The aerosol route is generally preferred during pregnancy.
pregnancy because high concentrations of the medication can be delivered directly to the site of activity in the airways, with relatively less drug delivered to the uteroplacental circulation.

The limited number of human studies investigating the fetal safety of long-term administration of a beta-adrenergic agonist have not shown significant adverse neonatal outcomes. In addition, the long history of use of these agents without reports of teratogenicity suggests that their use should not be restricted because of fetal concerns. Optimal control of maternal symptoms of asthma appears to be more important for the fetus than potential detrimental effects of beta-adrenergic agonists.

On the basis of the potential risks associated with long-term single-agent therapy with a beta-adrenergic agonist, a paradoxical approach to the treatment of asthma may involve long-term administration of a beta-adrenergic antagonist. This approach is analogous to the paradigm based in the cardiovascular system, in which long-term administration of a beta-adrenergic antagonist is beneficial in patients with congestive heart failure. Studies in asthmatic patients are ongoing.

**Methylxanthines** (e.g., theophylline, aminophylline) were used for many years in the long-term treatment of asthma. Although their mechanism of action is controversial, relaxation of airway smooth muscle is the most prominent effect. The ability of the agents to inhibit intracellular phosphodiesterase and increase concentrations of cyclic adenosine monophosphate (cAMP) is not the mechanism of bronchodilation, because these effects do not occur at clinically relevant concentrations in vivo. Furthermore, in the patient taking antiinflammatory agents and beta-adrenergic agonists, methylxanthines add little to optimal asthmatic control. Although their use is now limited to patients whose asthma responds poorly to other forms of therapy, methylxanthines do not appear to cause significant adverse fetal outcomes. Serum concentrations of theophylline should be monitored carefully, especially in the third trimester, when theophylline clearance decreases.

Bronchodilation with **anticholinergic agents** occurs through the blockade of muscarinic receptors on airway smooth muscle. Overall, anticholinergic agents alone are not as effective as beta-adrenergic agonists, but some patients show better response to anticholinergic agents. The effects of adding anticholinergic agents to beta-adrenergic agonists for acute and chronic asthma were evaluated in meta-analyses of randomized trials. Anticholinergic agents improved lung function in acute asthma but had little benefit in chronic asthma. The **quaternary anticholinergic agent ipratropium bromide** can be delivered as an aerosol, allowing higher concentrations in the lung with reduced systemic absorption and potential effects on the fetus. Human data on the safety of anticholinergic agents and on potential teratogenicity are lacking, but ipratropium bromide is not associated with teratogenicity in animal studies.

**Magnesium sulfate** relaxes airway smooth muscle, most likely via its antagonism of calcium entry into airway smooth muscle cells. Its use is limited primarily to acute bronchospasm.

### Antiinflammatory Agents

Proposed mechanisms of action for corticosteroids are (1) decreases in cellular infiltration and mediator release, (2) reduction in airway permeability, and (3) upregulation of the beta-adrenergic system. Unlike bronchodilators, corticosteroids not only reduce airway sensitivity to a constrictor stimulus but also decrease the maximal extent of airway narrowing, a feature that may predict severity of an acute asthmatic episode.

The use of **inhaled corticosteroids** has gained popularity. This route of administration is effective and may limit fetal side effects. Studies have assessed the effects of systemic and inhaled corticosteroids on the fetus. Neither systemic nor inhaled corticosteroids have been proven to increase the risk for congenital malformations in humans. Inhaled corticosteroids do not affect glucocorticoid-regulated pathways in the fetus and therefore are unlikely to cause adverse effects on fetal growth and development. Although oral corticosteroid use is associated with an increased incidence of LBW infants, inhaled corticosteroids do not appear to increase perinatal risk. Of interest, use of inhaled corticosteroids guided by measurements of exhaled nitric oxide reduce exacerbations, but improvements in perinatal outcomes have not been proven.

Corticosteroids may increase perinatal morbidity by exacerbating maternal glucose intolerance, especially in women who also receive treatment with a beta-adrenergic agonist. Thus, careful monitoring of maternal glucose concentration is indicated in asthmatic women who require treatment with a corticosteroid during pregnancy. However, because of the efficacy of corticosteroids in controlling severe asthma during pregnancy, these agents should not be withheld from the medical regimen.

Some authorities have recommended that corticosteroid-dependent asthmatic women receive large doses of parenteral corticosteroids during labor to prevent complications related to adrenal suppression. The scientific basis for this recommendation is questionable. Although physiologic glucocorticoid replacement reduced hemodynamic instability and mortality in adrenalectomized primates that underwent surgery, supraphysiologic doses provided no additional benefit. Furthermore, inhaled corticosteroids in moderate doses do not produce adenocortical suppression. There is little information about the benefit of corticosteroid replacement therapy during labor. The potential for adrenal insufficiency in infants of asthmatic mothers taking inhaled or oral corticosteroids appears to be very low, most likely owing to the widespread use of either prednisone or prednisolone. In the mother, prednisone is converted rapidly to prednisolone, which crosses the placental barrier to a very limited extent.

**Cromolyn sodium** and **nedocromil sodium** belong to a class of drugs that are thought to reduce inflammation and mediator release primarily by stabilizing mast cells and perhaps other inflammatory cells. Nedocromil also inhibits...
cellular chloride ion flux, a feature that may explain its ability to affect a range of airway cells, including nerve cells.83

Cromolyn and nedocromil are administered as aerosols. Limited studies suggest that cromolyn is safe during pregnancy,84 and clinical experience is greater with cromolyn than with nedocromil. Thus, use of cromolyn is preferred.

On the basis of the observation that leukotrienes are released into the airways by immune cells and contribute to the inflammatory process, other forms of antiinflammatory therapy are leukotriene receptor antagonists and leukotriene synthesis inhibitors. Safety data for the use of these agents in pregnancy are scarce. Bracken et al.48 did not observe adverse neonatal outcomes in nine women exposed to these agents. A later prospective study of 96 women showed that use of leukotriene receptor antagonists was not associated with a specific pattern of congenital abnormalities, but the investigators cautioned that extrapolation of the data to a large population would require additional studies because of the limited sample size of the study.

A recombinant monoclonal anti-IgE antibody, omalizumab, is used specifically in patients with allergic asthma that is refractory to inhaled corticosteroids. Experience in pregnancy is limited.85

Obstetric Management

The following aspects of obstetric management of the asthmatic parturient may differ from that of the nonasthmatic patient: (1) induction of labor, (2) management of postpartum hemorrhage, and (3) treatment of hypertension.

For induction of labor, prostaglandins should be administered cautiously in women with asthma. Prostaglandin F₂α constricts airways in vivo86 and in vitro.87 Airways of asthmatic subjects demonstrate greater sensitivity to prostaglandin F₂α, and its use to induce labor is associated with bronchospasm.88 Prostaglandin E₃ can have either dilating or constricting effects on the airways, perhaps because of its ability to activate a variety of different types of prostaglandin receptors.89 Because of the known risk for bronchospasm after exposure to prostaglandin F₂α and the possible risk after exposure to prostaglandin E₃, alternative methods of induction of labor are preferred in asthmatic women.

Likewise, asthma represents a relative contraindication to the administration of 15-methyl prostaglandin F₂α (carbo-prost, Hemabate) for the treatment of postpartum hemorrhage. The use of ergot alkaloids to treat postpartum hemorrhage in asthmatic women has also been questioned. Although controlled studies have not been performed, ergot alkaloids have been associated with episodes of acute bronchospasm.90,91 on the basis of either their tryptaminergic actions or their ability to activate alpha₁-adrenergic receptors on airway smooth muscle cells. Oxytocin, which does not significantly affect airway tone, is the preferred ecbolic agent in asthmatic patients.

Beta-adrenergic receptor antagonists are used to treat hypertension in some pregnant women. In asthmatic women, these agents may provoke bronchospasm when used acutely.92 Other antihypertensive agents, such as hydralazine, nifedipine, or nitroglycerin, do not seem to enhance airway responsiveness.

Anesthetic Management

Preoperative Assessment

During the preoperative evaluation, the anesthesia provider should assess the severity of the disease and whether an acute asthmatic episode is present. The medical history should include information about symptoms of wheezing, dyspnea, and cough. Further information should be sought about the frequency and severity of symptoms, the course of these symptoms during pregnancy, and the date of the most recent exacerbation. Patients who have frequent, severe attacks are at increased risk for morbidity in the peripartum period.

Physical examination should focus on the pulmonary system. Chest auscultation may demonstrate wheezing with or without a prolonged expiratory phase. However, wheezing may not be audible if air movement is markedly reduced. Additional signs of an acute exacerbation of asthma include tachypnea, an exaggerated (greater than 20 mm Hg) pulsus paradoxus, and the use of accessory respiratory muscles.

In a pregnant woman with stable asthma, laboratory tests add little to anesthetic management. However, if an acute exacerbation is suspected, chest radiographic examination, arterial blood gas measurements, and pulmonary function tests may assist with diagnosis and therapy. Chest radiographic examination helps diagnose precipitating or complicating conditions such as pneumonia, pneumothorax, and heart failure. During an episode of acute asthma, arterial blood gas measurements often show hypoxemia and respiratory alkalosis. After a prolonged, severe episode, arterial carbon dioxide tension increases as a result of fatigue. Spirometry measures the volume of gas exhaled over time (see Box 52.1). The most convenient indirect measurement for assessing airway obstruction during labor is the peak expiratory flow rate, which can be measured at the bedside with a Wright peak flowmeter.93

Management during Labor and Vaginal Delivery

The goals of analgesia for labor and delivery in asthmatic women include (1) provision of pain relief, (2) reduction in the stimulus to hyperpnea, and (3) prevention or relief of maternal stress. The goal of adequate pain relief does not differ for asthmatic women. It is important to prevent hyperpnea and stress in women who describe asthmatic episodes triggered by exercise or stress. These goals should be accomplished with minimal sedation, minimal paralysis of the muscles of respiration, and minimal depression of the fetus. Possible analgesic regimens include systemic opioids, paracervical block, pudendal nerve block, lumbar sympathetic block, and epidural or spinal analgesia using local anesthetic agents, opioids, or both.

Systemic opioids may provide reasonable pain relief and reduce the stimulus to hyperpnea, especially during the early part of the first stage of labor. In theory, opioids reduce the risk for bronchospasm in asthmatic subjects. Opiate receptors are believed to be present in the respiratory tract44 and to

85
inhibit release of excitatory neuropeptides. The clinical relevance of these findings is unknown, because moderate doses of inhaled morphine do not significantly alter airway tone. Conversely, high doses of some opioids (e.g., morphine) may increase the risk for bronchospasm by releasing histamine. The risk associated with using moderate doses of morphine does not seem excessive, because airway tone does not change in subjects with moderate to severe asthma after inhalation of morphine. An opioid that does not release histamine (e.g., fentanyl, remifentanil) may be a better choice for the asthmatic parturient. High doses of opioids are not desirable in subjects with active wheezing because of the risks for maternal and neonatal respiratory depression (see Chapter 22).

Paracervical block and pudendal nerve block performed by an obstetrician are acceptable choices for analgesia during the first and second stages of labor, respectively. These techniques provide analgesia without sedation or paralysis of the respiratory muscles. The problems with these techniques in asthmatic patients are similar to those in nonasthmatic parturients (see Chapter 24).

Lumbar sympathetic block also provides pain relief without sedation or motor block during the first stage of labor. This technique has the same limitations as for women without asthma (see Chapter 24).

Intrathecal and epidural opioid techniques are useful during the first stage of labor and do not produce motor block (see Chapter 23). The advantage of the absence of motor block should be weighed against the risk for respiratory depression in asthmatic subjects.

Advantages of the use of local anesthetic agents for lumbar epidural analgesia in asthmatic patients include continuous pain relief and a reduction in the stimulus to hyperventilation. These goals typically are achieved without maternal sedation or neonatal depression. Unlike other analgesic techniques, continuous lumbar epidural analgesia adds a margin of safety by providing the opportunity to extend the sensory block for cesarean delivery. The possibility of extension allows the anesthesia provider to avoid some of the risks associated with general anesthesia. The most significant disadvantage of epidural local anesthetics in an asthmatic subject is the risk for a high thoracic motor block and respiratory insufficiency. Use of an appropriate epidural catheter test dose and maintenance of a sensory level at the 10th thoracic dermatome minimize this risk. In addition, the use of a dilute concentration of local anesthetic combined with a modest dose of an opioid produces satisfactory analgesia with less motor block than local anesthetic alone.

Management during Cesarean Delivery

The choice between neuraxial anesthesia and general anesthesia for cesarean delivery depends on obstetric considerations and the respiratory status of the parturient. In general, avoidance of airway instrumentation is desirable, because tracheal intubation markedly increases airway tone in asthmatic subjects.

The most significant advantage of neuraxial anesthesia in the asthmatic patient is that this technique obviates the necessity for tracheal intubation. Neuraxial anesthesia is associated with a lower incidence of bronchospasm than general anesthesia in asthmatic subjects. Stable asthmatic patients can undergo either spinal or epidural anesthesia. In unstable asthmatic patients who require the use of accessory muscles of respiration, neuraxial anesthesia may be hazardous because of impaired ventilatory capacity in the presence of a high thoracic motor block. Intrathecal administration of either ropivacaine or levobupivacaine, which may produce less motor block than bupivacaine, does not confer any advantage with respect to pulmonary function in women receiving spinal anesthesia for cesarean delivery.

The adrenal medulla receives innervation from preganglionic sympathetic fibers arising from the sixth thoracic to the second lumbar spinal segment. Some authors have postulated that neuraxial anesthesia and the ensuing sympathetomy could precipitate or potentiate bronchospasm during cesarean delivery in asthmatic subjects by reducing adrenal output of epinephrine. This possibility seems remote. First, although epinephrine infusion can reduce airway reactivity in asthmatic subjects, epinephrine concentrations do not decrease during nonobstetric surgery performed with neuraxial anesthesia that achieves high thoracic sensory levels. Second, the idea that neuraxial anesthesia may prevent increases in circulating epinephrine that are required to compensate for stress-induced bronchospasm does not appear to be valid. Bronchoconstriction does not stimulate epinephrine secretion in human asthmatic subjects. Thus, neuraxial anesthesia is appropriate for cesarean delivery in stable asthmatic subjects.

General anesthesia for asthmatic women undergoing cesarean delivery requires a balance between the competing considerations of pulmonary aspiration and intraoperative bronchospasm. Although airway instrumentation provides a great stimulus for bronchospasm, the high risk for aspiration mandates tracheal intubation during administration of general anesthesia in parturients.

Most commonly, options for tracheal intubation include awake intubation and rapid-sequence induction, although mask induction of general anesthesia with sevoflurane has been described in a parturient with status asthmaticus. Indications for awake intubation in asthmatic subjects are similar to those for nonasthmatic patients, and pretreatment with a local anesthetic and a beta-adrenergic agonist can attenuate reflex-induced bronchoconstriction after awake intubation. The benefits of topical local anesthetics and airway nerve blocks for awake intubation should be weighed against a possible increase in the risk for aspiration from the loss of protective airway reflexes. Rapid-sequence induction for cesarean delivery in asthmatic patients is most often accomplished using either propofol or ketamine. A sympathomimetic agent, ketamine has long been considered the intravenous induction agent of choice for asthmatic subjects. Ketamine relaxes airway smooth muscle and inhibits neural reflexes. Propofol provides better protection than thiopental against bronchospasm associated with tracheal intubation in asthmatic patients, but it has not been compared directly.
with ketamine in humans. Beneficial airway effects of propofol, like those of ketamine, also appear to occur via inhibition of airway reflexes. Intravenous lidocaine, which also inhibits airway reflexes, attenuates irritant-induced bronchoconstriction, including tracheal intubation, and produces an additional protective effect above that of beta-adrenergic agonist pretreatment alone.109 In patients without asthma, maintenance of general anesthesia typically includes administration of a low concentration of a volatile halogenated anesthetic agent, with or without nitrous oxide, before delivery of the infant. After delivery, maintenance of anesthesia typically consists of nitrous oxide and an intravenous opioid, with or without a low concentration of a volatile halogenated agent. In asthmatic parturients, the volatile halogenated anesthetic agents are considered the agents of choice for the maintenance of anesthesia. These agents attenuate airway responsiveness through direct effects on airway smooth muscle,110–112 inhibition of airway reflexes,113 and effects on the epithelium.114

A high concentration of a volatile halogenated anesthetic agent has salutary effects on the airways but also increases the risk for hemorrhage during cesarean delivery by causing dose-dependent uterine relaxation.115 Alternatively, nitrous oxide, an intravenous opioid, and a low concentration of a volatile halogenated agent may be given. Although halothane and isoflurane are approximately equipotent bronchodilators at high concentrations, halothane produces greater bronchodilation at lower concentrations116 and therefore may be preferable for anesthesia for cesarean delivery. Sevoflurane acts as a bronchodilator in large and small airways117 and reverses airway constriction associated with tracheal intubation.118 Effects of desflurane are controversial. Desflurane protects against a direct stimulus to the airways119 but may be less effective against reflex stimuli, such as tracheal intubation.120 A bronchodilator can be added if bronchospasm occurs. The potential disadvantage of this technique is that the most effective bronchodilators (i.e., the beta-adrenergic agonists) also relax uterine smooth muscle. The administration of a beta-adrenergic agonist by aerosol delivers a relatively greater dose of drug to the airways and minimizes uterine relaxation.

Emergence from general anesthesia, as with induction, requires a balance between reducing the risk for aspiration and lowering the risk for bronchospasm. Exubtuation of the trachea when the patient is awake minimizes the risk for aspiration, but the tracheal tube may stimulate reflexes and precipitate bronchospasm as the depth of anesthesia is reduced. If bronchospasm occurs during emergence, bronchodilators can be administered. For refractory bronchospasm, continued mechanical ventilation in an intensive care unit may be required.

**CIGARETTE SMOKING**

**Epidemiology**

Cigarette smoking is a significant, preventable cause of maternal morbidity and perinatal morbidity and mortality.121 The prevalence of smoking among pregnant women in the United States declined from 18.1% in 1991 to 8.4% in 2014, and approximately 72% of women who smoke quit smoking during pregnancy.122

**Pathophysiology**

Cigarette smoke contains a large number of separate components that have a variety of biologic effects. Nonrespiratory effects of cigarette smoking are described in Chapter 53.

The primary respiratory effects of cigarette smoking include alterations in small airway function, increased mucus secretion, and impairment of ciliary transport.123 The precise mechanisms for these effects are unknown. Smoking also is associated with an increase in nonspecific airway reactivity, possibly through epithelial damage, altered airway geometry caused by increased mucus secretion, or upregulation of endothelin receptors.124 These changes lead to a marked increase in the incidence of postoperative pulmonary complications.

**Interaction with Pregnancy**

Few studies have documented the respiratory effects of cigarette smoking during pregnancy. In one study, reductions in forced expiratory flow rates suggested that pregnant women who smoke cigarettes have greater small airway resistance than those who do not smoke.125 These and other abnormalities were similar to the changes in airway function observed in nonpregnant smokers. Although further studies are warranted, other respiratory effects of cigarette smoking in pregnant women are likely to be similar to those effects in nonpregnant women.

Cigarette smoking adversely affects pregnancy in a number of ways. The association between smoking and LBW has a genetic influence, such that the specific variation of the nicotinic acetylcholine receptor gene cluster is associated with lower newborn birth weight in smokers but not in nonsmokers.126 One potential mechanism for these detrimental effects may be chronic, intermittent reductions in uterine perfusion. In a rodent model, reductions in uterine blood flow following inhaled nicotine were mediated by sympathetic nicotinic acetylcholine receptors.127 In addition, even low levels of cigarette smoke alter fetal metabolic pathways.128 Further details regarding adverse maternal and fetal effects of smoking are described in Chapter 53.

**Medical Management**

Cessation of smoking is the preferred form of medical management. Smoking cessation programs are effective in pregnant women.129 Nonpharmacologic methods are preferred to pharmacologic methods (e.g., nicotine patches) because of insufficient safety information for the latter. Das et al.130 demonstrated that smoking cessation before or early in pregnancy results in prompt improvement in maternal airway function. Smoking cessation reduces perioperative complications in the nonpregnant patient undergoing surgery,131 but no controlled studies have evaluated effects of smoking cessation on peripartum outcome.
Anesthetic Management

Tracheal intubation is associated with bronchospasm in smokers.\textsuperscript{132} For vaginal delivery, any of the analgesic techniques described earlier for asthmatic parturients are acceptable. For cesarean delivery, neuraxial anesthesia achieves the goal of avoiding airway instrumentation and is therefore preferable to general anesthesia, although no controlled studies have documented differences in peripartum morbidity. If general anesthesia is required, the methods for reducing the risk for intraoperative bronchospasm described previously may be considered. During induction of general anesthesia in smokers, the formulation of propofol containing sulfate results in greater respiratory resistance after tracheal intubation than the formulation containing ethylenediaminetetraacetic acid (EDTA).\textsuperscript{133} The clinical significance of this finding is unknown. One study noted that respiratory resistance did not decrease after tracheal intubation in smokers anesthetized with desflurane,\textsuperscript{120} suggesting that other volatile halogenated anesthetic agents might be preferable.

CYSTIC FIBROSIS

Epidemiology

Cystic fibrosis, a lethal genetic disorder that is transmitted as an autosomal recessive trait, affects approximately 1 in 3500 births in the United States.\textsuperscript{134} Because of improvements in diagnosis and therapy, a growing number of women with cystic fibrosis survive to reproductive age. From 2005 to 2014, the pregnancy rate in cystic fibrosis patients in the United States decreased approximately 2% per year, but whether this is limited to cystic fibrosis patients or simply reflects the U.S. trend has not been determined.\textsuperscript{135}

Pathophysiology

Clinical features of cystic fibrosis result from abnormalities of epithelial tissues, especially in the respiratory, digestive, and reproductive tracts. The underlying mechanism is a defect in cAMP-mediated activation of chloride (Cl\textsuperscript{−}) conductance in the epithelium.\textsuperscript{136,137} Normal epithelial cells secrete Cl\textsuperscript{−} in response to an increase in intracellular cAMP. In cystic fibrosis, a genetic mutation makes epithelial cells unable to alter Cl\textsuperscript{−} permeability in response to changes in cAMP. The gene responsible for cystic fibrosis is located on chromosome 7 and encodes a protein known as the cystic fibrosis transmembrane regulator (CFTR),\textsuperscript{138,139} which may be absent or dysfunctional as a result of multiple mutations. The CFTR acts as a Cl\textsuperscript{−} channel but also has a number of other actions. Cystic fibrosis is characterized by impaired water flow from the interior to the exterior of epithelial cells, leading to obstruction of exocrine glands with mucus.

In the lungs, abnormalities of electrolyte transport alter the composition of airway secretions. Inflammation, with infiltration of polymorphonuclear leukocytes, also contributes to changes in airway secretions.\textsuperscript{120} Large numbers of integrating neutrophils release DNA in quantities sufficient to overwhelm the ability of deoxyribonuclease I (DNase I), an endogenously released enzyme, to digest extracellular DNA. Undigested DNA increases the viscosity of airway secretions, which causes obstruction of small airways and reduced lung volumes. The ensuing ventilation-perfusion inequalities produce arterial hypoxemia. Some patients have hyperreactive airways. Spontaneous pneumothorax often occurs. Chronic airway obstruction and impaired mucus clearance increase the frequency of pulmonary infection. Most patients become colonized or infected with \textit{Pseudomonas aeruginosa}. Eventually, tissue damage leads to bronchiectasis and pulmonary insufficiency. Chronic hypoxemia and lung destruction may produce pulmonary hypertension and cor pulmonale. Nonrespiratory manifestations of cystic fibrosis include pancreatic exocrine insufficiency, intestinal obstruction, and infertility.

Diagnosis

Clinical criteria for the diagnosis of cystic fibrosis include (1) the presence of chronic obstructive lung disease and colonization with \textit{P. aeruginosa} before 20 years of age, (2) exocrine pancreatic insufficiency, and (3) a family history of cystic fibrosis. Laboratory findings include (1) sweat Cl\textsuperscript{−} concentrations greater than 60 mEq/L, (2) CFTR genotype with two known cystic fibrosis mutations, and (3) detection of CFTR dysfunction by the nasal potential difference test.\textsuperscript{141} Chest radiographic examination often demonstrates hyperinflation, and arterial blood gas measurements may show hypoxemia. Pulmonary function tests, which can reveal obstructive or restrictive lung patterns, are useful to assess the severity of the disease. With serial measurements, clinicians should look for evidence of an increased residual volume and a reduced FEV\textsubscript{1} (forced expiratory volume in 1 second).\textsuperscript{142}

Interaction with Pregnancy

Effect of Pregnancy on Cystic Fibrosis

The following factors may contribute to the deterioration of pulmonary function during pregnancy: (1) increased airway responsiveness and obstruction (as can occur in patients with asthma), (2) increased work of breathing, and (3) cardiovascular changes such as congestive heart failure and pulmonary hypertension associated with the increased blood volume of pregnancy.

In spite of potential negative effects of pregnancy on the course of cystic fibrosis, long-term maternal outcome does not appear to be affected.\textsuperscript{143} However, temporary reductions in FEV\textsubscript{1} in the immediate postpartum period may occur,\textsuperscript{144} and prepregnancy FEV\textsubscript{1} is a useful predictor of ability to tolerate pregnancy.\textsuperscript{145}

Effect of Cystic Fibrosis on Pregnancy

Cystic fibrosis has been associated with an increased risk for LBW infants and preterm delivery, but recent evidence suggests that improved care of these patients can mitigate these problems.\textsuperscript{146} Potential mechanisms for these complications include chronic hypoxemia and poor maternal nutrition.
Medical Management

Respiratory management of cystic fibrosis is primarily symptomatic. Patients with large volumes of mucus production undergo mechanical airway clearance. Some patients inhale recombinant human DNase I to reduce viscosity of lung secretions caused by accumulating DNA. Hypertonic saline inhalation aids clearance of airway mucus. Bronchodilators may help those patients who manifest a reversible component of airway obstruction. Continuous oxygen therapy may benefit patients with hypoxemia and cor pulmonale.

Long-term antibiotic therapy with inhaled tobramycin reduces both the incidence of recurrent pulmonary infection and the frequency of exacerbations in patients with cystic fibrosis. Long-term administration of oral azithromycin also decreases exacerbations from cystic fibrosis through either its antibiotic or its antiinflammatory properties. Effects of long-term antibiotic therapy on the fetus are unknown.

Other forms of therapy include gene therapy and lung transplantation. The goal of gene therapy is to improve function of the defective CFTR protein. Ivacaftor and lumacaftor/ivacaftor combination therapy are used for patients with certain specific mutations. With only anecdotal experience in pregnancy, the safety of these CFTR modulators for the fetus has not yet been established. Significant pulmonary deterioration sometimes leads to double-lung transplantation, although it is unclear whether transplantation alters survival.

Obstetric Management

Because of the influence of pregravid maternal health on pregnancy outcome, the primary obstetric issue centers on the advisability of pregnancy in patients with cystic fibrosis. Criteria for the termination of pregnancy are not clearly defined. Genetic counseling regarding the risk for cystic fibrosis in the offspring is another important component of obstetric management.

Anesthetic Management

Considerations for anesthetic management focus primarily on the pulmonary system. Because of the high incidence of hypoxemia in patients with cystic fibrosis, continuous monitoring of oxygen saturation and appropriate oxygen therapy are advisable.

The goals of pain relief during labor are to provide adequate analgesia and to prevent maternal hyperventilation while avoiding high thoracic motor block and respiratory depression. High thoracic motor block may impair the parturient’s ability to cough and eliminate thick secretions. Hyperventilation increases the work of breathing and may cause decompensation in patients with severe pulmonary dysfunction. For pain relief during labor, parenteral opioid analgesia may worsen pulmonary function by depressing respiratory drive and inhibiting cough. Intrathecal opioids have been used successfully, but patients should be monitored carefully for respiratory depression. Continuous lumbar epidural analgesia, with a sensory nerve block maintained at the level of the 10th thoracic dermatome, can provide excellent pain relief and reduce the stimulus for hyperventilation, with minimal motor block of the thorax. A dilute solution of bupivacaine, with or without an opioid, provides sensory analgesia with minimal motor block and is therefore nearly ideal in this setting. In healthy parturients, this technique actually improves respiratory function slightly.

Cesarean delivery necessitates the choice between general anesthesia and neuraxial anesthesia. Among patients with cystic fibrosis, no studies have documented differences in outcome between general anesthesia and neuraxial anesthesia. Neuraxial anesthesia offers the advantage of avoiding tracheal intubation, which may be associated with bronchospasm or obstruction of the tracheal tube with secretions. Neuraxial anesthesia also avoids positive-pressure ventilation, which may enlarge a preexisting pneumothorax. The primary consideration for neuraxial anesthesia during cesarean delivery is to avoid a high thoracic motor block, which may impair ventilation and the ability to cough. Effective spinal anesthesia for cesarean delivery slightly decreases vital capacity. Methods for reducing the risk for excessively high motor block include the use of a continuous catheter technique, which allows titration of the local anesthetic agent to achieve the desired sensory level, and the use of the lowest concentration of local anesthetic (with or without an opioid) that provides surgical anesthesia. Both epidural anesthesia and combined spinal-epidural anesthesia have been used in parturients with cystic fibrosis.

For general anesthesia, techniques to reduce the risk for bronchospasm, as described for patients with asthma (see earlier discussion), may be warranted. Additional considerations include (1) humidification of gases to prevent inspissation of mucus, (2) frequent suctioning to remove excess secretions, and (3) use of ventilator settings that allow an appropriately long expiratory phase to prevent air trapping and pneumothorax. It may also be prudent to avoid nitrous oxide in the parturient with cystic fibrosis, because of the risk for pneumothorax. Patients with cystic fibrosis should be allowed to awaken fully before extubation of the trachea. Chest physiotherapy may be required in the immediate postoperative period.

RESPIRATORY FAILURE

Epidemiology

The prevalence of respiratory failure during pregnancy is thought to be as many as 1 in 500. While the most common obstetric causes are hypertensive disease and hemorrhage, a significant number of patients suffer from acute respiratory distress syndrome (ARDS). A large database analysis of more than 55 million pregnancies from 2006 to 2012 revealed that the number of pregnant patients requiring mechanical ventilation as a result of ARDS increased from 36.5 cases per 100,000 live births in 2006 to 59.6 cases per 100,000 live births in 2012, and the in-hospital mortality rate was 9%.

Pathophysiology

The pathophysiology of respiratory failure depends on the underlying disorder. ARDS results from a group of conditions that cause widespread pulmonary inflammation and edema.
predisposing conditions. Damage to the alveolar and capillary membranes initiates a cascade of events leading to fluid transudation that often is accompanied by pulmonary venoconstriction. Direct injury to the alveolar and capillary membranes can result from pulmonary aspiration of gastric contents and perhaps oxygen toxicity. Indirect toxicity can result from humoral and cellular mechanisms caused by triggers such as sepsis and amniotic fluid embolism. Transudation of fluid leads to atelectasis, airway obstruction, reduced lung compliance, and altered ventilation-perfusion relationships. Both physiologic dead space and shunt fractions are increased.

**Diagnosis**

A variety of disorders can cause acute respiratory failure during pregnancy (Box 52.4). Specific diagnostic criteria depend on the disorder.

The diagnosis of ARDS requires the exclusion of other disorders. Prominent characteristics of ARDS include arterial hypoxemia, radiographic evidence of pulmonary infiltrates, and reduced lung compliance in the setting of a recognized predisposing condition.

**Interaction with Pregnancy**

Pregnancy is not known to alter the overall course of respiratory failure. However, differences in outcome between pregnant and nonpregnant patients have been observed in subsets of patients with respiratory failure. In a series of patients with severe acute respiratory syndrome (SARS), pregnant patients had greater morbidity. Mortality rates are similar in pregnant and nonpregnant subjects. Although delivery of the infant has been suggested as a means to improve maternal respiratory status, evidence indicates that improvement cannot be expected in every patient.

The most significant effect of respiratory failure on pregnancy is a reduction in oxygen delivery to the fetus. This reduction results most commonly from maternal arterial hypoxemia or maternal hypotension, which often accompanies respiratory failure. Hypotension may result from associated underlying conditions or from elevated mean airway pressures during mechanical ventilation. High rates of prenatal complications with or without preterm delivery have been reported.

**Medical Management**

Therapeutic strategies for managing respiratory failure during pregnancy do not differ qualitatively from those in nonpregnant patients. The primary goals of medical management are to (1) eliminate predisposing conditions, (2) limit fluid transudation, and (3) maintain maternal oxygen delivery. Fluid restriction and diuretics help limit fluid transudation, although this therapy must be used cautiously when the underlying cause of respiratory failure is associated with intravascular fluid depletion. The goals for maintenance of oxygen delivery may differ quantitatively during pregnancy. Oxygen delivery to the fetus worsens significantly when PaO₂ decreases below 70 mm Hg or oxygen saturation (SaO₂) falls below 95%. Standard methods of maintaining oxygen delivery include (1) administration of a higher inspired concentration of oxygen, (2) administration of bronchodilators in the presence of reversible airway obstruction, (3) administration of pharmacologic agents to support the circulation as needed, and (4) mechanical ventilation. A higher inspired oxygen concentration, delivered by face mask, is safe during pregnancy and may obviate the necessity of tracheal intubation and its risks for aspiration and difficult airway management. Bronchodilator therapy can also be used for respiratory failure, as described earlier for asthma. Pharmacologic agents for circulatory support include agents with both alpha- and beta-adrenergic receptor activity.

Indications for tracheal intubation and mechanical ventilation are similar for pregnant and nonpregnant patients with respiratory failure. Maternal and fetal effects of current approaches to mechanical ventilation, including use of low tidal volumes and permissive hypercapnia, have not been studied in pregnant patients. Positive end-expiratory pressure may be used if cardiac output is maintained to allow sufficient blood flow to the uterus.

Some pregnant patients with respiratory failure do not show adequate response to conventional methods of treatment. For these patients, treatment options include extracorporeal membrane oxygenation (ECMO), high-frequency
oscillatory ventilation,\textsuperscript{170} and inhaled nitric oxide.\textsuperscript{171} Nitric oxide relaxes vascular smooth muscle. Rapid inactivation of nitric oxide by binding to hemoglobin in the circulation allows inhaled nitric oxide to produce pulmonary vasodilation without systemic vascular effect. Selective pulmonary vasodilation in well-ventilated areas of the lung presumably would improve oxygen delivery. The safety of these alternative forms of treatment in pregnancy is unknown because reports of their use are anecdotal.

**Obstetric Management**

Because the beneficial effects of delivery on the course of respiratory failure have not been proven, indications for induction of labor or cesarean delivery in this setting are not well defined. Small observational studies have not clearly shown an association between delivery and improved respiratory status in pregnant women with respiratory failure.\textsuperscript{161,172,173} Further, data to support decisions regarding mode of delivery are limited. Vaginal delivery is possible during mechanical ventilation\textsuperscript{174,175} and may avoid complications of major intra-abdominal surgery in a critically ill woman.

**Anesthetic Management**

The anesthetic management of patients with respiratory failure requires appropriate medical management. During labor, analgesia for mechanically ventilated patients can be achieved with intravenous opioids, which are often used for sedation during mechanical ventilation. Lumbar epidural analgesia provides pain relief without the neonatal respiratory depression associated with high doses of opioids. Labor epidural analgesia also reduces oxygen consumption,\textsuperscript{176} which may be beneficial in hypoxemic patients. The use of labor epidural analgesia in patients with respiratory failure depends on underlying conditions and ongoing therapy. Close attention should be paid to intravascular volume, adequacy of coagulation, and presence or absence of infection.

In mechanically ventilated patients, general endotracheal anesthesia is often the most convenient choice for cesarean delivery. Aside from the issues of medical management (as discussed earlier), the techniques and pharmacologic agents do not differ substantially from those used in patients without respiratory failure.

**KEY POINTS**

- Patients with asthma, infection, respiratory failure, or cystic fibrosis and patients who smoke cigarettes may have reversible airway obstruction.
- In patients with airway hyperresponsiveness, tracheal intubation provides one of the most significant stimuli for bronchospasm during the perioperative period.
- Inhaled beta\textsubscript{2}-adrenergic agonists are the most effective therapy for perioperative bronchospasm.
- Most bronchodilators also produce uterine relaxation. However, their administration by aerosol should minimize their effects on uterine tone.
- Neuraxial anesthesia is often the anesthetic technique of choice in patients with respiratory disease because it does not require tracheal intubation.
- Techniques of neuraxial anesthesia should be modified to reduce the likelihood of a high thoracic motor block in patients with significant respiratory disease.

**REFERENCES**


95. Otuolana B, Okikawa J, Linn L, et al. Safety and pharmacokinetics of inhaled morphine delivered using the


Use of licit and illicit substances by pregnant women can pose a significant risk to maternal and fetal health. To improve diagnosis and reduce the moral tenor, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) replaced the term substance abuse with a continuum of mild, moderate, or severe substance use disorder. Estimates of the prevalence of maternal substance use vary depending on the particular licit or illicit substance, the maternal age group, the extent of use, and the data source. Overall, the rate of past-month illicit drug use in pregnant women as reported in the National Survey on Drug Use and Health in 2015 was 4.7% compared with 12.5% of nonpregnant women 15 to 44 years of age.

Anesthesia providers play a fundamental role in caring for these patients during labor and delivery and postpartum. Depending on the particular substance, pregnant women may experience little to no acute and chronic adverse effects, or alternatively, may manifest one or more of the following: (1) cardiovascular, pulmonary, and neurologic complications or (2) obstetric complications (e.g., fetal growth restriction, preterm labor, placental abruption, fetal death). Patients with substance use disorder may also have heightened sensitivity to pain and/or tolerance to opioid analgesics, which may impact acute postoperative pain management.

