OPERATIVE OBSTETRICS

SECOND EDITION

Edited by

JOHN PATRICK O'GRADY
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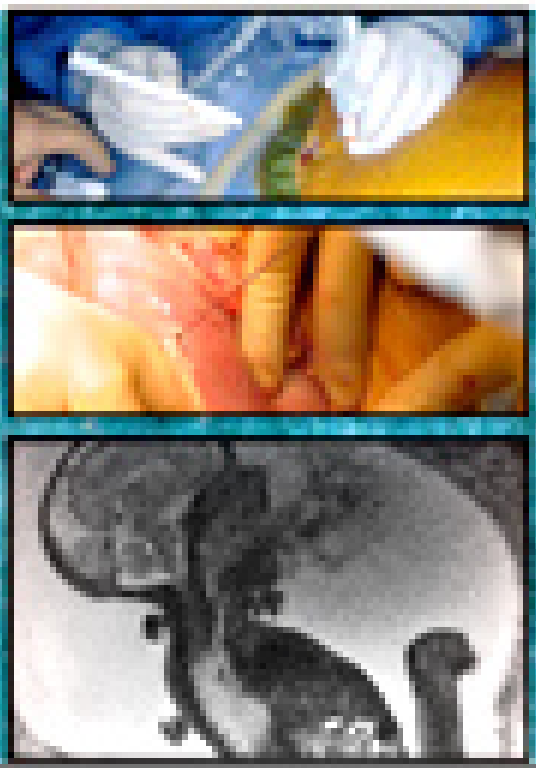

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Operative Obstetrics

Second Edition

Major changes in obstetric practice have occurred in the ten years since the publication of the first edition of *Operative Obstetrics*. Prospective clinical studies have improved clinical practice, and better techniques for antenatal fetal evaluation have been introduced. Yet, there are also less desirable trends. There has been a relentless increase in the rate of cesarean delivery, and persisting medicolegal and societal pressures continue to demand faultless performance. Our recognition of recent improvements in clinical practice and acknowledgement of the continuing challenges and limitations inherent in modern clinical management have prompted a new edition. This updated edition includes chapters on the important subjects of cesarean delivery, common surgical complications, ectopic pregnancy, birth injury, and instrumental delivery, among other topics. It features a new discussion of surgical procedures performed by non-physicians and a review of fetal surgery. The text also considers complicated and controversial subjects such as cervical insufficiency, pregnancy termination, and shoulder dystocia. In recognition of the realities of current practice, each of the four sections of the book has a chapter with an in-depth analysis of the legal issues underlying practice. An expanded appendix reviews general legal concepts pertinent to the practice of obstetrics.

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To JO: His son finally did become a surgeon. And to Molly for support and encouragement.

JPOG

For my family, Herakliusz, Stefania, Alexandria, and Madeline, for their patience and support during this endeavor.

LBZ

To Arlene, Alexis, and Matt. For your love and support.

MLG

To Marge and Bill, who sacrificed so much on my road to becoming an attorney.

KG

S

Looking back over a long clinical lifetime, one tends to forget or take for granted one's successes; it is the failures which stand out like keloid scars, never to be forgotten and, hopefully, a warning to others. I have to recognise that if there is any classic mistake which I have not myself made it is simply because of the lack of time in which to commit it. It makes one wondrously sympathetic toward others in trouble. No apology is therefore made for the highly personal emphasis in this book.

Ian Donald (1910–1987)

Practical Obstetric Problems

London: Lloyd-Luke, 1979, p. viii.

Note to Readers

The advancement of medical science brings continuous changes in management, methods of diagnosis and evaluation, and drug therapy.

The editors of and contributors to *Operative Obstetrics* Second Edition, have closely reviewed the information included in this textbook, consulted appropriate literature, and conferred with experienced clinicians in the effort to provide accurate information and practice recommendations in accordance with the generally accepted standards of medical practice. The reader is cautioned, however, that owing to the rapid changes in the science of medicine and the possibility of human error, the authors of the various chapters, the editors, and the publisher cannot guarantee that all information included in this text is in every respect complete or accurate. We do not accept responsibility for errors, omissions, or results obtained from the use of these data. For these reasons, the reader is encouraged to confirm our practice suggestions with other standard sources. Relying on his or her experience, education, and unique knowledge of the individual patient, the attending physician or certified nurse midwife must determine the best treatment for a specific obstetric condition.

Recommended drugs and dosing schedules for various medical conditions do appear in this text. Before a drug is administered, however, clinicians should review standard compendia of drug information and package inserts for any changes in drug use or additional warnings of potential adverse reactions or other precautions. To ensure patient safety, caution is especially necessary when the drug in question is new to the practitioner, infrequently administered, or has the potential for serious side effects.

– The Editors

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Foreword

THE PROCESS OF EVOLUTION affects not only the characteristics of a species but also the adaptive technology between a species and its environment. The practice of obstetrics is devoted to maximizing the ability of each human being to confront the environment and to be part of the creative, modulating path of evolution. It is almost, if not totally, impossible to discern evolutionary human changes within our own lifetimes; however, it is a different story with the technology of our interactions. Obstetrics has changed, and it has changed rapidly.

If the earth's lifetime were compressed into a single 24-hour day, humans would have appeared only 30 seconds ago. I cannot imagine what nanocalculation would be required to measure the history of operative obstetrics, yet that incredibly short measure of geologic time is packed with a geometrically increasing collection of events and stories. The interesting and comprehensive chapter on the history of operative delivery alone is worth the price of this book. Every contemporary obstetrician should know and learn from the history of obstetrics. Some might argue that this history is truly the past, and that operative obstetrics today is a matter of a few simple choices. Even that judgment, however, must be based on a critical analysis of the operative choices. Only then can the individual obstetrician understand the reasons behind modern decisions.

The modern focus on "evidence-based medicine" all too often fails to recognize the broad base of knowledge that is the foundation of clinical decision making. This book is an excellent example of the fact that medical knowledge is more than what we read in the literature. Although medicine tests the worth of specific procedures with appropriately designed clinical studies, physicians also learn from each and every clinical experience and modify their decisions according to an understanding of the individual patient's needs. Nowhere is this more important than in operative procedures. The authors of this book have solidified their recommendations with a comprehensive survey of the literature, but they have filtered this knowledge through the valuable experiences of multiple clinicians, finally offering clinical advice that is meaningful and useful.

Obstetric decisions today are not simpler. They are actually more complex, requiring an ever-expanding knowledge base. This book provides a knowledge base of operative obstetrics derived from the accomplishments of the past and the experiences of the present. In so doing, it serves an important purpose: to assist obstetricians in achieving the objective of a successful pregnancy and a healthy newborn.

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Preface

Obstetrics is not one of the exact sciences, and, in our penury of truth we ought to be accurate in our statements, generous in our doubts, tolerant in our convictions.

James Young Simpson (1811–1870)

MUCH TO OUR SURPRISE, more than ten years have passed since the publication of the first edition of *Operative Obstetrics*. Since the initial text appeared in 1995, new tests, surgical procedures, and novel methods of medical education have been introduced to the practice of obstetrics. In addition, there has been an expansion of roles for nonphysician personnel in the provision of care to pregnant women. There remain important unresolved controversies in the specialty, including elective or patient-choice cesarean delivery, trials of vaginal birth after cesarean, patient safety during hospitalization, pregnancy termination, and the recruitment and training of new practitioners, to list only a few. The influx of new ideas and the development of new techniques over the last decade have accompanied increasing demands by institutions, third-party payers, and governmental agencies for evidence-based, cost-efficient, and safe practice. Clinicians are thus pressured from many directions to rapidly incorporate new scientific advances into their management, rethink traditional concepts of best practice, follow increasingly restrictive protocols and practice guidelines, and even revisit basic ethical concepts. Because of the unresolved issues concerning appropriate practice and the risks associated with adverse outcomes, it is inevitable that medicolegal risks in obstetrics remain high and that increasingly few clinicians, with a decade or more of active practice, now escape litigation.

The stated goal of all recent textbooks is to define best practice by employing the techniques of evidence-based medicine. In fact, there is now a growing body of evidence-based data concerning obstetric practice, much to the improvement of the specialty; however, many areas of management have never been subjected to such systemic study. Experienced practitioners rapidly discover that there are obstetric and surgical practices and clinical problems that have not proved amenable to the rigid demands of evidence-based analysis. These observations emphasize the limitations of current methodologies and serve as a constant reminder of the incompleteness of physicians' knowledge and the need for continuous improvement through appropriately designed prospective studies.

This new edition required the amalgamation of data derived from quite different sources. Working with the editors, our many collaborators have strived to reconcile current scientific knowledge and data from evidence-based clinical studies with the rich heritage available from the past. Philosophically, the editors remain unrepentant advocates of combining essential elements of the art of traditional obstetrics and the accumulated experience of our predecessors with new concepts and methods of management derived from meta-analysis and other prospective and randomized clinical investigations. Reflecting the realities of modern practice, this new edition includes legal commentaries on areas of

special concerns, with recommendations for appropriate actions to help to avoid difficulty.

It is the editors' earnest anticipation that this new edition of *Operative Obstetrics* fulfills the demanding requirements of clinicians struggling with the many pressures of contemporary practice. Our aim is both to challenge and instruct our readers. The success of this endeavor will be measured by the extent to which we have constructively critiqued established ideas, fused the traditionally accepted with the scientifically proved aspects of practice, and sustained the reader's interest. Our measure of success is simple. If this textbook proves helpful in the management of a single case, our original expectations will be met, and we will consider our intense labors and those of our coworkers to have been amply rewarded.

John P. O'Grady
Martin L. Gimovsky
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Part I

ANTEPARTUM

Chapter 1 A HISTORY: OPERATIVE DELIVERY

John P. O'Grady

Norwithstanding that I would use all my Endeavours to deter Men from the rash and imprudent Practice of instrumental Operations in Midwifery; yet it is not to be denied, but that such Operations are very useful and necessary, when undertaken with Caution, Skill and Prudence;. . .

Fielding Ould (1710–1789)
A Treatise of Midwifery in Three Parts
Dublin: O. Nelson & C. Connor,
1742: 111, pg 142.

Prolonged or obstructed labor, undeliverable fetal positions, maternal hemorrhage from retained products of conception, delivery of the second of twins, and the problematic extraction of large infants are among the recurring problems in human labor and delivery that do not resolve without intervention. Assistive techniques to manage these and other complications of human parturition are rooted deep in antiquity. Over many years, various manipulations and specialized instruments were developed to expedite delivery of viable infants or to remove the fetus and the other products of conception from the uterus in case of fetal demise or incomplete delivery. A brief historical review of the origins of operative delivery techniques increases the appreciation of modern practitioners for the complex roots of the science and art that have led to modern practice.

THE HISTORY OF CESAREAN DELIVERY

Myth and Legend

Reports of the surgical removal of the fetus from the mother are common in history and legend. Such tales figure in the origin myths for important personalities from many cultures. For example, Brahma is described as emerging from his mother's umbilicus, and in 5636 B.C.E., Buddha is reported to have been delivered from his mother Maya's right flank [1]. Tall tales of preternatural or miraculous births are also common in our western Greco-Roman cultural heritage. Classic Greek mythology includes several descriptions of what could be termed cesarean deliveries of various gods, demigods, and mortals [2]. A representative example is the case of the inconstant princess Coronis. Upon receiving proof of her infidelity with another male suitor, her enraged paramour Apollo (Phoebus Apollo), god of prophecy, music, and archery, dispatched her with an arrow. In some versions of

this tale it is Apollo's twin sister, Artemis (Diana), daughter of Zeus and Leto, who was responsible for this murderous archery. In any event, Apollo next placed the body of the newly dead Coronis on a funeral pyre. As the flames leaped up, Apollo's rage rapidly changed to consternation for the fate of his unborn child. At Apollo's urgent request, Hermes (Mercury), the messenger of the gods and the patron of heralds, thieves, travelers, and merchants, intervened, and the infant was delivered from his mother's body by means of an abdominal incision. This child, who was the product of this unique perimortem delivery, was subsequently tutored in the healing arts by Chiron the centaur, son of Coronos and the nymph Philyra, and eventually became the most famous physician of antiquity, Asclepius. This tale has an ending that should serve as a warning to overly ambitious physicians. In his later life, Asclepius developed his medical abilities to the point where he could resurrect the dead. For his presumption in using his medical talents to thwart the will of the gods, Zeus killed him with a thunderbolt!

In another setting, Zeus prematurely delivered Dionysus (Bacchus), god of wine and ecstasy, from the abdomen of the dying Semele, the daughter of Cadmus and Harmonia. Zeus had actually fathered this child. Unfortunately, complications with the pregnancy led to disaster. In the sixth month of the pregnancy, malevolent advice was given to the young woman by the jealous Hera, Zeus's wife, who was masquerading as Semele's elderly nurse, Beroe. Under this influence, Semele refused Zeus her bed unless he would come to her in his true form. Zeus, trapped by her request, resumed his accustomed form as a thunderbolt, a dramatic process that proved fatal to the hapless Semele. Through the intervention of the ever-present Hermes, however, the unborn and premature Dionysis was removed from Semele's womb, sewn into the thigh of Zeus, and, through this unusual mechanism, carried to maturity as a bizarre type of ectopic pregnancy [3].

There are other unusual tales of obstetric interventions in Greek and Roman mythology. Adonis, famous for his great beauty, was born of his mother, Myrrha of Smyrna, after her transformation into a tree. Myrrha had conceived following an incestuous relationship with her father, Cinyras. Cinyras was a Cypriot king and originally one of the lesser suitors to Helen before her abduction and the beginning of the Trojan War. This unusual relationship between father and daughter developed because of the enmity of Aphrodite, the goddess of love, who punished the unfortunate Myrrha because of her lack of devotion [2]. Aphrodite's intervention caused the poor Myrrha to fall in love with her own father. Under what proved to be a maleficient influence, Myrrha developed a subterfuge whereby she shared Cinyras' bed without his recognizing her. The god's punishment for Adonis's mother was her transformation into a myrrh tree, thus arresting her father's unacceptable advances. Her father's eventual fate was also severe. When he discovered that he had been tricked into impregnating his own daughter, Cinyras committed suicide.

In terms of drama, myth, and legend, classic theater also contains many stories of unusual births. Perhaps the most famous occurs in the denouement of the play *Macbeth*. Shakespeare's protagonist Macduff is free from mortal risk from Macbeth, because Macduff was "from his mother's womb untimely ripp'd . . . . " [4] As he was not of woman born, Macduff fulfilled the prophecy of the witches and thus successfully defeated the regicidal Macbeth. This tale of ambition, greed, murder, and operative delivery has a long pedigree, with its origin well before the sixteenth century. Shakespeare had obtained the material for his tragedy from an earlier text, the *Chronicles of Holinshead*. From this reference, further sources for this Scottish tale can be traced to another text, *Scotorum*, *Historiae of Boece* (Paris, 1526); it can further be followed to a manuscript originally published in 1385! Doubtless, its roots are even earlier than the fourteenth century, in now lost sources.

History also includes many reports of unusual cesarean deliveries involving actural individuals. There are several well-documented cases in which women delivered themselves by conducting their own surgeries. Many if not most of these abdominal surgical deliveries would in current terminology be described as cesareans. Authentic reports from rural settings also describe traumatic deliveries when milkmaids were gored by cattle, the earliest dating back to 1647. In some of these latter cases, the mother, the infant, or both apparently survived [1].

Derivation of Terms *Cesarean* and *Section*

In common parlance transabdominal surgical deliveries are termed *cesareans*. How this nomenclature

came to be employed for abdominal surgical delivery is a long and complex tale. The derivation of the term *cesarean* has been ascribed to several sources. Ancient historians, including Pliny the Elder are largely responsible for the widely believed myth that a Roman emperor or Caesar – either Scipio Africanus (237–183 B.C.E.) or more commonly, the most famous emperor, Gaius Julius Caesar (102?–44 B.C.E.) – was delivered from his mother via an abdominal incision. Unfortunately, it is unlikely that these historical figures or many of the other famous persons reputed to have been delivered by a surgical procedure were actually born in that manner. In reference to the historical Roman Emperor Gaius Julius Caesar, it is virtually certain he was *not* delivered surgically from his mother, since the term *cesarean* predates him by centuries. Furthermore, published letters of Julius Caesar indicate that he corresponded with his mother, Aurelia, while he was in Gaul. Finally, Aurelia is known to have lived until 54 B.C.E., when Caesar, who was then more than 40 years old, attended her funeral [5]. Her long-term survival after an unsterile abdominal surgery in the first century is distinctly improbable. The reports by Pliny and other classical writers of successful abdominal delivery of culturally important people such as the historical Emperor Julius Caesar lack historical support and are best viewed as political fables.

There are various interpretations but no clear evidence to explain how the family of Gaius Julius Caesar received the cognomen *caesar* and how this family name at some point became associated with a surgical procedure. The name of Caesar might derive from several literary sources, such as from the Latin *caedere/caedo*, meaning "to cut, fall, or kill; to cut down or to strike mortally as in conflict," [6] possibly reflecting a traumatic or surgical delivery sometime in the family's past [7]. It is also possible that a legend of an abdominal delivery became associated with the family name simply as an honor. Preternatural births were thought to confer on the child certain special virtues, powers, or abilities – exactly what might be expected of a world leader such as an emperor. After all, the Julian family was noble and from a patrician clan. Caesar's father, once the governor of Asia, had served as praetor, the second most important post after counsul [8].

Another possible origin of the term *cesarean* derives from legal responses to the problem of peri- or postmortem delivery. The first law relating to postmortem delivery is reputed to have been promulgated by the quasi-legendary king of Rome, Numa Pompilius (715–673 B.C.E.), and termed the *lex regia* (and subsequently *lex caesarea*) [1]. This edict concerned the abdominal delivery of a child during an acute life-saving effort in the unusual circumstance of a dying or recently dead mother. The statute was a type of Good Samaritan law, requiring delivery of the unborn child from its mother and forbidding the burial of the dead woman until this was accomplished. The law also protected the person who performed such a perimortem procedure from an accusation of murder or manslaughter, assuming that the amateur surgeon acted in good faith.

Some English words with specialized meaning have their origin in the Latin roots that originally gave us the term *cesarean*. In musical notation, a *caesura* is a set of closely approximated parallel lines in the score that mark a sudden stop, or cut, in the course of the program. This term is also used to indicate an interruption, break, or pause between words within a metrical foot in poetry, or in the middle of a line of text. In a social/political context, both the titles of *Kaiser* and *Tsar* (C*zar*) have their origin in the original Latin C*aesar*. In English, both Kaiser and Tsar either describe an authority figure, usually a tyrannical one, or are used in their historical sense as the traditional titles for a Holy Roman, Austrian-German, or Russian Emperor, respectively.

Whatever the origin of the term, by the mid-sixteenth century, the term *cesarean* was used to describe abdominal surgical deliveries in medical literature. One of the earliest commentators or medical editors to refer to the abdominal delivery of an infant as a cesarean was Richard Jonas, who translated, edited, and expanded one of the many editions of the obstetric textbook usually termed the *Roszgarten*, which was originally authored by Eucharius Rösslin of Frankfurt-am-Main (discussed later in this chapter). First published in 1540 in its English editions as *The Byrth of Mankynde*, this text was thereafter frequently reprinted. In one of these reprintings, Jonas commented in reference to abdominal delivery "...that are borne after this fashion be called cesares, for because they be cut of theyr mothers belly, whervpon also the noble Romane cesar...of that name in Rome toke his name..." [9].

The second part of the usual term for obstetric abdominal surgery, *section*, probably has its origin in the Latin verb *secare/seco*, meaning "to light, strike, or reach," or "to cut into, separate, divide, or part" [10]. Another possibility is *incidere/incido*, meaning "to fall or on, happen, or occur" [6,10].

At some indeterminate time in the past, the terms used to describe the surgical operation for abdominal delivery, *cesarean* and *section*, became inextricably linked. Over time, however, the terms used to describe the surgery for abdominal deliveries have changed. In modern times, such surgical delivery of the fetus was referred to as a c*esarean operation* until the early twentieth century, when the term *cesarean section* became popular [1]. Currently, the term *cesarean birth* is frequently used in both lay and professional literature. Because of the redundancy inherent in the term *cesarean section*, we prefer to describe the surgical operation for the abdomen delivery of a child as a *cesarean delivery*, a *cesearean operation*, or simply as a *cesarean*. These conventions are used in the current text.

Cesarean Delivery in the Historical Record

Beyond the mythology of the origins of the cesarean-related terms is also a long historical record of successful and not-so-successful abdominal deliveries. The oldest reliably recorded operations date back to the Sumerians in the second millennium B.C.E. More than 1,000 years later, Gorgias (483–375 B.C.E.), a famous orator from Sicily, is reputed to have been delivered by a cesarean Records from as early as the second century C.E. report the operation several times, and in early Jewish literature Maimonides (1135–1204) mentioned cesarean surgery and commented on technique. It was not until the seventeenth century, however, that thoroughly documented cesarean deliveries are known to have been performed on living women with occasional maternal or fetal survivals. Many of the earlier reports are incomplete, wildly improbable, or so warped and embellished by multiple retellings that they remain suspect.

Commentary concerning cesarean delivery appears early in obstetric literature; however, many of the classic medical authors fail entirely to mention the procedure, attesting to its rarity. As an example, Soranus of Ephesus (98–138 C.E.) does not include cesarean operations in his review of surgical procedures. Sonanus did describe the management of obstetric malpresentation by version and extraction but did not mention the use of instruments or abnormal surgery for delivery. Aurelius Cornelius Celsus (27 B.C.E.–50 C.E.) in his book *De Re Medica* (c. 30 C.E.) is also silent on abdominal delivery yet provided instructions for the extraction of dead infants by the use of a hook or crochet. Cesareans are also not a part of the corpus of Hippocratic writings. Eucharius Rösslin the Elder's (also Roeslin, Roesslyn, or Rhodion) important, early obstetric textbook *Der Swangern Frawen und Hebammen Rosegarten*, published in Strassburg in 1513 and widely known as *The Roszgarten* (also *Roszgarten* or *Rosengarten*) does not mention the cesarean operation. As earlier noted, however, one of the many later editors or revisers of this book, Richard Jonas, did make such a reference in a commentary included in one of the many subsequent English language reprintings of this remarkably long-lived textbook.

There are various reports of cesarean deliveries from numerous sources before the seventeenth century. Unfortunately, most simply document the danger of the procedure and the extreme risk to the mother's life. In Sweden, a postmortem cesarean operation was first recorded in 1360. Scipio Mercurio (1550–1616?), a surgeon of Padua, claimed several successful cesarean operations in his textbook *La Commare o Riccoglitrice*, published in 1596. In 1578, Giulio Cesari Aranzio (1530–1589) reported a successful postmortem cesarean delivery on a mother who had died late in the third trimester. Jacques Guillemeau (1544–1612) was surgeon to Henry and a student of the noted barber-surgeon Ambroise Paré (1510–1590). Guillemeau included a chapter on cesarean delivery in an obstetric text that was later translated into English by Thomas Hatfield in 1612 and entitled C*hildbirth or, The Happie Deliverie of Women* [11]. Guillemeau stated that he had seen the operation carried out by various surgeons on a total of five women, all of whom had died. In his discussion of the procedure in this book, Guillemeau was among the first to introduce the word *section* into the medical literature.

The most controversial of the early reports of successful operative deliveries is that involving Jacob Nufer, a sow-gelder who is reputed to have performed a successful cesarean on his own wife circa 1500. The Jacob Nufer story was first related by Caspar Bauhin (1550–1624), more than 80 years after

the supposed event, in the appendix and commentary to Bauhin's Latin translation of a text entitled *Traité Nouveau de l'hysterotomokie ou l'enfantement Caesarienne* printed in Paris in 1581 and originally authored by François Rousset (1535–1590?), physician to the Duke of Savoy [12]. Rousset, although not himself a surgeon, recounted cases of cesarean deliveries performed by others and claimed to have been an observer in still more, including several with maternal and fetal survivals. He argued that a cesarean was not only "a feasible operation" but also could preserve the lives of both mother and infant. As the title of his text reflects, Rousset termed the procedure a *cesarean delivery* or "enfantement Caesarienne" presumably in homage to the legend involving the birth of Julius Caesar [13]. The Nufer story was retold as late as the mid-eighteenth century by the reviewer and critic John Burton (1710–1771) in his textbook of obstetrics, *An Essay towards a Compleate New System of Midwifry*, published in 1751 [14].

As the Nufer tale is usually related, both lithotomists and midwives were called in consultation when the labor of Nufer's wife was obstructed. None of these attendants was able to bring the child forth, however. In desperation, Nufer himself performed a surgical delivery. His wife is supposed to have not only survived the operation but also later to have delivered other children vaginally. Although this entire story is suspect, it might contain a kernel of hidden truth. Because of the nature of his work in animal husbandry, Nufer would have had rough surgical and birthing experience. Such people with a functional knowledge of delivery mechanics were occasionally called on in the sixteenth century to help manage obstructed human labors. This might explain his active involvement in his wife's confinement. But, can the rest of this remarkable story be believed? Perhaps what Nufer's wife had was an advanced abdominal pregnancy. This could explain both her survival following an unsterile laparatomy and her subsequent unimpaired fertility. What actually happened in that Swiss hamlet in 1500, and the degree to which the Nufer story has been embellished and distorted over time, cannot now be determined as no new information is likely to be forthcoming.

In 1610, a physician in Wittenberg, Jeremias Trautmann, conducted the earliest well-documented cesarean delivery [15]. Although a surgery is known to have been performed and a child delivered, the clinical details remain confusing. It is possible that what Trautmann actually found was an anterior uterine sacculation or an abdominal pregnancy. In other accounts the pregnancy was normal and the reason for surgery was a large ventral hernia that precluded normal labor. In fact, whether a pregnancy was even diagnosed before the operation is uncertain, and the infant might have been an unexpected discovery during a surgical exploration to relieve acute abdominal symptoms. In any event, an abdominal procedure was conducted, a child was delivered and is presumed to have survived although the extant records are at best incomplete. Unfortunately, the mother died some 25 days after the original operation, presumably from infection.

From the inception of the operation, controversy concerning the propriety of cesarean delivery has characterized the medical literature. It was recognized very early that postmortem operations on mothers dying in labor or late in pregnancy would rarely result in a normal and surviving child. Owing to the state of development of surgical technique, a cesarean was a virtual death sentence for both mother and infant until the early nineteenth century. To operate on a living woman was thus shunned, owing to the profound maternal risk from surgery and the uncertainty of success in salvaging a living infant. When labor was obstructed, version and extraction, fetal destructive procedures, and later symphysiotomy were the accepted methods for delivery. Whereas the mother often survived these obstetric manipulations and destructive procedures for vaginal delivery, in almost all cases the infant did not.

With this background, including horrific reports in the literature and their own experience with disastrous cesarean results, most of the influential obstetric educators of the sixteenth and seventeenth centuries, including Ambroise Paré (1510–1590), Jacques Guillemeau (1550–1630), Pierre Dionis (1643?–1718), and François Mauriceau (1637–1709), advised strongly against performing a cesarean operation on living women. Mauriceau, the most celebrated obstetrician of the late seventeenth century, discussed known obstetric procedures in his textbooks, *Traité Les Maladies des Femmes Grosses, et Accouchées* (Figure 1.1) [16] and *Observations Sur la Grossesse et l'Accouchement des Femmes, et sur Leurs Maladies, &; celles des Enfans Nouveau – Nez* [17].

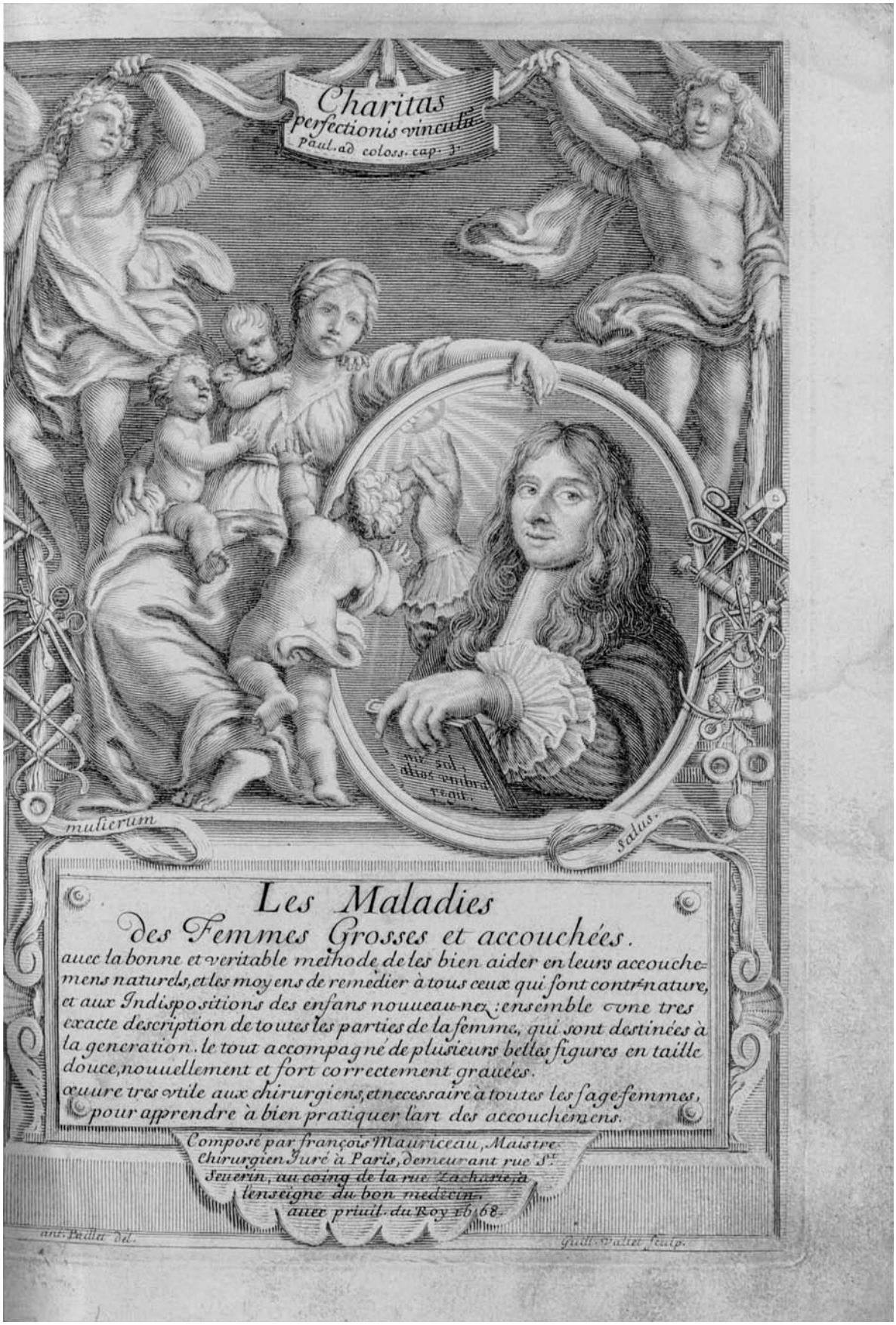

FIGURE 1.1.
Title page of the* Traité *of François Mauriçeau (c. 1668).

Mauriceau argued that only postmortem cesareans should be performed. He was well experienced in serious obstetric complications and knew firsthand of the limitations imposed by the inability of physicians to conduct abdominal deliveries. His own sister had experienced a serious antepartum hemorrhage from a placenta previa. When her attendants recoiled from intervention, Mauriceau had delivered her himself by version and extraction. Unfortunately, she did not survive this procedure [18].

In contrast, some early medical authors did support cesarean delivery. Jean-Louis Baudelocque (1746–1810) and André Levret (1703–1780) advocated cesareans for a contracted pelvis, in preference to the usual procedures of embryotomy, decapitation, or cranial decompression. The maternal and fetal results of most early cesarean operations were disastrous, however, reinforcing the argument for those who opposed such surgeries. According to Baskett [11], on one occasion, the noted French accoucheur Baudelocque was forced to defend himself in court when a contemporary called him an assassin because of Baudelocque's favorable opinions concerning cesarean delivery!

Cesarean deliveries were sporadically reported in the medical literature from the eighteenth through the mid-nineteenth century with generally poor results and often the loss of both mother and infant. In the early to mid-1700s cesarean deliveries were performed in Paris at a rate of approximately 1 per 4000 births. Unfortunately, the associated maternal mortality was 70% to 80%! A few successful abdominal deliveries did occur outside of the French capital between 1760 and 1814, however [19]. There were similarly grim statistics from the British Isles. There was not a cesarean delivery with documented maternal survival in Ireland until 1738, when a midwife, Mary Donally, operated on a 33-year-old multipara. In this case, Donally made a right paraumbilical incision with a razor; the incision subsequently closed with a tailor's needle and silk thread. The patient survived but later developed a ventral hernia. A cesarean delivery following a 6-day obstructed labor is also known to have occurred in England in 1737, but neither mother nor infant survived. In fact, a cesarean operation in England in which the mother is known to have survived did not occur until 1793 when the first case was reported. The mother in this instance had been in labor for three days when a surgeon, James Barlow delivered a dead child through a left paramedian incision [1]. From the same era there is an incompletely documented report of a successful cesarean delivery from America. Dr. Jesse Bennett (1769–1842) is supposed to have performed the procedure on his own wife in 1794 in Staunton, Virginia, following an unsuccessful effort at vaginal instrumental delivery. The details of this case are sketchy, and the documentation is poor. Thus, this claim is not generally considered credible. The first well-documented American report dates from 1827, when Dr. J. Cambert Richmond (1785–1855) performed an operation on a nulliparous eclamptic woman. Although the mother survived, the infant did not [20]. Another cesarean with maternal survival was performed before 1821 (exact date unknown) by the physician and surgeon James Miranda Barry in South Africa. Barry holds the unique distinction of being both an Edinburgh graduate and a woman who successfully masqueraded as a man from 1809 until her death in 1865 [18]. Africa is also the source for a report of another successful cesarean delivery performed by an unknown indigenous surgeon. In 1879, R. W. Felkin, a Scottish medical traveler in what later became Uganda in East Africa, witnessed and later published his observations concerning a cesarean delivery [21]. Preoperatively the surgeon cleansed his hands and the mother's abdomen with banana wine. The same fluid was administered orally to the mother before the surgery began, presumably to induce a degree of insensibility. After the delivery, which the surgeon performed through a midline incision, the uterus was not sutured. The abdominal incision was pinned together with iron needles and then secured by a bark-cloth string. Bleeding was controlled by cautery. Felkin claimed that the woman made a full recovery and noted the apparent expertise of the surgeon, concluding that the procedure was well established in that part of Africa.

In the late eighteenth century and into the early years of the nineteenth century, because of the serious risks of surgery, symphysiotomy vied with cesarean delivery as the best procedure for obstructed delivery. Intentional incision of the pubic symphysis was introduced to medical practice in 1768, when Jean René Sigault (1740–18??) described the technique in a single case [1,11,25]. Sigault successfully delivered a multiparous woman (a Madam Souchot), whose first child was lost owing

to an obstructed labor and a fetal demise, eventually terminated by an embryotomy. Her other deliveries had been equally unfortunate, resulting in stillbirths. For his efforts, Sigault received both a medal from the Facility of Medicine in Paris, and a government pension. A medal was given to his assistant, Alphonse LeRoy (1742–1816), and to complete the awards, a pension was provided for the patient, who, despite a rocky postpartum course, including abscesses and a vesicovaginal fistula, survived! Despite such occasional successes, because of the manner in which symphysiotomy was performed, maternal morbidity and mortality were high. For these reasons, the procedure soon fell into disfavor and was not revived until the twentieth century. Symphysiotomy is still occasionally performed in parts of the nonindustrialized world as an alternative to a cesarean [23,24].

Prior to the late nineteenth century, several serious technical problems precluded safe cesarean deliveries. First, the operation was viewed as the last resort. It therefore usually was not performed until after prolonged labor, multiple examinations, manipulations, and various unsuccessful efforts at vaginal instrumental delivery. Inevitably, many of these women were exhausted and dehydrated, and most were infected. Surgical procedures at that time were also primitive. Before the invention of inhalation anesthesia in the late 1840s, surgery needed to be rapid. Only laudanum and alcohol were available as analgesic agents and the patient had to be actively restrained during the procedure. Furthermore, nothing was known concerning aseptic methods of surgery, ensuring a serious risk of infection. In the usual technique, the maternal abdomen was opened by a vertical incision, lateral to the rectus muscle. Attendants restrained the mother and, once the abdomen was entered, endeavored to hold back the intestines with their hands. The uterus was incised vertically and the child removed. Usually, the uterine wound was specifically not sutured because sutures were believed to predispose to complications, but the edges of the abdominal wound were usually reapproximated. Because of the timing of the operation, the absence of aseptic technique, and the failure to close the uterus, mothers usually rapidly died of hemorrhage or, if they lingered for several days, of peritonitis.

