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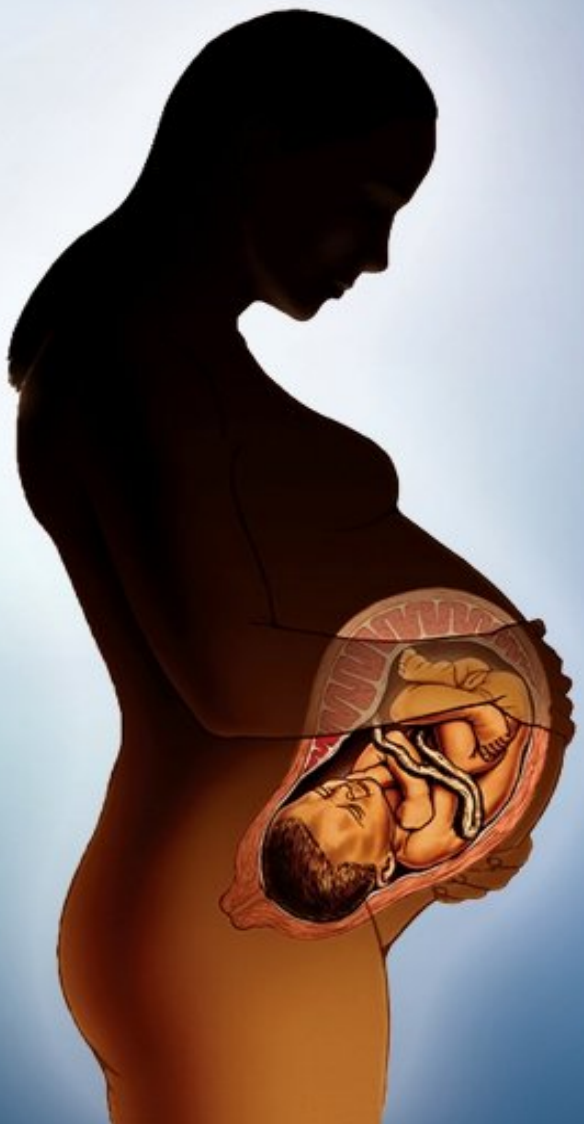
CHESTNUT'S OBSTETRIC ANESTHESIA

PRINCIPLES and PRACTICE



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CHESTNUT'S OBSTETRIC ANESTHESIA

PRINCIPLES and PRACTICE

1

The History of Obstetric Anesthesia

Donald Caton, MD

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

CHAPTER OUTLINE

"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 Haggard[1] 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

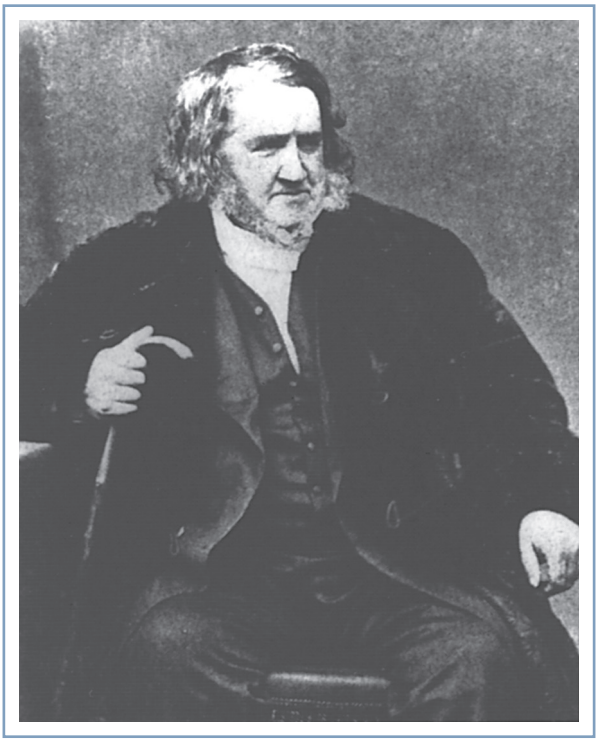


Fig. 1.1 James Young Simpson, the obstetrician who first administered a modern anesthetic for childbirth. He also discovered the anesthetic properties of chloroform. Many believe that he was the most prominent and influential physician of his day. (Courtesy of Yale Medical History Library.)

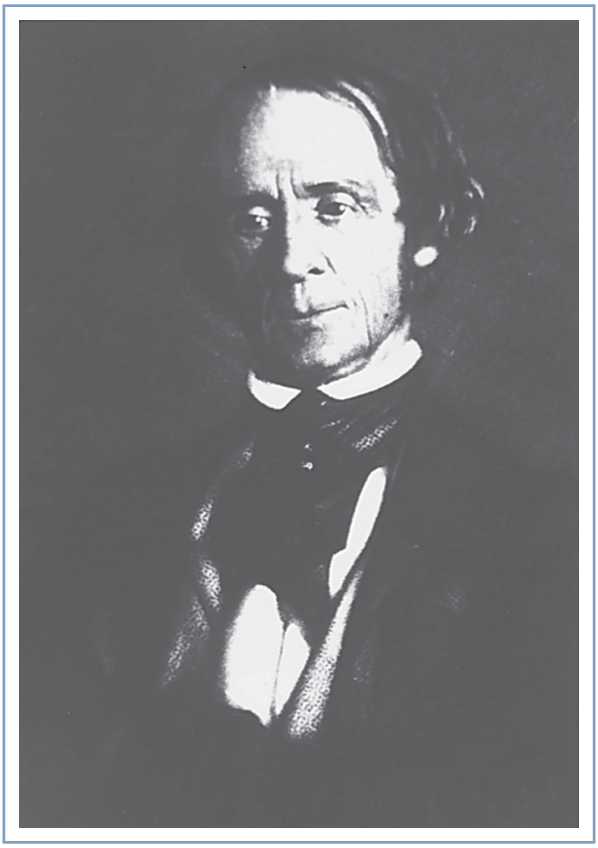


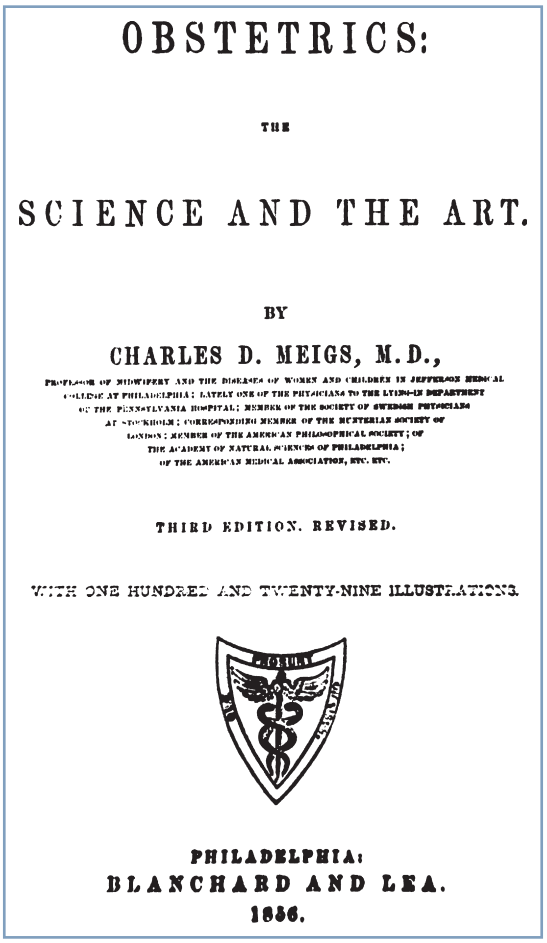
Fig. 1.2 Charles D. Meigs, the American obstetrician who opposed the use of anesthesia for obstetrics. He questioned the safety of anesthesia and said that there was no demonstrated need for it during a normal delivery. (Courtesy of Wood-Library Museum.)

stature, Meigs equaled Simpson. Born to a prominent New England family, Meigs' forebears included heroes of the American Revolutionary War, the first governor of the state of Ohio, and the founder of the University of Georgia. His descendants included a prominent pediatrician, an obstetrician, and one son who served the Union Army as Quartermaster General during the Civil War.[5]

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]

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.

