Management and Therapy of Early Pregnancy Complications

First and Second Trimesters

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Editors
Antonio Malvasi
Department of Obstetrics and Gynecology
Santa Maria Hospital
G.V.M. Care and Research
Bari
Italy

International Translational Medicine
and Biomodelling Research Group
Department of Applied Mathematics
Moscow Institute of Physics
and Technology (State University)
Moscow Region
Russia

Andrea Tinelli
Department of Obstetrics and Gynecology
Vito Fazzi Hospital
Lecce
Italy

Gian Carlo Di Renzo
Department of Obstetrics and Gynecology
Centre for Perinatal and
Reproductive Medicine
Santa Maria della Misericordia University
Hospiatal
Perugia
Italy

ISBN 978-3-319-31375-7 ISBN 978-3-319-31377-1 (eBook)
DOI 10.1007/978-3-319-31377-1

Library of Congress Control Number: 2016947178

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

This book is dedicated to all those who are wrongly accused of malpractice and who are not to blame, but are in love with their work and may encounter occasional complications. Those who work in obstetrics and take responsibility may cause complications; those who do not work do not cause injuries.

Preface

Obstetric complications have been clinically frequent since ancient times, as there are two patients to be treated: the mother and the fetus, which is a more complex situation to monitor and treat. The treatment of obstetric complications has evolved over the centuries with the advent of new technologies (i.e., ultrasound, laser, minimally invasive surgery, and cardiotocography). New demographic and sociological changes in different populations and new scientific findings have given rise to a specific new field, maternal-fetal medicine. In this book the authors aim to describe obstetric complications according to modern diagnostic and therapeutic aspects, such as minimally invasive surgery (surgical endoscopy, even in cervical cerclage), and assisted reproductive techniques (ARTs). Modern obstetrics is capable of simultaneously performing diagnosis and surgical treatment, as in the case of extrauterine pregnancy, adnexal pathology, and uterine fibroids. Some complications were unpreventable, even in the last century, such as rupture of the uterus. Today, because of the exponential increase in the number of cesarean deliveries performed, uterine rupture has become a more common and widespread problem and can determine the death of mother and fetus. In industrialized countries, the procreative age of women has grown to commonly exceed 40 years, thus increasing the incidence of some diseases in the past century, such as diabetes, hypertension, and thromboembolism. New uncommon complications, such as in the case of ARTs, which are now also performed in patients during menopause, and may result in a significant increase in maternal-fetal problems and pregnancy complications. A major health policy issue in high-resource countries is malpractice. Doctors working in obstetric units are often forced to work using "defensive medicine" to avoid the risk of being accused of malpractice. This entails an increase in medical, legal, and insurance costs, and a more stressful work environment. There is a blurred line between complication and malpractice, and many doctors are forced to defend themselves against unfair legal accusations, with significant economic and psychological consequences. This book extensively illustrates a debate on common topics that are also cited in the courts to receive fair financial compensation. Hopefully, this book sheds light on common complications in obstetrics during the first two trimesters of pregnancy, to help colleagues and professionals in their daily work.

Bari, Italy — Antonio Malvasi
Lecce, Italy — Andrea Tinelli
Perugia, Italy — Gian Carlo Di Renzo

Acknowledgments

The authors thank Antonio Dell'Aquila for the wonderful drawings that come from a long collaboration with Prof. Dr. Antonio Malvasi, in the Medical Graphics Academy.

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Contributors

Maria Andrikopoulou, MD, PhD Department of Obstetrics and Gynecology, Winthrop-University Hospital, Mineola, NY, USA

Domenico Baldini, MD Center for Medically Assisted Fertilization, MoMò Fertilife, Bisceglie, Italy

Cynthia Bean, MD Department of Obstetrics and Gynecology, Winfred L. Wiser Hospital for Women and Infants, The University of Mississippi Medical Center, Jackson, MS, USA

Juan Carlos Bello-Muñoz, MD, PhD Maternal-Fetal Medicine Unit – Obstetrics Department, Quiron University Hospital Barcelona, Barcelona, Spain

Vincenzo Berghella, MD, FACOG Department of Obstetrics and Gynecology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

Maria Pia Brisigotti, MD, PhD Course in Paediatric Science, Fetal-Perinatal and Paediatric Pathology, University of Genoa, Genoa, Italy

UOSD Feto-perinatal Pathology, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Howard Carp, MB, BS, FRCOG Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel

Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Daniela A. Carusi, MD Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Gian Carlo Di Renzo, MD, PhD Department of Obstetrics and Gynecology, Centre for Perinatal and Reproductive Medicine, Santa Maria della Misericordia University Hospiatal, Perugia, Italy

Jamil ElFarra, MD Department of Obstetrics and Gynecology, Winfred L. Wiser Hospital for Women and Infants, The University of Mississippi Medical Center, Jackson, MS, USA

Ezio Fulcheri, MD, PhD Division of Anatomic Pathology, Departement of Surgical and Diagnostic Science, University of Genoa, Genoa, Italy

UOSD Feto-perinatal Pathology, IRCCS Istituto Giannina Gaslini, University of Genoa, Genoa, Italy

Antonio R. Gargiulo, MD, PhD Center for Infertility and Reproductive Surgery and Center for Robotic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Sandro Gerli, MD, PhD Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy

Audrey Gilbert, MD, FRCSC Department of Obstetrics and Gynecology, McGill University, Montréal, QC, Canada

Stephanie H. Guseh, MD Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Paul W. Hendrix, DO Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

Bradley S. Hurst, MD Reproductive Endocrinology and Infertility, Carolinas HealthCare System, Charlotte, NC, USA

Louise P. King, MD, JD Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School and Center for Bioethics, Boston, MA, USA

Dimitrios Kiortsis, MD, PhD Department of Physiology, University of Ioannina Medical School, Ioannina, Greece

Ioannis P. Kosmas, MD, MSc, PhD Department of Obstetrics and Gynecology, Xatzikosta General Hospital, Ioannina, Greece

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Jun Kumakiri, MD, PhD Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan

Jessica Kuperstock, MD Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Keun-Young Lee, MD, PhD Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, South Korea

Antonio Malvasi, MD Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia

James N. Martin Jr, MD, FACOG, FRCOG Department of Obstetrics and Gynecology, Winfred L. Wiser Hospital for Women and Infants, The University of Mississippi Medical Center, Jackson, MS, USA

Ljiljana Mirković, MD Head of Obstetric Intensive Care Unit, Medical Faculty, University of Belgrade, Belgrade, Serbia

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

Ospan Mynbaev, MD, MSc, PhD, ScD Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Reshama Navathe, MD, FACOG Department of Obstetrics and Gynecology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

Camran Nezhat, MD Center for Special Minimally Invasive Surgery, Stanford Medical Center, Palo Alto, CA, USA

Farr R. Nezhat, MD Department of Obstetrics and Gynecology, Winthrop-University Hospital, Mineola, NY, USA

Department of Obstetrics and Gynecology, New York-Presbyterian/Weill Cornell, New York, NY, USA

Rie Ozaki, MD Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Hongo, Bunkyo-ku, Tokyo, Japan

Elena Pacella, MD Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy

Luis Alonso Pacheco Unidad Endoscopia, Centro Gutenberg, Malaga, Spain

Michael J. Paidas Division of Maternal Fetal Medicine, Yale Women and Children's Center for Blood Disorders and Preeclampsia Advancement, National Hemophilia Foundation – Baxter Clinical Fellowship Program at Yale, New Haven, CT, USA

Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

William H. Parker, MD Minimally Invasive Gynecologic Surgery, UCLA Medical Center, Santa Monica, CA, USA

Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, CA, USA

Leonardo Resta, MD Section of Pathological Anatomy, Department of Emergency and Organ Transplantation (DETO), University of Bari, Bari, Italy

Luis Cabero Roura, MD, PhD, FRCOG(hon), FACOG(hon) Department of Ob/Gyn and Center for Perinatal and Reproductive Medicine, Vall d'Hebron University Hospital, Universidad Autonoma de Barcelona, Barcelona, Spain

Stefan Iliev Savchev, MD, PhD Maternal-Fetal Medicine Unit – Obstetrics Department, Quiron University Hospital Barcelona, Barcelona, Spain

Stavros Sifakis, MD, PhD Department of Obstetrics and Gynecology, University Hospital of Heraklion, Crete, Greece

Ga-Hyun Son, MD Department of Obstetrics and Gynecology, Hallym University, Seoul, South Korea

Ji-Eun Song, MD Department of Obstetrics and Gynecology, Hallym University, Seoul, South Korea

Radmila Sparić, MD Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

Medical Faculty, University of Belgrade, Belgrade, Serbia

Satoru Takeda, MD Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan

Constantina Tatsi, MD Department of Obstetrics and Gynecology, Xatzikosta General Hospital, Ioannina, Greece

Andrea Tinelli, MD, PhD Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy

Abraham Tsur, MD Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel

Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Togas Tulandi Reproductive Medicine, McGill University, Montréal, QC, Canada

Department of Obstetrics and Gynecology, McGill University Health Center, Montréal, QC, Canada

Avinoam Tzabari, MD, PhD Department of Obstetrics and Gynecology, Medical Center Yoseftal Hospital, Eilat, Israel

Ughetta Vergari, PhD Department of Classical Philology and Philosophical Sciences, International Center of Bioethics and Human Rights, University of Salento, Lecce, Italy

Anthony M. Vintzileos, MD Department of Obstetrics and Gynecology, Winthrop-University Hospital, Mineola, NY, USA

Richard Viscarello, MD Department of Obstetrics and Gynecology, Maternal Fetal Care P.C., The Stamford Hospital, Stamford, CT, USA

A Brief History of Obstetric Complications

1

Stefan Iliev Savchev, Juan Carlos Bello-Muñoz, Gian Carlo Di Renzo, and Luis Cabero Roura

People have been writing about the diseases of women for as long as there has been medical writing. Nearly a fifth of the oldest collections of western medical texts since that attributed to Hippocrates are dedicated to the female body [63]. Soranus of Ephesus, a renowned medical author who died prior to the birth of Galen (Fig. 1.1a, b), wrote his most important texts precisely on gynecology [46].

There exists a significant body of specialized gynecological texts, with more than a hundred chapters produced between the fourth and fifteenth centuries [53]. It has to be acknowledged that most of those texts were focused on the childbirth and its complications; but no doubt, early and late obstetric complications have also played an important role in history. There are a few well-preserved documents that emphasize how important some of those cases and their treatment were: For example, in 408 A.D. empress Eudoxia, wife of Byzantine emperor Arcadius, suffered a well-described septic abortion which, eventually, led to her death (Fig. 1.2). According to the chronicle kept by Cedrenus and Zonaras [50], the empress' unborn child died, and a severe infectious process compromised the patient. "Blood mixed" with worms poured out from her genitals. So great was the malodour of the environment that all the herbs of India and the known perfumes could achieve nothing; her body smelled as if she had died many days previously. At the same time a high fever gripped her whole body, making it "a real pyre." Her condition worsened and her entourage "summoned Abbot Arsakios to give her the Holy Communion." After that, "the child was aborted, dead." Her entourage, satisfied, ordered a litany; unfortunately, during the ritual, the empress "vomited out her soul." This, of course, had an important impact on the succession line to the throne and, therefore, in history.

Another matter of truly particular interest to the ancient people was whether or not a woman was capable of becoming or was, indeed, pregnant. In the ancient Egypt [33, 54], physicians had recognized the procreative relationship between sexual intercourse and pregnancy. They regarded the male's contribution as a "seed" that is planted onto the fertile ground of the female uterus. The semen was believed to originate in the spinal cord (Fig. 1.3a, b). This misconception was set forward by Egyptian priests who were engaged with sacrifices of bulls to the gods. (They perceived the phallus of the bull as an extension of the spine, since bovine retractor penis muscles are attached to the sacral vertebrae.) Therefore, infertility was more a male nervous condition rather than a female tare. The maternal part in reproduction was unclear since they did not realize that sperm traveled to the uterus and to the tubes, nor did they recognize the ovaries. The female body served as an incubator for the fetus; the uterus was a vessel, but curiously the vital role of the placenta in fetal nourishment was already appreciated.

Just a few from the known methods for pregnancy diagnosis in ancient Egypt have survived to our days – a thorough account of the number of matinal vomits and the "onion test" which consisted in putting an onion deeply into the vagina and checking the woman's breath the morning after, thus considering an onion smell as a positive result (Fig. 1.4). No relationship between lack of menses and gestation is described in ancient texts. Consequently, early miscarriage was not taken into account, and pathologies as extrauterine pregnancy were not even considered possible.

The first description of pregnancy tests comes from the Berlin Papyrus, which also gives instructions for predicting the sex of the fetus: urine from a pregnant woman was poured on grains of barley and emmer wheat. If they sprouted, a pregnancy was confirmed. If barley sprouted first, the fetus

S.I. Savchev, MD, PhD • J.C. Bello-Muñoz, MD, PhD
Maternal-Fetal Medicine Unit – Obstetrics Department, Quiron University Hospital Barcelona, Barcelona, Spain

G.C. Di Renzo, MD, PhD
Department of Obstetrics and Gynecology, Centre for Perinatal and Reproductive Medicine, Santa Maria della Misericordia University Hospiatal, Perugia, Italy
e-mail: giancarlo.direnzo@unipg.it

L.C. Roura, MD, PhD, FRCOG(hon), FACOG(hon) (✉)
Department of Ob/Gyn and Center for Perinatal and Reproductive Medicine, Vall d'Hebron University Hospital, Universidad Autonoma de Barcelona, Barcelona, Spain
e-mail: lcaberor@sego.es

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_1

Fig. 1.1 Galen (**a**) and his book (**b**): "Galeni….omnia quae exant opera in Latinum sermonem conversa". Juntarum quarta editionem. Venetiis 1565. Folio 360×240, front. Inc.Voll. 11

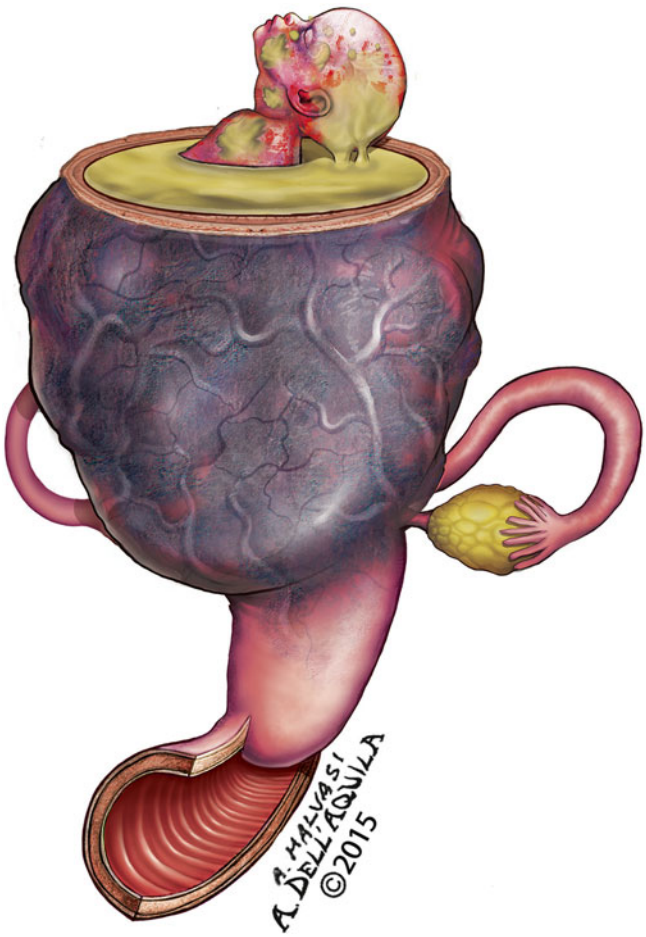

Fig. 1.2 Septic abortion

was a male. If the emmer wheat sprouted first, it meant a female, and if none grew the pregnancy would fail [85].