Progress was slow. The first reported instance of the successful use of uterine sutures at a cesarean was by the surgeon Jean LeBas (1717–1787). In a 1769 delivery, he applied silk thread sutures to a uterine incision to stop hemorrhage. The patient subsequently recovered. Inevitably, LeBas was heavily criticized by his contemporaries. After LeBas' report, several attempts at routine uterine suturing occurred in individual cases, usually with disastrous results [11].

From our vantage point, it is hard to understand why suturing of the uterine wound during a cesarean was considered inappropriate until almost the beginning of the twentieth century. This practice followed then-contemporary clinical experience and well-established surgical technique, however. A common reason given for not suturing the uterus routinely after a cesarean was the belief that rapid uterine involution would inevitably loosen any stitches, rendering them ineffective. Another problem was infection. In the eighteenth and well into the nineteenth century, sutures placed by a surgeon were routinely left long, protruding from the wound. This was believed necessary to facilitate drainage and to provide access for the eventual removal of the sutures, which usually were not absorbable and, of course, not sterile. Conventional wisdom and clinical observation held that deeply placed sutures invariably became infected, leading to abscess, cellulitis, or sepsis. A wound left open, with the suture ends exiting the skin, would eventually begin to develop what was termed laudable pus, however. With time, progressive tissue necrosis would eventually release the sutures. The usual practice was that several days after the surgery the surgeon would begin intermittently to pull gently on the suture ends. This process was subsequently repeated once or twice daily until local necrosis was sufficient to permit the extraction of the sutures without eliciting a hemorrhage. For patients who survived to the point of suture removal, eventual recovery was likely. After suture removal, the wound would slowly heal by secondary intention. Once the process of granulation was well advanced such wounds were quite resistant to infection and unlikely to lead to cellulitis or sepsis. Unfortunately, when such standard surgical techniques were used in cesarean deliveries, hemorrhage and infection were routine, with serious and usually fatal consequences for the mother.

When uterine reapproximation was finally introduced, silver wire became the initial suture material of choice, mirroring its use in nineteenth century

gynecology. Frank E. Polin of Springfield, Kentucky, first reported the use of silver wire in the closure of a uterine wound in 1852. Other than silver wire, many other types of suture were in use, derived from a wide range of materials including silk, carbolized gut, horsehair, and even hemp. What would now be considered as appropriate uterine approximation with nonpermanent suture materials was not introduced until the early 1880s.

Many important surgical innovations begun in the mid-nineteenth century eventually made safe cesarean deliveries possible. Ether was first used during labor in Boston in 1847 and subsequently popularized by the socially prominent New England obstetrician Walter Channing (1786–1876). The anesthetic properties of chloroform were discovered by James Young Simpson (1811–1870) and first employed by him in deliveries in Edinburgh beginning in 1847 [11].

A major breakthrough in the technique of cesarean surgery occurred in the early 1880s. Max Sänger (1853–1903), then an assistant to Carl Siegmund Franz Credé (1819–1892) in Leipzig, introduced an operative procedure in 1882 that is now considered the classic cesarean operation. In doing so, Sänger revolutionized standard cesarean surgical technique [26]. In a general review for a monograph concerning the cesarean operation, Sänger had collected published case reports of prior deliveries that he carefully reviewed and critiqued. Based on these data from the literature and his own experience, Sänger argued that operative complications from cesareans would occur less frequently if the myometrium were closed and a concerted effort made to avoid the spillage of intrauterine secretions into the peritoneal cavity [26]. His procedure featured a meticulous, water-tight reapproximation of the uterine wound, employing buried sutures. Sänger also exteriorized the uterus before delivering the infant and attempted to improve postoperative drainage by passing a drain from the fundus out through the cervix.

Although maternal morbidity and mortality from cesarean deliveries remained high even with Sänger's improvements, statistics were substantially better with his technique than the levels previously experienced. It was only after Sänger's 1882 paper that closure of the uterus was finally recognized as both a feasible and necessary part of cesarean technique [1].

Horatio R. Storer, of Boston, Masschusetts, first performed a cesarean hysterectomy in 1868, on a woman with a large leiomyoma that obstructed the birth canal. He removed the uterine corpus and adnexa during this procedure. The child was stillborn and "in an advanced state of decomposition." The mother died three days later. The first maternal survivor following cesarean hysterectomy occurred in 1876, when a woman with rickets and pelvic contracture was delivered by Eduardo Porro (1842–1901) [1,27]. What later was termed the *Porro operation* was a unique surgical procedure originally suggested by the Florentine surgeon Joseph Cavallini in 1768. Cavallini and later Porro had experimented with pregnant hysterectomy in animal models. Cavallini had operated on dogs and sheep; Porro had used rabbits. Each had proved to his satisfaction that the uterus was not necessary for life and that its surgical removal was technically possible.

In early 1876, Porro encountered a 25-year-old nullipara with a rachitic pelvis and a true conjugate of 4 cm or less, precluding vaginal delivery. Following careful consideration and preparations, including preliminary handwashing with carbolic acid, Porro performed a classic cesarean delivery by means of a midline abdominal incision, with the patient under chloroform anesthesia. After delivery of the baby, an iron-wire snare was passed around the uterus, tubes, and ovaries. All these structures were then amputated and the remaining cervical stump was bought out of the abdomen through the lower end of the midline incision. Drainage tubes were inserted and the abdominal wall was then closed around the residual stump with silver-wire sutures. The snare was removed on the fourth day and the sutures on the seventh. The exterialized cervical stump and lower portion of the abdominal wound were then permitted to heal by secondary intention. Six weeks later, the woman left the hospital with her infant. Remarkably, she was the first to survive a cesarean delivery performed at that clinic!

The Porro operation rapidly gained acceptance in Europe because it radically solved the problems of both hemorrhage and infection. Maternal losses with the Porro operation remained high but were substantially below those experienced before the procedure was introduced. By 1884, approximately 140 of these operations had been reported in Europe, with a maternal mortality rate of 56%. After 1882, the classic cesarean operation without

hysterectomy as popularized by Max Sänger began to replace Porro's operation as the surgical technique of choice because the rates of maternal morbidity and mortality were lower. By the onset of the twentieth century, the Porro operation had been entirely superseded.

Despite these and other innovations, cesarean delivery did not gain popularity with practitioners until well after the introduction of aseptic technique by Joseph Lister (1827–1912) and others in the latter decades of the nineteenth century. Drawing upon the new discoveries in bacteriology and the development of the germ theory of infection,the combination of improved anesthesia and new surgical methods finally blunted the horrific rates of maternal morbidity and mortality associated with cesarean operations [28]. The great safety of cesarean delivery still awaited changes introduced during the twentieth century.

The rapidly falling mortality rate of cesarean hysterectomy expanded the potential indications for the operation. Cesarean hysterectomy became progressively popular during the period from the late 1940s to the mid 1960s, and was often performed for sterilization. In recent decades, because of the substantial morbidity of the operation, cesarean hysterectomy has fallen from favor as an elective method of sterilization. At present, this procedure is generally restricted to management of uncontrolled hemorrhage, the rare case of nonreparable uterine injury, or for other reasons of severe uterine or cervical pathology. In recent years, the availability of potent uterotonics and broad-spectrum antibiotics, the development of embolization techniques, and new methods of vessel ligation have markedly reduced the need for emergency cesarean hysterectomy, although it still remains an important and potentially lifesaving procedure (See Chapter 18, Cesarean Delivery).

Other innovations in surgical technique lessened the risks of surgery. Maternal complications from cesarean deliveries were reduced by the development of the lower-segment cesarean operation, a procedure originally suggested by Johann F. Osiander of Goettingen (1759–1822). In 1805, Osiander opined that entry into the uterus through a vertical lower-segment incision could avoid the complications of the usual surgical technique, which then involved a vertical incision in the upper and thicker portion. More than a century later, Bernard Krönig (1912) revived this idea and proposed dissecting into the vesicouterine space and subsequently using the bladder serosa to cover the uterine incision, to protect the peritoneal cavity from exposure to the lochia. This combined technique of a lower-segment uterine entry and sequestration of the myometrial wound behind the peritoneum resulted in less immediate surgical morbidity and substantially reduced the risk of uterine rupture in subsequent pregnancies.

The extraperitoneal cesarean operation has an interesting history [20]. This procedure was first proposed by W. E. Horner in 1824. Such procedures were not performed until Alexander Johnston Chalmers Skene (1838–1900) successfully delivered a woman with a rachitic pelvis by this technique [7]. In 1909, the extraperitoneal operation gained support when Wilhelm Latzko of Vienna reported only two maternal deaths among thirty such procedures. Latzko's paravesical, extraperitoneal operation was later popularized in the years prior to World War by E. G. Waters [29] and J. F. Norton [30]. The theoretical advantage of this operation was to isolate the entire operative site retroperitoneally and thus potentially avoid the risk of peritoneal contamination. The progressively increasing safety of the transperitoneal approach, the rapidly decreasing incidence of protracted, dystocic labors, and the advent of antibiotics markedly reduced the importance and advantage of the extraperitoneal operation, however. It is now uncommonly attempted.

In recent decades, additional modifications in cesarean operative technique have been introduced. New and less tissue reactive suture materials are now available. In routine operations contemporary surgeons now frequently omit the serosal or vesicouterine flap closure and closure of the parietal peritoneum in an effort to reduce adhesion formation. The standard methods for both opening and closing both the fascia and uterus also have changed, at least for many surgeons, replacing the traditional sharp entry by techniques of blunt dissection and employing running as opposed to interrupted sutures for closure. Perhaps the most marked change in cesarean practice in the last 75 years has not been in surgical technique, however, but in the remarkable reduction in serious maternal morbidity and mortality associated with the operation by the administration of prophylactic antibiotics, the rapid

development of medical therapies to treat complications, and general improvements in anesthesia. The overall mortality risk for unselected cesarean operations has fallen to 1 per 1,000 or less owing to these various advances and improvements.

INSTRUMENTAL DELIVERY

The development of atraumatic delivery instruments is a complex and fascinating part of the history of obstetrics [31–36]. Beginning 200 years ago, a remarkably small group of innovators developed and perfected new types of obstetric instruments. Their trials, false starts, occasional successes, and many failures make for a rousing tale that involves trade secrets, professional jealousy, true altruism, a touch of scandal, and inevitably, the search for profit and fame. Beyond technical considerations concerning instruments or technique, practitioners of the past were also well aware of the potential risks and benefits of the use of instruments in obstetric practice and of the classic alternatives, either a cesarean or a destructive operation. They sought to develop vaginal delivery devices that were safe, effective, and ultimately lifesaving. The different approaches that contemporary accoucheurs have toward instrument-assisted delivery mirrors a two-century-old tension between contending philosophies of obstetric practice. This persisting and irresolvable controversy is between those willing to intervene versus those whose preferences are to wait and observe. The balance in the relative ascendancy between these positions is influenced by various advances in the field of obstetric practice, including the periodic publication of critical reevaluations of traditional obstetric procedures, the introduction of new instruments, the popularity of novel techniques or procedures, the complex pressures of society, and medicolegal trends.

Prior to the introduction of safe delivery instruments, intravenous fluid therapy, blood transfusion, potent antibiotics, and potent uterotonics, the options available to birth attendants when labor was obstructed were starkly limited. The mother could be permitted to continue to labor at high risk for her own injury and for the loss of her child in the hope of an eventual vaginal delivery. Alternatively, version and extraction, symphysiotomy, or a procedure destructive to the fetus could be performed. Such procedures might save the mother but often did so at the cost of severe or fatal fetal injuries. Furthermore, before the late nineteenth century, attempts at any intervention were often delayed until the situation was nearly hopeless, effectively determining the outcome. Abdominal operations such as cesareans were uncommon prior to the latter part of the nineteenth century. Surgery was brutal, far from safe, and performed without anesthesia. As discussed in the previous section, cesarean delivery did not become an acceptable option until after the mid 1880s owing to the horrific risks of hemorrhage and infection and the limitations of anesthesia. It was in this formidable setting that nondestructive delivery instruments were first invented.

Modern obstetric delivery forceps are the highly modified descendants of instruments destructive to the fetus that date from antiquity [31,32,34]. The term *forceps* most likely takes its origin from a contraction of a Latin root word, either *ferricepes* (*ferum*, meaning "iron," and *capio*, meaning "I take") or *formus* (meaning "hot") combined again with *capio*.

Although destructive instruments including hooks and other extraction devices are accepted as ancient, the date of invention for nontraumatic obstetric forceps is the subject of debate. Atraumatic instrumental delivery devices were unknown to the Greeks and probably to the Romans as well, although the latter is not completely certain. If the Romans ever had a nondestructive delivery forceps in their armamentarium, this device was lost over time and did not influence later developments. Destructive instruments, including cranial perforators, hooks and various cranial grasping devices, however, date to antiquity.

Various two-bladed, scissor-like metal instruments designed for obstetrical applications were in use by approximately 1000 C.E. and were known to Albucasis (1013–1106) and his contemporaries, Avicenna (c. 980–1037) and Maimonides (1135–1204). Jacob Rueff's (1500–1558) textbook *De Conceptu et Generatione Hominis* from 1544 illustrates such instruments (Figure 1.2). A surgeon and obstetrician in Zurich, Rueff drew his information largely from Soranus and from the previously mentioned text by Rösslin, usually entitled the *Rosengarten*, initially published in 1513. Unfortunately, devices depicted in this text were quite clearly designed for the destruction and removal of the fetus from the uterus and not to assist in the delivery of living infants. Atraumatic delivery required the

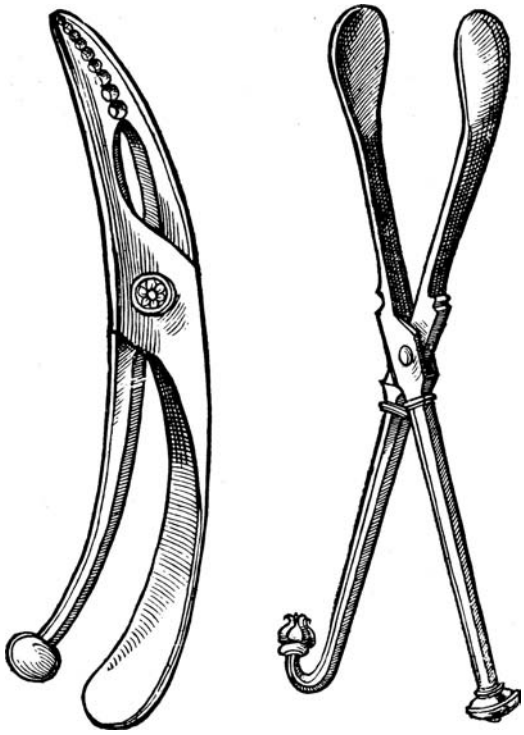

FIGURE 1.2.
Delivery instruments illustrated by Jacques Rueff in* De Conceptu et Generatione Hominis *(1554). (Courtesy of the Historical Division/ Cleveland Health Sciences Library, Cleveland, OH.)

development of instruments capable of two different but related tasks: grasping the fetal head securely and permitting cranial rotation and traction. Both of the tasks also had to be accomplished without resulting in serious maternal injury. Neither technical limitations nor the lack of surgeons delayed the development of safe delivery instruments, however. Europe had many talented medical fabricators in the flourishing armament industry of the sixteenth and seventeenth centuries who could easily have produced metal scissor-like instruments like forceps on demand. The problem was twofold: first, the requirement to identify the need for such instruments, and second, the recruitment of sufficiently skilled practitioners to direct the transformation of initially destructive instruments into atraumatic delivery instruments. These changes awaited the Chamberlens.

During the reign of Charles , religious persecution drove many Protestants from France, including William Chamberlen (c. 1540–1596), a medical practitioner who subsequently established his

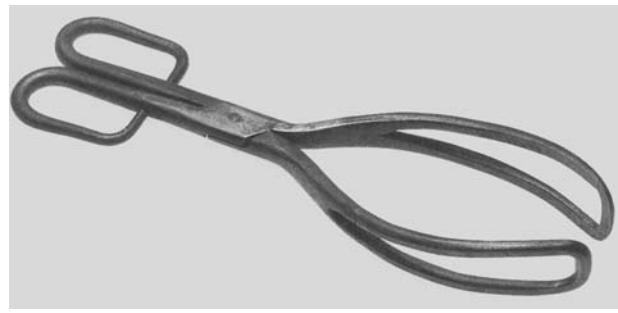

FIGURE 1.3.
Chamberlen delivery forceps c. 1610 (facsimile). (Courtesy of the Dittrick Museum of Medical History, Historical Division/Cleveland Health Sciences Library, Cleveland, OH.)

family in England [22,31,34,37]. By the late sixteenth century, the two sons of William Chamberlen were actively practicing medicine in London, working as barber surgeons and heavily involved in midwifery. Which of the brothers, Peter Chamberlen "the elder" (1560–1631) or Peter Chamberlen "the younger" (1572–1626) was the inventor of obstetric forceps is not clear, although Peter the Elder is usually give the credit. Although the process that led to the development of the Chamberlen instrument is unknown, it is believed that a practical forceps model was first developed after 1610 and then later modified several times based on clinical experience (Figure 1.3).

The Chamberlen delivery forceps were not released for general use after their invention, and for decades the instruments remained closely guarded as a family trade secret. The Chamberlen brothers and many of their descendants held themselves out as obstetric consultants. As such, they provided the public access to their secret method of delivery (the forceps) for a fee. Once they had been called in consultation, their "secret instrument" was delivered to the lying-in site in a large, gilded box [37]. All of the original birth attendants were then excluded from the room. The forceps were then removed from the box in such a fashion so as not to be seen by the parturient. As was usual continental practice, the delivery was conducted under the cover of a sheet that covered the parturient's bed and was tied behind the accoucheur's neck. His drape in place, the surgeon would sit at the end of the bed, grasp the forceps, and commence the procedure. Thus, both his manipulations and the delivery forceps were hidden under the sheet. After the delivery, the instrument

was replaced in its box and the delivery fee claimed. Because of this process, neither the woman nor her family or friends could attest to what had actually occurred, and thus the secret remained secure.

A later and somewhat unsavory member of the Chamberlen family, Hugh the Elder (1630–17??) was a notable entrepreneur and self-styled dealmaker. In 1670, hoping to raise money he went to Paris and offered to sell the family secret to the noted French obstetrician François Mauriceau for what was then a large sum of money [3,33]. Mauriceau provided a test case, a woman with a markedly deformed pelvis in obstructed labor. Despite Chamberlen's prolonged and heroic efforts, both the women and infant died. At a later postmortem examination, the uterus was found to be ruptured. Not surprisingly, this sale fell through. Despite this debacle, Chamberlen managed to secure an agreement from his French colleague to translate Mauriceau's textbook, the *Traité*, into English. On his return to London, Chamberlen published a version of this book in English, initially entitled *The Accomplish't Midwife* (1672). The text proved highly successful and at least eight subsequent editions were printed. This literary and professional coup was a substantial contribution to midwifery practice in England and improved Chamberlen's prominence in his profession while also helping to attract a large clinical practice, thus improving both his social and financial position [22].

Forever embroiled in political affairs and financial schemes, Hugh the Elder subsequently encountered sufficient difficulty in England to induce him to flee to Holland. During his five years on the Continent, it is suspected that he sold obstetric instruments to either Hendrik van Roonhuysen [also Roon-Huyse, Roonhuyse] (1615–1672) or more likely his son and successor Rogier van Roonhuysen (c. 1650–1709), both surgeons in Amsterdam [33,36]. This sale probably occurred after 1693 or perhaps 1695. Although details of this transaction are extremely sketchy, this commercial deal could have first introduced an atraumatic delivery device to Europe. It is also possible that no sale of an instrument actually occurred. The Amsterdam forceps might have been an independent invention. It is also possible that what van Roonhuysen received from Chamberlen was only the *idea* for a delivery instrument that he later independently refined, rather than an actual working model. Paralleling the example set by the Chamberlen family, the sale also permitted Roonhuysen and his successors to hold the use of this instrument (or perhaps instruments) as a local monopoly for more than 50 years. With the payment of a substantial fee, practitioners who passed the examination for the Amsterdam Surgeon's Guild were permitted introduction to this secret delivery instrument.

Various modifications to the original Chamberlen design or one or more vectus blades independently developed either by Roonhuysen or his close associates, Jean (or Joannes) de Bruin (1681–1753), Paulus deWind of Middleburg, and Regner Bloom of Amsterdam, eventually came to public notice in the Netherlands after 1747. This occurred partly because several practitioners, including a disgruntled applicant to the Amsterdam Surgeons Guild, John Peter (or Jan) Rathaw (also, Rathlaw, Rathlauw; 1720–1791), and Van der Suam (or Swam), a former pupil of Rogier van Roonhuysen, wished to finally break the Amsterdam monopoly [33,36]. As published by Rathaw and later independently by another surgeon in 1747, Daniel Schlichtingting (1703–1765), the revealed van Roonhuysen secret instrument consisted of a type of forceps, quite different from the known Chamberlen models, with thin, bandike parallel blades and no pelvic curve. This instrument was articulated only at the distal end of the handles.

On his deathbed in 1753, van Roonhuysen's closest pupil, Jean de Bruin, gave his original delivery instruments as a legacy to two friends, J. de Vischer and H. van de Poll. They subsequently published a description of one of these instruments in a text entitled *The Obstetric Secret of the Roonhuysens Discovered* (Leiden, 1753). What they revealed in this paper was a single-bladed device slightly curved at both ends and covered with dog leather. This instrument is best described as a modified lever or vectus blade.

The entire story of the van Roonhuysen's secret instrument(s), including what these instruments actually were, who was involved in the various transactions concerning these devices, and whether any of the "revealed" instruments were actually obtained from Hugh Chamberlen remains cloudy [36,38]. It is also uncertain if these forceps and vectus blades were actually invented independently by the van Roonhuysens or somehow inspired by their viewing an earlier model of the Chamberlen forceps.

Apparently, the Amsterdam group used two instruments, a vectus blade and a type of forceps. Part of the confusion lies in separating the "release," or publication of the description of these separate delivery instruments, from their actual invention (or modification?). Owing to the various claims and counterclaims by the people involved and our distance from the actual events, no resolution concerning what the Amsterdam cartel either purchased from Chamberlen or independently invented seems likely. Apart from the quibbles concerning its origin, the van Roonhuysen extractors proved to be poor competition for the Chamberlen forceps. Forceps based on the Amsterdam model never became popular and had little influence on future developments. While possibly representing a true independent invention, the van Roonhuysen forceps remain now as a historical curiosity only. Of interest, the use of levers or vectus blades remained common in the Netherlands well into the nineteenth century. These instruments might be the only lasting obstetric contribution that can be ascribed to the Amsterdam group (Figure 1.4).

Other delivery instruments also became available in the early to mid-eighteenth century. Independently of the Chamberlens, Johannes Palfyn of Ghent (1650–1730), a surgeon and anatomist with an uncertain interest in midwifery, developed a two-bladed delivery instrument, his *tire-tête* or *mains de fer* [11,22,36]. This device was demonstrated in Paris, probably in 1720, at a meeting of the Academie Royale de Sciences. This instrument was also presented to the Medical Faculty of Paris in 1723. Unfortunately, Palfyn never published anything on either the construction of this instrument or its clinical use. All information about his forceps comes from the comments of his contemporaries and his critics. Palfyn might have derived the inspiration for his invention from a vectus blade instrument originally developed by the noted French surgeon Ambroise Paré (1510–1590). Palfyn's innovation was to employ two blades, each with cephalic curve fitted to the sides of the fetal head. These blades were neither crossed nor otherwise articulated together, and they also lacked a pelvic curve. In its original description, the device was likened to a pair of "artificial hands" designed to assist the delivery of the fetal head. Thus their name, "iron hands" or *mains de fer*. Later, other practitioners including Guilles Le Doux of Ypres (c. 1710) and Grégoire the Elder (?–1730?) bound the two parallel blades together with a cloth tape or strap to try to increase their clinical utility. Parallel blades have a technical advantage over other forceps' designs since they avoid the cranial compression inherent in the scissor-like articulated blades of most instruments, including those of the Chamberlens. As a parallel-blade device, however, the Palfyn instrument had major technical problems. The lack of a pelvic curve restricted its potential use. Even with the wrapping of the shanks, the instrument proved unstable and was largely ineffective in clinical use.

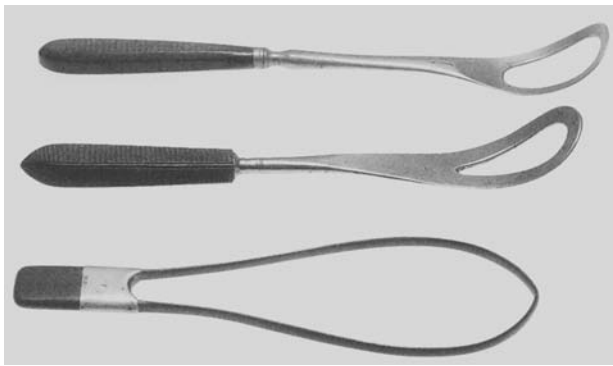

FIGURE 1.4.
Vectis blades and whale bone fillet c. 1850. (Courtesy of the Dittrick Museum of Medical History, Historical Division/Cleveland Health Sciences Library, Cleveland, OH.)

Palfyn's device never achieved popularity owing to its technical limitations, marginal utility, and professional opposition from distinguished contemporaries. One of the most vocal critics, the noted accoucheur Guillaume-Manquest de la Motte (1665–1737), publicly denounced the *mains de fer* as both impractical and dangerous, which they most likely were. After this unfortunate trial presentation, nothing further was heard concerning Palfyn's instrument, and it disappeared from obstetric history.

Instability is a design problem for all parallel-blade instruments because traction immediately drives the blades laterally, predisposing them to slippage. In addition, if parallel blades are unsupported by a firm locking mechanism they can be easily twisted, risking lacerations of the birth canal. Following redesign and crossing of the blades and the fitting of a screw-based lock (Duseé modification) a later modification of the Palfyn instrument actually was made clinically usable. This instrument never

gained popularity and had little influence on subsequent forceps design, however [36]. Many years later, once the problems of blade articulation and stability had been solved, Laufe, Shute, and others successfully revived the parallel-blade design for obstetric forceps [39–41].

In the mid-1730s, following the publication of several case reports and informal exchanges between several practitioners, obstetric forceps of varying types rapidly came into general use in England. Thus in 1733, in his text *A Treatise on the Improvement of Midwifery*, Edmund Chapman (1680–1756) mentioned that forceps were instruments well known to his contemporaries [22]. Other practitioners, including William Giffard (?–1731) and Benjamin Pugh (c. 1710–1775) also reported using forceps before 1750 [33,36]. Exactly how the secret of the forceps was revealed to these accoucheurs remains unknown. It cannot be simply a coincidence that the several physicians most involved in popularizing these early, Chamberlen-like instruments all worked in Essex, England, in reasonable proximity to the Chamberlen estate. Unfortunately, the details of this potentially fascinating part of the forceps story are now irretrievably lost.

Modifications to these early delivery instruments were required before they achieved popularity and utility. Both the Chamberlen and Palfyn forceps were short and straight and lacked a pelvic curve. Owing to these design limitations, they would have been useful only as low or outlet instruments. To improve performance, André Levret (1703–1780), William Smellie (1697–1763), and Benjamin Pugh (c. 1710–1775) independently added a pelvic curve [11]. This helped to accommodate the forceps blades to the birth canal, and the new instruments that incorporated this modification were capable of more accurate and less traumatic applications. This improvement was introduced at the same time as the French obstetrician Jean Louis Baudelocque (1746–1810) developed a technique for estimating pelvic capacity by taking external measurements with a large caliper or pelvimeter. His studies of pelvimetry demonstrated the importance of pelvic shape and various pelvic dimensions in the mechanism of labor, thus improving the understanding of how instruments should be used [22].

The newly modified cross-bladed forceps that incorporated the pelvic curve provided an attractive alternative to the dreary triad of heroically prolonged labors, attempted version and extraction, and destructive operations that had characterized earlier practice. Unfortunately, the indiscriminate use of instruments, often by the inexperienced, led to abuse. Knowledge of techniques for safe application and training to disseminate improvements in technique lagged well behind the enthusiastic application of these new devices.

Overuse of instruments provoked the expected response. An era of lively debate concerning the appropriate use of instruments ensued, much of which was strikingly similar to modern discussions. The result was that several of the best eighteenth century English practitioners, including William Smellie (1697–1763) and his student William Hunter (1718–1783), taught the conservative use of instruments. Although Hunter clearly knew how to use forceps, he took pride in noting that his pair was so little used that they were covered in rust. Practitioners of an even more conservative school of obstetric management, including Thomas Denman (1733–1815), William Osborn (1736–1808), and Richard Croft (1762–1818), favored extreme prolongations of labor rather than any resort to instrumental assistance [11]. In their view, the risks attendant to instrumentation outweighed any potential. The general guidelines for appropriate forceps use as designated by the conservative school would be quite unacceptable by modern standards [36]. These included

- No intervention is to be performed if any progress is noted, no matter how slowly, unless fetal demise is diagnosed;
- No intervention may be considered until the head has been on the perineum for >6 hours;
- Forceps are to be used only for the most urgent occasions, and then sparingly.

A famous and poignant reminder of the potentially serious error of failing to intervene despite strong indication was the childbirth death of George IV's only heir, Princess Charlotte, in 1817 [42]. The royal obstetrician, Sir Richard Croft, was a socially prominent and fashionably conservative practitioner. The Princess' labor lasted 50 hours, and the child was stillborn. Six hours following the delivery, Princess Charlotte died from what is now presumed to have been exhaustion, dehydration, and hemorrhage. Forceps were available but never

used. Later, in the face of intense public and professional criticism concerning his obstetric management, Croft committed suicide. Beyond the tragedy of these three related deaths, the event also presented a major political crisis. With the death of Charlotte, there was no legitimate heir for George . If no legitimate heir could be produced, the English crown would pass to a distant Hanoverian relative, the Duke of Brunswick, a young cousin of George . Eventually, after active intervention, a suitable bride of proven fertility for the king's brother was found. A successful pregnancy and delivery followed in 1819. Through this somewhat unusual mechanism, the English crown passed to the King's niece. In 1837, this woman assumed the English throne and was crowned as Queen Victoria, who proved to be the longest reigning of the English monarchs. The Princess Charlotte debacle and other similar events eventually discredited the ultraconservative school of obstetric management, and by the middle decades of the nineteenth century led to a more balanced view of the role of assisted delivery.

The extensive use of instrumental delivery was an event of the latter part of the nineteenth and the early twentieth century. Before the late 1840s, the incidence of forceps use both in England and the continent was 1% or less in large clinical services (Tables 1.1 and 1.2). Fleetwood Churchill was among the first practitioners to publish birth statistics. In his *Research on Operative Midwifery* (1841), he presented data summarizing experience in the late eighteenth and early nineteenth century (Table 1.1) [36]. These data indicate that both forceps and operations destructive to the fetus occurred in substantially fewer than 1% of all deliveries.

In 1875, T. More Madden of the Rotunda or Dublin Lying-in Hospital reported delivery data collected from 1787 to 1874 during the directorship of seven hospital masters (Table 1.2). As had been reported by Churchill, instrumental delivery was uncommon (0.5%) until midcentury. Thereafter, the rate rose from 1.6% for the interval 1847–1854 to 9.2% by 1868–1874.

During the interval from the eighteenth century until the latter decades of the nineteenth century, the percentage of procedures destructive to the fetus remained relatively stable, at approximately 0.4%. The increase in operative forceps deliveries probably reflects several factors:

TABLE 1.1 Frequency of Forceps Use and Craniotomy or Operations Destructive to the Fetus in the Late Eighteenth and Early Nineteenth Centuries*

Instrument Employed	Deliveries	Operations Performed (%)
Forceps		
British 1781–1840	42,196	120 (0.28)
French 1797–1831	44,736	277 (0.62)
German 1801–1837	261,224	1,702 (0.65)
Total	348,156	2,099 (0.60)
Perforator and Crotchet		
British 1781–1819	41,434	181 (0.45)
French 1797–1811	36,169	30 (0.08)
German 1801–1837	256,655	132 (0.05)
Total	334,258	343 (0.10)

*As reported by Churchill, 1841. *Modified from* Hibbard [36], reprinted with permission.

TABLE 1.2 Operative Deliveries at the Dublin Lying-in Hospital Under Various Masters: 1787–1874*†

Mastership	Deliveries	Forceps (%)	Perforator (%)
Joseph Clarke 1787–1794	10,387	14 (0.13)	49 (0.47)
Samuel Labatt 1815–1822	21,867	0	0
Robert Collins 1826–1833	16,654	24 (0.14)	118 (0.71)
Charles Johnson 1842–1833	6,702	18 (0.27)	54 (0.80)
Total	55,610	56 (0.10)	221 (0.40)
Robert Shekleton 1847–1854	13,748	220 (1.60)	54 (0.39)
A. H. McClintock 1854–1861	3,700	76 (2.05)‡	5 (0.14)
George T. Johnston 1868–1874	7,027	639 (9.1)	29 (0.41)
Total	24,475	935 (3.82)	88 (0.36)

*As reported by More Madden, 1875.

†From Hibbard [36], with permission.

‡Includes vectis blade operations.

the availability of anesthetic agents after 1849, the development of new delivery instruments, and changing concepts of obstetric management. The rate of destructive procedures remained unaltered because of technical problems in ascertaining fetal condition and the inability of clinicians to perform cesarean delivery without extreme maternal risk.

Of interest, and as a reflection of the difficult cases presented to these practitioners, Hibbard [36] reports that the maternal mortality from forceps procedures varied from 4.8% (14/294; England) to 7.3% (35/479; Germany and France). In comparison, maternal losses from destructive operations to the fetus (predominantly perforation) were an astounding 21% (52/251)!

In the middle and late nineteenth century, obstetrics underwent rapid changes. Advances in therapeutics accompanied the development of many new delivery instruments and techniques. The introduction of anesthesia in the late 1840s and the development of new instruments and aseptic practices in the 1880s profoundly changed obstetric practice, permitting both sufficient time and relative safety for various surgical procedures.

In the latter part of the nineteenth century, instrumental delivery by forceps became more common and the procedures more extensive. Both more difficult and ever-higher procedures were progressively attempted, including operations performed before full cervical dilation. Hibbard [36] suggests that this more aggressive use of forceps arose from a then general belief that once the membranes ruptured, uterine inertia was common. In this setting some type of intervention was therefore thought to be appropriate.

The English obstetrician James Young Simpson (1811–1870) and his American contemporary George T. Elliot (1827–1871) were among the most prominent practitioners of the mid-nineteenth century [11,43,44]. Simpson, a highly regarded and influential obstetrician working in Edinburgh, developed not only a type of forceps but also the first effective obstetric vacuum extractor. His specially designed forceps were introduced in 1848, rapidly became popular, and are still in use. A man of many interests, Simpson authored papers on hospital design, mesmerism, acupressure, and homeopathy, among other subjects. He also played a pivotal role in obstetric anesthesia, discovering the anesthetic properties of chloroform, which by 1848 he had employed during deliveries and in the treatment of eclamptic seizures.

George T. Elliot (1827–1871) introduced his midwifery forceps in 1858. To limit compression of the fetal head, he included a setscrew in the instrument handle to control the degree to which the handles of the forceps could be approximated. Both his instrument and Simpson's remain among the most popular designs and are in common use today [32].

In the waning years of the nineteenth century, awakening interest in the mechanism of labor was reflected in the design of new instruments. Following earlier designs of Louis Joseph Hubert of Louvain (1810–1876) and his son E. Hubert and others, Etienne Stephene Tarnier (1828–1897) and Charles P. Pajot (1816–1896) introduced axis-traction forceps. These devices were developed to align the vector of traction with the pelvic curve, thus improving success and using force in a more judicious and less traumatic manner.

Friedrich Wilhelm Scanzoni (1821–1891) popularized rotational maneuvers, especially for management of occiput posterior positions [11]. Modifications of his grand rotation are still occasionally performed today (see Chapter 17, Instrumental Delivery).