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. Although no one made a formal announcement of this fact, rumors surfaced and provoked strong public criticism. Thomas Wakley, the irascible founding editor of *The Lancet,* was particularly incensed. He "could not imagine that anyone had incurred the awful responsibility of advising the administration of chloroform to her Majesty during a perfectly natural labour with a seventh child."[9] (It was her eighth child, but Wakley


OBSTETRICS:

THE

SCIENCE AND THE ART.

BY

CHARLES D. MEIGS, M.D.,

PROFESSOR OF MIDWIFERY AND THE DISEASES OF WOMEN AND CHILDREN IN JEFFERSON MEDICAL COLLEGE AT PHILADELPHIA; LATELY ONE OF THE PHYSICIANS TO THE LYING-IN DEPARTMENT OF THE PENNSYLVANIA HOSPITAL; MEMBER OF THE SOCIETY OF SWEDISH PHYSICIANS AT STOCKHOLM; CORRESPONDING MEMBER OF THE MEDICAL SOCIETY OF LONDON; MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY; OF THE ACADEMY OF NATURAL SCIENCES OF PHILADELPHIA; OF THE AMERICAN MEDICAL ASSOCIATION, ETC. ETC.

THIRD EDITION. REVISED.

WITH ONE HUNDRED AND TWENTY-NINE ILLUSTRATIONS.

PHILADELPHIA:
BLANCHARD AND LEA.
1856.

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.[9]

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 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.[10]

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:

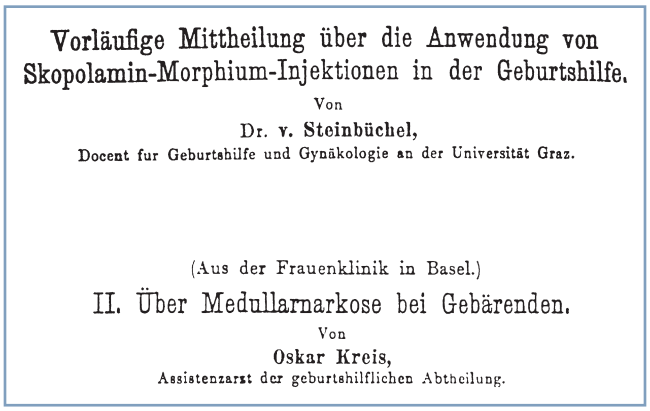
> *I am very sorry you all thought me so rash and naughty in trying the ether. Henry's faith gave me courage, and I had heard such a thing had succeeded abroad, where the surgeons extend this great blessing more boldly and universally than our timid doctors. … This is certainly the greatest blessing of this age.*[11]

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."[9] 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."[12]

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."[13] 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.

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[14] of Graz and popularized by Gauss[15] of Freiberg. It combined opioids with scopolamine to make women amnestic and somewhat comfortable during labor (Fig. 1.4). Until



Vorläufige Mittheilung über die Anwendung von Skopolamin-Morphium-Injektionen in der Geburtshilfe.

Von

Dr. v. Steinbüchel,

Docent fur Geburtshilfe und Gynäkologie an der Universität Graz.

(Aus der Frauenklinik in Basel.)

II. Über Medullarnarkose bei Gebärenden.

Von

Oskar Kreis,

Assistenzarst der geburtshilflichen Abtheilung.

Fig. 1.4 Title pages from two important papers published in the first years of the twentieth century. The paper by von Steinbüchel introduced twilight sleep. The paper by Kreis described the first use of spinal anesthesia for obstetrics.

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*, Sansom[17] 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,[18] 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[22] suggested that "nitro-aerial" particles from the mother nourish the fetus. By 1847, physiologists had corroborative evidence. Clinical experience gave more support. John Snow[23] 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

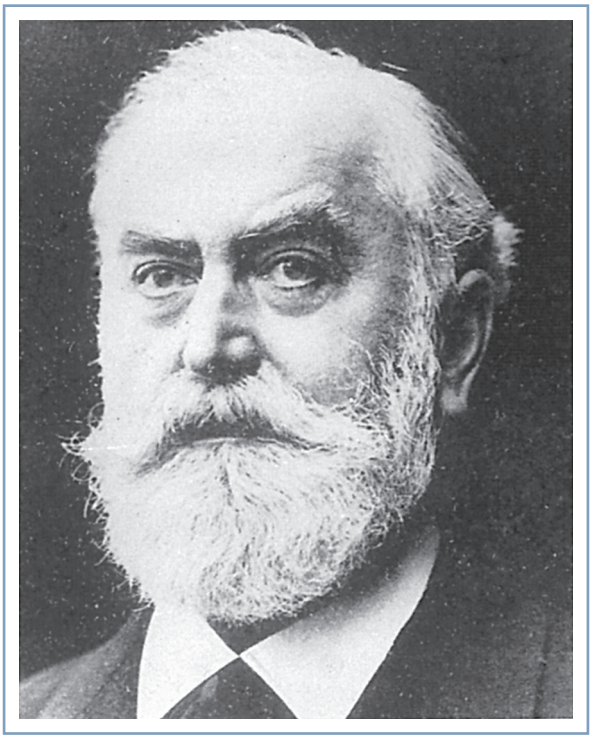


Fig. 1.5 Paul Zweifel, the Swiss-born obstetrician who performed the first experiments that chemically demonstrated the presence of chloroform in the umbilical blood and urine of infants delivered by women who had been anesthetized during labor. (Courtesy of J.F. Bergmann-Verlag, München, Germany.)

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.[24]

In 1874, Swiss obstetrician Paul Zweifel[25] 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, Zweifel[26] 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.[28] 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.[29] 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, Gillette[30] described 15 instances of neonatal depression that he attributed to morphine given during labor. Similarly, in a review article published in 1914, Knipe[31] 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]

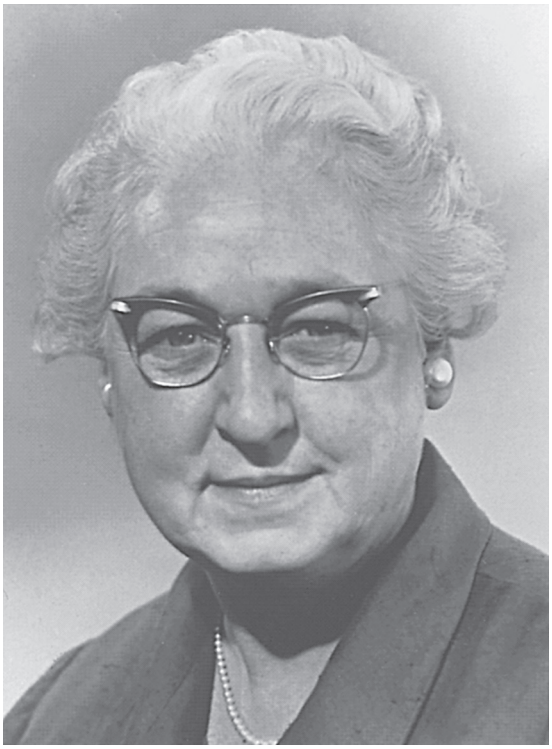
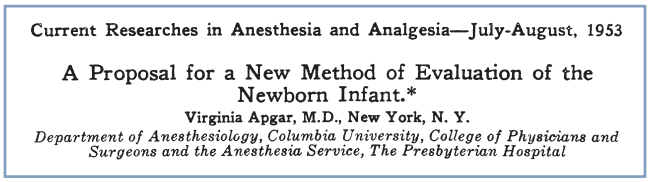


Fig. 1.6 Virginia Apgar, whose scoring system revolutionized the practice of obstetrics and anesthesia. Her work made the well-being of the infant the major criterion for the evaluation of medical management of pregnant women. (Courtesy of Wood-Library Museum.)