The correct diagnosis of the early pregnancy complications and their management are fairly recent, bound to the development of modern imaging techniques. We think it would be of readers' interest to have a historic perspective of the perceptions and the understanding of ancient physicians about spontaneous abortion, recurrent pregnancy loss (miscarriage), and later ectopic pregnancy and gestational trophoblastic disease.

1.1 Miscarriage

Ancient cultures have applied a variety of fascinating therapies to prevent the occurrence and reoccurrence of miscarriage. Ceremonies of ritual purification, special prayers, and a variety of medicinal therapies were employed throughout the ages to prevent this feared event. Rituals to memorialize and help mourn the lost pregnancy were developed in many cultures [33, 43, 79]. These rituals reinforce how deeply men and women were affected by early pregnancy loss [49].

The middle ages saw a big change to the attitude regarding early pregnancy loss, mainly because the interest of physicians, priests, and lawmen throughout was to determine whether there were criminal intentions or not behind the miscarriage. The actual causes of even recurrent miscarriages and the way to prevent or treat them remained largely neglected.

The figure of miscarriage was suspiciously scarcely considered in the nineteenth century. Jackson [44] looks at

Fig. 1.3 Ancient Egyptian (**a**) and their concept of male fertility: the semen was believed to originate in the spinal cord (**b**)

eighteenth-century British court records to document how women described pregnancy losses in defending themselves against infanticide charges. Dr. Shannon Withycombe [84] examined nineteenth-century medical and personal perspectives finding a veil upon the information regarding causes of miscarriage within the medical records of those times. Kastor argues from a close reading of sources from the Lewis and Clark expedition that Sacagawea was treated for a miscarriage on route (Fig. 1.5). Sacagawea was the hostage/wife of a Canadian mercenary hired by the explorers to guide them through the wild western territory of what today is the state of Nebraska. The chronicles from the expedition relate how the entire crowd was committed to stop because of a massive bleeding that had nearly cost the young woman her life and how she treated herself with "a tea made from roots and berries collected from the woods" [47].

Over the past five decades, scholars have begun to document the changing representations and experiences of miscarriage. Sources are thin for women's experiences before the 1960s, so historical conclusions are, by all means, fairly speculative, though well argued [66, 69]. Clearly, the subject remained in the underworld of medical science until as long as the beginning of the twentieth century. As Hedley [35] mentioned "Neglecting a threatened abortion is to increase the danger of the ovum being expelled from the uterus and in the case of actual abortions, there is the considerable risk of infection if no care is taken." It was, probably, the first mention of miscarriage as a pathological condition with its inherent risks.

As mentioned above, it was not until the first half of twentieth century when recurrent miscarriage and threatened abortion became medical subjects. The advent of hormones and hormonal therapy for conditions such as diabetes [55] or

Fig. 1.4 Onion test on dilute vaginal discharge morning after, thus considering an onion smell as a positive result

Fig. 1.5 Detail of "Lewis and Clark at Three Forks" by Edgar Samuel Paxson, mural in lobby of Montana House of Representatives

hypothyroidism [61] changed the prospects for successful pregnancy of affected patients. Few decades later, the interest switched to the immunology of recurrent miscarriage [2], which accepts the important role that autoimmune conditions played in the pathophysiology of this condition [1, 8].

Throughout the last few decades, with the mass implementation of ultrasonography in the practice of gynecology, the diagnosis of nonviable pregnancy became straightforward, and the term missed abortion was added to the medical terminology [28]. The awareness that 20–30 % of all pregnancies end up with loss in the first half of pregnancy led to many studies on its etiology and important changes on the current perception of miscarriage and its genetical, hemorheological, immunological, and hormonal background. It could be said that, currently, physicians are able to establish the cause for the vast majority of those events [67].

1.2 Abortion

The practice of abortion as the medical removal of a fetus has been known since ancient times. Many of the methods employed in early and primitive cultures were nonsurgical. Physical activities like strenuous labor, climbing, paddling, weight lifting, or diving were common techniques. Others included the use of irritant leaves, fasting, bloodletting, pouring hot water onto the abdomen, and other dangerous methods [19]. Documents from more recent time provide us with the wide choice of abortifacient used in different cultures throughout the world. In the nineteenth century, the advance in surgery and anesthesia gave another tool for ending undesirable pregnancy. The criminalization of abortion only served to make it clandestine, proving it to be a dangerous procedure and often having serious consequences or resulting in death. The twentieth century witnessed legalization of abortion in most of the developed world, refining of the surgical technique, antibiotic prophylaxis, and introduction of modern medical abortion methods. Unfortunately in the developing world, where access to medical facilities is difficult, abortion continues to be a dangerous act, still claiming lives. Abortion-related mortality will occur mainly or exclusively as a result of unsafe abortion, as spontaneous abortion is rarely a cause of death. Unsafe abortion-related mortality is rather likely to be underreported because of stigma attached to the procedure. The number of maternal deaths due to unsafe abortions was usually estimated from community reports or hospital data of abortion deaths as a percentage of all maternal deaths. Besides, there is a consistent relationship between sub-register of cases and higher mortality rates among poor communities from developing countries [6, 82].

1.3 Ectopic Pregnancy

From its indirect reference by Abulcasis (Fig. 1.6a, b) (936–1013) and until the nineteenth century, the ectopic pregnancy was known as a un iversally fatal accident. The first description of the mechanism of ectopic gestation comes from French physician Pierre Dionis (Fig. 1.7a, b), who in 1718 wrote, both accurately and poetically:

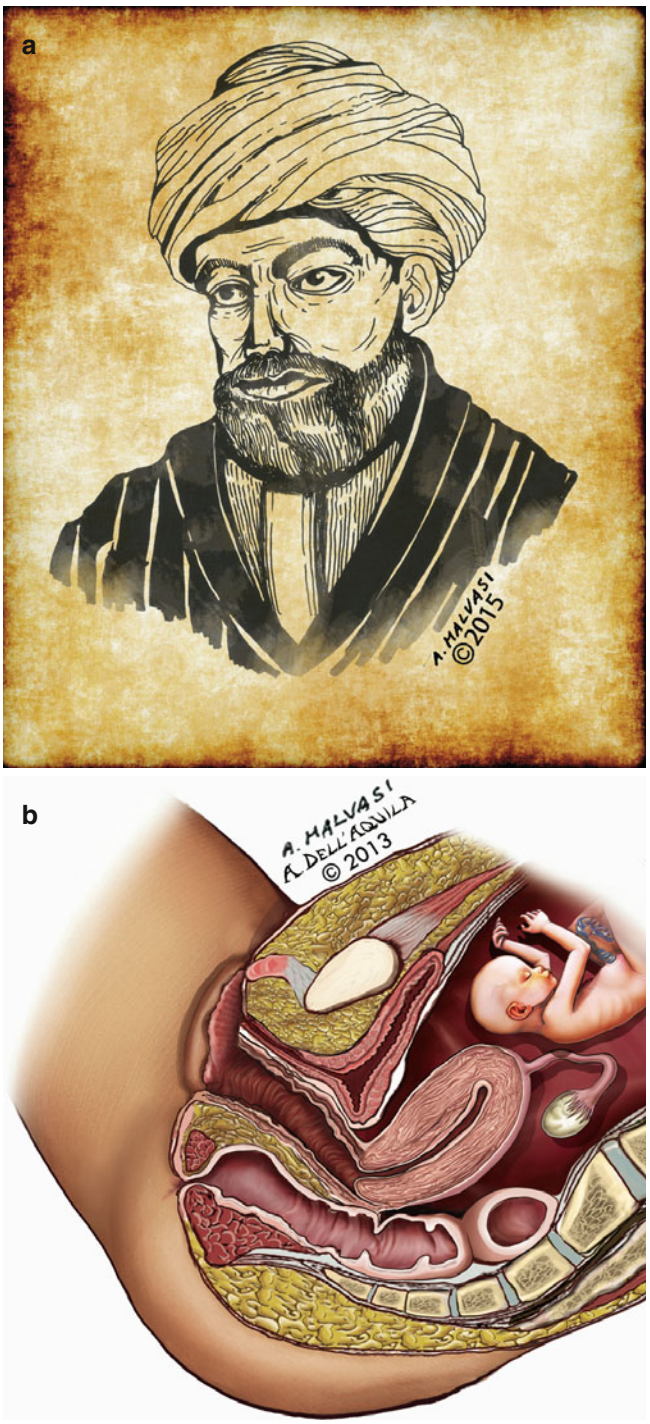

Fig. 1.6 Albucasis, based on "I grandi vecchi della medicina" by Luciano Sterpellone, 1988. (**a**) and abdominal pregnancy (**b**): Albucasis (936–1013), the Arab Muslim physician, is credited with first recognizing abdominal pregnancy which was apparently unknown to Greek and Roman physicians and was not mentioned in the writings of Hippocrates

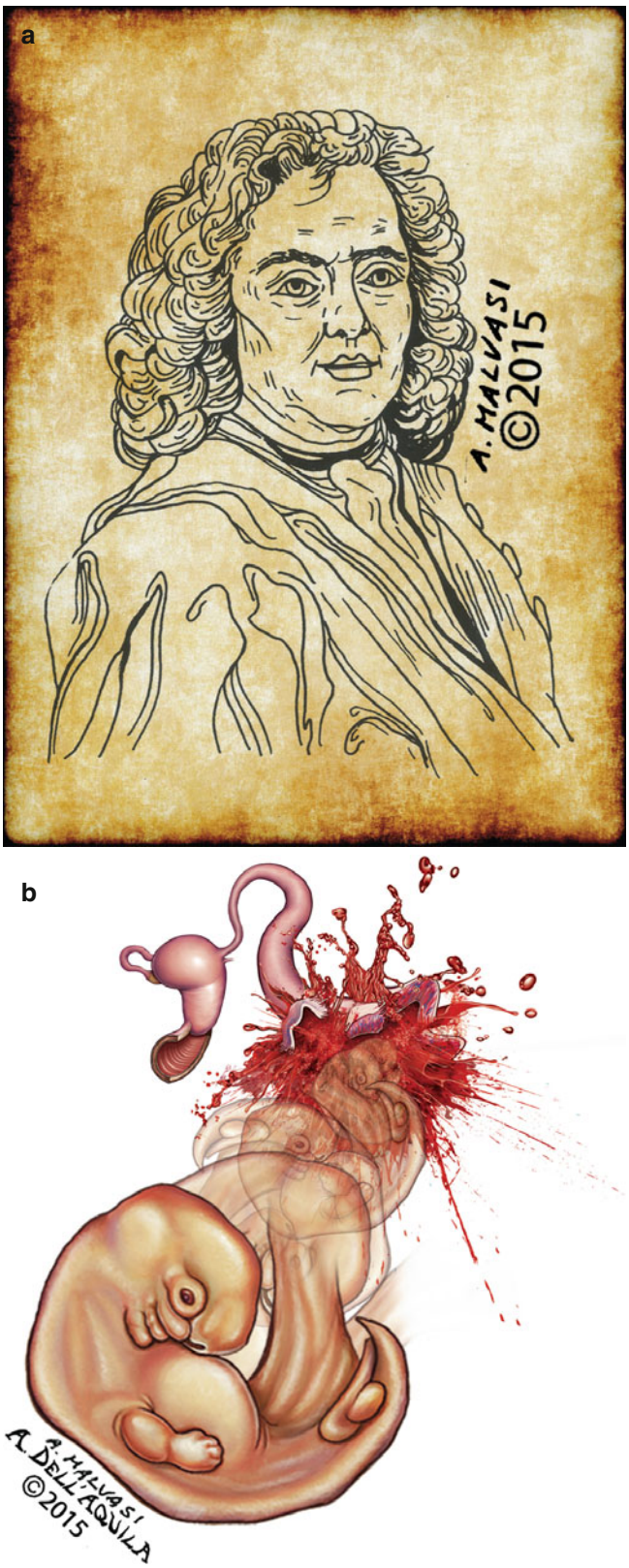

Fig. 1.7 Pierre Dionis (**a**) in 1718 described a rupture of a tubal pregnancy (**b**)

> If the egg is too big, or if the diameter of the tuba Fallopiana is too small, the egg stops and can get no farther, but shoots forth and takes root there; and, having the same communication with the blood vessels of the tuba that it would have had with those of the womb, had it fallen into it, it is nourished, and grows big to such a degree that the membrane of the tuba being capable of no such dilatation as that of the uterus, breaks at last, and the foetus falls into the cavity of the abdomen; which occasions the death of the mother by breaking open its prison [7].

By reporting successful treatment of tubal pregnancy with salpingectomy in 1884, Robert Lawson Tait (1845–1899) (Fig. 1.8a, b) started an era of almost 70 years of exclusively extirpative treatment of ectopic pregnancy. In 1888, Tait was able to report his results for 42 cases of laparotomy for ruptured ectopic pregnancy, with only two deaths, including that of his first case. In several of these cases, the pregnancy had clearly been discharged from the tube into the peritoneal cavity after some weeks of gestation, but had continued to grow until symptoms and signs demanded intervention. In another paper in 1888, Tait established clearly from a postoperative specimen that this course of events, hitherto only suspected, could indeed occur. Laparotomy remained the mainstay of treatment – and indeed of diagnosis – of ruptured ectopic pregnancy until the last two decades of the twentieth century. Diagnostic ultrasound (Fig. 1.9a, b), quantitative measurement of ß-hCG levels, and laparoscopic surgery now mean that in most cases of ectopic pregnancy, laparotomy can be avoided. Side by side our understanding of the natural history of ectopic pregnancy improved. Preservation of future fertility became possible with the introduction of conservative surgical procedures and with the use of methotrexate. In the 1980s, methotrexate was first used to treat ectopic pregnancies. A study by Stovall [77] described outpatient treatment of ectopic pregnancy with methotrexate. A single-dose protocol was developed subsequently. The advances in the surgical and medical treatment of ectopic pregnancy over the past 110 years achieved dramatic decrease in mortality rate from 72 to 90 % in 1880 to 0.14 % in 1990 [58].

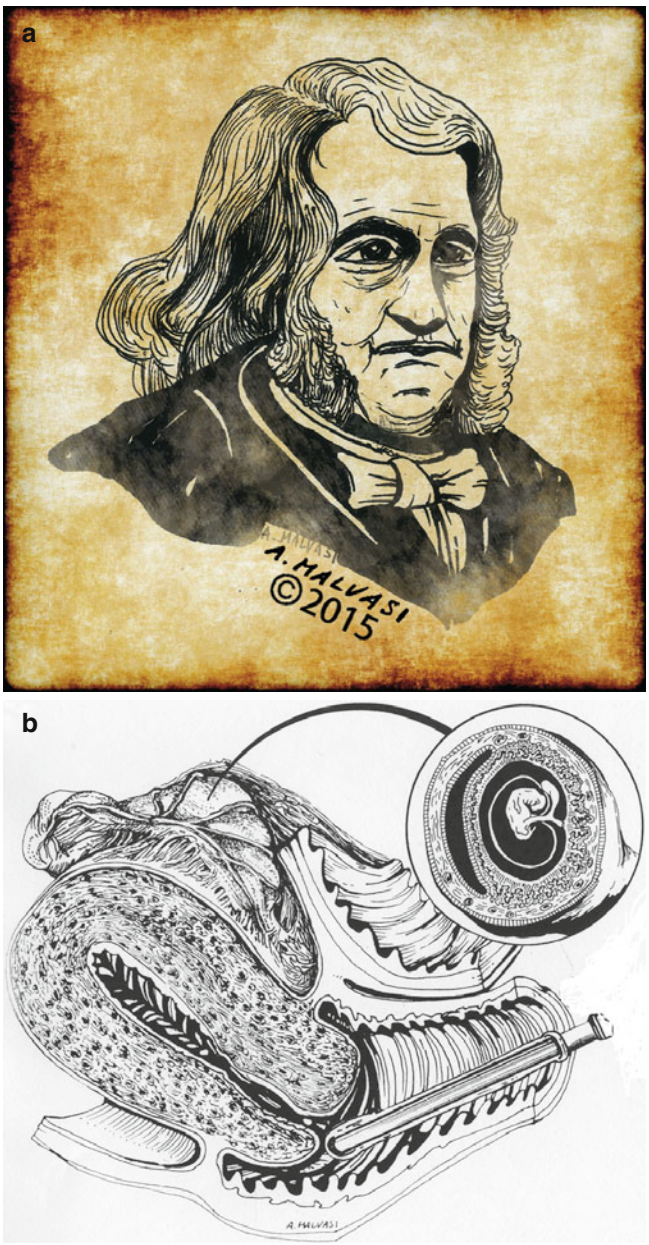

Fig. 1.8 Robert Lawson Tait (**a**) reported a successful treatment of tubal pregnancy with salpingectomy in 1884 (**b**)

1.4 Gestational Trophoblastic Disease

The term trophoblastic disease describes a continuum of tumors that arise in the fetal chorion of the placenta. They have been known since antiquity but have been poorly understood. In 400 BC, Hippocrates first described hydatidiform mole (Fig. 1.10a, b) as "dropsy of the uterus"; while in 600 AD, Aetius of Amida described a uterus "filled with bladder-like objects," which probably also represented this process.