Following an idea originally proposed in 1799, by Friedrich Osiander (1759–1822), solid-bladed forceps were popularized by James Woods McLane (1839–1912). To facilitate rotations, these forceps were modified with the addition of longer shanks by Ervin A. Tucker (1862–1902). Later, Ralph Herbert Luikart (1889–19??) modified these blades by selectively thinning the inner portion [45]. Such pseudofenestrated forceps blades retained the advantages of easy rotation inherent in the solid design yet maintained a firm grip on the fetal head. This modification remains popular and has been applied to several forceps types.

Rather than an inventor, the most important influence on American delivery practices in terms of instrumentation in the early part of the twentieth century was the medical educator, Joseph Bolivar DeLee (1869–1942). In the 1920s he described the prophylactic forceps operation [46]. Despite the lack of supporting data, DeLee championed the routine use of forceps combined with episiotomy for shortening the second stage once the fetal head had reached the pelvic floor, as a means of avoiding intracranial injury. This concept of routine operative

delivery for both maternal and fetal reasons – even though unsupported by data and based on theoretic concerns – was widely followed and strongly influenced North American practice for more than four decades.

Many other clinicians practicing in the early twentieth century designed modified forceps for specific clinical indications. These included the instruments introduced by Lyman Guy Barton (1866–1944) for transverse arrest, Arthur Holbrook Bill (1877–1961) for axis traction, Edmund Brown Piper (1881–1935) for breech delivery, and Christian Casper Gabriel Kielland (1871–1941) for midpelvic rotations. Recent years have seen the development of various new forceps designs, such as those of Laufe, Hays, Nargolkar, and Salinas, among others. These new devices attempt to improve maternal and fetal safety through specific aspects of their design.

HISTORY OF THE VACUUM EXTRACTOR

Vacuum delivery instruments have their origin in the very old practice of cupping [38,47]. In cupping, a metal or glass cup or globe is heated over an open flame and then pressed against the skin. As the cup cools, suction develops, extracting blood or other fluids. A century of experimentation with modifications of the vacuum principle inherent in cupping, combined with various technical advances of the nineteenth and twentieth centuries led to the development of modern obstetric vacuum extractors. Applications of cupping for assistance at deliveries were first reported in the late seventeenth century, when James Younge (1646–1721) and other surgeons performed vacuum deliveries using glass or metal cups [48]. These practitioners failed to publicize their successes, however, and nothing is known about either the construction of these instruments or the techniques used for application or traction [32].

Cupping faced serious technical limitations when the technique began to be applied to vaginal delivery. As this procedure was commonly performed, the cups were initially heated over an open flame before their application. Obstetric use, however, required both a vaginal application of the vacuum cup and a method for traction. Thus, a different technology was needed. Several important features had to be incorporated: easy insertion into the birth canal, the ability to form a firm seal to the fetal head, a means of continuous regeneration of the vacuum as a result of imperfections of the seal, and finally, a practical method for applying traction.

The vacuum principle was the subject of both experimentation and speculation in the early nineteenth century. It was recognized that evacuating either glass or metal globes could result in substantial pressure and that such devices could be used for traction in several important applications. It was not long before medical applications were suggested [49]. Based on contemporary experimentation and crude commercial vacuum-based devices, James Young Simpson, who developed a several obstetric devices, including the forceps that bear his name, invented the first practical obstetric vacuum extractor in 1849 [44,50,51]. His new device, which he termed an *air* or *suction tractor*, was proposed as an alternative to forceps for use in both cephalic and breech presentations when assisted delivery was required [44,50,51]. Simpson's device consisted of a piston syringe, probably derived from a breast pump, attached to a deep and flexible rubber cup (Figure 1.5). In use, the cup was placed firmly against the fetal head and the syringe was rapidly evacuated. Once suction was achieved, traction was applied by simply grasping the pump cylinder and pulling downward. The extractor was simple and, despite its limitations, successfully employed in several cases. Technical problems with traction, maintaining the vacuum, and the inability of the instrument to accommodate the pelvic curve as a result of its design eventually proved insurmountable, however. After a brief trial Simpson abandoned his vacuum device. Thereafter, despite the occasional introduction of various new designs, vacuum extraction essentially disappeared as an obstetric technique for nearly 100 years.

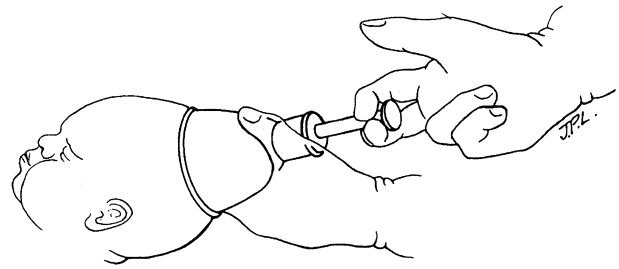

FIGURE 1.5.
Simpson's "air tractor" vacuum extractor (1849).
(*Reprinted from *O'Grady JP: Modern Vacuum Extraction. Parthenon, 1995; with permission.)

Several vacuum extractors were invented in the century following Simpson's original report, but none achieved either popularity or commercial success until the 1950s, when Malmström introduced his stainless steel cup [52]. The Malmström extractor rapidly became popular, especially in Europe. The device was rugged, successful, and could be used as an alternative to forceps [52–54]. Despite European success, metal cup extractors had a variable reception in the United States. After widespread interest in the early 1960s, vacuum extraction promptly fell into disfavor, largely because of reports of serious scalp injuries and other complications. The popularity of vacuum extraction resumed two decades later only when the soft-cup devices were introduced. At this time clinicians proved more receptive to an alternative for forceps, new instruments were available, and better techniques had been developed for vacuum-assisted delivery.

Malmström's device incorporated several important features now found on all vacuum devices. A protective disk was fitted into the interior of the cup to avoid injury to the fetal scalp. There was a separate vacuum source capable of continuous vacuum production, protected by a collecting bottle or trap. In addition, a pressure gauge was fitted to determine the degree of force generated. Finally, a metal chain firmly attached the cup to an easily grasped handle, permitting easy traction. In later years, other obstetricians including Bird, Lovset, Party, O'Neil, Halkin, and others invented, modified, and improved metal vacuum cups [55–57]. These modified instruments were intended to reduce the likelihood of detachment, facilitate application, or better protect the fetal scalp. Among the rigid metal cups, Bird's modification, in which the vacuum tube is attached to a lateral suction port independent of the traction chain, has proved to be the most popular and useful [55,57]. New models of rigid plastic extractors largely reprise the construction of the Malmström cup, extending the popularity of the original design.

An unknown number of Malmström-type metal cup extractors, predominantly of Bird's modified design, still remain in use. For several reasons, however, most American practitioners prefer to use the plastic cups that have been introduced in recent years [58]. These new designs are disposable single-use devices, constructed of polyethylene and/or Silastic polymer plastic. They are easy to use and have proven effective in most cases. As is always true when new devices become a commercial success, currently too many vacuum cup designs are available, with little if any significant difference between them.

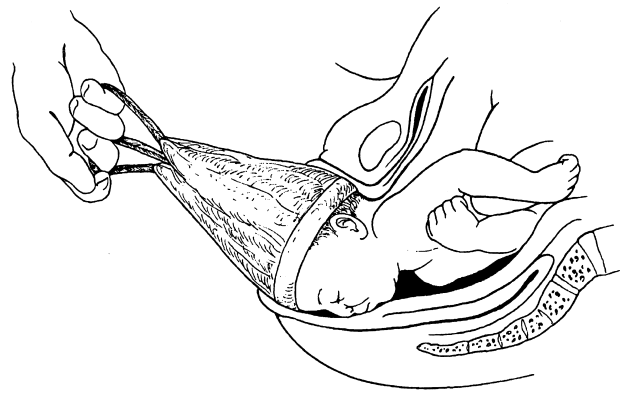

FIGURE 1.6.
Elliot's obstetric bonnet (1992). (*From *Elliott B, Ridgway LF, Berkus MD, Newton ER, Peairs W: The development and testing of new instruments for operative vaginal delivery. Am J Obstet Gynecol, 1992 Oct; 167(4 Pt 1): 1121–4; with permission.)

Experimentation with various types of vacuum traction devices has not ceased. Elliot recently described a vacuum-based instrument consisting of a rubber or plastic "bonnet" that lacks either a suction or vacuum port [59]. This unusual-appearing device is designed to be unrolled or fitted onto the fetal head like an inverted parachute. Tension on the handle flattens the membrane around the fetal cranium, providing the force necessary to assist parturition (Figure 1.6). The concept of inserting a net or bag to grasp the fetal head is certainly not new, as strikingly similar examples have appeared fleetingly in the obstetric literature for over two centuries, the earliest perhaps being the *tire-tête* of Pierre Amand from 1715 [36].

An important development in the use of vacuum extraction has been major improvements in practitioner education. These efforts reflect the increasing use of vacuum devices, an appreciation of their potential risks, and the need to better train practitioners in best techniques. Vacuum extraction has become increasingly popular in recent years, and instrumental delivery by vacuum extraction is now more common in the United States than forceps operations [60].

In recent years a greater appreciation of the risks and benefits of all types of assisted delivery has developed. This has prompted increased clinical study to define the best obstetric practices. The continued requirement for some means to accelerate or assist parturition in selected circumstances short of cesarean delivery ensures the continued use of vaginal delivery instruments for the foreseeable future (See Chapter 17, Instrumental Delivery).

REFERENCES

1. O'Dowd M, Phillip EE: The History of Obstetrics and Gynaecology. 1994, New York: The Parthenon Publishing Group.
2. Houtzager G: The Complete Encyclopedia of Greek Mythology. 2003, Edison, New Jersey: Chartwell Books, Inc.
3. Gottschalk W: Dystocia on Mount Olympus. Obstet Gynecol 1959 Mar; 13(3): 381–2.
4. Shakespeare W: *Macbeth*, 1606; V. vii. 44.
5. http://heraklia.fwsl.com.
6. http://www.perseus.Tufts.edu, 2006.
7. http://catholic.archives.nd.edu, 2006.
8. Grant M: Julius Caesar. 1992, New York: M. Evans and Company.
9. http://www.wordorigins.org/wordorc.htm, 2006.
10. http://catholic.archives.nd.edu, 2006.
11. Baskett TF: On the Shoulders of Giants: Eponyms and Names in Obstetrics and Gynecology. 1996, London: RCOG Press.
12. Rousset F: Traité Nouveau de l'Hystérotomokie ou l'Enfantement Caesarienne, qui Est Extraction de l'Enfant par Incision Laterale de Ventre et Matrice de la Femme Grosse. Pouvant Autrement Accoucher, et ce sans Préjudicer a la Vie de l'un de l'autre ni l'Empecher la Fécondité Maternelle par aprés. 1581, Paris: Demeys Duval.
13. Pottiee Sperry F: Biography: François Rousset. Hist Sci Med 1996; 30(2): 259–68.
14. Burton J: An Essay towards a Compleat New System of Midwifry. 1751, London: James Hodges.
15. Gordon BL: Medieval and Renaissance Medicine. 1959, New York: Philosophical Library.
16. Mauriceau F: Les Maladies des Femmes Grosses et Accouchées. 1668, Paris: Henavlt, D'Hovary, De Ninville and Coignard.
17. Mauriceau F: Observations sur La Grossesse et L'Accouchement des Femmes, et sur leurs Maladies, & celles des Enfants nouveau-nez. 1715, Paris: La Compagnie des Libraires Associez.
18. Drife J: The start of life: A history of obstetrics. Postgrad Med J 2002 May; 78(919): 311–15.
19. Huard P: sciences, Medicine, Pharmacie de la Revolution a l'Empire (1790–1815). 1970, Paris: Les Editions Roger Dacosta.
20. Speert H: Obstetrics and Gynecology in America. 1980, Washington, D.C.: American College of Obstetricians and Gynecologists.
21. Chipfakacha V: Abdominal deliveries in Africa: Food for thought to scholars of the history of medicine. Cent Afr J Med 1989 Feb; 35(2): 333–6.
22. Cutter IS, Viets HR: A Short History of Midwifery. 1964, Philadelphia: W.B. Saunders Company.
23. Mola G: Symphysiotomy or caesarean section after failed trial of assisted delivery. P N G Med J 1995 Sep; 38(3): 172–7.
24. Van Roosmalen J: Symphysiotomy – a reappraisal for the developing world. In Progress in Obstetrics and Gynaecology, J. Studd Editor. 1991, Edinburgh: Churchill-Livingstone. pp. 149–62.
25. Lauverjat T-E: Nouvelle Méthode de Practiquer L'Opération Césarienne, et Parallèlel de cette Opération & de la Section de la Symphyse des Os Pubis. Paris, 1788: pp. 150–1.
26. Sänger M: Der Kaiserschmitt. Arch Gynakol 1882; 19: 370.
27. Porro E: Della amputazione utero-ovarica come complemento di taglio Cesario. Ann Univ Med Chirurg 1876; 273: 289–350.
28. Lurie S, Glezerman M: The history of cesarean technique. Am J Obstet Gynecol 2003 Dec; 189(6): 1803–06.
29. Waters E: Retrovesical extraperitoneal cesarean section. Am J Obstet Gynecol 1940; 39: 423.
30. Norton J: Latzko extraperitoneal caesarean section. Am J Obstet Gynecol 1935; 30: 209.
31. Das K: Obstetric Forceps: Its History and Evolution. 1929, Calcutta: The Art Press.
32. O'Grady J: Modern Instrumental Delivery. 1988, Baltimore: Williams & Wilkins.
33. Radcliffe W: Milestones in Midwifery and the Secret Instrument. 1989, San Francisco: Norman Publishing.
34. Speert H: The obstetric forceps. Clin Obstet Gynecol 1960 Sep; 3: 761–6.
35. Drinkwater K: The midwifery forceps: Historical sketch. Med Chir J 1913; 64: 451–65.

36. Hibbard B: The Obstetrician's Armamentarium. 2000, San Anselmo, CA: Norman Publishing.
37. Speert H: Obstetrics and Gynecology: A History and Iconography. 1994, San Francisco: Norman Publishing.
38. Thiery M: Obstetric forceps and vectus: The roots. Acta Belg Hist Med 1992 Mar; 5(1): 4–20.
39. Shute W: Management of shoulder dystocia with the Shute parallel forceps. Am J Obstet Gynecol Oct 1; 84: 936–9.
40. Seidenschnur G, Koepcke E: Fetal risk in delivery with the Shute parallel forceps: Analysis of 1,503 forceps deliveries. Am J Obstet Gynecol 1979 Oct 1; 135(3): 312–7.
41. Shute W: An obstetrical forceps which uses new principle of parallelism. Am J Obstet Gynecol 1959 Feb; 72(2): 442–6.
42. Dewhurst J: Royal Confinements: A Gynaecological History of Britain's Royal Family. 1980, New York: St. Martin's Press.
43. Duns S: A Memoir of Sir James Y. Simpson. 1873, Edinburgh: Edmonston and Douglas. p. 288.
44. Chalmers J: James Young Simpson and the "suction tractor." J Obstet Gynaecol Br Commonw 1963; 70: 94–100.
45. Luikart R: A modification of the Kielland, Simpson and Tucker-McLane forceps to simplify their use and improve function and safety. Am J Obstet Gynecol 1937; 34: 686.
46. DeLee J: The prophylactic forceps operation. Am J Obstet Gynecol 1920; 1: 34–44.
47. O'Grady J, Gimovsky ML, McIlhargie CJ: Vacuum Extraction in Modern Obstetric Practice. 1995, New York: Parthenon Publishing Group Inc.
48. Younge J: An account of balls of hair taken from the uterus and ovaria of several women. Philos Trans R Soc (London) 1706–1707; 25: 2387.
49. Arnott N: Elements of Physics, or Natural Philosophy, General and Medical, Explained Independently of Technical Mathematics, and Containing New Disquisitions and Practical Suggestions, Vol 1. p. 543. 1831, Philadelphia: Carey and Lea.
50. Simpson J: On suction tractor or new mechanical power as a substitute for forceps in tedious labours. Edinburgh Monthly J Med Sci 1849; 32: 556–8.
51. Eustace D: James Young Simpson: The controversy surrounding the presentation of his Air Tractor (1848–849). J R Soc Med 1993 Nov; 86(11): 660–3.
52. Malmström T: The vacuum extractor: An obstetrical instrument. I. and the parturiometer, a tokographic device. . Acta Obstet Gynecol Scand 1957; 36(Suppl): 5–82.
53. Malmström T, Jansson I: Use of vacuum extractor. Clin Obstet Gynecol 1965; 8: 893–913.
54. Sjostedt J: The vacuum extractor and forceps in obstetrics: A clinical study. Acta Obstet Gynecol Scand 1967; 46(Suppl 10): 1–208.
55. Bird G: Modification of Malmström vacuum extractor. Br Med J: Online 1969; 3: 526–9.
56. Vacca A: Handbook of Vacuum Extraction in Obstetric Practice. 1992, London: Edward Arnold.
57. O'Neil A, Skull E, Michael C: A new method of traction for the vacuum cup. Aust N Z J Obstet Gynaecol 1981 Feb; 21(1): 24–5.
58. O'Grady J, Pope CS, Patel SS: Vacuum extraction in modern obstetric practice: A review and critique. Curr Opin Obstet Gynecol 2000 Dec; 12(6): 475–80.
59. Elliott B, Ridgway LF, Berkus MD, Newton ER, Peairs W: The development and testing of new instruments for operative vaginal delivery. Am J Obstet Gynecol 1992 Oct; 167(4 Pt 1): 1121–4.
60. Demissie K, Rhoads GG, Smulian JC, Balasubramanian BA, Gandhi K, Joseph KS, Kramer M: Operative vaginal delivery and neonatal and infant adverse outcomes: Population-based retrospective analysis. Br Med J 2004 Jul 3; 329(7456): 24–9.

Chapter 2 PRENATAL GENETIC TESTING

Gabriel M. Cohn

To some extent it may be said that the etiology of the transmitted foetal diseases is within our knowledge, and their diagnosis not altogether outside our grasp; with perseverence and skill their treatment will yet be hopefully undertaken by the well-informed physician.

John William Ballantyne (1861–1923)
Antenatal Pathology and Hygiene: The Embryo and the Foetus
Edinburgh: William Green and Sons, 1902.

The importance of genetics in clinical perinatal medicine has increased rapidly over the last three decades. Now, more than 6,000 genetic traits or disease entities have been identified (Figure 2.1) [1]. It is estimated that the incidence of genetic disease among newborns is 5%–6% [2]. Genetic disease has profound medical, financial, and societal consequences far greater than its actual numbers. With the progressive disappearance of many infectious and other diseases that in the past accounted for most hospital admissions, genetic disorders remain a serious contemporary social and medical problem. Studies examining inpatient pediatric admissions reveal that 33% to 52% of all pediatric hospitalizations result from complications of genetic disease [3]. If multifactorial disorders are eliminated, purely genetic diseases account for more than one in ten pediatric admissions [4]. Among adults, up to 11.5% of all inpatient admissions are due to genetically related abnormalities [5]. The contribution of genetic disorders to childhood mortality is edge with a substantial number of all pediatric deaths ascribed to genetic disease. Unfortunately, despite enhanced prenatal diagnostic capabilities and aggressive perinatal management, significant reductions in perinatal mortality associated with congenital malformations have not occurred [6].

In addition to its medical importance, genetic disease also has major financial and societal impact. Studies of patients with genetic diseases indicate that inpatient admissions for these patients are on average more common, more expensive, greater in duration, and, owing to geographic limitations of genetic services, require greater travel than similar treatment for persons with other types of illness. The loss of insurability following the diagnosis onset of genetic diseases doubles the likelihood that patients will pay out of pocket for medical services [3]. The societal cost is equally burdensome. Both years of work lost to impairment and years of life lost to disease span decades among persons afflicted with genetic disorders. In sum, the emotional, psychological, and financial impact of productivity lost

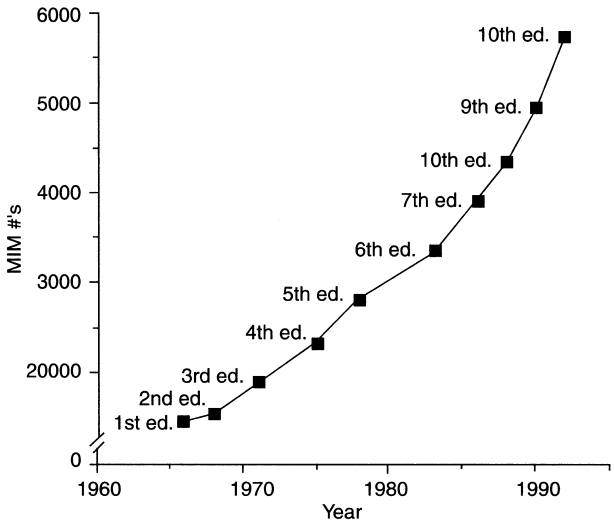

FIGURE 2.1.
Total number of entries in* Mendelian Inheritance in Man. *Since 1966 there has been a 3.8-fold increase in recognized human genetic traits and disorders.

to genetic disorders is extensive and often poorly appreciated.

With the improvement and automation of techniques in the fields of cyto- and molecular genetics and the identification of many genetic diseases, an understanding of the molecular pathophysiology of many disorders is now possible. Several molecular genetic assays have been developed in kit form to assist clinicians in the early diagnosis of genetic disease. It is believed that with this increased understanding of the mechanisms underlying many genetic entities and with the increasing accuracy of case identification, both pharmacogenetic and gene transfer interventions will progressively evolve. The introduction of such enhanced diagnostic and treatment capabilities will place increased reliance on prenatal diagnosis techniques as the basis for the *prevention* of genetic disease through termination of pregnancy or as the basis for the *treatment* of genetic disease through in-utero medical or surgical interventions. The questions of best practices in genetic screening as well as potential treatment for congenital disorders remain both complex and controversial. [7–10].

This chapter focuses on the procedures and techniques currently available to clinicians to evaluate genetic disorders. As our knowledge in molecular and clinical genetics progressively expands and as more potential therapies become available, the obstetrician plays a greater role in the identification of at-risk cases and in the prenatal diagnosis of genetic disease. Several currently investigative procedures that could become available for clinical use in the near future are also reviewed and their importance is discussed. For those desiring more extensive information, several excellent genetics resources are available free of charge.[1]

HISTORY

The development of prenatal diagnostic techniques has closely paralleled the advances in clinical genetics. Amniocentesis was first introduced in the 1880s as a treatment for hydramnios [11–14]. It was not until 1960, however, that amniocentesis for X-chromatin evaluation was first described [15–17]. Amniotic fluid sampling subsequently proved useful for the diagnosis and management of Rh isoimmunization and more recently as a technique for direct evaluation of fetal pulmonary maturity [18]. With the advent of X-chromatin analysis, amniocentesis was demonstrated to identify fetal sex acccurately, providing a technique for identifying fetuses at risk for X-linked recessive disorders, such as Duchenne muscular dystrophy and hemophilia [19,20]. In 1966, Steel and Berg [21] were successful in culturing and karyotyping amniocytes, suggesting that prenatal diagnosis of chromosomal aneuploidies was feasible. Jacobsen and Barter [22] subsequently introduced the first report of a fetal chromosomal anomaly identified on amniocentesis, a D/D translocation. In 1968, Valenti and coworkers [23] and Nadler [24] described the prenatal diagnosis of Down syndrome identified on amniocytes obtained by amniocentesis. A biochemical disorder, galactosemia, was similarly identified prenatally by

[1]Two invaluable Web sites include Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) and the GeneTest Web site (http://www.genetests.org). OMIM is an extensive database searchable by disease, gene, or by clinical feature(s). This database can be particularly useful in generating a differential diagnosis based on ultrasound or other clinical findings, or alternatively in providing a synopsis of the key clinical features associated with a given genetic diagnosis. In addition, an extensive review of the literature is provided for approximately 6,000 known phenotypes, as well as several thousand genetic markers. The GeneTest Web site provides an up-to-date listing of genetic tests that are clinically available, labs and clinical centers that provide genetic services, as well as extensive reviews of several hundred common genetic disorders.

Nadler [24], indicating that prenatal diagnosis by amniocentesis was not strictly limited to chromosomal abnormalities. The first report of a clinical trial of genetic amniocentesis was published by Nadler and Gerbie [25] in 1970. This study demonstrated that prenatal diagnosis by amniotic fluid analysis was an accurate and a low-risk procedure when performed between 16 and 20 weeks.

Fetal visualization was another significant advance. In the 1930s, amniotic infusion of contrast media for amniography was introduced, a procedure used to visualize the fetus and the placenta. Further development of various radiographic and radioactive tracer techniques over the following decades assisted in utero diagnosis. These tests and procedures were promptly abandoned with the advent of high-resolution ultrasonography, however.

Despite its introduction into medicine soon after the Second World War, ultrasound scanning did not make a major impact on obstetric management until real-time machines of high resolution became widely available in the 1970s. Today, ultrasound scan is the primary screening method for many fetal abnormalities and is considered a necessity in many obstetric procedures (e.g., version, amniocentesis, and cordocentesis).

The initial experience with amniocentesis was performed without the benefit of ultrasonography. "Blind" procedures were performed by arbitrarily inserting a spinal needle 3 cm above the pubis symphysis, at no earlier than 15 weeks' gestation. Although considered a reliable technique, midtrimester amniocentesis had the disadvantage of relatively late timing and hence late diagnosis. Societal pressures limiting pregnancy termination for genetic indications and medical considerations of the enhanced complications associated with midtrimester abortions stimulated interest in methods of first-trimester prenatal diagnosis. Unfortunately, initial attempts at transvaginal amniocentesis at $\leq$10 weeks of gestation and first-trimester endoscopic chorion biopsy resulted in significant pregnancy loss as well as high failure rates [25, 26]. New methods were needed.

In 1968, the technique of chorionic tissue biopsy (i.e., chorionic villous biopsy [CVS]) for prenatal diagnosis was introduced by Mohr [27]. In this procedure, an endoscope of 6 mm in diameter was introduced by way of one of the vaginal fornices or transcervically. The endoscope was positioned against the chorion, the optical device removed, and suction applied. A tubular knife was next introduced and used to biopsy tissue captured by the endoscopic suction. Success proved elusive, as only one half of the samples obtained were chorionic tissue, and many samples were found to contain amniotic membrane. Modifications of this technique were introduced, and a series of studies were performed on pretermination patients with only modest success [27–29]. Clinicians at Teitung Hospital in China [30] subsequently demonstrated that simple first-trimester placental biopsy was indeed feasible. In their original procedure, a 3-mm diameter metal cannula was blindly introduced through the cervix and advanced until "soft resistance" was encountered. A smaller-diameter inner catheter was then introduced to approximately 1 cm beyond the cannula tip, and tissue was then aspirated by syringe suction. This procedure was attempted in 100 pregnancies to determine fetal sex. In ninety-three patients, the appropriate fetal sex was assigned based on X-chromatin analysis. Of seventy continuing pregnancies, 4% were subsequently lost. Unfortunately, attempts to repeat this technique by other groups proved unsuccessful [31,32]. Attempts at procedure modification (e.g., endocervical lavage) were similarly without great success [33–35]. CVS remained investigational until new biopsy techniques and modified equipment were combined with modern ultrasonic visualization to improve both safety and success.

Direct ultrasonic visualization proved important in the development and acceptance of both amniocentesis as well as CVS. Combined with high-resolution ultrasonography, amniocentesis was directed either at a site identified as most suitable by a sonogram performed prior to the procedure (*ultrasound guided*) or by a sonogram performed during the procedure (*ultrasound monitored*). These modifications permitted localization of the placenta and allowed prenatal diagnosis prior to 14 weeks of gestation – the limit previously established by blind amniocentesis. In the early 1980s, Kazy [36] used ultrasonography to direct thin biopsy forceps (1.7 mm in diameter) at the chorion frondosum and successfully sampled a series of pregnancies. Among the patients studied were women carrying fetuses at risk for genetic disease. Thirteen such women who elected to continue their pregnancies after sampling experienced a successful pregnancy

outcome and the birth of a normal infant. Subsequently, Ward [37] and his London-based group introduced a method in which a blunt stainless steel malleable obturator served as a guide over which a 1.5-mm polyethylene catheter was threaded. Using continuous ultrasonographic guidance, this apparatus was introduced to abut the edge of the chorion frondosum. Once in position, the obturator was removed and a syringe applied. Chorionic villi were aspirated with negative pressure. Ward and coworkers [37] demonstrated that in pregnancies sampled between seven and 14 weeks, a 90% success in chorionic villus sampling was possible. Simoni and coworkers [38] subsequently compared four methods of villus biopsy, including blind insertion of the flexible catheter developed by Ward, blind insertion of an intravascular catheter, endoscopic sampling, and ultrasonographic introduction of the flexible Ward catheter. Using the first three approaches, maximal sampling success was limited to 76%, with bleeding occurring in 17% of attempts. With the Ward catheter used in conjunction with continuous ultrasonographic guidance, sampling success rates improved to 96%. In 1984, the technique of transabdominal CVS was introduced by Smidt-Jensen and coworkers (39) and proved to be a valuable alternative to transcervical sampling methods.

The role of CVS in early pregnancy diagnosis is developing. This issue is discussed in greater detail later, and the risk/benefit ratio is in the process of reconsideration. Recent evidence concerning possible fetal limb defects as a rare procedure-related complication continues to be closely analyzed.

Interest in transabdominal amniocentesis before 16 weeks was reawakened with the advent of improved ultrasound equipment. Subsequent evaluations have indicated, however, that early amniotic fluid sampling procedures ($\leq$14 weeks) entail more complications and these have largely been abandoned. The technologic advances that have had the most important influence on prenatal diagnosis, however, include new molecular and cytogenetic testing such as the polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH) studies. These and similar study methods, as well as other noninvasive techniques for the detection of genetic disease, are in the process of development. Such innovations include detection of fetal cells in maternal circulation, preimplantation diagnosis, polar body biopsy, and oocyte typing.

AMNIOCENTESIS

Transabdominal Procedures

Genetic amniocentesis usually is performed after 15 completed weeks of gestation. After ultrasonic study to confirm dates, fetal viability, fetal number, fetal anatomic survey and placentation, the patient is requested to empty her bladder. The abdomen is aseptically cleansed with a povidone-iodine or another antiseptic solution, and sterile drapes are applied. Ultrasound gel is applied to a transducer, which is subsequently inserted into a sterile surgical glove or sleeve. The sterile cover is tightly wrapped around the transducer and sterile surgical lubricant is applied onto the exterior of the gloved transducer. This permits the transducer to be applied to the maternal abdomen with minimal risk of contamination. A pocket of fluid free of fetus and placenta is next identified. If an area free of placenta cannot be found, an area containing the thinnest section of the placenta away from the cord insertion is localized. Once an ideal target is noted, the skin can be infiltrated with a local anesthetic, although the author has generally found this to be unnecessary. Thereafter, under direct visualization, a 22-gauge disposable spinal needle with stylet is passed through the patient's skin and into the amniotic cavity (see Figure 2.2) [40]. The length of the standard needle is 9 cm. A needle insertion of approximately 3.5 to 4.5 cm will usually suffice to tap fluid. Thus the standard needle is appropriate for most patients. In selected obese patients, however, a longer needle might be required. In these special circumstances, evaluation by an initial scan serves as a guide to estimating the required needle length. Once the sac is entered, 20 milliliters of fluid are generally withdrawn, using at least two separate syringes. The first few milliliters are discarded to avoid maternal cell contamination [41]. This initial aliquot can be used for alpha-fetoprotein evaluation, however. Once the complete sample is obtained, the needle is promptly withdrawn. The puncture site is then observed under real-time ultrasound for fetal hemorrhage and normal fetal cardiac activity confirmed. If all is normal, this author subsequently discharges patients to home, requesting that they report any fluid loss, lower abdominal pain, cramping, contractions, or fever. Strenuous activity or coitus is discouraged for the following 24 hours, and thereafter routine activity

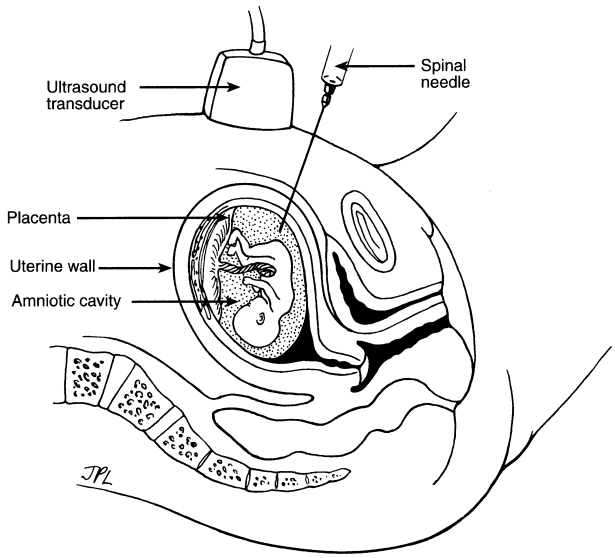

FIGURE 2.2.
Ultrasound-guided amniocenteses. Following aseptic preparations, a 5-gauge needle is guided into the amniotic cavity with the aid of real-time ultrasonography. (See text for details.)

may be resumed. Rh-negative patients subsequently receive Rh immunoglobulin (RhIG).

If, during the initial attempt, free-flowing amniotic fluid is not obtained, rotating the needle to reposition the bevel or minimal repositioning of the needle is often successful in achieving flow. Negative pressure should not be applied to the syringe during repositioning. If needle rotation or repositioning under ultrasonographic observation proves unsuccessful, a second tap attempt with a new needle is warranted. Whether repeat skin preparation is required for the second tap depends on the clinical circumstances. If a second attempt is unsuccessful, additional efforts are best postponed for 1 week [42,43]. Failure to obtain amniotic fluid is commonly due to needle misdirection, leiomyomas, uterine contractions, or membrane tenting [44,45]. The last problem problem occurs more frequently prior to 15 weeks of gestation.

Complications

The recent review by Alfirevic and Sundberg has examined the fetal loss rate associated with midtrimester amniocentesis and CVS [46]. To evaluate the clinical relevance of such studies, the baseline loss rate for ultrasonographically diagnosed viable pregnancies at that same gestation, for woman of the same age, must be known. Maternal age is a major factor in the incidence of spontaneous miscarriage. In established pregnancies, the overall spontaneous fetal loss rate is 13.6% among women 40 years of age and older, 4.5% in women in the 35- to 39-year-old group, and 1.5% among women younger than 35 years of age [47–50]. Further, *preamniocentesis maternal-serum alpha-fetoprotein* (MSAFP) elevations, if present, are associated with a significantly higher pregnancy loss rate. Read and coworkers [51] compared the outcome of 212 pregnant women undergoing amniocentesis for MSAFP elevation to the outcome of 219 pregnant women in whom a prior pregnancy had resulted in a fetus with an open neural tube defect (ONTD). The spontaneous loss rate following amniocentesis among patients with MSAFP elevation was 8% versus 2.8% among patients with prior ONTD fetus. These data suggest that many patients who undergo prenatal diagnosis (i.e., advanced maternal age and elevated MSAFP) are at increased risk for spontaneous pregnancy loss *independent* of the procedure-related risk.

Most spontaneous losses occur early in gestation. Evaluation of pregnancy loss rate by gestational age indicates that, of patients awaiting preamniocentesis counseling, 1.2% spontaneously aborted between 12 and 16 weeks. Sant-Cassia and coworkers [52] reported a 1% pregnancy loss rate between 16 and 28 weeks among controls for an amniocentesis study. These data should be included when counseling patients prior to any invasive prenatal testing.

Based on these data presented above, to evaluate studies examining procedure-related loss rates, study designs must incorporate appropriately matched control patients *not* undergoing amniocentesis. There are a number of studies addressing amniocentesis [46]. In 1976, the National Institute of Child Health and Human Development (NICHD) reported a prospective study of 1040 subjects undergoing amniocentesis compared with 992 controls matched for race, socioeconomic conditions, parity, and age [53]. The results suggested no significant differences in the fetal loss rate (3.2% in the control group versus 3.5% in the amniocentesis group), elective second-trimester termination (2.1% in the control group versus 2.3% in subjects), birthweight, 5-minute Apgar Scores, congenital

anomalies, neonatal complications, or developmental problems. Immediate maternal complications (e.g., vaginal bleeding, leakage of amniotic fluid) were reported in 2.4% of patients undergoing amniocentesis. In this series, the risk of vaginal bleeding was significantly related to the number of needle insertions. The authors concluded that mid-trimester amniocentesis was both accurate and "highly safe" and did not significantly increase the risk of pregnancy loss. Interestingly, the loss rate observed in the control group was higher than that observed in other large series, suggesting the recruitment of a high-risk control population or perhaps imperfect matching of the control group.