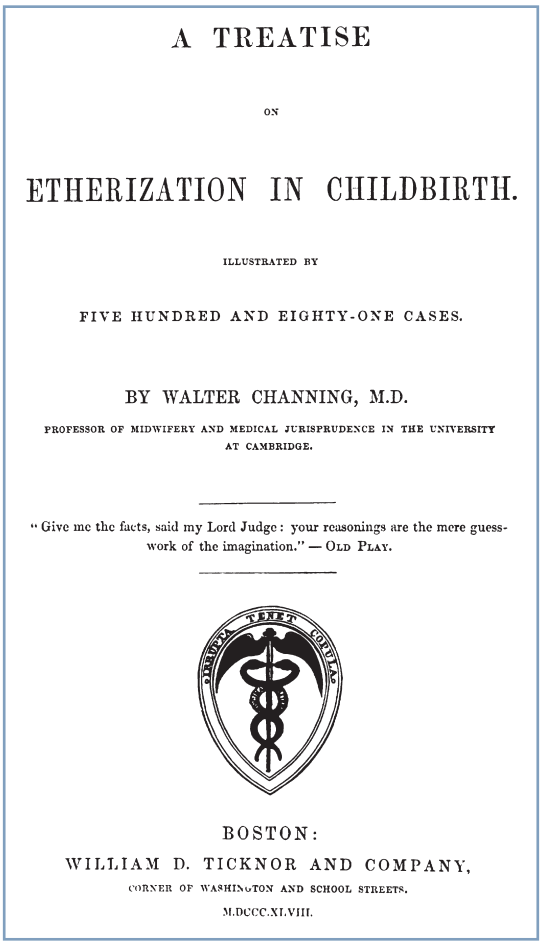
Current Researches in Anesthesia and Analgesia—July-August, 1953

A Proposal for a New Method of Evaluation of the Newborn Infant.*

Virginia Apgar, M.D., New York, N. Y.

Department of Anesthesiology, Columbia University, College of Physicians and Surgeons and the Anesthesia Service, The Presbyterian Hospital

Fig. 1.7 Title page from the paper in which Virginia Apgar described her new scoring system for evaluating the well-being of a newborn.



A TREATISE

ON

ETHERIZATION IN CHILDBIRTH.

ILLUSTRATED BY

FIVE HUNDRED AND EIGHTY-ONE CASES.

BY WALTER CHANNING, M.D.

PROFESSOR OF MIDWIFERY AND MEDICAL JURISPRUDENCE IN THE UNIVERSITY AT CAMBRIDGE.

"Give me the facts, said my Lord Judge: your reasonings are the mere guess-work of the imagination." — OLD PLAY.

BOSTON:

WILLIAM D. TICKNOR AND COMPANY,

CORNER OF WASHINGTON AND SCHOOL STREETS.

M.DCCC.XLVIII.

Fig. 1.8 Frontispiece from Walter Channing's book on the use of etherization for childbirth. Channing favored the use of etherization, and he persuaded others to use it, although evidence ensuring its safety was scant.

In 1953, Apgar[33] 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.[34] 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[35] 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 Snow[23] 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. Snow[23] 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 anesthesia 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 Head[38] 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 Koller[40] 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

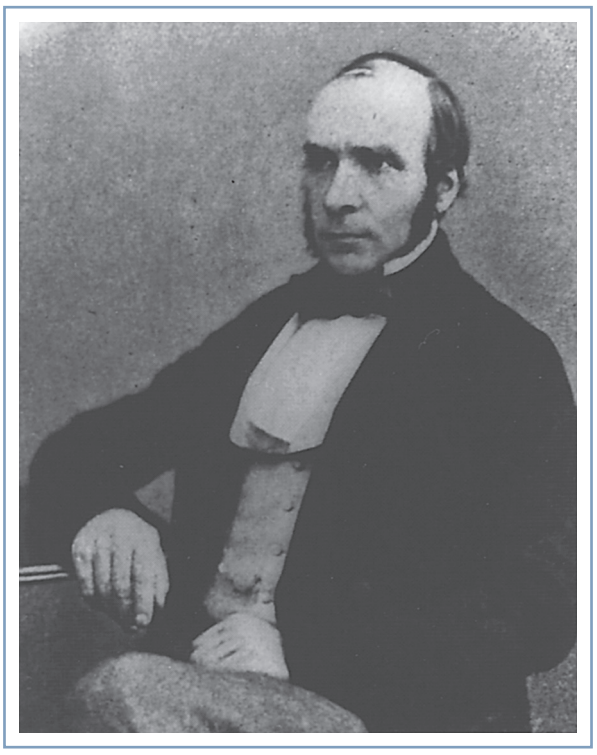


Fig. 1.9 John Snow, a London surgeon who gave up his surgical practice to become the first physician to devote all his time to anesthesia. He wrote many monographs and papers, some of which accurately describe the effects of anesthesia on the infant and mother. (Courtesy of Wood-Library Museum.)

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[44] 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 length of 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.[45]

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,[46] 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,[47] 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.[48] 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[49] 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[50] described and named it. The pathophysiology of the syndrome had already been described by Winternitz et al.,[51] 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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2

Physiologic Changes of Pregnancy

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CHAPTER OUTLINE

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

The mean maternal weight increase during pregnancy is 17% of the prepregnancy weight, or approximately 12 kg.[1] 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.[2] 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.[3]

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.[4] These changes, coupled with the elevation of the

TABLE 2.1 Recommended Weight Gain during Pregnancy

Prepregnancy Body Mass Index (kg/m^2)	Total Weight Gain in kg (lb)	Rate of Weight Gain during Second and Third Trimester in kg/wk (lb/wk)
< 18.5	12.7–18.2 (28–40)	0.45 (1)
18.5–24.9	11.4–15.9 (25–35)	0.45 (1)
25.0–29.9	6.8–11.4 (15–25)	0.27 (0.6)
≥ 30	5.0–9.1 (11–20)	0.23 (0.5)

Modified from Rasmussen KM, Yaktine AL, eds. *Weight Gain During Pregnancy: Reexamining the Guidelines.* Washington, DC: National Academies Press; 2009.

BOX 2.1 Changes in the Cardiac Examination in the Pregnant Patient

- Accentuation of first heart sound (S1) and exaggerated splitting of the mitral and tricuspid components
- Typical systolic ejection murmur
- Possible presence of third heart sound (S3) and fourth heart sound (S4); no clinical significance
- Leftward displacement of point of maximal cardiac impulse

diaphragm from the expanding uterus, cause several changes in the physical examination and in cardiac studies.

Changes in heart sounds include accentuation of the first heart sound with exaggerated splitting of the mitral and tricuspid components (Box 2.1).[5] 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[6]; 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[7] and an overall 50% increase in mass at term.[8] This eccentric hypertrophy results from an increase in the size of the preexisting cardiomyocytes, resembling the changes that occur from repeated, strenuous exercise.[1] The annular diameters of the mitral, tricuspid, and pulmonic valves increase; 94% of term pregnant women exhibit tricuspid and pulmonic regurgitation, and 27% exhibit mitral regurgitation.[9] 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.[10] Depressed ST segments and isoelectric low-voltage T waves in the left-sided precordial and limb leads are common.[11]

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.[12] There is significant heterogeneity in cardiac output measurement using different noninvasive devices; these differences should be taken into account when caring for individual patients.[13]

Cardiac output begins to increase by five weeks' gestation and is 35% to 40% above baseline by the end of the first trimester.[8,14] It continues increasing throughout the second trimester to approximately 50% greater than nonpregnant values (Figs. 2.1 and 2.2).[8,12,15,16] Cardiac output does not change further during the third trimester.[17] Some studies have reported a decrease in cardiac output 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.[8] 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.[8,12,14-16,18] 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.[8,12,14,18] The increased stroke volume correlates with increasing estrogen levels.[1] Stroke volume index decreases over the course of pregnancy, while cardiac index remains slightly increased from prepregnancy values.[17]

Left ventricular end-diastolic volume increases during pregnancy, whereas end-systolic volume remains unchanged, resulting in a larger ejection fraction.[8,12,14,15,18] Central venous, pulmonary artery diastolic, and pulmonary capillary wedge pressures are within the normal nonpregnant range.[16] 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 (Fig. 2.3).[8,15,18] Tissue Doppler imaging, which is relatively independent of preload, has been used to assess diastolic function.[19] A mild degree of diastolic dysfunction may be seen during the third trimester compared with earlier in pregnancy and nonpregnant controls.[17]