**DRUG DETECTION**

Optimal care requires developing a therapeutic bond with these patients and identifying what substances have been taken. Providers should ask questions in a respectful and nonjudgmental manner. It is vital to respect patient confidentiality, which may mean speaking to the patient without family or friends present. Self-reporting typically underrepresents the true prevalence of drug use. Therefore, health care providers should be familiar with the characteristic signs and symptoms associated with acute and chronic intoxication. Although analysis of urine, meconium, and hair are the most common methods to test pregnant patients and their infants for the presence of illicit drugs, analysis of saliva, umbilical cord tissue, amniotic fluid, and neonatal gastric aspirate can also be done (Tables 53.1 and 53.2). Caregivers should be aware that the immunoassays most commonly used in drug testing can have false-positive or false-negative results in the presence of structurally related drugs or additives. Gas chromatography with mass spectrometry ideally should be used to provide confirmation of positive results.

**PLIC SUBSTANCES**

**Alcohol**

**Epidemiology**

Since 1981, official advisories have warned against the use of alcohol by pregnant women or women considering pregnancy. Yet, the 2015 National Survey on Drug Use and Health noted that 9.3% of pregnant women 15 to 44 years of age reported past-month alcohol use, 4.6% reported binge drinking, and 0.8% reported heavy drinking. Not all of these women have alcohol use disorder or are drinking alcohol recklessly. Some may not be aware that they are pregnant, or
TABLE 53.1 Drug Detection: Overview

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine</strong></td>
<td>Detection of diverse group of illicit substances (except volatile alcohols)</td>
<td>Underrepresents most illicit drug use</td>
</tr>
<tr>
<td></td>
<td>Specimen and test readily available</td>
<td>Significant false-positive rate for phencyclidine (PCP)</td>
</tr>
<tr>
<td></td>
<td>Short turnaround time (30 min at point of care; 2 h for laboratory specimens)</td>
<td>Narrow detection window compared with that for meconium and hair</td>
</tr>
<tr>
<td></td>
<td>More sensitive test (compared with meconium and hair) for cannabis</td>
<td>Specimen can more easily be adulterated</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>Most commonly used for volatile alcohols (can detect other illicit substances)</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Specimen and test readily available</td>
<td>Narrow detection window compared with that for urine, meconium, and hair</td>
</tr>
<tr>
<td><strong>Meconium</strong></td>
<td>Highly sensitive (compared with urine testing) for cocaine and opioids</td>
<td>Report may be delayed (days)</td>
</tr>
<tr>
<td></td>
<td>Wide detection window</td>
<td>Low sensitivity and specificity for detecting cannabinoids, heroin, and amphetamines via immunoassay</td>
</tr>
<tr>
<td></td>
<td>No false-positive results for cocaine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noninvasive</td>
<td></td>
</tr>
<tr>
<td><strong>Hair</strong></td>
<td>Highly sensitive test for detecting cocaine (three times that of urine) and opioids</td>
<td>Multiple hairs required; harvested close to scalp</td>
</tr>
<tr>
<td></td>
<td>Wide detection window (reflects chronic cumulative use)</td>
<td>Environmental contamination may cause false-positive result</td>
</tr>
<tr>
<td></td>
<td>Samples can be stored at room temperature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Samples can be analyzed remote from collection</td>
<td></td>
</tr>
<tr>
<td><strong>Umbilical cord blood</strong></td>
<td>Comparable to meconium with more rapid results</td>
<td>Specimen not available before delivery</td>
</tr>
<tr>
<td></td>
<td>May reflect a wide window of detection</td>
<td>Lower sensitivity to methadone, cocaine, and opiates compared with meconium</td>
</tr>
<tr>
<td></td>
<td>Ability to detect codeine, morphine, 6-MAM (heroin metabolite), and meconin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noninvasive</td>
<td></td>
</tr>
<tr>
<td><strong>Oral fluid</strong></td>
<td>Highly sensitive for methamphetamine and other basic drugs</td>
<td>If mouth is dry, salivary stimulation may be associated with a decreased drug concentration in oral fluid</td>
</tr>
<tr>
<td></td>
<td>Easy, noninvasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primarily detects parent compound</td>
<td></td>
</tr>
</tbody>
</table>

6-MAM, 6-monoacetylmorphine.
Data from references 14,15,17,130,209–213

TABLE 53.2 Drug Detection Window in Urine*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analyte</th>
<th>Detection Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>Cotinine</td>
<td>19 h (urine $T_{1/2}$)</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>2 h (urine $T_{1/2}$)</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>3–6 h</td>
</tr>
<tr>
<td></td>
<td>Benzoylcegonine</td>
<td>IV use: 1–2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intrasanal use: 2–3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–3 days</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Amphetamine</td>
<td>Smoked: 60 h</td>
</tr>
<tr>
<td></td>
<td>Methamphetamine</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Methylenedioxymethamphetamine (MDMA, ecstasy)</td>
<td>MDMA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetrahydrocannabinol (THC)</td>
<td>Smoked: 10 h</td>
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<tr>
<td></td>
<td>THCCOOH</td>
<td>Up to 25 days</td>
</tr>
<tr>
<td>Marijuana (cannabis)</td>
<td>LSD</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>2-Oxo-3-DH-LSD</td>
<td>96 h</td>
</tr>
<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>6-monoacetyl morphine</td>
<td>IV use: 2–4.5 h</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>19–54 h</td>
</tr>
<tr>
<td>Prescription opioids</td>
<td>Oxycodone</td>
<td>2–4 days</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>24–72 h</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>2–4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flunitrazepam: 7-amino-flunitrazepam</td>
<td>&lt; 72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic use: 4–6 wk</td>
</tr>
<tr>
<td>γ-Hydroxybutyric acid (GHB)</td>
<td>Rapidly metabolized to CO₂ and H₂O</td>
<td>&lt; 12 h</td>
</tr>
</tbody>
</table>

*IV, Intravenously; $T_{1/2}$, half-life.

*Average values based on recent use; precise values may vary according to method of ingestion, assay employed, and duration of use.

*Detection of methadone, buprenorphine, oxycodone, and oxymorphone typically requires an additional screening test. Data from references 4,19,75,100,214
may not be knowledgeable of the ill effects on their pregnancy.

**Pharmacology**

Alcohol is absorbed through the gastrointestinal tract, primarily within the small intestine, and is then metabolized by alcohol and acetaldehyde dehydrogenases.\(^{21–23}\) This process leads to the production of acetaldehyde and the reduction of nicotinamide adenine dinucleotide (NAD\(^+\)) to NADH. The intracellular accumulation of NADH relative to NAD\(^+\) results in metabolic derangements, including the inhibition of fatty acid oxidation, resulting in a fatty liver and the inhibition of gluconeogenesis, leading to hypoglycemia or lactic acidosis. A small residual amount (2% to 8%) of alcohol is excreted via the lungs, urine, and sweat.

**Systemic Effects**

Legally defined “intoxication” implies a blood alcohol level of at least 80 to 100 mg/dL, although behavioral, cognitive, and psychomotor changes can occur at levels of 20 to 30 mg/dL (e.g., after one to two drinks)\(^{21–23}\) (Table 53.3).

Alcohol has complex effects on the central nervous system (CNS); it acts as both a depressant and a stimulant through a variety of neurotransmitter pathways.\(^{23}\) Consuming alcohol in conjunction with barbiturates or benzodiazepines compounds these effects. Endogenous opioids interact with alcohol to “reinforce” further alcohol use; this effect is blunted by opioid antagonists such as naltrexone, which can be used in the treatment of alcohol use disorder.

Alcohol and its metabolites (e.g., acetaldehyde) can be directly toxic to brain tissue.\(^{21,22}\) Chronic alcoholism is associated with brain atrophy that results in impairment of memory, abstract problem-solving, verbal learning, and visual-spatial processing. Additional adverse neurologic effects result from vitamin (e.g., thiamine, vitamin B\(_{12}\)) deficiencies.

Heavy alcohol consumption can result in hepatic cirrhosis, which, in turn, can lead to encephalopathy, coagulopathy, and esophageal varices (Table 53.4). Gastrointestinal mucosal injury, pancreatitis, and cardiomyopathy may also occur.\(^{2,22,24}\) In a retrospective cohort study of the Nationwide Inpatient Sample database, women with a diagnosis of alcohol use disorder undergoing cesarean delivery were twice as likely as women without alcohol use disorders to develop a hospital-acquired infection, including urinary tract infection or sepsis.\(^{25}\) The underlying pathophysiology was not reported but could involve an immunocompromised state in chronic alcohol users.

Symptoms of acute alcohol withdrawal (e.g., nausea, vomiting, tachycardia, hypertension, arrhythmias, tremor, hallucinations, agitation, seizures) usually occur within 6 to 48 hours after cessation of chronic consumption (Table 53.3).\(^{7,8}\) Pharmacologic therapy to minimize the signs and symptoms of alcohol withdrawal includes the use of benzodiazepines and alpha\(_2\)-adrenergic receptor agonists (e.g., clonidine).\(^{7}\) Dexmedetomidine, a potent alpha\(_2\)-adrenergic receptor agonist, has also been investigated as an adjunct therapy.\(^{26}\) The most severe form of withdrawal symptoms, delirium tremens, manifests as agitation, disorientation, hallucinations, and fever combined with autonomic instability. Delirium tremens, though rare in pregnant women, can lead to maternal and fetal death if untreated.\(^{7}\)

**Effects on Pregnancy and the Fetus**

Intrauterine alcohol exposure is the leading cause of preventable birth defects in the United States.\(^{27,28}\) No safe level of alcohol consumption by pregnant women has been identified as studies investigating minimal to moderate prenatal alcohol exposure during pregnancy have been limited by confounding variables.\(^{29,30}\) According to the National Organization on Fetal Alcohol Syndrome, fetal alcohol spectrum disorders (FASD) is the “umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications.”\(^{22,23}\) Fetal alcohol syndrome (FAS) refers to a clinical diagnosis and is based on the presence of particular neonatal facial features (e.g., small palpebral fissures, flat mid-face with a short upturned nose, thin upper lip) and significant impairment in neurodevelopment and physical growth.\(^{27,32}\) A recent meta-analysis identified a range of complications that occur with a high prevalence in children affected by FAS including disorders of conduct and language disorder, chronic serous otitis media, and peripheral nerve abnormalities.\(^{33}\) Education and screening for prenatal alcohol exposure can facilitate treatment and improve pregnancy outcomes by encouraging cessation of alcohol consumption as soon as pregnancy is recognized.

**Anesthetic Management**

Alcohol-intoxicated parturients are at increased risk for behavioral problems, electrolyte abnormalities, greater gastric acid secretion, and co-intoxication with other substances.\(^{7,8}\) Determining whether the patient can protect her airway is of paramount importance because acute intoxication increases the risk for pulmonary aspiration of gastric contents. In addition, these patients may have intravascular volume depletion secondary to vomiting, inadequate oral intake, diuresis, and hypoalbuminemia. Significant alcohol ingestion in the setting of poor oral intake may also manifest as severe hypoglycemia.\(^{22,24,34}\)

Neuraxial analgesia or anesthesia can be safely administered for labor or cesarean delivery in patients with alcohol use disorders provided that (1) the patient is cooperative, (2) there is no evidence of coagulopathy (as a result of liver disease), (3) the patient is volume replete, and (4) baseline neurologic deficits (e.g., peripheral neuropathy, cognitive deficits) are assessed and documented.\(^{7}\)

If emergency delivery is required and the patient is either uncooperative or too sedated to protect her airway, general anesthesia will be necessary. The patient should receive pharmacologic aspiration prophylaxis (e.g., nonparticulate antacid, histamine-2 (H\(_2\))-receptor antagonist, metoclopramide) and should undergo a rapid-sequence induction of general anesthesia.\(^{35}\)
Evidence from published reports is inconclusive about predictable differences in anesthetic requirements in patients with acute and chronic alcohol use. Acute alcohol intoxication is believed to decrease anesthetic requirement, in part because of the additive effect of alcohol and other CNS depressants. The notion that chronic alcoholics require more anesthesia than their non–alcohol-using counterparts is based primarily on data from an abstract published by Han in 1969, who demonstrated that the mean minimum alveolar concentration (MAC) for halothane in six chronic, nonpregnant, heavy alcohol users was significantly greater than that for six healthy adults. Subsequently, Swerdlow et al. assessed the response to thiopental in 11 nonpregnant, chronic alcohol users. After eliminating potential confounders such as acute intoxication, withdrawal, polysubstance use, and end-organ dysfunction, they found that chronic alcohol intake did not...
<table>
<thead>
<tr>
<th>Substance</th>
<th>Neurologic</th>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>Gastrointestinal</th>
<th>Hematologic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Peripheral neuropathy</td>
<td>Cardiomyopathy</td>
<td>—</td>
<td>Hepatitis</td>
<td>Anemia (± leukopenia, thrombocytopenia)</td>
<td>↑ Cortisol</td>
</tr>
<tr>
<td></td>
<td>Brain atrophy</td>
<td></td>
<td></td>
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<td></td>
<td>Encephalopathy</td>
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<tr>
<td>Tobacco</td>
<td>—</td>
<td>Atherosclerosis</td>
<td>Diffusion capacity abnormalities</td>
<td></td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>↓ Pulmonary immune function</td>
<td></td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>↑ Incidence of bronchitis, COPD</td>
<td></td>
<td>—</td>
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<td></td>
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<td></td>
<td>↑ Airway irritability</td>
<td></td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>↑ Risk for lung cancer</td>
<td></td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td>Cessation may produce withdrawal headache</td>
<td>Does not negatively affect cardiac health at moderate dose</td>
<td>—</td>
<td></td>
<td>—</td>
<td>↑ Risk for bladder dysfunction with high dose</td>
</tr>
<tr>
<td>Marijuana</td>
<td>↓ Attention, memory</td>
<td>—</td>
<td>If smoked: effects similar to</td>
<td>↑ Rare forms of</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>(cannabis)</td>
<td>↓ Ability to process complex information</td>
<td></td>
<td>those associated with tobacco</td>
<td>oropharyngeal</td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td>If smoked: effects similar to</td>
<td></td>
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<td></td>
<td>those associated with tobacco</td>
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<td>If snorted: mucosal and nasal</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>septal injury</td>
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<td>Cocaine</td>
<td>Brain atrophy</td>
<td>Cardiomyopathy</td>
<td>Myocarditis</td>
<td>Gastrointestinal</td>
<td>↓ Platelets (?)</td>
<td>Renal failure</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Blood vessel occlusion</td>
<td>ischemia/ulceration</td>
<td>↑ AST and ALT</td>
<td></td>
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<td>Amphetamines</td>
<td>Paranoid psychosis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑ Tooth decay (“meth mouth”)</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Impaired memory</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>(episodic use)</td>
<td>Delayed hallucinations</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Opioids</td>
<td>Abnormal pain sensitivity</td>
<td>Infective endocarditis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatitis or HIV infection with exposure to contaminated needles</td>
</tr>
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<td>Volatile</td>
<td>Visual loss</td>
<td>Cardiomyopathy</td>
<td>—</td>
<td>Nonviral hepatitis</td>
<td>Aplastic anemia</td>
<td></td>
</tr>
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<td>substances</td>
<td>Cranial neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Glue-sniffer’s” rash</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
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<td></td>
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<td></td>
<td>Renal failure</td>
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<tr>
<td></td>
<td>Autonomic dysfunction</td>
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<td></td>
<td>Ataxia</td>
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<td></td>
<td>Brain atrophy</td>
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<td>Encephalopathy</td>
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</tbody>
</table>

*ALT,* Alanine aminotransferase; *AST,* aspartate aminotransferase; *COPD,* chronic obstructive pulmonary disease; *HIV,* human immunodeficiency virus; ↑, increase in; ↓, decrease in; ?, questionable.
altered thioental dose requirements, pharmacokinetics, or pharmacodynamics. No large population studies have assessed dose requirements for volatile anesthetic agents or hypnotic agents in patients who chronically use alcohol. 

**Short-term** consumption of alcohol inhibits the metabolism of drugs by the liver (through competition for cytochrome P450), which results in higher plasma concentrations of hepatically metabolized drugs. **Long-term** consumption of alcohol increases the activity of cytochrome P450, resulting in decreased levels of medications such as diazepam and labetalol, and increased levels of toxic metabolites that occur from hepatic degradation of illicit drugs such as cocaine. Both pregnancy and liver disease can lead to decreased plasma concentrations of pseudocholinesterase; however, this does not seem to have a clinically significant effect on the degradation of succinylcholine or ester local anesthetics. 

Pregnant women who regularly consume large amounts of alcohol and undergo general anesthesia for cesarean delivery

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### TABLE 53.5 Symptoms of and Treatment for Substance Use Withdrawal

<table>
<thead>
<tr>
<th>Substance</th>
<th>Symptoms</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (ethanol)</td>
<td>Nausea, Vomiting, Tachycardia, Hypertension, Tremor, Hallucinations, Agitation</td>
<td>Benzodiazepines and alpha2-adrenergic agonist (e.g., clonidine)</td>
</tr>
<tr>
<td>Delirium tremens:</td>
<td>Autonomic instability/arrhythmias, Seizures, Severe tremors, Disorientation, Fever</td>
<td>Benzodiazepines and alpha2-adrenergic receptor agonists (e.g., clonidine), Antiarrhythmics, Anticonvulsants (e.g., phenytoin)</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Cravings, Irritability, Headache, Cough, Insomnia</td>
<td>Nicotine replacement therapies, including patch, gum, and inhalers</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Headache, Anxiety, Depressed mood, Fatigue</td>
<td>Supportive care, Caffeine ingestion</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Mild abstinence syndrome, Headache, Restlessness, Tremor, Anxiety, Autonomic effects</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Prolonged sleep phase, Hunger, Anxiety, Weakness, Headache, Tremors and seizures</td>
<td>Supportive care, Reintroduction of drug, if necessary, with slow taper</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Fatigue, Depression, Hunger, Intense cravings</td>
<td>Tricyclic antidepressants, dopaminergic agents (e.g., bromocriptine), and amino acid therapy (no therapy has proved to be successful)</td>
</tr>
<tr>
<td>Hallucinogens (e.g., phencyclidine [PCP], lysergic acid diethylamide [LSD])</td>
<td>No clearly associated withdrawal symptoms, although psychological dependence can occur</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Opioids (e.g., heroin)</td>
<td>Flu-like symptoms, such as fatigue, weakness, restlessness, rhinorrhea, perspiration, fever, diarrhea</td>
<td>Supportive therapy, Alpha2-adrenergic agonists (e.g., clonidine), Doxepin, Reintroduction of drug, if necessary, with slow taper</td>
</tr>
<tr>
<td>Volatile substances (e.g., ethylene glycol, toluene, glue)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
may be at high risk for awareness under anesthesia.39 The high doses of volatile anesthetics often recommended in nonpregnant, chronic alcohol-using patients can lead to significant uterine atony and potential increased blood loss. Therefore, a balanced anesthetic technique that combines induction with generous doses of a hypnotic agent with succinylcholine, followed by maintenance with a volatile anesthetic agent (limited to 0.5 to 0.8 MAC after delivery to prevent uterine atony), nitrous oxide, and an opioid and a benzodiazepine (for analgesia and amnesia), should be considered. Withholding additional muscle relaxation after induction and adding a brain function monitor if time and circumstance permit may help identify patients who could benefit from additional anesthesia.40

Caffeine
Epidemiology
On a daily basis, 80% to 98% of women drink caffeine-containing beverages.41 The prevalence of consumption of caffeine-containing beverages during pregnancy is unknown.

Pharmacology
Caffeine (1,3,7-trimethylxanthine) is a naturally occurring alkaloid found in coffee, tea, cocoa, and some soft drinks and medicines.41,42 The primary sources of caffeine in the adult diet are coffee (56 to 100 mg/100 mL if brewed) and tea (20 to 73 mg/100 mL). Caffeine is readily absorbed through the gastrointestinal tract with maximum blood concentrations 1 to 1.5 hours after ingestion. Caffeine undergoes hepatic metabolism and is then excreted in the urine.41,42 In pregnancy, the half-life increases from 4 hours in the first trimester to 11.5 to 18 hours by the third trimester.43 Caffeine crosses the placenta and can also be found in breast milk. The half-life in the neonate is prolonged compared with that in children and in nonpregnant women. Habitual use of caffeine at levels greater than 500 to 600 mg/day is defined in some studies as abuse.44,45

Systemic Effects
Caffeine acts as an antagonist at the adenosine receptor. In the absence of the inhibitory effects of adenosine, the neurotransmitters norepinephrine, dopamine, and serotonin are released in increased concentrations.41,46 Systemic effects of caffeine include CNS stimulation, changes in blood pressure and metabolic rate, and diuresis (see Table 53.3).42 The side effects attributed to caffeine vary among individuals, in part related to the doses ingested and the chronicity of use. Studies of the effects of caffeine on alertness, vigilance, mood, and memory have produced inconsistent results.41

Moderate caffeine intake (less than or equal to 200 mg/day or less than or equal to 4 cups of coffee/day) does not seem to negatively affect cardiovascular health in most people. Although some people who ingest caffeine report tachycardia and palpitations, doses lower than 450 mg/day do not appear to increase significant cardiac arrhythmias in healthy patients or those with ischemia or ventricular ectopy. Caffeine doses as low as 250 mg have been reported to have a hypertensive effect after acute ingestion (an increase in systolic blood pressure of 5 to 15 mm Hg and an increase in diastolic blood pressure of 5 to 10 mm Hg), particularly in caffeine-naïve individuals; however, epidemiologic studies have produced inconsistent results. Caffeine appears to affect bladder function in women. Moderate caffeine intake may exacerbate preexisting bladder symptoms, and excessive intake (greater than 400 mg/day) increases the risk for bladder dysfunction.45

Evidence suggests that caffeine is not a human carcinogen.42 The lethal dose of caffeine in humans has been estimated to be 10 g; however, only a few such cases have been reported.41

Caffeine withdrawal is associated with headache, anxiety, depressed mood, and fatigue (see Table 53.5). Typically, symptoms begin 12 to 24 hours after cessation of use, peak at 20 to 48 hours, and last up to 7 days. The severity and likelihood of symptoms are not predictable.41

Effects on Pregnancy and the Fetus
Caffeine readily crosses the placenta. Whereas animal studies have shown a teratogenic effect with very high doses, moderate doses do not appear to result in teratogenesis in humans.41,44,47 There is some evidence that caffeine at doses greater than 300 mg/day may result in fetal growth restriction and decreased birth weight, particularly in women who also smoke or drink significant amounts of alcohol,45 although previous studies have not shown an association between low or moderate caffeine intake (less than 300 mg/day) and greater risk for spontaneous abortion or preterm delivery.44 Weng et al.48 found that caffeine consumption greater than 200 mg/day was associated with an increased risk for miscarriage, particularly among pregnant women who did not have a previous history of miscarriage.

Moderate first-trimester caffeine intake was found to have either no significant effect or to have a protective effect on the development of maternal gestational diabetes mellitus, depending on the population studied.45 Moderate intake of caffeine in lactating women does not adversely affect postnatal development.41,42

Anesthetic Management
Caffeine may enhance the side effects of beta-adrenergic receptor agonists such as epinephrine and albuterol. Caffeine may also increase the risk for a hypertensive crisis in patients taking monoamine oxidase inhibitors (MAOIs). Chronic caffeine use causes an increase in CYP1A2 activity, which can have potential effects on medications degraded by this enzyme. The elimination of theophylline and acetaminophen can be slowed by habitual caffeine consumption, resulting in higher serum drug concentrations. In contrast, serum concentrations of lithium may be decreased secondary to caffeine-enhanced elimination.42

Perhaps of greatest significance to the anesthesia provider is the potential for caffeine withdrawal headache when caffeine intake is abruptly stopped during labor and delivery. Caffeine withdrawal should be considered in a postpartum
patient with a nonspecific, nonpositional headache without associated lateralizing neurologic findings (see Chapter 30). Evidence for the efficacy of caffeine in the treatment of postdural puncture headache is scant (see Chapter 30).49

**Tobacco**

**Epidemiology**

As public awareness has grown regarding the hazards of smoking during pregnancy, the prevalence of cigarette smoking during pregnancy has declined; an estimated 18% of pregnant women reported smoking (in the past month) in 2003,50 compared with 13.6% in 2015.2 The percentage of young pregnant and nonpregnant female smokers 18 to 25 years of age was equivalent (23%), but fewer older pregnant women (26 to 44 years of age) reported smoking than nonpregnant women of the same age range (8.1% versus 23.3%).2 Among the approximately 40% of patients who stop smoking when they discover that they are pregnant, 60% to 80% return to smoking by 6 months postpartum.51

**Pharmacology**

More than 4000 chemicals are found in tobacco, including nicotine, carbon monoxide, and cyanides.23 Tobacco is most often smoked, but it can also be chewed or sniffed. Nicotine, the principal component of tobacco, acts at peripheral and central nicotinic (acetylcholine) receptors throughout the body to affect the release of catecholamines. Nicotine's effects begin immediately on exposure, and the half-life is typically a few hours; it is then rapidly metabolized in the liver and the lungs and excreted by the kidneys. Nicotine's acute effects are of shorter duration in heavy smokers than in light smokers.

Carbon monoxide, another key component, interferes with oxygen delivery to the cells by competitively binding to hemoglobin, decreasing the latter's oxygen-binding capacity and shifting the oxyhemoglobin dissociation curve to the left.52 Depending on the extent of smoke inhalation, carbon monoxide may occupy 3% to 15% (or more) of the oxygen-carrying capacity of the blood.53

**Systemic Effects**

Smoking alters maternal physiology through tobacco’s acute pharmacologic action and its contribution to comorbid disease. Peripherally, nicotine increases sympathetic tone, thereby increasing maternal heart rate, blood pressure, and cardiac work (see Table 53.3).51 Nicotine affects neurotransmitter release in different areas of the brain, producing feelings of alertness, euphoria, and, ultimately, dependence.23,54

Increased production of carboxyhemoglobin is thought to be a major factor in the impaired wound healing observed in smokers.52 Smoking also promotes atherosclerosis. The pulmonary effects of tobacco smoking include changes in the increased volume of mucus, impaired mucociliary clearance, and an increased incidence of bronchitis and chronic obstructive pulmonary disease (see Table 53.4).54

Tobacco is addictive, and cessation of its use produces withdrawal symptoms of cravings, irritability, headache, cough, and insomnia (see Table 53.5). Smoking cessation interventions include counseling and therapy, hypnosis, acupuncture, and pharmacologic therapy. There is insufficient evidence to recommend nicotine replacement therapy (e.g., nicotine patch) in pregnancy55; the American College of Obstetricians and Gynecologists (ACOG) recommends that it be used only when nonpharmacologic interventions have failed.50

**Effects on Pregnancy and the Fetus**

Nicotine has a low molecular weight and readily crosses the placenta, eventually yielding higher fetal than maternal nicotine concentrations.3 Smoking may result in decreased fetal oxygenation as a result of increased concentrations of carboxyhemoglobin and reduced uteroplacental perfusion. This compromised state can lead to decreased uptake of nourishing amino acids by the placenta.56 Smoking also adversely affects fetal growth.56–58 Salihu et al.57 documented that infant mortality was 40% higher in the offspring of women who smoked than in the offspring of nonsmoking women; this risk increased in a dose-dependent fashion for infants that were small for gestational age (SGA). In a more recent study, smoking cessation in early pregnancy was associated with a greater reduction in risk for fetal growth restriction compared with cessation later in pregnancy.59

Smoking is also associated with higher incidences of spontaneous fetal loss, preterm labor, placental abruption, and sudden infant death syndrome (SIDS).50,55,60,61 Paradoxically, smoking has been associated with a reduced risk for preeclampsia, although this may be related to the higher rates of early pregnancy loss among pregnant smokers (see Chapter 35).52,63

Although the negative impact of fetal tobacco exposure on growth appears to resolve by 2 years of age,64 there may be other long-term effects. A growing number of studies indicate that prenatal smoking exposure may be associated with an increased risk for attention deficit/hyperactivity disorder, although it is not clear whether the relationship is causal. Holz et al.65 examined offspring exposed to prenatal smoking using functional magnetic resonance imaging in a prospective 25-year study. After controlling for confounders, including adversity and sex, prenatal smoking exposure appeared to have long-term effects on neural activity and development. A recent study by Quinn et al.66 suggested this association may be caused by confounding effects of other lifestyle and genetic issues; when cousins and siblings discordant on prenatal smoking and severe mental illness were compared, there was no increased risk for severe mental illness in the smoking-exposed newborns.

**Anesthetic Management**

Smoking is a risk factor for several perioperative complications, including respiratory sequelae and impaired wound healing.52,54 Smoking results in increased airway secretions, decreased ciliary motility, and impaired gas exchange.54 Smoking is also associated with an increase in nonspecific airway reactivity, and tracheal intubation may provoke
bronchospasm. Smokers may be more likely to cough following emergence from general anesthesia, but the data are mixed and may be related to the specific volatile agent used.67,68

The physiologic benefits of smoking cessation are progressive. Even brief smoke-free intervals can result in a reduction in the carboxyhemoglobin concentration, some improved ciliary function, and decreased small airway obstruction.69 However, 6 months of abstinence may be required before the function of alveolar macrophages and pulmonary cytokines during and after general anesthesia in former smokers is similar to that of nonsmokers.69 Neuraxial anesthesia avoids airway manipulation and is typically preferred in parturients who smoke.

ILLICIT SUBSTANCES AND MISUSE OF MEDICATIONS

Amphetamines and “Club” Drugs

Amphetamines have historically been prescribed as components of nasal decongestants, bronchodilators, weight-loss drugs, and therapies for narcolepsy and attention deficit/hyperactivity disorder.70 However, because of their high potential for misuse, amphetamines have been categorized by the U.S. Drug Enforcement Agency (DEA) as Schedule II stimulants since 1971.71 MDMA (3,4-methylenedioxymethamphetamine) (“ecstasy”) and methamphetamine are thought to be the most widely misused amphetamines.71

Epidemiology

Though the prevalence of MDMA in pregnant women is unknown, 5.7% of women 12 years of age and older reported past-year use of MDMA in 2015.7 Polydrug use in women who use methamphetamine and MDMA appears to be common.71,72

Pharmacology

Amphetamines (and related compounds) are amines that exist as either salts of various acids or free bases. Used illicitly, they can be ingested orally, inhaled, or, less commonly, injected, resulting in significant CNS penetration.23 The plasma half-life ranges from 5 to 30 hours. Metabolism is variable; up to 30% of the parent compound can be found in the urine. Detection of these compounds and their metabolites in the urine is possible up to several days after ingestion.4

Methamphetamine (“speed” or “crystal meth”) is a congener of amphetamine that contains a methyl radical.71 This white, odorless, bitter-tasting powder can be smoked, snorted, ingested orally, or administered rectally.72 The availability of this compound is facilitated by its production in low-cost home laboratories. Methamphetamine is more potent than amphetamine and has a longer half-life; 50% of the drug is cleared in 12 hours. When it is smoked or injected intravenously, the “flash” from this drug is intense and of short duration. Snorting produces euphoria within 5 minutes, and oral ingestion does so within 20 minutes.70

MDMA has grown in popularity, particularly among young women.73 MDMA has a methylenedioxy group attached to the aromatic ring of the amphetamine molecule that confers some of its hallucinogenic effects (see later).74 The effects of MDMA typically begin approximately 20 minutes after ingestion and last approximately 6 hours; large doses have effects for up to 2 days. MDMA is metabolized by the liver and excreted by the kidneys.4

The “club” drug, γ-hydroxybutyric acid (GHB), also known as liquid ecstasy or liquid X, is derived from gamma-aminobutyric acid (GABA), which readily enters the brain when ingested, producing hallucinogenic, anxiolytic, euphoric, and sedative effects.75 Severe cardiorespiratory depression, coma, and seizures can occur at high doses. Overdose is common, owing in part to the variable individual responses to the drug.75,76 Chronic use may be associated with a downregulation of GABA receptors, and withdrawal manifests as insomnia, tachycardia, hypertension, and nausea/vomiting.75

The newest designer drug of the phenethylamine class is 3,4-methylenedioxypyrovalerone (MDPV), also known as “bath salts.” Typically sold in crystal or powder form that can be snorted, smoked, or injected, this substance acts as a noradrenaline and dopamine reuptake inhibitor.77 It is not detected by common drug screening tests. Adverse effects resemble those of amphetamines (e.g., agitation, hypertension, and tachycardia), and dependence and withdrawal can occur.78 In rare instances, it can cause severe hyperthermia or hyponatremia. Until recently, bath salts could be purchased legally online, at some convenience stores, or in “head shops,” but its active ingredients were banned by the Drug Enforcement Administration (DEA) after several deaths were reported.79

Systemic Effects

Acute amphetamine ingestion leads to indirect sympathetic activation through the release of norepinephrine, dopamine, and serotonin from adrenergic nerve terminals (see Table 53.3).4,80 The physiologic effects of amphetamines are similar to those of cocaine and other stimulants, with two important differences: (1) amphetamines and their derivatives lack local anesthetic properties, and (2) amphetamine can inhibit monoamine oxidase activity, leading to decreased degradation of catecholamines.8 Amphetamine-induced seizures can masquerade as eclampsia.81

Long-term use of high doses of amphetamines can have a number of adverse maternal effects, including damage to the cardiovascular and neurologic systems, and behavioral changes such as hostility, violence, hallucinations, and paranoid psychosis (see Table 53.4).72 Methamphetamine has a much longer duration of action than cocaine, because a smaller fraction of the former drug is metabolized.70

The cardiovascular effects of amphetamines and their derivatives are similar to those of cocaine: vasoconstriction, tachycardia, and labile blood pressure.24 Patients are typically hypertensive, although catecholamine depletion can result in hypotension. Arrhythmias, myocardial ischemia, endothelial
damage, and acceleration of atherosclerosis can also occur. Recommendations for the management of cardiovascular complications associated with amphetamines and cocaine are similar, including resuscitation using intravenous fluids or judicious use of phenylephrine for hypotension. If pharmacotherapy is needed to treat hypertension, then labetalol, an alpha- and beta-adrenergic receptor antagonist, may be preferred over a pure beta-adrenergic receptor antagonist. Direct vasodilators (e.g., nitrates or hydralazine) can be used but may exacerbate tachycardia. Acute amphetamine or cocaine intoxication can mimic the signs and symptoms of severe preeclampsia or eclampsia with its associated hypertension, severe headache, and even seizures. Factors such as labile blood pressure and a positive toxicology screen should raise the index of suspicion for ingestion of amphetamines or cocaine.

The pleasurable effects of methamphetamine and the deleterious neurologic sequelae are believed to be the result of high levels of dopamine in the brain. In addition to positive feelings, patients who have taken methamphetamine may experience anxiety, mood disturbances, paranoia, and hallucinations. Severe intracranial hypertension and hemorrhagic stroke have been reported in the setting of acute use. Chronic use has been associated with impairment of motor function and verbal learning as well as with significant changes in the areas of the brain associated with memory and emotion (see Table 53.4). Volkow et al. observed that prolonged abstinence (12 to 17 months) resulted in significant recovery of brain dopamine transporters, although performance on neuropsychological tests did not improve to the same extent. In addition, psychotic features of long-time amphetamine use may be precipitated by stress in former users after months or even years of abstinence. MDMA use has been associated with numerous adverse effects, including hyperthermia, hyponatremia, and seizures. Healthy volunteers given MDMA in experimental settings have demonstrated central nervous system effects that include enhanced mood, heightened awareness, and hallucinations. Severe intracranial hypertension and hemorrhagic stroke have been reported in the setting of acute use. Chronic use has been associated with impaired motor function and verbal learning as well as with significant changes in the areas of the brain associated with memory and emotion (see Table 53.4).

Anesthetic Management
Amphetamines cause (indirect) sympathetic activation. Intoxicated patients are at risk for dangerous cardiovascular events, including hemodynamic instability and cardiac arrest. Recommendations for anesthetic management for patients with amphetamine and cocaine toxicity are similar.

A cooperative patient may be a candidate for neuraxial sedation.93 The authors attributed the response to downregulation of beta-adrenergic receptors and catecholamine depletion. As with cocaine, phenylephrine may be a better choice for the treatment of hypotension than ephedrine; as an indirect-acting agent, ephedrine may either cause an exaggerated hemodynamic response if circulating catecholamines are high, or be ineffective if the amphetamine-intoxicated patient is catecholamine-depleted.

Cocaine
Although the use of cocaine dates back to 600 AD, cocaine was formally introduced into clinical practice as a local anesthetic in the 1880s. During this period, Sigmund Freud also experimented with cocaine's ability to combat hunger, fatigue, and opiate addiction. Cocaine has both vasoconstrictive and local anesthetic properties as a result of its ability to block sodium channels during depolarization.
Epidemiology
The prevalence of cocaine use during pregnancy is difficult to estimate as 60% to 90% of pregnant cocaine users engage in polysubstance use, including tobacco. Survey data in 2015 reported the prevalence of past-month cocaine use in pregnant women 15 to 44 years of age as 1 in 1000.2

Pharmacology
Cocaine (benzoylmethylecgonine) is an ester of benzoic acid and the base ecgonine, which is the parent compound of atropine and scopolamine. When dissolved in hydrochloric acid to form a water-soluble powder (cocaine hydrochloride), cocaine can be chewed, administered intravenously (“mainlined”), or taken intranasally (“snorted”). Intrarectal and intravaginal use has also been reported. When cocaine is processed with either sodium bicarbonate (“crack”) or ammonia and ether (“free base”), the resulting cocaine alkaloid can be smoked. The amount (dose) and duration of exposure are more important determinants of the cocaine effects than is the chemical formulation. Smoked cocaine (“crack” or free base) is rapidly absorbed through the lungs and reaches the brain in 6 to 8 seconds; intravenous cocaine reaches the brain in 12 to 16 seconds; and snorted cocaine reaches the brain in 3 to 5 minutes. The typical half-life of cocaine is 30 to 90 minutes, although its effects can last as long as 6 hours.