Simpson and coworkers [54] reported the results of the Canadian Collaborative Group Study. A pregnancy loss rate of 3.2% was observed among 1,020 pregnancies in 900 women who underwent 1,223 amniocenteses. The immediate amniocentesis complication rate was 3.6%. A significantly higher fetal loss rate was observed in pregnancies sampled with needles of 19 gauge or larger, or when more than two needle insertions were undertaken in a single day. The authors concluded that amniocentesis was "... safe, accurate and reliable ..." at about 16 weeks of gestation when carried out by an experienced clinician and monitored by ultrasound scan. This study lacked a control group, however.

The Working Party on Amniocentesis (U.K. Collaborative Study Group) [55] demonstrated a 2.4% spontaneous abortion rate among patients undergoing amniocentesis versus a 1.2% loss rate among matched controls. Furthermore, an increased risk of infantile respiratory difficulties and orthopedic abnormalities were seen among test subjects. There were, however, problems with study design; specifically, patient matching was imperfect. A significant fraction of patients in the amniocentesis group were selected on the basis of MSAFP elevation and were significantly older than the controls. In addition, in the data analysis, matched controls who spontaneously aborted were replaced with controls who had not aborted. Some controls also entered the study at older gestational ages than their matched subjects. These selection biases alone probably account for the observed differences between this study and the others previously described, and these data are to be interpreted with care.

Tabor and coworkers [56] performed a randomized, controlled study of amniocentesis on over 4,500 women aged between 24 and 34 years. Subjects and controls were matched for gestational age at entry, maternal age, prior induced and spontaneous abortions, stillbirths, low-birthweight infants, live births, smoking history and socioeconomic status. The loss rate was 0.7% in the control group and 1.7% in the subject group ($p \leq 0.01$). The study suggested an increased pregnancy loss rate in patients estimated at approximately 1% undergoing amniocentesis.

Many smaller studies of the risk of amniocentesis also have been conducted, with findings suggestive of no minimal differences between patients undergoing amniocentesis and controls. Unfortunately, not all subjects were appropriately matched with controls, rendering these results difficult to interpret. The recent comprehensive review and meta-analysis of Mujezinovic and Alfirevic [57], which appeared in September of 2007, summarized MEDLINE data published after January 1, 1995, concerning both amniocentesis and CVS. These authors noted a wide range in reported risk for pregnancy complications from these diagnostic procedures. The pooled estimate for a pregnancy loss within 14 days of an amniocentesis was 0.6% (95% CI 0.5–0.7). This provides a reasonable benchmark for clinicians to use in counseling [58].

Blood-tinged amniotic fluid is detected in 2% of amniocentesis. This event is associated with an increased fetal loss rate and can be due to either maternal or fetal bleeding. Documentation of maternal blood in the sample is associated with an increased pregnancy loss rate from 1.7% (control population) to 6.6% (hemorrhage population) [59]. Fetal blood in amniotic fluid is associated with a loss rate of up to 14.3% [60]. Perhaps not surprisingly, transplacental amniocentesis has a significantly higher loss rate than non-transplacental amniocentesis (2.9% vs. 1.2% respectively, with the control group significantly lower than both at 0.4%) [56]. MSAFP elevation following amniocentesis is more common in sampled pregnancies with anterior placentas. Such elevations are believed to result from subclinical maternal-fetal hemorrhage and, if present, are associated with an increased fetal loss rate (14% vs. 1%) [59, 60].

Following second-trimester amniocentesis, Rh sensitization is a potential complication [61]. Both

Khalil and coworkers [62] and Golbus and coworkers [63] reported a decreased risk of sensitization in Rh-negative women who routinely received RhIG following amniocentesis. Tabor and coworkers [64] could not demonstrate a significant increase to Rh sensitization following amniocentesis in Rh-negative patients who had not received RhIG. Although there is no uniformity of opinion concerning RhIG administration following midtrimester amniocentesis, the consensus is that RhIG administration *is* indicated in at-risk pregnancies to prevent Rh sensitization. The American College of Obstetricians and Gynecologists recommends the administration of 300 μg of RhIG following the procedure [65]. It has been this author's practice in the past to treat at-risk pregnancies (i.e., Rh negative and a negative maternal indirect Coomb's test), and such treatment remains the current recommendation of this author.

Up to 6% of the specimens resulting from midtrimester amniocentesis have green or brown discoloration of the fluid (53,67–69). Biochemical analysis of the pigment found in the discolored fluid reveals it to be breakdown products of hemoglobin [70]. It is highly unlikely that this fluid discoloration is from meconium passage, an event virtually restricted to late gestation. A more plausible explanation is that the staining results from occult intrauterine hemorrhage, with subsequent transmembranous passage of heme pigments.

Several studies have investigated the association between amniotic fluid discoloration and pregnancy loss. In a case-controlled study, Hankins and coworkers [68] could demonstrate no increased risks among patients found to have discolored amniotic fluid at the time of genetic amniocentesis. Nevertheless, several other studies have demonstrated a significant increase in risk of pregnancy loss in instances in which amniotic fluid discoloration is noted during mid-trimester amniocentesis [64,67,65–70]. In these studies, the spontaneous abortion rates in the control groups ranged from 1.5% to 1.6%, whereas pregnancy loss rates in the stained-fluid group ranged from 9% to 100%. Thus, amniocentesis specimens complicated by fluid discoloration (i.e., fresh blood or green/brown discoloration presumably from chronic or occult bleeding) identifies a group at increased risk for pregnancy loss. Patients with this finding should be so counseled.

Although amniocentesis is frequently performed in conjunction with real-time ultrasonography, no adequately designed prospective study has been performed to assess the value of ultrasound use in this procedure. Nonetheless, there are substantial amounts of data reflecting clinical experience. Several studies have demonstrated a reduction in the number of dry taps, needle insertions, bloody taps, failed cultures, and pregnancy losses when ultrasonography is used routinely [40,67,69–77]. Other studies have demonstrated no benefit to amniocentesis [55,78,79]. Unfortunately, most of these studies are flawed in their design, with inadequate controls, improper randomization, inappropriate crossing over, or different operators performing amniocentesis with or without ultrasound scan. Although the benefits of ultrasonographically monitored amniocentesis have not been scientifically demonstrated, in this setting the rule of reason must apply. No reports of an *increased* incidence of adverse outcomes of ultrasonically directed procedures have been published. The important assistance of direct ultrasonic guidance for intrauterine procedure is clearly recognized by clinicians. The ability of scanning to localize the pocket to be entered by the sampling needle makes the procedure easier and the operator more confident. It is this author's firm opinion that amniocentesis should *always* be ultrasound monitored.

Maternal infection following amniocentesis is rare. The risk of amnionitis has been estimated to range between 1 in 1,000–8,000 procedures. One maternal death following amniocentesis has been reported [80]. Given the extreme low risk, the use of prophylactic antibiotics for this procedure is not warranted [81].

Vaginal leakage or spotting is reported in approximately 3% of patients who undergo mid-trimester amniocentesis. Although fluid leakage can result in either oligohydramnios or pregnancy loss, successful pregnancy outcome following conservative measures and monitoring of such pregnancies is also possible. Patients must be made aware of the potential risks of such management [82].

Accidental needling of the fetus potentially resulting in skin dimpling and minor scars is believed to occur in up to 2% to 9% of procedures [83]. The magnitude of the risk for resulting skin lesions is unknown, but it is believed to be very low. Rarely, more significant anomalies have been reported

anecdotally and attributed to amniocentesis. Ultrasound monitoring of the procedure was not reported in any of these cases. Controversy exists in the literature supporting and refuting claims that neonates exposed in utero to amniocentesis are at increased risk for respiratory distress and orthopedic disorders such as talipes [84]. Although a specific risk has yet to be established, patients should be aware of these concerns and the limitations of the available data.

CHORIONIC VILLUS SAMPLING

Procedure

Prior to the attempt at transcervical biopsy (TC-CVS), a ultrasonic scan is performed to evaluate fetal viability, fetal number, placentation, and dating by crown-rump length (CRL) and gestational sac size. The latter two measurements are compared with the expected gestational age estimated from the patient's last normal menstrual period (LMP). Scheduling of procedures beyond the 9th week of gestation eliminates a substantial percentage of spontaneously aborting embryos. In addition, there are other reasons for performing procedures beyond 9 weeks, including a possible reduced incidence of fetal injuries (discussed later).

The accuracy of the reported LMP is important. Wapner and Jackson [85] reported that a discrepancy in crown-rump length more than 1 week less than predicted by menstrual dates is predictive of increased risk for spontaneous pregnancy loss. Furthermore, in patients considered for chorionic sampling based on advanced maternal age, over 10% were observed to already have an embryonic demise on the initial preprocedural ultrasound assessment.

In addition to embryologic evaluation, ultrasound scanning establishes the sites of both the chorion frondosum and of the cord insertion. Cervical and uterine anatomic relationships are also noted. Cervical manipulation and either bladder distention or emptying usually facilitate both successful visualization and completion of the procedures.

Once a thorough ultrasonic assessment is completed, the patient is placed in the dorsal lithotomy position. A sterile speculum is introduced, and the cervix is swabbed with an aseptic solution of the clinician's choice. Some operators grasp the anterior lip of the cervix with a long Allis or other forceps as an aid in manipulating the uterus and directing the catheter to the chorion. Ultrasonic reevaluation confirms uterine position and the location of the chorion frondosum. For a successful biopsy procedure, the operator must coordinate his/her activity with that of the ultrasonographer. The operator next bends the distal portion of the catheter slightly to accommodate the demonstrated curvature of the lower uterine segment. The sampling catheter is then introduced through the endocervical canal beyond the internal os at which time a loss of resistance is perceived. Further advancement is delayed until the catheter tip can be visualized ultrasonographically. Once the tip is satisfactorily identified, the surgeon advances the catheter under direct visualization toward the homogenous, hyperechoic chorion frondosum. Where the location of the chorion is uncertain, identification of the cord implantation site serves as a valuable landmark. To assist in accurate placement, catheter rotation, cervical manipulation, or speculum adjustment all could be required. Once the catheter is positioned at the near distal end of the chorion frondosum, the obturator is removed, and a 20-ml syringe containing 5 ml of tissue culture media is attached to the catheter. Using continuous negative pressure on the syringe, the surgeon withdraws the catheter gradually. After a tissue examination confirms the presence of an adequate specimen, the instruments are removed, completing the procedure. As with routine amniocentesis, the patient is directed to call if fever, heavy vaginal bleeding or severe abdominal pain, or cramps develop. She is further instructed to avoid strenuous activity or coitus during the ensuing 24 hours; thereafter she may resume normal activities.

Transabdominal chorionic villus sampling (TA-CVS) is a procedure technically very similar to transabdominal amniocentesis. Two techniques were originally described. In both, a preliminary ultrasound survey is undertaken, and the patient's skin prepped in the usual manner. In the two-needle technique, an outer needle is used as a trochar. This is introduced into the myometrium adjacent to the sampling site. A thinner, inner needle is then guided through the outer needle toward the chorion frondosum under direct ultrasound guidance. Tissue is aspirated under negative pressure into a media-containing syringe. Several passes through the entire

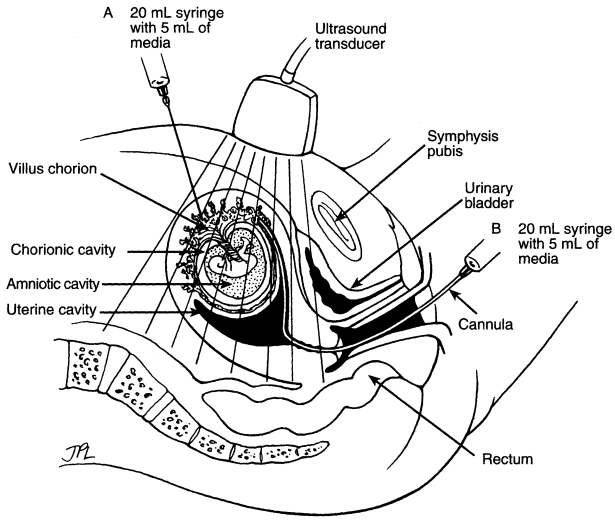

FIGURE 2.3.
Chorionic villus sampling. Using either a transcendent (A) or a transabdominal (B) approach, the chorion frondosom is sampled under 15 ml to 20 ml of negative pressure. (See text for details.)

length of the chorion are required to obtain an adequate sample.

The single-needle technique utilizes a regular 20-gauge spinal needle. The needle is simply inserted into the chorion frondosum under direct ultrasound guidance (See Figure 2.3). Once in the chorion, the stylet is removed, and a 20-ml syringe containing 5 ml of culture media is attached. Using continuous negative pressure, several passes through the entire length of the chorion frondosum are undertaken to obtain the specimen.

In both transabdominal and transcervical biopsy techniques, the specimen obtained is washed in a Petri dish and examined under sterile conditions, using a dissection microscope. An assessment of tissue type and quantity is performed immediately to ascertain the success of the biopsy. The specimen is subsequently submitted to the laboratory for processing.

There are certain contraindications to CVS. Absolute contraindications to transabdominal CVS include unavoidable myomas, a placenta not reachable through the maternal abdomen, and maternal intestines overlying the uterus. Relative contraindications include active bleeding, Rh isoimmunization, embryonic growth retardation, or maternal coagulopathy. Other possible contraindications includes low-lying myomas, a gestation greater than 12 weeks, a multiple gestation, or an overly curved sampling pathway. Contraindications unique to transcervical sampling include vaginal infection, cervical stenosis, vaginismus, the presence of an IUD, and sampling failure following two passes.

Transcervical CVS is technically possible in the window from 6 to 7 weeks' to 12 to 13 weeks' gestation. Recent reports of the association of congenital limb anomalies with CVS, in particular before the 10th week of gestation, have resulted in a restriction of CVS to gestations greater than or equal to 10 weeks in duration, however. Early and mid-trimester transabdominal CVS procedures have gained popularity as alternatives to early amniocentesis or cordocentesis in selected conditions such as severe oligohydramnios [84,86].

The overall efficacy of TA-CVS and TC-CVS are comparable. Single sampling success rates range from 96.4% to 99.5% in the TC group, and 99.4% to 99.7% in the TA group [87–96]. Although both TC-CVS and TA-CVS are equally effective, centers offering CVS should be well versed in both techniques, with a particular approach taken based on the anatomy and condition of the patient being sampled as well as the expertise of the operator.

The accuracy of CVS compares favorably with that of amniocentesis [97–100]. Amniocentesis is generally considered 99.5% accurate, whereas CVS exhibits an accuracy rate of 97.5% to 99.7% [101,102]. Maternal cell contamination (MCC) was initially a significant concern with as many as 13% of cases reported to have this complication. The incidence of MCC is now reported to range from 0.1% to 1.3% [103–106]. Most cases of MCC are found in long-term cultures, although MCC has also been found in direct preparations of chorionic villi. It is believed that the risk of MCC is reduced by meticulous dissection of the villi under a dissection microscope, comparison of both direct preparation and long-term cultures of villi, and comparison of heteromorphisms of 46XX villus cells and maternal lymphocytes. Placental mosaicism has been observed in <2% [107] of all CVS samples. On repeat testing by mid-trimester amniocentesis, approximately two thirds of suspected mosaic pregnancies are cytogenetically normal. Mosaicism noted exclusively in villi is considered *confined placental mosaicism* and is associated with an increased

risk for pregnancy loss (8.6% versus 3.5%) [107–109]. Placental mosaicism has not been proven to be associated with growth retardation, gestational hypertension, preterm labor and delivery, or abruptio placentae.

When the cytogenetic diagnosis following CVS is in doubt, amniocentesis should be offered as a confirmatory study. Up to 3% of patients who undergo CVS will require a follow-up mid-trimester amniocentesis to evaluate mosaicism, maternal cell contamination, or a subsequently elevated mid-trimester MSAFP [110]. Patients who are CVS candidates should be counseled about this possibility prior to undergoing testing.

Complications

Complications associated with CVS include vaginal bleeding, amniotic fluid leakage, infection, fetal-maternal transfusion, teratogenic effects, and fetal loss [110–113].

Vaginal spotting or bleeding occurs in up to 32% of patients with TC-CVS but is reported in only 4% to 5% of women undergoing transabdominal procedures. Intrauterine hematomas detectable at the first follow-up ultrasound scan have been noted in 3.1% to 4.0% of TC-CVS and 0.3% of TA-CVS cases. Fluid leakage is a rare complication of both procedures but is more common following transcervical operations [97]. Uterine infection ranges from 0.05% to 0.5% in TC-CVS cases. Infection has not been reported in TA-CVS. Changing of the sampling catheter with each passage through the cervix has reduced the incidence of maternal infection. Administration of 50 μg RhIG is recommended following CVS procedure in Rh-negative patients. Perinatal risks including small for dates, preterm labor, low birthweight and perinatal mortality are not increased in patients undergoing either CVS procedure.

The fetal loss rate following CVS has been examined in several studies [46, 57, 84, 86, 99, 100, 111, 114–116]. In considering these studies, remember that as in mid-trimester transabdominal procedures, both the gestational timing and maternal age are important in establishing the a priori risk. An important additional factor is operator experience.

The Canadian Collaborative CVS study [114] was the first major prospective study to appear in the literature. In this study, random assignment of 2,979 women to either CVS or to amniocentesis was undertaken. All centers performed transcervical procedures. The physicians were required to have performed a minimum of successful procedures prior to their acceptance as coinvestigators. The data revealed that the overall loss rate was 0.6% higher in the CVS group in comparison to the amniocentesis group. This difference was not statistically significant.

A similar study design was conducted by the NICHD [115]. In the NICHD study, however, acceptable randomization of the amniocentesis group could not be accomplished. The observed fetal loss rate was 7.2% for the TC-CVS group and 5.7% for the amniocentesis group. After the data for maternal age differences are adjusted, the TC-CVS group had a 0.8% higher loss rate, again not statistically significant.

The subsequent BMRC study [111] noted a significant difference in fetal loss rate between the CVS group and the amniocentesis group (13.6% and 9.0%, respectively). A careful evaluation of this study reveals that unlike the Canadian or American study, a standard method of villous sampling was not employed. Either TC-CVS or TA-CVS was performed according to operator preference. Furthermore, no criteria for operator inclusion based on experience was established in the study protocol. As TC-CVS has been shown to have a significant learning curve, this omission is believed to have influenced the results. A subsequent Danish study bears this out [116]. In this latter investigation, the fetal loss rate among patients undergoing amniocentesis was 6.4%, those undergoing TA-CVS 6.3%, and TC-CVS 10.9%. In the last group there was an inverse relationship between the fetal loss rate and the amount of tissue obtained. These data suggest that operator experience played a significant role in the observed increase in fetal loss.

In the major studies comparing TA-CVS to TC-CVS, therefore, a significant outcome difference was noted only in the Danish study. In the other studies, operators were skilled in TC-CVS before beginning the investigation, and no significant difference in outcomes for the two techniques was detected. Recent investigations with experienced practitioners have found similar outcomes [46, 57, 86, 99, 100].

Special Issues

Several studies have reported an association between CVS procedures and limb anomalies and oromandibular-limb hypogenesis [112,113]. These complications were attributed initially to procedures performed between 56 and 66 days of gestation. Vascular compromise during limb development was believed to be the causative factor [129].

Kuliev and colleagues [117] reported the results of a WHO-sponsored registry established in Philadelphia. More than 80,000 of an estimated 150,000 CVS-exposed pregnancies worldwide were reported up to May of 1992. Although clusters of limb anomalies following CVS were reported from various centers, the overall incidence among CVS-exposed pregnancies was 6/10,000 live births, comparable with the background incidence rate reported by the British Columbia Registry (5.42/10,000 live births) [118].

A retrospective cohort study performed in five obstetric centers from 1984 to 1991 reported by Gruppo Italiano Diagnosi Embrio Fetal (GIDEF) [110] analyzed the association between CVS and transverse limb reduction defects (TLRD). Outcome data were available on 2,759 of 3,420 pregnancies exposed to CVS. Assuming normal outcome in all patients lost to follow-up, a minimum overall crude rate of TLRD was found to be four times higher in the CVS-exposed group (1/1,143) than in the general Italian population (1/4,458). The rate of limb defects was higher for CVS performed at 9 weeks' gestation (2.9/1000) than at 10 weeks (1/1,000). The rate of TLRD in CVS-exposed pregnancies with completed follow-up was 1/619, representing a sevenfold increase compared with the general population.

In 1995, the Centers for Disease Control and Prevention published the results of a study of CVS-exposed pregnancies from 1988 to 1992. It was found that the risk of limb defects among CVS-exposed pregnancies ranged from 0.03% to 0.10% and represented at least a sixfold greater risk than that in the general population (0.005%). The risk and severity of limb defects appears to correlate with the timing of CVS, with a 0.20% risk observed prior to 10 weeks' gestation and a 0.07% risk at 10 weeks' gestation or greater. Furthermore, most of the defects noted following CVS at 10 weeks or greater are limited to the digits [112].

To contrast CVS and amniocentesis, the increased risk of pregnancy loss and of limb anomalies should not preclude consideration of other important issues such as the desirability to obtain results with early gestation (particularly for women with medical conditions for which pregnancy poses a substantial risk), the advantages of first-trimester pregnancy termination (particularly interruption of pregnancy by the administration of antiprogestins and prostaglandins if early CVS is considered), and the type of genetic disorders in question.

Early Amniocentesis

In the attempt to introduce first-trimester prenatal diagnosis in areas lacking a CVS program, several centers have investigated early amniocentesis as an alternative. Although technically similar to routine mid-trimester amniocentesis, early procedures are more likely to be complicated by the tenting of the amniotic sac. Needle insertion therefore must be more precise. Furthermore, most operators limit the amount of amniotic fluid aspirated to one milliliter per week of gestation. The initial experience indicated a fetal loss rate ranging from 0% to 4.7%. Success in obtaining fluid is as high as 95% with cytogenetic success rates of approximately 99%, comparing favorably with amniocentesis and CVS. Technically, amniocentesis becomes increasingly difficult before the 13th week of gestation and the rate of complications is increased, indicating that this method has a limited role in prenatal diagnosis, only partially bridging the gap between CVS and routine abdominal amniocentesis at the mid-trimester [57, 86, 99, 100].

Cochrane Review and Comparison

The Cochrane Database of Systemic Review recently updated its comprehensinve review and comparison of amniocentesis and CVS for prenatal diagnosis. The objective of this review was to assess the comparative safety and accuracy of CVS (TC and TA) and amniocentesis (early and second trimester). A total of fourteen randomized studies were included in the analysis [120].

In a comparison of amniocentesis versus control, the authors noted that an increase in spontaneous miscarriages of 0.8% among those undergoing amniocentesis relative to controls was statistically

significant (relative risk [RR] 1.6, 95% confidence interval [CI] 1.02–2.52). A 1% increase in total pregnancy loss was not statistically significant, however. Leakage of amniotic fluid was more common following amniocentesis (1.7% vs. 0.4%; RR 3.9, 95% CI 1.9–7.8), although there was no difference in vaginal bleeding between the two groups.

A comparison between early and second-trimester amniocentesis revealed that mid-trimester amniocentesis was technically less demanding and safer. Multiple needle insertions were required in 4.7% of early amniocentesis procedures, compared with only 1.7% for mid-trimester amniocentesis. Total pregnancy loss following early amniocentesis was 7.6% compared with 5.9% following mid-trimester amniocentesis (RR 1.29, 95% CI 1.03–1.61). The number of congenital anomalies (particularly the number of infants born with talipes equinovarus) was significantly higher in the early amniocentesis group (4.6% vs. 2.7%). Early amniocentesis was also associated with a higher rate of laboratory failures (1.8%) and a higher false-negative rate, compared with a 0.2% failure rate and no false-negative cytogenetic results following mid-trimester amniocentesis.

A comparison of CVS to second-trimester amniocentesis was evaluated in one of three ways: Second-trimester amniocentesis versus CVS (any route), second-trimester amniocentesis versus TC-CVS and second-trimester amniocentesis versus TA-CVS. In the comparison between second-trimester amniocentesis versus CVS by any route, the overall loss rate was significantly higher following CVS (11% vs. 8.2% RR 1.43, 95% CI 1.22–1.67) An increase in spontaneous miscarriages was the primary contributing factor to this increase (RR 1.51, 95% CI 1.23–1.85). CVS also presented greater technical challenges relative to amniocentesis. Repeated sampling was more common following TC-CVS (6.3% versus 0.2%), and laboratory failure occurred more frequently in CVS samples compared with amniocentesis samples (1.7% vs. 0.07%). There were more false-positive and false-negative results in the CVS group (2.2% vs. 0.2% and 0.3% vs. 0%, respectively) as well as more cytogenetic abnormalities confined to the placenta (2.3% vs. 0.4%). Maternal complications were uncommon following either procedure, and life-threatening complications were not reported. Vaginal bleeding was more common following TC-CVS, although no significant difference was noted in the incidence of vaginal bleeding later in pregnancy. It appears that the route of CVS might contribute to the increased loss rate observed relative to amniocentesis. TC-CVS was associated with a higher risk of pregnancy loss and risk of spontaneous miscarriage compared with amniocentesis (14.5% vs. 11%; RR 1.40 CI 1.09–1.81 and 12.9% vs. 9.4%; RR 1.50, 95% CK 1.07–2.11). No statistically significant difference in the risk of pregnancy loss and miscarriage was found in a comparison between TA-CVS and second-trimester amniocentesis, however. Studies comparing TC-CVS and TA-CVS corroborate this observation. Overall, the risk of pregnancy loss, spontaneous miscarriages, vaginal bleeding, and rate of multiple insertions appears higher in the transcervical group compared with the transabdominal group. Finally, a comparison of early amniocentesis and transabdominal CVS revealed a higher risk of pregnancy loss and spontaneous miscarriage following early amniocentesis. Furthermore, the mean number of days required for culture was two to three days greater in the early amniocentesis group compared with the TA-CVS group.

On the basis of these findings, the authors concluded that second-trimester amniocentesis is safer than early amniocentesis or TC-CVS, but that if earlier diagnosis is required, TA-CVS is preferable. When TA-CVS cannot be performed, TC-CVS or second-trimester CVS are the "preferred options."

SPECIAL CONSIDERATIONS

Multiple Gestations

The presence of a multiple gestation complicates prenatal genetic assessment and subsequent management. The ratio of dizygotic to monozygotic twins per 1,000 births approximates 2–3:1. The frequency of dizygotic twinning increases with parity and maternal age [121–125]. Based on these considerations, Rodis and colleagues [125] reconsidered the age-related risk of chromosomal aneuploidy in twin gestations, specifically the age-related risk that one or both fetuses is affected. In estimating the corresponding risks, the authors calculated that the percentage of dizygotic twinning was 80% in the population evaluated. Unfortunately, no adjustment for increased dizygotic twinning with increased age or parity was undertaken in these calculations. Hook's

[124] data on the risk of chromosomal abnormalities in singleton gestations was subsequently recalculated and weighted for the risk of monozygosity/dizygosity and for the possibility that neither, either, or both fetuses were aneuploid. In addition, a retrospective review of cytogenetic results from twin amniocentesis was undertaken.

According to the tables generated from this complex analysis, the risk to a patient at 33 years of age with a twin gestation of having at least one twin with Down syndrome is equivalent to that for a 35-year-old with a singleton pregnancy. In addition, the risk of having at least one twin with any chromosomal abnormality at the age of 32 years is 1:179 for live-born infants and 1:156 at the time of mid-trimester amniocentesis. This risk is higher than that estimated for the procedure-related fetal loss rate owing to standard mid-trimester amniocentesis in a singleton pregnancy (approximately 1:200) [125]. Although initial studies suggested the possibility of an increased risk of pregnancy loss in twin gestations because of amniocentesis [126,127], more recent data using more appropriate controls (i.e., using twin gestations, not singleton pregnancies, as the control group to assess the baseline pregnancy loss rate) indicates that there is no significant difference in fetal loss rate from amniocentesis in twin gestations, despite the need for at least two punctures. Specifically, Ghidini and coworkers [128] observed a baseline fetal loss rate of 3.2% among controls with twin gestations versus a 3.5% loss rate observed following amniocentesis of twin pregnancies. Interestingly, the loss rate of the amniocentesis group was similar to figures previously reported (3.2%–3.57%) [127], but that had previously compared unfavorably to the 0.6% loss rate observed among singleton gestations. Preliminarily, these data suggest that all patients with a twin gestation should undergo genetic counseling and be offered amniocentesis of both twins *beginning at a maternal age of 32*, because the risk of aneuploidy to at least one fetus is greater at that time than the procedure risk for amniocentesis. Unfortunately, with a background fetal loss rate of 3.2%, a study evaluating 2,300 patients in each group would be required to detect a 50% increase above baseline in the procedure-related fetal loss rate. Such studies have yet to be conducted. In counseling at the author's institution, we inform patients of these risk/benefit calculations and generally offer amniocentesis for twin pregnancies based on the earlier maternal age.

Technically, amniocentesis of a twin gestation differs from that of a singleton gestation only in the importance of the identification of the specific fetus being sampled. The standard approach to twin sampling is to identify the membrane separating both fetuses and subsequently perform sequential needle insertions into each sac. With the first insertion, amniotic fluid is aspirated and indigo carmine dye is introduced. The dye serves as a marker when performing the needle insertion into what is believed to be the second sac. The aspiration of stained fluid with the second tap suggests an inadvertent reintroduction of the needle into the original sac. Alternatively, the presence of clear fluid indicates that the second sac is being sampled. Careful documentation of the fetal relationships is necessary because the specific identification of an affected versus an unaffected fetus might be required should selective termination be considered.

As an alternative to the two-stick-and-dye procedure, Jeanty and colleagues [129] proposed a single-puncture method. In this technique, the membrane separating both sacs is visualized. A single needle insertion is undertaken, and fluid is withdrawn from the first sac. Subsequently, the same needle is simply advanced through the separating membrane under direct ultrasonic guidance and into the second sac, which is then sampled. A prospective study comparing these two techniques for efficacy and safety has yet to be performed. There have been few published studies that have examined the safety of second-trimester amniocentesis in twins. In a controlled study in which the dual puncture and dye method was used, Ghidini and coworkers did not find a significant difference in outcome [128]. Yukobowich and associates published the results of their retrospective cohort analysis. Pregnancy outcomes at 4 weeks following mid-trimester amniocentesis in twins were compared with the 4-week outcomes of a control group of twin pregancies in which amniocentesis was not performed, and compared with a control group of singleton pregnancies in which amniocentesis was performed. The rates of miscarriage for the three groups were reported to be 2.73%, 0.6%, and 0.67%, respectively ($p = 0.01$ for both comparisons). These data suggest that the

risk of miscarriage associated with amniocentesis in twins is greater than the risk of miscarriage associated with twin pregnancy alone and is greater than the risk of miscarriage following amniocentesis in singleton pregnancies [130].

Twin sampling by CVS is reliably accurate only with a monochorionic placenta or with two distinct placentas. Difficulty is encountered in attempting to sample dichorionic twins with a fused placenta. In such situations, if sampling is attempted it is best done near each of the umbilical cord insertion sites. Under these circumstances, the sampling error ranges from 2.6% to 16.6%. This underscores the need to limit such sampling to the most experienced centers or to abandon the attempt at CVS except in unusual circumstances and to use conventional amniocentesis for genetic analysis at a more advanced gestational age [131].

The technique of prenatal testing in the higher multiple gestations is similar to that for twin gestation. Unfortunately, series sufficiently large to evaluate these methods are not available. Technical problems in sampling each sac of the higher multiples are common, and successful taps are usually difficult and tedious. The procedure(s) used must be individualized.

Selective Pregnancy Termination

With genetic testing of twin pregnancies and the increased likelihood of detecting an abnormality in only one fetus, or with multifetal pregnancies from ovulation induction, the option of selective pregnancy termination needs consideration. As with all types of pregnancy termination, there are important ethical issues in selective reduction. Careful patient selection and counseling are required. Procedures, if attempted, should be performed only by experienced operators. Several methods are available, including intracardiac potassium chloride injection, cardiac tamponade, air embolization, and, most recently, percutaneous cord occlusion [132]. Although the data are limited, they do suggest relative safety for these procedures. Significant maternal complications have been reported, however. The safest and most efficacious approach to this problem awaits carefully controlled prospective studies. In the interim, selective termination can be considered in multiple gestations of four or more, or in instances in which fetal abnormalities are diagnosed in one of a twin or a triplet gestation. Not surprisingly, the earlier the procedure can be performed, the lower the risk of complications.

LABORATORY PROBLEMS

A detailed technical discussion of the laboratory aspects of prenatal genetic testing is beyond the scope of this text but is covered by several excellent reports [133–136]. Errors in prenatal diagnosis can arise in the laboratory from simple mislabeling of tubes or cultures, maternal cell contamination, pseudomosaicism, mosaicism, or misinterpretation of results. Similarly, CVS can be associated with misdiagnosis primarily because of maternal cell contamination, pseudomosaicism, and true mosaicism. Maternal cell contamination (MCC) has been reported to range from 0.1% to 1.3% of CVS specimens [134,135]. The rate of mosaicism on CVS specimens ranges from 0.6% to 0.8%. On repeat testing usually by mid-trimester amniocentesis, approximately three fourths of suspected mosaic pregnancies prove to be cytogenetically normal [114].

In cytogenetic results obtained from the randomized Danish study of TA-CVS and TC-CVS and amniocentesis, mosaicism was detected in 1% of all cases of CVS [136]. Of these, 90% were found to be confined to the placenta, 0.7% of mosaicism/pseudomosaicism were seen in amniotic fluid specimens, and only 40% of the latter were confirmed in the fetus. Pseudomosaicism was similar in cultures of chorionic villi and amniocytes (0.5 and 0.6%); MCC was more common following transcervical sampling (4.5%) compared with transabdominal sampling (1.5%).

Laboratory experience of early amniocentesis indicates that the overall culture success rates have been reported to range from 98.6% to 99.8%. Mean turn-around time ranges from 8.2 to 8.4 days compared with 6.59 to 8.3 days for amniocentesis performed after the 14th week of gestation [137, 138]. Kerber and Held [137] noted a significant increase in the number of numerical and structural aberrations in single cells and a significant increase in the frequency of numerical aberrations in multiple cells. Lockwood and Neu [138] reported abnormal karyotypes in 4.9% of their specimens but had no

clinical follow-up on these patients. Their experience is consistent with prior reports that found that 1.1% to 5% of early amniocenteses are associated with chromosomal abnormalities.

SERVICE ORGANIZATION AND QUALITY ASSURANCE

As knowledge in genetics and its clinical application increases, greater demands will be placed on developing comprehensive prenatal genetics programs. These programs will be required to provide timely, accurate information, in a format that patients can readily understand and use to make informed decisions. Toward this end, a multidisciplinary team composed of persons skilled and specialized in genetics (i.e., geneticist, genetic counselors) maternal fetal medicine (i.e., perinatologists, perinatal nurses, ultrasonographers), neonatology (i.e., neonatologists and neonatal nurses), and grief and abortion counseling (i.e., social workers and gynecologic-specialty nurses) is needed to address the issues and complications raised by this new technology. In addition, a strong referral network must be established with qualified subspecialty physicians capable of managing unique diagnosable medical and surgical complications of the fetus or newborn (e.g., pediatric neurosurgeons, urologists, and others). Technical capabilities should include high-resolution ultrasound; the technical ability for early and routine amniocentesis; CVS and mid-trimester placental biopsy capabilities; and proficiency in cordocentesis. A close working relationship with a licensed, certified cytogenetics laboratory capable of providing timely cytogenetic, molecular genetic, and prenatal screening services is essential. Twenty-four hour emergency access to the system is also necessary.

Quality assurance is an essential part of maintaining a perinatal diagnostic service. A perinatal database allowing for population estimates of specific genetic and congenital anomalies and hence identifying areas of needed services addresses this issue. Furthermore, by using a regional perinatal database prospectively, the service can routinely evaluate and compare the sensitivity and specificity of services provided (i.e., genetic consultation, ultrasound, prenatal screening and testing) to national standards, so that specific areas of strength or weakness can readily be identified and corrected. Patient satisfaction should be assessed regularly, and service adjustments made to better accommodate the special needs of families during such difficult times. Timely and effective communication among providers and between providers and the patient is essential. Systems must be in place to ensure that all relevant information is conveyed to all essential parties in a timely and accurate fashion while safeguarding the patient's confidentiality. Finally, establishing specific algorithms or protocols for certain high-volume clinical problems can standardize solutions to problems in management.