In 1700, Smellie first related the terms hydatid and mole, but it was not until 1827 that Velpeau and Boivin first recognized hydatids as cystic dilations of chorionic villi. Sanger in 1889, coined the term sarcoma uteri deciduocellulare as a malignant tumor derived from the decidua of pregnancy. In 1895, Marchand demonstrated these tumors to be the sequelae of pregnancy, abortion, or hydatidiform mole and described the proliferation of the syncytium and cytotrophoblast. In 1903, Teacher confirmed Marchand's work and negated Sanger's theory of sarcomatous degeneration of the decidua. Finally, Fels, Ernhart, Reossler, and Zondek (Fig. 1.11) demonstrated excessive levels of gonadotropic hormone in the urine of patients with these processes [34].

Historically, trophoblastic disease has been classified as either hydatidiform mole or gestational choriocarcinoma.

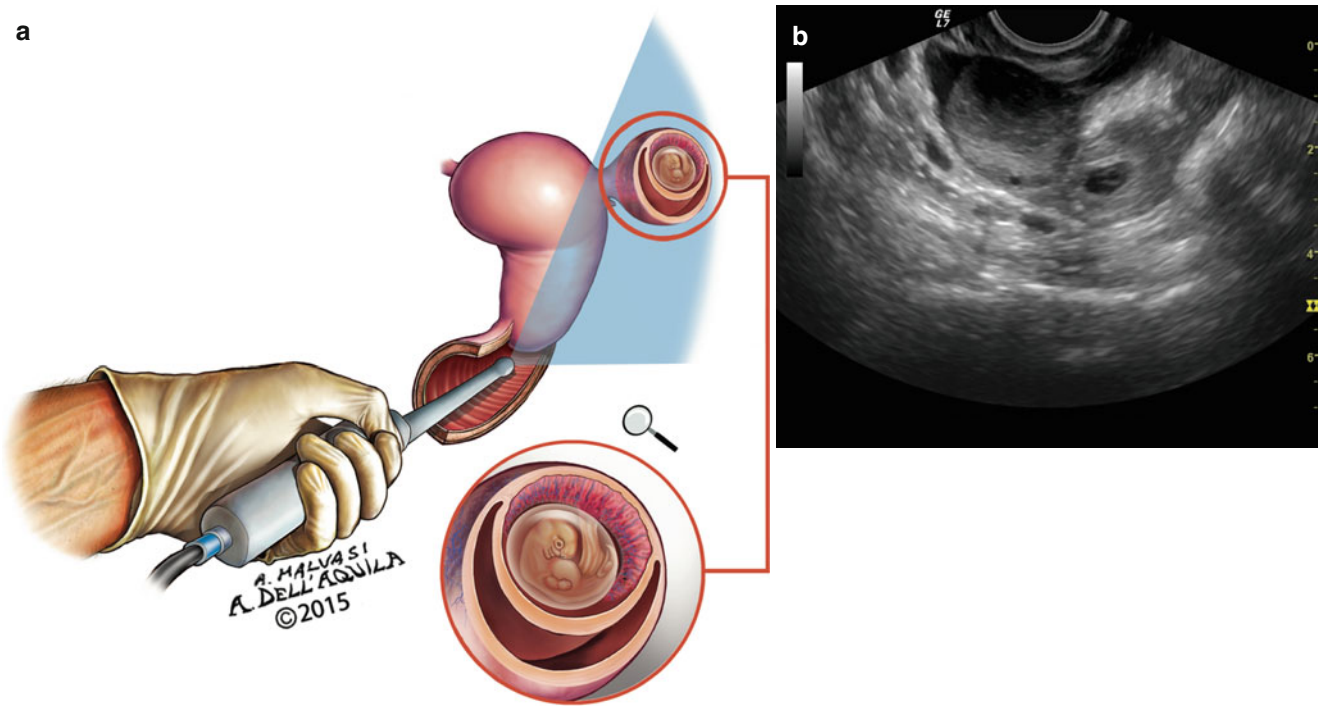

Fig. 1.9 Diagnostic ultrasound of a tubaric pregnancy: (**a**) draw representing the transvaginal examination of a tubal pregnancy; (**b**) an ultrasonographic tubaric pregnancy image

They share three unusual characteristics as follows: (1) curability with chemotherapy, (2) production of human chorionic gonadotropin (hCG), and (3) origin in tissue genetically different from the host.

Metastatic gestational trophoblastic disease was first reported as showing a complete response to chemotherapy after treatment with methotrexate in 1956 [37, 48]. This initial report was followed in 1961 by documentation that approximately 50 % of the patients with this condition remained free of disease, and for the first time, there were 5-year survivors [36]. These tumors produce hCG, and measurement of this hormone was the basis for establishing the diagnosis, determining the response to chemotherapy, defining complete remission, and detecting the rare recurrences. hCG became the perfect "tumor marker" for this disease. Finally, because of its origin in fetal tissue, these tumors contain histocompatibility antigens derived from the father, which could elicit stronger immune responses than normally would be made to tumor-associated antigens.

Early in the history of successful chemotherapy for these tumors, it was assumed that the unparalleled success of chemotherapy was the result of synergistic effects between cytotoxic chemotherapy and immunologic rejection. Despite their rarity, these cases became interesting to many types of medical specialists. Because they can arise in any type of pregnancy (term delivery, abortion, and ectopic or molar pregnancy), obstetrician-gynecologists are responsible for the management of the pregnancy event and the detection of trophoblastic disease sequelae. Medical and gynecologic oncologists have continued to develop more effective chemotherapeutic programs for these tumors with the stated goal of curing all patients, an achievement which currently is possible except for the few patients at highest risk of not responding to treatment. Endocrinologists are involved in studying the biology and chemistry of hCG and its subunits and in developing sensitive and specific assays for these measurements. Pathologists are essential for diagnosing the various forms of trophoblastic neoplasm and differentiating these tumors from others that also may produce hCG. Cytogeneticists have contributed enormously to our understanding of the fertilization events that lead to the varieties of molar pregnancies. Finally, immunobiologists actively study the effects of the presence of paternal antigens in the tumor as a cause, part of the natural history, and in relation to the response to therapy of these tumors [52, 64].

1.4.1 Puerperal Infections

Considering the little available evidence and as the existing historical documents permit one to judge, childbed fever is a modern disease. The cases reported by Hippocrates generally identified as such were not indeed puerperal fever. Hippocrates himself never identified it as a separate and distinguishable disease [18].

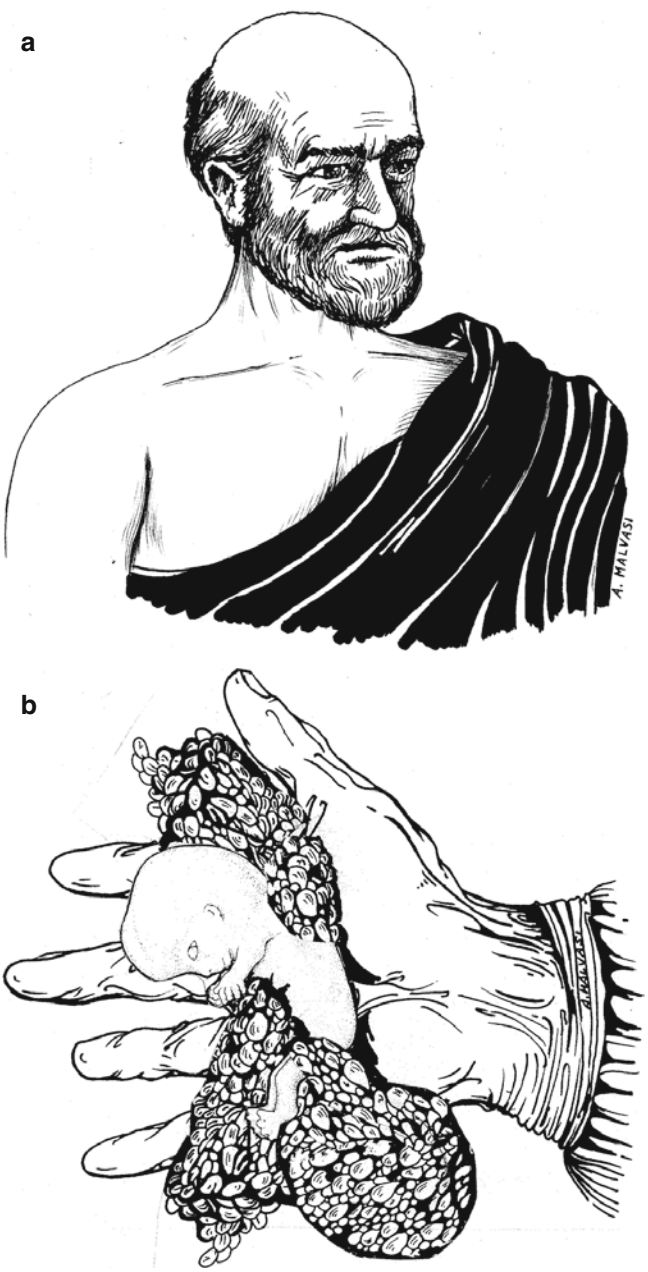

Fig. 1.10 Hippocrates, based on a sculpture, (**a**) first described hydatidiform mole (**b**)

Fig. 1.11 Bernhard Zondek, based on a photograph

Scholars have suspected first the existence of yet unclear disease of childbed fever in the second half of the seventeenth century at the Hôtel-Dieu in Paris. Phillipe Peu relates that mortality among childbearing women was very high, the year 1664 being particularly devastating [32]. The mortality because of puerperal fever continued to rise with the development of big teaching hospitals across Europe. So one could say that puerperal fever was, likely, the first nosocomial disease. Nonetheless, it took decades and hundreds of thousands of lives to realize that. It is impossible to write about the history of puerperal fever without mentioning one of the most unfairly treated heroes in the history of medicine: Dr. Ignaz Philipp Semmelweis (Fig. 1.12).

Dr. Semmelweis worked at the Vienna General Hospital's maternity clinic on a 3-year contract from 1846–1849. There, as elsewhere in European and North American hospitals, puerperal fever was rampant, sometimes killing as many as 40 % of admitted patients. He was disturbed by these mortality rates and eventually developed a theory of infection, in which he theorized that decaying matter on the hands of doctors, who had recently conducted autopsies, was brought into contact with the genitals of birthgiving women during the medical examinations at the maternity clinic. Then he proposed a radical hand-washing theory using chlorinated lime [3, 45].

From his theory, he was able to explain other features in the dataset, for instance, why mortality rates were remarkably higher during winter than summer, because of increased student activity and scheduled autopsies immediately before the rounds at the maternity clinic. He also registered how the second obstetrical clinic at Vienna General Hospital, which instructed midwife students, evidently had a lower mortality rate than the first one, where physicians were instructed.

He managed to oblige the assistants of the first clinic to avoid the morgue in the months of December 1846 and January, February, and March 1847. Restricting examinations to the minimum also reduced the opportunity for the

Fig. 1.12 Ignaz Philipp Semmelweis, based on a photograph, 1861

patients to be touched by contaminated hands. With these simple interventions, mortality in the first clinic was dramatically reduced during those months [70].

He was also able to explain why women with extended dilation invariably died: "Infection occurs most often during dilation. […]..it is frequently necessary to penetrate the uterus in manual examination (Fig. 1.13) to determine the location and position of the fetus. Thus, before chlorine washings, almost every patient whose period dilation was extended died of childbed fever."

At that time, however, the germ theory of infection had not been developed, and Semmelweis' ideas ran contrary to key medical beliefs and practices. His ideas were rejected and ridiculed. Quite unusually, his contract was not renewed, effectively expelling him from the medical community in Vienna. He died as an outcast in a mental institution a few years later [5].

In 1878 Robert Koch discovered that most infection-causing microbes were not airborne, but instead they were transferred from one surface to the other through direct contact. Consequently, there was a large transformation of the surgical field from antisepsis to asepsis, a process that attempted to create a germ-free environment in the operating room and the obstetrical ward.

Sir Joseph Lister (Fig. 1.14), between 1883 and 1897, was a British surgeon and a pioneer of antiseptic surgery

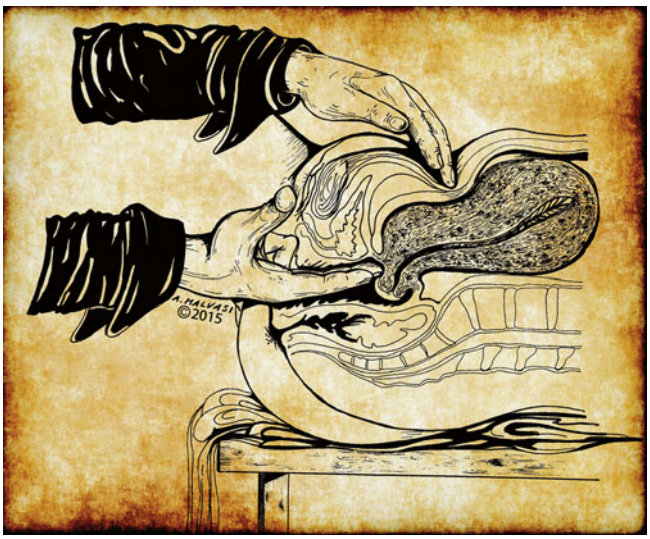

Fig. 1.13 Uterine manual examination in puerperium, by hands of doctors, who had recently conducted autopsies

(Fig. 1.15). By applying Louis Pasteur' s advances in microbiology, he promoted the idea of sterile portable ports while working at the Glasgow Royal Infirmary. Lister successfully introduced carbolic acid (now known as phenol) to sterilize surgical instruments and to clean wounds, which led to a reduction in postoperative infections and made surgery safer for patients.

Finally, obstetricians in the United Kingdom succeeded in probing what Semmelweis seeked to demonstrate: that the advent of pathological anatomy, and consequently the increase in autopsies, was correlated to the incidence of childbed fever. Consequently hereto, maternity hospitals in the United Kingdom were independent institutions, removed from general hospitals. The students were forced to concern themselves exclusively with obstetrics, thus not carrying out germs from pathological autopsies.

The advent of asepsis and the later arrival of antisepsis changed definitively the face of puerperal fever. And numbers remained mainly unchanged until the middle of the twentieth century when antibiotics made their entrance in history.