Cocaine is metabolized to ecgonine esters and benzoylgonine (biologically inactive) by plasma and hepatic cholinesterases and to norcocaine (biologically active) by nonenzymatic hydrolysis. Only small amounts of cocaine are excreted unchanged in the urine. In the presence of alcohol, cocaine is transesterified to cocaethylene, which has a longer half-life and greater physiologic effects than cocaine.

Systemic Effects
Cocaine has complex actions on the central and peripheral nervous systems and on nerve conduction. The powerful sympathomimetic effects of cocaine are caused by the drug’s inhibition of the reuptake of norepinephrine, dopamine, and serotonin, which allows these neurotransmitters to accumulate at the synaptic clefts and produce sustained stimulation. This process can result in as much as a fivefold increase in circulating concentrations of catecholamines, which, in turn, may lead to feelings of euphoria, increased energy, and decreased fear. Repetitive use of cocaine eventually leads to depletion of neurotransmitter stores, upregulation of receptors, and a higher dose requirement to achieve the desired euphoric effects.

The peripheral nervous system effects of cocaine and its derivatives result from binding to tissue receptors involved in monoamine reuptake, which results in hypertension and/or labile blood pressure and tachycardia. Cocaine produces widespread small and large vessel occlusion through vasospasm, thrombosis, and endothelial injury, which may result in significant end-organ damage.

Cocaine has profound effects on the cardiovascular system, and pregnancy appears to enhance them. Acute administration of cocaine increases peripheral vascular resistance, cardiac contractility, and myocardial oxygen demand (see Table 53.3). Coronary vasoconstriction also occurs; a greater effect occurs in diseased vessel segments than in nondiseased segments. Studies in vitro have indicated that cocaine can have a procoagulant effect in small and large vessels. This may lead to thrombus formation and coronary plaque rupture in the setting of cocaine-induced hypertension.

Cocaine-induced chest pain is a common complaint among young people presenting to the emergency department. Mittleman et al. found that cocaine use was associated with a significant, abrupt, and transient increase in the risk for acute myocardial infarction in patients who were otherwise at low risk. The occurrence of cocaine-induced electrocardiographic changes is fairly common and is not necessarily associated with true ischemia. If ischemia is suspected, treatment with supplemental oxygen, aspirin, and vasodilators, with or without reperfusion therapy, as well as measurement of troponin levels, is indicated. Although cocaine users who suffer a myocardial infarction have fewer postinfarction sequelae than the general population, the incidence of major cardiovascular complications is not trivial; 5% to 7% have congestive heart failure, 4% to 17% have ventricular arrhythmias, and up to 2% die.

Prompt recognition of acute cocaine-induced cardiovascular toxicity facilitates management. Not all cocaine-induced hypertension in pregnant women requires immediate intervention, but if pharmacotherapy is used, it is important to understand the potential undesired consequences. Beta-adrenergic receptor blockade may result in unopposed alpha-adrenergic receptor–mediated vasoconstriction that can lead to coronary artery vasoconstriction and myocardial failure. Labetalol, an alpha- and a beta-adrenergic receptor antagonist, may be preferred, although it does not ameliorate cocaine-induced coronary artery vasoconstriction. Direct vasodilators (e.g., nitrates, hydralazine) can be used but may cause further tachycardia. Hydralazine treated the hypertension in cocaine-intoxicated pregnant ewes but did not restore uterine blood flow. Calcium entry–blocking agents, such as nifedipine and nimodipine, have been found to potentiate the toxic effects of cocaine in animal models, although the mechanism has not been determined. Sedatives (e.g., benzodiazepines) or magnesium sulfate may ameliorate cocaine’s cardiovascular effects.

Other acute cardiovascular effects of cocaine include QT prolongation, bradycardia, and arrhythmias, including supraventricular or ventricular tachycardia and ventricular fibrillation. Severe bradycardia can be treated with atropine or electrical pacing. Stable supraventricular tachycardia (SVT) can be treated with vagal maneuvers or the use of adenosine. In the unstable patient with SVT, direct current (DC) cardioversion may be required.

In a retrospective multicenter study, Shih et al. found that the use of lidocaine in nonpregnant patients with cocaine-induced myocardial infarction was not associated with significant cardiovascular or CNS toxicity. Although
amiodarone therapy for maternal and fetal arrhythmias has been described as having only minor adverse effects in some patients, there are also reports of associated fetal hypothyroidism and fetal growth restriction. Thus, amiodarone in pregnant women is reserved for malignant arrhythmias that are refractory to other therapies.

Long-time cocaine use can cause left ventricular hypertrophy or dilated cardiomyopathy with accompanying systolic dysfunction (see Table 53.4). Aortic dissection has also been reported. Intravenous use of cocaine and other injectable drugs increases the risk for development of infective endocarditis. Noncardiogenic pulmonary edema, pulmonary hypertension, and right-sided heart failure can also occur in the setting of cocaine use.

The neurologic complications of cocaine may be transient or permanent. Morbidity and mortality may result from subarachnoid hemorrhage, intracerebral hemorrhage, cerebral vasculitis, and/or transient ischemic attacks. Many cocaine-using patients in whom cerebral infarct(s) and hemorrhage developed had additional risk factors for stroke, including hypertension, alcohol use, or smoking. Cocaine-induced seizures, if self-limited, are typically treated with supportive care and benzodiazepines.

Respiratory complications occur in 25% of cocaine users. Smoking cocaine can have profound respiratory effects, which include bronchospasm, chronic cough, and diffusion capacity abnormalities. Cocaine-using parturients are at increased risk for peripartum wheezing. Inhaled cocaine vapor can produce thermal airway burns. “Snorting” cocaine can lead to epistaxis, oral ulcers, and nasal septal injury. The intense pulmonary and bronchial arterial vasoconstriction produced by cocaine can cause interstitial and alveolar hemorrhage. Pneumothorax, pneumomediastinum, and pneumopericardium have also been reported.

Cocaine ingestion can result in serious gastrointestinal complications, such as ischemia, ulceration, and perforation. In addition, cocaine's anticholinergic effects include delayed gastric emptying and an increased risk for aspiration. Although some cocaine users have abnormal liver enzyme levels, cocaine is not clearly hepatotoxic.

Hematologic consequences of cocaine exposure during pregnancy may, on rare instances, include thrombocytopenia. Cocaine-induced thrombocytopenia has a clinical course similar to that of idiopathic thrombocytopenic purpura, and is responsive to therapy with corticosteroids and, in one published case, splenectomy. Whereas Kain et al. found the rate of thrombocytopenia to be higher in the cocaine group than in the drug-free group (6.7% versus 1.5%, respectively), Gershon et al. found that in pregnant women who tested positive for cocaine, only 2.5% had a platelet count lower than 140,000/mm³, compared with 4.7% in the cocaine-negative group.

Renal failure can result from cocaine use secondary to rhabdomyolysis, renal infarction, or impaired immunologic function. Cocaine-using patients have a higher prevalence of syphilis, human immunodeficiency virus (HIV) infection, and other infectious diseases compared with non–cocaine-using patients, even after controlling for intravenous drug use. Studies of the endocrine system in gravid ewes have shown that cocaine exposure results in increases in maternal adrenocorticotropic hormone and cortisol as well as maternal and fetal plasma glucose and lactate.

Cocaine also impairs cutaneous vasodilation and sweating. The lethal effects of cocaine are related, in part, to the drug's tendency to produce hyperthermia, particularly in hot weather. Cocaine use has been associated with sudden death from several of the factors discussed earlier, including cardiac arrhythmias, respiratory arrest, status epilepticus, and impaired thermoregulation.

Cocaine withdrawal can be difficult to recognize because of its nonspecific signs and symptoms: extreme fatigue followed by hunger, anxiety, weakness, headache, tremors, and seizures (see Table 53.5). Recommended therapy involves supportive care and reintroduction of the drug, if necessary, followed by a slow taper over days to weeks.

Effects on Pregnancy and the Fetus

Pregnant women metabolize cocaine to norcocaine to a greater extent than their nonpregnant counterparts, exposing both mother and fetus to this more potent metabolite. With its low molecular weight and high lipophilicity, it is mostly un-ionized at physiologic pH and readily crosses the placenta.

Woods et al. demonstrated that cocaine increases both heart rate and myocardial oxygen consumption and decreases cardiac output to a greater extent in gravid ewes than in nonpregnant ewes. Cocaine also increases maternal blood pressure and decreases uterine blood flow in gravid ewes.

In a 2011 meta-analysis, Gouin et al. found that cocaine use during pregnancy was associated with significantly higher risk for preterm birth. Obstetric complications associated with maternal cocaine use include a higher incidence of placental abruption and preterm labor; the latter occurs in 17% to 29% of women who use cocaine. Acute cocaine toxicity can mimic preeclampsia or eclampsia when pregnant women present with hypertension, headache, blurred vision, and/or seizures but can be differentiated through a positive urine test result for cocaine, the presence of normal laboratory measurements, and rapid resolution of symptoms without delivery. There is also an association between cocaine use and an increased risk for sexually transmitted diseases and failure to obtain prenatal care.

The impact of maternal use of cocaine (particularly “crack”) on the fetus has been the subject of intense legal, political, and scientific debate since the 1980s. Initial animal data and retrospective human studies suggested an increased risk for major congenital anomalies (e.g., genitourinary and abdominal wall defects) in fetuses exposed to cocaine. However, these reports are confounded by concurrent use of other drugs and low statistical power. Subsequent studies found no significant difference in type or number of congenital anomalies between infants with exposure to cocaine in
direct-acting vasopressor, such as phenylephrine.10,141 volume resuscitation, and, if needed, careful titration of an anesthetic. Treatment of hypotension should include for labor analgesia can usually be utilized for a cesarean delivery. During labor, early administration of neuraxial anesthesia should be encouraged if the patient is cooperative and has a platelet count above the threshold of concern for the anesthesia provider.10,116 Neuraxial anesthesia can reduce levels of circulating catecholamines and mitigate some of the systemic effects of cocaine.6 Also, an epidural catheter placed for labor analgesia can usually be utilized for a cesarean delivery anesthetic. Treatment of hypotension should include volume resuscitation, and, if needed, careful titration of a direct-acting vasopressor, such as phenylephrine.

In terms of physical health measures, Bauer et al.133 found that infectious complications, such as hepatitis, syphilis, and, to a lesser extent, HIV infection, were more common in infants of cocaine-abusing mothers.

Anesthetic Management
Cocaine-using patients are at risk for acute and chronic multiorgan system dysfunction21 and the need for urgent cesarean delivery. During labor, early administration of neuraxial anesthesia should be encouraged if the patient is cooperative and has a platelet count above the threshold of concern for the anesthesia provider.10,116 Neuraxial anesthesia can reduce levels of circulating catecholamines and mitigate some of the systemic effects of cocaine.6 Also, an epidural catheter placed for labor analgesia can usually be utilized for a cesarean delivery anesthetic. Treatment of hypotension should include volume resuscitation, and, if needed, careful titration of a direct-acting vasopressor, such as phenylephrine.

When an ester local anesthetic (or succinylcholine) is administered to a patient who has ingested cocaine, these medications may compete with cocaine for available plasma cholinesterase6,106; however, the clinical significance of these effects is not reported. Despite the theoretical risk for altered metabolism of succinylcholine, a standard intubating dose should be administered.99 Changes in μ- and κ-opioid receptors and altered baseline endorphin levels may result in an increased perception of pain in cocaine-using patients despite the presence of an apparently satisfactory level of neuraxial anesthesia.60 Ross et al.142 observed a reduction in duration of intrathecal sufentanil analgesia during labor in cocaine-abusing women, although the quality of analgesia was not diminished.

Cocaine-using patients who receive general anesthesia are at greater risk for hypertension and tachycardia during and after laryngoscopy and tracheal intubation.62 If general anesthesia is required, premedication with a benzodiazepine or an opioid may help attenuate the acute physiologic effects of cocaine. As the anticholinergic effects of cocaine can delay gastric emptying and may also increase the risk for aspiration, pharmacologic prophylaxis and a rapid-sequence induction of general anesthesia are indicated. Propofol may be well tolerated, whereas ketamine may potentiate the CNS vasoconstrictive effects of cocaine, potentially increasing the risk for cerebrovascular morbidity.116 Both etomidate and cocaine can result in disinhibition of the CNS control of extrapyramidal activity, and their effects may be additive.143 Dexmedetomidine, an alpha-2-adrenergic receptor agonist, has been shown in animal studies to delay the onset of cocaine-induced seizures and may be useful in selected patients.144 Early studies in dogs demonstrated that acute cocaine ingestion can cause hyperthermia in both laboratory animals and humans97,124; therefore, core temperature should be monitored in cocaine-abusing patients. However, given the propensity for nasal septal defects in these patients, temperature probes (and other tubes and monitors) should not be inserted intranasally. Active warming should be used only if the patient is hypothermic.

Marijuana (Cannabis)
Marijuana is the most common illicit drug used in pregnancy, with 4.7% of pregnant women between 15 and 44 years of age reporting past-month marijuana use in 2015.4 Although marijuana use is lower in the pregnant than in nonpregnant population (12.5%), the use in pregnancy is increasing. Contributing factors are thought to include the legalization of medical marijuana, the decriminalization of recreational marijuana, and the drug’s antiemetic properties.

Pharmacology
Marijuana contains more than 400 compounds, including 60 cannabinoids. Most of the psychotropic effects are caused by 9-tetrahydrocannabinol (THC).10,145 The THC content in marijuana has tripled since 1995.146 Noncannabinoid constituents of marijuana are similar to those in tobacco without the nicotine. Inhaled THC is absorbed through the lungs and reaches the brain within minutes. Oral ingestion of marijuana results in blood THC concentrations that are 25% to 30% of those obtained by smoking, but with a delayed onset of up to 2 hours. The lipid-soluble cannabinoids are sequestered in fatty tissues and gradually released into other tissues. Thus, a single ingestion can have an elimination half-life of up to 7 days; complete elimination of the inactive metabolite 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) takes as long as 25 to 30 days. Metabolism occurs in the liver, with excretion in the urine. Measured concentrations of metabolites in the blood and urine correlate poorly with the degree of intoxication.143 Synthetic cannabinoids feature the primary psychoactive component of cannabis and are not detected on routine urine assays for THC.147

Systemic Effects
Cannabis interacts with specific cannabinoid receptors in the brain and peripheral nerves. Psychoactive effects include

utero and infants without exposure, after accounting for confounding variables.133,134

Frank et al.135 reviewed studies published between 1984 and 2000 to assess the possible relationships between maternal cocaine use during pregnancy and childhood outcome. After controlling for possible confounding factors, they found no consistent negative association with physical growth, developmental test scores, or the expressive or receptive language skills. They observed less optimal motor performance up to 7 months of age, after which the differences between cocaine-exposed and nonexposed infants disappeared.

Studies investigating trajectories of motor, mental, or behavioral development in infants with prenatal cocaine exposure have had conflicting results, in part related to confounding risk factors such as exposure to adverse postnatal environments.136–138 In a 15-year follow-up study of adolescents prenatally exposed to cocaine, Richardson et al.139 noted that exposure to violence partially mediated the impact on (self-reported) delinquent behaviors by the adolescents. In addition, the first-trimester exposed adolescents had poorer performance on tests related to problem solving and abstract thinking.

In terms of physical health measures, Bauer et al.133 found that infectious complications, such as hepatitis, syphilis, and, to a lesser extent, HIV infection, were more common in infants of cocaine-abusing mothers.
anxiolysis, analgesia, appetite stimulation, euphoria, and, sometimes, dysphoria (see Table 53.3). Marijuana intoxication impairs cognitive and psychomotor function. Impairment of memory, attention, and the ability to process complex information can occur with long-time heavy use (see Table 53.4). It is unclear whether these effects are reversible.

Acute intoxication with marijuana appears to have a biphasic effect on the autonomic nervous system; low doses cause tachycardia and higher cardiac output caused by increased sympathetic and decreased parasympathetic tone. In contrast, high doses produce sympathetic inhibition and parasympathetic stimulation, resulting in bradycardia and hypotension. Although ventricular ectopy can occur, life-threatening arrhythmias in patients without preexisting cardiac disease are rare, and autonomic disturbances are generally well tolerated. Reversible ST-segment and T-wave abnormalities may occur, perhaps as a result of the higher heart rate associated with marijuana use. Synthetic cannabinoids produce more exaggerated physiologic effects. Although large studies are lacking, case reports indicate the dangers of its use. For example, two separate cases are reported of otherwise healthy women who developed ischemic stroke after first-time use.

As with tobacco, the respiratory consequences of smoking marijuana include mucociliary dysfunction, increased susceptibility to bronchitis, and chronic obstructive pulmonary disease (see Table 53.4). Acute intoxication may cause conjunctival vasodilation and visible reddening of the eyes. Although high doses of marijuana can cause hallucinations and psychosis, fatal overdose has not been documented.5,145

Withdrawal from long-time marijuana use may produce a mild abstinence syndrome that includes headache, restlessness, tremor, anxiety, and autonomic effects, similar to those of withdrawal from benzodiazepines and hypnotic drugs (see Table 53.5).4,149

**Effects on Pregnancy and the Fetus**

It is difficult to ascertain specific effects of marijuana on pregnancy, because women who use marijuana often engage in polysubstance use. Although marijuana use is not associated with congenital abnormalities, some studies have shown use in pregnancy to be associated with an increased risk for stillbirth, preterm birth, and neurobehavioral abnormalities. However, a recent retrospective cohort study of 8138 pregnant women did not find marijuana use to be associated with poor neonatal outcomes, such as low birth weight or low Apgar scores, after adjusting for confounders. Long-term associated effects in children include inattentiveness and impulsivity, deficits in problem solving, academic underachievement, and a predisposition to smoking marijuana and tobacco. There is no safe amount of marijuana recommended during pregnancy or lactation, and the ACOG discourages the use of marijuana during pregnancy and lactation.

**Anesthetic Management**

Neuraxial analgesia is typically preferred during labor and delivery and can be safely performed in patients who use marijuana, in the absence of other contraindications. Drug-related changes in heart rate and blood pressure are usually well tolerated in otherwise healthy, acutely intoxicated patients. However, the administration of atropine, pancuronium, and ketamine can exacerbate existing tachycardia.

Long-time marijuana smokers are at risk for similar respiratory complications during and after general anesthesia as tobacco smokers, specifically, increased airway secretions, impaired mucociliary clearance, and potentially increased airway reactivity. Persistent postextubation laryngospasm in a patient with a history of heavy marijuana smoking has been reported.

As acute intoxication with marijuana can have additive effects with those of sedative agents and volatile anesthetic agents, including myocardial depression, careful titration to clinical effect is recommended. The effect of marijuana on pain perception has been explored in an experimental model of human pain. Wallace et al. found that smoked marijuana had a differential effect on pain scores; a low dose had no effect, a medium dose reduced pain, and a high dose significantly increased pain. The clinical implications of these findings are unclear.

**Hallucinogens**

LSD (lysergic acid diethylamide), PCP (phencyclidine), psilocybin, ayahuasca, and mescaline are each hallucinogens. As discussed earlier in the amphetamine section, 3,4-methylenedioxymethamphetamine (MDMA) also has hallucinogenic effects.

**Epidemiology**

Hallucinogen use in pregnancy is thought to be uncommon. Survey data from 2015 reported a 0.1% prevalence of past month hallucinogen use in pregnant women compared with 0.5% in nonpregnant women ages 15-44.

**Pharmacology**

The hallucinogens are a diverse group of drugs notable for their complex mechanism of actions that include agonist, partial agonist, and antagonist effects at serotonergic, dopaminergic, and adrenergic receptors. Overall, the adrenergic effects of these drugs are mild compared with those of cocaine and amphetamines.

Both psilocybin, the hallucinogen in some wild mushrooms, and the synthetic compound LSD, are indole derivatives that chemically resemble serotonin. When ingested orally, intranasally, intravenously, or rectally, or smoked, they evoke auditory, visual, and tactile hallucinations. Clinical effects usually develop over 15 to 60 minutes and last for 6 to 12 hours. LSD is 100 times more potent than psilocybin and can be detected in urine or plasma for up to 3 days. LSD is metabolized by the liver and has a plasma half-life of 100 minutes. The potency of individual samples of psilocybin varies with physiologic effects typically occurring at doses of 20 to 60 mg. Most of the drug is excreted in the first 8 hours, although small amounts are excreted for up to 1 week. Ayahuasca (DMT) is a psychoactive brew used in ritual healing ceremonies and is composed primarily of two Amazonian
plants; the key ingredients are β-carboline and tryptamine derivatives. Its potency and effects are greatly dependent on the relative concentrations of its constituents. Phencyclidine, initially developed as a general anesthetic agent, was removed from the legal market in 1978. Ketamine, a related compound, is an anesthetic agent that is also a drug of abuse. Both bind to the N-methyl-D-aspartate (NMDA) receptor. The psychological effects of PCP typically last 12 to 48 hours. Ketamine has a shorter duration of action than PCP.

Unlike the phenylethylamines MDMA and GHB, which also have properties of amphetamines, mescaline is exclusively hallucinogenic. Found as the active ingredient in peyote cactus buttons, mescaline is typically eaten or drunk as a tea. The effects of mescaline, which last approximately 12 hours, include visual hallucinations, nausea, and vomiting.

Systemic Effects
Ingestion of hallucinogens causes activation of the sympathetic nervous system, which results in hypertension, tachycardia, dilated pupils, and increased core body temperature (see Table 53.3). The cardiovascular effects of these drugs are rarely serious, although some instances of supraventricular tachycardia and acute myocardial infarction have been reported. Myocardial infarction may result from vasoconstriction and increased platelet aggregation.

Carotid artery occlusion has been reported after the use of LSD. PCP use has been associated with seizures, delayed hypertensive crisis, and intracerebral hemorrhage. Overdose with PCP can be associated with confusion and combativeness, which may progress to seizures and catatonia. Some users of LSD experience a “bad trip,” which is likely to be a manifestation of an acute anxiety reaction. Other users report “flashbacks” or systemic effects of these drugs that occur months or even years after ingestion. Some of these episodes are likely a result of delayed release of small amounts of drug from fatty tissues. The use of LSD may unmask an underlying psychiatric disorder in vulnerable patients.

The psychological effects of psilocybin include giddiness, visual hallucinations, and gastrointestinal dysfunction. Morbidity is associated primarily with inadvertent ingestion of toxic species of mushrooms. Although psychological dependence on these drugs has been observed, no clearly associated withdrawal symptoms occur with abstinence (see Table 53.5).

A direct causal relationship between use of these drugs and death has not been documented; however, hallucinogens can cause feelings of paranoia and panic that can lead to accidents or fatalities. Confirmed by later studies. The effect of prenatal exposure of ayahuasca has led to active discussion in the literature without a definitive conclusion.

Anesthetic Management
Management of a hallucinogen-intoxicated patient is primarily supportive and noninterventional. Stressful situations can provoke panic attacks, which in turn can intensify the physiologic effects of these drugs. Specific recommendations include provision of a quiet, supportive environment and administration of a benzodiazepine if needed. Neuroleptic medications are relatively contraindicated as they can intensify toxic reactions.

Either neuraxial or general anesthesia can be administered for vaginal or cesarean delivery in the usual fashion, as the clinical situation warrants.

Opioids
Opioids refer to the class of naturally occurring and synthetic drugs that are structurally and functionally related to morphine. The term opiate specifically describes any of the narcotic alkaloids found in the juice of poppy plants, including morphine and codeine.

Epidemiology
As in the general population, the frequency of opioid use disorders in pregnant women has increased dramatically; a large population-based study revealed a 12.7% increase in prevalence (from 0.17% in 1998 to 0.39% in 2011 in the 20 to 34 years age group) and an increased risk for in-hospital mortality (Fig. 53.1). Historically, opioids were thought to be safe for pregnant women and were liberally prescribed for treatment of back and abdominal pain and headache.

Pharmacology
The naturally occurring opioids are metabolized to morphine, which has a plasma half-life of 2 to 3 hours. Morphine then undergoes rapid metabolism in the liver and is excreted in the urine, where both active and inactive metabolites can be detected for up to 2 days in occasional users, and longer in chronic users.

Heroin (diacetylmorphine or diamorphine) is a commonly used and highly addictive semisynthetic analogue of morphine that has no legal use in the United States. It can be smoked, snorted, or injected intravenously or intramuscularly. The speed of onset varies from less than 1 minute to 15 minutes, depending on the delivery method. The elimination half-life is typically 1 to 2 hours. Heroin is more lipid soluble...
Substance Use Disorders

Cardiac QTc interval prompting the lethal arrhythmia, torsades de pointes.

Unlike morphine, methadone undergoes biotransformation (rather than conjugation) in the liver and is excreted primarily by the fecal route. Methadone has been used since the 1960s for medication-assisted therapy for patients suffering from opioid-use disorders and since the 1970s for this indication in pregnant patients. Methadone must be dispensed daily from a certified clinic, when used for medication-assisted therapy. Methadone is also used as an analgesic in patients with chronic pain.170,172 Pregnancy is associated with greater methadone metabolism and reduced bioavailability because of greater maternal blood volume and changes in hepatic enzymatic activity and glomerular filtration rate.23,172,173

Buprenorphine (Subutex) is a semisynthetic opioid that acts as a partial µ-opioid receptor agonist (with low intrinsic opioid activity) and κ-opioid receptor antagonist that can also be used for medication-assisted therapy for patients suffering from opioid-use disorders.174–176 Suboxone, one of the two sublingual formulations of this drug, contains naloxone, which is biochemically active only if the user attempts to snort, inject, or cook the drug.175 Buprenorphine binding to the µ-opioid receptor is up to 1000 times greater than that of morphine, with a slow dissociation half-life of approximately 166 minutes.175 Primary metabolism of buprenorphine occurs in the liver with excretion in the bile.177 Like methadone, buprenorphine can prolong the QTc interval. Buprenorphine has a ceiling effect at 24 to 32 mg, which decreases the risk for respiratory depression.175,178 Buprenorphine is prescribed by physicians who have taken an 8-hour training course to become a certified provider. These courses

are available from the American Academy of Addiction Psychiatry, the American Society of Addiction Medicine, and the American Osteopathic Academy of Addiction Medicine.

Fentanyl is a highly potent synthetic opioid that can be delivered by intravenous, transmucosal, intranasal, buccal, epidural, intrathecal, or inhalational routes. Though fentanyl has a rapid speed of onset, its duration of action is limited by redistribution (half-life ranging from 3.1 to 7.9 hours). Highly lipid soluble, this opioid is primarily metabolized by the liver, although 10% of fentanyl is excreted by the kidneys. Fentanyl has increasingly become a drug of misuse, as its components are easy and inexpensive to obtain, and its effects are powerful. Work is currently underway on a fentanyl vaccine to protect against its lethal effects. Carfentanil, an elephant tranquilizer that is 100 times more potent than fentanyl, has also appeared as an opioid of misuse.

Systemic Effects
Opioids mimic the activity of endogenous peptides and exert their effects through binding to \( \mu \), \( \delta \), and \( \kappa \)-opioid receptors. Morphine and heroin exert their euphoric, analgesic, and reinforcing effects primarily through stimulation of the \( \mu \)-opioid receptor. Long-time opioid misuse causes neuroadaptations in the brain that may explain the manifestations of withdrawal.

Opioids act in the CNS to reduce sympathetic activity and increase parasympathetic activity; they also promote histamine release from mast cells. The resulting cardiovascular effects include bradycardia, hypotension, and, in some cases, potentially lethal tachyarrhythmias and bradyarrhythmias (see Table 53.3). Noncardiogenic pulmonary edema has been observed in some cases of overdose and is believed to be caused by hypoxia, intense pulmonary vasoconstriction, and, in some cases, the use of reversal agents (e.g., naloxone). Opioid-induced respiratory depression occurs through a direct effect on the brainstem that reduces the ventilatory response to hypercarbia. Opioid overdose can progress from miosis and respiratory depression to obtundation and death. As opioid overdose deaths in the general population have increased by almost threefold (2002 to 2015), one aspect of the public health response has been a proliferation of more easily accessible, opioid antagonist (i.e., naloxone) therapy. Treatment of overdose also includes maintenance of a patent airway and provision of hemodynamic support as needed.

Women who use opioids or other drugs intravenously are at risk for infective endocarditis (usually affecting right-sided valves), HIV infection, viral hepatitis, septic emboli, and pulmonary abscess formation. In addition, hiliar adenopathy may develop as a result of ingestion of additives such as quinine and starch. Opioid-dependent patients may have additional end-organ damage and may exhibit opioid tolerance, physical dependence, and withdrawal. Studies have found an association between opioid administration and abnormal pain sensitivity, including opioid-induced hyperalgesia (OIH) and allodynia (see Table 53.4). Opioid tolerance develops with chronic use and is related to amount and duration of drug exposure; tolerance results from changes in drug distribution and metabolism (pharmacokinetics) and in receptor density and activity (pharmacodynamics). However, tolerance to side effects such as sedation does not develop to the same degree. Both opioid-induced hyperalgesia and tolerance can lead to challenges in pain management in the peripartum period, specifically after cesarean delivery or other surgery.

Acute opioid withdrawal results from sympathetic hyperactivity, resulting in flulike signs and symptoms such as fatigue, weakness, restlessness, rhinorrhea, perspiration, fever, and diarrhea (see Table 53.5). These manifestations can persist for several days if not treated. The onset and duration of withdrawal symptoms vary with the opioid taken; morphine or heroin withdrawal symptoms typically begin within 6 to 18 hours after the last dose, reach their peak intensity by 3 days, and last for 7 to 10 days. Methadone withdrawal symptoms are delayed, with onset within 24 to 48 hours, peak intensity within 3 to 21 days, and duration up to 6 to 7 weeks. Clonidine, an alpha-2-adrenergic receptor agonist, can modulate these effects, although postural hypotension may result. Acute withdrawal can also be treated by administration of a short-acting opioid and initiation of a gradual dose taper.

Whereas medically supervised opioid detoxification during pregnancy is reported, it is generally not recommended primarily because of the high rate of relapse. Instead, the ACOG recommends medication-assisted therapy in combination with behavior modification therapy. Several studies have shown that methadone-assisted therapy promotes better medical and prenatal care, fewer unplanned pregnancies, decreased neonatal opioid withdrawal syndrome (NOWS) symptoms, and less maternal illicit drug use at delivery. Medication-assisted therapy with buprenorphine has also shown favorable results with particular advantages regarding neonatal outcomes.

Effects on Pregnancy and the Fetus
In 2010, Jones et al. performed a landmark, multicenter, randomized controlled trial comparing the neonatal effects of methadone and buprenorphine therapy on NOWS when used as part of an opioid dependence program during pregnancy. Although the percentage of neonates requiring treatment for NOWS did not differ between groups, the infants of buprenorphine-treated mothers spent 58% less time in the hospital and received 89% less morphine therapy for NOWS compared with those of methadone-treated mothers.

When obstetric complications were compared in methadone- and buprenorphine-treated pregnant women, maternal weight gain, cesarean delivery rates, birth weights, and Apgar scores were similar. However, more favorable neonatal growth outcomes and fewer medical complications and overdoses were present in women treated with buprenorphine. Based on these data, the ACOG suggests that buprenorphine be considered “a potential first-line medication for pregnant opioid-dependent women who are new to treatment.”
Neonatal opioid withdrawal syndrome (NOWS), which occurs in neonates repeatedly exposed to opioids in utero, is characterized by irritability, poor feeding, abnormal sleep patterns, diarrhea, fever, and seizures. Affected neonates may also have autonomic symptoms such as yawning and mottling. If prolonged and untreated, NOWS can result in death.3,189

In general, published reports have not shown an increased risk for birth defects after prenatal exposure to oxycodone, meperidine, or propoxyphene, but they have shown an association between congenital heart defects and early use of codeine.186 Two retrospective population-based studies showed an association between maternal therapeutic use of opioid medications early in pregnancy and spina bifida, cardiac defects, and gastroschisis,190,191 but data were obtained retrospectively via maternal interviews and did not control for dose, therapeutic indication, duration, or frequency of opioid exposure. A separate large population-based study showed an increased risk for several adverse pregnancy outcomes in women with opioid misuse or dependence, including preterm labor, fetal growth restriction, transfusion, and in-hospital mortality.165

Heroin use during pregnancy is associated with first-trimester spontaneous abortion, preterm delivery, and fetal growth restriction, in part as a result of poor maternal nutrition.3,171,187,189 Maternal and neonatal infection and NOWS have also been described. Children born to women using heroin were found to have normal development at the time of entry into school.3 In utero heroin exposure may be associated with a high rate of attention deficit/hyperactivity disorder.192

Anesthetic Management

Preadmission assessment and communication. Establishing trust and effective communication is critical in the care of opioid-tolerant or methadone- or buprenorphine-maintained patients and may improve the ability to elicit a more complete drug history. Ideally, the anesthesia provider would meet the patient before she presents for delivery and develop a mutually agreeable strategy for pain management with appropriate goals for pain intensity scores. Providers, family, and patients may express concern that exposure to opioids or other sedatives will prompt cravings or a frank relapse. Although withholding appropriate analgesic and anxiolytic medications from such a patient is not justified, patient monitoring (e.g., drug screens, pill counts) may be necessary.184

Opioid maintenance requirements. Chronic opioid requirements or pharmacologic maintenance therapy should be continued throughout the hospitalization and postpartum,135,170,171,184 with additional therapies for acute pain management. The precise dose of methadone must be confirmed with the dispenser, because improper dosing can result in inadequate analgesia, withdrawal phenomena, or life-threatening overdose.179 Any methadone or buprenorphine dose adjustments during pregnancy or postpartum must be done in close consultation with the prescribing physicians.186 Some providers may advocate for the substitution of an equivalent dose of a pure opioid agonist for buprenorphine in advance of delivery to maximize the effect of peripartum opioid analgesics. As in the nonobstetric population, this approach requires the careful coordination of the involved providers, an explicit protocol that outlines when the buprenorphine should be stopped and resumed, and which opioid and at what dose should be substituted in the interim. Proponents of maintaining buprenorphine therapy throughout the delivery period note that most admissions for delivery are unplanned, which can complicate efforts to enact this plan. It can also be challenging to safely manage this predelivery transition from buprenorphine to opioid-agonist therapy in the outpatient setting without increasing the risk for maternal or fetal withdrawal or relapse. Similarly, reintroduction of buprenorphine therapy in the early postpartum period may promote acute withdrawal or relapse at a vulnerable time.190 An alternative approach is to continue the buprenorphine therapy through delivery and the postpartum period. Buprenorphine or methadone doses can then be divided (e.g., buprenorphine three times daily) to maximize the analgesic properties of the medication.175,186 However, this strategy should only be attempted if administration of the correct total dose can be ensured. In all cases, the use of multimodal pain management techniques, described later, is crucial.

Anesthetic technique and dose requirements. The peripartum anesthetic goals for chronic opioid-using parturients or those receiving methadone or buprenorphine maintenance therapy include, as for all patients, provision of a safe environment that maximizes maternal comfort and bonding with her neonate. Neuraxial analgesia or anesthesia is the technique of choice for those undergoing vaginal or cesarean delivery, assuming that the patient is cooperative and has no evidence of coagulopathy or other contraindication.186 In a review of relevant publications, Cassidy and Cyna194 catalogued the needs of opioid-dependent patients across a broad range of anesthetic techniques and modes of delivery. The proportion of these women that required general anesthesia for cesarean delivery, or the number who requested epidural labor analgesia, did not differ compared with the proportions in non- opioid-dependent women. However, a significant incidence of pain management challenges was observed, particularly after cesarean delivery; 26% of the patients required consultation for inpatient pain management in addition to usual labor analgesia, and 74% of the patients had difficulties with postcesarean analgesia. These women also had significant vascular access problems and generated more emergency calls for fainting and collapse.

Labor analgesia. Meyer et al.11,12 noted that pregnant women on methadone or buprenorphine maintenance therapy had similar pain scores and analgesia requirements during labor and vaginal delivery compared with matched controls. It is therefore reasonable to expect that patient reports of inadequate labor epidural analgesia should be treated as they would be in patients without opioid use disorder. Epidural catheter replacement should be promptly offered as needed. In contrast, mixed opioid agonist/antagonist drugs (e.g., nalbuphine) that
are commonly employed for labor analgesia or in some cases treatment of neuraxial opioid-induced pruritus should be avoided in patients with a history of opioid use disorder because they can precipitate withdrawal. If neuraxial techniques are contraindicated for labor, inhaled nitrous oxide or intravenous patient-controlled analgesia with opioid agonists can be used, acknowledging that the opioid requirement is likely to be considerably higher. Multimodal therapy, including a fixed schedule of nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (paracetamol), should be used after vaginal delivery. 181

**Cesarean delivery anesthesia.** Whenever feasible, neuraxial anesthesia (spinal, epidural, or combined spinal–epidural anesthesia) should be utilized for cesarean delivery anesthesia. If general anesthesia is needed, there is the potential for decreased MAC in a patient with acute opioid intoxication as well as the potential for cross-tolerance with CNS depressants in a patient with a history of long-time opioid use. 7 However, given that obstetric patients are, in general, a group at high risk for awareness under general anesthesia, it is prudent to prioritize an adequate depth of anesthesia. 195

**Postoperative analgesia.** Postoperative pain management can be particularly challenging in patients with a history of chronic opioid use. Both methadone- and buprenorphine-maintained women had higher pain scores and received 70% and 47% more opioids, respectively, after cesarean delivery. 11,12 For cesarean delivery, multimodal analgesia with a fixed schedule of NSAID and acetaminophen therapy is highly recommended. Although perioperative use of gabapentin, an NMDA receptor antagonist, has not produced significant additional benefits with neuraxial opioids in the general obstetric population, 196 it is possible that these high-risk patients would benefit from gabapentin administration. (However, cumulative increased risk for respiratory depression with high-dose neuraxial morphine, gabapentin, and any additional opioids has been reported in the nonpregnant population. 197,198) Similarly, these patients may benefit from the higher neuraxial opioid dosing strategy described by Booth et al. 199 for patients predicted to have severe pain after cesarean delivery (i.e., 300 μg spinal morphine and 1 g acetaminophen every 6 hours for 24 hours). Low-dose ketamine, another NMDA antagonist, has also been used as a single intraoperative dose 200 or as a low-dose postoperative infusion to augment analgesia. 201 Other strategies include using patient-controlled epidural analgesia (consider placing a low thoracic epidural catheter for this purpose), transversus abdominis plane (TAP) blocks (single shot or via a continuous catheter), or IV patient-controlled opioid analgesia, similar to that in women who are not chronic opioid users (see Chapter 27).