A continuous improvement model has been established by Boehm and coworkers [139] for a CVS program. Using a computerized database for the continuing analysis of complications and patient input, modifications in timing, type of procedure, and genetic counseling content were undertaken, with an overall improvement in outcome. Furthermore, areas of laboratory weakness were identified as well, with a subsequent improvement in specimen quality and turn-around time.

FUTURE TRENDS

Recent reports have demonstrated evolving technologies and screening methods in prenatal diagnosis [140–143]. As an example, the detection of nucleated fetal red blood cells in maternal blood has generated great interest. With the enhancement of cell isolation and cell culture techniques, such cells could serve as a noninvasive source for prenatal diagnosis [144]. Currently, modifications in cell sorting and isolation, and the analysis techniques of FISH and PCR are being refined, to allow these technologies to serve as a prenatal screening tests. Such capabilities would permit the screening of a far larger number of abnormalities than is currently available and would help to better identify high-risk candidates for invasive prenatal testing. In brief, these techniques involve the use of fluorescent or biotinylated monoclonal antibodies directed at fetal cells. Using a fluorescent or magnetic activated cell sorter, the antibody-labeled cells are separated from unlabeled cells. Once isolated, tagged cells are subjected to genetic tests to assess whether specific chromosomal aneuploidies (e.g., trisomy 13, 18, or 21) are present. Recent reports have demonstrated

some limited clinical success with these techniques [144]. Problems and controversy continue to arise in the sensitivity of the technique, as well as concerns about the presence of fetal cells in maternal circulation for several years after each of a woman's several pregnancies [145].

In the field of assisted reproductive technology (i.e., in vitro fertilization [IVF] programs), the use of FISH and PCR holds great promise for prefertilization (polar body biopsy) and preimplantation (blastocyst biopsy) [146,147] diagnosis of genetic abnormalities. This could help identify ideal specimens for fertilization and implantation and potentially reduce the need for subsequent invasive prenatal testing. Several reports have been published in which post-IVF biopsy of one or two cells at the eight-cell blastocyst stage was undertaken. Using appropriate DNA primers and PCR, the identification of the sex of the embryos of couples at risk of having a child with an X-linked recessive disorder has been undertaken [148]. More recently, identification of cystic fibrosis in embryos of a couple at risk has been performed [149]. In all cases, embryos believed to be genetically unaffected were selected and implanted, with the subsequent birth of a normal child. Follow-up genetic testing has confirmed the preimplantation diagnosis.

The future for prenatal genetics is clearly one of high technology and continued controversy. Whether the specific technologies discussed here will develop is less important than the overall trend they represent. The aim for genetic services is to provide a maximum of genetic diagnostic capabilities for any given pregnancy, with a minimum of fetal risk. It is worthwhile to recall that technical ability commonly is far in advance of our ability to understand and manage the ethical, social, and personal implications of such studies, however. Physicians must continue to embrace new technologies while carefully weighing these abilities, to be certain that the advances and benefits for patient and practitioner are real and within our capacity to manage.

REFERENCES

1. McKusik VA: A 40-year prospective on the evolution of a medical specialty from a basic science. JAMA 1993; 270:2351–2356.
2. Baird PA, Anderson TW, Newcombe HB, Lowry B: Genetic disorders in children and young adults: A population study. Am J Hum Genet 1988; 42:677–693.
3. Hall JG, Powers EK, McIlvaine RT, Ean VH: The frequency and financial burden of genetic disease in a pediatric hospital. Am J Med Genet 1978; 1:417–436.
4. Reich E, Wallace S, Ben-Yishay M, Schlesinger S, Marks J, Bloom A: Genetic disease in a pediatric hospital. Am J Hum Genet 1972; 26: 71A.
5. Emery AEH, Rimoin DL (eds): Principles and Practice of Medical Genetics, Second Edition. Edinburgh: Churchill Livingstone, 1990.
6. Nevin NC: Trends in prevalence of congenital abnormalities. In: Drife JO, Donnai D (eds): Antenatal Diagnosis of Fetal Abnormalities. London: Springer-Verlag, 1991; 3–11.
7. Liston R, Sawchuck D, Young D, Society of Obstetrics and Gynaecologists of Canada; British Columbia Perinatal Health Program: Fetal health surveillance: Antepartum and intrapartum, consensus guideline. J Obstet Gynaecol Can 2007; 29(9 Suppl 4):53–56.
8. Sekizawa A, Purwosunu Y, Matsuoka R, Koide K et al: Recent advances in non-invasive prenatal DNA diagnosis through analysis of maternal blood. J Obstet Gynaecol Res 2007; 33(6):747–764.
9. Williams C: Dilemmas in fetal medicine: Premature application of technology or responding to women's choice? Social Health Iiin 2006; 28(1):1–20.
10. Mennuti MT: Genetic screening in reproductive health care. Clin Obstet Gynecol 2008; 51(1):3–23.
11. Lambl D: Ein seltener fall von hydramnios. Zent Fur Gynakol 1881; 5:329–334.
12. Schatz F: Eine besondere Art von einseitiger polyhydramnie mit anderseitiger oligohydramnie bei einagueu Zwillingen. Arch Gynakol 1882; 19:329–369.
13. Prochownick L: Beitrage zur lehre vom fruchtwasser und seiner entsellung. Arch Gynakol 1887; 11:305–345.
14. Henkel M: Akutes hydramnion, leberkompression, enges becken, punkition des hydramnion. Zenrt Fur Gynakol 1919; 43:841–846.
15. Fuchs F, Riis P: Antenatal sex determination. Nature. 1956; 117:330.

16. Makowsi EL, Perm K, Kaiser IH: Detection of sex of fetus by the incidence of sex chromatin in nuclei of cells in amniotic fluid. Science 1956; 123:542–543.
17. Shettles LB: Nuclear morphology of cells in human amniotic fluid in relation to sex of infant. Am J Obstet Gynecol 1956; 71:834–838.
18. Bevis DCA: The antenatal prediction of haemolytic disease of the newborn. Lancet 1952; 1:395–398.
19. Riis P, Fuchs F: Antenatal determination of foetal sex in prevention of hereditary disease. Lancet 1960; ii:180–182.
20. Serr DM, Margolis E: Diagnosis of fetal sex in a sex-linked hereditary disorder. Am J Obstet Gynecol 1964; 88:230–232.
21. Steele MW, Berg WR, JR: Chromosome analysis of human amniotic fluid cells. Lancet. 1966; 1:383–385.
22. Jacobson CB, Barter RN: Intrauterine diagnosis and management of genetic defects. Am J Obstet Gynecol 1967; 99:795–807.
23. Valenti C, Schutta EJ, Kehaty T: Prenatal diagnosis of Down's syndrome. Lancet 1968; 2:220.
24. Nadler HL: Antenatal detection of hereditary disorders. Pediatrics 1968; 42:912–918.
25. Nadler HL, Gerbie AB: Role of amniocentesis in the intrauterine detection of genetic disorders. N Engl J Med 1970; 282:596–599.
26. Johnson A, Gomilow L: Genetic amniocentesis at 14 weeks of less. Clin Obstet Gynecol 1988; 31: 345–352.
27. Mohr J: Foetal genetic diagnosis: development of techniques for early sampling of foetal cells. Acta Pathol Microbiol Scand 1968; 73:73–77.
28. Hahnemann N: Early prenatal diagnosis; a study of biopsy techniques and cell culturing from extraembryonic membranes. Clin Genet 1974; 6:294–306.
29. Kullander S, Sandahl B: Fetal chromosome analysis after transcervical placental biopsies during early pregnancy. Acta Obstet Gynecol Scand 1973; 52:355–359.
30. Department of Obstetrics and Gynecology, Tietung Hospital of Anshan Iron and Steel Co. Anshan, China: Fetal sex prediction by sex chromatin of chorionic villi cells during early pregnancy. Chinese Med J 1975; 1:117–126.
31. Horwell DH, Loeffler FE, Coleman DV: Assessment of a transcervical aspiration technique for chorionic villus biopsy in the first trimester of pregnancy. Br J Obset Gynaecol 1983; 90:196–198.
32. Liu DT, Mitchell J, Johnson J, Wass DM: Trophoblast sampling by blind transcervical aspiration. Br J Obstet Gynaecol 1983; 90:1119–1123.
33. Rhine SA, Cain JL, Cleary RE, Palmer CG, Thompson JF: Prenatal sex detection with endocervical smears: Successful results utilizing Y-body fluorescence. Am J Obstet Gynecol 1975; 122: 155–160.
34. Rhine SA, Palmer CG, Thompson JF: A simple alternative to amniocentesis for first-trimester prenatal diagnosis. Birth Defects 1977; 12:231–247.
35. Goldberg MF, Chen ATL, Ahn YW, Reidy JA: First-trimester fetal chromosomal diagnosis using endocervical lavage: A negative evaluation. Am J Obstet Gynecol 1980; 138:436–439.
36. Kazy Z, Rozovsky IS, Bahkarev VA: Chorion biopsy in early pregnancy: A method of early prenatal diagnosis for inherited disorders. Prenat Diagn 1982; 2:39–40.
37. Ward RHT, Modell B, Petrou M, Karagozlu F, Douratsos E: Method of sampling chorionic villi in the first trimester of pregnancy under guidance of real-time ultrasound. Br Med J 1983; 286:1542–1544.
38. Simoni G, Brambati B, Daesino C, et al: Efficient direct chromosome analyses and enzyme determinations from chorionic villi samples in the first trimester of pregnancy. Hum Genet 1983; 63:349–357.
39. Smidt-Jensen S, Hahnemann N, Jensen PKA, Therkelsen AJ: Experience with transabdominal fine-needle biopsy from chorionic villi in the first trimester – an alternative to amniocentesis. Clin Genet 1984; 26:272–274.
40. Jeanty P, Rodesch F, Romero R, Venus I, Hobbins JC: How to improve your amniocentesis technique. Am J Obstet Gynecol 1983; 146:593–596.
41. Benn PA, Hsu LYF: Maternal cell contamination of amniotic fluid cell cultures: Results of a US nationwide survey. Am J Med Genet 1983; 15:297–305.
42. Verp MS, Gerbie AB: Amniocentesis for prenatal diagnosis. Clin Obstet Gynecol 1981; 24:1007–1020.
43. Turnbull AC, MacKenezie IZ: Second trimester amniocentesis and termination of pregnancy. Br Med Bull 1983; 39:315–321.
44. Finberg HJ, Frigoletto FD: Sonographic demonstration of uterine contraction during amniocentesis. Am J Obstet Gynecol 1981; 9:740–742.

45. Platt LD, DeVore GR, Gimovsky ML: Failed amniocentesis: The role of membrane tenting. Am J Obstet Gynecol 1982; 144:479–480.
46. Alfirevic Z, Sundberg K, Brigham S: Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2003; 3, CD 003252.
47. Wilson RD, Kendrick V, Wittmann BK, McGillivray BC: Risk of spontaneous abortion in ultrasonically normal pregnancies. Lancet 1984; 2:920–921.
48. Stein ZA: A woman's age: Child bearing and child rearing. Am J Epidemiol 1985; 327–342.
49. Gilmore DH, McNay MB: Spontaneous fetal loss rate in early pregnancy. Lancet 1985; 1:107.
50. MacKenzie WE, Holmes DS, Newton JR: Spontaneous abortion rate in ultrasonographically viable pregnancies. Obstet Gynecol 1988; 71:81–83.
51. Read AP, Donnai D, Harrs R, Donnai P: Comparison of pregnancy outcome after amniocentesis for previous neural tube defect or raised maternal serum alpha fetoprotein. Br J Obstet Gynaecol 1980; 87:372–376.
52. Sant-Cassia LJ, MacPherson MBA, Tyack AJ: Midtrimester amniocentesis: Is it safe? A single-centre controlled prospective study of 517 consecutive amniocentesis. Br J Obstet Gynaecol 1984; 736–744.
53. NICHD National Registry for Amniocentesis Study Group: Midtrimester amniocentesis for prenatal diagnosis-safety and accuracy. JAMA 1976; 239:1471–1476.
54. Simpson NE, Dallaire L, Miller JR et al: Prenatal diagnosis of genetic disease in Canada: Report of a collaborative study. Can Med Assoc J 1976; 115:739–746.
55. Working Party on Amniocentesis: An assessment of hazards of amniocentesis. Br J Obstet Gynaecol. 1978; 85(Suppl):1–41.
56. Tabor A, Philip J, Madser M, Bang J, Obel EB, Norgaard-Pedersen B: Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986; 1:1287–1289.
57. Mujezin Ovic F, Alfirevic Z: Procedure-related complications of amniocentesis and chorionic villus sampling: A systems review. Obstet Gynecol 2007 Sept 110(3):687–694.
58. American College of Obstetricians and Gynecologists: Invasive prenatal testing for aneuploidy Practice Bulletin Number 88, December 2007. Washington, DC: American College of Obstetricians and Gynecologists.
59. Zipursky A, Pollock J, Chown B, Israes LG: Transplacental fetal hemorrhage after placental injury during delivery amniocentesis. Lancet 1963; 2:493–498.
60. Mennuti MT, DiGaetano A, McDonnell A, Cohen AW, Liston RM: Fetal-maternal bleeding associated with genetic amniocentesis. Obstet Gynecol 1983; 62:26–30.
61. Hill LM, Platt LD, Kellogg B: Rh-sensitization after genetic amniocentesis. Obstet Gynecol 1980; 56:459–461.
62. Khalil MA, Tabsh K, Lobherz TB, et al: Risks of prophylactic anti-D immunoglobulin after second-trimester amniocentesis. Am J Obstet Gynecol. 1984; 149:225–226.
63. Golbus MS, Stephens JD, Cann HM, et al: Rh-isoimmunization following genetic amniocentesis. Prenat Diagn 1982; 2:149–156.
64. Tabor A, Jerne D, Bok JE: Incidence of rhesus immunization after genetic amniocentesis. Br Med J 1986; 293:533–536.
65. American College of Obstetricians and Gynecologists: Prevention of D Isoimmunization. Practice Bulletin. Number 4, May 1999. Washington DC: American College of Obstetricians and Gynecologists.
66. Karp LE, Schiller HS: Meconium staining of amniotic fluid at mid-trimester amniocentesis. Obstet Gynecol 1977; 50:47s–49s.
67. Cruikshank DP, Varner MW, Cruikshank JE, et al: Midtrimester amniocentesis: an analysis of 923 cases with neonatal follow-up. Am J Obstet Gynecol 1983; 146:204–211.
68. Hankins GD, Rowe J, Quirk JG, et al: Significance of brown and/or green amniotic fluid at the time of second-trimester genetic amniocentesis. Obstet Gynecol 1984; 64:353–358.
69. Dacus JV, Wilroy RS, Summit RL, et al: Genetic amniocentesis: A twelve years' experience. Am J Med Genet 1985; 20:443–452.
70. Zorn EM, Hanson FW, Greve LC, et al: Analysis of the significance of discolored amiotic fluid detected at mid-trimester amniocentesis. Am J Obstet Gynecol 1986; 154:1234–1240.
71. Milunsky A, Atkins L: Prenatal diagnosis of genetic disorders: An analysis of experience with 600 cases. JAMA 1974; 230:232–235.

72. Kerenyi TD, Walker B: The preventability of "bloody taps" in second-trimester amniocentesis by ultrasound scanning. Obstet Gynecol 1977; 50:61–64.
73. Crandall BF, Howard J, Lebhertz TB, et al: Follow up of 2000 second-timester amniocenteses. Obstet Gynecol 1980; 56:625–628.
74. Benaceraff BR, Frigoletto FD: Amniocentesis under continuous ultrasound guidance: A series of 232 cases. Obstet Gynecol 1983; 62:760–763.
75. McDicken WN, Anderson T, MacKenzie WE, et al: Ultrasonic identification of needle tips in amniocentesis. Lancet 1984; 2:198–199.
76. Romero R, Jeantly P, Reece EA, et al: Sonographically monitored amniocentesis to decrease intraoperative complications. Obstet Gynecol 1985; 65:426–430.
77. Williamson RA, Varner MW, Grant SS: Reduction in amniocentesis risks under real-time guide procedure. Obstet Gynecol 1985; 65:751–755.
78. Gerbie AB, Shkolnik AA: Ultrasound prior to amniocentesis for genetic counseling. Obstet Gynecol 1975; 46:716–719.
79. Karp LE, Rothwell R, Conrad SH, Hoehn HW, Hickok DE: Ultrasonic placental localization and bloody taps in mid-trimester amniocentesis for prenatal diagnosis. Obstet Gynecol 1977; 50:589–593.
80. Thorp JA, Helfgott AW, King EA, King AA, Minyard AN: Maternal death after second-trimester genetic amniocentesis. Obstet Gynecol 2005; 105(5 Pt 2):1213–1215.
81. MacLachlan NA: Amniocentesis. In: Brock DJH, Rodeck CH, Ferguson-Smith MA (eds): Prenatal Diagnosis and Screening. Edinburgh: Churchhill Livingstone, 1992; 17.
82. Simpson JL, Socol ML, Aladjem S, et al: Normal fetal growth despite persistent amniotic fluid leakage after genetic amniocentesis. Prenat Diagn 1981; 1:277–279.
83. Raimer SS, Raimer BG: Needle puncture scars from mid-trimester amniocentesis. Arch Dermatol 1984; 120:1360–1362.
84. Philip J, Silver RK, Wilson RD, Thom EA et al. for the NICHD EATA Trial Group: Late first trimester invasive prenatal diagnosis: Results of an international randomized trial. Obstet Gynecol 2004; 103(6):1164–1173.
85. Wapner RJ, Jackson L: Chorionic villus sampling. Clin Obstet Gynecol 1988; 31:328–344.
86. Cauqhey AB, Hopkins LM, Norton ME: Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. Obstet Gynecol 2006; 108(3 Pt 1):612–616.
87. Dalpra L, Nocera G, Tibiletti MG, et al: "Late" chorionic villus sampling: Cytogenetics aspects. Prenat Diagn 1993; 13:239–246.
88. Smidt-Jensen S, Ludsteen C, Lind AM, Dinesen K, Philip J: Transabdominal chorionic villus sampling in the second and third trimester of pregnancy: Chromosome quality, reporting time and feto-maternal bleeding. Prenat Diagn 1993; 13: 957–969.
89. Bovicelli L, Rizzo N, Montacuti V, et al: Transabdominal chorionic villus sampling: Analysis of 350 consecutive cases. Prenat Diagn 1988; 8: 495–500.
90. Green JE, Dorfmann A, Jones SL, et al: Chorionic villus sampling: Experience with an initial 940 cases. Obstet Gynecol 1988; 71:208–212.
91. Jahoda MGJ, Pijpers L, Reuss A, et al: Evaluation of transcervical chorionic villus sampling with a completed follow-up of 1550 consecutive pregnancies. Prenat Diagn 1989; 9:621–628.
92. Leschot NJ, Wolf H, Van Prooijen-Knejt AC, et al: Cytogenetic findings in 1250 chorionic villus samples obtained in the first trimester with clinical follow-up of the first 1000 pregnancies. Br J Obstet Gynaecol 1989; 96:663–670.
93. Miny P, Basaran S, Pawlowitzki IH, et al: Validity of cytogenetic analysis from trophoblastic tissue throughout gestation. Am J Med Genet 1989; 33:136–141.
94. Brambati B, Lanzani A, Tului L: Transabdominal and transcervical chorionic villus sampling: Efficiency and risk evaluation of 2411 cases. Am J Med Genet 1990; 35:160–164.
95. USNICHD Collaborative CVS Group: Transcervical and transabdominal chorionic villus sampling are comparably safe procedures for first-trimester prenatal diagnosis: Preliminary analysis. Am J Hum Genet 1990; 47:A278.
96. Brambati B, Terzian E, Tognoni G: Randomised clinical trial of transabdominal versus transcervical chorionic villus sampling methods. Prenat Diagn 1991; 11:285–293.
97. Brambati B, Tului L, Simoni G, Travi M: Prenatal diagnosis at 6 weeks. Lancet 1988; 2: 397.

98. Monni G, Ibba RM, Lai R, Cau G, Mura S, Olla G, et al: Early transabdominal chorionic villus sampling in couples at high genetic risk. Am J Obstet Gynecol 1993; 168:170–173.
99. Brambati B, Tului L: Chorionic villus sampling and amniocentesis: Prenatal diagnosis: Curr Opinion Obstet Gynecol 2005;17(2):197–201.
100. Wapner RJ: Invasive prenatal diagnostic techniques. Semin Perinatol 2005; 29(6):401–404.
101. Holzgreve W, Miny P, Gerlach B, Wensterdorp A, Ablert D, Horst J: Benefits of placental biopsy for rapid karyotyping in the second and third trimester (late chorionic villus sampling) in high-risk pregnancies. Am J Obstet Gynecol 1990; 162:1188–192.
102. Williams J III, Medearis AL, Chu WH, Kovacs AD, Kaback MM: Maternal cell contamination in cultured chorionic villi: Comparison of chromosome Q-polymorphisms derived from villi, fetal skin and maternal lymphocytes. Prenat Diagn 1987; 7:315–322.
103. Roberts E, Duckett DP, Lang CD: Maternal cell contamination in chorionic villus samples assessed by direct preparation and three different culture methods. Prenat Diagn 1988; 8:635–640.
104. Wright DJ, Bradley BA, Koppitich FC, Drugan A, Johnson M, Evans MI: Interpretation of chorionic villus sampling laboratory results are just as reliable as amniocentesis. Obstet Gynecol 1989; 74:739–744.
105. Ledbetter DH, Martin AO, Verlinsky Y, et al: Cytogenetic results of chorionic villus sampling; high success rate and diagnostic accuracy in the United States collaborative study. Am J Obstet Gynecol 1990; 2:495–501.
106. Ledbetter DH, Zachary JM, Simpson JL, et al: Cytogenetics results from the US Collaborative Study on CVS. Prenat Diagn 1992; 12:317–345.
107. Boris BT, Ch R, Williamssss S III: Mosaicism in chorionic villus sampling; an analysis of incidence and chromosomes involved in 2612 consecutive cases. Prenat Diagn 1993; 13:179–190.
108. Johnson A, Wapner RJ, Davis GH, Jackson LG: Mosaicism in chorionic villus sampling: An association with poor perinatal outcome. Obstet Gynecol 1990; 75:573–577.
109. Wapner RJ, Simpson JL, Golbus MS, et al: Chorionic mosaicism: Association with fetal loss but not with adverse outcome. Prenat Diagn 1992; 12:347–355.
110. Ammala P, Hilesmaa VK, Liukkonen S, Saisto T, Teramo K, Vonkoskull H: Randomized trial comparing first-trimester transcervical chorionic villus sampling and second-trimester amniocentesis. Prenat Diagn 1993; 13:919–927.
111. Medical Research Council Working Party on the Evaluation of Chorion Villus Sampling: Medical Research Council European trial of chorionic villus sampling. Lancet 1991; 377:1491–1496.
112. Olney RS, Khoury MJ, Alo CJ, Costa P, Edmonds LD, et al: Increased risk for transverse digital deficiency after chorionic villus sampling: Results of the United States Multistate Case-Controlled Study, 1988–1992. Teratology 1995; 51(1): 20–29.
113. Golden CM, Ryan LM, Holmes LB: Chorionic villus sampling: A distinctive teratologic effect on fingers? Birth Defects Res A Clin Mol Teratol 2003; 67(8)557–562.
114. Canadian Collaborative CVS–Amniocentesis Clinical Trial Group: Mullticentre randomized clinical trial of chorion villus sampling and amniocentesis. Lancet 1989; 1:1–6.
115. Rhoads GG, Jackson LG, Schlesselman SE, et al: The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. N Engl J Med 1989; 320:609–617.
116. Smidt-Jensen S, Permin M, Philip J, et al: Randomised comparison of amniocentesis and transabdominal and transcervial chorionic villus sampling. Lancet 1992; 340:1237–1244.
117. Kuliev AM, Modell B, Jackson L, Simpson JL, Brambati B, Rhoads G, et al: Risk evaluation of CVS. Prenat Diagn 1993; 13:197–208.
118. Froster-Iskenius VA, Baird PA: Limb reduction defects in over one million consecutive live births. Teratology 1989; 39:127–135.
119. Mastroiacovo P, Tozzi AE, et al: Transverse limb reduction defects after chorionic villus sampling: a retrospective cohort study. Prenat Diagn 1993; 13:1051–1056.
120. Alfirevic, Z, Sundberg K, Birgham S: Amniocentesis and chorionic villus sampling for prenatal diagnosis [Review]. The Cochrane Library 2005; 4. Update Software, Oxford.
121. Waterhouse JAH: Twinning in twin pedigrees. Br J Soc Med 1950; 4:197–216.

122. Bulmer MG: Twinning rate in Europe during the war. Br Med J 1959; 1:29–30.
123. Myrianthopoulos NC: An epidemiologic survey of twins in a large prospectively studied population. Am J Hum Genet 1970; 22:611–629.
124. Nicolaides KH: The 11–14 weeks scan 2004; London: Fetal Medicine Foundation. pg. 10.
125. Rodis JF, Egan JFX, Craffey MS, Ciarleglio L, Greenstein RM, Scorza WE: Calculated risk of chromosomal abnormalities in gestations. Obstet Gynecol 1990; 76:1037–1041.
126. Palle C, Andersen JW, Tabor A, Lauritsen JG, Bang J, Phillips J: Increased risk of abortion after genetic amniocentesis in twinpregnancies. Prenat Diagn 1983; 3:83–89.
127. Anderson RL, Goldberg JD, Golbus MS: Prenatal diagnosis in multiple gestation: 20 years' experience with amniocentesis. Prenat Diagn 1991; 11:263–270.
128. Ghidini A, Lynch L, Hicks C, Alvarez M, Lockwood CJ: The risk of second-trimester amniocentesis in twin gestations: A case-control study. Am J Obstet Gynecol 1993; 169:1013–1016.
129. Jeanty P, Shah D, Roussis P: Single-needle insertion in twin amniocentesis. J Ultrasound Med 1990; 9:511–517.
130. Yukobowich E, Anteby EY, Cohen SM, Lavy Y, Granat M, Yagel S: Risk of fetal loss in twin pregnancies undergoing second-trimester amniocentesis. Obstet Gynecol 2001; 98:231–234.
131. Brambati B, Tului L, Travi M, et al: First-trimester genetic diagnosis in multiple pregnancy: Principles and potential pitfalls. Prenat Diagn 1991; 11:767–774.
132. Quintero RA, Reich H, Puder KS, Bardneff M, Evans MI, Cotton DB, Romero R: Brief report: Umbilical cord ligation of an acardiac twin by fetoscopy at 19 weeks' gestation. N Engl J Med 1994; 330:469–471.
133. Hsu LYF: Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Milunsky A (ed): Genetic Disorders and the Fetus. Third Edition. Baltimore: Johns Hopkins University Press, 1992; pp. 155–210.
134. Wright DJ, Brindley BA, Koppitch FC, Drugan A, Johnson MP, Evans MI: Interpretation of chorionic villus sampling laboratory results are just as reliable as amniocentesis. Obstet Gyencol 1989; 74:739–744.
135. Ledbetter DH, Martin AO, Verlinsky Y, et al: Cytogenetic results of chorionic villus sampling: High success rate and diagnostic accuracy in the United States collaborative study. Am J Obstet Gynecol 1990; 162:495–501.
136. Smidt-Jensen S, Lind AM, Permin M, Zachary JM, Windsteen C, Philip J: Cytogenetic analysis of 2928 CVS samples and 1075 amniocentesis from randomized studies. Prenat Diagn 1993; 13:723–740.
137. Kerber S, Held KR: Early genetic amniocentesis – 4 years experience. Prenat Diagn 1993; 13:21–27.
138. Lockwood DH, Neu RL: Cytogenetic analysis of 1375 amniotic fluid specimens from pregnancies with gestational age less than 16 weeks. Prenat Diagn 1993; 13:801–805.
139. Boehm F, Salyer SL, Dev VG, Reed CW: Chorionic villus sampling: Quality control – a continuous improvement model. Am J Obstet Gynecol 1993; 168:1766–1777.
140. Weisz B, Rodeer CH: An update on antenatal screening for Down's syndrome and specific implications for assisted reproduction pregnancies. Hum Reprod Update 2006; 12(5):513–518.
141. Ball RH, Caughey AB, Malone FD et al: FASTER research consortium. First and second trimester evaluation of risk for Down syndrome. Obstet Gynecol 2007; 110(1):10–17.
142. Natarajan G, Klein MD: The fetus as a patient: Prenatal diagnosis and fetal therapy. Medicine (imedicine.com) 2006, topic-2953.
143. Breathnach FM, Malone FD, Lambert Messerlian G, et al, FASTER research consortium: First and second trimester screening: Detection of aneuploidies other than Down syndrome. Obstet Gynecol 2007; 40(3): 651–657.
144. Simpson JL, Elias S: Isolating fetal cells from maternal blood: Advances in prenatal diagnosis through molecular technology. JAMA 1993; 270:2357–2361.
145. Hamada H, Arirami T, Hamaguchi H, Kubo T: Fetal nucleated cells in maternal peripheral blood after delivery. Am J Obstet Gynecol 1994; 170:1188–1193.
146. Navidi W, Arnheim N: Using PCR in preimplantation genetic disease diagnosis. Hum Reprod 1991; 6:836–849.
147. Marik JJ: Preimplantation genetic diagnosis. emedicine (imedicine.com) 2005, Topic-3520.

148. Hardyside AH, Kontogianni EH, Hathy K, Winston AML: Pregnancies from biopsied human perimplantation embryos sexed by 4 specific DNA amplification. Nature 1990; 344:768–770.

149. Handyside AH, Lesko JG, Tarin JJ, Winston RMC, Hughes MR: Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis. N Engl J Med 1992; 327:909.

Chapter 3 ULTRASOUND EXAMINATION

Alisa B. Modena
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Stuart Weiner

. . . For a diagnostic technique to be acceptable it must not involve the patient in pain, indignity or hazard. Sonar meets these requirements admirably.

Ian Donald (1910–1987)
Practical Obstetric Problems
London: Lloyd – Luke, 5th Edition, 1979, p. 1020

Traditionally, ultrasonography has been a means to guide antepartum obstetric management. Recently, investigators have focused on expanding its use in the labor and delivery suite, from the triage of high-risk patients to its assistance in the third stage of labor and postpartum evaluation. Additionally, the use of ultrasound scanning in the intrapartum assessment of patients in labor and its invaluable utility to guide invasive procedures are being examined. This chapter reviews several of these recent advances: cervical length evaluation as a predictor of preterm delivery and for the selection of appropriate induction of labor candidates; the evaluation of uterine bleeding; the monitoring of intrapartum fetal weight, presentation, and fetal well-being; and the guidance of invasive procedures. Furthermore, the authors wish to demonstrate the role of ultrasonography in aiding the understanding of aberrations from the expected course of descent and rotation of the fetus, choosing the proper operative delivery technique, guiding delivery of the second of twins, assessing retained placental tissue, and monitoring the maternal anal sphincter for nonapparent damage that could benefit from repair in the puerperium.

CERVICAL LENGTH ASSESSMENT

Assessment of the uterine cervix has been accomplished with the assistance of ultrasonography for the past three decades. As technology has improved significantly, newer and more reliable techniques of evaluation have become the standard care for the evaluation of this portion of female anatomy. Why is accurate assessment of this particular structure important?

Determination of the length of the uterine cervix is vital to the evaluation of patients with obstetric pathologies. It is important in the assessment of the patient experiencing preterm uterine contractions and is crucial in the estimation of the risk of premature delivery in women with a history of prior preterm delivery. Sonographic assessment of the cervix has been established as a reliable means of measuring the cervical length and as an important component in the prediction of preterm labor.

It has been postulated and confirmed in the literature that as the cervix shortens in length, the risk for preterm birth increases [1]. Traditionally, digital examination was the method of choice to evaluate the cervix; unfortunately, this technique is limited by both significant variation among examiners and the inability to assess the proximal portion of the cervix and the internal os [2].

Cervical length measurement as a tool for predicting cervical readiness for induction of labor has also been evaluated. Investigation of cervical length to predict outcome in labor induction has demonstrated this parameter to be associated with the more accurate prediction of successful induction beyond more traditional methods, including the Bishop score [3–5]. Finally, sonography of the uterine cervix can delineate numerous anatomic features and establish relationships to other pelvic organs efficiently and reproducibly.

There are three ways to evaluate the cervix by ultrasound scan: *transabdominal*, *transvaginal*, and *transperineal*. Initially, sonographers imaged the uterine cervix by a transabdominal approach. Although not as challenging technically as other methods, accurate transabdominal imaging of the cervix requires the gravida have a full bladder to provide an acoustic window through which cervical length and anatomy can be seen. Visualization of the cervix by a transabdominal approach can be limited by partial fullness of the patient bladder, maternal body habitus, or shadowing from a fetal presenting part. Conversely, overdistention of the bladder can artificially extend and flatten the underlying lower uterine segment and cervix, yielding an incorrect assessment of its length and dilatation. Currently, transabdominal sonography of the cervix is used to screen the length of the cervix during an examination, whereas other techniques of measuring the cervix are used for more definitive evaluation. Owing to the difficulty in obtaining an accurate image for the reasons listed previously, transvaginal or transperineal sonography are typically preferred over transabdominal or are used as complementary examinations.

Transvaginal sonography replaced transabdominal sonographic evaluation of the cervix once it was established to provide a more accurate assessment of cervical length and pathology [6–8]. Transvaginal sonography can be performed with a variety of transducer types using higher sound frequencies than transabdominal sonography because the region of interest is nearer to the probe. This characteristic confers better anatomic resolution of the cervix. It can be difficult at first for the sonographer to adapt to the more restricted field of view obtained with this type of probe, however. Initially, it was thought that inserting an ultrasound probe into the vagina could be potentially hazardous in specific circumstances. Several studies have looked at potential contraindications to transvaginal sonography, including preterm labor, chorioamnionitis in preterm ruptured membranes, and placenta previa, and found that there is no true clinical risk or contraindication to performing this procedure in these groups of patients [9–10].

In a transvaginal examination, the patient is placed in a supine position with hips abducted; a full bladder is not required. A 3.5- to 8-MHz transducer (properly sterilized according to the manufacturer's recommendations) sheathed in a probe cover is inserted halfway between the introitus and cervix. Initial insertion can be done by or with the assistance of the gravida herself. The operator should handle the probe lightly, taking care to avoid excessive pressure on the anterior cervical lip, which can lead to a falsely increased measurement of cervical length. Guidelines have been established for transvaginal sonography to reduce interobserver variability. The entire length of the cervical canal should be visualized (see Figure 3.1); the external os should appear symmetric, and the distance from the surface of the posterior lip to the cervical canal is equal to the distance from the surface of the anterior lip to the

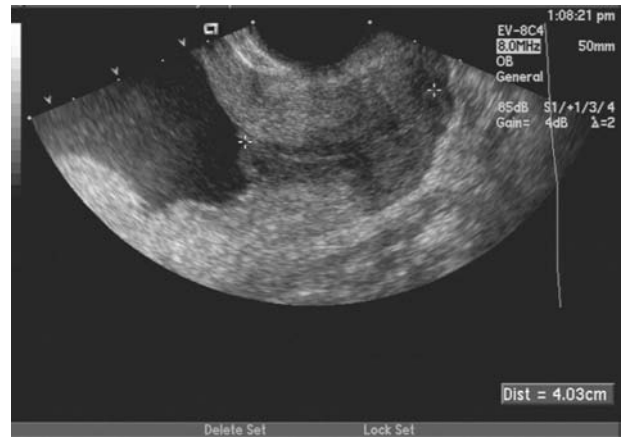

FIGURE 3.1.
Normal cervix.

cervical canal. Finally, the internal os should be visualized as a flat dimple or an isosceles triangle [11].

Transperineal or translabial sonography is typically well tolerated by the patient and should be considered when there are any concerns about the risk of infection or inciting bleeding, or when a vaginal probe transducer is not available. A 3.5- to 5.0-MHz sector or curvilinear transducer covered with a sheath is applied in the sagittal plane to the patient's perineum. Partial fullness of the bladder assists in the visualization of the cervix by conveying sound waves toward the cervix and by being an identifiable landmark. The cervical canal is generally oriented at a right angle from the distal vagina and can be assessed using the same landmarks described above for transvaginal sonography. Transperineal sonography has been observed to have a good correlation with transvaginal sonography for accurate cervical length measurement [12]; however, it remains technically more challenging because of the less familiar orientation of the anatomy and thus is less frequently performed.