Sir Alexander Fleming (6 August 1881–11 March 1955) was a Scottish biologist, pharmacologist, and botanist. His best-known discoveries are the enzyme lysozyme in 1923 and the antibiotic substance benzylpenicillin (penicillin G) from the mold *Penicillium notatum* in 1928, for which he shared the Nobel Prize in Physiology or Medicine in 1945 with Howard Florey and Ernst Boris Chain (Fig. 1.16).

Puerperal fever remains among the first five causes of maternal death around the world, but percentages have fallen far below the 0.01 % of deliveries in the developed world.

Fig. 1.14 Sir Joseph Lister. Based on "Trattato di Medicina Minore" by E. Cova, 1947

Fig. 1.15 Lister was the pioneer of antisepsis, using, primarily, the sterilization by fire. Based on "Manuale di Ostetricia" by Spirito. Edizioni Idelson, 1948

1.4.2 Obstetrics as a Medical Specialty

Midwifery remained an artisanal female role during the entire middle age. The figure of a "Man-Midwife" was equally feared and ridiculed for centuries. The role for the physician summoned to the bedside of a childbirthing woman was, mainly, the desperate surgical attempt to extract a dead fetus (usually in pieces) in order to save the mother's life (Fig. 1.17).

During the sixteenth century, the French military surgeon Ambroise Paré (1510–1590) founded a school for midwives in Paris. Paré (Fig. 1.18) wrote about podalic version and breech extraction and about cesarean section (Fig. 1.19), which he is said to have either performed or supervised not

Fig. 1.16 Sir Alexander Fleming discovered antibiotic substance benzylpenicillin (penicillin G) from the mold *Penicillium notatum* in 1928. Based on "I grandi vecchi della medicina", by Luciano Sterpellone, 1988

only after the death of the mother but also, at least twice, on living women. One of Pare's pupil midwives went on to attend the French court, and one of the babies she delivered – a girl named Henrietta Maria – eventually became queen of England at the age of 16 when she married King Charles I in 1625 [23].

The best known of the French *accoucheurs* was Francois Mauriceau (Fig. 1.20) (1637–1709), whose name is familiar to today's obstetricians by reason of the so-called Mauriceau-Smellie-Veit maneuver for dealing with the aftercoming head in a breech delivery. In 1668 Mauriceau published his celebrated text, *traite des maladies des femmes grosses*, which was translated into several languages and went through many editions. Mauriceau was a visionary and a pioneer; nonetheless, he rejected the idea of performing cesarean section and, the only opportunity he had in his life to work with obstetric forceps, disappointed him forever.

1.4.3 Operative Vaginal Delivery

Operative vaginal delivery has been described as far back as the sixth century BC in Hindu medicine. Further reference to instrumental delivery can be found in writings of Hippocrates during the Greek and Roman era between 500 BC and 500 AD. Intervention in these circumstances involving the use of surgical instruments or even kitchen utensils would serve purely to remove the dead fetus in an attempt to avoid maternal mortality [57]. The establishment of forceps-assisted

Fig. 1.17 Midwife attending a cesarean section. Based on a 15th century German woodcut

delivery as a means of avoiding both maternal and neonatal morbidity has developed over several centuries and for many years was kept a closely guarded secret by its inventors.

Forceps In the sixteenth century, the French Huguenot William Chamberlen fled to England from Catherine de Medici after her ban on Protestant physicians, and it is with his two sons Peter Chamberlen, "the elder" (Fig. 1.21), and Peter Chamberlen, "the younger," that the story of forceps as an instrument to deliver live infants begins. Both were members of the Barber Surgeons Company, and both fell out of favor with the College of Physicians for nonattendance at lectures. Despite this, Peter the elder and Peter the younger were both to have significant roles in the practice of "man-midwifery" or as it later became known, obstetric [24, 38].

While it is not entirely clear which of the brothers invented forceps, it is often accredited to Peter the elder. The Chamberlain quest to protect their invention led to extensive means of concealment. The instruments themselves were always carried in a gilded chest and revealed once the woman had been blindfolded. The birth subsequently took place under blankets with only the Chamberlens in attendance of the patient. It was through these elaborate measures that the Chamberlens were able to keep the secret of forceps for nearly a century (Fig. 1.22).

Fig. 1.18 Ambroise Paré. Based on "Deux livres de chirurgie, de la génération de l'homme, et manière d'extraire les enfans hors du ventre de la mère", 1573

Fig. 1.19 Extraction of a fetus in breech presentation, during a cesarean section. Based on "Foetus description" by J.P. Maygrier, 1822

On 19 August 1670, Moriceau had a historic meeting with Hugh Chamberlen, who boasted of making a woman give birth in 8 min and offered to sell his secret invention, the forceps, for a large amount of money. So he was invited by Moriceau to apply the forceps on a stunted woman that he had failed to give birth to. Hugh Chamberlen was locked in a room together with the woman in labor, and, after 3 h of attempts, he failed to carry out the delivery. The patient died the following day, due to a uterine rupture. Hugh Chamberlen returned to London, and her family hid the invention of forceps for another two centuries, until forceps were found in the ceiling of a London house.

He did however gain a copy of "Observations sur la grossesse et l'accouchement"; Mauriceau's 1668 (Fig. 1.23) text which he translated into English under the title "The Accomplish't Midwife." In the preface he publicly alludes to his secret instrument and says, "My lather, brothers, and myself (though none else in Europe, as I know) have, by God's blessing and our industry, attained to, and long practised a way to deliver women in this case without any prejudice to them or their infants : though all others (being obliged, for want of such an expedient, to use the common way) do or must endanger, if not destroy one or both with hooks." He thus apologizes for not having divulged this secret: "there being my father and two brothers living that practise this art, I cannot esteem it my own to dispose of nor publish it without injury to them."

In 1673 following the success of the translated text, Hugh became the physician in ordinary to King Charles II and in 1685 was elected a fellow of the Royal Society. Later while supporting James II, Hugh was accused by the College of Physicians of practicing without a license after the King's forced abdication. This led him to flee to Holland where he is said to have sold some instruments to a Dutch obstetrician named Van Roonhuysen, to Cornelius Bokelman, and to Frederik Ruysch (a celebrated anatomist). In their hands, and in those of their successors, it remained a profound secret until 1753, when it was purchased by two Dutch physicians, Jacob de Visscher and Hugo van de Poll, for the purpose of making it universally known. Very likely, all the known forceps from then and until our days are, somehow, heirs of that original model.

Several illustrious names were added to the list of improvers of the device, such as Dr. Simpson from Edinburgh, Dr. Franz Naegele from Heidelberg, or Dr. Kjelland from Oslo. With the improvement of surgical technique for cesarean section, operative delivery fell in decay. Nowadays, nearly a 10 % of deliveries around the world are assisted with forceps or, more recently, by vacuum cups [15, 23].

Turning (*obstetric version*) on its original conception was a procedure related to changing the position of a living child so that the feet were brought down foremost into the vagina. There is little evidence of its use at the antiquity. In the writings of Aspasia and Philumenus, we find directions for turning the child. Thus Philumenus states, "Si caput foetus locum obstruxerit ita ut prodire nequeat infans in pedes vertatur atque educa-

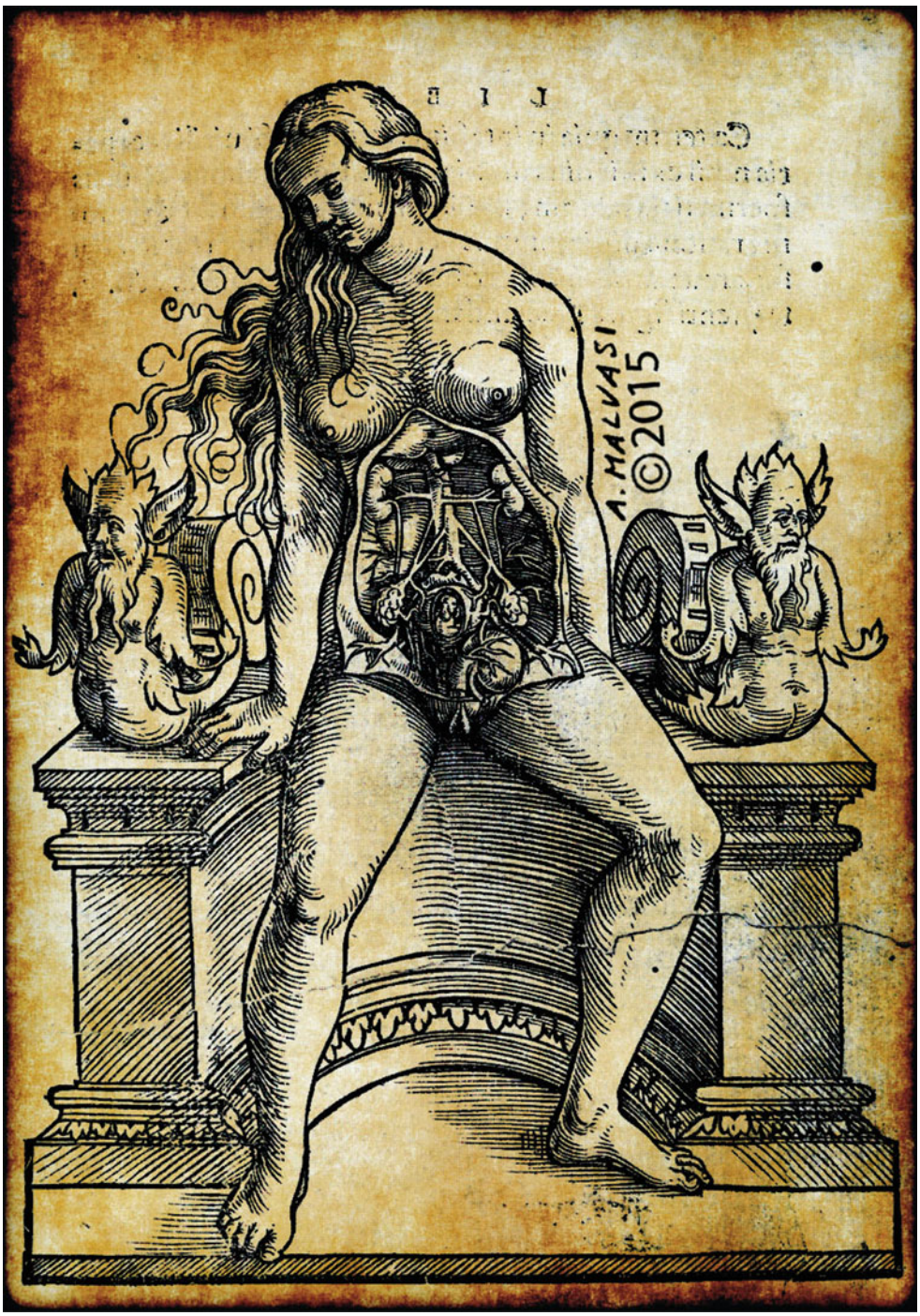

Fig. 1.20 The female anatomy. Based on "De conceptu et generatione hominis" by Jacob Roof, Zurich, 1554

tur." At a still later period, Celsus (Fig. 1.24a, b) gave similar directions, but to all appearance they also merely apply to a dead child "Medici vero propositum est, ut infantem manu dirigat, vel in caput vel etiam in pedes si forte aliter compositus est," and again he says, "Sed in pedes quoque conversus infans, non difficulter ex- trahitur. Quibus apprehensis per ipsas manus commode educitur" (Celsus, de Medicina, lib. vii. cap. 29.). From that time the whole subject seemed to sink into oblivion, until Pierre Franco in his work on surgery proposed the extraction of the child with the turning. Nowadays, obstetric version on its original inception is no longer considered a safe procedure. More recently the external cephalic version was developed as a mean for reducing the requirements of cesarean section because of breech presentation [81].

Cesarean Section Although the early records of the cesarean operation are not very distinct, still we possess sufficient data to pronounce it of very considerable antiquity. The earliest mention of it shows that it was at first used merely for the purpose of saving the child by extracting it from the

Fig. 1.21 Peter Chamberlen. Based on "Trattato di Ostetricia e Ginecologia", 1968

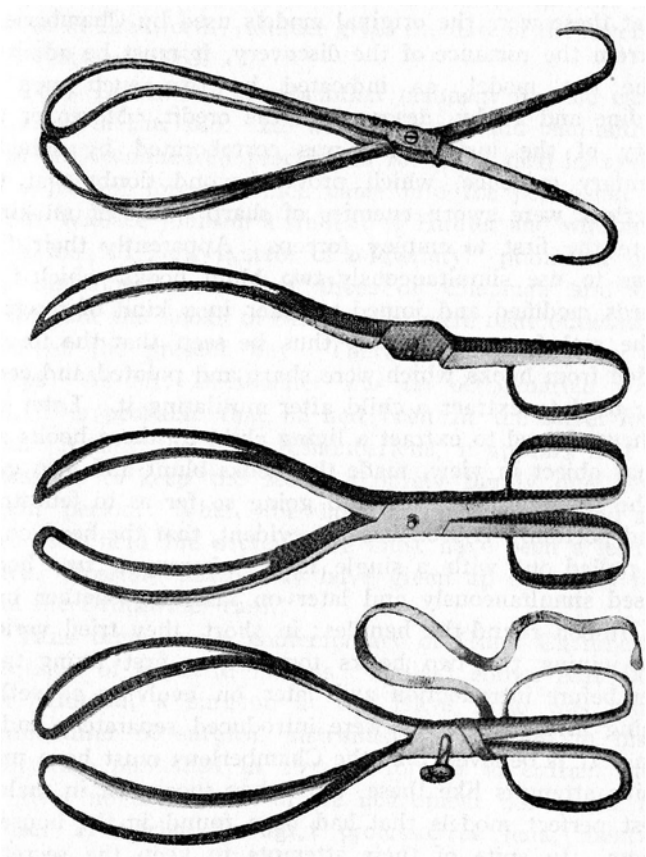

Fig. 1.22 Chamberlen Forceps, from "Obstetric Forceps", Kedarnath DAS, 1929

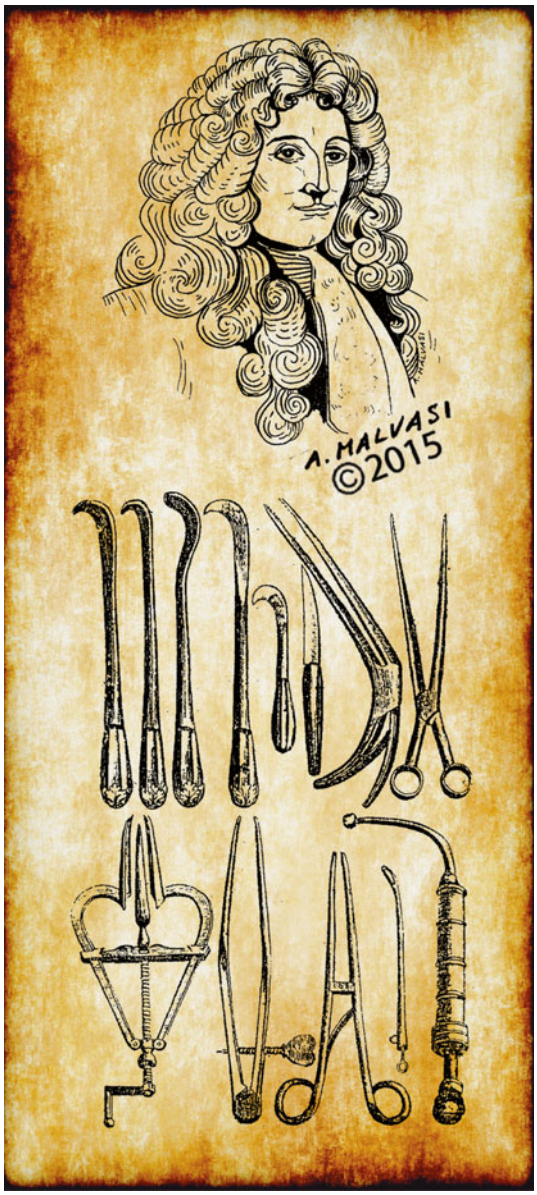

Fig. 1.23 Francois Mauriceau and its instruments. Based on "Des maladies des femmes grosses et accouchées" by Mauriceau, 1668

womb of its dead mother, a law having been made by Numa Pompilius, the second king of Rome, forbidding the body of any female far advanced in pregnancy to be buried until the operation had been performed (Fig. 1.25). The oldest authentic record is the case of Georgius, a celebrated orator born at Leontium in Sicily, 508 BC Scipio Africanus (Fig. 1.26), who lived about 200 years later and is said to have been born in a similar manner. There is no reason to suppose that Julius Caesar (Fig. 1.27) was born by this operation, or still less that it derived its name from him, for at the age of thirty, he speaks of his mother Aurelia as being still alive, which is very unlikely if she had undergone such a mode of delivery. We would rather prefer the explanation of Professor Naegele: that