**Volatile Substances**

Volatile substances are chemically diverse and readily available and can be sniffed, aerosolized, or ingested to produce feelings of euphoria, excitement, and invulnerability. 202-204 The five classes of these substances include aromatic hydrocarbons (e.g., toluene), halocarbons (e.g., trichloroethylene-TCY), aliphatic hydrocarbons (e.g., propane), inhaled anesthetics (e.g., halogenated ethers and nitrous oxide), and alkyl nitrites (e.g., amyl nitrite). 204

### Epidemiology

The 2015 National Survey on Drug Use and Health reported that 0.7% of the general population 12 years of age and older used inhalants in the past year; the prevalence of use in pregnant women is unknown.

### Pharmacology

Volatile substances act by diverse mechanisms, although they commonly have low vapor pressure and high volatility at room air, which facilitates rapid absorption. Excretion is primarily through the lungs. 204 Exposure is typically to very high concentrations, for short durations (e.g., 15 minutes). Detection, although difficult, can be enhanced by the presence of the “glue sniffer’s” facial rash 203 or the odor of the inhalant. 203 Laboratory assays can detect many solvents in the blood within 10 hours of exposure. Urine assays are available only for certain volatile substances (e.g., toluene, chlorinated solvents) but may provide a longer window of detection. 4

**Toluene,** a primary component of household paint and cleaning agents, is sniffed or ingested orally for its transient euphoric effects. 10 Whereas animal studies suggest that only a small fraction of the original vapor reaches the brain, the effects on GABA, glutamate, and other neurotransmitter systems are profound. 204 **Ethylene glycol,** a bittersweet-tasting component of antifreeze, brake fluids, and industrial solvents, is sometimes used as an inexpensive substitute for alcohol. Readily absorbed via the gastrointestinal tract, this solvent reaches maximal blood concentrations within 1 to 4 hours. It is metabolized by the hepatic enzyme alcohol dehydrogenase to four toxic organic acids. Primary screening for ethylene glycol intoxication includes serum anion-gap metabolic acido- sis, high urine osmolality with an osmol gap, and the presence of calcium oxalate crystals in the urine. 205,206

### Systemic Effects

Typically, the user of volatile substances feels an initial sense of euphoria followed by a brief period of disinhibition and impulsivity. Intoxication can be prolonged through repeated inhalation of the solvent. As the dose increases, dizziness, diplopia, and disorientation manifest, followed by headache, nausea, vomiting, drowsiness, and sleep. 203

Mucous membrane irritation can result in rhinorrhea, epistaxis, excessive salivation, and conjunctival redness. Nausea, vomiting, and diarrhea can also occur. 203 Ingestion of volatile substances can lead to potentially lethal tachyarrhythmias, likely secondary to sympathetic stimulation, or bradycardia rhythms from decreased sinoatrial node automaticity or direct vagal stimulation and myocardial depression (see Table 53.3). Hyoxemia may occur as a result of formation of carboxyhemoglobinemia, methemoglobinemia, or suffocation. 4,203,207

Chronic inhalant use can cause multiorgan system disease, with cardiac (e.g., cardiomyopathy, arrhythmias, myocardial...
infarction), pulmonary (e.g., wheezing, acute respiratory distress syndrome, pulmonary hypertension), central and peripheral nervous system (e.g., cognitive impairment, ataxia, muscle weakness, peripheral neuropathy), and autonomic dysfunction (see Table 53.4). Renal toxicity, aplastic anemia, and hepatocellular carcinoma have also been reported. Imaging studies have demonstrated loss of brain mass, white matter degeneration, and subcortical abnormalities in long-term users. Significant methemoglobinemia with attendant cyanosis can also occur from exposure to some compounds.4,203,207

Cessation of chronic use can lead to reversal of many of the pathophysiologic changes, although the CNS effects may persist. Death from inhalant use typically occurs from suffocation, aspiration, or accidental injury. Sudden sniffing death syndrome, likely secondary to a fatal arrhythmia in the setting of a sensitized myocardium, electrolyte abnormalities, and hypoxemia, has been reported in both new and long-term users.203

With ingestion of ethylene glycol, inebriation and accumulation of the toxic metabolite glycolic acid occurs, resulting in CNS depression and seizure activity. Cardiopulmonary manifestations occurring 12 to 24 hours after ingestion may be fatal. Renal failure is likely to occur 24 to 72 hours after ingestion in survivors. The estimated lethal dose of undiluted ethylene glycol is 1.4 mL/kg. Treatment of ethylene glycol ingestion may require the induction of emesis with ipecac or the use of gastric lavage. The conversion of ethylene glycol to its toxic metabolites can be prevented with the use of the antidote fomepizole or ethanol. Hemodialysis may be warranted.206

Ingestion of toluene can similarly cause cardiac arrhythmias, acute respiratory distress syndrome, hepatic failure, cerebral edema, and death.10

**Effects on Pregnancy and the Fetus**

In animal studies, acute and chronic toluene exposure during pregnancy results in the presence of toluene in the fetal brain.208 Volatile substance use has been associated with human fetal growth restriction, preterm delivery, and perinatal mortality.7

Ethylene glycol intoxication was misdiagnosed as eclampsia in a patient who presented at 26 weeks’ gestation with hypertension and seizures followed by coma.205 Her course, complicated by hemodynamic instability, severe metabolic acidosis, and acute renal failure, eventually prompted suspicion of intoxication. Toxicology investigation confirmed ethylene glycol poisoning. The patient was successfully treated with hemodialysis and intravenous ethanol, and the neonate was treated with diuresis and replacement transfusion.

**Anesthetic Management**

Identification of volatile substance use in the parturient is critical to safe anesthetic care.207 Decontamination of skin and clothing is required.203 A careful physical examination, including the oropharynx and documentation of preexisting neurologic deficits, should be undertaken, and electrolyte abnormalities should be corrected.7

If the patient is cooperative and able to protect her airway, neuraxial labor analgesia can be administered. Initial treatment of hypotension should include intravenous fluids first, and then phenylephrine, given the propensity toward arrhythmias. Atropine should be readily available but used with caution. In a stable patient with sustained tachyarrhythmias, selective beta-adrenergic receptor antagonists should be the first-line therapy.4

In intoxicated or otherwise uncooperative patients, rapid-sequence induction of general anesthesia for cesarean delivery may be indicated.7 Propofol or etomidate may be preferred induction agents to ketamine as the latter may exacerbate tachyarrhythmias. Oxygenation and ventilation can be complicated by preexisting pulmonary complications.

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**KEY POINTS**

- Licit and illicit substance use by pregnant women may result in significant maternal and fetal risks.
- Anesthesia providers often care for women with substance use disorders during labor or cesarean delivery.
- Maternal self-reporting underestimates the true incidence of substance use. Drug testing (e.g., urine, blood, oral fluid, hair, meconium) should be employed if substance use disorder is suspected.
- Optimal care of these patients requires developing a therapeutic bond and an explicit pain management plan. Anesthesia providers should ask patients questions about substance use disorder in a respectful and nonjudgmental manner.
- Neuraxial anesthetic techniques are the preferred methods for labor analgesia and cesarean delivery anesthesia for most patients with a history of substance use disorder, provided that the patient is cooperative, is able to protect her airway, and does not have a coagulopathy or a platelet count below the threshold of concern for the anesthesia provider.
- Although patients with alcohol or other substance use disorder may have abnormal pain sensitivity, providers should not assume that the etiology of inadequate neuraxial labor analgesia is solely a result of the patient’s disorder. Opioid-tolerant patients can have inadequate (failed) neuraxial analgesia and anesthesia just like their opioid-naïve counterparts.
- Smoking during pregnancy negatively affects fetal growth. Pregnant women who smoke are more likely to suffer respiratory complications and impaired wound healing.
• Moderate maternal caffeine intake (less than 300 mg/day) does not appear to have adverse maternal or fetal effects.
• Marijuana is thought to be the most common illicit substance used by pregnant women. Smoking marijuana increases maternal respiratory comorbidities. There may be long-term effects on exposed offspring including attention and impulsivity, deficits in problem solving, and academic underachievement.
• Cocaine use has been associated with sudden death from a variety of factors, including cardiac arrhythmias, respiratory arrest, status epilepticus, and impaired thermoregulation. Maternal cocaine use increases the likelihood of placental abruption and urgent cesarean delivery.
• Acute cocaine intoxication can mimic preeclampsia, eclampsia, or malignant hyperthermia.
• Evidence is conflicting as to whether intrauterine hallucinogen exposure has deleterious effects on the fetus.

• Volatile substance use can lead to severe maternal hypoxemia and potentially lethal arrhythmias.
• Ingestion of amphetamines results in high levels of circulating catecholamines, leading to hemodynamic instability and, in some cases, cardiac arrest.
• Care of the opioid-dependent patient should involve maintenance of long-term opioid requirements, multimodal management of acute pain, and avoidance of opioid antagonists and mixed agonist/antagonist agents (unless the patient shows signs of overdose).
• Buprenorphine is increasingly becoming the opioid medication-assisted therapy of choice in patients who use heroin or have other opioid use disorders. Goals of care in these and methadone-maintained patients include continuing their methadone or buprenorphine treatment, adding multimodal acute pain therapy, and avoiding opioid antagonists and mixed agonists/agonist-antagonist agents.

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2. Results from the 2015 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration. Rockville, MD: Center for Behavioral Health Statistics and Quality; 2016.


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The management of critically ill obstetric patients most commonly involves treatment of disease processes that occur as a direct consequence of pregnancy. Although sometimes life-threatening, these conditions are usually reversible. Delivery of the infant often attenuates or ablates the disease process, and the mother typically recovers with supportive and resuscitative measures. Primary obstetric disorders account for 50% to 80% of intensive care unit (ICU) admissions for pregnant patients; approximately 80% of these admissions result from preeclampsia, sepsis, and/or hemorrhage (Box 54.1). The estimated ICU admission rate for obstetric patients is 0.5% to 1% in the United States; the mortality rate among this population is 12% to 20%.2

Trauma accounts for 45% to 50% of all maternal deaths in the United States, and it is the most common nonobstetric cause of maternal death; as many as 20% of affected women require emergency surgery.5,6 It is likely that the reported incidence of maternal trauma is underestimated due to underreporting, especially in cases of domestic violence.7 Motor vehicle accidents are the most common cause of injury-related maternal death (49% to 70%), followed by domestic violence (11% to 25%) and falls (9% to 23%).8–11 Not using a seat belt is a major risk factor for maternal and fetal injury in motor vehicle trauma.12 Penetrating trauma and burns are less common than blunt mechanisms of injury.11

The rate of maternal trauma admission to an ICU increases with each trimester: 8% occur in the first trimester, 40% in the second trimester, and 52% in the third trimester.13 Most women are able to continue their pregnancy at home, but up to 38% are hospitalized until delivery.

Risk factors for maternal trauma include age younger than 25 years, low socioeconomic status, minority race, use of illicit drugs or alcohol, and domestic violence.13,14 It is important to remember that any female patient of reproductive age who is a victim of trauma could be pregnant at the time of injury.

Complications and Outcomes
As in the general population, hemorrhagic shock and brain injury are the most common mechanisms of death in pregnant patients. The management of critically ill obstetric patients must include maternal shock, transfusion of blood products, and early gestational age at the time of critical maternal illness.2–4

TRAUMA DURING PREGNANCY

Epidemiology
Trauma affects 5% to 7% of pregnancies in the United States and is the leading nonobstetric cause of maternal death; as many as 20% of affected women require emergency surgery.5,6

It is likely that the reported incidence of maternal trauma is underestimated due to underreporting, especially in cases of domestic violence.7 Motor vehicle accidents are the most common cause of injury-related maternal death (49% to 70%), followed by domestic violence (11% to 25%) and falls (9% to 23%).8–11 Not using a seat belt is a major risk factor for maternal and fetal injury in motor vehicle trauma.12 Penetrating trauma and burns are less common than blunt mechanisms of injury.11

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Risk factors for maternal trauma include age younger than 25 years, low socioeconomic status, minority race, use of illicit drugs or alcohol, and domestic violence.13,14 It is important to remember that any female patient of reproductive age who is a victim of trauma could be pregnant at the time of injury.

Complications and Outcomes
As in the general population, hemorrhagic shock and brain injury are the most common mechanisms of death in pregnant patients.
trauma victims. Pelvic and acetabular fractures also pose a significant risk. Injuries and complications that are unique to pregnant trauma victims include uterine rupture, placental abruption, preterm labor, and direct fetal injury. Although rare (0.6% of injuries), uterine rupture is a major threat to the life of both the mother (10% mortality) and the fetus (near 100% mortality). Placental abruption complicates 1% to 5% of minor injuries and 20% to 60% of major trauma and usually occurs from 16 weeks’ gestation onward. Placental abruption can cause major overt and occult hemorrhage and coagulopathy and should be considered as a possible source of bleeding in the unstable pregnant trauma patient. Preterm labor is a common (25%) complication of trauma and can be precipitated even in cases of apparently minor injury. Premature rupture of membranes (PROM) increases the risk for both preterm labor and infection. Amniotic fluid embolism is a rare complication of maternal trauma, but it should be considered as part of the differential diagnosis in patients who are refractory to resuscitation.

Fetal-maternal (transplacental) hemorrhage can occur after trauma and result in maternal isoimmunization with the D antigen of the fetal red blood cell Rhesus protein complex (Rhe(D)) in the Rh-negative mother (see Chapter 6). The Kleihauer-Betke test is used to identify fetal blood in the maternal circulation after maternal injury. Acid applied to a positive Kleihauer-Betke test. Essentially all patients with a positive test had uterine contractions, whereas patients with a negative Kleihauer-Betke test did not have contractions. The investigators concluded that the Kleihauer-Betke test was a sensitive and specific predictor of preterm labor in pregnant trauma patients and should be performed in all victims regardless of blood Rh phenotype.

**Fetal Trauma and Outcome**

The fetal mortality rate after maternal blunt trauma has been reported to range from 3.4% to 38.0%; placental abruption, uterine rupture, maternal shock, and maternal death are the most frequent factors associated with fetal demise (Box 54.2). The risk for direct fetal trauma increases with gestational age because the bony pelvis protects the uterus and fetus before 13 weeks’ gestation. Pregnant women who sustain blunt trauma have a lower risk for bowel injury than non-pregnant patients because the uterus acts as a shield and pushes the abdominal contents into the upper abdomen. Maternal pelvic fractures are associated with uteroplacental injury and fetal skull fractures. Skull fracture is the most common direct fetal injury and has a reported fetal mortality rate of 42%. The relationship between the Injury Severity Score (ISS) (see later discussion) and fetal outcome is controversial. Some studies have shown a direct relationship between the ISS and the incidence of fetal demise, whereas others have not. Analysis of outcomes from 1075 pregnant trauma victims showed that an ISS of greater than 15 was associated with increased risk for fetal demise. In contrast, a study using data from the state of Washington found no correlation between ISS and pregnancy outcomes. Fetal demise occurred even in women with low ISS. Evidence suggests that decreased serum bicarbonate, an indicator of systemic hypoperfusion, is associated with fetal demise after maternal trauma. Altered

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**BOX 54.1 Causes of Critical Illness in Pregnancy**

**Obstetric Causes**
- Acute fatty liver of pregnancy
- Amniotic fluid embolism
- Cardiomyopathy
- Chorioamnionitis
- HELLP syndrome
- Hemorrhage
- Pelvic septic thrombophlebitis
- Placental abruption
- Pre-eclampsia/eclampsia
- Puerperal sepsis

**Nonobstetric Causes**
- Acute renal failure
- Autoimmune disorders
- Chronic respiratory disease
- Diabetic ketoacidosis
- Drug abuse
- Pneumonia
- Pulmonary thromboembolism
- Trauma
- Urinary tract infection

**HELLP** Hemolysis, elevated liver enzymes, low platelet count.

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**BOX 54.2 Factors Associated with Fetal Demise after Trauma**

- Ejection from vehicle
- Maternal pelvic fracture
- High maternal Injury Severity Score (> 15)
- Maternal death
- Maternal hypotension
- Uterine rupture
- Uterine tenderness
- Placental abruption
- Vaginal bleeding
- Abnormal fetal heart rate pattern
- Amniotic fluid on pelvic examination
- Maternal history of alcohol use
- Maternal history of smoking
maternal mental status and the presence of head trauma have also been linked to adverse fetal outcomes.

It is crucial to preserve maternal cardiac output, blood pressure, and oxygen delivery to optimize maternal recovery and protect fetal well-being. However, fetal loss can occur even if the mother has not incurred serious injuries. Thus, all pregnant women should be evaluated in a medical setting after trauma, regardless of the apparent severity of injury. The fetus remains at risk for delayed complications after maternal discharge from the hospital. Delayed complications include a twofold increase in the risk for preterm delivery and a ninefold increase in the risk for fetal death. Late complications of trauma, such as cerebral palsy, have also been reported in children born to mothers who experienced trauma during pregnancy.

**Initial Assessment and Resuscitation**

The initial assessment and resuscitation should focus on the mother; it is axiomatic that maternal resuscitation typically facilitates fetal resuscitation. A systematic approach to initial resuscitation and stabilization should be used (Fig. 54.1). Immediate interventions are initiated to identify and

**Fig. 54.1** Algorithm for management of the pregnant woman after trauma. A, B, C, Airway, breathing, circulation; FHR, fetal heart rate. (Modified from Chames MC, Pearlman MD. Trauma during pregnancy: outcomes and clinical management. Clin Obstet Gynecol. 2008;51:398–408.)
treat life-threatening conditions based on the principles of Advanced Trauma Life Support (ATLS). Initial focus should be placed on ensuring adequate airway protection, ventilation (breathing), and circulation (the “ABCs” of resuscitation). Pregnant women experience significant changes in cardio-pulmonary and metabolic function that must be considered during resuscitation (Table 54.1).

**Airway**

Airway patency, stabilization, and protection should be ensured as quickly as possible in all critically injured patients, including those who are pregnant. The status of the patient’s airway can be quickly assessed by eliciting a verbal response. The inability to speak is an indication of severely impaired mental status or the inability to move adequate air to mediate phonation, either of which should prompt interventions to secure and protect the airway. Additional means of assessing airway patency include auscultation of the chest, assessment of chest movement, and assessment of air movement at the mouth and nose. Immediate interventions to establish airway patency include head-tilt and jaw-thrust maneuvers, as well as placement of an oral or nasopharyngeal airway to facilitate bag-and-mask ventilation and oxygenation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect of Pregnancy</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>Decreased by 20%</td>
<td>More rapid oxyhemoglobin desaturation during periods of apnea</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>Increased by 15%–20%</td>
<td>Tracheal intubation more difficult</td>
</tr>
<tr>
<td>Airway edema</td>
<td>May be present</td>
<td></td>
</tr>
<tr>
<td>Lower esophageal sphincter tone</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Decreased during labor</td>
<td></td>
</tr>
<tr>
<td><strong>Breathing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphragm</td>
<td>Displaced cephalad</td>
<td>Place chest tubes at higher intercostal space</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Tidal volume</td>
<td>Increased 35%–45%</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.42–7.46, partially compensated respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>28–32 mm Hg</td>
<td>Reflects normal hyperventilation</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>19–22 mEq/L</td>
<td>Reduced buffering capacity</td>
</tr>
<tr>
<td>Base deficit</td>
<td>2–3 mEq/L</td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>100–107 mm Hg</td>
<td></td>
</tr>
<tr>
<td><strong>Circulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood volume</td>
<td>Increased by 40%–50%</td>
<td>Significant blood loss may occur before onset of symptoms and hypotension</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Increased by 40%–50%</td>
<td>Early diagnosis of hypovolemia more difficult</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Increased by 15%–25%</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Decreased by 5–15 mm Hg (more pronounced during mid-pregnancy)</td>
<td>Physiologic anemia</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Decreased by 5–15 mm Hg (more pronounced during mid-pregnancy)</td>
<td>Decreased cardiac output in the supine position; left uterine displacement required</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10–12 g/dL</td>
<td></td>
</tr>
<tr>
<td>Gravid uterus</td>
<td>Aorto caval compression</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation factors</td>
<td>Increased</td>
<td>Hypercoagulable state</td>
</tr>
<tr>
<td>BUN, creatinine</td>
<td>Decreased</td>
<td>Abnormal measurements often overlookeda</td>
</tr>
<tr>
<td>Symphysis pubis/sacroiliac joints</td>
<td>Widened</td>
<td>May alter radiographic interpretations</td>
</tr>
</tbody>
</table>

*BUN, Blood urea nitrogen.

The reported measurements may fall within the normal range for the hospital laboratory, but the measurements may actually be abnormally high for a pregnant patient.
It is essential to consider the possibility of cervical spine injury, facial fractures, and skull base injuries. Excessive head-tilt maneuvers can worsen injury if a cervical spine fracture is present. Patients who have sustained severe trauma should be suspected of having a cervical spine injury until proven otherwise. Cervical spine injury must be ruled out by radiographic and physical examination criteria. The cervical spine should be stabilized with a hard collar and in-line stabilization until the severity of injury has been established. In cases of documented cervical spine injury, great care must be taken not to worsen spinal cord injury. A nasopharyngeal airway should not be placed in patients with suspected facial or skull base fractures to avoid further trauma and worsening of preexisting conditions.

Most patients who require interventions to open or support the airway, as just described, will ultimately require tracheal intubation. Indications for tracheal intubation include impaired mental status, airway obstruction, inability to clear secretions or blood from the airway, inadequate spontaneous ventilation, and hypoxemia that is refractory to supplemental oxygen administration. Tracheal intubation of pregnant patients is complicated by changes in respiratory system structure and function (see Table 54.1) (see Chapter 29). Among the most prominent alterations are airway (including vocal cord) edema, decreased functional residual capacity, and increased oxygen consumption. Airway edema impairs vocal cord visualization, thus complicating laryngoscopy and tracheal intubation. Decreased functional residual capacity and increased oxygen consumption result in more rapid oxyhemoglobin desaturation during periods of apnea. These factors increase the risk for failed tracheal intubation and hypoxemia.

Gastric emptying is normal in pregnant women before the onset of labor. However, lower esophageal sphincter tone is commonly decreased in pregnant women (see Table 54.1). Thus, pregnant women are at increased risk for regurgitation and pulmonary aspiration of gastric contents, and similar to all trauma victims, are considered to have a full stomach on arrival in the emergency department or operating room. Therefore, in most cases, rapid-sequence induction of general anesthesia is performed to facilitate tracheal intubation. However, the specific tracheal intubation technique will depend on the practitioner’s skills and resources, as well as on the location of the patient’s injuries. Alternative approaches to rapid-sequence induction include awake tracheal intubation and tracheostomy.

Several factors can complicate tracheal intubation in the trauma patient. The patient may be combative, which complicates awake tracheal intubation strategies. Blood in the airway can also limit the use of a fiberoptic bronchoscope and impair visualization of the glottis when using a standard or video laryngoscope. The presence of facial fractures, direct airway injuries, trauma-induced airway edema, and tracheal deviation can limit access to the airway.

Finally, airway management, including tracheal intubation, is more challenging in the presence of cervical spine injury. If cervical spine injury is present or suspected, it is crucial to avoid flexion, extension, or lateral movement of the neck. The spine is protected using in-line stabilization and/or a hard cervical collar. Airway management devices such as a gum elastic bougie, a video laryngoscope, a lighted intubating stylette, and/or an intubating supraglottic airway (SGA), among others, should be available for use if standard laryngoscopy is difficult or impossible. An SGA such as a laryngeal mask airway can be used to temporarily provide ventilation in cases in which mask ventilation and tracheal intubation have failed, but an SGA will not provide protection from aspiration and should be replaced by a secure airway device as soon as possible. In some cases, cricothyroidotomy or tracheostomy may be necessary to provide a secure airway.

Breathing

Adequate ventilation and oxygenation should be ensured for the benefit of both the mother and the fetus. Supplemental oxygen should be administered immediately, even if the patient is breathing spontaneously. Mechanical ventilation is often necessary after tracheal intubation in patients with respiratory failure and/or hypoxemia. Ventilation can be compromised by trauma-associated factors such as pneumothorax, hemothorax, lung contusion, mediastinal compression, and chest wall injuries. These problems must be identified during the primary survey and treated to optimize ventilation and oxygenation. In women with advanced pregnancy, it may be necessary to place chest tubes more cephalad than normal owing to the cephalad displacement of the diaphragm and intraabdominal structures by the gravid uterus. Pregnant trauma patients should be ventilated to maintain $\text{PaO}_2$ at a level that is normal for pregnancy (28 to 32 mm Hg) (see Table 54.1). Positive end-expiratory pressure (PEEP) may be added to improve oxygenation, if indicated; however, PEEP should be titrated carefully in the hypovolemic patient because it may impair venous return and worsen cardiac output and organ perfusion.

Circulation

Once respiratory stabilization has been achieved, it is essential to assess cardiovascular function and to determine whether the patient is in shock. Two large-bore peripheral intravenous catheters should be placed in the upper extremities to facilitate resuscitation. Central venous access facilitates rapid resuscitation but may be difficult to obtain. Intraosseous cannulation should be considered if it is difficult or impossible to obtain peripheral or central venous access.

Fluid resuscitation should be initiated using crystalloid solution, but blood transfusion should be considered if significant blood loss is apparent or suspected. Left uterine displacement should be initiated immediately to prevent or minimize aortocaval compression by the gravid uterus. The adverse effects of aortocaval compression may be exacerbated during periods of trauma-associated hypovolemia. The use of the pneumatic antishock garment to stabilize fractures or control hemorrhage is relatively contraindicated in pregnant women owing to its adverse effects on venous return.
Pelvic fractures can be identified by chest and pelvic radiographs and external sites of bleeding. Thoracic blood loss and uterine rupture are also potential sources of hemorrhage. The most common locations of exsanguinating blood loss are the chest, abdomen, retroperitoneum, long bones, and external sites. In the pregnant trauma patient, placental abruption and uteroplacental perfusion. Because of the physiologic anemia of pregnancy, oxygen-carrying capacity may be significantly impaired at the time that hypovolemia becomes evident. Intrauterine bleeding. Finally, ultrasonography facilitates assessment of cardiac filling and recognition of cardiac tamponade in patients with thoracic trauma.

The hallmark clinical signs of shock are listed in Box 54.3. The presence of these signs indicates a need for timely and appropriate fluid resuscitation. A rapid assessment of sources of blood loss should be performed. In trauma victims, the most common locations of exsanguinating blood loss are the chest, abdomen, retroperitoneum, long bones, and external sites. In the pregnant trauma patient, placental abruption and uterine rupture are also potential sources of hemorrhage. A brief physical examination will identify fractures of the long bones and external sites of bleeding. Thoracic blood loss and pelvic fractures can be identified by chest and pelvic radiographs, respectively. Focused abdominal sonography in trauma (FAST) or diagnostic peritoneal lavage can be used to identify intra-abdominal bleeding. However, diagnostic peritoneal lavage may be difficult to perform safely in advanced pregnancy. FAST can be rapidly performed to assess the hepatorenal, splenorenal, and pelvic spaces, which are the most common sites of major hemorrhage in trauma patients. FAST can also be used to assess uteroplacental integrity and the presence of intrauterine bleeding. Finally, ultrasonography facilitates assessment of cardiac filling and recognition of cardiac tamponade in patients with thoracic trauma.

It is important to recognize that pregnant trauma patients may lose a significant amount of blood before the development of hypotension. Pregnant patients have a 40% to 50% increase in blood volume by the third trimester. Classic signs of hypovolemia such as tachycardia, hypotension, and poor capillary refill may not be evident until blood loss approaches 1.5 to 2 liters. Therefore, it is likely that a pregnant trauma victim will have lost significantly more blood volume and oxygen-carrying capacity than a comparable nonpregnant patient when signs of cardiovascular deterioration become evident. Resuscitation should be guided by apparent blood loss to maintain adequate maternal cardiac output and uteroplacental perfusion. Because of the physiologic anemia of pregnancy, oxygen-carrying capacity may be significantly impaired at the time that hypovolemia becomes evident. In addition, maternal perfusion of vital organs is often sustained at the expense of uteroplacental perfusion. Uterine blood flow may decrease by as much as 30% before the mother shows signs of hypovolemia. Therefore, a nonreassuring fetal heart rate (FHR) pattern may be the first sign of significant intravascular volume loss. Fluids should be warmed to minimize the risk for hypothermia, which can contribute to coagulopathy, arrhythmias, and altered drug responses.

**Fluid resuscitation.** Current practice supports the use of crystalloid solutions to resuscitate the hypovolemic trauma victim during the early phases of resuscitation. However, the crystalloid versus colloid debate remains to be fully resolved. The Saline versus Albumin Fluid Evaluation (SAFE) did not show any difference in survival in nonpregnant trauma patients randomized to receive resuscitation with colloid or crystalloid, with the exception of patients with head trauma, who had poorer outcomes when resuscitated with albumin. The CRISTAL trial also did not demonstrate differences in 28-day mortality when comparing crystalloid to colloid, but 90-day mortality was lower in patients who received colloid. However, the authors considered the results exploratory and cautioned against conclusions about the efficacy of colloid solutions until further investigations are completed. Colloid solutions are anecdotally preferred in some trauma centers.

**Balanced salt solutions** (lactated Ringer’s solution, PlasmaLyte) are typically preferred over normal saline in patients without closed head injury. Balanced salt solutions have significant buffering properties and are less likely than normal saline solution to cause hyperchloremic metabolic acidosis during high-volume resuscitation. A 2018 trial showed that use of balanced crystalloids for resuscitation of critically ill patients was associated with a lower incidence of the composite outcome (death, need for renal-replacement therapy, or renal dysfunction) compared with normal saline. Other buffered salt solutions such as Ringer’s ethyl pyruvate and Ringer’s hydroxybutyrate also may have value. Currently, no evidence supports the use of one buffered isotonic crystalloid solution over another.

The use of hypertonic crystalloid solutions such as 3% sodium chloride is controversial; currently no evidence supports their use in pregnant trauma victims. Hypernatremia is a risk in patients resuscitated with hypertonic saline, and some studies have shown increased mortality in patients resuscitated with hypertonic crystalloid solutions. In a 2017 systematic review, Wu et al. did not identify significant survival or complication risk associated with hypertonic saline resuscitation compared with isotonic saline in patients with hemorrhagic shock. Nevertheless, a recent paper by Asehnoune et al. reported improved adjusted 90-day survival in trauma patients with intracranial hypertension treated with continuous hyperosmolar therapy. In general, hypertonic resuscitation does not appear to be beneficial to trauma patients without traumatic brain injury but may benefit patients with traumatic brain injury and elevated intracranial pressure (ICP).

Some practitioners have advocated hypovolemic resuscitation in patients with major hemorrhage after trauma. This technique employs permissive hypotension (systolic blood pressure of 80 to 90 mm Hg) until hemorrhage can be controlled in the operative setting. The underlying premise of
Hypovolemic (hypotensive) resuscitation is that overresuscitation worsens ongoing blood loss as a result of higher perfusion pressure and dilution of clotting factors. Small boluses of fluids are administered to maintain perfusion in patients without evidence of closed head injury. The use of hypotensive resuscitation is likely detrimental in patients with closed head injury because it is crucial to maintain adequate cerebral perfusion pressure (CPP) in patients with elevated ICP.³⁶ (CPP is the difference between mean arterial pressure [MAP] and ICP.) No definitive published data support the use of hypotensive resuscitation in pregnant trauma patients. Current guidelines do not support this approach because it may compromise uteroplacental perfusion.

The resuscitative endovascular balloon occlusion of the aorta (REBOA) catheter is a large-vessel occlusion device that is typically deployed into the aorta during periods of severe intraabdominal and pelvic hemorrhage, and is becoming increasingly utilized in cases of major trauma.²⁵ A proximal pressure transducer is used to titrate balloon inflation to maintain central pressures and limit downstream bleeding as reparative procedures are executed. The device is a less invasive alternative to emergency department thoracotomy and aortic cross-clamping to temporize noncompressible torso hemorrhage. In patients without penetrating thoracic injury, Brenner et al.³⁸ reported a survival benefit for REBOA compared with patients who received resuscitative thoracotomy. The efficacy of the approach remains to be fully determined in all subsets of trauma patients with hemorrhage; a prospective study of the device is underway. The effectiveness and safety of the REBOA catheter remains to be established in critically injured pregnant patients.

**Damage control principles and resuscitation.** The traditional approach to treatment of traumatic life-threatening injuries has been definitive operative repair. However, some patients experience progressive physiologic decline during long surgical procedures and develop severe derangements such as hypothermia, metabolic acidosis, and coagulopathy, a combination that has become known as the deadly triad.³⁹ These pathologic alterations require rapid and effective treatment to prevent severe morbidity and death. More recently, practitioners have advocated the use of a more targeted surgical approach, termed damage control surgery, which is initiated to control hemorrhage without providing early definitive repair of injuries.⁴⁰ Major surgical bleeding is controlled, and the thoracic and abdominal cavities are packed to provide hemostasis. Gastrointestinal diversion is performed, and body cavities are temporarily closed, often using vacuum-type closure systems. Active volume resuscitation is performed using blood products rather than crystalloids, an approach known as damage control resuscitation, to achieve metabolic homeostasis. Once stable hemodynamic and acid-base status, coagulation function, and temperature are achieved, the patient is returned to the operating room for definitive repair of injuries.

**Blood products.** All trauma centers should have rapid access to type O, Rh-negative blood for emergency use before type-specific or cross-matched blood is available. Recently, trauma specialists have advocated damage-control resuscitation using packed red blood cells (PRBCs), platelets, and fresh frozen plasma mixed in equal proportions (1:1:1) (see Chapter 37). Several investigators have reported the value of this approach in military practice, and they have specifically observed that this approach results in more effective resuscitation, less coagulopathy, and improved survival than more traditional approaches.⁴¹ Based on experience over the last few years, damage-control resuscitation is also considered to be the optimal strategy for managing civilian patients with exsanguinating trauma.³² The Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) trial showed that damage-control surgery and balanced blood product resuscitation (1:1:1 ratio) is associated with improved hemostasis at 3 hours after intervention and a decreased incidence of death by exsanguination at 24 hours after injury, although overall mortality at 24 hours and 30 days after injury was not improved compared with patients receiving damage-control surgery with blood products in a 1:1:2 ratio.⁴³ Based on current evidence, the Eastern Association for the Surgery of Trauma recommends the use of balanced blood product resuscitation in exsanguinating trauma patients.⁴⁴

Despite implementation of damage-control resuscitation, coagulopathy remains a significant problem for trauma patients requiring large-volume resuscitation. Damage-control resuscitation provides clotting factors via transfused plasma and direct administration of platelets. However, tissue injury and release of endogenous anticoagulants often results in sustained alterations in coagulation. Consequently, some practitioners advocate adopting a goal-directed approach to treat trauma-induced coagulopathy based on viscoelastic monitoring, either with thromboelastography (TEG) or rotational thromboelastometry (ROTEM) (see Chapter 44).⁴⁵ Gonzalez et al.⁴⁶ reported that goal-directed treatment of trauma-associated coagulopathy, compared with standard assessment of coagulation status, was associated with lower mortality and decreased use of plasma and platelets during the acute phase of resuscitation.⁴⁶ However, there were limitations associated with the study, and further work is needed to define the benefits of goal-directed treatment of coagulopathy in the trauma patient suffering large-volume hemorrhage.

**Secondary Survey**

As in all trauma cases, it is crucial to evaluate the mother for significant abdominal, thoracic, orthopedic, and neurologic injuries. A head-to-toe examination should be performed to determine the presence of injuries and the need for intervention. A more detailed evaluation of neurologic function, as well as examination of the head and neck, should be performed. This survey includes examination of posterior structures that may be obscured by the supine position and the presence of a cervical collar. The torso should be examined to identify thoracic and abdominal injuries. The thoracic examination should include chest auscultation, inspection, and palpation. Palpation of the abdomen should be performed to evaluate abdominal tenderness, and a rectal examination should be performed to identify evidence of intraluminal bleeding.
The extremities must be examined to identify deformities, and each joint should be manipulated. Distal perfusion of the extremities must be continuously monitored, especially in limbs that show signs of significant injury. This is accomplished by evaluation of distal pulses and capillary refill. In cases of penetrating injury, the sites of entry and exit should be identified. It is especially important to examine carefully the areas that are difficult to access such as the oral cavity, perineum, axilla, scalp, and back. Once the secondary survey has been performed, more targeted assessments of suspected injuries can be performed using radiologic imaging.

Fetal survey. After initial stabilization of the mother, information about the pregnancy should be gathered through a focused history and physical examination. The history should include the date of the last menstrual period, expected date of delivery, and status of the pregnancy. In cases in which there is uncertainty regarding fetal age, an approximate determination can be made by measuring fundal height. The fetal age is estimated to be 1 week for each centimeter of fundal height above the symphysis pubis. In addition to the assessment of fundal height, the abdominal examination should include an assessment of uterine tenderness and consistency, the presence or absence of uterine contractions, and fetal position and movement.