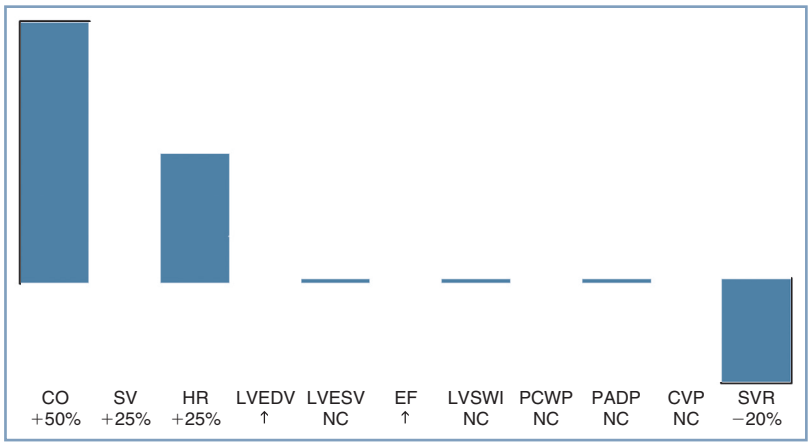

Fig. 2.1 Central Hemodynamic Changes at Term Gestation. Changes are relative to the nonpregnant state. *CO,* cardiac output; *SV,* stroke volume; *HR,* heart rate; *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume; *EF,* ejection fraction; *LVSWI,* left ventricular stroke work index; *PCWP,* pulmonary capillary wedge pressure; *PADP,* pulmonary artery diastolic pressure; *CVP,* central venous pressure; *SVR,* systemic vascular resistance; *NC,* no change. (Data from Conklin KA. Maternal physiological adaptations during gestation, labor, and puerperium. *Semin Anesth.* 1991;10: 221–234.)

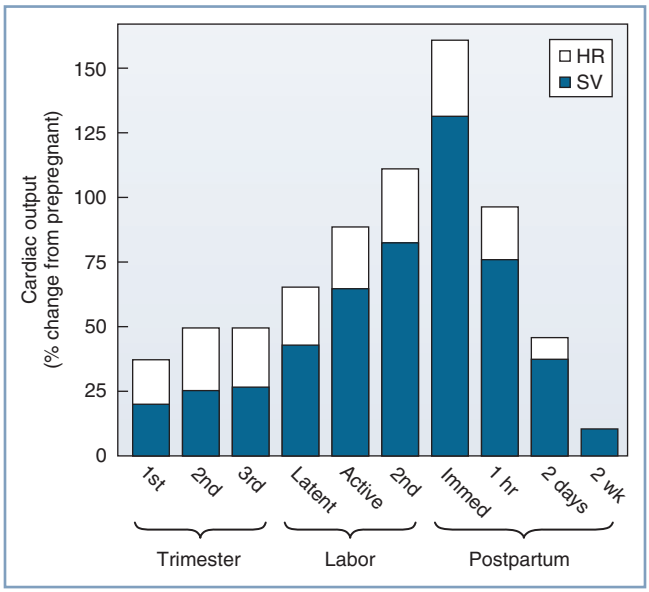

Fig. 2.2 Cardiac Output during Pregnancy, Labor, and the Puerperium. Values during pregnancy are measured at the end of the first, second, and third trimesters. Values during labor are measured between contractions. For each measurement, the relative contributions of heart rate *(HR)* and stroke volume *(SV)* to the change in cardiac output are illustrated.

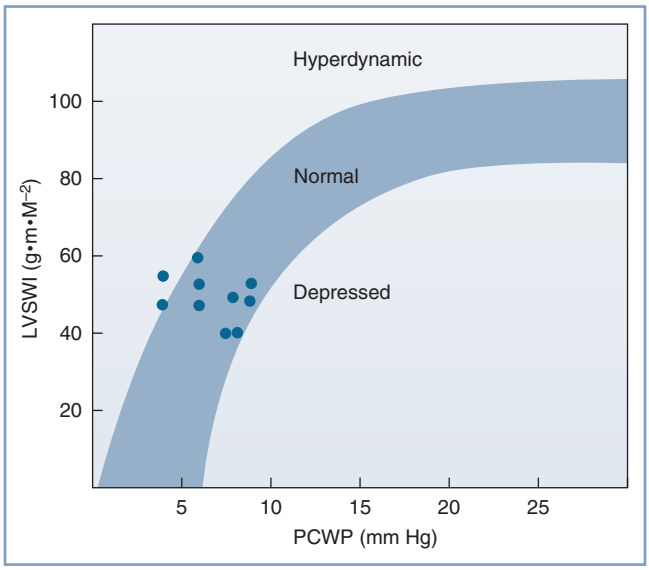

Fig. 2.3 Left ventricular function in late phase of third-trimester normotensive pregnant patients. *LVSWI,* left ventricular stroke work index; *PCWP,* pulmonary capillary wedge pressure. (Modified from Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of cardiac function. *Am J Obstet Gynecol.* 1989;161:439–442.)

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.[20–22] During the second half of pregnancy, the proportion of cardiac output distributed to the uterine circulation increases from 5% to 12%.[23] Approximately 90% of this flow perfuses the intervillous space, with the balance perfusing the myometrium.[21] At term, skin blood flow is approximately three to four times the nonpregnant level, resulting in higher skin temperature.[24] Renal plasma flow is increased by 80% at 16 to 26 weeks' gestation but is only 50% above the prepregnancy baseline at term.[25]

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,[26] and the American College of Obstetricians and Gynecologists recommends 20 to 30 minutes per day[27]; 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.[28] 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.[29] Exercise is safe for the fetus[29,30]; 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.[30]

During exercise, maximal oxygen consumption is greater in pregnancy,[31] especially during cardiovascular exercise. The rate of increase in minute ventilation is greater with exercise during pregnancy.[32] Cardiac output is also greater, primarily

from increased stroke volume[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.[34] Blood pressure increases with maternal age, and for a given age, nulliparous women have a higher mean pressure than parous women.[35] Systolic, diastolic, and mean blood pressure decrease during mid-pregnancy and return toward baseline as the pregnancy approaches term.[36] Diastolic blood pressure decreases more than systolic blood pressure, with early- to mid-gestational decreases of approximately 20%.[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.[12,16] 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.[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.[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.[39] This finding is consistent with the 75% elevation above baseline of femoral venous and lower inferior vena cava pressures.[40] Despite caval compression, collateral circulation maintains venous return, as reflected by the right ventricular filling pressure, which is unaltered in the lateral position.[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.[41]

In the supine position, significant and sometimes complete compression of the inferior vena cava is evident at term.[42,43] Blood returns from the lower extremities through the intraosseous, vertebral, paravertebral, and epidural veins.[44] However, this collateral venous return is less than would occur through the inferior vena cava, resulting in a decrease in right atrial pressure.[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).[46] By term, femoral venous and lower inferior vena caval pressures are approximately 2.5 times the nonpregnant measurements in the supine position.[40,46] 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.[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.[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.[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.[43]

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.[50] Women who assume the supine position at term gestation experience a 10% to 20% decline in stroke volume and cardiac output,[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%.[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.[54] The adverse hemodynamic effects of aortocaval compression are reduced once the fetal head is engaged.[47,48] The sitting position has also been shown to result in aortocaval compression, with a decrease in cardiac output of 10%.[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**.[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.

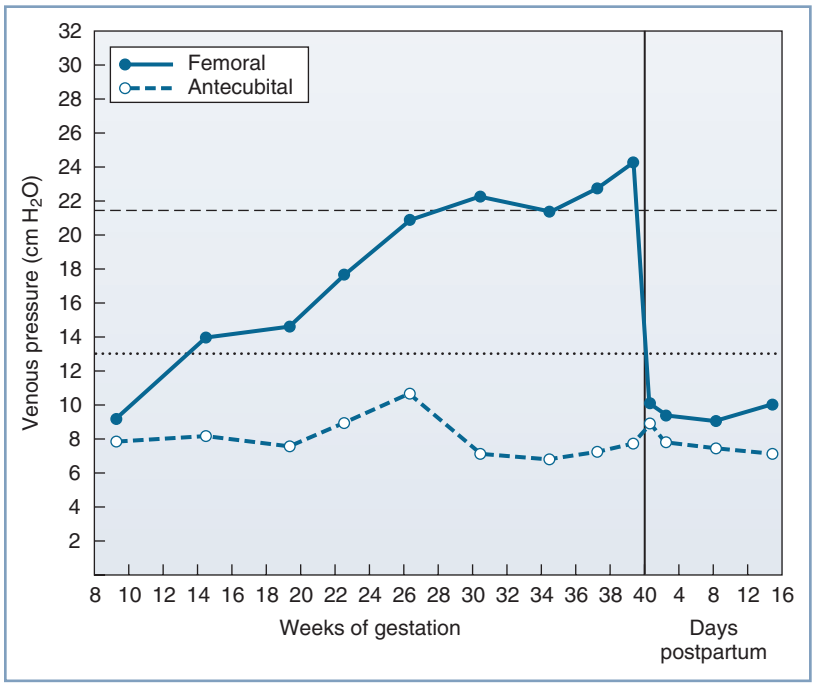

Fig. 2.4 Femoral and antecubital venous pressures in the supine position throughout normal pregnancy and the puerperium. (Modified from McLennan CE. Antecubital and femoral venous pressure in normal and toxemic pregnancy. *Am J Obstet Gynecol.* 1943; 45:568–591.)