Endocervical length varies by modality used. Transvaginal sonography has been shown to be the method most amenable to standardization, providing the highest degree of consistency for cervical measurement. Several studies described cervical lengths by transabdominal sonography (mean 3.2 cm–5.3 cm), transvaginal sonography (mean 3.2 cm–4.8 cm) and transperineal sonography (mean 2.9 cm–3.5cm) [8,12–14]. Additionally, cervical length can vary within different subpopulations; it depends on parity, obstetric history, maternal age, maternal nutritional status, and history of drug use [15].

To obtain an accurate measurement of the cervix, one should obtain a true longitudinal view, including both the internal os and the external os. The image should be enlarged to fill at least one half of the ultrasound screen and oriented, by convention, so that the patient's head (cephalad) is on the left side of the screen. Undue pressure on the cervix by a vaginal ultrasound probe can artificially increase its apparent length and can be avoided by first obtaining a satisfactory image, withdrawing the probe until the image begins to blur, and then reapplying only enough pressure to restore the image clarity. Amniotic fluid and the lowest edge of the empty maternal bladder should be identified as landmarks, and the presence of membranes in the cervical canal or beyond the cervix should be noted. The *internal os* is often located just below the lowest edge of the bladder and is the point at which the cervical canal and the amniotic sac or fetal presenting parts meet. Proceeding from the internal os, one should then locate the endocervical canal and external os. The *external os* is the point within the vaginal canal at which the anterior and posterior ends of the cervix meet. The appropriate sagittal views are obtained by locating the V-shaped notch at the internal os, and the triangular area of echodensity at the external os. The canal appears as a faint line of echodensity or echolucency between the two.

The cervix should be measured at least three times; the *cervical length to record is the shortest one that clearly displays both the internal and external cervical os and the entire length of the cervical canal*. The sum of two separate measurements or the trace function of the ultrasound calipers might be required if the cervical canal is not straight. In the presence of funneling or dilation of the internal os (see Figure 3.2), the residual (i.e., closed) cervical length should be measured. The depth of a funnel and whether it is static or dynamic should also be noted. If a funnel does not develop spontaneously, one can be induced by asking the patient to perform the Valsalva maneuver or by applying moderate fundal pressure. Prolonged observation of the cervix for 3 to 5 minutes is recommended because dynamic changes manifesting as dilation of the internal os or funneling can occur during the course of an examination [16].

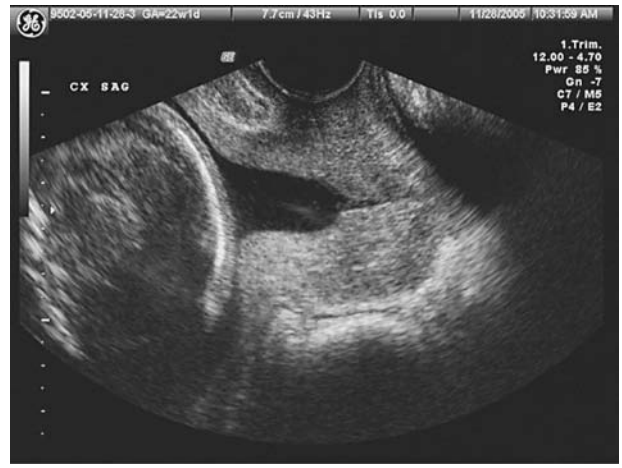

FIGURE 3.2.
Funneled cervix.

When clinically indicated, cervical length measurement by ultrasound, used in conjunction with digital examination, is an invaluable tool. With digital examination only, the practitioner cannot obtain an accurate evaluation of the supravaginal portion of the cervix. The length of this segment of the cervix can be assessed by sonography. Furthermore, early cervical changes such as subtle dilation and funneling typically begin at the level of the internal os, which might not be perceived on digital examination. Using receiver operator curves, Iams and Gomez determined that cervical sonography was a better predictor of preterm birth than digital assessment of cervical dilation and effacement [1,17]. This advantage remains with even early changes of the uterine cervix. The overwhelming advantage of sonography over digital examination is chiefly confined to early labor, when cervical dilation is less than 3 cm [13].

The process of cervical effacement is visualized sonographically as funneling of the cervical canal, typically materializing once the amniotic sac begins to protrude into the cervical canal. On ultrasound scan, this can appear as a change from a closed cervix to a wedge-shaped opening of the internal os followed by progressive shortening of the cervix craniocaudally. The process of effacement described as initially V shaped and then U shaped on ultrasound examination depends on the descent of the fetal presenting part [18]. Criteria for defining a funneled cervix have been described in an effort to standardize measurement and reporting. *Funnel width* is described as the dilation of the internal os, whereas *residual cervical length* is the closed cervical length distal to the funnel. *Funnel length* is the length of an imaginary line that connects the apex of the funnel to the cephalad-most edge of the base of the funnel. The percentage of funneling is the total funnel length divided by the residual cervical length plus the funnel length, that is, the total length of the cervix [19]. A funnel percentage of greater than 40% is a significant predictor of preterm delivery [19].

Sonographic assessment of cervical length as a predictor of preterm delivery has been studied in low- and high-risk women who are asymptomatic or symptomatic. There are a multitude of prospective studies showing that cervical length assessment by ultrasonography is not only reproducible but is an extremely valuable technique in terms of its predictive value. Normal cervical length is relatively stable in the late second and early third trimester but begins to shorten slightly with increasing gestational age during the third trimester. After 16 weeks' gestation, the median cervical length is between 40 mm and 45 mm. As pregnancy progresses, the median cervical length decreases to 35 mm to 40 mm at 24 to 28 weeks, and 30 mm to 35 mm after 32 weeks [1].

Standardization of cervical length using transvaginal sonography was performed in approximately 3000 women to determine these normal lengths [1]. Iams et al. described normal cervical length between 22 and 30 weeks' gestation by a bell-shaped curve; the 90 percentile is 45 mm; the 50 percentile is 35 mm; the 10 percentile is 25 mm; the 5 percentile is 20 mm. Furthermore, they established the lack of clinical utility in measuring cervical length prior to 16 weeks' gestation because cervical shortening and funneling typically do not occur prior to that gestational age.

In asymptomatic high-risk women (i.e., those gravidas with a history of a prior preterm birth), their risk of preterm delivery in the subsequent pregnancy correlates with the cervical length measured during that pregnancy [20]; furthermore, the relative risk of preterm birth increases as the cervical length decreases. Additionally, the degree of "shortness" of the cervix is associated with the gestational age at delivery in the previous preterm birth, that is, the earlier the gestational age of the previous delivery, the shorter the cervix in the subsequent pregnancy [20–21]. Conversely, there appears to be little correlation between cervical length on ultrasound examination and the risk of preterm birth in asymptomatic low-risk women. These women were analyzed in the Preterm Prediction Study for their risk for preterm delivery based on cervical length assessment at 24 weeks' gestation. Cervical length on ultrasound examination was found to have a low sensitivity in this population for predicting preterm delivery at less than 35 weeks [22].

Finally, symptomatic women, that is, those who report preterm uterine contractions, have been assessed to determine the utility of evaluating the cervical length on labor and delivery. There appears to be a significant benefit from sonographic evaluation of cervical length when managing women whose diagnosis of preterm labor is uncertain. Of *symptomatic* women whose cervical lengths are

measured with ultrasonography, those whose cervices are found to be greater than 15 mm have a low likelihood of delivering within seven days of the examination [23–26]. Conversely, approximately 50% of symptomatic women with a cervical length of less than or equal to 15 mm will deliver within seven days of the examination [24]. The same group analyzed different risk factors and found that the only significant predictor of preterm delivery within 48 hours of initial examination was cervical length [25]. Furthermore, Gomez et al found that vaginal ultrasonographic examination of the uterine cervix was more accurate than digital examination of the cervix in the assessment of the risk for preterm delivery in patients with preterm labor and intact membranes [17]. The findings of these studies provide important clinical information to the obstetrician on labor and delivery in terms of assessing symptomatic patients and planning their management strategy.

Cervical length assessment for predicting the outcome of labor induction has been evaluated in numerous studies. There are mixed results in the literature; some authors have found a significant benefit to cervical length assessment [3–5,27–28], whereas others have found little additional assistance in guiding labor induction management [29–32]. In 2004, Rane et al. determined that preinduction cervical length was an independent predictor of the likelihood of vaginal delivery within 24 hours [27]. In this same cohort of more than 600 patients, those authors found that cervical length was an independent predictor of cesarean delivery. They concluded that sonographic parameters, including cervical length assessment, were superior to the Bishop score for the prediction of these labor outcomes. In separate studies by Yang, Ware, and Gabriel, cervical length performance was directly compared to the Bishop score [3–5]. All together these studies measured the cervical length in 350 patients prior to labor induction. They found a more significant relationship between vaginal delivery and cervical length than the Bishop score and concluded that cervical length measured by transvaginal ultrasonography was a useful and independent predictor of successful labor induction. Gabriel found that in women having an unfavorable Bishop score, a cervical length of less than 26 mm was associated with a lower risk of cesarean delivery and a shorter duration of labor, whereas Ware found that women with a cervical length of less than 30 mm were more likely to be delivered vaginally and had significantly shorter labors. Bartha et al. specifically looked at cervical length measurement as a means of defining cervical ripeness [28]. They employed a cervical length cutoff of greater than 30 mm for the use of prostaglandin for cervical ripening and found that using transvaginal cervical length significantly reduced the need for intracervical prostaglandin treatment for patients whose cervices were deemed ripe on sonographic assessment.

Nevertheless, there are an equivalent number of studies that have not found cervical length ultrasound measurement to be more accurate at predicting the outcome of labor induction than digital examination or Bishop score. In postterm patients, Chandra et al. found that transvaginal ultrasound did not predict successful labor induction as well as digital cervical examination [31]. Additionally, several studies found the Bishop score to be a better predictor of the time interval from induction to delivery [29–30,32]. At this time, the use of cervical length in the assessment of preinduction cervical readiness should be used with caution.

ASSESSMENT OF FETAL STATUS

Amniotic Fluid Index

Evaluation of fetal amniotic fluid quantity is an essential fetal assessment tool for the obstetrician. Amniotic fluid serves numerous functions vital to the normal development of the fetus, including musculoskeletal and lung function. Pathologic quantities of amniotic fluid should alert the physician to the possibility of impending harm to the pregnancy. Traditionally, amniotic fluid volume has been a reliable predictor of perinatal outcome.

The origin of amniotic fluid during the first trimester is a combination of maternal plasma transudate through the chroioamnion and fetal plasma through permeable fetal skin. By the mid-trimester, amniotic fluid production and excretion are entirely managed by the fetus. Production of fluid occurs mainly in the fetal kidneys and lungs; removal of fluid occurs by the fetal gastrointestinal system and through the amniochorionic membrane, thus distributing it to the maternal circulation. Amniotic

fluid assessment is most typically accomplished by quantitative measurement of the volume of fluid, because this provides direct insight into the status of fetal physiology. In the average pregnancy, the mean amniotic fluid volume increases from 30 ml to 1000 ml between 10 and 37 weeks; the average volume remains stable up to 39 weeks, after which it declines to approximately 500 ml by 42 weeks. The rate of amniotic fluid production is also gestational age dependent; at 8 weeks' gestation, the rate increases by 10 ml/week; at 13 weeks it is 25 ml/week; and at 21 weeks the rate of production reaches a maximum of 60 ml/week. Postterm the volume declines at a rate of approximately 8% per week [33].

Many factors can influence amniotic fluid volume; fetal metabolism, fetal blood volume, maternal hydration, and certain maternal disease states have all shown associations with amniotic fluid volume. For example, it has been postulated that maternal hydration not only improves amniotic fluid volume by improving uteroplacental blood flow but also increases the transfer of water across the placenta into the amniotic cavity. Studies have shown that maternal rehydration can alter amniotic fluid volume significantly [34].

An accurate measurement of amniotic fluid volume is crucial to assist in clinical decision making. In lieu of the risk and difficulty in obtaining measurements through invasive means such as amniocentesis with dye-dilution studies, ultrasonography, a noninvasive technique, has become an objective and safe procedure to determine fluid quantity. Although experienced sonographers can make a subjective estimation of the amount of fluid, an objective measurement is preferable in most instances. In 1981, Manning et al. described a technique called the *maximum vertical pocket* (MVP), which involved the selection, under ultrasound guidance, of the single deepest amniotic fluid pocket [35]. The quantitative depth was determined as the largest dimension of this pocket measured with the ultrasound transducer perpendicular to the floor. In 1987, Phelan et al. devised a semiquantitative sonographic assessment of the amniotic fluid volume called the *amniotic fluid index* (AFI) [36]. The AFI is a measurement based on the division of the gravid uterus into four quadrants using the external landmark of the maternal umbilicus and linea nigra to divide the quadrants. The AFI is obtained by the summation of the deepest vertical pocket in each quadrant that is free of umbilical cord or extremities. Many sonographers make use of color Doppler mapping, if available, to ensure an umbilical-cord–free pocket.

Studies have found modest differences in the assessment accuracy of AFI and MVP. In 1990, Moore found that AFI became less accurate at lower fluid volumes, decreasing the sensitivity for the detection of oligohydramnios to less than 50% [37]. Similarly, Miyamura et al. found that an MVP measurement of $\leq$3 cm was more useful for establishing oligohydramnios than AFI measurement [38]. In 2004, Chauhan found no difference in the two semiquantitative measurements in their ability to predict perinatal outcome; however, they did find that oligohydramnios was diagnosed more frequently with AFI than MVP [39]. The same author found, however, that both the AFI and MVP were relatively inaccurate predictors of oligohydramnios or polyhydramnios when compared with dye-dilution calculations of actual amniotic fluid volume [40]. Despite these limitations, AFI and MVP quantitative assessments are preferred over the highly invasive approach of amniocentesis with dye instillation since this latter approach confers a significant risk of pregnancy loss to the patient.

Regardless of which quantitative assessment of amniotic fluid volume the practitioner chooses, what is the relationship between an abnormal volume and poor perinatal outcome? There are numerous conditions that can cause decreased placental perfusion, thus decreasing the oxygen and substrate flow to the fetus and resulting in relatively hypoxemic blood flowing to the fetal organs. The fetus subsequently redistributes its cardiac output to ensure adequate oxygen delivery to the most vital organs, increasing blood flow to the brain, heart, and adrenal glands while decreasing the relative flow to the abdomen and kidneys. The decreased renal perfusion and increased antidiuretic hormone release from this hypoxemia result in decreased urine output and oligohydramnios [41]. In the presence of hypoxemia, fetal lung resorption of fluid increases, adding to the low amniotic fluid volume.

A variety of thresholds has been described to define an AFI diagnosis of oligohydramnios and polyhydramnios. In Manning's original work from 1980, oligohydramnios was defined as the absence of

a single pocket of amniotic fluid with a depth ≤1.0 cm [48]. When this definition was thought to be too restrictive, Manning redefined the MVP definition to be the absence of a 2.0 cm by 2.0 cm pocket of fluid [42]. Using amniotic fluid index, oligohydramnios was defined as an AFI ≤5.0 cm [36]. In 1990, Moore obtained AFIs in almost 800 normal pregnancies and defined oligohydramnios as an AFI below the fifth percentile for gestational age [37]. This value varies between 7.9 cm at 16 weeks' and 6.3 cm at 40 weeks' gestation. Although an AFI of ≤5 cm as Phelan suggested would include ≤1% of term gestations, this AFI definition of oligohydramnios is the one most commonly used by obstetricians.

Several studies have reported that intrapartum oligohydramnios is associated with a poor perinatal outcome [43–44]. These studies show increased rates of fetal heart rate abnormalities, a higher risk of low birthweight percentile, and an increased risk of cesarean delivery when oligohydramnios is present. A meta-analysis of the relationship between amniotic fluid volume and perinatal outcome found an association between oligohydramnios and an increased incidence of cesarean delivery for nonreassuring fetal heart rate patterns and low Apgar score [45].

Prior to ultrasound, *polyhydramnios* or excessive amniotic fluid, was diagnosed when the fundal height exceeded expectations for the patient's gestational age or there was difficulty palpating fetal parts. Ultrasonography allowed for a more quantitative assessment of polyhydramnios; the definition is either a deepest vertical pocket measurement of greater than 8 cm or an AFI greater than 24 cm. Numerous conditions, both maternal and fetal, are associated with polyhydramnios, including maternal diabetes mellitus, fetal structural and chromosomal abnormalities, erythroblastosis fetalis, twins, and certain medications. In a study by Carlson et al., an AFI of >24 cm predicted 49/50 cases of true polyhydramnios confirmed at delivery and included 92% of all anomalies and 100% of all trisomies, fetal and neonatal deaths [46]. A recent publication assessed the relationship of amniotic fluid volume and perinatal outcome [47]. They found a significant relationship between the identification of polyhydramnios and large-for-gestational age fetuses as well as fetuses at risk for congenital anomalies and cesarean delivery.

Biophysical Profile

The fetal *biophysical profile* (BPP) is a tool used by obstetric practitioners to evaluate fetal well-being both antepartum and on labor and delivery. More recently, BPP assessment of fetal status has even been attempted intrapartum and is discussed later in this chapter. The ultimate goal in establishing an investigation to assess the fetal condition is to distinguish between the healthy versus the hypoxemic fetus. Furthermore, avoidance of a low rate of false-negative test results so that asphyxiated fetuses are not missed and a low rate of false-positive results to avoid unnecessary anxiety and operative procedures is imperative. With a non-stress test (NST) or a contraction stress test (CST), both of which are associated with high false-positive rates, only the fetal heart rate is evaluated, forcing the clinician to estimate fetal health based on simply one parameter.

With the addition of ultrasound appraisal of fetal activity and amniotic fluid volume to the evaluation of the fetal heart rate, it is feasible for the obstetrician to gain more insight into fetal welfare. Manning et al. were the first to describe the use of multiple biophysical parameters of the fetus on ultrasound examination in an attempt to predict perinatal outcome [48]. The authors observed 216 patients with high-risk pregnancies who were delivered within 1 week of the ultrasound assessment. They studied five different variables: fetal breathing, fetal movement, fetal tone, qualitative amniotic fluid volume, and the non-stress test. They found that using the five parameters in combination showed the greatest accuracy for predicting five-minute Apgar score, fetal distress in labor, and perinatal mortality versus using any of the parameters alone. Furthermore, these investigators introduced the use of a scoring system in which each activity was scored either as 0 if absent or abnormal, or 2 if present or normal. They continued the examination until all parameters were deemed present or until 30 minutes had elapsed. This assessment of fetal health continues to be widely used today, exploiting the same five parameters, time limitation, and scoring system first described over two decades ago.

How is the BPP a useful predictor of perinatal morbidity and asphyxia? The BPP, unlike the NST or CST, combines evaluation of both acute and chronic markers for fetal well-being. Amniotic fluid volume is a signal of chronic fetal health not

typically altered by acute changes in fetal acid–base status. The presence of a low amniotic fluid volume, or oligohydramnios, is considered to be the result of chronic fetal stress most likely reflecting the presence of long-term fetal hypoxia, resulting in the shunting of oxygenated blood to the fetal heart, brain, and adrenal glands, reducing perfusion of the fetal kidneys. This renal hypoperfusion results in decreased fetal urine output and oligohydramnios.

The other four parameters of the BPP, fetal breathing, movement, tone, and heart rate, are more acute markers of unbalanced fetal acid–base status. Individually, these markers are regulated by different regions of the fetal central nervous system and as such mature and respond to fetal hypoxemia and acidemia at different stages in fetal development. The earliest of the parameters established is fetal tone, which can be observed 8 weeks following the last menstrual period. Fetal body movements accelerate over the following gestational week, followed by fetal breathing, which typically commences at approximately 21 weeks' gestation. The fetal heart rate reactivity is the final biophysical portion to mature, typically doing so by the end of the second trimester. Vintzileos and others observed that the order in which the parameters characteristically disappear in response to acute fetal acidemia is the reverse order of when they emerge throughout gestation, implying that the first factor to regress is classically fetal heart rate reactivity, followed by fetal breathing, movement, and tone [49–51].

Although there are numerous confounders to consider when interpreting the value of a BPP, such as gestational age of the fetus, diurnal variation, specific disease states, and maternal drug administration, the overall benefit to using the BPP in the assessment of fetal status has been established. In their original study in 1980, Manning et al. found that when the BPP score was 10 out of 10, the perinatal and fetal death rates were zero [48]. Conversely, when the score was 0 out of 10, the perinatal loss rate rose to 60% and fetal death rate was 40%. In a prospective, blinded study of more than 700 patients comparing fetal BPP with NST, the same authors found that BPP had a significantly higher positive predictive value than NST with regard to low Apgar scores [52]. Furthermore, those authors pointed out that because BPP uses ultrasound examination to evaluate the fetus, the added benefit of detecting fetal congenital anomalies is included. Baskett et al. managed 4,184 high-risk pregnancies with BPP and found that a normal BPP (score of 8 or 10 out of 10) was associated with a perinatal mortality rate of 0.1%, an intermediate score (6 out of 10) was associated with a perinatal mortality rate of 3.1%, and abnormal scores (0–4 out of 10) were associated with a perinatal mortality rate of 20% [53]. They also found an overall low false-negative rate of 0.7/1,000.

Intrapartum BPP has recently been studied in an effort to assess its role as an instrument for evaluating fetal status during labor as well as a method of assessing the effect of oxytocics, regional anesthesia, and ruptured membranes on fetal behavior [54]. Kim et al. prospectively performed BPPs on 100 non-anomalous, singleton pregnancies and blinded the managing physicians to the results. They observed that the ascertainment of the BPP was not influenced by the use of oxytocics, prostaglandins, and the presence of meconium or epidural anesthesia. Additionally, they found that fetal breathing and gross fetal movement decreased with rupture of amniotic membranes. Furthermore, they established that a BPP score of 6 or less was associated with a relative risk for cesarean delivery of 8.0. They also found that cessation of any component of the BPP significantly increased the risk of cesarean delivery and admission to the neonatal intensive care unit. With further evaluation, BPP could prove to be a clinically useful adjunctive tool in the assessment of fetal well-being not only during the antepartum period but also intrapartum.

DOPPLER FLOW STUDIES

Doppler ultrasonography uses the principle described by Christian Doppler in 1842, which elucidates the physical properties associated with the changes in sound frequency emitted or reflected from a moving source. Sonographically, this property can be manipulated to observe the velocity of blood flow in both maternal and fetal blood vessels and translated to a frequency shift of the reflected sound waves. Because this section concerns sonographic fetal assessment of labor and delivery, the discussion of Doppler ultrasound is limited to the examination of relevant fetal vessels.

Clinically, the two vessels most often used to predict perinatal outcome are the fetal umbilical artery and the middle cerebral artery, although numerous

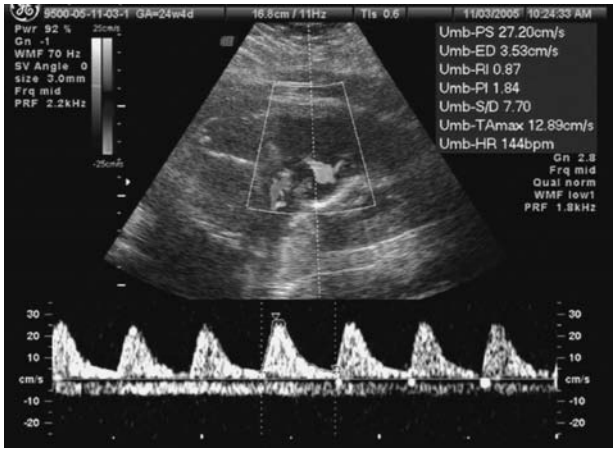

FIGURE 3.3.
Normal uterine artery Doppler.

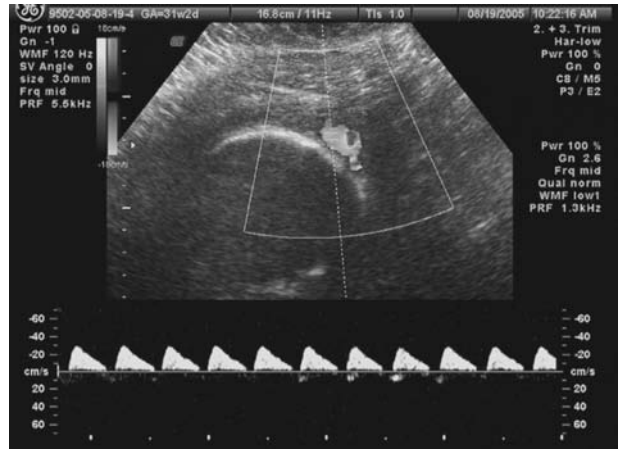

FIGURE 3.4.
Abnormal uterine artery Doppler.

other vessels have been investigated for their role in evaluating the fetus in utero (see Figures 3.3 and 3.5). Doppler ultrasonography measurement of the umbilical arterial blood flow uses real-time Doppler velocimetry, providing information on perfusion of the fetoplacental unit. With advancing gestational age and trophoblastic invasion of the uterine decidual layer, the volume of flow in the umbilical arteries increases. Consequently, the high vascular impedance that can be detected early in the first and early second trimesters gradually declines until term. The relatively low vascular impedance in the placenta overall allows for continuous forward flow in the umbilical arteries throughout the cardiac cycle in most normal pregnancies.

How does measuring Doppler flow in the umbilical arteries help to assess fetal status? By using Doppler velocimetry, the obstetrician can measure and interpret vascular impedance in the umbilical arteries, thus determining the fetoplacental response to multiple obstetric and medical conditions that can adversely influence pregnancy. For example, with maternal hypertensive disorders, including preeclampsia, there is a substantial increase in the vascular resistance of the placenta, which leads to a decrease in the end-diastolic velocity of blood flow in the umbilical arteries that can be quantified by Doppler ultrasonography (see Figure 3.4). If this resistance continues to increase, the end-diastolic forward flow could eventually cease or even reverse and travel back toward the fetus, transporting deoxygenated blood away from the placenta. This change in flow pattern in the umbilical artery impairs transplacental oxygen transfer between the fetus and placenta and can lead to significant hypoxemia and growth restriction of the fetus.

Once the endpoint of reversed end-diastolic flow is obtained by Doppler interrogation of the umbilical artery, the perinatal mortality rate in a nonanomalous fetus is approximately 35% [55]. Meta-analysis of published randomized controlled studies indicates that antepartum umbilical artery Doppler assessment in high-risk patients reduces the perinatal mortality risk by more than 30% without increasing the rate of unnecessary obstetric interventions [56]. Conversely, there are studies that show no beneficial role of antepartum Doppler velocimetry as a screening test for low-risk pregnancies [57].

Intrapartum umbilical Doppler velocimetry assessment as a predictor of adverse perinatal outcome has been studied in a limited fashion. In 1999, Farrell et al. hypothesized that increased placental vascular resistance during late pregnancy would be expected to persist into the intrapartum period in both low- and high-risk patients [58]. They performed a meta-analysis to determine the clinical value of intrapartum umbilical artery Doppler analysis in identifying compromised infants at delivery. They determined that intrapartum umbilical artery Doppler velocimetry had minimal ability to predict low Apgar scores at 1 and 5 minutes, small for gestational age infants, fetal heart rate abnormalities during labor, umbilical arterial acidosis at delivery, or the resort to a cesarean for fetal distress. Unfortunately, the heterogeneity of the sample that these authors entered into the analysis, both

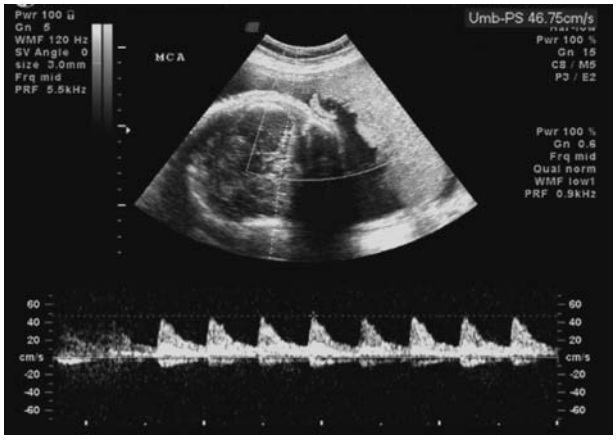

FIGURE 3.5.
Normal Doppler of the middle cerebral artery.

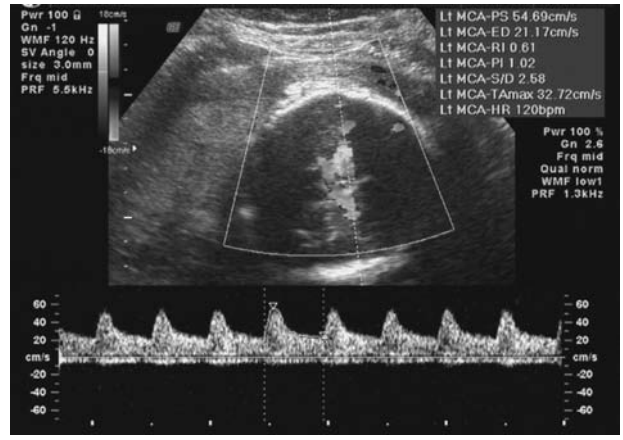

FIGURE 3.6.
Abnormal Doppler of the middle cerebral artery.

low- and high-risk patients, might have distorted the outcome. A more recent study correlated umbilical artery Doppler with fetal pulse oximetry and external cardiotocography and observed alterations in the umbilical artery Doppler measurements in fetuses with labor-induced fetal hypoxia [59]. These authors thought that umbilical artery velocimetry indices correlated with perinatal outcome; their study, however, was limited by a small sample size (35 fetuses). With further study, umbilical artery Doppler velocimetry could prove to be a predictor of adverse perinatal outcome during the intrapartum period in certain high-risk pregnancies.

Blood flow through the umbilical arteries gives the practitioner an overview of the placenta and its ability to perfuse the fetus adequately. If one wishes to obtain information directly about the fetal response to decreased blood flow or oxygen content, however, the fetal middle cerebral artery can be evaluated (see Figure 3.5). The middle cerebral artery has a high sensitivity for the detection of fetal intrauterine growth restriction and related complications. In the normally developing fetus, the brain is an area of high vascular impedance with minimal forward flow at end diastole. Hypoxemia in the fetus causes a redistribution of fetal blood flow to the fetal brain by cerebral vasodilation at the expense of other fetal organs, such as kidneys, subcutaneous tissue, skeletal muscle, and liver. This response, evident by a decrease in cerebrovascular impedance, can be measured by Doppler flow studies (see Figure 3.6). The association between abnormal middle cerebral artery Doppler waveform and fetal hypoxemia has been explored with the use of cordocentesis [60]. Rizzo et al. looked at growth-restricted fetuses and correlated Doppler findings with fetal blood parameters, concluding that hypoxemia and acid–base status in the fetus could be predicted by abnormalities in the flow pattern of the middle cerebral artery.

Furthermore, a Doppler cerebroplacental ratio, a ratio of the middle cerebral artery pulsatility index to the umbilical artery pulsatility index, has been developed and evaluated in its ability to identify the fetal redistribution of blood flow in the presence of hypoxemia. Bahado-Singh and coauthors found that Doppler identification of the fetal redistribution using the cerebroplacental ratio strongly predicted outcome in fetuses at risk for intrauterine growth restriction [61]. The clinical significance of fetal hypoxia in the middle cerebral artery as measured by Doppler during labor has also been studied. Siristatidis et al. found that middle cerebral artery Doppler showed significantly decreased vascular impedance in those fetuses with oxygen saturation values below 30% and abnormal cardiotocographic patterns [62]. They concluded that middle cerebral artery Doppler investigation is an important predictor of adverse fetal outcome, especially fetal hypoxia, and could help the clinician to manage these patients intrapartum.

GESTATIONAL AGE/FETAL WEIGHT ASSESSMENT

The management of a pregnant patient with little or no prenatal care who presents to labor and delivery

in the third trimester or in labor is frequently of concern. It is not only of the utmost consequence for the obstetrician to determine an accurate gestational age of the pregnancy to manage issues such as preterm labor, but it is imperative to the pediatricians who will assume care once the infant is born. Ultrasonography can facilitate obtaining an accurate gestational age and estimating fetal weight as well as diagnosing any gross abnormalities of the fetal anatomy. Studies have looked at less traditional ultrasound measurements and markers to help establish gestational age in the third trimester. The distal femoral and proximal tibial epiphyseal ossification centers in the fetus have been studied in the third trimester of pregnancy. It was determined that the distal femoral epiphysis was not identifiable before 28 weeks but was observed in 72% of fetuses at 33 weeks and in 94% of fetuses at 34 weeks [63]. The proximal tibial epiphysis was absent before 34 weeks and observed in 56% of fetuses at 36 weeks, 80% of fetuses at 37 weeks, and 100% of fetuses at 39 weeks gestation [63]. Other have looked at the proximal humeral ossification centers of the fetus and found that this center could be visualized after the 38th week with a specificity of 99%, sensitivity of 58%, and with a positive predictive value of 91% and negative predictive value of 93% [64].

Finally, an investigation was published that questioned the traditional dogma that third-trimester gestational age dating is relatively inaccurate with a 95% confidence interval of ± 3 weeks. Mongelli et al. derived third-trimester ultrasound dating algorithms from pregnancies conceived with artificial reproductive techniques [65]. They found that a formula using a combination of the measurements of the femur length and the head circumference had a 95% confidence interval of -13 to $+17$ days. Smulian et al. compared the accuracy of three different sonographic circumference measurement techniques to predict birthweight in term fetuses [66]. They found that measurement of the abdominal circumference within 24 hours of delivery showed a percent deviation from the actual birthweight of 1.9% (SD $\pm$ 8.0%). This measurement was within 10% of actual birthweight in 80% of cases. These measurements along with identification of the fetal ossification centers can aid the clinician in making a relatively accurate assessment of gestational age in the third trimester.

ULTRASONOGRAPHY OF THE PLACENTA

"Ultrasound is the most sensitive diagnostic tool for detecting abnormalities of the placenta, yet it may be unable to demonstrate the most clinically significant abnormalities (placenta accreta, abruption) even if one is highly skilled in placental sonography" [67].

Placental Abruption

Placental abruption (abruptio placentae) is the premature separation of the normally implanted placenta. Most often a clinical suspicion and diagnosis, placental abruption can be catastrophic. The risk of preterm delivery is 20% to 40% with placental abruption [68]. Although it is one of the leading causes of perinatal mortality, accounting for 15% to 20% of perinatal deaths [69], the incidence of abruption is only 0.5% to 1% in the general population [70]. Abruption classically presents with the triad of vaginal bleeding, abdominal or pelvic pain, and uterine contractions and tenderness.

Ultrasound examination for placental abruption is helpful only if a retroplacental hematoma is seen, but the absence of this finding does not exclude abruption (see Figure 3.7). Historically, the sensitivity of ultrasonography for visualizing intrauterine hemorrhage has been reported as approximately 50% [67]. More recently, the sensitivity and specificity of sonography for identifying abruption have been reported as 24% and 96% respectively, and the

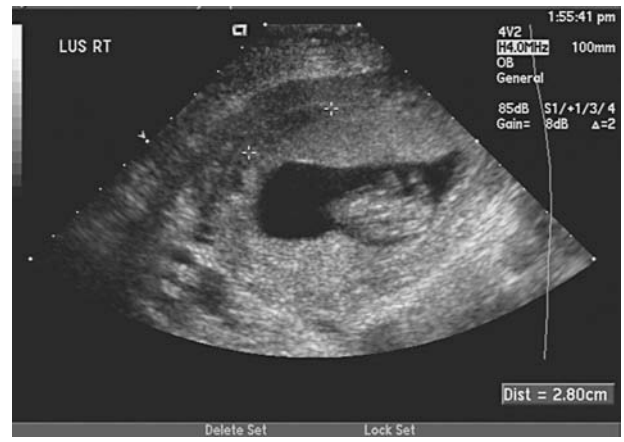

FIGURE 3.7.
Abruptio placentae.

positive and negative predictive values were 88% and 53%, respectively [71].