A pelvic examination should be performed to evaluate cervical dilation and effacement, fetal station, and the presence of amniotic fluid and blood. The FHR is assessed by Doppler auscultation or ultrasonography. If maternal stability permits, ultrasonography facilitates estimation of fetal age and assessment of uteroplacental injury.

If no fetal cardiac activity is identified, fetal resuscitation should not be attempted (see Fig. 54.1). In a series of 441 pregnant trauma patients, the absence of a detectable FHR was associated with fetal death in all cases. When an FHR is detected, an assessment of fetal viability should be performed. An estimated gestational age of 23 to 24 weeks and an estimated fetal weight of 500 g are common thresholds for extrauterine fetal viability. The FHR should be monitored in cases in which the fetus is determined to be viable. In cases in which a nonviable fetus is present, the importance of FHR monitoring is unclear. However, alterations in FHR and FHR variability may signal maternal deterioration and serve as a good monitor of the effectiveness of maternal resuscitation.

FHR monitoring is generally performed with external Doppler auscultation, and a tocdynamometer is used to assess uterine contractions. Adverse fetal outcomes are unlikely in cases with a reassuring FHR tracing and no early warning signs of uteroplacental injury (bleeding, abdominal pain). In contrast, an abnormal FHR tracing or evidence of uteroplacental injury (vaginal bleeding, uterine contractions, uterine tenderness, presence of amniotic fluid on vaginal examination) predicts poor fetal outcome in approximately 50% of cases.

Fetal Monitoring
Continuous electronic FHR monitoring is the current standard of care for pregnant trauma victims with a viable fetus. FHR monitoring should be initiated as soon as maternal stabilization allows, because placental abruption can occur early during the course of resuscitation. Continuous electronic FHR monitoring is more sensitive for placental abruption than ultrasonography, physical examination, or Kleihauer-Betke testing. Occasional uterine contractions are common after trauma and are usually not associated with poor fetal outcome. Random uterine contractions usually resolve within a few hours of the accident. However, regular and prolonged uterine contractions (eight contractions per hour for more than 4 hours) are associated with placental abruption, which has a high fetal mortality rate. The diagnosis of placental abruption should trigger immediate cesarean delivery for both fetal and maternal indications; a large percentage of viable fetuses can be rescued if expedited delivery is performed, and placental abruption will exacerbate maternal hemorrhage and coagulopathy. The presence of fetal bradycardia and/or frequent late FHR decelerations should also prompt delivery if the mother is stable and adequately resuscitated.

The ideal duration of FHR monitoring has not been determined. However, a common practice, based on a prospective study of 60 pregnant trauma patients at more than 20 weeks’ gestation, is to monitor the FHR for 4 hours. If maternal-fetal abnormalities are not detected within 4 hours, it is generally considered safe to discontinue FHR monitoring because a normal FHR tracing has a negative predictive value of 100% when combined with a normal maternal physical examination. However, the presence of abnormalities such as vaginal bleeding, spontaneous rupture of membranes, category II and III FHR patterns, persistent uterine contractions, uterine tenderness, abdominal pain, and/or need for maternal analgesia should prompt further FHR monitoring. The sensitivity of ultrasonography for placental abruption ranges from 50% to 80%, but ultrasonography is a safe and effective means of assessing fetal viability, FHR, placental location, gestational age, and amniotic fluid volume. It is particularly valuable in the presence of maternal tachycardia, when it can be difficult to differentiate maternal and fetal heart rates using Doppler auscultation.

Laboratory Studies
Laboratory evaluation in pregnant trauma patients does not differ from the evaluation for nonpregnant patients, with a few exceptions. As for all trauma patients, the laboratory evaluation will be driven by the type and severity of injury. For most patients with significant injury, standard analysis includes a complete blood cell count, coagulation studies, serum electrolyte measurements, blood glucose and lactate levels, liver function tests, arterial blood gas analysis, urinalysis, and toxicology screening, as well as sending a blood sample for typing and cross-matching for compatible blood products (Box 54.4).

The presence of disseminated intravascular coagulation (DIC) and low blood bicarbonate levels is associated with poor fetal outcome. Both abnormalities reflect severe maternal injury and should prompt aggressive maternal...
resuscitation. Of special consideration in pregnant trauma patients is maternal-fetal hemorrhage. The Kleihauer-Betke test is used to detect the entry of fetal blood into the maternal circulation. Although typically performed in Rh(D) antigen-negative mothers to detect transplacental hemorrhage and the potential for developing Rh(D) sensitization, this test may help predict adverse fetal outcomes in all pregnant trauma patients (see earlier discussion).

**Imaging**

The pregnant trauma patient often requires imaging to evaluate orthopedic, head, thoracic, and abdominal injuries. Although many patients and physicians are concerned about the fetal effects of ionizing radiation, the risks for teratogenesis, malignancy, and gene mutation are small with a radiation exposure less than 5 to 10 rads (see Chapter 17). Less than 1% of trauma patients receive more than 3 rads of radiation exposure. When possible, the fetus should be shielded with lead. Intravenous pyelography subjects the fetus to as much as 1.4 rads of exposure, but the test can be invaluable in diagnosing injuries to the kidneys, ureters, and bladder. Computed tomography (CT) is associated with greater radiation exposure than plain radiography, but exposure levels are generally below that considered to be dangerous to the fetus. Modern multidetector (multislice) CT results in higher fetal radiation exposure, but it has significant advantages in speed and image resolution. Overall, the small risk for fetal radiation exposure is outweighed by the benefits to the injured mother and, by extension, the fetus.

**Injury Scoring**

Several injury scoring scales have been developed over the past 40 years. The scoring systems provide a framework for standardizing clinical management, benchmarking outcomes, and planning research. Presently, no reliable scoring tool exists for predicting maternal or fetal outcome after trauma. Currently used scoring systems include (1) anatomic injury scales that rely on physical examination and diagnostic procedures, (2) physiologic injury scales that rely on assessment of physiologic responses and function, and (3) combination injury scales.

One of the first anatomy-based injury scales was the **Abbreviated Injury Scale (AIS)** developed by the Association for the Advancement of Automotive Medicine. Each of nine body regions is given a injury severity score that ranges from 1 (minor) to 6 (maximal [currently untreatable]). Although the AIS effectively describes the severity of injuries at specific locations, it provides a limited assessment of the overall pathophysiologic impact of all injuries. The **Injury Severity Score (ISS)**, which was developed to address this issue, is obtained by summing the square of the three highest severity scores from the AIS. The ISS ranges from 1 to 75. Minor injuries are classified as an ISS of less than 9; moderate, from 9 to 15; serious, from 16 to 25; and severe, greater than 25. The ISS correlates with the risk for preterm delivery after trauma, but its value in predicting fetal death, placental abruption, and other adverse outcomes is controversial.

The American Association for the Surgery of Trauma developed the **Organ Injury Scale (OIS)**; this is an organ-based severity scale designed to facilitate clinical investigation and outcomes research.

The value of injury scoring scales in predicting adverse maternal and fetal outcomes remains to be established. Distelhorst et al. reported improved birth outcomes in pregnant patients treated at dedicated trauma centers. However, after controlling for the ISS, the level of trauma designation was not associated with any differences in most birth outcomes, with the exception of higher risk for preterm labor and meconium-stained amniotic fluid at level 1 and 2 centers compared with level 3 and 4 centers.

Anatomic scoring systems have value in describing the extent and severity of injuries to specific organ systems. However, physiologic scoring systems may add prognostic value. The **Glasgow Coma Scale (GCS)**, which is among the most widely used physiologic scoring systems, evaluates the neurologic status of the trauma patient. The GCS evaluates eye opening, verbal response, and motor activity; scores range from 3 to 15, with 3 indicating the absence of neurologic activity and 15 representing intact neurologic function. A GCS score of less than 9 reflects severe impairment, whereas a score of 9 to 12 reflects moderate disability. However, concerns have been raised about interrater reliability and lack of prognostic utility for the GCS. Some researchers have proposed that a simplified motor score would be more reliable.

**Traumatic Brain Injury**

Brain injury is the most common severe injury in patients who suffer from motor vehicle accidents, and it is a major cause of mortality among pregnant trauma victims. It is important to perform a thorough neurologic examination
with particular attention to level of consciousness. Altered mental status may be an indicator of evolving intracranial pathology, intoxication, hypoperfusion, and/or metabolic disturbances. Mental status should be reevaluated frequently because intracranial pathologic processes may not be apparent on initial evaluation and may evolve during the course of resuscitation.

Elevated ICP is a common finding in patients with traumatic brain injury and may be a significant threat to life. Head CT is the imaging study of choice for identifying the site and severity of intracranial pathologic processes in trauma patients, and it should be performed within 1 hour of arrival in the emergency department.

Crystalloid fluid resuscitation should be used for resuscitation in patients with traumatic brain injury; resuscitation with albumin is deleterious in patients with traumatic brain injury (see earlier discussion). The use of hypertonic crystalloids to resuscitate patients with traumatic brain injury is controversial. Hypotensive resuscitation is contraindicated in patients with traumatic brain injury and elevated ICP. It is crucial to maintain mean arterial pressure and CPP to minimize the risk for brain ischemia and permanent brain injury. The extent of brain injury will worsen if CPP is not maintained. It is also important to maintain cerebral oxygen delivery by optimizing maternal cardiac output and blood oxygen-carrying capacity.

It may be necessary to intubate the trachea of patients with deteriorating mental status for airway protection and provision of ventilatory support. Hypoventilation should be avoided because it increases ICP. Hyperventilation to a PaCO2 level of ventilatory support. Hypoventilation should be avoided because it increases ICP. Hyperventilation to a PaCO2 of 30 mm Hg will provide a transient decrease in ICP and may be useful until definitive treatment can be initiated. However, hyperventilation can be disadvantageous for the fetus because it can decrease uteroplacental blood flow by decreasing maternal cardiac output and blood pressure, and perhaps by causing uteroplacental vasoconstriction. Therefore, it is prudent to maintain PaCO2 at levels that are normal in pregnant women (28 to 32 mm Hg). Additional maneuvers to decrease ICP include treatment with a diuretic such as mannitol or furosemide and elevation of the head 40 to 45 degrees. Treatment with hypertonic saline can also decrease intracranial volume and ICP, and may improve outcomes in patients with traumatic brain injury.

Corticosteroids are no longer recommended for patients with traumatic brain injury because their administration in this setting is associated with increased mortality. Barbiturates decrease cerebral oxygen use and blood flow and may provide cerebral protection in patients with severe impairment. Both mannitol and furosemide cross the placenta and could cause alterations in fetal plasma osmolality and decrease fetal intravascular volume. However, concern regarding adverse fetal effects should be overridden by the needs of the mother in cases of traumatic brain injury.

### Cardiopulmonary Resuscitation

The incidence of cardiac arrest in pregnancy is reported to be 1:20,000 to 1:40,000 patients in industrialized countries. Cardiac arrest during hospitalization for delivery is more common, because it includes postpartum cardiac arrest. The most frequent causes are trauma, peripartum hemorrhage, embolic phenomena, stroke, preeclampsia/eclampsia, sepsis, status asthmaticus, and anesthesia-related complications.

Cardiopulmonary resuscitation should be initiated immediately (see Chapter 41). The 2015 American Heart Association (AHA) guidelines highlight the importance of initiating high-quality chest compressions to facilitate circulation. Recent guidelines have simplified the list of modifications to cardiopulmonary resuscitation during pregnancy (Box 54.5), for the most part, pregnant women benefit from standard high-quality cardiopulmonary resuscitation similar to that performed in nonpregnant patients. Hands should be placed in the usual location on the center of the victim’s chest; there is no scientific evidence to support changing the hand position from that used to resuscitate nonpregnant patients. Chest compressions should be performed at a rate of 100 per minute at a depth of at least 5 cm. Interruptions should be minimized. Cardiac arrest in the pregnant patient is complicated by the physiologic changes of pregnancy, particularly the effect of the gravid uterus on aortocaval blood flow. Well-performed chest compressions in the nonpregnant patient typically result in cardiac output that is approximately 30% of normal. In pregnant patients, aortocaval compression reduces the cardiac output that results from chest compressions. Therefore, the AHA guidelines advocate manual left uterine displacement with the patient in the supine position (Fig. 54.2).

In the hospital setting, the airway should be secured and the mother ventilated with 100% oxygen. Chest impedance is unchanged during pregnancy; therefore, the usual voltage levels for defibrillation should be used in pregnant patients.

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**Box 54.5 Modification of Cardiopulmonary Resuscitation during Pregnancy**

- Perform manual left uterine displacement.
- Anticipate difficult airway management.
- Obtain intravenous access above the diaphragm.
- If patient is receiving magnesium sulfate, discontinue magnesium infusion and administer calcium chloride or calcium gluconate.
- Remove all fetal monitors before delivery; internal fetal monitors may be cut externally. Fetal monitor removal should not delay defibrillation.
- If spontaneous circulation does not return within 4 minutes of cardiac arrest, immediate resuscitative hysterotomy or cesarean delivery should be performed if gestational age is 20 weeks or greater, aiming for delivery within 5 minutes of cardiac arrest.
- Continue all resuscitation efforts during and after cesarean delivery.

Management of the Brain-Dead Patient

Brain death in the pregnant patient is a rare occurrence. Esmaeilzadeh et al. summarized 30 cases published between 1982 and 2010. Nontraumatic brain injury, primarily intracranial hemorrhage, was the cause of death in 26 of 30 cases. The mean gestational ages at times of injury and delivery were 22 and 29.5 weeks, respectively. Twelve viable infants survived beyond the neonatal period.

In cases of maternal brain death, care providers should focus on saving the life of the fetus; maternal organ preservation for harvest and donation is a secondary consideration. Maintenance of vital functions in mothers with catastrophic brain injury is justified to meet these two goals, but in many cases ethical and legal concerns must be addressed. Consideration must be given to gestational age and the chance for fetal survival. Before 23 weeks’ gestation, the chance for extraterine fetal survival is small. In general, management should follow current guidelines for organ preservation therapy.

The question of whether to preserve maternal circulation and organ function to facilitate fetal development is an ethical dilemma. A fundamental issue relates to the support of the brain-dead mother as an incubator for the unborn fetus. Some professionals argue such an approach is unethical, whereas others view prolonged somatic support as a case of organ donation with the fetus as the recipient. In many cases, the mother’s wishes are not known. If the mother indicated a wish to donate organs, prolonged somatic maternal support may be appropriate. Currently, there is no generally accepted lower limit of gestational age for maintenance of maternal support. Each case must be addressed on an individual basis, with close communication among the family, a cohort of care providers, and the hospital ethics committee.

CRITICAL CARE DURING PREGNANCY

Ischemic Stroke

Pregnant women are at increased risk for ischemic stroke compared with their nonpregnant counterparts. Pregnancy is a hypercoagulable state characterized by decreased fibrinolysis, increased levels of clotting factors, and decreased levels of certain natural anticoagulants (e.g., protein S). Clinical manifestations of ischemic stroke are similar to those seen in the nonpregnant population and include focal neurologic symptoms, seizures, decreased level of consciousness, and abnormal cranial nerve function. Once the diagnosis is suspected, and initial evaluation and therapy—including airway protection—have been addressed, non–contrast-enhanced CT should follow immediately. If CT shows no evidence of hemorrhagic stroke, the patient is assumed to have an ischemic stroke. Magnetic resonance imaging is more sensitive in detecting early ischemic events; however, the test is more time-consuming and not widely available. Consideration of thrombolytic therapy should follow, including evaluation of contraindications for thrombolytic therapy (Box 54.6). Thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) has been reported during pregnancy and appears to be safe for the fetus; transplacental passage of r-tPA is minimal. However, retroplacental bleeding with pregnancy
loss has been reported.70–72 Consultation with an experienced neurologist is recommended.

The r-tPA is administered intravenously at a dose of 0.9 mg/kg (maximum, 90 mg) over 1 hour (10% of the dose is commonly administered as an initial bolus over the first minute).69 The therapeutic window (i.e., time from onset of symptoms to administration of the agent) is 4.5 hours. Patients who are candidates for this therapy should be watched closely in an ICU environment that includes fetal surveillance by a maternal-fetal medicine specialist. Blood pressure should be maintained below 180/105 mm Hg during r-tPA therapy with the use of agents such as labetalol or nicardipine.72 Neurologic deterioration during thrombolytic infusion should raise suspicion of hemorrhagic transformation; the infusion should be stopped immediately, and the head CT should be repeated. If hemorrhagic transformation is present, reversal of r-tPA is achieved with administration of cryoprecipitate (10 units) with the goal of maintaining a serum fibrinogen level above 150 mg/dL. The added benefit of platelet transfusion is not clear. If cryoprecipitate is not available, tranexamic acid 1 gram intravenously may be administered.73

Patients with ischemic stroke who are not candidates for r-tPA therapy should receive aspirin (162 to 325 mg/day) for 1 to 2 weeks; subsequently, the dose may be decreased to 100 mg/day.72 Deep vein thrombosis prophylaxis with unfractionated heparin should also be started on admission unless contraindicated. Outcome data related to blood pressure management in patients with acute ischemic stroke are inconsistent. In 2018 the AHA and the American Stroke Association recommended that, in patients who are not receiving thrombolytic therapy, emergency antihypertensive medication should be withheld unless the blood pressure is higher than 220/120 mm Hg.69 This recommendation does not apply to women with ischemic stroke in the presence of preeclampsia, in whom current guidelines recommend treatment with antihypertensive agents if the blood pressure is greater than 160/110 mm Hg. If the patient has received thrombolytic therapy, aspirin and prophylactic doses of heparin should be withheld for 24 hours after completion of the infusion. Fever should be aggressively treated to achieve normothermia. Blood glucose control with a target between 140 to 180 mg/dL is recommended in the setting of ischemic stroke. Intravenous insulin may be used as needed. Seizure prophylaxis in ischemic stroke is not recommended.69

Cerebral sinus and vein thrombosis may occur during pregnancy and the puerperium, but most cases occur postpartum. The practitioner should suspect cerebral sinus thrombosis in the presence of severe headache, focal neurologic signs, and/or papilledema. The diagnostic test of choice is magnetic resonance venography (MRV). Most cases involve the transverse sinuses. Initial imaging reveals concomitant areas of hemorrhage in as many as 40% of these cases. Despite the latter, treatment involves immediate therapeutic anticoagulation with unfractionated heparin or low-molecular-weight heparin unless massive hemorrhage is present.74,75 Ischemic strokes that involve more than 50% of the territory of the middle cerebral artery are known as “malignant strokes.” They occur more commonly in young people. In the vast majority of cases, these patients require early decompression hemicraniectomy because the stroke is usually associated with massive cerebral edema that frequently is not responsive to medical therapy.76

Hemorrhagic Stroke

Pregnancy typically is accompanied by a 40% to 50% increase in both cardiac output and effective blood volume. These changes, coupled with hormone-induced increased fragility of vessel wall structures (secondary to increased levels of estrogen, progesterone, matrix metalloproteinases, and relaxin), may render pregnant patients more susceptible to hemorrhagic stroke resulting in intracerebral and subarachnoid hemorrhage.77

Intracerebral hemorrhage. Intracerebral hemorrhage is usually a secondary complication of hypertensive emergencies (e.g., preeclampsia, hypertensive encephalopathy). Clinical presentation is similar to that in nonpregnant individuals. The diagnosis is confirmed with non–contrast-enhanced CT.

As in any other stroke victim, initial management involves securing the airway and facilitating oxygenation and ventilation. Intracranial pressure monitoring should be considered in patients with a GCS score less than 8, clinical evidence of transtentorial herniation, and evidence of significant intraventricular hemorrhage or hydrocephalus.78

Blood pressure control in the setting of intracerebral hemorrhage is controversial. Past evidence suggested that
acute blood pressure control with the aim of reducing systolic pressure to 140 mm Hg is safe and could be associated with improved functional outcomes. Recent evidence from recent clinical trials does not support benefit from strict blood pressure control (systolic blood pressure goal below 140 mm Hg) compared with traditional management (systolic blood pressure goal below 180 mm Hg). In some studies, patients randomized to strict blood pressure control had a higher risk for acute kidney injury.

Blood pressure control is currently recommended in patients with intracerebral hemorrhage and a systolic blood pressure above 160 to 200 mm Hg. In cases of intracerebral hemorrhage associated with preeclampsia, most practitioners recommend maintenance of systolic and diastolic blood pressures between 140 to 160 mm Hg and 90 to 110 mm Hg, respectively, to maintain uteroplacental perfusion pressure (see Chapter 35). Blood pressure should be monitored invasively and treated with a titratable intravenous agent such as labetalol or nicardipine.

In the setting of intracerebral hemorrhage secondary to the use of warfarin, rapid reversal of the anticoagulation effect is of paramount importance. Vitamin K (10 mg intravenously over a minimum of 20 minutes) should be administered, along with prothrombin complex concentrate, which contains the vitamin K–dependent clotting factors II, VII, IX, and X. Advantages of prothrombin complex concentrate compared with plasma transfusion to replete vitamin K–dependent clotting factors include no requirement for blood typing and cross-matching, a lower risk for bloodborne infection, fewer complications, faster correction of the international normalized ratio (INR), and little risk for volume overload. Prothrombin complex concentrate can be infused over 15 to 30 minutes. The role of recombinant activated factor VII (rFVIIa) in this setting is limited, and its use cannot be recommended at this time.

The risk for seizures after intracerebral hemorrhage is higher in cases of lobar hemorrhage; the risk is small if hemorrhage is localized to the basal ganglia, and even less if limited to the posterior fossa. Unless clinical seizures are observed or nonconvulsive activity is noted on the electroencephalogram (EEG), routine seizure prophylaxis in patients with intracerebral hemorrhage is not recommended; therapy may be associated with poorer long-term functional outcome. The exception is intracerebral hemorrhage in the setting of preeclampsia, for which magnesium is indicated for seizure prophylaxis. As with most brain injuries, glucose control is paramount in the management of intracerebral hemorrhage. Blood glucose should be maintained between 140 and 180 mg/dL in critically ill patients with brain injuries. Once bleeding cessation is documented by repeat imaging, deep vein thrombosis prophylaxis with unfractionated heparin or low-molecular-weight heparin should be initiated (usually 1 to 4 days after the intracerebral hemorrhage). Patients should also receive mechanical prophylaxis with sequential compression devices.

**Subarachnoid hemorrhage.** A subarachnoid hemorrhage may be traumatic or nontraumatic. This discussion is limited to nontraumatic forms of subarachnoid hemorrhage. The most common cause of nontraumatic subarachnoid hemorrhage is rupture of a berry aneurysm. The clinical presentation varies from the complaint of the “worst headache in my life” to profound coma. The diagnosis is made by CT followed by cerebral angiography to locate the source of the bleeding; CT angiography detects aneurysms as small as 2 mm. Abdominal shielding is essential during all radiographic procedures to limit fetal radiation exposure. Once the aneurysm is located, two management options exist. Cranial clipping with clipping of the aneurysm has been the traditional treatment. More recently, coiling of the aneurysm has emerged as a less invasive option. Controversy exists regarding which option results in the most favorable outcome. A large randomized study comparing both treatment modalities found that endovascular coiling resulted in a lower risk for death at 5 years; however, the risk for rebleeding was higher in the endovascular coiling group. Endovascular coiling is currently the preferred treatment option as it has been associated with better long-term neurologic outcomes and less mortality.

Endovascular coiling has not been specifically studied in the pregnant population, although several cases of successful endovascular treatment of ruptured intracranial aneurysms in pregnant women have been reported.

Regardless of the treatment modality, it is crucial to secure the aneurysm as early as possible. Before the aneurysm is secured, blood pressure control should target a systolic blood pressure below 160 mm Hg.

**Delayed vasospasm** is one of the most serious complications of subarachnoid hemorrhage. The onset is usually 3 to 5 days after the hemorrhage and manifests as worsening of the neurologic examination (either new focal symptoms or decreased level of consciousness). If a change in the neurologic status is noted, immediate CT should be performed to rule out rebleeding or hydrocephalus; if absent, vasospasm is likely. Vasospasm is confirmed with cerebral angiography. All patients should be treated with nimodipine (60 mg orally every 4 hours for 21 days) as prophylaxis against delayed-onset ischemia secondary to cerebral vasospasm. Nimodipine is the only agent that has shown improved outcomes in the treatment of delayed cerebral ischemia. Recent data do not lend support to the efficacy of magnesium sulfate or statins.

Once surgical or endovascular treatment is completed, blood pressure control may be less rigorous because hypertension may be a compensatory mechanism to maintain cerebral perfusion pressure in the setting of vasospasm. During pregnancy, extremely high blood pressure may lead to placental abruption and should be avoided. Maintaining a systolic blood pressure below 160 mm Hg may be reasonable during pregnancy after securing the aneurysm.

Historically, patients presenting with symptomatic delayed cerebral vasospasm have been treated with “triple H therapy.” Triple H therapy consists of inducing hypervolemia (through administration of crystalloids or colloids), leading to hemonodilution, accompanied by induced hypertension (by using vasopressors) in an attempt to increase cerebral perfusion. Evidence of the efficacy of triple H therapy is extremely limited.
The use of hypervolemia and subsequent hemodilution may even be detrimental as a result of a decrease in arterial oxygen content.\textsuperscript{87} Instead, many practitioners recommend induced hypertension with intravenous infusion of norepinephrine, phenylephrine, or dopamine, and titration of systolic blood pressure to measurements higher than 180 mm Hg (MAP \textgreater{} 120 mm Hg). However, during pregnancy, the use of high-dose vasopressors to induce hypertension may lead to uteroplacental vasoconstriction and hypoperfusion and subsequent fetal demise. Additionally, the hypertension may increase the risk for placental abruption. Pregnant patients requiring induced hypertension for delayed vasospasm present a significant clinical dilemma. If the fetus is sufficiently mature (e.g., more than 32 weeks' gestation), it may be advisable to deliver the fetus before initiation of induced hypertension. If delivery is not an option, balloon angioplasty of the constricted vessels by an interventional radiologist may be considered in lieu of induced hypertension.

Subarachnoid hemorrhage may also lead to extracerebral manifestations, the most common of which are hyponatremia, cardiac dysfunction, and neurogenic pulmonary edema. Hyponatremia occurs secondary to increased secretion of atrial and ventricular natriuretic peptides (cerebral salt-wasting syndrome).\textsuperscript{88} Treatment with isotonic sodium replacement (0.9\% saline) usually suffices. Rarely, hypertonic saline may be required.

The massive liberation of catecholamines that accompanies subarachnoid hemorrhage is believed to cause subendocardial ischemia, leading to “cardiac stunning” with concomitant arrhythmias and decreased cardiac output. Patients may require inotropic support and antiarrhythmic therapy. Neurogenic pulmonary edema usually occurs within hours of the bleeding event, and has both a hydrostatic component (from cardiac stunning and pulmonary venous constriction as a result of increased catecholamine secretion) and a noncardiogenic component (from endothelial injury owing to activation of the inflammatory cascade secondary to the presence of severe brain injury). Treatment of neurogenic pulmonary edema is supportive and requires low tidal volume ventilation strategies and the use of PEEP to improve oxygenation.

Subarachnoid hemorrhage may also occur secondary to rupture of brain arteriovenous malformations.\textsuperscript{89} General intensive care provided to these patients is similar to that used in aneurysmal subarachnoid hemorrhage, with a few exceptions. The risk for vasospasm after subarachnoid hemorrhage from arteriovenous malformations is lower and rarely warrants therapy. Once removed (surgically), adjacent brain tissue will be exposed to increased cerebral blood flow leading to cerebral edema. Localized cerebral edema may be prevented by avoidance of severe hypertension. The decision to surgically treat a ruptured arteriovenous malformation is controversial and depends on the location and type of venous drainage (superficial or deep).\textsuperscript{89} The risk for rebleeding during pregnancy is increased, and treatment (e.g., surgical resection, embolization) is commonly recommended for accessible lesions.\textsuperscript{90}

As with intracerebral hemorrhage in general, normothermia should be maintained and the maximum blood glucose level should be maintained between 140 and 180 mg/dL. Seizure prophylaxis in the setting of subarachnoid hemorrhage is controversial. Prolonged use of phenytoin has been associated with poor neurologic outcomes and should be avoided.\textsuperscript{91} A systematic review suggested that 3 days of seizure prophylaxis therapy provides similar seizure prevention with more favorable outcomes compared with longer-term treatment.\textsuperscript{91} In general, widespread use of seizure prophylaxis in subarachnoid hemorrhage is not recommended.

**Status Epilepticus**

*Status epilepticus* is defined as a continuous, generalized convulsive seizure lasting more than 5 minutes or two or more seizures with no return to baseline consciousness between the seizures.\textsuperscript{92} Status epilepticus may be caused by noncompliance with antiepileptic medications, stroke, brain tumor, central nervous system infection, head trauma, metabolic derangements (e.g., uremia, hepatic encephalopathy, electrolyte abnormalities), cerebral hypoxia, and hypoglycemia/hyperglycemia. Rarely, eclamptic seizures may progress to status epilepticus.

Initial management should include protecting the airway and arresting the epileptic convulsions. Intravenous access should be obtained and hypoglycemia ruled out promptly. If in doubt, a 50-mL bolus of intravenous 50\% dextrose with 100 mg of thiamine should be administered. Adequate hydration is of paramount importance because seizure-induced muscle breakdown may lead to myoglobin-induced kidney injury.\textsuperscript{92} Initial pharmacologic therapy includes an intravenous benzodiazepine (e.g., lorazepam 0.1\ mg/kg) followed by a standard intravenous antiepileptic agent (e.g., phenytoin, valproic acid). If intravenous access is difficult, intramuscular drug administration is an option. Intramuscular midazolam (10 mg) is at least as effective as intravenous lorazepam in the prehospital management of status epilepticus.\textsuperscript{93} If seizure control is not achieved, a continuous infusion of propofol, midazolam, or a barbiturate may be required.\textsuperscript{94} There is no agreement on the recommended EEG titration goal (burst suppression versus seizure control).\textsuperscript{94} Many practitioners recommend 24 to 48 hours of seizure control documented by EEG before slowly weaning the infusion.

**Acute Respiratory Distress Syndrome**

*Acute respiratory distress syndrome* (ARDS) is a severe form of noncardiogenic pulmonary edema; it is a common cause of mortality in the critically ill obstetric patient. ARDS is defined as the acute onset (within 7 days of known clinical insult) of noncardiogenic pulmonary edema (usually secondary to an inflammatory insult) with bilateral pulmonary infiltrates and a partial pressure of oxygen to inspired fraction of oxygen ratio (P/F ratio) less than 300 with PEEP of at least 5 cm H$_2$O.\textsuperscript{95} Mild ARDS is defined as a P/F ratio between 200 and 300, moderate ARDS between 100 and 200, and severe ARDS as a ratio below 100. The term *acute lung injury* is no
longer used. The mortality rate from severe ARDS is approximately 45%.95

ARDS may occur secondary to a pulmonary or extrapulmonary pathologic process. The common denominator is activation of the inflammatory cascade, leading to inflammation-induced endothelial/epithelial injury in the lung with subsequent leaking of protein-rich fluid into the alveoli. Direct (pulmonary) insults that may lead to ARDS include pneumonia, aspiration pneumonitis, pulmonary contusion, and smoke inhalation during burns. Indirect (extrapulmonary) causes include sepsis, pancreatitis, trauma, and massive transfusion. Similar to the nonobstetric population, the most common cause of ARDS in pregnant women is sepsis.96 Certain obstetric conditions (e.g., placental abruption, amniotic fluid embolism, preeclampsia) may also cause ARDS because these conditions are associated with inflammation and subsequent diffuse endothelial injury. Also, patients with severe placental abruption or amniotic fluid embolism complicated by DIC are at increased risk for massive transfusion of blood products.

Initial treatment for the patient with acute hypoxic respiratory failure of noncardiac origin falls into ventilatory and nonventilatory strategies (Box 54.7). Of vital importance, the underlying cause of the ARDS must be addressed simultaneously with institution of supportive measures (e.g., broad-spectrum antibiotics and surgical drainage if indicated in cases of sepsis-related ARDS; immediate delivery in patients with chorioamnionitis).

**Ventilatory Strategies**

The only intervention that has convincingly decreased mortality in ARDS is lung-protective mechanical ventilation.97 ARDS is a heterogeneous disease in which some areas of the lung are affected (consolidated with edema) and others are not. During tidal volume delivery, gas flow is predominantly distributed to unaffected portions of the lung. If large tidal volumes are used, these “normal” areas of the lung are exposed to excessive volumes and pressures that lead to volutrauma and barotrauma, respectively. Overdistention of the lung provokes a local inflammatory response that further injures the lung parenchyma; locally produced inflammatory mediators (i.e., cytokines) may translocate to the systemic circulation and provoke worsening multiorgan failure (biotrauma).98 If large tidal volumes are used with low PEEP, the constant opening and closing of the recruited alveoli (atelectrauma) will also worsen lung inflammation. These four insults (volutrauma, barotrauma, biotrauma, and atelectrauma) constitute what is known as ventilator-induced lung injury.99

In a randomized clinical trial involving 861 patients with ARDS, patients randomized to receive mechanical ventilation with a small tidal volume (6 mL/kg ideal body weight) and a limitation of plateau pressure to less than 30 cm H2O had a mortality of 31% compared with 40% in the group randomized to receive a larger tidal volume (12 mL/kg ideal body weight).77 Since the publication of this trial, intensivists have adopted strategies that limit tidal volumes to decrease ventilator-induced lung injury and improve outcomes in patients with ARDS. By limiting tidal volumes, minute ventilation is invariably decreased, leading to hypercarbia and respiratory acidemia. To improve minute ventilation, the operator may increase the respiratory rate up to 35 breaths per minute to maintain, ideally, an arterial pH above 7.3.99

Significant maternal hypercarbia may result in decreased removal of carbon dioxide from the fetus, leading to fetal acidemia. Tidal volumes from 6 to 8 mL/kg (ideal body weight) can be used to ventilate pregnant women with ARDS; attempts should be made to maintain maternal Paco2 below 60 mm Hg. Because of decreased compliance of the chest wall during pregnancy, plateau pressures of up to 35 cm H2O may

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**BOX 54.7 Management Strategies in Patients with Acute Respiratory Distress Syndrome during Pregnancy**

**Ventilatory Strategies**

- Lung-protective mechanical ventilation
  - Limit tidal volume to 6 to 8 mL/kg (ideal body weight). If possible, maintain Paco2 < 60 mm Hg. Limit plateau pressures to 30 to 35 cm H2O.
- Oxygenation goals
  - Maintain Paco2 ≥ 55 mm Hg and SpO2 ≥ 88% as long as the electronic FHR tracing is reassuring. A higher Paco2 may be required in patients with nonreassuring fetal status.
- Provide adequate PEEP
- Titrate according to oxygen requirements.
- Rescue therapies
  - Prone ventilation, extracorporeal membrane oxygenation, airway pressure release ventilation, recruitment maneuvers.

**Nonventilatory Strategies**

- Limit fluid administration
- Avoid excessive fluids, especially after the initial phase of resuscitation.
- Neuromuscular blockade (cisatracurium)
  - May consider early use of cisatracurium for 48 hours. Avoid coadministration of corticosteroids and aminoglycosides.
- Corticosteroids (no consistent evidence of improved survival)
  - Methylprednisolone 1 mg/kg bolus over 30 minutes followed by a continuous infusion of 1 mg/kg/day for 14 days. The dose is then decreased by half for 1 week, then decreased by half again for 4 days, and finally decreased by half one last time for 3 days.
- Inhaled prostacyclin/nitric oxide
  - Despite improvements in oxygenation, data on survival benefit are lacking. Avoid intravenous vasodilators (e.g., epoprostenol) because these drugs may worsen oxygenation by increasing the shunt fraction.

FHR, Fetal heart rate; PEEP, positive end-expiratory pressure.

*Ideal body weight in kilograms (females) = 45.5 + 0.91 (height in centimeters – 152.4).
be tolerated. Continuous electronic FHR monitoring is recommended because abnormal FHR patterns may occur during periods of fetal acidemia.

The use of low tidal volumes to limit ventilator-induced lung injury must be accompanied by the use of adequate levels of PEEP to recruit alveolar units. A discussion of optimization of PEEP is beyond the scope of this chapter, but the reader may access FiO$_2$-PEEP tables that titrate PEEP according to oxygen requirements. Alternatively, PEEP may be increased gradually provided it does not result in increased plateau pressures (as this indicates overdistention as opposed to recruitment). The oxygenation goal is to achieve a PaO$_2$ of at least 55 mm Hg or higher with an SaO$_2$ (as measured by pulse oximetry) of at least 88% or higher. The use of high PEEP (levels up to 15 cm H$_2$O or higher) has been associated with decreased mortality in the subset of patients with the most severe forms of ARDS.

When patients with ARDS are turned from the supine to the prone position, oxygenation often greatly improves, likely secondarily to anterior displacement of the heart with resultant recruitment of the posterior lung segments and improved ventilation-perfusion matching. Decreased mortality from ARDS was observed in patients with P/F ratios less than 150 when prone ventilation was applied early in the course of the disease and for at least 16 hours per day. Use of prone ventilation during the second half of pregnancy is obviously technically demanding (and may not be possible) because of the enlarged gravid uterus. Currently, prone ventilation is recommended as one of the strategies in severe ARDS that is associated with decreased mortality.

Other ventilatory strategies that may be used in ARDS, but have not been associated with reduced mortality, include the use of recruitment maneuvers, airway pressure release ventilation, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO). HFOV is not recommended as it has been associated with either no benefit or increased mortality. Evidence regarding the use of ECMO for treatment of ARDS is inconclusive; a large ongoing trial will answer whether or not venous ECMO improves outcomes compared with lung protective mechanical ventilation. Delivery of the fetus has not been shown to improve maternal oxygenation; however, in cases of life-threatening hypoxemia with a viable fetus and nonreassuring fetal status (especially after 32 weeks’ gestation), delivery to prevent stillbirth may be warranted.