Hemodynamic Changes during Labor and the Puerperium

Cardiac output during labor (but between uterine contractions) increases from prelabor values by approximately 10% in the early first stage, by 25% in the late first stage, and by 40% in the second stage of labor.[57–59] In the immediate postpartum period, cardiac output may be as much as 75% above predelivery measurements and 150% above prepregnancy baseline.[58] These changes result from an increase in stroke volume caused by greater venous return and alterations in sympathetic nervous system activity. During labor, uterine contractions displace 300 to 500 mL of blood from the intervillous space through the ovarian venous outflow system into the central circulation ("autotransfusion").[60–62] The postpartum increase in cardiac output results from relief of vena caval compression, diminished lower extremity venous pressure, sustained myometrial contraction, and loss of the low-resistance placental circulation.[59] Cardiac output decreases to just below prelabor values at 24 hours postpartum[60] and returns to prepregnancy levels between 12 and 24 weeks postpartum[12] (see Fig. 2.2). Heart rate decreases rapidly after delivery, reaches prepregnancy levels by 2 weeks postpartum, and is slightly below the prepregnancy rate for the next several months.[12,57] Other anatomic and functional changes of the heart are also fully reversible.[23,63]

THE RESPIRATORY SYSTEM

Despite the multiple anatomic and physiologic changes that occur during pregnancy, it is remarkable that pregnancy has a relatively minor impact on lung function.

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[68] 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,[69] forced expiratory volume in 1 second (FEV_1),

TABLE 2.2 Effects of Pregnancy on Respiratory Mechanics

Parameter	Change[a]
Diaphragm excursion	Increased
Chest wall excursion	Decreased
Pulmonary resistance	Decreased 50%
FEV_1	No change
FEV_1/FVC	No change
Flow-volume loop	No change
Closing capacity	No change

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity.
[a]Relative to nonpregnant state.
Modified from Conklin KA. Maternal physiological adaptations during gestation, labor, and the puerperium. *Semin Anesth.* 1991;10:221–234.

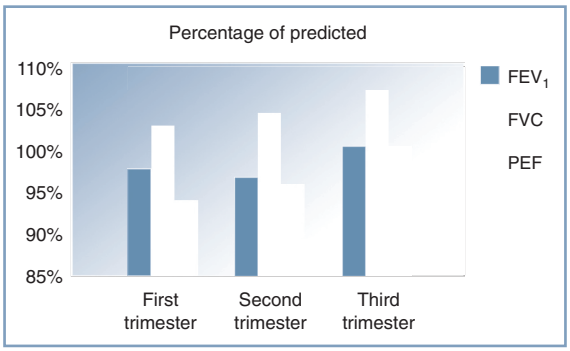

Fig. 2.5 Changes in airflow mechanics during pregnancy. The magnitude of the increase in flow rates is small. The forced expiratory volume in one second *(FEV_1)* is within the normal range of predictive values for nonpregnant individuals. *FVC,* forced vital capacity; *PEF,* peak expiratory flow. (Based on data from Grindheim G, Toska K, Estensen ME, Rosseland LA. Changes in pulmonary function during pregnancy: a longitudinal study. *BJOG.* 2012;119:94–101.)

the ratio of FEV_1 to forced vital capacity (FVC), and closing capacity are unchanged during pregnancy.[70] There is no significant change in respiratory muscle strength during pregnancy despite the cephalad displacement of the diaphragm. Furthermore, despite the upward displacement of the diaphragm by the gravid uterus, diaphragm excursion actually increases by 2 cm.[71]

The peak expiratory flow (PEF) rate achieved with a maximal effort after a maximal inspiration is often considered a surrogate for the FEV_1 and can be used to monitor asthma therapy. Studies of changes in PEF rate during pregnancy show conflicting results, likely reflecting differences in measurement devices and patient position. Harirah et al.[72] found that peak expiratory flow rate declined throughout gestation in all positions and that flow rates in the supine position were lower than those during standing and sitting. The mean rate of decline was 0.65 L/min per week, and PEF rate remained below normal at 6 weeks postpartum. By contrast, Grindheim et al.[73] reported that PEF rate increased throughout pregnancy starting at an average of 6.7 L/s in the early second trimester and peaking at 7.2 L/s at term (Fig. 2.5). These authors also reported that the FVC increased by 100 mL after 14 to 16 weeks' gestation, with the change being greater in parous than in primigravid women.[73]

Lung Volumes and Capacities

Lung volumes can be measured using body plethysmography or by inert gas techniques with slightly differing results.[74] By term, total lung capacity is slightly reduced,[75] whereas tidal volume increases by 45%, with approximately half the change occurring during the first trimester (Table 2.3 and Fig. 2.6). The early change in tidal volume is associated with a transient reduction in inspiratory reserve volume. Residual volume tends to decrease slightly, a change that maintains vital capacity. Inspiratory capacity increases by 15% during the third trimester because of increases in tidal volume and inspiratory reserve volume.[76,77] There is a corresponding decrease in expiratory reserve volume.[76,77] The functional 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]

TABLE 2.3 Changes in Respiratory Physiology at Term Gestation

Parameter	Change[a]
Lung Volumes	
Inspiratory reserve volume	+5%
Tidal volume	+45%
Expiratory reserve volume	–25%
Residual volume	–15%
Lung Capacities	
Inspiratory capacity	+15%
Functional residual capacity	–20%
Vital capacity	No change
Total lung capacity	–5%
Ventilation	
Minute ventilation	+45%
Alveolar ventilation	+45%

[a]Relative to nonpregnant state.
From Conklin KA. Maternal physiological adaptations during gestation, labor and the puerperium. *Semin Anesth.* 1991;10:221–234.

Ventilation and Blood Gases

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

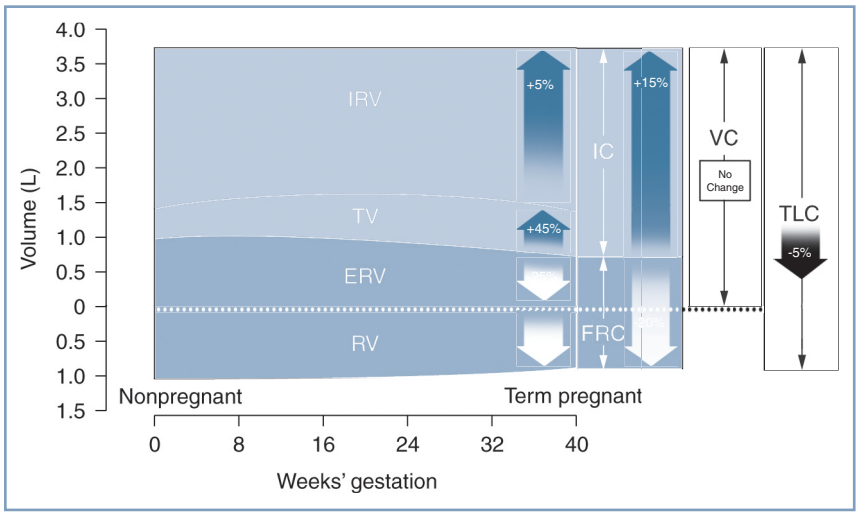

Fig. 2.6 Lung volumes and capacities during pregnancy. *ERV,* expiratory reserve volume; *FRC,* functional residual capacity; *IC,* inspiratory capacity; *IRV,* inspiratory reserve volume; *RV,* residual volume; *TLC,* total lung capacity; *TV,* tidal volume; *VC,* vital capacity.