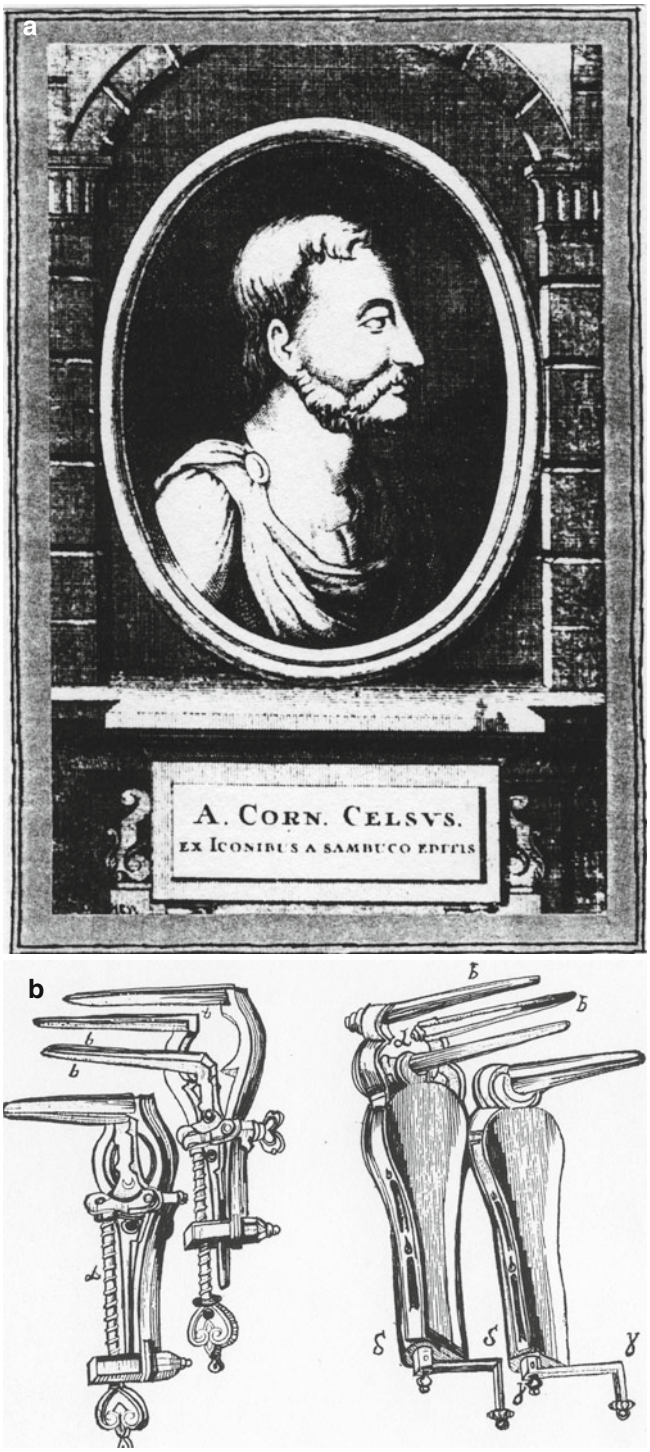

Fig. 1.24 Aurelius Cornelius Celsus (**a**), letterpress. Wellcome Library, London. Uterine dilatators (**b**), based on "Histoire des accouscements chez tout le peuples" by Witkkowski G.J., 1887

one of the noble patricians of Julian families at Rome had been delivered *ex caso matris utcro* and had been named Caesarea ("born through a cut") from this circumstance, so that the name was derived from the operation, not the operation from the name. The earliest account of it in any medical work is that in the *Chirurgia Guidonis de Cauliaco*, published about the middle of the fourteenth century. Here, however, the practice is only spoken of as proper after the death of the mother. The first authentic operation upon a living woman in later times was the one by Jacob Nufer upon his own wife in 1500. Dismayed by the agony and pain of his wife's labour, he sought the help of no less than thirteen midwives to deliver their child and relieve his wife. For days they tried, and failed. When he could stand no longer to see his wife suffer, Nufer asked his wife if she would have the confidence in him to perform the operation. She agreed. Nufer seeked permission from the local authorities, who initially refused but eventually relented to Nufer's persistent pleas. Nufer's wife lived following the operation and eventually gave birth to five more children, all vaginally, including one set of twins. Owing to its fatal character ande the strong feeling against it, cesarean section was performed but rarely; still however sufficient evidence existed to mark its occasional success and urge its repetition in similar cases. The best documented surgical experience on cesarean section with some reports of survival is attributable to Francois Russet (1525–1598) in France [80]. In the second part of the nineteenth century, maternal mortality following classical cesarean section was still nearly 100 %.

In 1876, the Italian obstetrician, Eduardo Porro (Fig. 1.28) developed a cesarean section technique consisting of uterine corpus amputation and suturing of the cervical stump into the abdominal wall incision in an attempt to prevent life-threatening hemorrhage and infection (Fig. 1.29).

The first operation was on patient named Giulia Cavallini (Fig. 1.30). She was born in Adria in Veneto and arrived at San Matteo in Pavia in April of 1876, newly married and pregnant for months. Giulia Cavallini has his chance: "High 1.48, had the pelvis deformed because of rickets that had struck her as a child" and Porro "soon becomes clear that the situation was dramatic: the birth canal is too narrow," so Porro called this pelvis "the lost space." Porro operated Giulia by cesarean section (Fig. 1.31) with the birth of Maria Alessandrina Cesarina: a healthy baby, that was fine, as well as her mother Giulia.

The successful outcome in Porro's test case was due to his adherence to surgical principles that are well recognized today, but were not firmly established in 1876. Despite the lack of blood products, intravenous fluids, and antibiotics, the Porro operative technique subsequently decreased maternal mortality to 58 %. His innovative, carefully planned approach for cesarean hysterectomy was a major innovation in obstetric surgery.

Until the latter part of the nineteenth century, cesarean delivery was regarded as one of the most hazardous obstetric operations, to be undertaken only as a last resort. The operation was carried out 80 times in the United States before 1878, with a maternal mortality of 53 %. Abdominal hysterectomy, likewise, achieved medical respectability only in the closing decades of the nineteenth century. Before 1863,

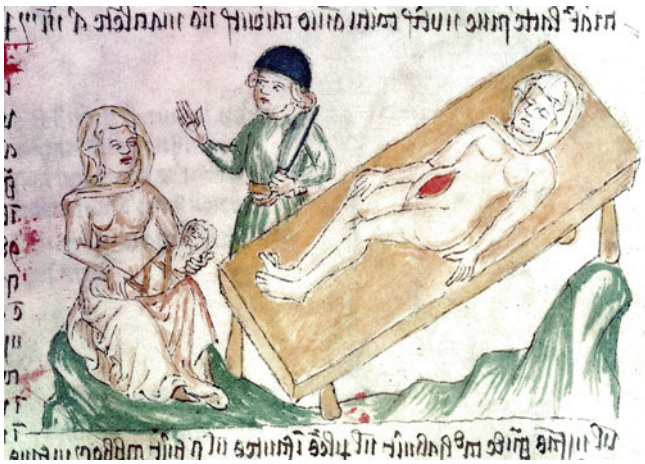

Fig. 1.25 Representation of cesarean section on dead mother. From Gynaecological texts, Caesarean section. Wellcome Library, London

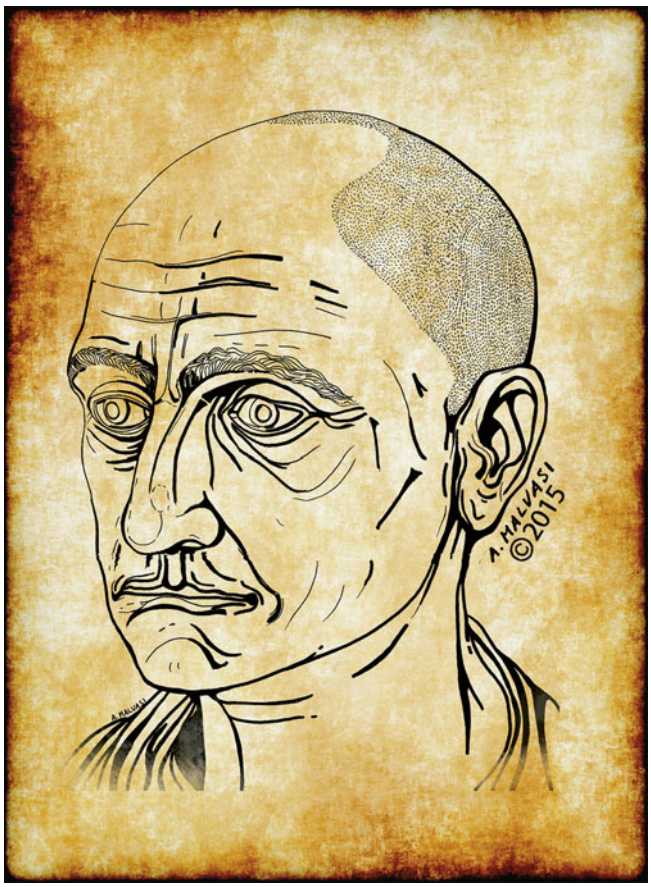

Fig. 1.26 Scipio Africanus. Based on the sculpture in Musei Archeologici, Naples

Fig. 1.27 Julius Caesar. Based on a coin, 47 b.C.

abdominal hysterectomy had proved fatal in almost 90 % of the patients in whom it was attempted; in only three cases had it been performed successfully in the United States. Cesarean hysterectomy becomes something of a paradox, therefore, when viewed in historical perspective, for it evolved from efforts to circumvent the mortal danger of abdominal delivery by the addition to it of a similarly formidable and dangerous procedure: uterine extirpation [71].

It was Max Sanger (Fig. 1.32) in 1882 who insisted that correctly suturing of the uterus was essential. Then, the advent of cesarean section without hysterectomy came along in the twentieth century. With the introduction of improved surgical techniques, asepsis, modern transfusion techniques, and Harris' principle of early operation prior to possible infection, the mortality rates improved to be as low as 0.1 %, between the years 1943 and 1952.

Edwin Craigin, in 1916, stated the most quoted dictum in obstetrics: "Once a cesarean,always a cesarean" [59]. The dictum was valid as long as the typical cesarean section included a classical (upper segment) incision in the uterus. With the introduction of the transverse lower uterine segment incision by John Munro Kerr (Fig. 1.33) and recognition that this type of incision was not associated with an excessively high rate of uterine rupture during labor, a trial of vaginal birth after one previous cesarean section became and still is the most accepted policy.

1.4.4 Development of Modern Care for the Premature Infant and of the Fetal Monitoring

The nineteenth century saw shifting of the care for the future mother and her newborn from reducing mortality to focusing on morbidity. The best illustration for this is probably the fascinating birth and development of the care for the premature infant (Fig. 1.34). At the turn of the twentieth century, a baby born prematurely had dismal prospects for survival. Except for

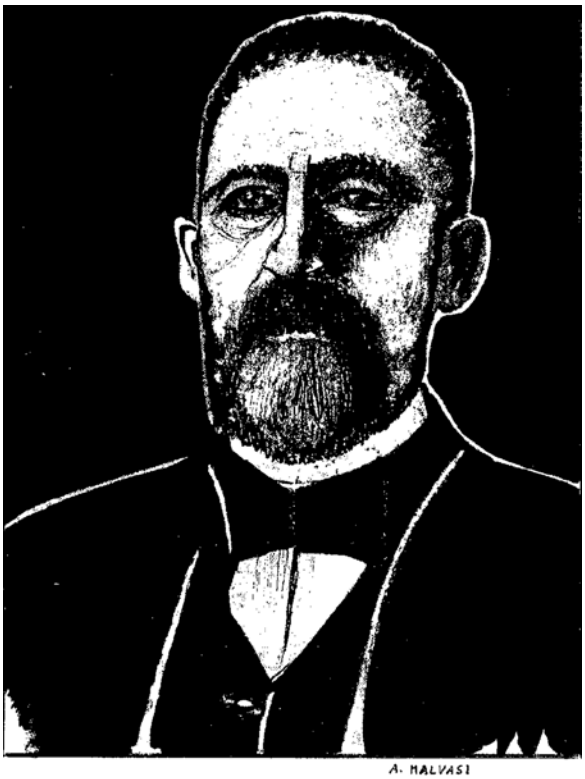

Fig. 1.28 Eduardo Porro improved the so-called cesarean operation by excision of the uterus and adnexa, described in *Della amputazione utero-ovarica come complemento di taglio cesareo* (1876), the best known of his writings. In 1891, he was named senator of the kingdom by King Humbert I. Based on a portrait, Clendering Library Portrait Collection

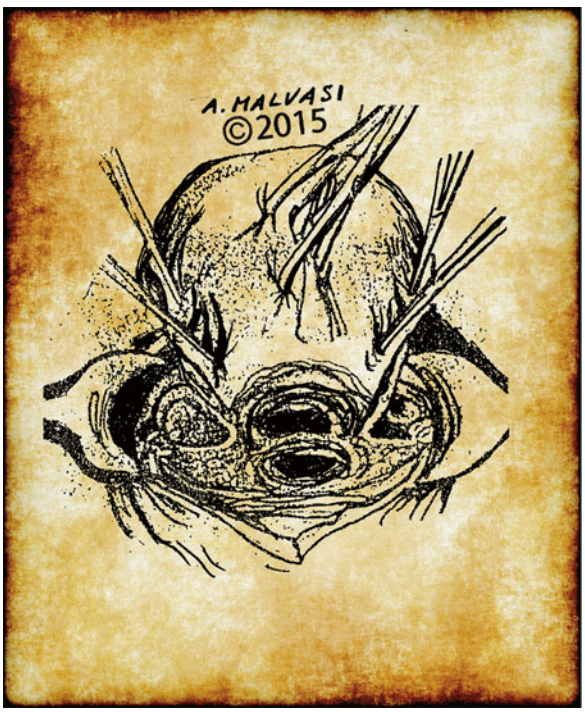

Fig. 1.29 The cesarean section Porro's technique. Based on "Dell' amputazione utero-ovarica come completamento del taglio cesareo" by Edoardo Porro