Nonventilatory Strategies

Nonventilatory strategies play an important role in the management of patients who suffer ARDS (see Box 54.7). The early use of neuromuscular blockade improves survival in patients with ARDS. A possible advantage of cisatracurium is its significant antiinflammatory activity; the infusion should be limited to the first 48 hours of mechanical ventilation. Pregnancy is not a contraindication to application of this treatment, if required.

Because ARDS occurs secondary to inflammation-mediated lung injury, interest has risen regarding the possible benefits of corticosteroid therapy. Theoretically, low-dose corticosteroids could be immunomodulatory (not immunosuppressive), leading to downregulation of excessive inflammation, and thus limiting acute lung injury. Overall, published evidence indicates that low-dose corticosteroids reduce systemic inflammation, improve oxygenation, reduce multiorgan dysfunction, and decrease the duration of mechanical ventilation and ICU stay in patients with ARDS. If used, low-dose corticosteroids (see Box 54.7) should be initiated before day 14 of the disease; after day 14, corticosteroid therapy is not recommended. The effect on survival is controversial, although some evidence suggests that corticosteroids decrease mortality in patients with ARDS. Interestingly, the use of these low doses has not been associated with an increased risk for gastrointestinal hemorrhage, hyperglycemia, nosocomial infection, or myopathy. At the current time, the use of steroids cannot be universally recommended in ARDS as the effects on mortality are not consistent. During pregnancy, the physician should consider the possible risk for fetal cleft lip (with and without cleft palate) associated with corticosteroid administration during the first trimester of pregnancy.

Management of fluid balance is fundamental in the care of patients with ARDS. A randomized trial found that conservative fluid management (mean fluid balance in the first 7 days, −136 mL) was associated with a shorter duration of mechanical ventilation and a shorter length of stay in the ICU than liberal fluid management (mean fluid balance, +6992 mL). At the time of enrollment, most patients had been fluid resuscitated and were hemodynamically stable. The incidence of adverse effects (e.g., shock, need for renal dialysis) did not differ between groups.

Fluid restriction in patients with ARDS is usually initiated on day 2 to 3 of the disease process; the first several days are commonly associated with hypotension and shock that invariably requires fluid resuscitation. Provided shock has resolved and vasopressors are not required to support blood pressure, fluids should be restricted to the amount required to maintain hemodynamic stability. Enteral feeding should be the main source of fluids in lieu of “maintenance fluids.” If a diuretic is used to achieve a negative fluid balance, judicious use is recommended. Continuous electronic FHR monitoring is recommended to assess the adequacy of uteroplacental perfusion.

Right ventricular failure may be seen in up to 25% of patients with ARDS. Alveolar “flooding” limits oxygenation with resultant hypoxic pulmonary vasoconstriction. The increase in pulmonary vascular resistances may lead to acute cor pulmonale and right ventricular failure, accompanied by a severe decrease in cardiac output (from both right-sided failure and left ventricular diastolic dysfunction). The administration of an inhaled pulmonary vasodilator such as nitric oxide or prostacyclin often leads to improved oxygenation and right ventricular function. However, there is no evidence that these interventions improve survival. Pregnancy is not a contraindication for pulmonary vasodilator therapy. Pharmacological therapy for ARDS (e.g., omega-3 fatty acids,
linolenic acid, antioxidants) has not been shown to be beneficial and is not recommended.12

**Nutrition and Glucose Control**

Critically ill patients require nutrition to heal. Early aggressive enteral nutrition is of paramount importance and should be implemented within 24 to 48 hours of admission to the ICU.13 Enteral nutrition (either through a nasogastric tube or a Dobhoff tube with the tip placed in the duodenum) helps maintain gut barrier integrity, thus preventing bacterial and cytokine translocation from the intestine. Enteral nutrition is generally preferred over parenteral nutrition because it is associated with less infectious morbidity and mortality. Enteral nutrition should be discontinued in patients requiring high doses of vasopressors because of a possible increase in the risk for bowel ischemia.13

The total amount of calories needed during critical illness is unknown.114 More than 200 formulas exist to calculate daily energy requirements while in the ICU; many of these formulas coincide with a simple calculation of 25 Kcal/kg/day (ideal body weight).13 An extra 300 Kcal/day should be added during pregnancy (500 Kcal/day in patients with multiple gestation). Overfeeding should be avoided because it may lead to fatty liver, volume overload, excessive carbon dioxide production, hyperglycemia, infection, and immunosuppression. Protein delivery should not be restricted, and critically ill patients should receive 1.2 to 2.0 g/kg/day of protein.113 Most available enteral feeding formulas do not contain sufficient protein; it may be necessary to add additional protein to standard formulas. In the setting of ARDS, either trophic feeding or full-calorie feeding is acceptable during the first week of the disease.

**Stress hyperglycemia** refers to the elevation in blood glucose concentration associated with critical illness. Stress hyperglycemia is caused by multiple factors, including massive catecholamine release and systemic inflammation. Hyperglycemia is commonly worsened with initiation of nutritional support. Hyperglycemia worsens oxidative injury and potentiates inflammation and clotting. In 2001, a landmark study suggested that tight glycemic control during critical illness (intravenous use of an insulin infusion to maintain blood glucose level between 80 and 110 mg/dL) was associated with decreased mortality and other benefits.115 These findings were not replicated in later studies; the largest available randomized controlled trial actually found that tight glucose control led to a 2.6% increase in mortality compared with less stringent glucose control. Maintaining blood glucose between 80 and 110 mg/dL commonly leads to episodes of iatrogenic hypoglycemia, which may worsen outcome.116 Current guidelines recommend a target blood glucose level between 140 and 180 mg/dL in ICU patients.113

**Transfusion Triggers**

Most PRBC transfusions in the ICU are used to treat anemia in hemodynamically stable patients who are not actively bleeding.117 The efficacy of such an approach has not been demonstrated. Anemia in the critically ill patient commonly results from inflammation-induced inhibition of erythropoiesis and excessive phlebotomy.117 Administration of PRBCs theoretically leads to an increase in arterial blood oxygen content, oxygen delivery, and, ultimately, oxygen consumption. Unfortunately, no clear evidence indicates that PRBC transfusions improve oxygen consumption.118,119 In reality, significant risks are associated with transfusion of blood products in the ICU (Table 54.2).119

The largest published trial to date evaluating the role of PRBC transfusion in hemodynamically stable ICU patients found no difference in outcome between patients randomized to a liberal transfusion strategy (transfuse to maintain hemoglobin greater than 10 g/dL) or a restrictive strategy (transfuse to maintain a hemoglobin greater than 7 g/dL).120 A subgroup analysis revealed that mortality was increased with the liberal transfusion strategy in the subgroup of patients younger than 50 years of age and with less severe disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score less than 20). Based on these findings, most intensivists do not transfuse hemodynamically stable patients in the ICU until the hemoglobin level is less than 7 g/dL. (In patients with acute coronary syndrome, the threshold may be higher at 8 g/dL.)117 Although each case should be individualized, it seems reasonable to apply these guidelines to critically ill pregnant patients. Plasma, cryoprecipitate, and platelets should not be transfused for the sole purpose of correcting laboratory measurements in patients who are not actively bleeding and are not undergoing an invasive procedure.

**Sepsis**

Sepsis occurs as the result of a maladaptive systemic inflammatory response to an infectious insult. It is the leading cause of mortality in ICUs in developed countries, and the incidence is increasing worldwide.121 Sepsis is also one of the leading causes of maternal mortality.122 The incidence of death from sepsis in obstetric patients is lower than that in nonobstetric patients. This likely reflects the fact that pregnant women are younger and have fewer co-existing medical pathologic processes.

Pregnancy affects both humoral and cell-mediated immunologic functions. The white blood cell count rises as pregnancy progresses, and some authors have described neutrophils in pregnant patients as “activated,” thus favoring severe inflammatory reactions to infectious stimuli.123 Cellular immunity is altered as a consequence of a decline in T-helper type 1 cell and natural killer cell function. The impaired cellular immunity may predispose pregnant women to infections from viruses and parasites. In contrast, antibody-mediated immunity is enhanced in pregnancy despite depressed levels of immunoglobulins (likely from hemodilution). Pregnancy is not a state of generalized immunosuppression; rather, it is a state of immunomodulation with compromised cellular and enhanced humoral immunity. Unfortunately, published information regarding the management of sepsis in pregnant women is limited; pregnant women typically have been excluded from large trials that have guided the evolution of the management of sepsis over the past several decades.
**Definitions**

Sepsis is currently defined as an inflammatory response secondary to an infectious insult that results in organ dysfunction. The Sequential Organ Failure Assessment (SOFA) score evaluates dysfunction of the brain, kidney, liver, lung, platelet count, and mean arterial blood pressure. Organ dysfunction is defined as an acute increase by two or more points in the SOFA score (see Table 36.1). The term **severe sepsis** is no longer used. **Septic shock** is defined as sepsis-induced hypotension requiring the use of vasopressors with a serum lactate level greater than 2 mEq/L. A recently introduced term is the **quick SOFA score**. The quick score does not define sepsis but has been used to identify patients with potential sepsis at risk for developing complications. Patients are deemed at risk if they have two or more of confusion, tachypnea (respiratory rate above 22/min), and hypotension (systolic blood pressure below 100 mm Hg).  

SOFA score thresholds for defining organ dysfunction may require modifications during pregnancy. For example, a serum creatinine level greater than 0.8 mg/dL may be abnormal in pregnancy (the SOFA score considers kidney injury if above 1.2 mg/dL). Similarly, a mean arterial blood pressure below 70 mm Hg (considered abnormal in the SOFA score) may be normal in mid-pregnancy. The other SOFA parameters used to define organ dysfunction (GCS less than 15, P/F ratio less than 400, platelet count less than 150,000/mm³, and bilirubin greater than 1.2 mg/dL) likely do not require significant modification during gestation.

**Pathophysiology**

The pathophysiology of sepsis is complicated and not fully understood. After exposure to a microorganism (bacteria, virus, parasite, fungus), the inflammatory cascade is activated. Massive production and release of inflammatory cytokines (interleukin-1 beta [IL-1β], tumor necrosis factor-alpha [TNF-α], IL-6, IL-8), antiinflammatory cytokines (IL-4, IL-10), endothelial factors (nitric oxide), and other mediators (prostaglandins, leukotrienes, complement) result in loss of vasomotor tone, profound vasodilation, and increased vascular permeability (secondary to cytokine-induced injury of both the endothelium and the glycocalix). Fluids subsequently move out of the vascular space, resulting in so-called “third spacing.”

The profound decrease in systemic vascular resistance and accompanying tachycardia results in the so-called “hyperdynamic state” seen in septic patients. However, myocardial function is profoundly altered by the actions of nitric oxide, IL-1, oxygen-derived free radicals, and TNF-α. Up to 60% of patients with sepsis have an ejection fraction less than 45%. Both systolic and diastolic dysfunction may occur. Not

### TABLE 54.2 Potential Complications Associated with Transfusion of Blood Products

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion-related acute lung injury (TRALI)</td>
<td>Noncardiogenic pulmonary edema that occurs within 6 hours of transfusion</td>
</tr>
<tr>
<td>Transfusion-related circulatory overload (TACO)</td>
<td>Hydrostatic pulmonary edema secondary to volume overload</td>
</tr>
<tr>
<td>Transfusion-related immunomodulation (TRIM)</td>
<td>After transfusion, decreased immunity with increased risk for nosocomial infections</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Viral (hepatitis B and C, HIV, cytomegalovirus, parvovirus B19, West Nile virus, human T-lymphotropic virus) or bacterial (Staphylococcus species, E. coli, Pseudomonas species, Yersinia)</td>
</tr>
<tr>
<td>Febrile reactions</td>
<td>Secondary to leukocytes and cytokines accumulated during storage. May decrease with leukoreduction.</td>
</tr>
<tr>
<td>Allergic nonhemolytic reactions</td>
<td>Urticaria and pruritus, secondary to soluble antigens in the donor plasma</td>
</tr>
<tr>
<td>Hemolytic reactions</td>
<td>Secondary to preexisting recipient alloantibodies against donor erythrocytes</td>
</tr>
<tr>
<td>Posttransfusion purpura</td>
<td>Purpura and bleeding manifestations after transfusion of blood products</td>
</tr>
<tr>
<td>Increased risk for multiorgan system failure</td>
<td>Likely secondary to cytokines contained in stored blood products</td>
</tr>
<tr>
<td>Graft-versus-host reaction</td>
<td>Lymphocytes transfused to patient not recognized as foreign; such cells react against host tissues, leading to pancytopenia, rash, hepatitis, and diarrhea</td>
</tr>
<tr>
<td></td>
<td>Mainly seen in patients with profound immunosuppression or in patients receiving blood products from close relatives who share human leukocyte antigens</td>
</tr>
<tr>
<td></td>
<td>May be prevented with leukoreduction and gamma radiation of blood products.</td>
</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulopathy; HIV, human immunodeficiency virus.

infrequently, myocyte injury from proinflammatory cytokines may lead to leakage of troponins. Typically, patients with systolic dysfunction tend to present with biventricular dilation. This dilation appears to be an adaptive response that allows for increased intracavitary filling, leading to an increased stroke volume despite a decrease in ejection fraction (preload recruitment). These cardiac changes tend to resolve spontaneously among survivors of sepsis.

Almost all patients with sepsis have coagulation abnormalities, ranging from asymptomatic changes to severe DIC.125 Activation of the clotting cascade results from tissue factor expression by macrocytes, neutrophils, and the endothelium as part of the inflammatory response. Tissue factor expressed on the surface of these cells binds factor VII, thus activating the clotting cascade. Excessive activation of the clotting cascade may lead to consumptive coagulopathy and multiorgan system failure.

Natural anticoagulant proteins are often consumed in patients with severe sepsis21; alterations in protein C, antithrombin III, and plasminogen activator inhibitor have been described. Consumption of activated protein C has been associated with poor outcomes in septic patients. Protein C is activated secondary to the interaction of thrombin (generated as a result of clotting activation) with the endothelial surface receptor thrombomodulin. Activated protein C inhibits factors V and VIII, promotes fibrinolysis, and has anti-inflammatory properties. Thus, the decrease in activated protein C observed in severe sepsis results in amplified inflammation and a disruption in the normal balance between procoagulant and anticoagulant activity.

Mitochondrial dysfunction is also common in severe sepsis.126 Even in the presence of adequate oxygen delivery, oxygen consumption cannot be guaranteed if the mitochondria are dysfunctional and cannot extract oxygen and use it in oxidative respiration. This pathologic process explains why patients with sepsis may have normal or above-normal oxyhemoglobin saturation in the central or pulmonary circulation despite poor tissue oxygen utilization.

Management

Of pivotal importance in the management of sepsis is achieving early infection source control and instituting adequate antibiotic therapy and resuscitation. Infected fluid collections or tissues should be drained/excised if clinically indicated.127 Broad-spectrum antibiotics should be initiated quickly (ideally after cultures have been obtained); narrow-spectrum antibiotic administration should follow once culture results are available.

Fluid management. The cornerstone of resuscitation in sepsis is early fluid therapy. Premature initiation of vasopressors may worsen tissue ischemia. Current guidelines recommend the early administration of 30 mL/kg of crystalloid solution; vasopressors are indicated if a mean arterial blood pressure of at least 65 mm Hg is not achieved.127 The placenta should be regarded as the maternal end organ that is most sensitive to hypoperfusion. For this reason, FHR decelerations are often an early sign of maternal hypoperfusion.

Fluid resuscitation improves tissue perfusion by increasing driving pressure and modulating early inflammation by decreasing concentrations of proinflammatory cytokines. Crystalloids (normal saline, lactated Ringer’s solution, PlasmaLyte) have an intravascular half-life of 30 to 60 minutes compared with 16 hours for colloids such as albumin. Theoretically, the use of colloid leads to a more efficient resuscitation. The largest published trial comparing the use of crystalloids and colloids in critically ill patients found no difference in outcomes between groups.29 However, a subgroup analysis suggested that patients with sepsis might benefit from albumin administration.29 A recent randomized clinical trial found no benefit of albumin use in sepsis.124 Currently, there is no evidence that colloids (mainly albumin) are superior to crystalloids for fluid resuscitation in septic patients.

The use of hydroxyethyl starch in septic patients is associated with increased rates of kidney injury and mortality, and is not recommended.128,130 The use of balanced crystalloid solutions (lactated Ringer’s solution and PlasmaLyte) is currently recommended; normal saline is associated with increased adverse renal effects among critically ill patients.21

In the past, early goal-directed therapy (defined as “adjustments in cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand” to achieve a normal central venous mixed oxygen concentration) was advocated. More recent evidence shows that this approach does not improve outcomes, and may be harmful as it introduces the risks associated with central line insertion.131,132

Excessive fluid resuscitation and a positive fluid balance have consistently been associated with increased mortality in critically ill patients. A trial in patients with ARDS showed that after the initial phase of resuscitation, patients who were randomized to receive a conservative fluid regimen had improved lung function and a shorter duration of mechanical ventilation and ICU stay compared with patients who received a liberal fluid regimen.110 The study did not have sufficient power to identify a difference in 60-day mortality.

Thus, it appears that early in sepsis (the first 6 hours), patients benefit more from aggressive initial fluid resuscitation. Later, a conservative fluid strategy may be beneficial, with fluid administration guided by dynamic rather that static measurements of preload.133 For example, in mechanically ventilated patients with sinus rhythm and who are not triggering the ventilator, pulse pressure variation above 13% accurately predicts fluid responsiveness. Similarly, in nonintubated patients or patients not in sinus rhythm, an increase in stroke volume (usually 10% to 15%) as assessed by transthoracic echocardiography or noninvasive cardiac output monitoring during passive leg raising (or after administration of a fluid bolus) accurately predicts fluid responsiveness.133

Vasopressors and inotropes. If a MAP greater than 65 mm Hg is not achieved with fluid therapy alone, vasopressors are indicated.127 The vasopressor of choice in septic shock is norepinephrine. Norepinephrine increases blood pressure primarily by increasing systemic vascular resistance.
Obstetricians have traditionally expressed concern regarding the potential adverse effects of vasopressors on uteroplacental perfusion. However, in the setting of septic shock, restoration of maternal organ perfusion pressure is essential for fetal survival. Multiple case reports have described improved fetal status with the use of vasopressors to increase MAP.

**Vasopressin** is a peptide hormone synthesized in the hypothalamus and stored in the pituitary gland. A relative deficiency of vasopressin has been described during septic shock. Vasopressin causes direct vascular smooth muscle constriction via stimulation of V1 receptors. It also increases the response to catecholamines, likely by increasing cortisol secretion through its action on V2 receptors in the pituitary gland. Additionally, vasopressin causes vasoconstriction by closing ATP-dependent potassium channels. Observational studies have shown that the addition of low-dose vasopressin (0.03 U/min) to traditional vasopressor therapy can raise blood pressure in vasopressor-refractory septic shock. A large randomized clinical trial reported no difference in mortality in patients with vasopressor-dependent septic shock who were randomized to receive either vasopressin or norepinephrine in addition to open-label vasopressor therapy. However, the trial did not address the use of vasopressin as rescue therapy for septic shock that is resistant to conventional vasopressors. Vasopressin is commonly used in catecholamine-refractory septic shock and in patients who experience significant tachyarrhythmias with the use of catecholamines.

No good data exist regarding the use of vasopressin during septic shock in pregnant women. Theoretically, it may activate uterine V1 receptors, leading to uterine contractions. Caution is recommended if this agent is used during pregnancy.

Myocardial contractility is compromised in septic shock (see earlier discussion). **Septic cardiomyopathy** may be “unmasked” when vasopressors are used to increase systemic vascular resistance. Assessment of cardiac output (e.g., bedside transthoracic echocardiography) is beneficial when vasopressors (primarily norepinephrine and vasopressin) are used without concomitant inotropic support. If worsening cardiac output is noted after initiating vasoconstrictor therapy, inotropic support (dobutamine or milrinone) may be beneficial.

Anecdotal data suggest that catecholamines may not be effective in patients with severe acidemia. However, data do not support the use of sodium bicarbonate therapy during resuscitation. In septic patients, bicarbonate therapy is not indicated if the pH is above 7.15. If the pH is less than 7.15, the use of sodium bicarbonate should be individualized. Particular care should be taken if the practitioner chooses to use bicarbonate during pregnancy because bicarbonate does not cross the placenta, but the carbon dioxide generated from its administration crosses the placenta to the fetal compartment, leading to potential fetal acidemia.

**Corticosteroids.** Approximately 50% to 75% of patients with sepsis/septic shock have critical illness–related corticosteroid insufficiency. Cytokines lead to a dysfunctional hypothalamic-pituitary-adrenal axis with a consequent decrease in cortisol secretion. Cortisol plays a pivotal role in the upregulation of catecholamine receptors at the vascular level (leading to an increased response to endogenous and exogenous catecholamines).

The use of corticosteroid therapy in patients with septic shock has long been controversial. In the past, large doses of corticosteroids were used; however, evidence suggested that the use of high-dose corticosteroids in patients with sepsis/septic shock may be harmful. Studies performed in the past decade suggest that low-dose corticosteroids (hydrocortisone 200 mg/day) may be beneficial. Currently, physiologic doses of corticosteroids are recommended in patients who fail to respond to catecholamine therapy. The agent of choice is hydrocortisone (50 mg bolus intravenously every 6 hours or a continuous intravenous infusion at 10 mg/h) together with oral fludrocortisone 50 μg daily. This low dose of glucocorticoid is believed to be immunomodulatory; the excessive inflammatory response that leads to shock is downregulated without causing immunosuppression. Once begun, treatment should be maintained for 7 days; tapering is not necessary. The practitioner should be cognizant of the possible association between corticosteroid use during the first trimester of pregnancy and the development of fetal cleft lip and palate. The adrenocorticotropic hormone (ACTH) stimulation test should not be used to identify patients with septic shock who should receive glucocorticoids.

**Monitoring resuscitation.** Traditionally, the main goal of resuscitation efforts in sepsis has been to achieve “normal” vital signs (MAP greater than 65 mm Hg, urine output greater than 0.5 mL/kg/h, normal heart rate). Unfortunately, clinical signs and symptoms lack sensitivity for detection of tissue hypoperfusion. Patients may have normal vital signs and still have organ hypoperfusion and anaerobic metabolism. Different strategies have been proposed to detect these patients with “occult shock.” Resuscitation may be guided by blood lactate levels. Patients with persistent lactic acidosis, despite apparently normal vital signs, may require further resuscitation to increase tissue oxygen delivery.

Another option is to optimize hemodynamic support using central (ScvO2) and mixed venous (SvO2) oxyhemoglobin saturation monitoring. SvO2 is the saturation of hemoglobin obtained from blood sampled from the pulmonary artery. It requires placement of a pulmonary artery catheter; a normal value is greater than 65%. Pregnancy per se does not alter the SvO2.

ScvO2 is the oxyhemoglobin saturation of a blood sample obtained from the junction of the superior vena cava and the right atrium. This measurement is readily achieved by obtaining a blood sample from a central venous catheter. The normal value is greater than 70%. To our knowledge, normal values for ScvO2 during pregnancy have not been described. Patients with tissue hypoperfusion will extract more oxygen in an attempt to increase aerobic metabolism. The increased extraction will lead to a decrease in the oxygen saturation of hemoglobin returning to the central circulation.
The Fetus during Critical Maternal Illness

In the vast majority of cases, therapeutic interventions in the critically ill pregnant patient should not be withheld because of fetal concerns. When the alternative is death or severe injury, very few drugs or diagnostic or therapeutic maneuvers are contraindicated. Most medications (sedatives, neuromuscular blocking agents, corticosteroids, vasopressors, inotropes, antibiotics) may be used safely (or with minimal risks that are commonly outweighed by the benefits) during pregnancy. Some of the common agents used in the ICU setting, and the associated fetal risks, are listed in Table 54.3.

Imaging studies should be performed as needed with the use of abdominal shielding to limit fetal radiation exposure. When possible, ultrasonography and magnetic resonance imaging (MRI) are preferred because no ionizing radiation is used. Radiation exposure from common studies, such as a chest or abdominal radiography or CT of the head or chest, are all below the upper limit of safety (5 rads) recommended by the American College of Obstetricians and Gynecologists (ACOG).54 Similarly, the use of radiopaque (iodide containing) or paramagnetic contrast media during pregnancy is acceptable, provided the study is considered fundamental to the care of the patient.54

Critically ill pregnant patients should receive continuous electronic FHR monitoring after 24 weeks’ gestation (lower age limit of viability) to continuously evaluate fetal well-being. The presence of fetal bradycardia, tachycardia, or persistent FHR decelerations may signal uterine hypoperfusion that requires improved resuscitation efforts. Each case should be evaluated individually with the aid of a maternal-fetal medicine specialist. Pregnant women beyond 20 weeks’ gestation should be positioned either in the left or right decubitus position to avoid uterine compression of the inferior vena cava, which results in a decrease in cardiac preload.

Acknowledgment

We would like to acknowledge the contributions of Dr. Paul Howell to a previous edition of this chapter.

### TABLE 54.3 Common Medications Used during Critical Illness

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Uterine vessels are very sensitive to vasoconstriction because they are rich in alpha-adrenergic receptors. As with any vasopressor, this agent may be used after adequate volume resuscitation and with continuous electronic FHR monitoring. Norepinephrine is the preferred agent in sepsis.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dopamine is associated with more tachyarrhythmias than norepinephrine. As with norepinephrine, it should be used after adequate fluid resuscitation and with continuous electronic FHR monitoring. Not currently recommended as a first-line pressor in critical care.</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Low doses used for the treatment of diabetes insipidus have not been associated with fetal harm. No data exist on its use as a continuous infusion for septic shock in pregnancy. Potentially, vasopressin may lead to activation of V1a receptors and uterine contractions; thus, extreme caution is recommended if used during pregnancy. Continuous electronic FHR monitoring is highly desirable.</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Provides inotropic support</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Provides inotropic support</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Pure vasopressor, no inotropic support</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Both vasopressor and inotropic support</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Some data suggest an association between corticosteroid use during the first trimester and fetal cleft lip/palate. However, if required to improve maternal outcomes, use should not be deferred.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>No clear correlation between the use of midazolam and fetal anomalies has been described. Use of any sedative close to the time of delivery is associated with neonatal depression.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Limited data have associated prolonged use with fetal anomalies. It is unlikely that its use during a few days of critical illness outside the first trimester is teratogenic.</td>
</tr>
<tr>
<td>Propofol</td>
<td>May result in hypotension</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>This agent crosses the placenta, but no published studies link dexmedetomidine to fetal malformations.</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>May have antiinflammatory properties (beneficial in treatment of ARDS)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Accumulates in renal and/or liver failure</td>
</tr>
<tr>
<td>Morphine</td>
<td>Histamine release may result in hypotension</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Minimal hemodynamic disturbances</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Minimal hemodynamic disturbances</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Commonly used to treat agitated delirium</td>
</tr>
</tbody>
</table>

FHR, Fetal heart rate.
**KEY POINTS**

- Trauma is the most common nonobstetric cause of maternal death.
- Head injury and hemorrhagic shock are the most common causes of death in the pregnant trauma victim.
- Even minor trauma increases the risk for placental abruption and preterm labor.
- Resuscitation of the critically ill or injured obstetric patient should be based on the premise that optimized maternal resuscitation will be most beneficial to the fetus.
- Care of the pregnant trauma patient should be based on Advanced Trauma Life Support principles. Additional attention should be given to complications that are specific to pregnancy, such as uterine rupture and placental abruption.
- In addition to standard Advanced Cardiac Life Support guidelines for cardiac arrest, considerations for resuscitation of the pregnant patient include maintenance of left uterine displacement and evacuation of the uterus. If spontaneous circulation does not return within 4 minutes of cardiac arrest, immediate hysterotomy or cesarean delivery should be performed if the gestational age is 20 weeks or greater, aiming for delivery within 5 minutes of cardiac arrest.
- Neurologic emergencies during pregnancy require prompt intensive care to avoid secondary brain injury caused by hypoxia, hypercarbia, seizures, hyponatremia, hyperglycemia, and rebleeding episodes.
- Patients with ARDS should receive lung-protective mechanical ventilation. When possible, excessive fluid administration should be avoided.
- Early enteral nutrition and glucose control are basic tenants of contemporary critical care.
- Transfusion of blood products in critically ill patients should follow a restrictive strategy.
- Prompt diagnosis, infection source control, adequate antibiotic therapy, and early fluid resuscitation are fundamental principles of the early management of sepsis.
- Fetal heart rate monitoring is indicated in pregnant trauma victims and critically ill obstetric patients beginning at 24 weeks’ gestation; altered fetal heart rate patterns can serve as a valuable indicator of inadequate resuscitation.

**REFERENCES**


American Society of Anesthesiologists
Guidelines for Neuraxial Anesthesia in Obstetrics*1

COMMITTEE OF ORIGIN:
OBSTETRIC ANESTHESIA

These guidelines apply to the use of neuraxial anesthesia and labor anesthesia or analgesia in which local anesthetics are administered to the parturient during labor and delivery. They are intended to encourage quality patient care but cannot guarantee any specific patient outcome. Because the availability of anesthesia resources may vary, members are responsible for interpreting and establishing the guidelines for their own institutions and practices. These guidelines are subject to revision from time to time as warranted by the evolution of technology and practice.

GUIDELINE I
NEURAXIAL ANESTHESIA SHOULD BE INITIATED AND MAINTAINED ONLY IN LOCATIONS IN WHICH APPROPRIATE RESUSCITATION EQUIPMENT AND DRUGS ARE IMMEDIATELY AVAILABLE TO MANAGE PROCEDURALLY RELATED PROBLEMS.

Resuscitation equipment should include, but is not limited to: sources of oxygen and suction, equipment to maintain an airway and perform endotracheal intubation, a means to provide positive pressure ventilation, and drugs and equipment for cardiopulmonary resuscitation.

GUIDELINE II
NEURAXIAL ANESTHESIA SHOULD BE INITIATED AND MAINTAINED BY A PHYSICIAN WITH APPROPRIATE PRIVILEGES OR UNDER THE MEDICAL DIRECTION2 OF SUCH AN INDIVIDUAL.

Physicians should be approved through the institutional credentialing process to initiate and direct the maintenance of obstetric anesthesia and to manage procedurally related complications.

GUIDELINE III
NEURAXIAL ANESTHESIA SHOULD NOT BE ADMINISTERED UNTIL: (1) THE PATIENT HAS BEEN EXAMINED BY A QUALIFIED INDIVIDUAL3; AND (2) A PHYSICIAN WITH OBSTETRIC PRIVILEGES TO PERFORM OPERATIVE VAGINAL OR CESAREAN DELIVERY, WHO HAS KNOWLEDGE OF THE MATERNAL AND FETAL STATUS AND THE PROGRESS OF LABOR AND WHO AGREES WITH THE INITIATION OF LABOR ANESTHESIA, IS READILY AVAILABLE TO SUPERVISE THE LABOR AND MANAGE ANY OBSTETRIC COMPLICATIONS THAT MAY ARISE.

Under circumstances defined by department protocol, qualified personnel may perform the initial pelvic examination. The physician responsible for the patient’s obstetric care should be informed of her status so that a decision can be made regarding present risk and further management.3

GUIDELINE IV
AN INTRAVENOUS INFUSION SHOULD BE ESTABLISHED BEFORE THE INITIATION OF NEURAXIAL ANESTHESIA AND MAINTAINED THROUGHOUT THE DURATION OF THE NEURAXIAL ANESTHETIC.

GUIDELINE V
NEURAXIAL ANESTHESIA FOR LABOR AND/OR VAGINAL DELIVERY REQUIRES THAT THE PARTURIENT’S VITAL SIGNS AND THE FETAL HEART RATE BE MONITORED AND DOCUMENTED BY A QUALIFIED INDIVIDUAL. MONITORING TECHNIQUE, FREQUENCY OF RECORDING, AND ADDITIONAL MONITORING SHOULD BE CHOSEN WITH REGARD TO THE CLINICAL CONDITION OF THE PARTURIENT AND FETUS AND IN ACCORDANCE WITH INSTITUTIONAL POLICY. WHEN EXTENSIVE NEURAXIAL

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*Approved by the ASA House of Delegates on October 12, 1988, and last amended on October 16, 2013.
1Guidelines for Neuraxial Anesthesia in Obstetrics/2013 is reprinted with permission of the American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068-2573.
2The Anesthesia Care Team (Approved by ASA House of Delegates October 18, 2006, and last amended October 21, 2009).
GUIDELINE VIII
A PHYSICIAN WITH APPROPRIATE PRIVILEGES SHOULD REMAIN READILY AVAILABLE DURING THE NEURAXIAL ANESTHETIC TO MANAGE ANESTHETIC COMPLICATIONS UNTIL THE PATIENT’S POSTANESTHESIA CONDITION IS SATISFACTORY AND STABLE.

GUIDELINE IX
ALL PATIENTS RECOVERING FROM NEURAXIAL ANESTHESIA SHOULD RECEIVE APPROPRIATE POSTANESTHESIA CARE. FOLLOWING CESAREAN DELIVERY AND/OR EXTENSIVE NEURAXIAL BLOCKADE, THE STANDARDS FOR POSTANESTHESIA CARE5 SHOULD BE APPLIED.

GUIDELINE X
THERE SHOULD BE A POLICY TO ASSURE THE AVAILABILITY IN THE FACILITY OF A PHYSICIAN TO MANAGE COMPLICATIONS AND TO PROVIDE CARDIOPULMONARY RESUSCITATION FOR PATIENTS RECEIVING POSTANESTHESIA CARE.

†Standards for Basic Anesthetic Monitoring (Approved by ASA House of Delegates October 21, 1986, and last amended October 20, 2010).

‡Standards for Postanesthesia Care (Approved by ASA House of Delegates October 27, 2004, and last amended October 21, 2009).

The primary responsibility of the anesthesia provider is to provide care to the mother. If the anesthesia provider is also requested to provide brief assistance in the care of the newborn, the benefit to the child must be compared to the risk to the mother.
Appendix

Practice Guidelines for Obstetric Anesthesia: an Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology

What other guidelines are available on this topic?
- Other guidelines on the topic for the anesthetic management of the parturient have been published by the American College of Obstetricians and Gynecologists in 2002 and reaffirmed in 2010 and 2013.

Why was this guideline developed?
- In October 2014, the ASA Committee on Standards and Practice Parameters, in collaboration with the Society for Obstetric Anesthesia and Perinatology, elected to collect new evidence to determine whether recommendations in the existing practice guidelines continue to be supported by current evidence. The resultant guidelines, presented in this issue, incorporate an analysis of current scientific literature and expert consultant survey results.

How does this statement differ from existing guidelines?
- This statement presents new findings from the scientific literature since 2006 and surveys of both expert consultants and randomly selected ASA members.
- This document represents the first practice guideline to be developed as a collaborative effort between the ASA and a subspecialty society (Society for Obstetric Anesthesia and Perinatology) with content expertise relevant to the recommendations.
- The American College of Obstetricians and Gynecologists Practice Bulletin focuses on limited aspects of cesarean anesthesia (e.g., when an anesthesiology consult is appropriate) and of labor analgesia (e.g., parenteral opioids) that an obstetrician would use to counsel their patients.
- These guidelines also include perianesthetic management of other obstetric procedures and emergencies.

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to the clinical needs and constraints and are not intended to replace local institutional policies. In addition, practice guidelines developed by the American Society of Anesthesiologists (ASA) are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome. Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to the clinical needs and constraints and are not intended to replace local institutional policies. In addition, practice guidelines developed by the American Society of Anesthesiologists (ASA) are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome.

Excerpted from Practice Guidelines for Obstetric Anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. Anesthesiology 2016;124(2):270-300. ©2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All rights reserved.

Updated by the American Society of Anesthesiologists Committee on Standard and Practice Parameters: Jeffrey L. Apfelbaum, MD (Committee Chair), Chicago, Illinois; Joy L. Hawkins, MD (Task Force Chair), Denver, Colorado; Madhulika Agarkar, MPH, Schaumburg, Illinois; Brenda A. Bucklin, MD, Denver, Colorado; Richard T. Connis, PhD, Woodinville, Washington; David R. Gambling, MBBS, San Diego, California; Jill Mhyre, MD, Little Rock, Arkansas; David G. Nickinovich, PhD, Bellevue, Washington; Heather Sherman, PhD, Schaumburg, Illinois; Lawrence C. Tseng, MD, Boston, Massachusetts; and Edward (Ted) A. Yaghmour, MD, Chicago, Illinois.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the journal’s website (www.anesthesiology.org). A complete bibliography used to develop these updated guidelines, arranged alphabetically by author, is available as supplemental digital content 1. http://links.lww.com/ALN/B219.

Submitted for publication October 28, 2015. Accepted for publication October 28, 2015. Approved by the ASA House of Delegates on October 28, 2015.
guidelines are subject to revision as warranted by the evolution of medical knowledge, technology, and practice. They provide basic recommendations that are supported by a synthesis and analysis of the current literature, expert and practitioner opinion, open-forum commentary, and clinical feasibility data.

This document updates the “Practice Guidelines for Obstetric Anesthesia: An Updated Report by the ASA Task Force on Obstetric Anesthesia,” adopted by ASA in 2006 and published in 2007.²

**METHODOLOGY**

**Definition of Perioperative Obstetric Anesthesia**

For the purposes of these updated guidelines, obstetric anesthesia refers to peripartum anesthetic and analgesic activities performed during labor and vaginal delivery, cesarean delivery, removal of retained placenta, and postpartum tubal ligation.

**Purposes of the Guidelines**

The purposes of these guidelines are to enhance the quality of anesthetic care for obstetric patients, improve patient safety by reducing the incidence and severity of anesthesia-related complications, and increase patient satisfaction.