TABLE 2.4 Blood Gas Parameters during Pregnancy

		TRIMESTER		
Parameter	**Nonpregnant**	**First**	**Second**	**Third**
$Paco_2$ in mm Hg (kPa)	40 (5.3)	30 (4.0)	30 (4.0)	30 (4.0)
Pao_2 in mm Hg (kPa)	100 (13.3)	107 (14.3)	105 (14.0)	103 (13.7)
pH	7.40	7.44	7.44	7.44
Bicarbonate (mEq/L)	24	21	20	20

tidal volume from 450 to 600 mL and a small increase in respiratory rate of 1 to 2 breaths/min.[79] 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 CO_2 production at rest by approximately 30% to 300 mL/min. The former is closely related to the blood level of progesterone,[80] 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 CO_2-ventilatory response curve. This change occurs early in pregnancy and remains constant until delivery.[69]

Dyspnea is a common complaint during pregnancy, affecting up to 75% of women.[81] Contributing factors include increased respiratory drive, decreased $Paco_2$, 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.[82] Exercise has no effect on pregnancy-induced changes in ventilation or alveolar gas exchange.[83] The hypoxic ventilatory response is increased during pregnancy to twice the normal level, secondary to elevations in estrogen and progesterone levels.[84] This increase occurs despite blood and cerebrospinal fluid (CSF) alkalosis.

During pregnancy, Pao_2 increases to 100 to 105 mm Hg (13.3 to 14.0 kPa) as a result of greater alveolar ventilation and a decline in $Paco_2$ (Table 2.4).[85–87] 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 Pao_2 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 volume ventilation.[85] 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.

$Paco_2$ 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 CO_2 tension and $Paco_2$ in nonpregnant women, the two measurements are equivalent during early pregnancy,[88] at term gestation,[89] and in the postpartum period.[90] 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 Pco_2 is 6 to 8 mm Hg (0.8 to 1.1 kPa)

TABLE 2.5 Changes in Gastrointestinal Physiology during Pregnancy[a]

Parameter	TRIMESTER First	Second	Third	Labor	Postpartum (18 h)
Barrier pressure[b]	Decreased	Decreased	Decreased	Decreased	?
Gastric emptying	No change	No change	No change	Delayed	No change
Gastric acid secretion	No change	No change	No change	?	?
Proportion of women with gastric volume > 25 mL	No change	No change	No change	Increased	No change
Proportion of women with gastric pH < 2.5	No change	No change	No change	No change	No change

[a]Relative to nonpregnant state.
[b]Difference between intragastric pressure and tone of the lower esophageal high-pressure zone.

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 arterial[85] 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.[94] Pain, anxiety, and coached breathing techniques all increase minute ventilation. $Paco_2$ 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.[94,95] 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 Pco_2 values increase slowly after delivery and are still slightly below prepregnancy levels at 6 to 8 weeks postpartum.[1]

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 acetaminophen[103–105] and by studies that assessed the emptying of a test beverage or meal by radiographic,[106] ultrasonographic,[105,107] dye dilution,[108] epigastric impedance,[109] and applied potential tomographic[110] 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.[107] Up to 40% of women suffer from constipation at some time during their pregnancy.[113] 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.[114] Van Thiel et al.[115] 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.[116] 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.[117]

Nausea and Vomiting

Approximately 80% of pregnant women will experience nausea and vomiting during pregnancy.[118] The symptoms typically start between 4 to 9 weeks' gestation and may last until 12 to 16 weeks' gestation.[119] 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.[120,121] Direct measurements show that the mean gastric volume increases.[122] 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.[123] Gastric acid secretion may decrease during labor because only 25% of parturients who are in labor have a gastric pH of 2.5 or lower.[124] Gastric emptying is also delayed during the early postpartum period but returns to prepregnancy levels by 18 hours postpartum.[125] Fasting gastric volume and pH values are similar to nonpregnant patients at 18 hours postpartum.[126–128] The effects of opioids and neuraxial analgesia on gastric emptying are discussed in Chapters 23 and 28.

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.[129] 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.[130]

Biliary stasis and greater secretion of bile with cholesterol increase the risk for gallbladder disease during pregnancy.[131] The incidence of gallstones is 5% to 12% in pregnant women.[132] 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.[133] The size of the total bile acid pool increases by about 50% during pregnancy, and the relative proportions of the various bile acids change.[134] 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%.[135] 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. Hydronephrosis may occur in 80% of women by mid-pregnancy.[136]

Both the glomerular filtration rate (GFR) and the renal plasma flow increase markedly during pregnancy secondary to reduced renal vascular resistance.[25] 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.[137] The role of nitric oxide in the renal vasodilation was tested and confirmed in a rat model.[138] Renin and aldosterone also both increase during pregnancy.[139]

Creatinine clearance is increased to 150 to 200 mL/min from the normal baseline values of 120 mL/min.[140] 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.[137] 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.[140] 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 rise in GFR, to 2.0 to 3.0 mg/dL by 24 weeks' gestation.[141] 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).[142,143] Proteinuria (> 300 mg/24 h) has been described without the diagnosis of preeclampsia.[144] 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.[145] The degree of proteinuria in normal pregnancy correlates with gestation. Baba et al.[146] suggested that in normotensive patients, a P:C ratio of > 0.75 may be the "rule-in" threshold for significant proteinuria.[146] Women with twin pregnancies have greater protein excretion compared with those with singleton pregnancies.[147]

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 and normal glucose excretion when not pregnant, approximately half will exhibit a doubling of glucose excretion. Most of the remainder have increases of 3 to 10 times the nonpregnant amount, and a small proportion (< 10%) excrete as much as 20 times the nonpregnant amount.[148] 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).[149–152] 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

TABLE 2.6 Hematologic Parameters at Term Gestation

Parameter	Change[a] or Actual Measurement
Blood volume	+45%[a]
Plasma volume	+55%[a]
Red blood cell volume	+30%[a]
Hemoglobin concentration (g/dL)	11.6
Hematocrit	35.5%

[a]Relative to nonpregnant state.
Modified from Conklin KA. Maternal physiological adaptations during gestation, labor, and puerperium. *Semin Anesth.* 1991;10:221–234.

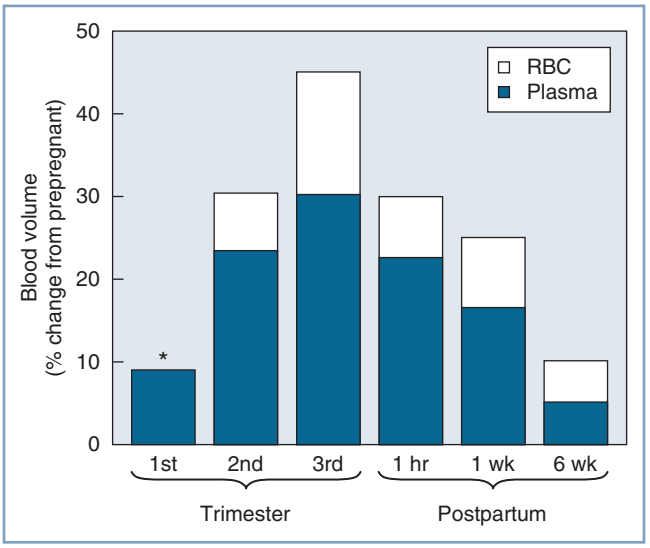

Fig. 2.7 Blood Volume during Pregnancy and the Puerperium. Values during pregnancy measured at the end of the first, second, and third trimesters. Postpartum values measured after a vaginal delivery. The values for red blood cell volume *(RBC)* and plasma volume *(Plasma)* do not represent the actual percentage of change in these parameters but rather reflect the relative contribution of each to the change in blood volume. The asterisk indicates that RBC volume is below the prepregnancy volume at the end of the first trimester.