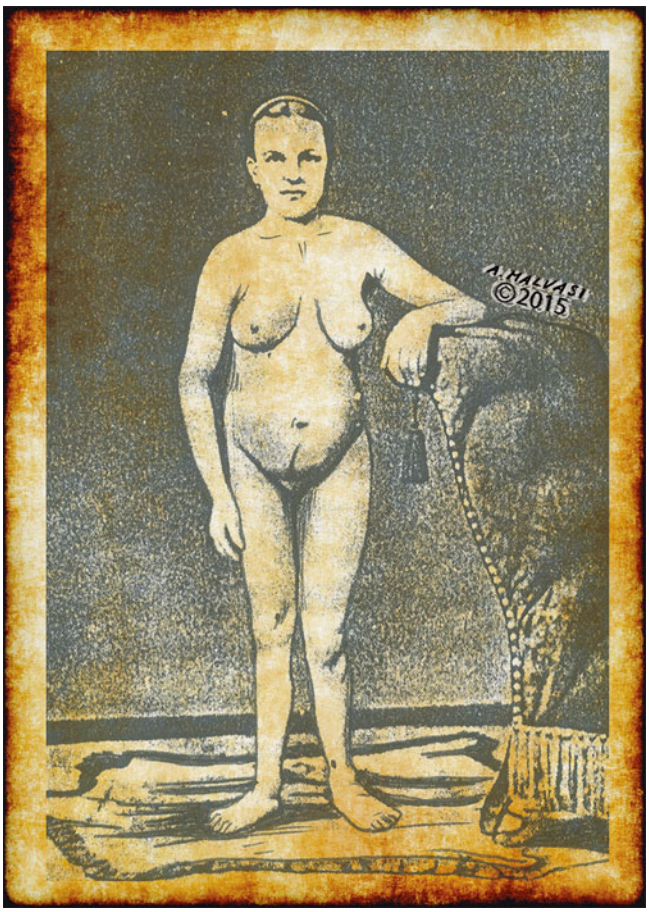

Fig. 1.30 Giulia Cavallini, the first patient operated by Porro. Based on a photograph in "Dell'amputazione utero-ovarica come completamento del taglio cesareo" by Edoardo Porro

Fig. 1.31 Porro cesarean method

Fig. 1.32 Max Sanger. Based on "Trattato di Ostetricia e Ginecologia", 1968

Fig. 1.33 The transverse lower uterine segment incision. Based on "Cesarean Section: Lower Segment Operation" by Marshall J.M., 1939

Fig. 1.34 Fragment of a crater of the late fifth century BC, preserved in the archaeological museum of the University of Bonn (Germany), representing the second birth of Dionysus who "disengaged" from the right thigh of Zeus

a few scattered pockets of medical interest, the knowledge, expertise, and technology necessary to help these infants was not available. "Preemies" who survived more than a day or two were often labeled "weaklings" or "congenitally debilitated" implying an inherent frailty. Survival of these tiny infants depended on many factors, mainly the degree of prematurity and the infant's weight at birth. Many physicians pointed to the example of congenital syphilis to suggest premature birth to be nature's way of expelling a defective fetus [62].

The premature infant occupied an ambiguous position between physician and mother as well as between fetus and newborn. These infants, like other newborns, were almost always born at home, unless the mother was so destitute to turn to the resources of a lying-in hospital. Although obstetricians were increasingly likely to be present at the birth of these infants over the course of the nineteenth century, their focus on the mother rarely allowed attention to the infant beyond initial resuscitation [51].

The first significant challenge to this equilibrium between doctor and mother was the invention in Paris of a medical technology directed at premature infants, the incubator. Its invention was associated with the French obstetrician Stephane Tarnier (Fig. 1.35), who in the 1870s sought to find a means to warm the numerous premature infants who routinely succumbed to hypothermia on the wards of Paris' Maternité hospital. A visit to the chicken incubator display in the Paris zoo inspired him to have the zoo's instrument maker install a similar device for the care of infants in 1880 (Fig. 1.36). The design of this incubator was hardly a novelty but Tarnier did two important contributions: He statistically compared premature infant mortality before and after the introduction of the device, showing reduced mortality by nearly a half, and placed the spotlight on premature infant. The second innovation was the use of Louis Antoine Champetier de Ribes' balloon (Fig. 1.37) to promote the stimulation of childbirth, by mechanical expansion.

In Nice, France, Alexandre Lion, a physician and son of an inventor, developed in the 1890s a much more sophisticated incubator than that of Tarnier (Fig. 1.38). A large

Fig. 1.35 Stephane Tarnier. Based on a photograph by Pierre Petit, with permission, Library of London

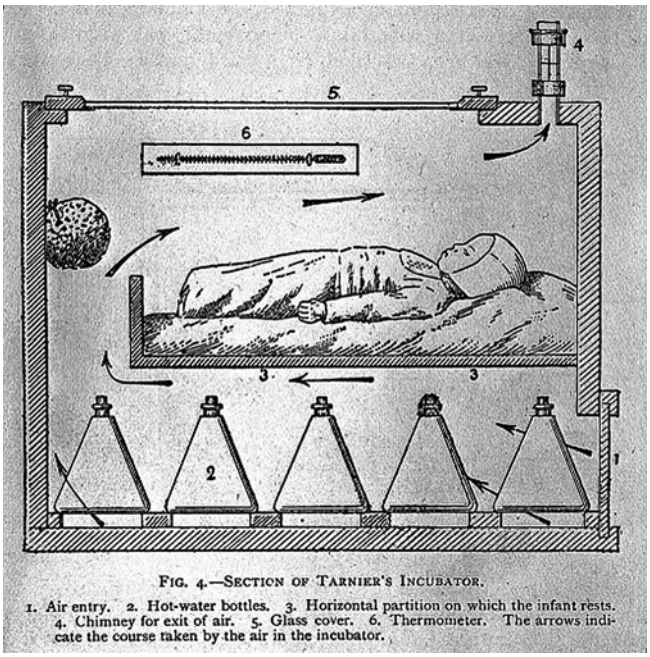

Fig. 1.36 Section of Tarnier's incubator. Budin, The Nursling, 1907. Wellcome Library, London.

Fig. 1.37 Louis Antoine Champetier de Ribes' balloon. Based on "Trattato di Ostetricia" by I. Clivio, 1945

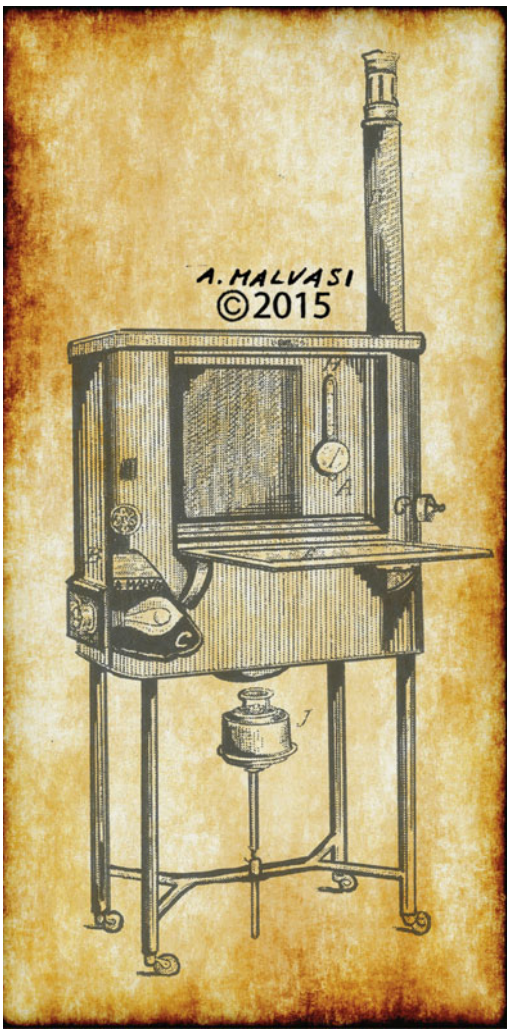

Fig. 1.38 A much more sophisticated incubator of the last century. Based on "Cuveuse" by Rommel, 1913

metal apparatus equipped with a thermostat and an independent forced ventilation system, the Lion incubator was designed to compensate for less-than-optimal nursing or environment. The high point of Lion's career was his opening of the *Kinder-brutenstalt* ("child hatchery"), an elaborate incubator baby show that became the surprise sensation of the Berlin Exposition of 1896. Medical professionals might have scoffed, but so great was the show's popularity that similar (or still larger) shows became a regular feature of World Fairs at the turn of the century. International interest in the incubator, as measured by journal articles, surged far more dramatically than it had at the time of Tarnier's invention [9, 73].

Since the beginning of the nineteenth century, the design of the incubator changed remarkably by incorporating the ever evolving new technology. However, it cannot be viewed as the sole reason for dropping mortality rates for the premature born infants. A variety of supportive technologies came into being, both within the nursery (intravenous lines, monitors, and micromethod blood sampling) and outside (transport systems and referral networks) [76].

Another technological invention proved to change the practice of obstetrics for the decades to follow. The auscultation of the fetal heart rate and later the electronic fetal monitoring (EFM), introduced the concept of fetal well-being, fetal intrapartum distress, and means to prevent it.

Fetal heart sounds were reportedly first detected by Marsac in the 1600s. The idea that fetal heart rate could be used to determine fetal well-being was first proposed by Killian in the 1600s, but this went unnoticed until 1818 when Mayor and Kergaradec described the method of auscultating fetal heart sounds by placing the ear next to the maternal abdomen (Fig. 1.39). By 1833, Evory Kennedy, an English physician, published guidelines for fetal distress and recommended auscultation of the fetal heart rate as a tool of intrapartum monitoring. Few years earlier, Nauche and Maygrier conducted studies on fetal auscultation through the vagina, but were unsuccessful for aesthetic and functional reasons.

It is mandatory to mention the invention of Adolphe Pinard, an important Paris obstetrician, known for describing a significant number of obstetric maneuvers and signs and also for his devotion to public medicine and his life as a defender of medical care for pregnant women with little or no financial resources. In 1895 he invented the *stethoscope*, a simple, bell-shaped, conic device used to amplify the fetal heartbeat. It is likely the most widely used obstetric device in history has been a useful tool for fetal monitoring until the late 1970s in the developed world and still is in developing countries.

Fig. 1.39 J.A. de Kergaradec (1787–1877), the forgotten inventor and pioneer of the obstetrical stethoscope (*upper figure*) and the obstetrical stethoscopes of Pinard (*image down*). Based on "Trattato di Ostetricia Minore" by E. Cova, 1947

In 1893, von Winkel, working with the Pinard's stethoscope, established criteria for fetal distress that remained unchanged until the advent of electronic fetal monitoring (tachycardia, FHR >160; bradycardia, FHR <100; irregular heart rate; passage of meconium; and gross alteration of fetal movement). By the turn of the twentieth century, various authors had described fever as a cause of fetal tachycardia, head compression and cord compression as a cause of bradycardia, and hyperstimulated uterine activity associated with a characteristic fetal heart rate response and asphyxia.

The fetal stethoscope – or fetoscope – was first described by David Hillis in 1917 at the Chicago Lying-In Hospital. Amid much controversy, in 1922, Joseph DeLee, Hillis' superior at the same institution, described the device again, taking priority for its creation [16]. The device eventually became known as the DeLee-Hillis fetoscope and was at the forefront of intrapartum fetal monitoring for the next half century. Intermittent auscultation (IA) of the fetal heart rate during labor became widely recommended. Electric, amplified fetoscopes of Matthews, Marvel, and Kirschbaum made the task of fetal monitoring easier by the 1940s when IA became the emerging standard of care. It remained so until well into the 1970s and is used in some form even today [4, 65].

However, in 1968, Benson et al. published results of a review of 24,863 labors in which IA was used throughout the 1950s. Their results concluded that IA was not a "reliable … indicator of fetal distress" except in the extreme situation of terminal bradycardia. This damning report emerged at a time when true electronic fetal monitoring (EFM) was being developed, and experts were quick to dismiss IA in favor of the hoped-for promise of EFM [17, 42].

In 1906 Cremer described the use of the fetal electrocardiogram using abdominal and intravaginal electrical leads that led other investigators to attempt to determine fetal status using electrocardiographic patterns only to conclude that fetal distress did not yield any consistent electrocardiographic patterns. In 1958, Hon, the pioneer of modern EFM, first described a system for capturing continuously the fetal ECG. In 1964, Callagan described a commercially viable system for capturing the FHR with Doppler technology. In the 1960s, EFM systems were made commercially available by Hon in the United States (1968), by Hammacher in Germany, and by Caldeyro-Barcia in Uruguay, father of, among other things, the Montevideo units and long-and short-term variability.

The spiral electrode or fetal scalp electrode (Fig. 1.40) as used today was introduced by Hon in 1972. More complex electronic methods of differentiating between genuine fetal signal and artifact were introduced over time to work in tandem with Doppler technology, giving rise to modern electronic autocorrelation. By 1975, just over twenty percent of labors were monitored with EFM, a number that now stands at well over eighty percent.

Until recently, as new technologies have emerged, they have been adopted into clinical practice before large studies were carried out regarding their efficacies. IA was widely used for four decades before the first randomized clinical trials (RCTs), and EFM was used over a decade before the first RCT was available.

Many of the RCTs designed for EFM compare it to IA, though it should be remembered that Benson et al. were highly critical of IA in 1968. Cochrane has published a meta-analysis comparing EFM to IA which showed no difference between the two in low Apgar scores, NICU admissions, perinatal deaths, or the development of cerebral palsy (CP). There were a 50 % reduction in neonatal seizures, but a significant increase in operative vaginal delivery and cesarean delivery rates. Vintzeileos et al. did show a reduction in perinatal death in the EFM group as compared to IA, on the order of one perinatal death prevention for every 1000 births, but with an associated increase in the cesarean delivery rate of two- to threefold. Notwithstanding these controversies, EFM continues to be widely used today as a routine monitor of fetal well-being [26].

Despite the widespread use of electronic fetal monitors (Fig. 1.41a, b), uniformity of terminology and standards were not firmly established until 1997 when the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN) along with other professional organizations adopted the terminology of the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop for use in describing fetal heart rate patterns [60].

Ultrasonography was revolution in obstetrics (Fig. 1.42), since it monitored physiological and pathological pregnancy.

Another important revolution was the obstetric locoregional and general anesthesia, born at 1800 by William Thomas Green Morton (1819–1868) (Fig. 1.43). At the beginning of the technique, it was used by chloroform with the mask (Fig. 1.44), made by Dr. David Lang who advised colleagues to continue anesthesia while he was dying.