**Focus**

These guidelines focus on the anesthetic management of pregnant patients during labor, nonoperative delivery, operative delivery, and selected aspects of postpartum care and analgesia (i.e., neuraxial opioids for postpartum analgesia after neuraxial anesthesia for cesarean delivery). The intended patient population includes, but is not limited to, intrapartum and postpartum patients with uncomplicated pregnancies or with common obstetric problems. The guidelines do not apply to patients undergoing surgery during pregnancy, gynecological patients, or parturients with chronic medical disease (e.g., severe cardiac, renal, or neurologic disease). In addition, these guidelines do not address (1) postpartum analgesia for vaginal delivery, (2) analgesia after tubal ligation, or (3) postoperative analgesia after general anesthesia (GA) for cesarean delivery.

**Application**

These guidelines are intended for use by anesthesiologists. They also may serve as a resource for other anesthesia providers and health care professionals who advise or care for patients who will receive anesthetic care during labor, delivery, and the immediate postpartum period.

**Task Force Members and Consultants**

In 2014, the ASA Committee on Standards and Practice Parameters requested that the updated guidelines published in 2007 be reevaluated. This current update consists of a literature evaluation and the reporting of new survey findings of expert consultants and ASA members. A summary of recommendations is found in Appendix 1.

This update was developed by an ASA-appointed Task Force of 11 members, consisting of anesthesiologists in both private and academic practices from various geographic areas of the United States, and consulting methodologists from the ASA Committee on Standards and Practice Parameters. The Task Force developed these updated guidelines by means of a multistep process. First, original published research studies from peer-reviewed journals published subsequent to the previous update were reviewed. Second, a panel of expert consultants was asked to (1) participate in opinion surveys on the effectiveness of various anesthetic management strategies and (2) review and comment on a draft of the update developed by the Task Force. Third, survey opinions about the guideline recommendations were solicited from a random sample of active members of the ASA. Finally, all available information was used to build consensus within the Task Force to finalize the update.

**Availability and Strength of Evidence**

Preparation of these guidelines followed a rigorous methodologic process. Evidence was obtained from two principal sources: scientific evidence and opinion-based evidence.

**Scientific Evidence**

Scientific evidence used in the development of these updated guidelines is based on cumulative findings from literature published in peer-reviewed journals. Literature citations are obtained from PubMed and other healthcare databases, direct Internet searches, Task Force members, liaisons with other organizations, and manual searches of references located in reviewed articles.

Findings from the aggregated literature are reported in the text of the guidelines by evidence category, level, and direction. Evidence categories refer specifically to the strength and quality of the research design of the studies. Category A evidence represents results obtained from randomized controlled trials (RCTs), and Category B evidence represents observational results obtained from nonrandomized study designs or RCTs without pertinent comparison groups. When available, Category A evidence is given precedence over Category B evidence for any particular outcome. These evidence categories are further divided into evidence levels. Evidence levels refer specifically to the strength and quality of the summarized study findings (i.e., statistical findings, type of data, and the number of studies reporting/replicating the findings within the evidence categories). In this document, only the highest level of evidence is included in the summary report for each intervention–outcome pair, including a directional designation of benefit, harm, or equivocality for each outcome.

**Category A.** Randomized controlled trials report comparative findings between clinical interventions for specified outcomes. Statistically significant (\(P < 0.01\)) outcomes are
designated as either beneficial (B) or harmful (H) for the patient; statistically nonsignificant findings are designated as equivocal (E).

Level 1: The literature contains a sufficient number of RCTs to conduct meta-analysis, and meta-analytic findings from these aggregated studies are reported as evidence.

Level 2: The literature contains multiple RCTs, but the number of RCTs is not sufficient to conduct a viable meta-analysis for the purpose of these updated guidelines. Findings from these RCTs are reported separately as evidence.

Level 3: The literature contains a single RCT, and findings are reported as evidence.

Category B. Observational studies or RCTs without pertinent comparison groups may permit inference of beneficial or harmful relations among clinical interventions and clinical outcomes. Inferred findings are given a directional designation of beneficial (B), harmful (H), or equivocal (E). For studies that report statistical findings, the threshold for significance is a P value of less than 0.01.

Level 1: The literature contains observational comparisons (e.g., cohort and case-control research designs) with comparative statistics between clinical interventions for a specified clinical outcome.

Level 2: The literature contains noncomparative observational studies with comparative statistics (e.g., relative risk, correlation, or sensitivity/specificity).

Level 3: The literature contains noncomparative observational studies with descriptive statistics (e.g., frequencies and percentages).

Level 4: The literature contains case reports.

Insufficient literature. The lack of sufficient scientific evidence in the literature may occur when the evidence is either unavailable (i.e., no pertinent studies found) or inadequate. Inadequate literature cannot be used to assess relations among clinical interventions and outcomes because a clear interpretation of findings is not obtained due to methodologic concerns (e.g., confounding of study design or implementation), or the study does not meet the criteria for content as defined in the “Focus” of the guidelines.

Opinion-Based Evidence.

All opinion-based evidence (e.g., survey data, Internet-based comments, letters, and editorials) relevant to each topic was considered in the development of these updated guidelines. However, only the findings obtained from formal surveys are reported in the current update. Identical surveys were distributed to expert consultants and a random sample of ASA members who practice obstetric anesthesia.

Category A: Expert opinion. Survey responses from Task Force-appointed expert consultants are reported in summary form in the text, with a complete listing of the consultant survey responses reported in Appendix 2.

Category B: Membership opinion. Survey responses from active ASA members are reported in summary form in the text, with a complete listing of ASA member survey responses reported in Appendix 2.

Survey responses from expert and membership sources are recorded using a 5-point scale and summarized based on median values.4

Strongly Agree: Median score of 5 (at least 50% of the responses are 5)

Agree: Median score of 4 (at least 50% of the responses are 4 or 4 and 5)

Equivocal: Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contain least 50% of the responses)

Disagree: Median score of 2 (at least 50% of responses are 2 or 1 and 2)

Strongly Disagree: Median score of 1 (at least 50% of responses are 1)

Category C: Informal opinion. Open-forum testimony obtained during the development of these guidelines, Internet-based comments, letters, and editorials are all informally evaluated and discussed during the formulation of guideline recommendations. When warranted, the Task Force may add educational information or cautionary notes based on this information.

GUIDELINES

Perianesthetic Evaluation and Preparation

Perianesthetic evaluation and preparation topics include (1) a focused history and a physical examination, (2) an intrapartum platelet count, (3) a blood type and screen, and (4) perianesthetic recording of fetal heart rate patterns.

History and Physical Examination

Literature findings. Although it is a well-accepted clinical practice to review medical records and conduct a physical examination, comparative studies are insufficient to directly evaluate the impact of these practices. Studies with observational findings suggest that certain patient or clinical characteristics (e.g., hypertensive disorders of pregnancy such as preeclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome, obesity, and diabetes mellitus) may be associated with obstetric complications (Category B2/B3-H evidence).1-14

Survey findings. The consultants and ASA members both strongly agree (I) to conduct a focused history and physical examination before providing anesthesia care and (2) that a communication system should be in place to encourage early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team.

4When an equal number of categorically distinct responses are obtained, the median value is determined by calculating the arithmetic mean of the two middle values. Ties are calculated by a predetermined formula.
Intrapartum Platelet Count

**Literature findings.** The literature is insufficient to assess whether a routine platelet count can predict anesthesia-related complications in uncomplicated parturients. An observational study reported that platelet count and fibrinogen values are associated with the frequency of postpartum hemorrhage (Category B2 evidence). Other observational studies and case reports suggest that a platelet count may be useful for diagnosing hypertensive disorders of pregnancy, such as preeclampsia; hemolysis, elevated liver enzymes, and low platelet count syndrome; and other conditions associated with coagulopathy (Category B3/B4-B evidence).

**Survey findings.** The consultants and ASA members strongly agree that the anesthesiologist’s decision to order or require a platelet count should be individualized and based on a patient’s history (e.g., preeclampsia with severe features), physical examination, and clinical signs.

Blood Type and Screen

**Literature findings.** The literature is insufficient to determine whether obtaining a blood type and screen is associated with fewer maternal anesthetic complications. In addition, the literature is insufficient to determine whether a blood cross-match is necessary for healthy and uncomplicated parturients.

**Survey findings.** The ASA members agree and the consultants strongly agree that (1) a routine blood cross-match is not necessary for healthy and uncomplicated parturients for vaginal or operative delivery and (2) the decision whether to order or require a blood type and screen or cross-match should be based on maternal history, anticipated hemorrhagic complications (e.g., placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies.

Perianesthetic Recording of Fetal Heart Rate Patterns

**Literature findings.** Studies with observational findings and case reports indicate that fetal heart rate patterns may change after the administration of neuraxial anesthetics (Category B3/B4 evidence).

**Survey findings.** The consultants and ASA members strongly agree that fetal heart rate patterns should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor.

Aspiration Prevention

Aspiration prevention includes (1) clear liquids, (2) solids, and (3) antacids, H₂-receptor antagonists, and metoclopramide.

Clear Liquids

**Literature findings.** There is insufficient published literature to examine the relation between fasting times for clear liquids and the risk of emesis/reflux or pulmonary aspiration during labor.

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2A specific platelet count predictive of neuraxial anesthetic complications has not been determined.
Survey findings. ASA members agree and the consultants strongly agree that (1) oral intake of moderate amounts of clear liquids may be allowed for uncomplicated laboring patients and (2) the uncomplicated patient undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) may have moderate amounts of clear liquids up to 2 h before induction of anesthesia.

Solids

Literature findings. A specific fasting time for solids that is predictive of maternal anesthetic complications has not been determined. There is insufficient published literature to address the safety of any particular fasting period for solids in obstetric patients.

Survey findings. The consultants and ASA members strongly agree that (1) the patient undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6 to 8 h depending on the type of food ingested (e.g., fat content); (2) laboring patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes mellitus, and difficult airway) or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis; and (3) solid foods should be avoided in laboring patients.

Antacids, H2-Receptor Antagonists, and Metoclopramide

Literature findings. Randomized controlled trials indicate that preoperative nonparticulate antacids (e.g., sodium citrate and sodium bicarbonate) are associated with higher gastric pH values during the peripartum period (Category A2-B evidence)\(^{32-35}\) and are equivocal regarding gastric volume (Category A2-E evidence).\(^{32-35}\) Randomized placebo-controlled trials indicate that H2-receptor antagonists are associated with higher gastric pH values in obstetric patients (Category A2-B evidence) and are equivocal regarding gastric volume (Category A2-E evidence).\(^{36-38}\) Randomized placebo-controlled trials indicate that metoclopramide is associated with reduced peripartum nausea and vomiting (Category A2-B evidence).\(^{39-41}\) Literature is not available that examines the relationship between reduced gastric acidity and the frequency of pulmonary aspiration, emesis, morbidity, or mortality in obstetric patients who have aspirated gastric contents.

Survey findings. The consultants and ASA members both agree that before surgical procedures (e.g., cesarean delivery or postpartum tubal ligation), consider the timely administration of nonparticulate antacids, H2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis.

Recommendations for Aspiration Prevention\(^b\)

Clear Liquids

- The oral intake of moderate amounts of clear liquids may be allowed for uncomplicated laboring patients.

- The uncomplicated patient undergoing elective surgery may have clear liquids up to 2 h before induction of anesthesia.

- Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sports drinks.

- The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested.

- Laboring patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes mellitus, and difficult airway) or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

Solids

- Solid foods should be avoided in laboring patients.

- The patient undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6 to 8 h depending on the type of food ingested (e.g., fat content).\(^1\)

Antacids, H2-Receptor Antagonists, and Metoclopramide

- Before surgical procedures (e.g., cesarean delivery or postpartum tubal ligation), consider the timely administration of nonparticulate antacids, H2-receptor antagonists, and/or metoclopramide for aspiration prophylaxis.

Anesthetic Care for Labor and Vaginal Delivery

Anesthetic care for labor and vaginal delivery includes (1) timing of neuraxial analgesia and outcome of labor, (2) neuraxial analgesia and trial of labor after prior cesarean delivery, and (3) anesthetic/analgesic techniques. Appendix 3 contains an overview of anesthetic care for labor and vaginal delivery.\(^1\)

Timing of Neuraxial Analgesia and Outcome of Labor

Literature findings. Meta-analyses of RCTs report equivocal findings for spontaneous, instrumented, and cesarean delivery when comparing early administration (i.e., cervical dilations of less than 4 or 5 cm) with late administration (i.e., cervical dilations of greater than 4 or 5 cm) of epidural analgesia (Category A1-E evidence).\(^{44-48}\) An RCT comparing cervical dilations of less than 2 cm with greater than or equal to 2 cm also reports equivocal findings (Category A3-E evidence).\(^{49}\) Finally, RCTs comparing early versus late combined spinal-epidural (CSE) analgesia administration report equivocal findings for cesarean, instrumented, and spontaneous delivery (Category A2-E evidence).\(^{50,51}\)

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\(^{b}\)The Task Force recognizes that in laboring patients the timing of delivery is uncertain; therefore, adherence to a predetermined fasting period before nonselective surgical procedures is not always possible.
Survey findings. The consultants and ASA members strongly agree to (1) provide patients in early labor (i.e., less than 5 cm dilation) the option of neuraxial analgesia when this service is available; (2) offer neuraxial analgesia on an individualized basis; and (3) not withhold neuraxial analgesia on the basis of achieving an arbitrary cervical dilation.

Neuraxial Analgesia and Trial of Labor after Prior Cesarean Delivery

Literature findings. Nonrandomized comparative studies are equivocal regarding mode of delivery, duration of labor, and adverse outcomes when epidural analgesia is used in a trial of labor for previous cesarean delivery patients (Category B1-E evidence).32-56

Survey findings. The consultants and ASA members strongly agree (1) to offer neuraxial techniques to patients attempting vaginal birth after previous cesarean delivery and (2) that for these patients, it is appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia or for anesthesia in the event of operative delivery.

Analogesic/anesthetic techniques. Considerations for analogesic/anesthetic techniques include (1) early insertion of a neuraxial (i.e., spinal or epidural) catheter for complicated parturients, (2) continuous infusion epidural (CIE) analgesia, (3) epidural local anesthetics combined with opioids, (4) higher versus lower concentrations of local anesthetics, (5) single-injection spinal opioids with or without local anesthetics, (6) pencil-point spinal needles, (7) CSE analgesia, and (8) patient-controlled epidural analgesia (PCEA).

Early Insertion of a Neuraxial Catheter for Complicated Parturients

Literature findings. The literature is insufficient to assess whether, when caring for the complicated parturient, the early insertion of a neuraxial catheter, with immediate or later administration of analgesia, improves maternal or neonatal outcomes.

Survey findings. The consultants and ASA members strongly agree to consider early insertion of a neuraxial catheter for obstetric (e.g., twin gestation or preeclampsia) or anesthetic indications (e.g., anticipated difficult airway or obesity) to reduce the need for GA if an emergent procedure becomes necessary.

CIE Analgesia

Literature findings. Randomized controlled trials indicate that CIE local anesthetics are associated with reduced maternal pain and discomfort compared with single-shot IV opioids during labor (Category A2-B evidence).37,58 The literature is insufficient to evaluate CIE compared with continuous infusion of IV opioids. An RCT reports greater pain relief during labor for CIE when compared with intramuscular opioids (Category A3-B evidence), with equivocal findings for duration of labor and mode of delivery (Category A3-E evidence).79 A nonrandomized comparative study reports equivocal findings for duration of labor and mode of delivery when CIE local anesthetics are compared with single-injection spinal opioids (Category B1-E evidence).60

Survey findings. The consultants and ASA members strongly agree that (1) continuous epidural infusion may be used for effective analgesia for labor and delivery, and (2) when a continuous epidural infusion of local anesthetic is selected, an opioid may be added.

Analgesic Concentrations

Literature findings. Meta-analyses of RCTs report improved analgesic quality31-45 when comparing epidural local anesthetics combined with opioids versus equal concentrations of epidural local anesthetics without opioids (Category A1-B evidence). Findings were equivocal for frequency of spontaneous delivery, hypotension, pruritus, and 1-min Apgar scores (Category A1-E evidence).62-73

Randomized controlled trials are equivocal for analgesic efficacy and duration of labor when continuous epidural infusion of low concentrations of local anesthetics with opioids are compared with higher concentrations of local anesthetics without opioids for maintenance of analgesia (Category A2-E evidence).74-77 Meta-analyses of RCTs are also equivocal regarding spontaneous delivery and neonatal Apgar scores when continuous epidural infusion of low concentrations of local anesthetics with opioids are compared with higher concentrations of local anesthetics without opioids (Category A1-E evidence).74-80 A lower frequency of motor block was found for lower concentrations of local anesthetics (Category A1-B evidence).74-76,78-80 The literature is insufficient to determine the effects of epidural local anesthetics with opioids on other maternal outcomes (e.g., hypotension, nausea, pruritus, respiratory depression, and urinary retention).

Survey findings. The consultants and ASA members strongly agree to use dilute concentrations of local anesthetics with opioids to produce as little motor block as possible.

Single-Injection Spinal Opioids with or without Local Anesthetics

Literature findings. An RCT reports a longer duration of analgesia when a spinal opioid is compared with an IV opioid (Category A1-B evidence).61 Nonrandomized comparisons are equivocal for duration of labor, mode of delivery, and other adverse outcomes such as nausea, vomiting, headache, and pruritus (Category B1-E evidence).62-84 The literature is not sufficient to compare single-injection spinal opioids with local anesthetics versus single-injection spinal opioids without local anesthetics.

Survey findings. The consultants and ASA members agree that single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated. The ASA members agree and the consultants strongly agree that a local anesthetic may be added

4The Task Force notes that the addition of an opioid to a local anesthetic infusion allows an even lower concentration of local anesthetic for providing equally effective analgesia.
to a spinal opioid to increase duration and improve quality of analgesia.

Pencil-Point Spinal Needles

**Literature findings.** Meta-analysis of RCTs indicate that the use of pencil-point spinal needles reduces the frequency of postdural puncture headache when compared with cutting-bevel spinal needles (Category A1-B evidence).\(^{117-122}\)

**Survey findings.** The consultants and ASA members strongly agree to use pencil-point spinal needles instead of cutting-bevel spinal needles to minimize the risk of postdural puncture headache.

CSE Analgesia

**Literature findings.** Meta-analyses of RCTs report improved analgesia and a faster onset time (Category A2-B evidence) when CSE local anesthetics with opioids are compared with epidural local anesthetics with opioids,\(^{90-96}\) with equivocal findings for maternal satisfaction with analgesia, mode of delivery, hypotension, pruritus, and 1-min Apgar scores (Category A1-E evidence).\(^{90-101}\) Meta-analysis of RCTs report an increased frequency of motor block with CSE (Category A1-H evidence).\(^{90,92,93,96,101}\)

**Survey findings.** The consultants and ASA members strongly agree that (1) if labor is expected to last longer than the analgesic effects of the spinal drugs chosen, or if there is a good possibility of operative delivery, then consider a catheter technique instead of a single-injection technique and (2) CSE techniques may be used to provide effective and rapid onset of analgesia for labor.

Patient-Controlled Epidural Analgesia

**Literature findings.** Meta-analysis of RCTs report reduced analgesic consumption (Category A1-B evidence) when PCEA is compared with CIE.\(^{102-107}\) Meta-analysis of RCTs report equivocal findings for duration of labor, mode of delivery, motor block, and 1- and 5-min Apgar scores when PCEA is compared with CIE (Category A1-E evidence).\(^{103-116}\) Meta-analysis of RCTs indicate greater analgesic efficacy for PCEA with a background infusion compared with CPEA without a background infusion (Category A1-B evidence)\(^{117-121}\) and is equivocal regarding mode of delivery and frequency of motor block (Category A1-E evidence).\(^{117-122}\)

**Survey findings.** The consultants and ASA members strongly agree that (1) PCEA may be used to provide an effective and flexible approach for the maintenance of labor analgesia and (2) the use of PCEA may be preferable to fixed-rate CIE for providing fewer anesthetic interventions and reducing dosages of local anesthetics. The consultants and ASA members agree that PCEA may be used with or without a background infusion.

Recommendations for Anesthetic Care for Labor and Vaginal Delivery

**Timing of Neuraxial Analgesia and Outcome of Labor**

- **Provide patients in early labor (i.e., less than 5 cm dilation) the option of neuraxial analgesia when this service is available.**
- **Offer neuraxial analgesia on an individualized basis regardless of cervical dilation.**
- **Reassure patients that the use of neuraxial analgesia does not increase the incidence of cesarean delivery.**

**Neuraxial Analgesia and Trial of Labor after Prior Cesarean Delivery**

- **Offer neuraxial techniques to patients attempting vaginal birth after previous cesarean delivery.**
- **For these patients, consider early placement of a neuraxial catheter that can be used later for labor analgesia or for anesthesia in the event of operative delivery.**

**Analgesia/Anesthetic Techniques**

**Early insertion of a neuraxial catheter for complicated parturients**

- **Consider early insertion of a neuraxial catheter for obstetric (e.g., twin gestation or preeclampsia) or anesthetic indications (e.g., anticipated difficult airway or obesity) to reduce the need for GA if an emergent procedure becomes necessary.**
- **In these cases, the insertion of a neuraxial catheter may precede the onset of labor or a patient’s request for labor analgesia.**

**CIE analgesia**

- **Continuous epidural infusion may be used for effective analgesia for labor and delivery.**
- **When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the concentration of local anesthetic, improve the quality of analgesia, and minimize the motor block.**

**Analgesic concentrations**

- **Use dilute concentrations of local anesthetics with opioids to produce as little motor block as possible.**

**Single-injection spinal opioids with or without local anesthetics**

- **Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated.**
- **If labor duration is anticipated to be longer than the analgesic effects of the spinal drugs chosen, or if there is a reasonable possibility of operative delivery, then consider a catheter technique instead of a single-injection technique.**
- **A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia.**

**Pencil-point spinal needles**

- **Use pencil-point spinal needles instead of cutting-bevel spinal needles to minimize the risk of postdural puncture headache.**

**CSE analgesia**

- **If labor duration is anticipated to be longer than the analgesic effects of the spinal drugs chosen, or if there is a reasonable possibility of operative delivery, then consider a catheter technique instead of a single-injection technique.**
- **CSE techniques may be used to provide effective and rapid onset of analgesia for labor.**
Nitroglycerin for Uterine Relaxation

Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue.

- Initiating treatment with incremental doses of IV or sublingual (i.e., tablet or metered dose spray) nitroglycerin may be done to sufficiently relax the uterus.

Anesthetic Care for Cesarean Delivery

Anesthetic care for cesarean delivery consists of (1) equipment, facilities, and support personnel; (2) general, epidural, spinal, or CSE anesthesia; (3) IV fluid preloading or coloading; (4) ephedrine or phenylephrine; and (5) neuraxial opioids for postoperative analgesia after neuraxial anesthesia.

Equipment, Facilities, and Support Personnel

- Nitroglycerin may be used to provide an effective and flexible approach for the maintenance of labor analgesia.
- The use of PCEA may be preferable to fixed-rate CIE for administering reduced dosages of local anesthetics.
- PCEA may be used with or without a background infusion.

Removal of Retained Placenta

Techniques for removal of retained placenta include (1) anesthetic techniques for removal of retained placenta and (2) nitroglycerin for uterine relocation.

Anesthetic Techniques

**Literature findings.** The literature is insufficient to assess whether a particular anesthetic technique is more effective than another for removal of retained placenta.

**Survey findings.** The consultants and ASA members strongly agree (1) that the hemodynamic status should be assessed before administering neuraxial anesthesia and (2) if an epidural catheter is in place and the patient is hemodynamically stable, consider providing epidural anesthesia. The consultants and ASA members agree to consider aspiration prophylaxis. The consultants and ASA members strongly agree that (1) titration of sedation/analgesia should be performed carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period and (2) in cases involving major maternal hemorrhage with hemodynamic instability, GA with an endotracheal tube may be considered in preference to neuraxial anesthesia.

**Nitroglycerin for Uterine Relaxation**

**Literature findings.** Randomized controlled trials comparing IV or sublingual nitroglycerin with placebo for the purpose of uterine relaxation report inconsistent findings for the successful removal of retained placenta (*Category A2-E evidence*).123-125 Observational studies and case reports indicate successful uterine relaxation and successful placental removal after IV or sublingual nitroglycerin administration (*Category B3/B4 evidence*).126-130

**Survey findings.** The ASA members agree and the consultants strongly agree that nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue.

**Recommendations for Removal of Retained Placenta**

**Anesthetic Techniques for Removal of Retained Placenta**

- In general, there is no preferred anesthetic technique for removal of retained placenta.
- If an epidural catheter is in place and the patient is hemodynamically stable, consider providing epidural analgesia.
- Assess hemodynamic status before administering neuraxial anesthesia.
- Consider aspiration prophylaxis.

- Titrate sedation/analgesia carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period.
- In cases involving major maternal hemorrhage with hemodynamic instability, GA with an endotracheal tube may be considered in preference to neuraxial anesthesia.
Survey findings. The consultants and ASA members strongly agree that IV ephedrine and phenylephrine both may be used for treating hypotension during neuraxial anesthesia.

Neuraxial Opioids for Postoperative Analgesia

Literature findings. Randomized controlled trials comparing epidural opioids with intermittent injections of IV or intramuscular opioids report improved postoperative analgesia for epidural opioids after cesarean delivery (Category A2-B evidence)\(^{200-204,206-211}\); meta-analysis of RCTs reports equivocal findings for nausea, vomiting, and pruritus (Category A1-E evidence)\(^{200-204,206-211}\). RCTs report improved postoperative analgesia when PCEA is compared with IV patient-controlled analgesia (Category A2-B evidence)\(^{200-204,206-211}\) with equivocal findings for nausea, vomiting, pruritus, and sedation (Category A2-E evidence)\(^{200-204,206-211}\).

Survey findings. The consultants and ASA members strongly agree that for postoperative analgesia after neuraxial anesthesia for cesarean delivery, selecting neuraxial opioids rather than intermittent injections of parenteral opioids should be considered.

Recommendations for Anesthetic Care for Cesarean Delivery

Equipment, Facilities, and Support Personnel

- Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite.
- Resources for the treatment of potential complications (e.g., failed intubation, inadequate analgesia/anesthesia, hypotension, respiratory depression, local anesthetic systemic toxicity, pruritus, and vomiting) should also be available in the labor and delivery operating suite.
- Appropriate equipment and personnel should be available to care for obstetric patients recovering from neuraxial or GA.

General, Epidural, Spinal, or CSE Anesthesia

- The decision to use a particular anesthetic technique for cesarean delivery should be individualized, based on anesthetic, obstetric, or fetal risk factors (e.g., elective versus emergency), the preferences of the patient, and the judgment of the anesthesiologist.
- Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used.
- Consider selecting neuraxial techniques in preference to GA for most cesarean deliveries; (4) if spinal anesthesia is chosen, use pencil-point spinal needles instead of cutting-bevel spinal needles; (5) for urgent cesarean delivery, an indwelling epidural catheter may be used as an alternative to initiation of spinal anesthesia; and (6) GA may be the most appropriate choice in some circumstances (e.g., profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption, umbilical cord prolapse, and preterm foetal breech).

IV Fluid Preloading or Coloading

Literature findings. Randomized controlled trial findings are inconsistent regarding the frequency of maternal hypotension when IV fluid preloading or coloading for spinal anesthesia is compared with no fluids (Category A2-E evidence)\(^{163-169}\). Meta-analyses of RCTs are equivocal for maternal hypotension when IV fluid preloading is compared with coloading (Category A2-E evidence)\(^{168,170-176}\).

Survey findings. The consultants and ASA members agree that IV fluid preloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery. The ASA members agree and the consultants strongly agree that, although fluid preloading reduces the frequency of maternal hypotension, it does not delay the initiation of spinal anesthesia in order to administer a fixed volume of IV fluid.

Ephedrine or Phenylephrine

Literature findings. Meta-analysis of double-blind placebo-controlled RCTs report reduced maternal hypotension during anesthesia for cesarean delivery when IV ephedrine is administered compared with placebo (Category A1-B evidence)\(^{177-181}\). RCTs are equivocal for hypotension when intramuscular ephedrine is compared with placebo (Category A2-E evidence)\(^{182-184}\). RCTs comparing phenylephrine with placebo report a lower frequency of hypotension when higher dosages of phenylephrine are administered (Category A2-B evidence)\(^{185-187}\) and equivocal findings when lower dosages are administered (Category A2-E evidence)\(^{182,185-187}\). Meta-analysis of double-blind RCTs report lower frequencies of patients with hypotension when infusions of phenylephrine are compared with ephedrine (Category A1-B evidence)\(^{188-193}\); higher umbilical artery pH values are reported for phenylephrine when compared with ephedrine (Category A1-H evidence)\(^{194-199}\).

Survey findings. The consultants and ASA members strongly agree that IV ephedrine and phenylephrine both may be used for treating hypotension during neuraxial anesthesia.
IV Fluid Preloading or Colloading
- IV fluid preloading or colloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery.
- Do not delay the initiation of spinal anesthesia in order to administer a fixed volume of IV fluid.

Ephedrine or Phenylephrine
- Either IV ephedrine or phenylephrine may be used for treating hypotension during neuraxial anesthesia.
- In the absence of maternal bradycardia, consider selecting phenylephrine because of improved fetal acid-base status in uncomplicated pregnancies.

Neuraxial Opioids for Postoperative Analgesia
- For postoperative analgesia after neuraxial anesthesia for cesarean delivery, consider selecting neuraxial opioids rather than intermittent injections of parenteral opioids.

Postpartum Tubal Ligation
  
  **Literature findings.** The literature is insufficient to evaluate the benefits of neuraxial anesthesia compared with GA for postpartum tubal ligation. In addition, the literature is insufficient to evaluate the impact of the timing of the postpartum tubal ligation on maternal outcome.
  
  **Survey findings.** The consultants and ASA members strongly agree that before postpartum tubal ligation, the patient should have no oral intake of solid foods within 6 to 8 h of the surgery, depending on the type of food ingested (e.g., fat content), and (2) that both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., neuraxial versus general) should be individualized based on anesthetic risk factors, obstetric risk factors (e.g., blood loss), and patient preferences. The ASA members agree and the consultants strongly agree to consider selecting neuraxial techniques in preference to GA for most postpartum tubal ligations.

Recommendations for Postpartum Tubal Ligation
- Before a postpartum tubal ligation, the patient should have no oral intake of solid foods within 6 to 8 h of the surgery, depending on the type of food ingested (e.g., fat content).
- Consider aspiration prophylaxis.
- Both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., neuraxial versus general) should be individualized, based on anesthetic and obstetric risk factors (e.g., blood loss), and patient preferences.
- Consider selecting neuraxial techniques in preference to GA for most postpartum tubal ligations.
- Be aware that gastric emptying will be delayed in patients who have received opioids during labor.
- Be aware that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals.
- If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, do not attempt the procedure at a time when it might compromise other aspects of patient care on the labor and delivery unit.

Management of Obstetric and Anesthetic Emergencies
Management of obstetric and anesthetic emergencies consists of (1) resources for management of hemorrhagic emergencies, (2) equipment for management of airway emergencies, and (3) cardiopulmonary resuscitation.

Resources for Management of Hemorrhagic Emergencies
Studies with observational findings and case reports suggest that the availability of resources for hemorrhagic emergencies may be associated with reduced maternal complications (Category B3/B4-B evidence). Survey findings. The consultants and ASA members strongly agree that institutions providing obstetric care should have resources available to manage hemorrhagic emergencies.

Equipment for Management of Airway Emergencies
Case reports suggest that the availability of equipment for the management of airway emergencies may be associated with reduced maternal, fetal, and neonatal complications (Category B4-B evidence). Survey findings. The consultants and ASA members strongly agree that labor and delivery units should have personnel and equipment readily available to manage airway emergencies consistent with the ASA Practice Guidelines for Management of the Difficult Airway, to include a pulse oximeter and carbon dioxide detector.

Cardiopulmonary Resuscitation
  
  **Literature findings.** The literature is insufficient to evaluate the efficacy of cardiopulmonary resuscitation in the obstetric patient during labor and delivery. In cases of cardiac arrest, the American Heart Association has stated that 4 to 5 min is the maximum time rescuers will have to determine whether the arrest can be reversed by Basic Life Support and Advanced Cardiac Life Support interventions. Delivery of the fetus may improve cardiopulmonary resuscitation of the mother by relieving aortocaval compression. The American Heart Association further notes that the best survival rate for infants more than 24 to 25 weeks in gestation occurs when the

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1The American College of Obstetricians and Gynecologists (ACOG) has indicated that postpartum tubal ligation “should be considered an urgent surgical procedure given the consequences of a missed procedure and the limited time frame in which it may be performed.” ACOG Committee Opinion No. 530: Access to postpartum sterilization. Obstet Gynecol 2012;120:212-215.

delivery of the infant occurs no more than 5 min after the mother’s heart stops beating.

Survey findings. The consultants and ASA members strongly agree that (1) basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units, and (2) if cardiac arrest occurs during labor and delivery, to initiate standard resuscitative measures with accommodations for pregnancy such as left uterine displacement and preparing for delivery of the fetus.

Recommendations for Management of Obstetric and Anesthetic Emergencies

Resources for Management of Hemorrhagic Emergencies
- Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies (Box B.1).
  - In an emergency, type-specific or O-negative blood is acceptable.
  - In cases of intractable hemorrhage, when banked blood is not available or the patient refuses banked blood, consider intraoperative cell salvage if available.

Equipment for Management of Airway Emergencies
- Labor and delivery units should have personnel and equipment readily available to manage airway emergencies consistent with the ASA Practice Guidelines for Management of the Difficult Airway to include a pulse oximeter and carbon dioxide detector.
  - Basic airway management equipment should be immediately available during the provision of neuraxial analgesia (Box B.2).
  - Portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units (Box B.3).
  - A preformulated strategy for intubation of the difficult airway should be in place.
  - When tracheal intubation has failed, consider ventilation with mask and cricoid pressure or with a supraglottic airway device (e.g., laryngeal mask airway, intubating laryngeal mask airway, or laryngeal tube) for maintaining an airway and ventilating the lungs.
  - If it is not possible to ventilate or awaken the patient, a surgical airway should be performed.

Cardiopulmonary Resuscitation.
- Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units.

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**BOX B.1 Suggested Resources for Obstetric Hemorrhagic Emergencies**

- Large-bore IV catheters
- Fluid warmer
- Forced-air body warmer
- Availability of blood bank resources
- Massive transfusion protocol
- Equipment for infusing IV fluids and blood products rapidly. Examples include, but are not limited to, hand-squeezed fluid chambers, hand-inflated pressure bags, and automatic infusion devices.

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

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**BOX B.2 Suggested Resources for Airway Management during Initial Provision of Neuraxial Analgesia in a Labor Delivery Room Setting**

- Laryngoscope and assorted blades
- Endotracheal tubes, with stylets
- Oxygen source
- Suction source with tubing and tonsil suction tip
- Self-inflating bag and mask for positive-pressure ventilation
- Medications for blood pressure support, muscle relaxation, and hypnosis

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

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**BOX B.3 Suggested Contents of a Portable Storage Unit for Difficult Airway Management for Cesarean Delivery Rooms**

- Rigid laryngoscope blades of alternate design and size
- Videolaryngoscopic devices
- Endotracheal tubes of assorted size
- Endotracheal tube guides. Examples include (but are not limited to) semirigid stylets, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube.
- At least one device suitable for emergency nonsurgical airway ventilation consisting of a face mask or supraglottic airway device (e.g., laryngeal mask airway, intubating laryngeal mask airway, and laryngeal tube).
- Equipment suitable for emergency surgical airway access (e.g., cricothyotomy)

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

If cardiac arrest occurs, initiate standard resuscitative measures.
- Uterine displacement (usually left displacement) should be maintained.
- If maternal circulation is not restored within 4 min, cesarean delivery should be performed by the obstetrics team.

APPENDIX 1 SUMMARY OF RECOMMENDATIONS

PERIANESTHETIC EVALUATION AND PREPARATION

History and Physical Examination
- Conduct a focused history and physical examination before providing anesthesia care.
  - This should include, but is not limited to, a maternal health and anesthetic history, a relevant obstetric history, a baseline blood pressure measurement, and an airway, heart, and lung examination, consistent with the American Society of Anesthesiologists (ASA) “Practice Advisory for Preanesthesia Evaluation.”
  - When a neuraxial anesthetic is planned or placed, examine the patient’s back.
  - Recognition of significant anesthetic or obstetric risk factors should encourage consultation between the obstetrician and anesthesiologist.
  - A communication system should be in place to encourage the early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team.

Intrapartum Platelet Count
- The anesthesiologist’s decision to order or require a platelet count should be individualized and based on a patient’s history (e.g., preeclampsia with severe features), physical examination, and clinical signs.
  - A routine platelet count is not necessary in the healthy parturient.

Blood Type and Screen
- A routine blood cross-match is not necessary for healthy and uncomplicated parturients for vaginal or operative delivery.
- The decision whether to order or require a blood type and screen or cross-match should be based on maternal history, anticipated hemorrhagic complications (e.g., placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies.

Perianesthetic Recording of Fetal Heart Rote Patterns
- Fetal heart rate patterns should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor.
  - Continuous electronic recording of fetal heart rate patterns may not be necessary in every clinical setting and may not be possible during placement of a neuraxial catheter.

ASPIRATION PREVENTION

Clear Liquids
- The oral intake of moderate amounts of clear liquids may be allowed for uncomplicated laboring patients.
- The uncomplicated patient undergoing elective surgery may have clear liquids up to 2 h before induction of anesthesia.
  - Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sports drinks.
  - The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested.
- Laboring patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes mellitus, and difficult airway) or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

Solids
- Solid foods should be avoided in laboring patients.
- The patient undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6 to 8 h depending on the type of food ingested (e.g., fat content).