30% above the prepregnancy level at term.[150,152,153] The red blood cell volume increases in response to elevated erythropoietin concentration[154] 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).[150,152,153,155] Women who do not receive iron supplements during pregnancy have greater decreases in hemoglobin concentration and hematocrit.[152]

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

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]

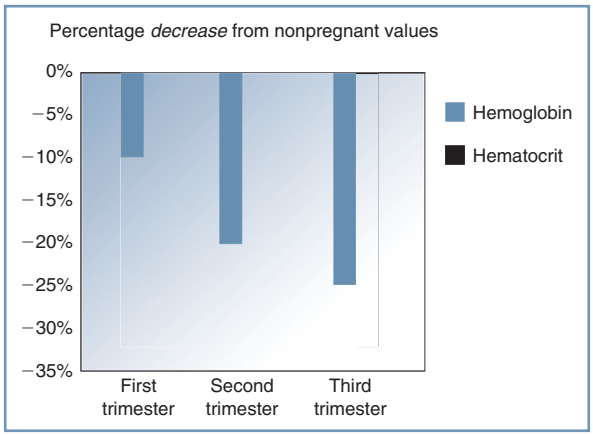

Fig. 2.8 The Decrease in Both Hemoglobin Concentration and Hematocrit during Pregnancy Underlies the Physiologic Anemia of Pregnancy. The decrease is greater for hematocrit, and the greatest decreases occur during the third trimester. (Based on data from Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol.* 2009;114:1326–1331.)

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.

BOX 2.2 Changes in Coagulation and Fibrinolytic Parameters at Term Gestation[a]

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

[a]Relative to nonpregnant state.

TABLE 2.7 Plasma Protein Values during Pregnancy

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

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.[163–165] Platelet aggregation in response to collagen, epinephrine, adenosine diphosphate, and arachidonic acid is increased.[166] Some investigators have noted a decrease in platelet count,[165,167] whereas others have noted no change,[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^3 and 0.9% of pregnant women having a platelet count less than 100,000/mm^3.[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.[169] Gestational thrombocytopenia is an exaggerated normal response.

The concentrations of most coagulation factors, including fibrinogen (factor I), proconvertin (factor VII), antihemophilic factor (factor VIII), Christmas factor (factor IX), Stuart-Prower 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).[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.[171–173] An increase in most factor concentrations, shortening of the prothrombin time (PT) and activated partial thromboplastin time (aPTT),[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).[174] Protein S activity decreases steadily during pregnancy, reaching the lowest values at delivery.[175]

Thromboelastrography (TEG) demonstrates evidence of hypercoagulability in pregnancy. These changes (decrease in R and K values, increase in the α 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).[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.[179] *In vitro,* exogenous oxytocin decreases R and K values, while increasing the α angle.[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.[181]

The greater concentration of fibrin degradation products signals increased fibrinolytic activity during gestation.[163]

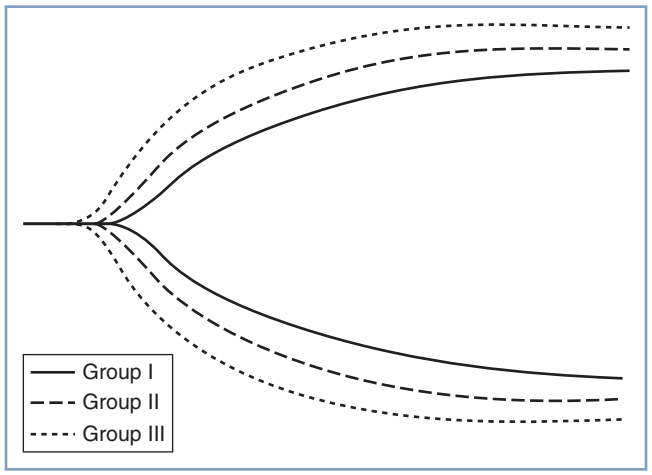

Fig. 2.9 Comparative thromboelastographs in nonpregnant (Group I), nonlaboring term pregnant (Group II), and laboring (Group III) women. (From Steer PL, Krantz HB. Thromboelastrography and Sonoclot analysis in the healthy parturient. *J Clin Anesth.* 1993;5:419–424.)

D-dimer values increase across gestation and remain higher than prepregnancy values in the postpartum period.[182,183] The marked elevation in the plasminogen concentration also is consistent with enhanced fibrinolysis.[184]

Hematology and Coagulation during the Puerperium

Blood loss during normal vaginal delivery and the early puerperium is approximately 600 mL.[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).[186]

Blood volume decreases to 125% of the prepregnancy level during the first postpartum week,[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.[187]

Cesarean delivery results in a blood loss of approximately 1000 mL within the first few hours of delivery.[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.[185]

Albumin and total protein concentrations and colloid osmotic pressure decline after delivery and gradually return to prepregnancy levels by 6 weeks postpartum.[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.[162] Globulin concentrations are elevated throughout the first postpartum week.[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.[188] Clotting times remain shortened during the first postpartum day,[189] 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 nonpregnant state by 2 weeks postpartum.[188]

THE IMMUNE SYSTEM

The blood leukocyte count increases progressively during pregnancy from the prepregnancy level of approximately 6000/mm^3 to between 9000 and 11,000/mm^3.[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/mm^3 during labor and increases further to an average of 15,000/mm^3 on the first postpartum day.[187] By the sixth postpartum day, the leukocyte count decreases to an average of 9250/mm^3, 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.[191]

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 (T_3) and thyroxine (T_4) concentrations during the first trimester, which are maintained until term.[198] The concentrations of free T_3 and T_4 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 T_4 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]

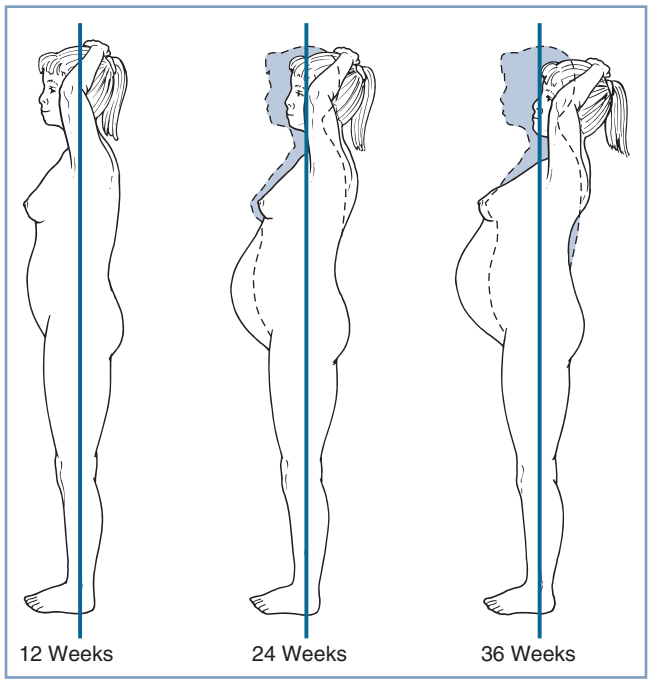

Fig. 2.10 Changes in Posture during Pregnancy. The first and the subsequent dotted-line figures represent a woman's posture before growth of the uterus and its contents have affected the center of gravity. The second and third solid figures show that as the uterus enlarges and the abdomen protrudes, the lumbar lordosis is enhanced and the shoulders slump and move posteriorly. (Modified from Beck AC, Rosenthal AH. *Obstetrical Practice.* Baltimore, MD: Williams & Wilkins; 1955:146.)