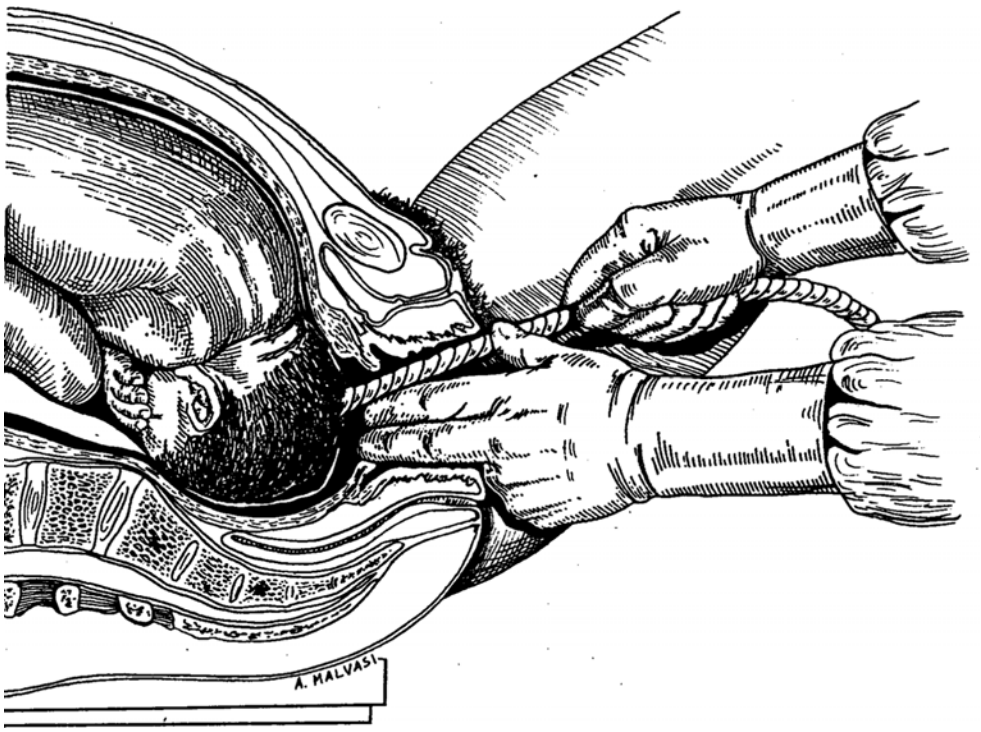

Fig. 1.40 The spiral electrode or fetal scalp electrode

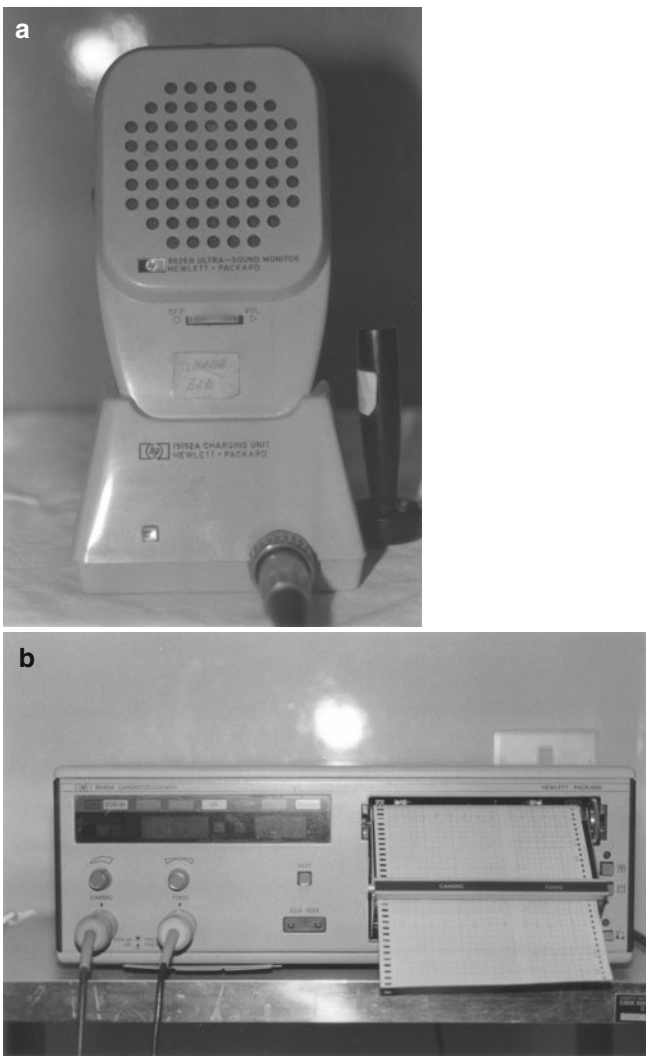

Fig. 1.41 Major and oldest electronic fetal monitors: Sonicaid (**a**) and HP 8040A (**b**) compact EFM with printer

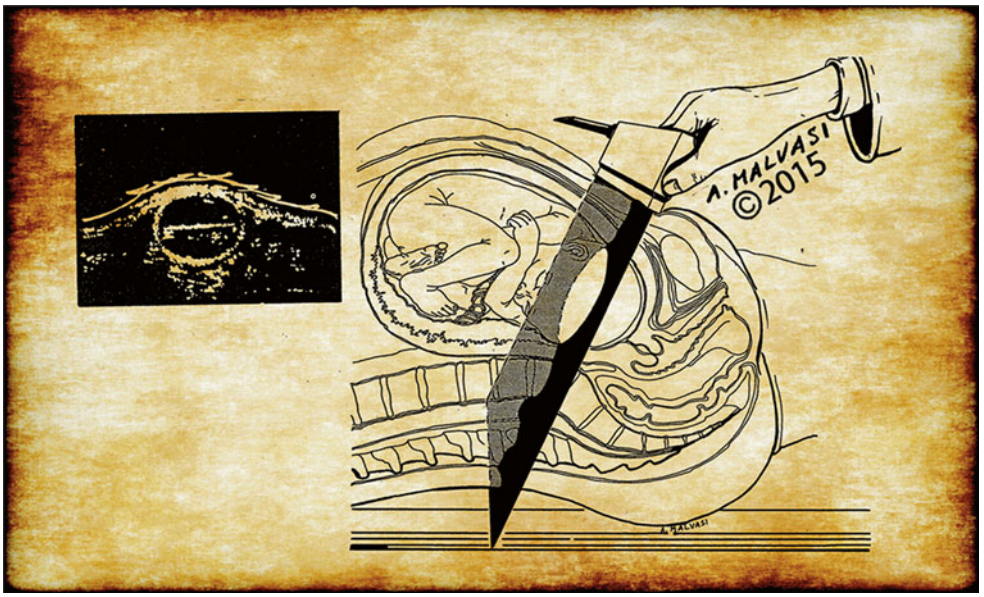

Fig. 1.42 An old ultrasound machine with linear probe. Modified from "Ecografia Ostetrica" by D'Addario, Kuriak. Piccin Nuova Libraria, 1989

Fig. 1.43 William Thomas Green Morton. Based on a photograph

Fig. 1.44 The technique was used by chloroform with the mask of Dr. David Lang

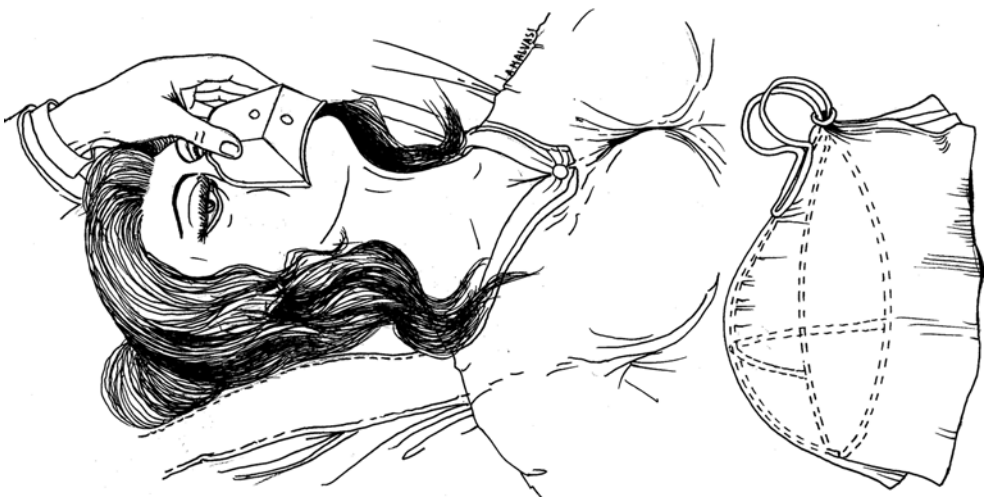

Fig. 1.45 Lang advised colleagues to c ontinue anesthesia while he was dying

1.5 Some "Forgotten" Conditions

Many complications of pregnancy have been considered as overcome given that they are no longer prevalent in the developed world. However, some endemic diseases still carry an important burden on pregnancy risk when the pregnant women live in remote rural areas at the developing countries. Conditions such as *Plasmodium falciparum* malaria, schistosomiasis, Chagas' disease, or leishmaniasis are still playing a part among the causes of maternal morbidity and even mortality worldwide [16, 22, 23].

Last century witnessed the almost complete disappearance of some pregnancy complications like the false pregnancy (pseudocyesis) and puerperal fever (Fig. 1.46). Documented since antiquity, this pathology was still occurring once in 250 pregnancies in 1940s in the United States (Daley 1946) (Fig. 1.45). Nowadays pseudocyesis is all but disappeared, probably as a direct result of widespread access to ultrasound equipment.

The understanding of pregnancy complications has advanced enormously throughout the last century. Nowadays establishing early pregnancy units is widespread in the referral hospitals, and management of those

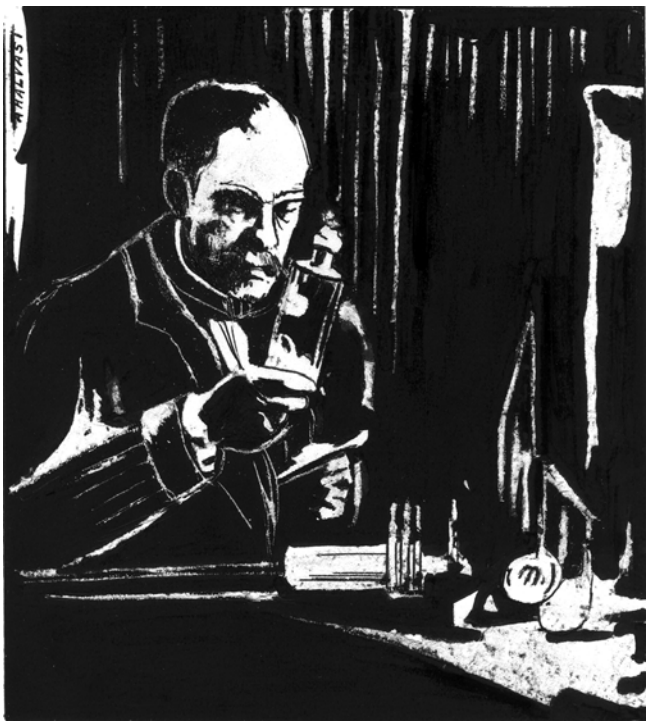

Fig. 1.46 Louis Pasteur was the first scientist to study infections in developing countries. Based on a photograph

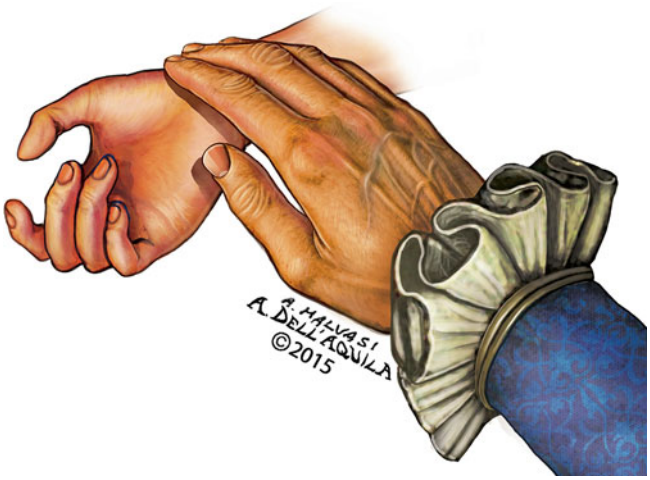

Fig. 1.47 In the past centuries, the evaluation of the arterial pulse was one of the few methods to clinically evaluate the maternal conditions

complications is firmly evidence based. Unfortunately, in the developing world a number of those complications can still cost the lives of women, and there is much work to be done in order to improve the access to medical care in a timely manner (Fig. 1.47).

In the following chapters the readers will find up-to-date articles about the specific early pregnancy complications, their diagnosis, and management, presented by leading specialists in the field.

Overall, the goal of this textbook is to continue providing, in a readable, understandable, and well-illustrated format, the clinical and basic information on early pregnancy complications that can serve as a reference for the clinicians involved in the care of pregnant patients.

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Spontaneous Abortion Complications

2

Abraham Tsur, Antonio Malvasi, Ughetta Vergari, and Howard Carp

2.1 Introduction

Miscarriage, the most common complication of pregnancy, is the loss of a pregnancy before fetal viability (Fig. 2.1). The term therefore includes all pregnancy losses from conception up to 20 weeks in North America and 24 weeks of gestation in Europe (Fig. 2.2). Although 15 % of clinical pregnancies miscarry, up to 50 % of conceptuses may be lost [1]. The causes of miscarriage are numerous, but include the presence of an abnormal embryo which is incompatible with life or a hostile maternal environment which does not support life (Fig. 2.3). The fetal causes include chromosomal aberrations which may account for up to 60 % of miscarriages or lethal structural malformations. However, whatever the cause, there is a final common pathway which includes uterine contractions, placental separation, and expulsion of the uterine contents. Fetal demise may precede expulsion, in a "missed miscarriage"; alternatively contractions may occur in the presence of a live embryo. Expulsion of the embryo and placenta is accompanied by varying degrees of bleeding, which may vary from a few drops of blood to torrential hemorrhage. Expulsion of the contents may be complete or incomplete (with only partial expulsion of the gestational products). If incomplete, intervention may be required such as curettage. Each of the above may have complications which may compromise the mother's well-being and future fertility. Some of the complications are described in this chapter.

A. Tsur, MD • H. Carp, MB, BS, FRCOG (✉)
Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: carp@netvision.net.il

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

U. Vergari, PhD
Department of Classical Philology and Philosophical Sciences, International Center of Bioethics and Human Rights, University of Salento, Lecce, Italy

2.2 Early Complications

2.2.1 Excessive Blood Loss and Disseminated Intravascular Coagulation

Incomplete miscarriage, with heavy bleeding, should be treated with surgical evacuation promptly. Risks of delayed intervention include excessive blood loss subsequently requiring transfusion of blood products or DIC (disseminated intravascular coagulation). Obstetrical DIC (Fig. 2.4a, b) is relatively rare in first-trimester miscarriages but can occur in midtrimester losses, especially if there are fetal demise and retention in utero for a long period. DIC can follow placental abruption or septic abortion and may lead to severe hemorrhage [1] and possibly amniotic fluid embolism. Severe DIC can lead to multiple organ failure and even mortality [2]. In extreme cases even hysterectomy may be required. These can be prevented by prompt diagnosis and treatment. The clinical presentation of DIC is acute bleeding combined with the following laboratory changes: decreased platelet count, prothrombin time prolongation, decreased fibrinogen levels, and increased markers of fibrin breakdown such as D-dimer. In order to facilitate early diagnosis and standardize assessment and treatment, several DIC scoring systems have been introduced [3]. Recently Erez et al. have introduced a new scoring system adjusted to pregnancy [4].

Management of DIC related to incomplete abortion or septic abortion includes the following four steps:

(a) Treating the underlying condition predisposing to DIC – including the surgical removal of retained products of conception and broad-spectrum intravenous antibiotics in the case of suspected sepsis.