Antacids, H₂-Receptor Antagonists, and Metoclopramide
- Before surgical procedures (e.g., cesarean delivery and postpartum tubal ligation), consider the timely administration of nonparticulate antacids, H₂-receptor antagonists, and/or metoclopramide for aspiration prophylaxis.

APPENDIX B Practice Guidelines for Obstetric Anesthesia


A specific platelet count predictive of neuraxial anesthetic complications has not been determined.

Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk or pulmonary aspiration: An updated report by the American Society of Anesthesiologists Task Force on Preoperative Fasting. Anesthesiology 2011;114:495-511.
ANESTHETIC CARE FOR LABOR AND DELIVERY

Timing of Neuraxial Analgesia and Outcome of Labor
- Provide patients in early labor (i.e., less than 5 cm dilation) the option of neuraxial analgesia when this service is available.
- Offer neuraxial analgesia on an individualized basis regardless of cervical dilation.
- Reassure patients that the use of neuraxial analgesia does not increase the incidence of cesarean delivery.

Neuraxial Analgesia and Trial of Labor after Prior Cesarean Delivery
- Offer neuraxial techniques to patients attempting vaginal birth after previous cesarean delivery.
- For these patients, consider early placement of a neuraxial catheter that can be used later for labor analgesia or for anesthesia in the event of operative delivery.

Analgesia/Anesthetic Techniques
Early Insertion of a Neuraxial (i.e., Spinal or Epidural) Catheter for Complicated Parturients
- Consider early insertion of a neuraxial catheter for obstetric (e.g., twin gestation or preeclampsia) or anesthetic indications (e.g., anticipated difficult airway or obesity) to reduce the need for general anesthesia if an emergent procedure becomes necessary.
- In these cases, the insertion of a neuraxial catheter may precede the onset of labor or a patient’s request for labor analgesia.

Continuous Infusion Epidural Analgesia
- Continuous epidural infusion may be used for effective analgesia for labor and delivery.
- When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the concentration of local anesthetic, improve the quality of analgesia, and minimize motor block.

Analgesic Concentrations
- Use dilute concentrations of local anesthetics with opioids to produce as little motor block as possible.

Single-Injection Spinal Opioids with or without Local Anesthetics
- Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated.
- If labor duration is anticipated to be longer than the analgesic effects of the spinal drugs chosen, or if there is a reasonable possibility of operative delivery, then consider a catheter technique instead of a single-injection technique.
- A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia.

Pencil-Point Spinal Needles
- Use pencil-point spinal needles instead of cutting-bevel spinal needles to minimize the risk of postdural puncture headache.

Combined Spinal-Epidural Analgesia
- If labor duration is anticipated to be longer than the analgesic effects of the spinal drugs chosen, or if there is a reasonable possibility of operative delivery, then consider a catheter technique instead of a single-injection technique.
- Combined spinal–epidural techniques may be used to provide effective and rapid onset of analgesia for labor.

Patient-Controlled Epidural Analgesia
- Patient-controlled epidural analgesia (PCEA) may be used to provide an effective and flexible approach for the maintenance of labor analgesia.
- The use of PCEA may be preferable to fixed-rate continuous infusion epidural analgesia for administering reduced dosages of local anesthetics.
- PCEA may be used with or without a background infusion.

REMOVAL OF RETAINED PLACENTA

Anesthetic Techniques
- In general, there is no preferred anesthetic technique for removal of retained placenta.
- If an epidural catheter is in place and the patient is hemodynamically stable, consider providing epidural anesthesia.
- Assess hemodynamic status before administering neuraxial anesthesia.
- Consider aspiration prophylaxis.
- Titrate sedation/analgesia carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period.
- In cases involving major maternal hemorrhage with hemodynamic instability, general anesthesia with an endotracheal tube may be considered in preference to neuraxial anesthesia.

Nitroglycerin for Uterine Relaxation
- Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue.
- Initiating treatment with incremental doses of IV or sublingual (i.e., tablet or metered dose spray) nitroglycerin may be done to sufficiently relax the uterus.
ANESTHETIC CARE FOR CESAREAN DELIVERY

Equipment, Facilities, and Support Personnel

• Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite.
• Resources for the treatment of potential complications (e.g., failed intubation, inadequate analgesia/anesthesia, hypotension, respiratory depression, local anesthetic systemic toxicity, pruritus, and vomiting) should also be available in the labor and delivery operating suite.
• Appropriate equipment and personnel should be available to care for obstetric patients recovering from neuraxial or general anesthesia.

General, Epidural, Spinal, or Combined Spinal-Epidural Anesthesia

• The decision to use a particular anesthetic technique for cesarean delivery should be individualized, based on anesthetic, obstetric, or fetal risk factors (e.g., elective versus emergency), the preferences of the patient, and the judgment of the anesthesiologist.
• Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used.
• Consider selecting neuraxial techniques in preference to general anesthesia for most cesarean deliveries.
• If spinal anesthesia is chosen, use pencil-point spinal needles instead of cutting-bevel spinal needles.
• For urgent cesarean delivery, an indwelling epidural catheter may be used as an alternative to initiation of spinal or general anesthesia.
• General anesthesia may be the most appropriate choice in some circumstances (e.g., profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption, umbilical cord prolapse, and preterm footling breech).

IV Fluid Preloading or Coloading

• IV fluid preloading or coloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery.
• Do not delay the initiation of spinal anesthesia in order to administer a fixed volume of IV fluid.

Ephedrine or Phenylephrine

• Either IV ephedrine or phenylephrine may be used for treating hypotension during neuraxial anesthesia.
• In the absence of maternal bradycardia, consider selecting phenylephrine because of improved fetal acid-base status in uncomplicated pregnancies.

Neuraxial Opioids for Postoperative Analgesia

• For postoperative analgesia after neuraxial anesthesia for cesarean delivery, consider selecting neuraxial opioids rather than intermittent injections of parenteral opioids.

POSTPARTUM TUBAL LIGATION

• Before a postpartum tubal ligation, the patient should have no oral intake of solid foods within 6 to 8 h of the surgery, depending on the type of food ingested (e.g., fat content).2
• Consider aspiration prophylaxis.
• Both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., neuraxial versus general) should be individualized, based on anesthetic and obstetric risk factors (e.g., blood loss) and patient preferences.
• Consider selecting neuraxial techniques in preference to general anesthesia for most postpartum tubal ligation.
• Be aware that gastric emptying will be delayed in patients who have received opioids during labor.
• Be aware that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals.
• If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, do not attempt the procedure at a time when it might compromise other aspects of patient care on the labor and delivery unit.1

MANAGEMENT OF OBSTETRIC AND ANESTHETIC EMERGENCIES

Resources for Management of Hemorrhagic Emergencies

• Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies (Box B.1).
• In an emergency, type-specific or O-negative blood is acceptable.
• In cases of intractable hemorrhage, when banked blood is not available or the patient refuses banked blood, consider intraoperative cell salvage if available. n

Equipment for Management of Airway Emergencies

• Labor and delivery units should have personnel and equipment readily available to manage airway emergencies consistent with the ASA Practice Guidelines for Management of the Difficult Airway,4 to include a pulse oximeter and carbon dioxide detector.
• Basic airway management equipment should be immediately available during the provision of neuraxial analgesia (Box B.2).
• Portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units (Box B.3).
• A preformulated strategy for intubation of the difficult airway should be in place.
• When tracheal intubation has failed, consider ventilation with mask and cricoid pressure or with a supraglottic airway device (e.g., laryngeal mask airway,
intubating laryngeal mask airway, and laryngeal tube) for maintaining an airway and ventilating the lungs.
• If it is not possible to ventilate or awaken the patient, a surgical airway should be performed.

Cardiopulmonary Resuscitation
• Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units.
• If cardiac arrest occurs, initiate standard resuscitative measures.
• Uterine displacement (usually left displacement) should be maintained.
• If maternal circulation is not restored within 4 min, cesarean delivery should be performed by the obstetrics team.²

APPENDIX 2 METHODS AND ANALYSES

For these updated guidelines, a review of studies used in the development of the previous update was combined with studies published subsequent to approval of the update in 2006.² The scientific assessment of these guidelines was based on evidence linkages or statements regarding potential relations between clinical interventions and outcomes. The interventions listed below were examined to assess their relation to a variety of outcomes related to obstetric anesthesia.³

PREANESTHETIC EVALUATION AND PREPARATION
• Conducting a focused history (patient condition)
• Conducting a physical examination
• Communication between anesthetic and obstetric providers
• Laboratory tests
  • Routine intrapartum platelet count
  • Platelet count for suspected preeclampsia or coagulopathy
  • Blood type and screen or cross-match
  • Recording of fetal heart rate patterns

ASPIRATION PREVENTION
• Oral intake of clear liquids for laboring patients
• Oral intake of solids for laboring patients
• A fasting period for solids of 6 to 8 h before an elective cesarean
• Nonparticulate antacids versus no antacids before operative procedures (excluding operative vaginal delivery)
• H₂-receptor antagonists (e.g., cimetidine, ranitidine, or famotidine) versus no H₂ antagonists before operative procedures (excluding operative vaginal delivery)
• Metoclopramide versus no metoclopramide before operative procedures (excluding operative vaginal delivery)

ANESTHETIC CARE FOR LABOR AND VAGINAL DELIVERY
• Early versus late administration of neuraxial analgesia (e.g., cervical dilations of less than 5 versus greater than 5 cm or less than 4 versus greater than 4 cm)
• Neuraxial techniques for labor for patients attempting vaginal birth after prior cesarean delivery
• Prophylactic neuraxial catheter insertion for obstetric (e.g., twin gestation or preeclampsia) or anesthetic indications (e.g., anticipated difficult airway or obesity)
• Continuous infusion epidural (CIE) of local anesthetics
  • CIE of local anesthetics (with or without opioids) versus intramuscular opioids for labor
  • CIE of local anesthetics (with or without opioids) versus IV opioids for labor
  • CIE of local anesthetics with or without opioids versus spinal opioids with or without local anesthetics for labor
• Analgesic concentrations
  • Induction of epidural analgesia using local anesthetics with opioids versus equal concentrations of epidural local anesthetics without opioids for labor
  • Induction of epidural analgesia using local anesthetics with opioids versus higher concentrations of epidural local anesthetics without opioids for labor
  • Maintenance of epidural infusion of lower concentrations of local anesthetics with opioids versus higher concentrations of local anesthetics without opioids for labor
  • Maintenance of epidural infusion with bupivacaine concentrations less than 0.125% with opioids versus bupivacaine concentrations greater than 0.125% without opioids for labor
• Single-injection spinal opioids
  • Single-injection spinal opioids with or without local anesthetics versus parenteral opioids for labor
  • Single-injection spinal opioids with local anesthetics versus spinal opioids without local anesthetics for labor
• Pencil-point spinal needles
  • Pencil-point spinal needles versus cutting-bevel spinal needles
• Combined spinal-epidural (CSE) local anesthetics with opioids
  • CSE local anesthetics with opioids versus epidural local anesthetics with opioids for labor
• Patient-controlled epidural analgesia (PCEA)
  • PCEA versus CIE for labor
  • PCEA with a background infusion versus PCEA without a background infusion for labor
• Removal of retained placenta
• Anesthetic techniques
• Administration of nitroglycerin for uterine relaxation

¹Unless otherwise specified, outcomes for the listed interventions refer to the reduction of maternal, fetal, and neonatal complications.
ANESTHETIC CARE FOR CESAREAN DELIVERY

- Equipment, facilities, and support personnel
  - Availability of equipment, facilities, and support personnel
- General, epidural, spinal, or CSE anesthesia
  - General anesthesia (GA) versus epidural anesthesia
  - Epidural versus spinal anesthesia
  - CSE anesthesia versus epidural anesthesia
  - CSE anesthesia versus spinal anesthesia
- In situ epidural catheter versus no epidural anesthesia in hemodynamically stable patients for removal of retained placenta
- GA versus neuraxial anesthesia in cases involving major maternal hemorrhage for removal of retained placenta
- IV fluid preloading or coloading
  - IV fluid preloading or coloading versus no IV fluid preloading or coloading for spinal anesthesia to reduce maternal hypotension
  - IV fluid preloading versus coloading
- Ephedrine or phenylephrine
  - Ephedrine versus placebo or no ephedrine
  - Phenylephrine versus placebo or no ephedrine
  - Ephedrine versus phenylephrine
- Neuraxial opioids for postoperative analgesia
  - Neuraxial opioids versus intermittent injections of parenteral opioids for postoperative analgesia after neuraxial anesthesia for cesarean
  - PCEA versus IV patient-controlled analgesia for postoperative analgesia after neuraxial anesthesia for cesarean
  - Addition of nonsteroidal antiinflammatory drugs versus no nonsteroidal antiinflammatory drugs for postoperative analgesia after neuraxial anesthesia for cesarean

POSTPARTUM TUBAL LIGATION

- A fasting period for solids of 6 to 8 h before postpartum tubal ligation
- Aspiration prophylaxis for postpartum tubal ligation
- Neuraxial anesthesia versus GA for postpartum tubal ligation
- Postpartum tubal ligation within 8 h of delivery

MANAGEMENT OF OBSTETRIC AND ANESTHETIC EMERGENCIES

Resources for Management of Hemorrhagic Emergencies

- Equipment, facilities, and support personnel available in the labor and delivery suite comparable to that available in the main operating suite
- Resources for management of hemorrhagic emergencies (e.g., red blood cells, platelets, and cell salvage)
- Invasive hemodynamic monitoring for severe preeclamptic patients

Resources for Management of Airway Emergencies

- Equipment for management of airway emergencies

Cardiopulmonary Resuscitation

- Basic and advanced life-support equipment in the labor and delivery suite

State of the Literature

For the literature review, potentially relevant clinical studies were identified via electronic and manual searches of the literature. The updated searches covered an 11-yr period from January 1, 2005 to July 31, 2015. New citations were reviewed and combined with pre-2005 articles used in the previous update, resulting in a total of 478 articles that contained direct linkage-related evidence. Search terms consisted of the interventions indicated above guided by the appropriate inclusion/exclusion criteria as stated in the “Focus” section of these Guidelines. A complete bibliography used to develop these guidelines, organized by section, is available as Supplemental Digital Content 2, http://links.lww.com/ALN/B220.

Each pertinent outcome reported in a study was classified by evidence category and level, and designated as either beneficial, harmful, or equivocal. Findings were then summarized for each evidence linkage. Literature pertaining to 13 evidence linkages contained enough studies with well-defined experimental designs and statistical information sufficient to conduct meta-analyses. These linkages were (1) early versus late epidural anesthetics, (2) epidural local anesthetics with opioids versus equal concentrations of epidural local anesthetics without opioids, (3) CIE of local anesthetics with opioids versus higher concentrations of local anesthetics without opioids, (4) pencil-point versus cutting-bevel spinal needles, (5) CSE local anesthetics with opioids versus epidural local anesthetics with opioids, (6) PCEA versus CIE anesthetics, (7) PCEA with a background infusion versus PCEA, (8) GA versus epidural anesthesia for cesarean delivery, (9) CSE anesthesia versus epidural anesthesia for cesarean delivery, (10) fluid preloading versus coloading for cesarean delivery, (11) ephedrine versus placebo for cesarean delivery, (12) ephedrine versus phenylephrine for cesarean delivery, and (13) neuraxial versus parenteral opioids for postoperative analgesia.

General variance-based effect-size estimates or combined probability tests were obtained for continuous outcome measures, and Mantel–Haenszel odds ratios were obtained for dichotomous outcome measures. Two combined probability tests were used as follows: (1) the Fisher combined test, producing chi-square values based on logarithmic transformations of the reported $P$ values from the independent studies, and (2) the Stouffer combined test, providing weighted representation of the studies by weighting each of the standard normal deviates by the size of the sample. An odds ratio procedure based on the Mantel–Haenszel method for combining study results using 2 x 2 tables was used with
outcome frequency information. An acceptable significance level was set at a P value of less than 0.01 (one tailed). Tests for heterogeneity of the independent studies were conducted to assure consistency among the study results. DerSimonian–Laird random-effects odds ratios were obtained when significant heterogeneity was found (P < 0.01). To control for potential publishing bias, a “fail-safe n” value was calculated. No search for unpublished studies was conducted, and no reliability tests for locating research results were done. To be accepted as significant findings, Mantel–Haenszel odds ratios must agree with combined test results whenever both types of data are assessed. In the absence of Mantel–Haenszel odds ratios, findings from both the Fisher and weighted Stouffer combined tests must agree with each other to be acceptable as significant.

For the previous update, interobserver agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a κ statistic for two-rater agreement pairs were as follows: (1) type of study design, κ = 0.83 to 0.94; (2) type of analysis, κ = 0.71 to 0.93; (3) evidence linkage assignment, κ = 0.87 to 1.00; and (4) literature inclusion for database, κ = 0.74 to 1.00. Three-rater chance-corrected agreement values were as follows: (1) study design, Sav = 0.884, Var (Sav) = 0.004; (2) type of analysis, Sav = 0.805, Var (Sav) = 0.009; (3) linkage assignment, Sav = 0.911, Var (Sav) = 0.002; (4) literature database inclusion, Sav = 0.660, Var (Sav) = 0.024. These values represent moderate to high levels of agreement.

Consensus-Based Evidence

For the previous update, consensus was obtained from multiple sources, including (1) survey opinion from consultants who were selected based on their knowledge or expertise in obstetric anesthesia or maternal and fetal medicine, (2) survey opinions solicited from active members of the American Society of Anesthesiologists (ASA), (3) testimony from attendees of publicly-held open forums at two national anesthesia meetings, (4) Internet commentary, and (5) Task Force opinion and interpretation. The survey rate of return was 75% (n = 76 of 102) for the consultants, and 2,326 surveys were received from active ASA members. Results of the surveys are reported in the guidelines.

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the guidelines were instituted. The rate of return was 35% (n = 36). The percent of responding consultants expecting no change associated with each linkage were as follows: perianesthetic evaluation: 97%; aspiration prophylaxis: 83%; anesthetic care for labor and delivery: 89%; removal of retained placenta: 97%; anesthetic choices for cesarean delivery: 97%; postpartum tubal ligation: 97%; and management of complications: 94%. Ninety-seven percent of the respondents indicated that the guidelines would have no effect on the amount of time spent on a typical case. One respondent indicated that there would be an increase of 5 min in the amount of time spent on a typical case with the implementation of these guidelines.

APPENDIX 3 OVERVIEW OF ANESTHETIC CARE FOR LABOR AND DELIVERY

Not all women require anesthetic care during labor or delivery. For women who request pain relief for labor and/or delivery, there are many effective analgesic techniques available. Maternal request represents sufficient justification for pain relief. In addition, maternal medical and obstetric conditions may warrant the provision of neuraxial techniques to improve maternal and neonatal outcome.

The choice of analgesic technique depends on the medical status of the patient, progress of labor, and resources at the facility. When sufficient resources (e.g., anesthesia and nursing staff) are available, neuraxial catheter techniques should be one of the analgesic options offered. The choice of a specific neuraxial technique should be individualized and based on anesthetic risk factors, obstetric risk factors, patient preferences, progress of labor, and resources at the facility.

When neuraxial techniques are used for analgesia during labor or vaginal delivery, the primary goal is to provide an adequate maternal analgesia with minimal motor block (e.g., achieved with the administration of local anesthetics at low concentrations with or without opioids).

When a neuraxial technique is chosen, appropriate resources for the treatment of complications (e.g., hypotension, systemic toxicity, and high spinal anesthesia) should be available. If an opioid is added, treatments for related complications (e.g., pruritus, nausea, and respiratory depression) should be available. An IV infusion should be established before the initiation of neuraxial analgesia or general anesthesia and maintained throughout the duration of the neuraxial analgesic or anesthetic. However, administration of a fixed volume of IV fluid is not required before neuraxial analgesia is initiated.

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Competing Interests
The authors declare no competing interests.

Correspondence
Address correspondence to the American Society of Anesthesiologists: 1061 American Lane, Schaumburg, Illinois 60173. These updated Practice Guidelines, and all ASA Practice Parameters, may be obtained at no cost through the Journal Website, www.anesthesiology.org.

The information in this appendix is intended to provide overview and context for issues concerned with anesthetic care for labor and delivery and are not guideline recommendations.
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Abstract: Good obstetric care requires the availability of qualified personnel and equipment to administer general or neuraxial anesthesia. The extent and degree to which anesthesia services are available varies widely among hospitals. However, for any hospital providing obstetric care, certain optimal anesthesia goals should be sought. These include the following:

I. Availability of a licensed practitioner who is credentialed to administer an appropriate anesthetic whenever necessary. For many women, neuraxial anesthesia (epidural, spinal, or combined spinal-epidural) will be the most appropriate anesthetic.

II. Availability of a licensed practitioner who is credentialed to maintain support of vital functions in any obstetric emergency.

III. Availability of anesthesia and surgical personnel to permit the start of a cesarean delivery in a timely manner in accordance with clinical needs and local resources.

IV. Because the risks associated with trial of labor after cesarean delivery (TOLAC) and uterine rupture may be unpredictable, the immediate availability of appropriate facilities and personnel (including obstetric anesthesia; nursing personnel; and a physician capable of monitoring labor and performing cesarean delivery, including an emergency cesarean delivery) is optimal. When resources for immediate cesarean delivery are not available, patients considering TOLAC should discuss the hospital’s resources and availability of obstetric, anesthetic, pediatric, and nursing staff with their obstetric provider; patients should be clearly informed of the potential increase in risk and the management alternatives. The definition of immediately available personnel and facilities remains a local decision based on each institution’s available resources and geographic location.

V. Appointment of a qualified anesthesia provider to be responsible for all anesthetics administered. There are many obstetric units where physicians or physician-supervised nurse anesthetists administer labor anesthesia. The administration of general or neuraxial anesthesia requires both medical judgment and technical skills. Thus, a physician with privileges in anesthesiology should be readily available.

Persons administering or supervising obstetric anesthesia should be qualified to manage the infrequent but occasionally life-threatening complications of neuraxial anesthesia, such as respiratory and cardiovascular failure, toxic local anesthetic convulsions, or vomiting and aspiration. Mastering and retaining the skills and knowledge necessary to manage these complications requires adequate training and frequent application.

To ensure the safest and most effective anesthesia for obstetric patients, the physician Director of Anesthesia Services, with the approval of the medical staff, should develop and enforce written policies regarding provision of obstetric anesthesia. These include the following:

I. A qualified physician with obstetric privileges to perform operative vaginal or cesarean delivery who concurs with the patient’s management and has knowledge of the maternal and fetal status and progress of labor should be readily available during administration of anesthesia. Readily available should be defined by each institution within the context of its resources and geographic location. Neuraxial and/or general anesthesia should not be administered until the patient has been examined and the fetal status and progress of labor evaluated by a qualified individual.

II. Availability of equipment, facilities, and support personnel equal to that provided in the surgical suite. This should include the availability of a properly equipped and staffed recovery room capable of receiving and caring for all patients recovering from neuraxial or general anesthesia. Birthing facilities, when used for labor anesthesia services or surgical anesthesia, must be appropriately equipped to provide safe anesthetic care during labor and delivery or postanesthesia recovery care.
III. Personnel, other than the surgical team, should be immediately available to assume care of the newborn. The obstetric provider and anesthesia provider are responsible for the mother and may not be able to leave her to care for the newborn.

In larger maternity units and those functioning as high-risk centers, 24-hour in-house anesthesia, obstetric, and neonatal specialists are usually available. Preferably, the obstetric anesthesia services should be directed by an anesthesia provider with special training or experience in obstetric anesthesia. These units will also frequently require the availability of more sophisticated monitoring equipment and specially trained nursing personnel.

Finally, good interpersonal relations between obstetric providers and anesthesia providers are important. Joint meetings between the two departments should be encouraged. Anesthesia providers should recognize the special needs and concerns of obstetric providers, who in turn should recognize the anesthesia provider as a consultant in the management of pain and life-support measures. Both should recognize the need to provide high-quality care for all patients.

REFERENCES

A variety of information technology–based resources exist for obstetric anesthesia clinicians, offering information regarding clinical practice, ongoing research, and recent publications, and providing avenues for professional interaction among clinicians, patients, the media, and others. This appendix should serve as a brief guide to some of these resources, which include websites, mobile computing applications, and social media resources, including Facebook, Twitter, and LinkedIn, where available. We have chosen to organize these resources into four sections for ease of navigation: (1) societies and organizations, (2) journals and online information resources, (3) multimedia learning resources, and (4) online communities of practice.

These sites were active at the time this guide was prepared (November, 2018). The authors of this appendix, and the editors and publisher of this textbook, bear no responsibility for the accuracy (or lack thereof) of any information found in these sites. Publication of this list does not imply endorsement of these sites.

For long web addresses, we have used URL-shortening (Bit.ly) to facilitate web browser entry.

**Section I: Societies and Organizations**

**Obstetric Anesthesia Societies**

The Society for Obstetric Anesthesia and Perinatology (SOAP)

Web: [http://soap.org](http://soap.org)

Facebook: [http://www.facebook.com/soaphq](http://www.facebook.com/soaphq)

Twitter: @SOAPHQ


The Obstetric Anaesthetists Association (OAA)

Web: [http://www.oaa-anaes.ac.uk](http://www.oaa-anaes.ac.uk)


Twitter: @OAAInfo

The OAA provides both education and training for anesthesia clinicians in the United Kingdom and other countries, and serves as a resource for women seeking information about analgesia for
OTHER PROFESSIONAL SOCIETIES OF INTEREST

The American Academy of Pediatrics (AAP)
Web: http://www.aap.org
Facebook: https://www.facebook.com/AmerAcadPeds
Twitter: @AmerAcadPeds

The AAP promotes the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults. Significant amounts of educational material are freely available.

The American College of Obstetricians and Gynecologists (ACOG)
Web: http://www.acog.org
Facebook: http://www.facebook.com/ACOGNational
Twitter: @ACOGNews

The ACOG promotes health care for women through policy and guideline development, education, and advocacy. A password is required for access to much of the online information, including committee opinions and practice bulletins and guidelines.

The American Society of Anesthesiologists (ASA)
Web: http://www.asahq.org
Facebook: https://www.facebook.com/AmericanSocietyofAnesthesiologists
Twitter: @ASALifeline
LinkedIn: http://www.linkedin.com/company/american-society-of-anesthesiologists

The ASA encourages education, research, and scientific progress in anesthesiology. The ASA strives to be an advocate for all patients who require anesthesia or relief from pain. The majority of documents, policies, and guidelines are freely available; some sections require a password for access. The ASA practice guidelines for obstetric anesthesia can be found at http://bit.ly/ASAOBGuidelines, and are included in Appendix B of this text.

The American Society of Regional Anesthesia and Pain Medicine (ASRA)
Web: http://www.asra.com
Twitter: @asra_society

The ASRA provides clinical and professional education for physicians and scientists, promotes excellence in patient care, and encourages research to advance the scientific basis of regional anesthesia and pain medicine. The ASA/ASRA practice advisory regarding infectious complications of neuraxial blockade can be found at http://bit.ly/ASAASRAInfectious.

The Anesthesia Patient Safety Foundation (APSF)
Web: http://www.apsf.org
Facebook: https://www.facebook.com/APSForg/
Twitter: @APSFOrg

The APSF seeks to improve patient safety during anesthesia care by encouraging and conducting research and education, programs and campaigns, and national and international exchange of information and ideas. Significant amounts of educational material are freely available for all users. The APSF Newsletter can be found at https://www.apsf.org/apsf-newsletter/.

The Association of Women’s Health, Obstetric and Neonatal Nurses (AWHONN)
Web: http://www.awhonn.org
Facebook: https://www.facebook.com/AWHONN
Twitter: @AWHONN
LinkedIn: https://www.linkedin.com/company/awhonn

The AWHONN seeks to improve the health of women and newborns, and to strengthen the nursing profession through advocacy, research, education, and provision of other professional and clinical resources for nurses and other health care professionals. Some content is freely available for all users. The AWHONN position statement on Nursing Support of Laboring Women is available at http://bit.ly/AWHONNSupport. The AWHONN position statement on the role of the registered nurse in the care of the pregnant woman receiving analgesia/anesthesia by neuraxial catheter techniques is available at http://bit.ly/AWHONN-Neuraxial.

The Canadian Anesthesiologists’ Society (CAS)
Web: http://www.cas.ca
Facebook: https://www.facebook.com/CanadianAnesthesiologistsSociety/
Twitter: @CASUpdate

The Canadian Anesthesiologists’ Society (CAS)
Web: http://www.cas.ca
The CAS promotes science, vigilance, and compassion in the practice of anesthesiology. Significant amounts of information (including practice guidelines) are freely available for all users. The CAS guidelines for regional (neuraxial) analgesia in obstetric patients can be found as a section in the CAS Guidelines to the Practice of Anesthesia at http://www.cas.ca/English/Page/Files/97_Guidelines-2017.pdf.

The International Anesthesia Research Society (IARS)
Web: http://www.iars.org
The IARS encourages the development and dissemination of current, state-of-the-art basic and clinical research data and the newest advances in all areas of clinical anesthesia care.

The International Fetal Medicine and Surgery Society (IFMSS)
Web: http://ifmss.org
The IFMSS promotes education and research related to the field of fetal diagnosis and therapy.

The North American Society of Obstetric Medicine (NASOM)
Web: http://www.nasom.org
The NASOM promotes and supports research collaboration, communication, and teaching concerning the medical care of pregnant women. General internists from the United States and Canada form the core membership of the society.

The Society for Maternal-Fetal Medicine (SMFM)
Web: http://www.smfm.org
Twitter: @MySMFM
The SMFM seeks to promote and expand education and research in maternal-fetal medicine and encourages the exchange of new ideas and research concerning the most recent approaches and treatments for obstetric problems.

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)
Web: http://www.somanz.org
The SOMANZ seeks to advance clinical and scientific knowledge of hypertensive diseases and medical disorders in pregnancy and to foster collaboration with other regional and international societies interested in hypertension in pregnancy and obstetric medicine.

GOVERNMENTAL REGULATORY ORGANIZATIONS

The Centers for Disease Control and Prevention (CDC)
Web: http://www.cdc.gov
Facebook: https://www.facebook.com/CDC
Twitter: @CDCgov
The CDC provides extensive information on most health-related subjects. For example, information is available on assisted reproductive technologies, birth rates, birth defects, breast-feeding, medication use during pregnancy, nutrition in pregnancy, preterm labor, maternal mortality, and various disease processes in pregnancy.

Mothers and Babies: Reducing Risk Through Audits and Confidential Enquiries Across the UK (MBRRACE-UK)
Web: https://www.npeu.ox.ac.uk/mbrrace-UK
MBRRACE-UK has replaced CMACE as the organization through which severe maternal and perinatal morbidity and mortality are reported and studied in the United Kingdom. They provide extensive information on maternal and perinatal mortality statistics, including anesthesia-related deaths, in the United Kingdom.

SECTION II: JOURNALS AND ONLINE INFORMATION RESOURCES

JOURNALS AND SCIENTIFIC LITERATURE

Obstetric Anesthesia Journals

Anesthesia & Analgesia (the Official Journal of IARS and SOAP)
Web: http://www.anesthesiaanalgesia.org
Facebook: http://bit.ly/AnesAnalgFacebook
Twitter: @IARS_journals
Content more than 12 months old is freely available without a subscription or password.

The International Journal of Obstetric Anesthesia (the Official Journal of the OAA)
Web: http://www.obstetanesthesia.com
This is the only peer-reviewed journal devoted solely to obstetric anesthesia. A subscription is required for most text.

The Obstetric Anesthesia Digest
Web: http://journals.lww.com/obstetricanesthesia/
Twitter: @OBAnesDigest
Recent publications of interest to obstetric anesthesia providers are cited, reviewed, and discussed by a panel of experts. A subscription is required for access to full text.
Related Journals

The American Journal of Obstetrics and Gynecology (the Official Journal of the SMFM)
Web: http://www.ajog.org
Facebook: https://www.facebook.com/AJOGthegray
Twitter: @AJOGthegray
A subscription is required for most text.

Anesthesiology (the Official Journal of the ASA)
Web: http://www.anesthesiology.org
Facebook: https://www.facebook.com/ASAanesthesiology
Twitter: @ALNAAnesthesia
Content more than 6 months old is freely available without a subscription or password.

The Canadian Journal of Anesthesia (the Official Journal of the CAS)
Web: https://link.springer.com/journal/12630
Content more than 12 months old is freely available without a subscription or password.

Obstetrics & Gynecology (the Official Journal of the ACOG)
Web: http://www.greenjournal.org
Facebook: https://www.facebook.com/greenjournal
Twitter: @greenjrnl
New or updated ACOG practice bulletins and committee opinions are frequently published in Obstetrics & Gynecology. A subscription is required for most text.

Pediatrics (the Official Journal of the AAP)
Web: http://pediatrics.aappublications.org
Facebook: https://www.facebook.com/aappeds
Twitter: @AAPJournals
Content more than 12 months old is freely available without a subscription or password (for a rolling 8-year period).

Other Information Sources

The Cochrane Collaboration
Web: http://www.cochrane.org
The Cochrane Collaboration provides frequently updated reviews of current literature in a variety of medical specialties, including anesthesiology and obstetrics. Most information in abstract form is freely available; however, a subscription is required for access to full-text documents.

LabourPains.com
Web: http://www.labourpains.com
Twitter: @labourpainsoaa
LabourPains.com is the public information site of the OAA. It is a source of accurate, unbiased patient information regarding delivery of obstetric anesthesia. In addition, it provides translations of much of this information, in the form of patient handouts/leaflets, into almost 50 languages.

Obstetric Anesthesia Fellowship Program Listings
This webpage is hosted by the Society for Obstetric Anesthesia and Perinatology. It is a listing of obstetric anesthesia fellowship opportunities in the United States and Canada, and it was created to help residents interested in pursuing advanced training in obstetric anesthesia.

PubMed (a Medical Literature Search Resource Supported by the National Institutes of Health)
Web: https://www.ncbi.nlm.nih.gov/pubmed
This site provides citations and abstracts; the user must go to the original source to obtain the full text of most articles.

SECTION III: MULTIMEDIA LEARNING RESOURCES

Anesthesia and Critical Care Reviews and Commentary
Web: http://accr.ac.com/
Created by Jed Wolpaw, MD, MEd, an anesthesiologist at Johns Hopkins University School of Medicine, this podcast series aims to help trainees who are preparing for their board certifications as well as provide a forum for interesting debates and interviews in the areas of anesthesiology and critical care medicine.

Anesthesia Illustrated–SOAP
Web: http://www.anesthesiaillustrated.com/soap/
This collaboration between Anesthesia Illustrated and SOAP includes a large number of obstetric anesthesia videos including many of the major presentations from the Sol Shnider and SOAP annual meetings. No registration or password is required. The website includes lectures from the 2015, 2016, and 2017 Sol Shnider annual meetings.
OpenAnesthesia
Web: http://www.openanesthesia.org
Twitter: @OpenAnesthesia

OpenAnesthesia is a wide-ranging multimedia educational platform sponsored by the IARS. The Obstetric Anesthesia Subspecialty section has extensive multimedia educational content including a well-developed online obstetric anesthesia curriculum, a library of virtual grand rounds, and a series of obstetric anesthesia podcasts.

California Maternal Quality Care Collaborative
Web: https://www.cmqcc.org/

The California Maternal Quality Care Collaborative uses research, quality improvement toolkits, statewide outreach collaboratives, and its innovative Maternal Data Center to improve health outcomes for mothers and infants. A variety of documents is available providing comprehensive advice on topics such as, but not limited to, preeclampsia, maternal hemorrhage, maternal cardiovascular disease, and venous thromboembolism.

SimStat–Labor and Delivery

The ASA has created a novel screen-based simulation multimedia experience to evaluate how well participants manage a patient involved in an obstetric crisis. Examples of activities include development of a differential diagnosis and management therapies for hypertension during pregnancy, and demonstration of adherence to ACLS guidelines in a pregnant patient. Completion of the activity confers five Part II and IV activity points toward American Board of Anesthesiology (ABA) Maintenance of Certification in Anesthesiology (MOCA).

Neuraxial Ultrasound

Brendan Carvalho, MBBCh, FRCA, MDCH, an obstetric anesthesiologist at Stanford University School of Medicine, shares his insights on “Neuraxial Ultrasound: Time to Learn and Not Get Left Behind,” in this Sol Shnider lecture for the Society for Obstetric Anesthesiology and Perinatology (SOAP).

SECTION IV: ONLINE COMMUNITIES OF PRACTICE

Duke Anesthesiology Twitter Journal Club Series
Web: https://anesthesiology.duke.edu/?page_id=830505
Twitter: @Duke_Anesthesia #AnesJC

Duke Anesthesiology presents one of a growing number of Twitter-based journal clubs, allowing discussion of research articles from around the world. The website contains an archive of curated discussions of prior articles.

Obstetric Anesthesia Social Media Influencers List
Web: https://twitter.com/larrychu/lists/ob-anesthesia-list

This is a Twitter list compiled and maintained by Larry Chu, MD, MS, an anesthesiologist at Stanford University School of Medicine. It is based on social media metrics data of obstetric anesthesia influencers from the Symplur Signals database. The tweets posted by members of this social media list yield information that is highly relevant to obstetric anesthesia practice.

Obstetric Anesthesia Facebook Interest Page
Facebook: https://www.facebook.com/obstetricanesthesia/

This Facebook page is dedicated to the science, practice, and research of obstetric anesthesia. It is curated by Alex Butwick, MBBS, FRCA, an anesthesiologist at Stanford University School of Medicine.

Symplur Healthcare Hashtags
Web: https://www.symplur.com/healthcare-hashtags/

The Healthcare Hashtag project is a free and open platform presented by Symplur that allows interested parties (clinicians, patients, advocates, and others) to participate in social media discussions. It is an easy way to follow trending topics and conferences.