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

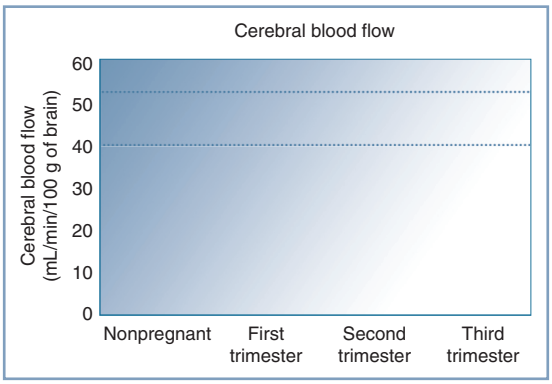

Fig. 2.11 Cerebral Blood Flow during Pregnancy. Cerebral blood flow increases as pregnancy progresses and is attributable to vasodilation from the hormonal changes of pregnancy. This increase in cerebral blood flow explains the increased risk for complications in patients with intracranial pathology 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.)

was shorter in the third trimester (7.0 ± 1.2 hours) compared with the baseline period between 6 and 20 weeks' gestation (7.4 ± 1.2 hours).[219]

Sleep characteristics change as pregnancy progresses.[220] 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.[220] Sleep may be poor for up to 3 months postpartum.[221] 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.[222]

Central Nervous System

Cerebral blood flow increases in pregnancy. Nevo et al.[223] 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.[224]

Women experience an elevation in the threshold to pain and discomfort near the end of pregnancy and during labor.[225] 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,[226] and opioid antagonists abolish pregnancy-induced analgesia to visceral stimulation in experimental animals.[227]

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.[42]

In the lateral position, lumbar epidural pressure is positive in term pregnant women but negative in more than 90% of nonpregnant women.[228] 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 nonpregnant women.[229] 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.[230–232] 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.[233–235] Studies performed with pregnant women placed in the lateral position have not shown major decreases in cardiac output.[236,237] 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.[238] 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).[43,238]

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

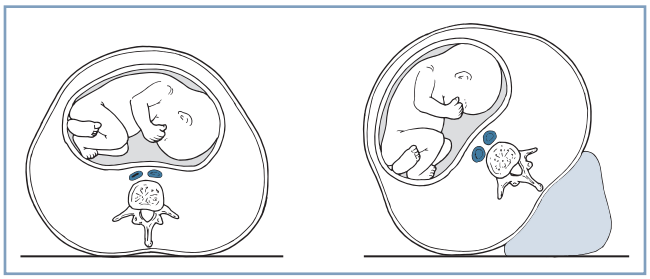

Fig. 2.12 Compression of the aorta and inferior vena cava in the supine *(left)* and lateral tilt *(right)* positions. (Redrawn from Camann WR, Ostheimer GW. Physiologic adaptations during pregnancy. *Int Anesthesiol Clin.* 1990;28:2–10.)

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 vasopressors
  - Decreased sensitivity

Tracheal Intubation

- Increased rate of decline of Pa_{O_2} 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. Hemoconcentration 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.[150]

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.[239] Vascular engorgement of the airway results in edema of the oral and nasal pharynx, larynx, and trachea,[240] 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.

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, Pa_{O_2} decreases twice as rapidly (139 versus 58 mm Hg/min [18.5 versus 7.7 kPa/min]) in pregnant versus nonpregnant women.[241] 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 Pa_{CO_2} 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 Pa_{CO_2} in nonpregnant women.[242] Decreased plasma bicarbonate concentration reduces buffering capacity in pregnancy. Allowing the Pa_{CO_2} to increase to the normal level for nonpregnant women results in respiratory acidosis.

Intravenous and Inhalation Anesthetics

The **propofol** requirement decreases 10% during the first trimester[243]; this decrease does not correlate with progesterone levels. The elimination half-life of propofol is unaffected by pregnancy, though clearance may be higher.[244]

The rate of rise of alveolar to inspired anesthetic concentration ratio (F_A/F_I) 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.[245–247] Although MAC is a spinal nociceptive reflex that involves both sensory and motor components,[248] 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.[249] 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.

Laboring women may differ from nonlaboring women. Yoo et al.[250] 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.[251] 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.[252] 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.**[253,254] 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.[255] The mean onset time and clinical duration of **cisatracurium** are significantly shorter in women immediately after delivery than in nonpregnant women.[256]

Chronotropic Agents and Vasopressors

Pregnancy reduces the chronotropic response to **isoproterenol** and **epinephrine** because of down-regulation of beta-adrenergic receptors.[257] 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 (Fig. 2.14). 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.[229] However, flow rate may increase during a uterine contraction because of increased CSF pressure.

BOX 2.4 Neuraxial Anesthesia: Anesthetic Implications of Maternal Physiologic Changes

Technical Considerations
- Lumbar lordosis increased[a]
- Apex of thoracic kyphosis at higher level[a]
- Head-down tilt when in lateral position

Treatment of Hypotension
- Decreased sensitivity to vasopressors[a]

Local Anesthetic Dose Requirements[b]
- Subarachnoid dose reduced 25%[a]
- Epidural dose unaltered or slightly reduced[a]

[a]Compared with nonpregnant women.
[b]Change in the segmental dose requirement.
Modified from Conklin KA. Maternal physiologic adaptations during gestation, labor, and the puerperium. *Semin Anesth.* 1991;10:221–234.

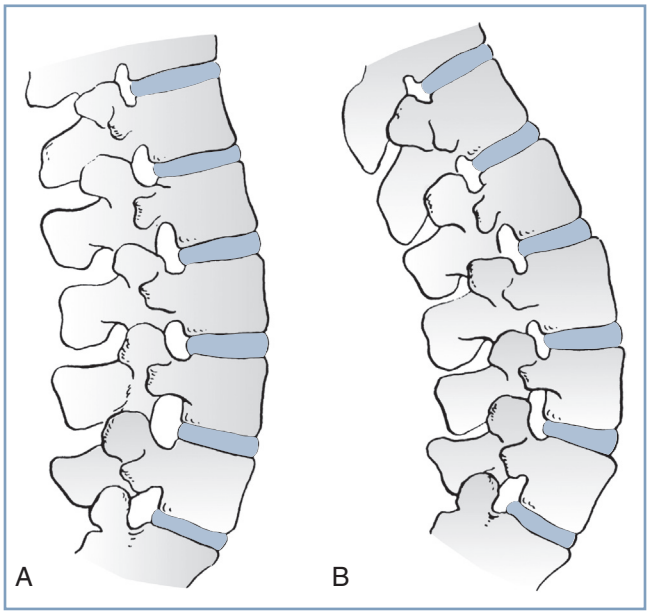

Fig. 2.13 Effects of Pregnancy on the Lumbar Spine. **A,** Nonpregnant. **B,** Pregnant. There is a marked increase in lumbar lordosis and a narrowing of the interspinous spaces during pregnancy. (Modified from Bonica JJ. *Principles and Practice of Obstetric Analgesia and Anesthesia,* Volume 1. Philadelphia, PA: FA Davis; 1967:35.)

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,[258] suggesting that there are pregnancy-induced alterations in nerve tissue sensitivity, either directly or indirectly from changes in hormone concentrations.[259]

Pregnant women exhibit a more rapid onset and a longer duration of spinal anesthesia than nonpregnant women who

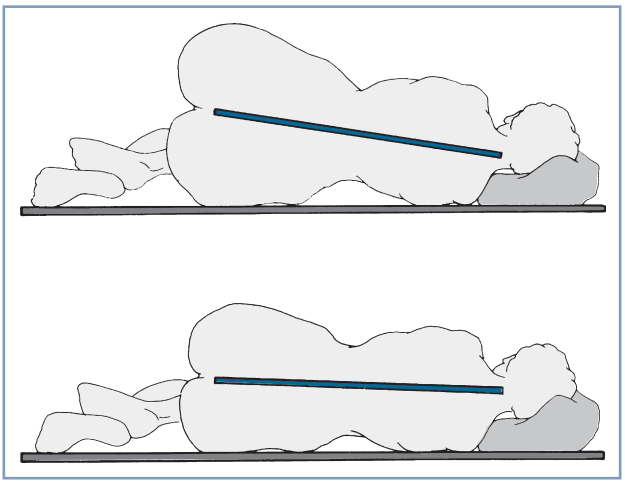

Fig. 2.14 Pelvic widening and resultant head-down tilt in the lateral position during pregnancy. *Upper panel,* pregnant; *lower panel,* nonpregnant. (Modified from Camann WR, Ostheimer GW. Physiological adaptations during pregnancy. *Int Anesthesiol Clin.* 1990;28:2–10.)

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.[260–262] The dose of hyperbaric local anesthetic required in term pregnant women is 25% lower than that in nonpregnant women.[263,264] This is attributed to the following factors: (1) reduction of spinal CSF volume, which accompanies distention of the vertebral venous plexus[42]; (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[265]; 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).[266] Spinal dose requirements change rapidly in the postpartum period, with segmental dose requirements returning to those of nonpregnant women within 24 to 48 hours[267] 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.[268,269]

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.[270]

Hypotension during Neuraxial Analgesia and Anesthesia

Pregnancy increases dependence on the sympathetic nervous system for the maintenance of venous return and systemic vascular resistance.[231] This, together with the effects of aortocaval 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.[271–273]

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 Pao_2 during periods of apnea.
- Pregnant women are at increased risk for failed tracheal intubation.
- Pregnant women are less responsive to vasopressors than nonpregnant women.

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