Normally, there is a complex hypoechoic retroplacental collection that consists of uteroplacental vessels and myometrium that measures 1 cm to 2 cm in thickness. Increased thickening of this area can be caused by a uterine contraction, fibroid, or hematoma. Thickening secondary to contractions can be identified by the transient nature of its appearance or a hypervascular area of myometrium on color Doppler. Fibroids can appear more rounded, with a distinct border or capsule, and demonstrate greater vascularity than a hematoma but less than a contraction.

Sonographic appearance of hemorrhage varies depending on the age of the hematoma, location, and the transducer used. Acutely, hemorrhage appears hyperechoic at 0 to 48 hours, becoming isoechoic at 3 to 7 days, and then hypoechoic at 1 to 2 weeks [72]. The most common site of placental abruption is at the placental margin.

PLACENTA PREVIA

The nomenclature of placenta previa describes its etiology: a placenta that is "previous" to or in front of the fetus relative to the birth canal. Placenta previa is the primary cause of third-trimester bleeding and is easily detectable on ultrasound examination, especially transvaginal or translabial ultrasound (see Figure 3.8). The only contraindication to transvaginal ultrasound scan is bulging or arguably ruptured membranes.

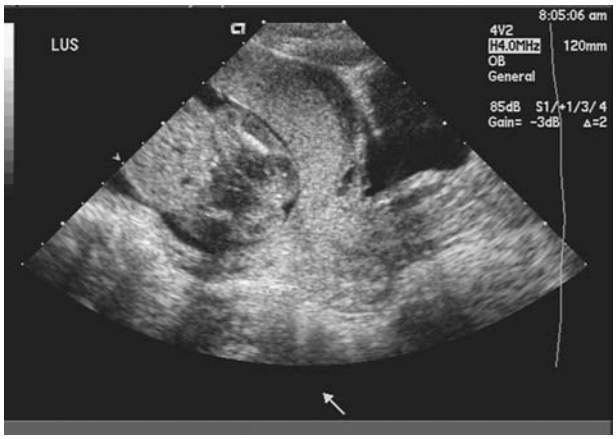

FIGURE 3.8.
Placenta previa.

The type of previa is defined by the actual distance between the placental edge and internal os. A *complete placenta previa* covers the entirety of the internal os. *Incomplete placenta previa*, a more inclusive term that includes both marginal and partial placenta previa, describes a placenta that impinges on some part of the internal os but does not completely cover it. *Low-lying placenta* denotes a placental edge that is within 2 cm of the internal os but does not cover a significant portion of it. Despite these definitions, the identification of the type of placenta previa is still somewhat subjective.

The incidence of abnormal placentation varies by gestational age. Placenta previa or low-lying placenta is usually physiologic and transient, with most placentas experiencing migration and resolution at term. In fact, the incidence of placenta previa in each trimester is approximately 42% at 11 to 14 weeks, 4% at 20 to 24 weeks, and 2% at term [73]. The clinical implications of any asymptomatic previa or low-lying placenta identified prior to 35 weeks should therefore be expectantly managed and followed for resolution. Conversely, given that abnormal placentation is the most common cause of second- and third-trimester bleeding, all patients presenting to the labor and delivery suite with this history should have a transvaginal or translabial ultrasound to identify placental location.

Transvaginal and translabial ultrasonography are superior to transabdominal ultrasonography in identifying and qualifying placenta previa. Transabdominal ultrasound examination will misdiagnose placenta previa in 25% of cases [74]. Transvaginal ultrasonography has a sensitivity and specificity of approximately 88% and 99%, respectively, and positive and negative predictive values of 93% and 98%, respectively [75]. The sensitivity and specificity of translabial ultrasonography is similar: 100% and 70% respectively when the distance between the placental edge and internal os is less than 2 cm, and 90% and 95% respectively when the distance is less than 1 cm [76].

PLACENTA ACCRETA

Ultrasonography can be helpful in the detection and evaluation of abnormal placental adherence to the

uterus. Categorized by depth of invasion, *placenta accreta* denotes a placenta attached to but not yet invading the myometrium. *Placenta increta* occurs when the villi invade the myometrium. *Placenta percreta* is the penetration of the villi through the myometrium with possible attachment to adjacent structures, including the bladder or rectum. The overall prevalence is estimated to be 1 in 2,500 pregnancies. This risk increases in the presence of previa, when the prevalence is 10% and can be as high as 35% in women with a history of a previous cesarean delivery and subsequent pregnancy with previa.

The pathophysiology of placenta accreta is an absence or weakening of the decidua basalis and incomplete development of the fibrinoid layer. In addition to the site of the previous uterine scar from a cesarean delivery, any area of prior uterine surgery (i.e., myomectomy) is a risk for accreta if subsequent placental implantation occurs at that site.

There are three primary ultrasound findings that are used as markers for placenta accreta (see Figure 3.9). First, obliteration of the retroplacental clear space describes the loss of any portion of the echolucent area between the myometrium and placenta [77,78]. Second, presence of *lacunae*, defined as multiple, linear, irregular hypoechoic vascular spaces within the placenta giving it its euphemistic "Swiss-cheese" appearance [79]. Third, interruption of the posterior bladder wall and myometrial interface can distort the normal continuous echolucent line, making it appear as a series of dashes [80]. Comparing these findings at both 15 to 20 weeks and 15 to 40 weeks, the findings of placental lacunae have the highest sensitivity and positive predictive value for placenta accreta. At 15 to 20 weeks, the presence of lacunae has a sensitivity of 79% and positive predictive value of 92%. At 15 to 20 weeks, the sensitivity and positive predictive value of placental lacunae increase to 93% each [80].

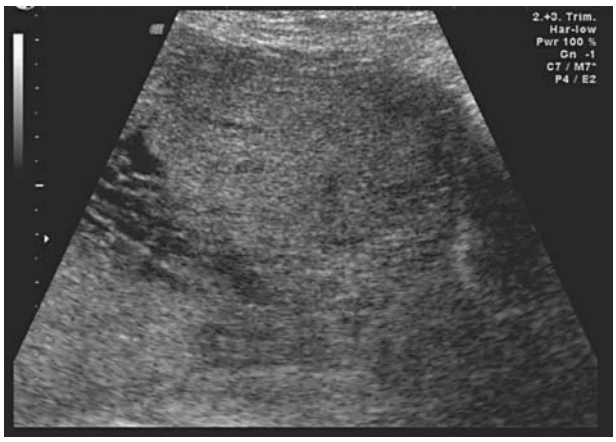

FIGURE 3.9.
Placenta accreta.

The use of color Doppler and magnetic resonance imaging (MRI) also have been proposed as adjuncts to aid in diagnosis. Although the use of color Doppler enhances the appearance of placental lacunae and perhaps fetoplacental blood vessels invading the myometrium, it has not been shown to increase the accuracy already exhibited by gray-scale ultrasonography [78]. Similarly, MRI has been shown to confirm ultrasound findings but has not been shown to be superior to gray-scale [81]. In fact, gray-scale ultrasonography has been shown to be superior to MRI in some studies [78].

Ultimately, the diagnosis of placenta accreta and its counterparts can be made only by pathologic examination in the laboratory after hysterectomy. Until then, ultrasound findings can raise suspicions, aid in identification and preliminary diagnosis, and thereby prepare physicians and patients for the possibility of the presence of accreta, so that appropriate surgical facilities are available.

ASSESSMENT OF FETAL POSITION

Fetal Presentation

Presentation denotes the fetal part that directly overlies the pelvic inlet. With a fetus in longitudinal lie, the presentation can be vertex, breech, or shoulder. Less common presentations include fundic and compound presentation. In a vertex fetus, the presentation is classified according to the leading bony landmark of the skull: occiput, mentum, or brow.

Leopold's maneuvers and vaginal examination are the two most common means of identifying fetal presentation. Transabdominal ultrasonography is most often used for confirmation. Additionally, ultrasound scan can be used as the primary tool for assessing presentation in the patient with rupture of membranes not in labor, preterm or term, when vaginal examination could be potentially harmful.

Position of the Fetal Occiput

Intrapartum assessment of the fetal occipital position is an essential part of managing labor. Correct

determination influences induction, progress of labor, and mode of delivery. To date, most obstetricians rely on transvaginal digital examination to determine the position of the occiput. Numerous recent investigations comparing digital examination and transabdominal ultrasound scan, however, have shown that digital examination is accurate in only 24% to 61% of cases, depending on stage of labor and position [82–85].

Digital examination is least accurate in the first stage of labor. In active labor (with the cervix ≥4 cm dilated) with fetal head at ischial spine station −2 or lower, 24% of assessments of position were correct when compared with transabdominal ultrasound examination (see Figures 3.10 and 3.11). This rate increased to 47% if digital examination assessments within 45 degrees of the ultrasound assessment were considered correct [83].

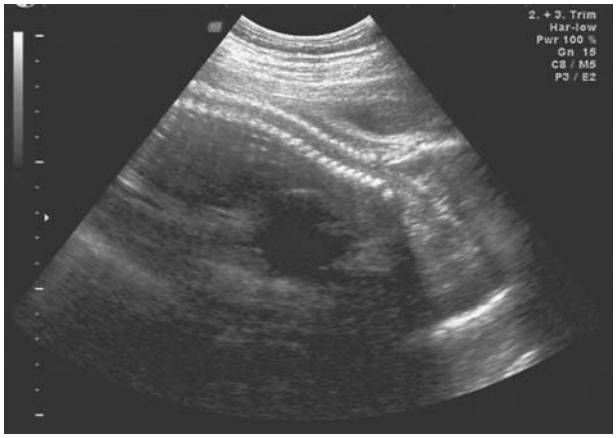

FIGURE 3.10.
Occiput anterior.

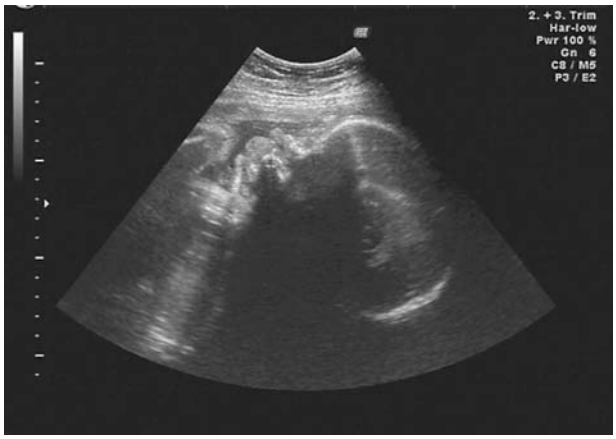

FIGURE 3.11.
Occiput posterior.

The accuracy of transvaginal digital examinations increases in the second stage of labor but remains suboptimal. The accuracy rate was 35% in 112 patients by digital examination versus transabdominal ultrasound scan. This rate increased to 61% when digital examination assessments within 45 degrees of the transabdominal ultrasound assessment were considered correct [84]. Transabdominal ultrasound and digital examination have also been compared with the actual occiput position at delivery after spontaneous resolution during a vaginal delivery or at the time of cesarean section. Vaginal examination was correct in 72% of cases, compared with 92% with ultrasound examination, when position assessments were within 45 degrees of the delivery position. (The 8% error rate for transabdominal ultrasonography occurred in fetuses that delivered in a variation of occiput anterior position and could be accounted for by unobserved spontaneous rotation occurring subsequent to the examination.) If the actual position was occiput posterior, the accuracy rates were only 31% of vaginal versus 100% of ultrasound examinations [85]. The improved accuracy of digital examination in the second stage of labor when compared with examination in the active phase of the first stage of labor is most likely due to the increased surface area of the fetal head and accompanying lower station that is palpable at 10 cm.

Management of the second stage of labor, particularly the safe and successful performance of an operative vaginal delivery, is contingent on correct assessment of fetal position. Incorrect placement of forceps or vacuum causes both fetal and maternal morbidity [86]. When transvaginal digital examination is compared with transabdominal ultrasongraphy prior to instrumental delivery, digital examination was correct in approximately 73% of cases [87]. Not surprisingly, accuracy varied according to position. For occiput anterior positions (see Figure 3.10), the accuracy was 83%. For occiput posterior (see Figure 3.11) or transverse, the accuracy was only 54%. In this study as in many others, a liberal definition of accurate was applied; the digital examination was considered correct if it was within 45 degrees of the transabdominal ultrasound assessment. Transabdominal ultrasound scan has also been shown to increase the accuracy of identifying engagement of the fetal head for both nulliparous and multiparous women [88]. Using

transabdominal ultrasonography to confirm fetal occiput position and station prior to instrumental delivery should be incorporated into the preprocedural evaluation of operative vaginal delivery.

While accumulated data clearly show the superiority of transabdominal ultrasonography over digital vaginal examination for the assessment of fetal occiput position prior to and during all stages of labor, transvaginal ultrasound scan provides even more information during the second stage of labor. Transvaginal ultrasound has been found to determine occiput position accurately in all cases of labor, whereas position could not be determined in 12% of digital exams ($p \leq 0.03$) and 15% ($p \leq 0.008$) of transabdominal ultrasound examinations. Transvaginal ultrasound examination also required the least time for performance, averaging less than 10 seconds per examination [89].

Determination of the fetal position by transabdominal ultrasonography could impact the ability to predict successful labor, either spontaneous or induced, by identifying fetuses in an occiput posterior position. Multiple studies have demonstrated the increased maternal and fetal morbidity of malposition in labor, including the increased risk for cesarean section. Occiput posterior position carries a statistically significant increased risk for prolonged first and second stage of labor, oxytocin augmentation, use of epidural analgesia, chorioamnionitis, assisted vaginal deliveries, third- and fourth-degree perineal lacerations, cesarean section, excessive blood loss, postpartum infection, and lower one-minute Apgar scores [90]. When combined with the parameters of cervical length and traditional maternal characteristics, ultrasonographically determined occiput position prior to induction can be predictive of the induction-to-delivery interval, and the likelihood of vaginal versus cesarean delivery [91]. Risk of cesarean delivery can be estimated in the early part of active labor (3 cm–5 cm) by sonographically determined occiput posterior position. In fact, fetuses that are occiput posterior at 3 cm to 5 cm of cervical dilatation have been found to have an odds ratio of 2.2 (CI 1.3–3.7, $p = 0.004$) for cesarean section [92]. Although most occiput posterior positions at delivery are a consequence of persistence of this position and not malrotation, remember that most (53%–87%) of occiput posterior positions will rotate to occiput anterior during labor, even at 10 cm [93–95]. Future research on the impact of alternative methods of induction or labor management for occiput posterior fetuses diagnosed by ultrasonography prior to labor could be useful in the prediction, diagnosis, and management of labor dystocia.

Most studies used the following landmarks to identify fetal occiput position: fetal orbits or cerebellum and posterior fossa for occiput-posterior position, midline cerebral echo for occiput-transverse positions, and cerebellum or occiput confirmed by tracing the spine for occiput-anterior positions. Additional views by a transperineal approach can be used to obtain landmarks when the vertex is below the level of the ischial spines. Assessment of the fetal occiput by transabdominal ultrasound examination is also easily reproducible. Interobserver agreement on sonographically determined fetal occipital position during labor (3 cm–10 cm) is within 15 degrees in 90% of cases and within 30 degrees in all cases [95].

Transvaginal sonographic examination is performed by inserting a sheath or glove-covered probe into the vagina until the resistance of the fetal head is felt. After applying the probe to the sagittal or coronal suture, a coronal or semicoronal section of the fetal brain is obtained. The most important landmark is a symmetric view of the midline and its structures, such as the pedunculi cerebri, or thalami and third ventricle. The exact position of the occiput is then calculated by determining the angle to which the transducer has to be turned clockwise to obtain the desired plane. The cerebellum and orbits can be used for confirmation [89].

Twin Gestation

Because the presentation of a twin gestation prior to delivery often dictates the mode of delivery, all twin pregnancies must have presentation verified by ultrasound examination on admission to labor and delivery. Twin presentations can be classified as vertex/vertex, vertex/nonvertex, nonvertex/other, where the leading fetus' position (A) is described first. Cesarean deliveries are frequently performed when twin A is nonvertex.

If twin B is nonvertex, ultrasound examination is first used to evaluate eligibility for vaginal delivery; namely, ultrasound measurement for estimated fetal weight for both fetuses is performed. Vaginal delivery is relatively contraindicated when the

discordance between twins is greater than 500 g with twin B as the larger twin [96].

The ultrasound machine should be present in the delivery room of any twin pregnancy. After the delivery of twin A, ultrasound examination will identify the presentation and position of twin B immediately and accurately and also provides direct visual monitoring of twin B's heart rate as it settles into its possibly new presentation, thereby allowing accurate assessment of fetal well-being [97].

Depending on the presentation of twin B after delivery of twin A, ultrasound scan can aid in the management of twin B's delivery. External cephalic version (especially from a transverse or oblique lie) can be accomplished with ultrasound assistance by applying gentle pressure to the ultrasound transducer and using it to guide the fetal head physically toward the pelvic inlet and into the vertex presentation [98].

Internal podalic version can also be performed for a nonengaged vertex or transverse presentation under ultrasound guidance. With one hand held abdominally and one hand vaginally, the fetal head is displaced from the pelvic inlet. Ultrasound examination can then identify the fetal feet, which are grasped by the internal hand and guided caudally toward the lower birth canal. This eliminates the confusion of a blind grasp for fetal small parts, which could lead to grasping of one or both fetal hands. Amniotomy is then performed, and total breech extraction begun [97–98].

If a breech extraction is attempted for twin B, ultrasound examination can ensure that the fetal head is flexed [98]. The angle between the upward extension of the main axis of the thoracic vertebrae and a coronal slice through the skull parallel to its base is measured. If the angle is greater than 90 degrees, the head is extended [98]. Other potential complications of a twin delivery that benefit from ultrasound guidance are umbilical cord prolapse and premature placental separation prior to delivery of twin B.

ULTRASONOGRAPHY FOR PROCEDURE GUIDANCE

Prenatal Diagnosis

There are a variety of invasive procedures used to diagnose and treat different fetal genetic, infectious, and hematologic pathologies. Several of these procedures are necessarily done by physicians on a labor and delivery unit, particularly if that procedure is being performed on a fetus at or beyond a viable gestational age (greater than 23 weeks). Performing these invasive procedures in the labor and delivery suite allows the physician to work in conjunction with the neonatologist, anesthesiologist, and the labor and delivery staff if expedited delivery is necessary. Achieving a positive outcome and reducing the procedure-related pregnancy loss rate for each of these procedures is the principal objective, and ultrasonography is of often an invaluable adjunct.

Prior to the performance of any invasive procedure during pregnancy, it is vital that the clinician obtain the greatest amount of information available about that gestation. Ultrasound examination allows the obstetrician to identify many characteristics, including gestational age, number of fetuses, gross anatomic abnormalities, abnormal amniotic fluid volume, fetal viability, and location of the placenta. Similarly, after delivery, ultrasonography is useful in the determination of retained pregnancy products within the uterine cavity and is invaluable to the surgeon performing a dilation and curettage for retained placental tissue.

Amniocentesis and chorionic villus sampling (CVS) are techniques in which a needle is inserted into the gestational sac to withdraw either a sample of amniotic fluid or a sample of placental tissue early in the pregnancy to determine genetic characteristics of the fetus, as well as later in the pregnancy to establish hematologic, infectious, and maturity characteristics. With amniocentesis, amniotic fluid from the uterine cavity is withdrawn using a needle inserted transabdominally. Although the most common indication for amniocentesis is for prenatal genetic studies, the assessment of fetal lung maturity, evaluation of the fetus for infection, degree of hemolytic anemia, blood or platelet type, and neural tube defects can be done using this procedure during pregnancy. Amniocentesis can also be executed as a therapeutic technique to remove excess amniotic fluid. CVS is a procedure in which a small sample of the placenta is obtained for genetic analysis. Whereas amniocentesis can safely be performed at any point in the gestation beyond 15 weeks, CVS is generally performed during the first trimester, between 10 and 13 weeks. In addition to a placental sample obtained transabdominally with a needle,

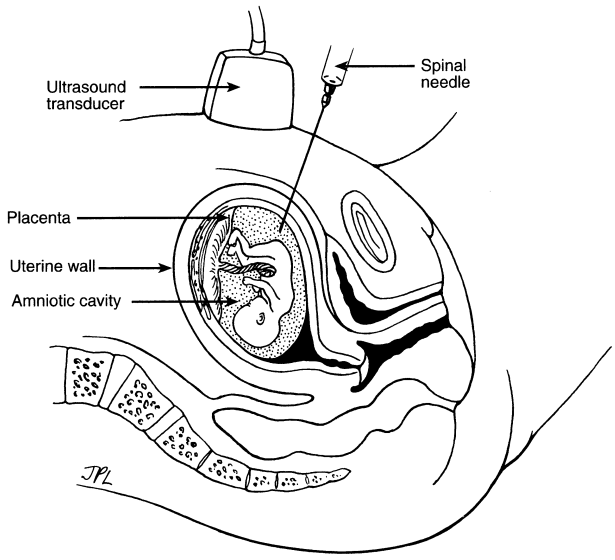

FIGURE 3.12.
Amniocentesis.

CVS can be performed transcervically, using ultrasound scan to guide a specialized catheter into the placenta.

When an amniocentesis or a CVS is performed, continuous ultrasonographic visualization of the needle should be maintained throughout the procedure (see Figure 3.12). The ultrasound probe is typically covered with nonsterile gel and placed within a sterile probe cover, while sterile gel is placed on the outer surface of the cover in contact with the sterilized maternal skin. The optimal position for attainment of the sample is confirmed by ultrasound visualization prior to insertion of the needle. For abdominally approached CVS and amniocentesis, some practitioners prefer a free-hand technique because it allows adjustment in the path of needle insertion. Many ultrasound machines are also outfitted with a needle-guiding attachment that can be placed on the transducer to facilitate obtaining the optimal amount of fluid or tissue during difficult procedures. Those ultrasound machines are typically programmed to display an on-screen template of the needle tract that can be used to target the chosen sampling route and site. Although most proceduralists prefer a co-planar approach to guidance (i.e., aligning the long axis of the needle within the same plane as the ultrasound beam), a transverse (or cross-beam) alignment can sometimes offer more precision. Once the procedure is successfully completed, ultrasound examination should be used to assess and document fetal viability and to rule out any gross tissue damage or hemorrhage.

The use of concurrent ultrasound guidance for amniocentesis rather than pre-procedure ultrasound evaluation has been studied and has not been shown to be associated with a reduced rate of fetal loss [99]. Ultrasonographic monitoring with continuous visualization of the needle throughout the procedure has become the standard of care in most regions of the United States, however, owing to the potential to reduce direct fetal injury, the number of punctures, and the incidence of bloody fluid. Furthermore, ultrasonography is important in identifying tenting of the membranes by the needle, fetal movement, or a uterine contraction during the procedure, allowing the operator to adjust the course of the needle to obtain a specimen. Finally, ultrasonography is a reliable means of ensuring that as little of the placenta is traversed as possible, the importance of which studies have suggested by demonstrating a greater risk of fetal complications with transplacental passage of the needle during invasive procedures [100–101].

PERCUTANEOUS UMBILICAL BLOOD SAMPLING

Fetal blood sampling is an ultrasound-guided procedure that is classically performed in the labor and delivery unit, where rapid delivery of a viable fetus can occur if necessary. Fetal blood sampling is a practice used to gain access to the fetal blood for various indications; classically, obtaining a fetal blood sample can assist in the diagnosis of genetic disorders using a technique of rapid karyotyping, as well as to diagnose fetal infection and determine fetal blood type. Because amniocentesis and CVS are invasive techniques that have a lower procedure-related pregnancy loss rate, they are typically used for determination of fetal genetic disorders. Fetal blood sampling, however, is typically reserved for the diagnosis and treatment of fetal blood disorders such as anemia and thrombocytopenia. This procedure requires precise ultrasound visualization of the fetus; traditional ultrasound examination provides a two-dimensional image by which the clinician can identify the relative location of key components within the uterine cavity, including the fetus, placenta, and umbilical cord.

Fetal blood sampling is achieved by direct needle insertion into the fetal umbilical cord, also called *cordocentesis* or *percutaneous umbilical blood sampling* (PUBS), fetal heart, or fetal intrahepatic blood vessels. Before ultrasonography was used, fetal blood sampling was carried out by fetoscopic-guided puncture of the umbilical vessels, with a 5% procedure-related risk of pregnancy loss. The current approach of sampling fetal vessels under direct ultrasound guidance reduces the loss rate to approximately 1% per procedure [102]. The umbilical cord is the most frequently used site to obtain a fetal blood sample; the choice of whether to sample the umbilical artery or vein depends on the gestational age, presentation, and the indication for the procedure. The operator typically will identify and aim for a fixed segment of the umbilical cord 1 cm to 2 cm from the placental cord insertion, because the risk of maternal blood contamination is minimal and the cord is anchored there, offering the greatest stability for insertion of the needle, withdrawal of an adequate sample, and, if necessary, ease of transfusion of blood products. The Doppler color function of the ultrasound machine can be used to confirm the cord insertion site and flow of transfusion products through the fetal vessels.

Prenatal diagnosis using ultrasound-guided cordocentesis was studied by Daffos and coauthors, who performed more than 600 fetal blood sampling procedures from 17 to 38 weeks' gestation [102]. They established a procedure-related loss rate of 1.1% and a premature delivery rate of 5% for their cohort of patients. Similarly, Watts et al. published the outcomes of 77 fetal transfusions in 35 pregnancies managed with direct ultrasound guidance [103]. They reported no immediate transfusion-related deaths, and 5 transfusion-related complications, none of which required the immediate delivery of the fetus. The same group reported a 0% procedure-related mortality rate in nonhydropic fetuses.

Three- and Four-dimensional Ultrasonography

Recently the techniques of three- and four-dimensional (3D, 4D) ultrasound examination have become an important addition to obstetric sonography, increasing its ability to identify fetal structures and guide invasive procedures. A two-dimensional ultrasound monitor display of three-dimensional data is termed *3D ultrasonography*. Surface rendering of the fetus, placenta, or umbilical cord with 3D sonography can better demonstrate abnormalities that were previously undetectable with traditional two-dimensional sonography. The real-time imaging of three perpendicular planes of view simultaneously is termed *4D ultrasonography*. The theoretical benefit to using 3D or 4D visualization during invasive obstetric procedures is to increase the precision of needle placement when the target is relatively small. 2D ultrasound procedure guidance is prone to lateralization; this occurs when the width of the ultrasound beam is wider than the width of the needle tip, resulting in the needle image appearing to be within a tissue structure (e.g., umbilical cord) when it is actually adjacent to that structure.

In 2005, Dolkart et al. studied the feasibility of using 4D real-time, multiplanar ultrasonographic imaging to reduce lateralization during invasive procedures. They utilized 4D ultrasound examination in 99 patients undergoing amniocentesis, CVS, or cordocentesis procedures [104]. A historical control group of 99 patients whose procedure was carried out using 2D ultrasound were used for comparison. They found no difference in the number of needle insertions performed during amniocentesis, CVS, or cordocentesis in either the 2D or 4D groups; however, operator satisfaction with needle-tip visualization was improved in the 4D group. They concluded that it is indeed feasible and perhaps beneficial to use 4D ultrasonography for guiding these procedures more precisely. Similarly, Kim et al. published the results of 93 invasive procedures done under 4D ultrasound guidance and concluded that such imaging could significantly reduce the amount of time required to complete the procedure, thus reducing the associated pregnancy risks [105]. Although this could prove to become the standard of care, at this time, the role of 3D and 4D ultrasound technology for procedure guidance has not been optimally defined nor has the benefit been proved for widespread use.

Retained Products/Dilation and Evacuation

A prolonged third stage of labor can be due to retained placental tissue, defined as a placenta that has not been fully expelled 30 minutes after delivery [106]. It occurs on labor and delivery units in 0.5% to 1% of all deliveries and is a common reason for

postpartum hemorrhage. Postpartum hemorrhage from retained uterine products occurs because the remaining tissue prohibits the uterus from contracting, thus inhibiting normal constriction of vascular beds that are subsequently left exposed and allowed to continue bleeding. The treatment of retained tissue requires removal of that tissue either manually or surgically to reduce the risk of severe bleeding and hypotensive shock that can occur with prolonged expectant management.

Ultrasound assessment of the uterus during the third stage of labor to verify the presence of retained placental tissue or membranes can assist the obstetrician in achieving the safest course of management while avoiding unnecessary and risky instrumentation of the postpartum uterus and minimizing bleeding. Transabdominal ultrasound examination immediately following delivery of the infant can demonstrate placental detachment, which allows the practitioner to comfortably pull on the umbilical cord without fear of uterine inversion or placental dismemberment. Separation of the placenta was studied with real-time ultrasonography during the third stage of labor in 100 patients [107]. In 97 of these patients, the authors found that separation of the placenta was multiphasic, beginning mostly in the lower pole of the placenta and then propagating upwards.

In addition to following the normal course of placental separation, several authors have used ultrasound examination to predict which patients might have difficulty with placental separation and to diagnose placental tissue retention. Krapp et al. used color Doppler to correlate the cessation of blood flow in placental basal plate vessels to the complete separation of the placenta from the myometrium [108]. They determined that continued blood flow in these vessels was associated with placenta adherence and the need for manual or instrumental removal. In a study of 39 women with suspected placental retention, Shen and coauthors performed ultrasound examination prior to exploration and found that sonography was an effective tool for identifying postpartum patients with retained placental fragments [109]. They found a sensitivity of 93.8% and specificity of 73.9% for ultrasound detection of this tissue. Determining the progression of placental separation and following it in real-time with ultrasound scan during the third stage of labor, as well as using Doppler techniques to monitor cessation of blood flow to placental tissue, might allow the practitioner to predict which patients are destined for retained placental fragments. Furthermore, ultrasonography has proved to be helpful in the diagnosis of failed placental separation, allowing for expeditious surgical management prior to severe hemorrhage.

Endoanal Ultrasound

Damage to the anal sphincter at the time of vaginal delivery predisposes women to fecal incontinence, especially when this damage goes undiagnosed and therefore is not repaired [110]. Disruption of the anal sphincter is clinically diagnosed in approximately 5% of all vaginal deliveries [111]. Endoanal ultrasound examinations in women without clinically recognized anal sphincter disruption after delivery have shown the prevalence to be as high as 44%, however [110]. *Anal sphincter rupture* is defined as a gap in the hyperechogenic ring of the internal or external anal sphincter [112]. Anal incontinence is subsequently reported in up to 50% of women with clinically unrecognized sphincter damage [110].

Recent studies have shown that performing routine endoanal ultrasound examination in women with second-degree perineal tears identifies clinically occult sphincter damage, allowing immediate surgical intervention. This intervention significantly decreases severe fecal incontinence from approximately 9% at 3 months and 7% at one year in women randomized to the control group, versus 3% at 3 months and one year ($p = 0.002$, $p = 0.03$ respectively) in women randomized to endoanal ultrasound and surgical repair when a defect was found [113]. Ultrasound examination of the perineum after childbirth improves the diagnosis of anal sphincter tears, and their immediate repair decreases the risk of severe fecal incontinence [113]. Endoanal ultrasonography needs to be performed in 29 women to prevent 1 case of severe fecal incontinence [113]. Adding routine endoanal ultrasound examination to the standard clinical examination after delivery has the potential to decrease occult sphincter damage and therefore fecal incontinence.

The aim of this chapter is to demonstrate the importance of ultrasonography in the proper assessment and management of the gravida in the labor and delivery suite. The proper use of this valuable

tool requires the same level of expertise, documentation, and state-of-the-art equipment (including transvaginal, pulsed and color Doppler, and 3D ultrasound capabilities) as is expected in the prenatal clinic. Use of these techniques in the labor and delivery suite will certainly lead to better management of the mother and fetus, reducing complications and leading to a healthier outcome for both.

REFERENCES

1. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery: National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996 Feb 29;334(9):567–72.
2. Phelps JY, Higby K, Smyth MH, Ward JA, Arredondo F, Mayer AR. Accuracy and intraobserver variability of simulated cervical dilatation measurements. Am J Obstet Gynecol. 1995 Sep; 173(3 Pt 1):942–5.
3. Yang SH, Roh CR, Kim JH. Transvaginal ultrasonography for cervical assessment before induction of labor. J Ultrasound Med. 2004 Mar;23(3):375–82.
4. Gabriel R, Darnaud T, Chalot F, Gonzalez N, Leymarie F, Quereux C. Transvaginal sonography of the uterine cervix prior to labor induction. Ultrasound Obstet Gynecol. 2002 Mar;19(3):254–7.
5. Ware V, Raynor BD. Transvaginal ultrasonographic cervical measurement as a predictor of successful labor induction. Am J Obstet Gynecol. 2000 May; 182(5):1030–2.
6. Brown JE, Thieme GA, Shah DM, Fleischer AC, Boehm FH. Transabdominal and transvaginal endosonography: Evaluation of the cervix and lower uterine segment in pregnancy. Am J Obstet Gynecol. 1986 Oct;155(4):721–6.
7. Leibman AJ, Kruse B, McSweeney MB. Transvaginal sonography: Comparison with transabdominal sonography in the diagnosis of pelvic masses. AJR Am J Roentgenol. 1988 Jul;151(1):89–92.
8. Andersen HF. Transvaginal and transabdominal ultrasonography of the uterine cervix during pregnancy. J Clin Ultrasound. 1991 Feb;19(2):77–83.
9. Timor-Tritsch IE, Yunis RA. Confirming the safety of transvaginal sonography in patients suspected of placenta previa. Obstet Gynecol. 1993 May;81(5 (Pt 1)):742–4.
10. Carlan SJ, Richmond LB, O'Brien WF. Randomized trial of endovaginal ultrasound in preterm premature rupture of membranes. Obstet Gynecol. 1997 Mar;89(3):458–61.
11. Burger M, Weber-Rossler T, Willmann M. Measurement of the pregnant cervix by transvaginal sonography: An interobserver study and new standards to improve the interobserver variability. Ultrasound Obstet Gynecol. 1997 Mar;9(3):188–93.
12. Kurtzman JT, Goldsmith LJ, Gall SA, Spinnato JA. Transvaginal versus transperineal ultrasonography: A blinded comparison in the assessment of cervical length at midgestation. Am J Obstet Gynecol. 1998 Oct;179(4):852–7.
13. Mahony BS, Nyberg DA, Luthy DA, Hirsch JH, Hickok DE, Petty CN. Translabial ultrasound of the third-trimester uterine cervix: Correlation with digital examination. J Ultrasound Med. 1990 Dec;9(12):717–23.
14. Kushnir O, Vigil DA, Izquierdo L, Schiff M, Curet LB. Vaginal ultrasonographic assessment of cervical length changes during normal pregnancy. Am J Obstet Gynecol. 1990 Apr;162(4):991–3.
15. Heath VC, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation: Relation to demographic characteristics and previous obstetric history. Ultrasound Obstet Gynecol. 1998 Nov;12(5):304–11.
16. Parulekar SG, Kiwi R. Dynamic incompetent cervix uteri. Sonographic observations. J Ultrasound Med. 1988 Sep;7(9):481–5.
17. Gomez R, Galasso M, Romero R, Mazor M, Sorokin Y, Goncalves L, et al. Ultrasonographic examination of the uterine cervix is better than cervical digital examination as a predictor of the likelihood of premature delivery in patients with preterm labor and intact membranes. Am J Obstet Gynecol. 1994 Oct;171(4):956–64.
18. Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: A new perspective. J Ultrasound Med. 1995 Oct;14(10):719–24.
19. Berghella V, Kuhlman K, Weiner S, Texeira L, Wapner RJ. Cervical funneling: Sonographic criteria predictive of preterm delivery. Ultrasound Obstet Gynecol. 1997 Sep;10(3):161–6.
20. Iams JD, Johnson FF, Sonek J, Sachs L, Gebauer C, Samuels P. Cervical competence as a continuum: A study of ultrasonographic cervical length and

obstetric performance. Am J Obstet Gynecol. 1995 Apr;172(4 Pt 1):1097–103.
21. Owen J, Yost N, Berghella V, MacPherson C, Swain M, Dildy GA 3rd, Miodovnik M, Langer O, Sibai B. Maternal-Fetal Medicine Units Network: Can shortened midtrimester cervical length predict very early spontaneous preterm birth? Am J Obstet Gynecol. 2004 Jul;191(1):298–303.
22. Iams JD, Goldenberg RL, Mercer BM, Moawad AH, Meis PJ, Das AF, et al. The preterm prediction study: Can low-risk women destined for spontaneous preterm birth be identified? Am J Obstet Gynecol. 2001 Mar;184(4):652–5.
23. Iams JD. Prediction and early detection of preterm labor. Obstet Gynecol. 2003 Feb;101(2):402–12.
24. Tsoi E, Akmal S, Rane S, Otigbah C, Nicolaides KH. Ultrasound assessment of cervical length in threatened preterm labor. Ultrasound Obstet Gynecol. 2003 Jun;21(6):552–5.
25. Tsoi E, Fuchs IB, Rane S, Geerts L, Nicolaides KH. Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes. Ultrasound Obstet Gynecol. 2005 Apr;25(4):353–6.
26. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW. Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor. Ultrasound Obstet Gynecol. 2004 Oct;24(5):554–7.
27. Rane SM, Guirgis RR, Higgins B, Nicolaides KH. The value of ultrasound in the prediction of successful induction of labor. Ultrasound Obstet Gynecol. 2004 Oct;24(5):538–49.
28. Bartha JL, Romero-Carmona R, Martinez-Del-Fresno P, Comino-Delgado R. Bishop score and transvaginal ultrasound for preinduction cervical assessment: A randomized clinical trial. Ultrasound Obstet Gynecol. 2005 Feb;25(2):155–9.
29. Roman H, Verspyck E, Vercoustre L, Degre S, Col JY, Firmin JM, et al. The role of ultrasound and fetal fibronectin in predicting the length of induced labor when the cervix is unfavorable. Ultrasound Obstet Gynecol. 2004 Jun;23(6):567–73.
30. Reis FM, Gervasi MT, Florio P, Bracalente G, Fadalti M, Severi FM, et al. Prediction of successful induction of labor at term: Role of clinical history, digital examination, ultrasound assessment of the cervix, and fetal fibronectin assay. Am J Obstet Gynecol. 2003 Nov;189(5):1361–7.
31. Chandra S, Crane JM, Hutchens D, Young DC. Transvaginal ultrasound and digital examination in predicting successful labor induction. Obstet Gynecol. 2001 Jul;98(1):2–6.
32. Rozenberg P, Chevret S, Chastang C, Ville Y. Comparison of digital and ultrasonographic examination of the cervix in predicting time interval from induction to delivery in women with a low Bishop score. BJOG. 2005 Feb;112(2):192–6.
33. Weissman A, Itskovitz-Eldor J, Jakobi P. Sonographic measurement of amniotic fluid volume in the first trimester of pregnancy. J Ultrasound Med. 1996 Nov;15(11):771–4.
34. Magann EF, Doherty DA, Chauhan SP, Barrilleaux SP, Verity LA, Martin JN Jr. Effect of maternal hydration on amniotic fluid volume. Obstet Gynecol. 2003 Jun;101(6):1261–5.
35. Manning FA, Hill LM, Platt LD. Qualitative amniotic fluid volume determination by ultrasound: Antepartum detection of intrauterine growth retardation. Am J Obstet Gynecol. 1981 Feb 1;139(3):254–8.
36. Phelan JP, Ahn MO, Smith CV, Rutherford SE, Anderson E. Amniotic fluid index measurements during pregnancy. J Reprod Med. 1987 Aug;32(8):601–4.
37. Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. Am J Obstet Gynecol. 1990 May;162(5):1168–73.
38. Miyamura T, Masuzaki H, Miyamoto M, Ishimaru T. Comparison between the single deepest pocket and amniotic fluid index in predicting fetal distress in small-for-gestational age fetuses. Acta Obstet Gynecol Scand. 1997 Feb;76(2):123–7.
39. Chauhan SP, Doherty DD, Magann EF, Cahanding F, Moreno F, Klausen JH. Amniotic fluid index vs. single deepest pocket technique during modified biophysical profile: A randomized clinical trial. Am J Obstet Gynecol. 2004 Aug;191(2):661–7.
40. Chauhan SP, Magann EF, Morrison JC, Whitworth NS, Hendrix NW, Devoe LD. Ultrasonographic assessment of amniotic fluid does not reflect actual amniotic fluid volume. Am J Obstet Gynecol. 1997 Aug;177(2):291–6.
41. Brace RA. Physiology of amniotic fluid volume regulation. Clin Obstet Gynecol. 1997 Jun;40(2):280–9.
42. Manning FA. Dynamic ultrasound-based fetal assessment: The fetal biophysical profile score. Clin Obstet Gynecol. 1995 Mar;38(1):26–44.

43. Voxman EG, Tran S, Wing DA. Low amniotic fluid index as a predictor of adverse perinatal outcome. J Perinatol. 2002 Jun;22(4):282–5.
44. Locatelli A, Vergani P, Toso L, Verderio M, Pezzullo JC, Ghidini A. Perinatal outcome associated with oligohydramnios in uncomplicated term pregnancies. Arch Gynecol Obstet. 2004 Jan;269(2): 130–3.
45. Chauhan SP, Sanderson M, Hendrix NW, Magann EF, Devoe LD. Perinatal outcome and amniotic fluid index in the antepartum and intrapartum periods: A meta-analysis. Am J Obstet Gynecol. 1999 Dec;181(6):1473–8.
46. Carlson DE, Platt LD, Medearis AL, Horenstein J. Quantifiable polyhydramnios: diagnosis and management. Obstet Gynecol. 1990 Jun;75(6): 989–93.
47. Ott WJ. Reevaluation of the relationship between amniotic fluid volume and perinatal outcome. Am J Obstet Gynecol. 2005 Jun;192(6):1803–9.
48. Manning FA, Platt LD, Sipos L. Antepartum fetal evaluation: development of a fetal biophysical profile. Am J Obstet Gynecol. 1980 Mar 15;136(6): 787–95.
49. Vintzileos AM, Gaffney SE, Salinger LM, Campbell WA, Nochimson DJ. The relationship between fetal biophysical profile and cord pH in patients undergoing cesarean section before the onset of labor. Obstet Gynecol. 1987 Aug;70(2):196–201.
50. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. Am J Obstet Gynecol. 1991 Sep;165(3):707–13.
51. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relationship of fetal biophysical profile and blood gas values at cordocentesis in severely growth-retarded fetuses. Am J Obstet Gynecol. 1990 Aug; 163(2):569–71.
52. Manning FA, Lange IR, Morrison I, Harman CR. Fetal biophysical profile score and the nonstress test: A comparative trial. Obstet Gynecol. 1984 Sep;64 (3):326–31.
53. Baskett TF, Allen AC, Gray JH, Young DC, Young LM. Fetal biophysical profile and perinatal death. Obstet Gynecol. 1987 Sep;70(3 Pt 1):357–60.
54. Kim SY, Khandelwal M, Gaughan JP, Agar MH, Reece EA. Is the intrapartum biophysical profile useful? Obstet Gynecol. 2003 Sep;102(3): 471–6.
55. Kurkinen-Raty M, Kivela A, Jouppila P. The clinical significance of an absent end-diastolic velocity in the umbilical artery detected before the 34th week of pregnancy. Acta Obstet Gynecol Scand. 1997 May; 76(5):398–404.
56. Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: Systematic review with meta-analysis. Am J Obstet Gynecol. 1995 May; 172(5):1379–87.
57. Mason GC, Lilford RJ, Porter J, Nelson E, Tyrell S. Randomised comparison of routine versus highly selective use of Doppler ultrasound in low-risk pregnancies. Br J Obstet Gynaecol. 1993 Feb; 100(2):130–3.
58. Farrell T, Chien PF, Gordon A. Intrapartum umbilical artery Doppler velocimetry as a predictor of adverse perinatal outcome: A systematic review. Br J Obstet Gynaecol. 1999 Aug;106(8):783–92.
59. Siristatidis C, Salamalekis E, Kassanos D, Creatsas G. Alterations in Doppler velocimetry indices of the umbilical artery during fetal hypoxia in labor, in relation to cardiotocography and fetal pulse oximetry findings. Arch Gynecol Obstet. 2005 Sep; 272(3):191–6.
60. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. Br J Obstet Gynaecol. 1995 Dec;102(12): 963–9.
61. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J Obstet Gynecol. 1999 Mar;180(3 Pt 1):750–6.
62. Siristatidis C, Salamalekis E, Kassanos D, Loghis C, Creatsas G. Evaluation of fetal intrapartum hypoxia by middle cerebral and umbilical artery Doppler velocimetry with simultaneous cardiotocography and pulse oximetry. Arch Gynecol Obstet. 2004 Dec;270(4):265–70.
63. Goldstein I, Lockwood C, Belanger K, Hobbins J. Ultrasonographic assessment of gestational age with the distal femoral and proximal tibial ossification centers in the third trimester. Am J Obstet Gynecol. 1988 Jan;158(1):127–30.
64. Nazario AC, Tanaka CI, Novo NF. Proximal humeral ossification center of the fetus: Time of appearance and the sensitivity and specificity of

this finding. J Ultrasound Med. 1993 Sep;12(9): 513–5.
65. Mongelli M, Chew S, Yuxin NG, Biswas A. Third-trimester ultrasound dating algorithms derived from pregnancies conceived with artificial reproductive techniques. Ultrasound Obstet Gynecol. 2005 Aug; 26(2):129–31.
66. Smulian JC, Ranzini AC, Ananth CV, Rosenberg JC, Vintzileos AM. Comparison of three sonographic circumference measurement techniques to predict birth weight. Obstet Gynecol. 1999 May; 93(5 Pt 1):692–6.
67. Callen PW (ed.): Ultrasonography in Obstetrics and Gynecology. Philadelphia, W. B. Saunders Company; 4th edition: 20, p 597.
68. Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. JAMA. 1999 Nov 3;282(17):1646–51.
69. Knab DR. Abruptio placentae. An assessment of the time and method of delivery. Obstet Gynecol. 1978 Nov;52(5):625–9.
70. Abu-Heija A, al-Chalabi H, el-Iloubani N.: Abruptio placentae: Risk factors and perinatal outcome. J Obstet Gynaecol Res. 1998 Apr;24(2):141–4.
71. Glantz C, Purnell L. Clinical utility of sonography in the diagnosis and treatment of placental abruption. J Ultrasound Med. 2002 Aug;21(8):837–40.
72. Nyberg DA, Cyr DR, Mack LA, Wilson DA, Shuman WP. Sonographic spectrum of placental abruption. AJR Am J Roentgenol. 1987 Jan;148(1): 161–4.
73. Mustafa SA, Brizot ML, Carvalho MH, Watanabe L, Kahhale S, Zugaib M. Transvaginal ultrasonography in predicting placenta previa at delivery: A longitudinal study. Ultrasound Obstet Gynecol. 2002 Oct;20(4):356–9.
74. Smith RS, Lauria MR, Comstock CH, Treadwell MC, Kirk JS, Lee W, Bottoms SF. Transvaginal ultrasonography for all placentas that appear to be low-lying or over the internal cervical os. Ultrasound Obstet Gynecol. 1997 Jan;9(1):22–4.
75. Leerentveld RA, Gilberts EC, Arnold MJ, Wladimiroff JW. Accuracy and safety of transvaginal sonographic placental localization. Obstet Gynecol. 1990 Nov;76(5 Pt 1):759–62.
76. Dawson WB, Dumas MD, Romano WM, Gagnon R, Gratton RJ, Mowbray RD. Translabial ultrasonography and placenta previa: Does measurement of the os–placenta distance predict outcome? J Ultrasound Med. 1996 Jun;15(6):441–6.
77. Cox SM, Carpenter RJ, Cotton DB. Placenta percreta: Ultrasound diagnosis and conservative surgical management. Obstet Gynecol. 1988 Mar;71(3 Pt 2):454–6.
78. Levine D, Hulka CA, Ludmir J, Li W, Edelman RR. Placenta accreta: Evaluation with color Doppler US, power Doppler US, and MR imaging. Radiology. 1997 Dec;205(3):773–6.
79. Guy GP, Peisner DB, Timor-Tritsch IE. Ultrasonographic evaluation of uteroplacental blood flow patterns of abnormally located and adherent placentas. Am J Obstet Gynecol. 1990 Sep;163(3):723–7.
80. Comstock CH, Love JJ Jr, Bronsteen RA, Lee W, Vettraino IM, Huang RR, Lorenz RP. Sonographic detection of placenta accreta in the second and third trimesters of pregnancy. Am J Obstet Gynecol. 2004 Apr;190(4):1135–40.
81. Kirkinen P, Helin-Martikainen HL, Vanninen R, Partanen K. Placenta accreta: Imaging by gray-scale and contrast-enhanced color Doppler sonography and magnetic resonance imaging. J Clin Ultrasound. 1998 Feb;26(2):90–4.
82. Rayburn WF, Siemers KH, Legino LJ, Nabity MR, Anderson JC, Patil KD. Dystocia in late labor: Determining fetal position by clinical and ultrasonic techniques. Am J Perinatol. 1989 Jul;6(3):316–9.
83. Sherer DM, Miodovnik M, Bradley KS, Langer O. Intrapartum fetal head position I: Comparison between transvaginal digital examination and transabdominal ultrasound assessment during the active stage of labor. Ultrasound Obstet Gynecol. 2002 Mar;19(3):258–63.
84. Sherer DM, Miodovnik M, Bradley KS, Langer O. Intrapartum fetal head position II: comparison between transvaginal digital examination and transabdominal ultrasound assessment during the second stage of labor. Ultrasound Obstet Gynecol. 2002 Mar;19(3):264–8.
85. Chou MR, Kreiser D, Taslimi MM, Druzin ML, El-Sayed YY. Vaginal versus ultrasound examination of fetal occiput position during the second stage of labor. Am J Obstet Gynecol. 2004 Aug;191(2): 521–4.
86. Cunningham FG, Gant N, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD. Forceps Delivery and Vacuum Extraction. Williams Obstetrics, 21st Edition. New York, McGraw-Hill, 2001, 485–508.
87. Akmal S, Kametas N, Tsoi E, Hargreaves C, Nicolaides KH. Comparison of transvaginal digital examination with intrapartum sonography to determine

fetal head position before instrumental delivery. Ultrasound Obstet Gynecol. 2003 May;21(5):437–40.
88. Sherer DM, Abulafia O. Intrapartum assessment of fetal head engagement: Comparison between transvaginal digital and transabdominal ultrasound determinations. Ultrasound Obstet Gynecol. 2003 May;21(5):430–6.
89. Zahalka N, Sadan O, Malinger G, Liberati M, Boaz M, Glezerman M, Rotmensch S. Comparison of transvaginal sonography with digital examination and transabdominal sonography for the determination of fetal head position in the second stage of labor. Am J Obstet Gynecol. 2005 Aug;193(2): 381–6.
90. Ponkey SE, Cohen AP, Heffner LJ, Lieberman E. Persistent fetal occiput posterior position: Obstetric outcomes. Obstet Gynecol. 2003 May;101(5 Pt 1):915–20.
91. Rane SM, Guirgis RR, Higgins B, Nicolaides KH. The value of ultrasound in the prediction of successful induction of labor. Ultrasound Obstet Gynecol. 2004 Oct;24(5):538–49.
92. Akmal S, Kametas N, Tsoi E, Howard R, Nicolaides KH. Ultrasonographic occiput position in early labour in the prediction of caesarean section. BJOG. 2004 Jun;111(6):532–6.
93. Akmal S, Tsoi E, Howard R, Osei E, Nicolaides KH. Investigation of occiput posterior delivery by intrapartum sonography. Ultrasound Obstet Gynecol. 2004 Sep;24(4):425–8.
94. Gardberg M, Laakkonen E, Salevaara M. Intrapartum sonography and persistent occiput posterior position: A study of 408 deliveries. Obstet Gynecol. 1998 May;91(5 Pt 1):746–9.
95. Akmal S, Tsoi E, Nicolaides KH. Intrapartum sonography to determine fetal occipital position: Interobserver agreement. Ultrasound Obstet Gynecol. 2004 Sep;24(4):421–4.
96. Ramsey PS, Repke JT. Intrapartum management of multifetal pregnancies. Semin Perinatol. 2003 Feb;27(1):54–72.
97. Warenski JC, Kochenour NK. Intrapartum management of twin gestation. Clin Perinatol. 1989 Dec;16(4):889–97.
98. Berkowitz RL, Hobbins JC. Delivering twins with the help of ultrasound. Contemporary Ob-Gyn. 1982 February; 19: 128–131.
99. Seeds JW. Diagnostic mid-trimester amniocentesis: How safe? Am J Obstet Gynecol. 2004 Aug;191(2): 607–15.
100. Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet. 1986 Jun 7;1(8493):1287–93.
101. Kappel B, Nielsen J, Brogaard Hansen K, Mikkelsen M, Therkelsen AJ. Spontaneous abortion following mid-trimester amniocentesis: Clinical significance of placental perforation and blood-stained amniotic fluid. Br J Obstet Gynaecol. 1987 Jan;94(1): 50–4.
102. Daffos F, Capella-Pavlovsky M, Forestier F. Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: A study of 606 consecutive cases. Am J Obstet Gynecol. 1985 Nov 15; 153(6):655–60.
103. Watts DH, Luthy DA, Benedetti TJ, Cyr DR, Easterling TR, Hickok D. Intraperitoneal fetal transfusion under direct ultrasound guidance. Obstet Gynecol. 1988 Jan;71(1):84–8.
104. Dolkart L, Harter M, Snyder M. Four-dimensional ultrasonographic guidance for invasive obstetric procedures. J Ultrasound Med. 2005 Sep;24(9): 1261–6.
105. Kim SR, Won HS, Lee PR, Kim A. Four-dimensional ultrasound guidance of prenatal invasive procedures. Ultrasound Obstet Gynecol. 2005 Nov;26(6):663–5.
106. Combs CA, Laros RK. Prolonged third stage of labor: Morbidity and risk factors. Obstet Gynecol. 1991 Jun;77(6):863–7.
107. Herman A, Zimerman A, Arieli S, Tovbin Y, Bezer M, Bukovsky I, Panski M. Down-up sequential separation of the placenta. Ultrasound Obstet Gynecol. 2002 Mar;19(3):278–81.
108. Krapp M, Baschat AA, Hankeln M, Gembruch U. Gray-scale and color Doppler sonography in the third stage of labor for early detection of failed placental separation. Ultrasound Obstet Gynecol. 2000 Feb;15(2):138–42.
109. Shen O, Rabinowitz R, Eisenberg VH, Samueloff A. Transabdominal sonography before uterine exploration as a predictor of retained placental fragments. J Ultrasound Med. 2003 Jun;22(6):561–4.
110. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. N Engl J Med. 1993 Dec 23;329(26): 1905–11.
111. MacArthur C, Bick DE, Keighley MR. Faecal incontinence after childbirth. Br J Obstet Gynaecol. 1997 Jan;104(1):46–50.

112. Sultan AH, Nicholls RJ, Kamm MA, Hudson CN, Beynon J, Bartram CI. Anal endosonography and correlation with in vitro and in vivo anatomy. 1993 Br J Surg (79):104–106.

113. Faltin DL, Boulvain M, Floris LA, Irion O. Diagnosis of anal sphincter tears to prevent fecal incontinence: A randomized controlled trial. Obstet Gynecol. 2005 Jul;106(1):6–13.

Chapter 4 ECTOPIC PREGNANCY

Samantha F. Butts
David B. Seifer

. . . one should regard sudden collapse associated with symptoms of abdominal hemorrhage in a woman during the childbearing period as prima facie evidence of a ruptured tubal pregnancy. By so doing, and operating promptly in suitable cases, a number of lives will be saved which otherwise would inevitably be lost.

J. Whitridge Williams (1866–1931)
Obstetrics: A Text-Book for the Use of Students and Practitioners,
New York: D. Appleton and Company, 1903, p. 553.

The initiation of a normal pregnancy requires exquisitely timed coordination of several endocrine-sensitive tissues. After fertilization of the ovum in the fallopian tube, cleavage and embryonic development occur, followed by uterine implantation approximately six days later. Following fertilization and implantation, the syncytiotrophoblast begins to produce human chorionic gonadotropin (hCG), which eventually rescues and maintains the corpus luteum beyond its normal 14-day life span. When this course of physiologic events occurs normally, a pregnancy can progress, allowing the fetus to develop until birth. The development of an *ectopic pregnancy* is an aberration of this process, in which embryonic implantation occurs outside of the uterus, most commonly in the fallopian tube but also in extratubal locations. Ectopic pregnancy is an extremely serious threat to the general and reproductive health of a woman. The objective of this chapter is to provide a comprehensive discussion of the contemporary approach to ectopic pregnancy. Diagnosis and treatment options and the epidemiology and pathophysiology of the condition are also reviewed.

EPIDEMIOLOGY

Ectopic pregnancies comprise approximately 2% of all pregnancies reported to the Centers for Disease Control and Prevention (CDC). Several important trends have emerged from data collected by the CDC with respect to ectopic incidence, and related morbidity and mortality. Notably, the incidence of ectopic pregnancy appears to have steadily and persistently risen since 1970, the first year that data on this subject were collected by the CDC (Figure 4.1). Between 1970 and 1992, the rate of ectopic pregnancy increased from 4.5 to 19.7 per 1,000 reported pregnancies (including live births, legal abortions, and ectopic pregnancies) [1,2]. This trend is likely due to the emergence of several key elements, including enhanced diagnostic capability to detect ectopic pregnancies early in gestation, the rising incidence of gonorrhea and chlamydial infections in reproductive-aged women, and the growing use

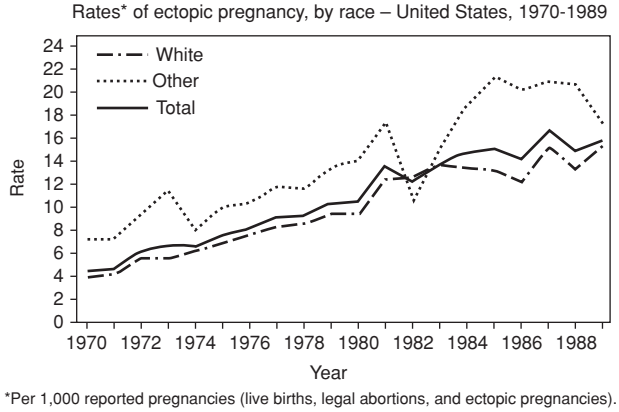

FIGURE 4.1.
Incidence of ectopic pregnancy from 1970–1989 overall and stratified by race. (*From *Goldner TE, et al. Surveillance for Ectopic Pregnancy – United States, 1970–1989. MMWR 1993;73–78; with permission.)

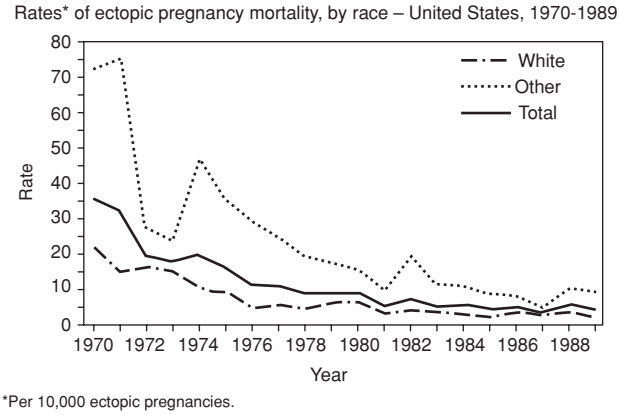

FIGURE 4.2.
Ectopic pregnancy mortality overall and stratified by race 1970–1989. (*From *Goldner TE, et al. Surveillance for Ectopic Pregnancy – United States, 1970–1989. MMWR 1993;73–82; with permission.)

of treatments to circumvent infertility, including in vitro fertilization.

Determination of the overall incidence of ectopic pregnancy is not straightforward, because data on nonhospitalized cases are inconsistently recorded. After a reported increase in hospitalizations for ectopic pregnancy over a twenty-year period starting in 1970, there has been a steady decline from 1990 forward. The number of hospitalizations appears to have peaked at 88,400 in 1989, followed by a significant drop the following year to 64,400 admissions. This trend in reduced hospitalization is due to the increased use of conservative approaches to the treatment of ectopic pregnancy, including the use of laparoscopy and methotrexate. In addition, prompt diagnosis early in gestation makes the occurrence of tubal rupture less common, allowing many more ectopic pregnancies to be treated before rupture and hemodynamic instability ensue.

Despite these notable successes, ectopic pregnancy remains a source of serious maternal morbidity and mortality in the United States. Complications of ectopic pregnancy have made this condition the leading cause of maternal mortality in the first trimester of pregnancy. From 1991 to 1999, there were 237 ectopic-related deaths, which constituted 6% of all pregnancy-related deaths. In most cases, the proximate cause of death is hemorrhage (93.3%), and, less commonly, infection (2.5%) or embolism (2.1%) [3]. Fortunately, the risk of ectopic-related mortality appears to be declining despite the increase in incidence of this condition. From 1970 to 1989, the case fatality rate of ectopic pregnancy drastically declined from 35.5 deaths/10,000 ectopics to 3.8 deaths/10,000 (Figure 4.2) [2].

Another dominant theme in the demographics of ectopic pregnancy is the presence of disparities in incidence and mortality by race. The relative risk of ectopic pregnancy for African American women is up to 1.6 times that for white women [2]. This disparity is consistent across all age categories and extends to differences in mortality related to ectopic pregnancy. As concerns ectopic-related mortality, the health disparity by race is even more prominent. From 1970 to 1989, the risk of death caused by ectopic pregnancy was 3.4 times greater for African-American women and other minorities as it was for white women [2,3]. The sharp decline in ectopic-related mortality experienced by all women in recent years has been insufficient to eliminate this persistent racial gap.

PATHOPHYSIOLOGY

Although the exact etiology of ectopic pregnancy is not completely understood, both maternal and embryonic factors are thought to contribute to its development. Abnormalities of tubal function and ovum quality or an altered hormonal milieu may each contribute to the development of an ectopic pregnancy [4]. Although this discussion focuses on tubal ectopic pregnancies, extrauterine pregnancies

can occasionally localize to the abdomen, cervix, ovary or uterine cornua. These less common presentations of ectopic pregnancy are discussed separately.

Normal embryo transport can be disrupted by damage to the structural integrity of the mucosal portion of the fallopian tube. It is easily understood that scarring secondary to infection or trauma could lead to trapping of a conceptus within intratubal adhesions or diverticulae. More subtle insults might not overtly disrupt normal anatomy but could cause ciliary dysfunction and compromise tubal transport. This type of insult could be most significant within the ampullary portion of the tube, where cilia are most concentrated and fertilization and early cleavage of the embryo take place.

Although defectively fertilized ova are logistically difficult to assess, the concept deserves further inquiry. It has been speculated that perhaps immature or postmature ova are more likely to implant prior to reaching the endometrial cavity [4]. This hypothesis requires further investigation, since the incidence of chromosomal abnormalities among ectopic pregnancies has not been found to be any greater than those noted in induced abortions [5].

Alteration of the hormonally mediated events leading to implantation offers another mechanism for consideration. A change in the estrogen-to-progesterone ratio could theoretically affect smooth muscle activity in the fallopian tube, immobilizing ciliary activity. The occurrence of this phenomenon would be particularly influential in the isthmic portion of the tube, which is suspected to contribute to the retention of the fertilized ovum for several days prior to implantation.

Any of these processes could be responsible for the detainment of the embryo and its developing trophoblast within the tube and subsequent mucosal invasion. Determination of whether tubal ectopic pregnancies are intraluminal or extraluminal in location has been studied. Initial evidence based on retrospective examination of tissue blocks directed attention to the extraluminal location between the muscularis and serosa [6]. Pauerstein and associates [7] examined this issue prospectively, however, and found most cases of unruptured ectopic pregnancies to be intraluminal. In contrast, ruptured ectopic pregnancies are located in both the intraluminal and extraluminal sites.

TABLE 4.1 Risk Factors for Ectopic Pregnancy

Risk Factors for Ectopic Pregnancy	Odds Ratio
Tubal surgery	4.7–21.0
Surgery for ectopic pregnancy	6.6–8.3
Documented tubal pathology	3.5–25
In utero DES exposure	5.6
Previous gonorrhea infection	2.9
Previous chlamydia infection	2.8–3.7
Previous PID infection	1.7–2.5
Infertility	2–2.5
Smoking	1.6–2.5

DES, diethylstilbestrol; PID, pelvic inflammatory disease.
From Ankum WM et al. Risk factors for ectopic pregnancy: A meta-analysis. Fertil Steril 1996;65:1093; with permission.

Of note with regard to implantation of the trophoblast within the fallopian tube is that most tubal pregnancies do not consist of ongoing viable gestations but are in fact in the process of abortion within a confined area. Although some blood accumulates both medially and laterally to the implantation site, most luminal accumulation of blood is lateral, allowing collection in the most distensible portion of the tube and often leading to leakage of blood from the fimbria [8].

RISK FACTORS

The decline in morbidity and mortality from ectopic pregnancy is related mostly to widespread awareness of important risk factors, facilitating early diagnosis. Conversely, changes in the prevalence of these risk factors are associated with the increased incidence of ectopic pregnancy in the United States. Some of the most significant risk factors for the development of ectopic pregnancy include history of pelvic inflammatory disease (PID), prior fallopian tube surgery, increasing age, and a history of infertility. These risk factors and others must be elicited from the patient to exclude alternative diagnoses and prevent a delay in diagnosis (Table 4.1).

Pelvic Infection

PID is the most common cause of tubal abnormalities and can lead to deciliation, intratubal and extratubal adhesions, and fimbrial injury. The offending organisms are most likely Chlamydia,

gonorrhea, or mixed anaerobic and aerobic organisms [9,10]. Westrom and associates [11] demonstrated the association of laparoscopically verified PID with tubal obstruction and ectopic pregnancy. In a study of 415 women with PID, the incidence of tubal occlusion after one, two, and three episodes was 13%, 35%, and 75% respectively. After one episode of PID, the ratio of ectopic-to-intrauterine pregnancies has been demonstrated to change from 1:147 to 1:24 by one group of investigators. This same group noted that women with laparoscopically proven salpingitis had a six- to sevenfold increase in the incidence of ectopic pregnancy after the episode of salpingitis [12].

Prior Ectopic Pregnancy

A history of ectopic pregnancy is a powerful risk factor for women who have experienced an ectopic pregnancy; such women have a 7- to 13-fold increased risk of subsequent ectopic pregnancy compared with the general population. On average, after one ectopic pregnancy the odds of recurrence range from 9% to 27% [13,14]. After two ectopic pregnancies, a repeat ectopic pregnancy occurs in 36% to 40% of subsequent pregnancies [15,16]. High rates of infertility often follow single or recurrent ectopic pregnancies as well [14,17].

Contraception and Surgical Sterilization

In general, the risk of ectopic pregnancy in women using any form of contraception is diminished compared with women using no contraception [17]. Nevertheless, different forms of birth control have very distinct degrees of risk of ectopic pregnancy when they fail. Contraceptive failure with the birth control pill is associated with a very low risk of ectopic pregnancy (0.005 ectopic pregnancies/1,000 woman-years) compared with much higher risks associated with the intrauterine device (IUD) and tubal sterilization (1.02 ectopics/1,000 woman-years and 0.3 ectopics/1,000 woman-years, respectively). Despite the fact that IUDs are highly effective at preventing pregnancy, when a pregnancy does occur, 6% to 50% are ectopic. This risk appears to be higher with the levonorgestrel IUD than the copper IUD [18].

Data from the U.S. Collaborative Review of Sterilization [19], which followed a cohort of greater than 10,000 women, demonstrated that tubal ligation failure results in an ectopic pregnancy in one third of cases. The 10-year cumulative risk of ectopic pregnancy was 18.5/1,000 pregnancies. Variables that modify the risk of ectopic pregnancy after tubal sterilization include patient age at the time of procedure and length of time since surgery. The risk of ectopic pregnancy after tubal sterilization is inversely proportional to the age of the patient at the time of surgery. Moreover, ectopic pregnancies associated with failed tubal ligations are more likely to occur with the interval of time from the procedure, with most developing more than four years after the initial surgery [19].

The incidence of ectopic pregnancy also varies with the type (i.e., fulguration) of procedure that is performed [20–23]. As a result, interval laparoscopic tubal electrocautery poses the highest risk of all available methods, whereas postpartum tubal ligation is the least likely to result in development of an ectopic pregnancy. In a study of over 35,000 tubal sterilizations, 51% of pregnancies following laparoscopic tubal electrocautery were noted to be ectopic compared with 12% following nonlaparoscopic, nonfulgurative tubal ligations [20]. Coagulation sterilization failures are associated with a higher incidence of uteroperitoneal fistulas that can be large enough to allow sperm access to the oocyte but small enough to preclude the transport of the conceptus [20]. Corroborative evidence supporting this theory is the 75% of pregnancies following coagulation sterilization failures noted in the distal portion of the fulgurated tube [24]. It bears emphasizing that while these data demonstrate that a greater percentage of pregnancies following laparoscopic sterilization are ectopic, the absolute rate of ectopic pregnancies in this group is still much lower than in women using no contraception [23].

PRIOR TUBAL SURGERY

Prior tubal surgery results in an increased risk of ectopic implantation. Risk for ectopic pregnancy varies depending on the type of reconstructive surgery and the extent of the underlying disease. Examples of reported rates of ectopic pregnancies following distal salpingostomies range between 12% and 18% [25], and approach 5% following a tubal anastamosis [26]. Ectopic rates following lysis of pelvic adhesions appear to depend on the

extent of peritubular adhesions [27]. Excluding a ruptured appendix, previous nontubal abdominal surgery does not appear to increase ectopic risk [28].

INFERTILITY AND INFERTILITY TREATMENT

Infertility alone or in combination with treatment is a risk factor for ectopic pregnancy. Several studies have suggested an association between medications used for superovulation and ectopic pregnancy [29–30]. In one case–control study, investigators found a twofold increased risk of ectopic pregnancy associated with the administration of fertility drugs [31]. These studies were limited, however, by lack of detailed drug data (types and doses) and failed to control for a history of previous ectopic pregnancy or pelvic infection. Additional data to support an association with fertility medications came from a recent case–control study demonstrating a nearly fourfold risk of ectopic pregnancy in patients exposed to drugs for ovulation induction [32]. One possible explanation for this association could reside in the influence of higher-than-normal preovulatory levels of estradiol in these patients, which might adversely affect tubal peristalsis.

There has been concern regarding a possible association between in vitro fertilization (IVF) and ectopic pregnancy. Notably, the first pregnancy conceived as a result of IVF in 1976 was an ectopic pregnancy [33]. Several descriptive studies document the incidence of ectopic pregnancy to be 5% to 7% in IVF cases, two to three times the general population risk [34–35]. It has been postulated that reverse embryo migration toward an abnormal fallopian tube following embryo transfer is associated with the development of ectopic pregnancies after IVF [36]. In addition, heterotopic pregnancies, considered extremely rare in the general population, occur with greater frequency (0.3%–1% of pregnancies) in women who conceive with infertility treatments, especially IVF [37].

AGE

As women delay childbearing beyond the age of 35 years, there appears to be a decrease in fertility accompanied by an increase in the rate of pregnancy complications, including spontaneous abortions and ectopic pregnancies [38–40]. It has been observed that women between the ages of 35 and 44 years have a threefold increase in the incidence of ectopic pregnancy compared with women aged 15 to 24 years, when controlling for race [41]. Changes in tubal function resulting in impaired ovum transport could be a possible component in this age-related increase in risk [39,41]. Undoubtedly, the risk also represents additional acquired risks that are present in this age group compared with their younger counterparts.

SMOKING

Smoking has emerged in recent years as an important risk factor for ectopic pregnancy, with an estimated relative risk of 2.5 [42]. Although the role of smoking in the etiology of ectopic pregnancy is less obvious than some of the other risk factors described, it has been theorized that nicotine or other additives in cigarettes might cause abnormal tubal motility and increase the odds of tubal implantation. Secondarily, nicotine could alter cellular and humoral immunity, diminishing the ability of the tubal epithelium to contain pathogens capable of causing inflammation and tubal scarring [43–45].

MATERNAL DIETHYLSTILBESTROL EXPOSURE

Maternal diethylstilbestrol (DES) exposure has been described as having a potential role in increasing the odds of ectopic pregnancy in female offspring. Although maternal use of DES has been related to the development of numerous tubal abnormalities in daughters of exposed women, an association with ectopic pregnancy has not been well elucidated [43].

UNUSUAL ECTOPIC PREGNANCIES

As they are far less common than tubal ectopic pregnancies, cervical, abdominal, ovarian, cornual, and heterotopic pregnancies often present significant diagnostic and therapeutic challenges. Overall, ectopic pregnancies in these locations compose less than 5% of all extrauterine pregnancies but are often associated with significant morbidity and mortality (Figure 4.3). Approaches to treatment of these special cases of ectopic pregnancy are discussed later in this chapter.