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_2

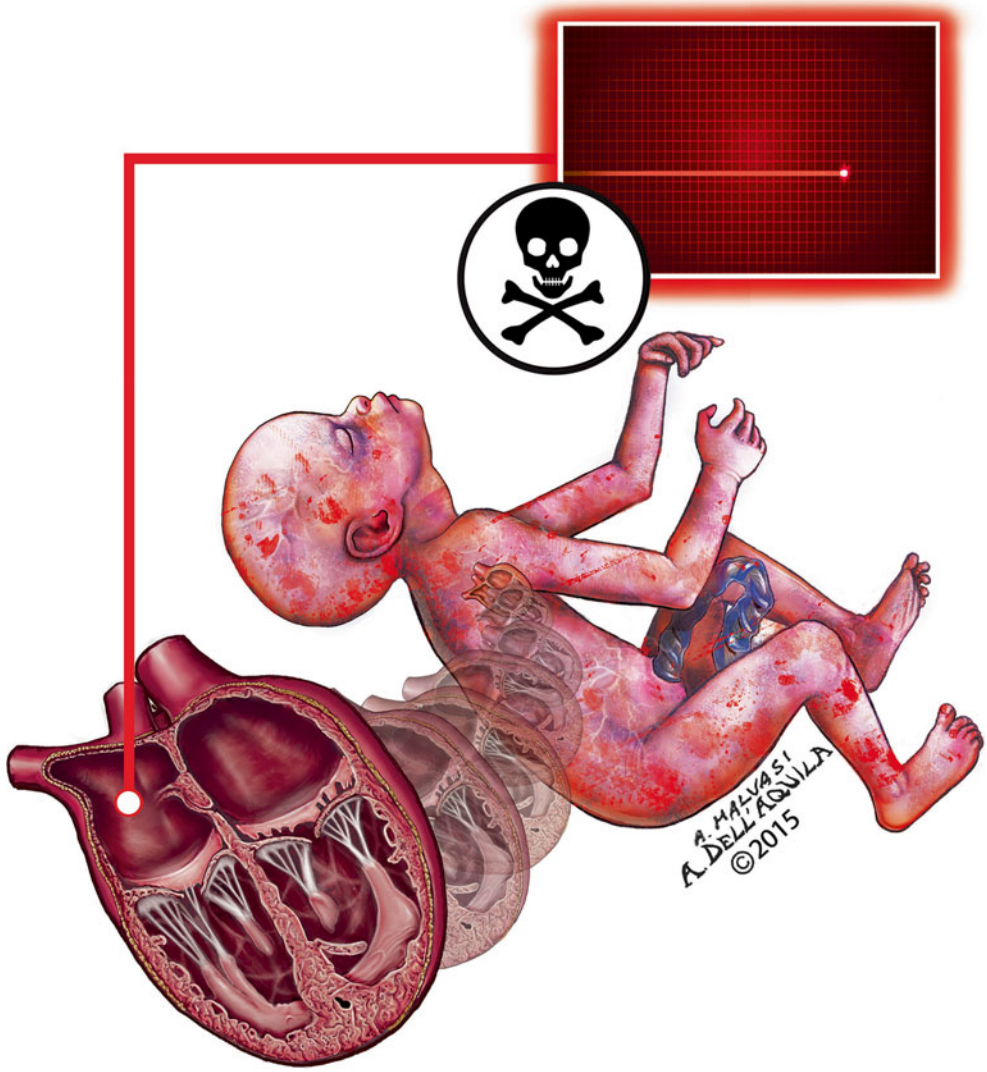


Fig. 2.1 The abortion is the loss of a pregnancy before fetal viability

(b) Clinical and laboratory intensive follow-up.
(c) Transfusion of blood products – packed cells, platelets, fresh frozen plasma, and cryoprecipitate – should be transfused promptly as needed.
(d) Hematologic interventions.

Tranexamic acid is widely used for the treatment and prevention of obstetrical hemorrhage. However, there is no evidence regarding its safety and efficacy in the scenario of incomplete or septic abortion. There is an ongoing international randomized, double-blind placebo-controlled trial aiming to determine the effect of early administration of tranexamic acid on mortality, hysterectomy, and other complications in women with postpartum hemorrhage (The WOMAN Trial [5]). The results are eagerly awaited and may have implications for the use of tranexamic acid in other conditions such as septic and incomplete abortions.

Recombinant activated factor VII (*rFVIIa*) was originally developed for the treatment of hemophilia. Similarly to tranexamic acid, there is lack of high-quality evidence regarding its efficacy and safety in the setting of DIC complicating incomplete or septic abortion. There is concern regarding the possibility of arterial thrombosis. Recent guidelines for the treatment of PPH stated that rFVIIa may be used as an adjunct to other surgical treatments [6].

2.2.1.1 Role of Oxytocin During Surgical Evacuation of the Uterus

Oxytocin is often used to enhance uterine contraction at the time of curettage. However, a randomized controlled blinded trial comparing the impact of 5 IU (international unit) of oxytocin and no oxytocin on bleeding, pain, and nausea after surgical termination of first-trimester pregnancies found oxytocin injection to confer no significant advantage [7].

However, in the Sheba Medical Center, we do administer oxytocin (in a dose of 5–10 IU depending on gestational age and size of the fetus) to most women undergoing surgical evacuation of the uterus as the contraction of the myometrium

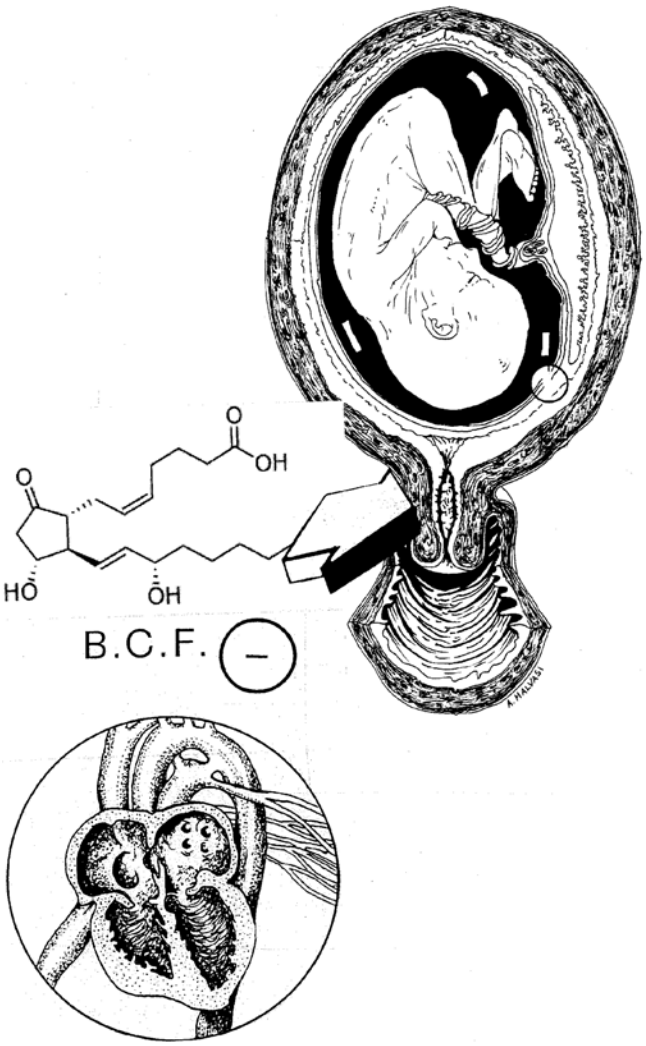


Fig. 2.2 Prostaglandins are often used to induce abortion after fetal demise to soften or dilate the cervix. BCF, fetal heartbeat stopped

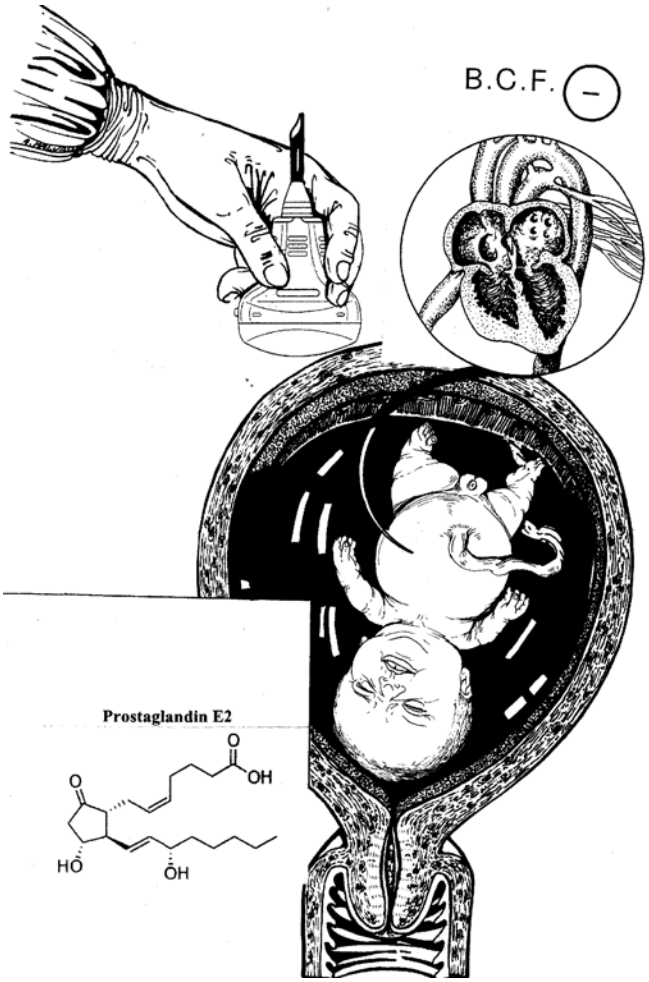


Fig. 2.3 Severe fetal anomalies or chromosomal aberrations may lead to fetal demise presenting as abortion. BCF, fetal heartbeat stopped

facilitates the procedure by clearly identifying the uterine border with the curette.

2.2.2 Infection and Septic Abortion

Septic abortion (Fig. 2.5) is defined as infection of the products of conception of a provable pregnancy. If not treated promptly, the infection can spread to the uterus and pelvis. Further spread may lead to systemic infection presenting as bacteremia, sepsis, septic shock, and potential failure of distal vital organs. Sepsis can spread rapidly if infected tissue is retained in the uterus [8]. The organisms involved are usually common vaginal bacteria. However clinicians should be alert to potentially lethal infection by bacteria that produce toxins, such as *Staphylococcus aureus*, that may be resistant to some penicillin: *Clostridium perfringens* and *Clostridium sordellii*; group A streptococcus; and also some toxin-producing strains of *E. coli* [8, 9].

The treatment of septic abortion includes fluid replacement, culture collection, and antibiotic therapy, followed promptly with curettage in order to evacuate the infected products of conception. A common feature in reported cases of death from septic abortion is delayed treatment [10].

2.2.2.1 The Role of Prophylactic Antibiotics

The role of antibiotic cover at curettage (Fig. 2.6) has been controversial; supporters of antibiotic cover have argued that antibiotics prevent infection. However, the counterargument is that if an infection occurs under antibiotic cover, it will be resistant to the simple antibiotics and therefore much harder to treat. However, a meta-analysis of 12 randomized trials by Sawaya et al. [11] reported that prophylactic antibiotics have a significant protective effect in preventing postaborted infections and can prevent up to one half of postaborted infection cases. This effect was found to be significant even in low-risk women. The choice of antibiotic regimen is less evidence based. In Sawaya et al.'s [11] meta-analysis, both the tetracycline and metronidazole (Fig. 2.7) were found to have significant and comparable protection against upper

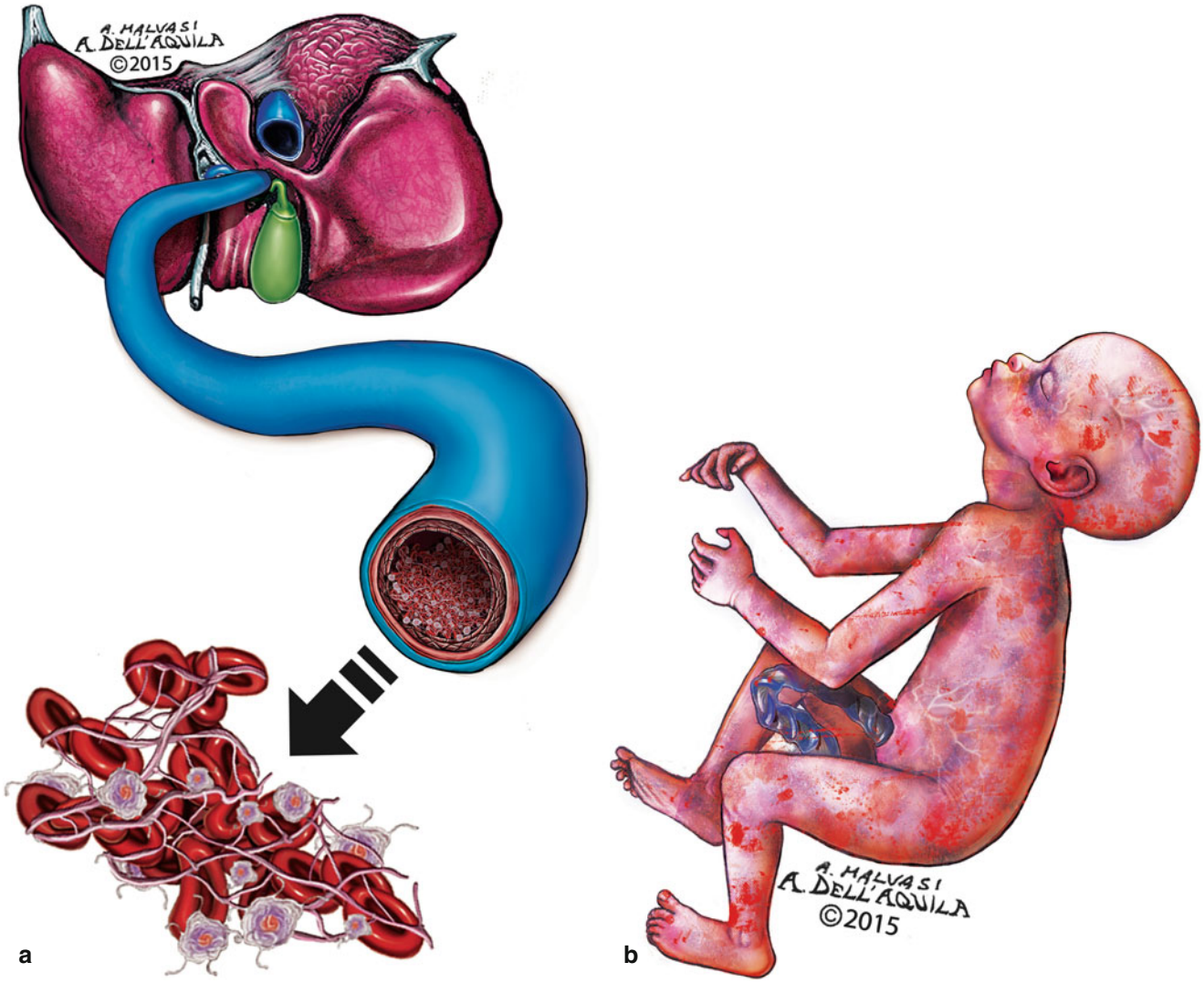


Fig. 2.4 Venous vein thrombosis and Diffuse Intravascular Coagulation may be a consequence of fetal death particularly in the second trimester, as thromboplastin is released into the maternal circulation from the degenerating placenta DIC with hepatic vein thrombosis (**a**) and fetal death (**b**)

genital tract infection. An American College of Obstetrics and Gynecology Practice Bulletin (No. 104) states that the choice of doxycycline 100 mg orally a few hours before the procedure followed by 200mg after the procedure is effective and inexpensive [12].

2.2.3 Mortality

In the developed world, death is rarely associated with spontaneous or induced abortion. The incidence is less than 1 per 100,000 procedures in the United States, whether spontaneous or induced [13]. In the recently published data regarding pregnancy-related mortality in the United States between the years 2006–2013 – the pregnancy-related mortality was 16 deaths per 100,000 women. Only 2.7 % of pregnancy-related deaths were attributed to induced or spontaneous abortion [14]. However, worldwide the percentage of maternal death attributed to abortion is higher, and it is estimated that complications of abortion are responsible for 7–14 % of maternal deaths [15, 16]. The lower mortality in the developed world may be due to better prevention of infection, aseptic techniques, and better availability of blood products and antibiotics. Unsafe and illegal abortions (Fig. 2.8) are still taking place in many parts of the world utilizing unsterile instruments, lack of appropriate conditions, and procedures being performed by individuals lacking the necessary skills as defined by the WHO [17].

2.3 Complications of Intervention

2.3.1 Uterine Perforation and Pelvic Organ Damage

Uterine perforation has been reported to occur in less than 0.5 % of patients in both first- and second-trimester procedures [18, 19]. The most common site of perforation is the uterine fundus. The uterine perforation can be by hysterometer

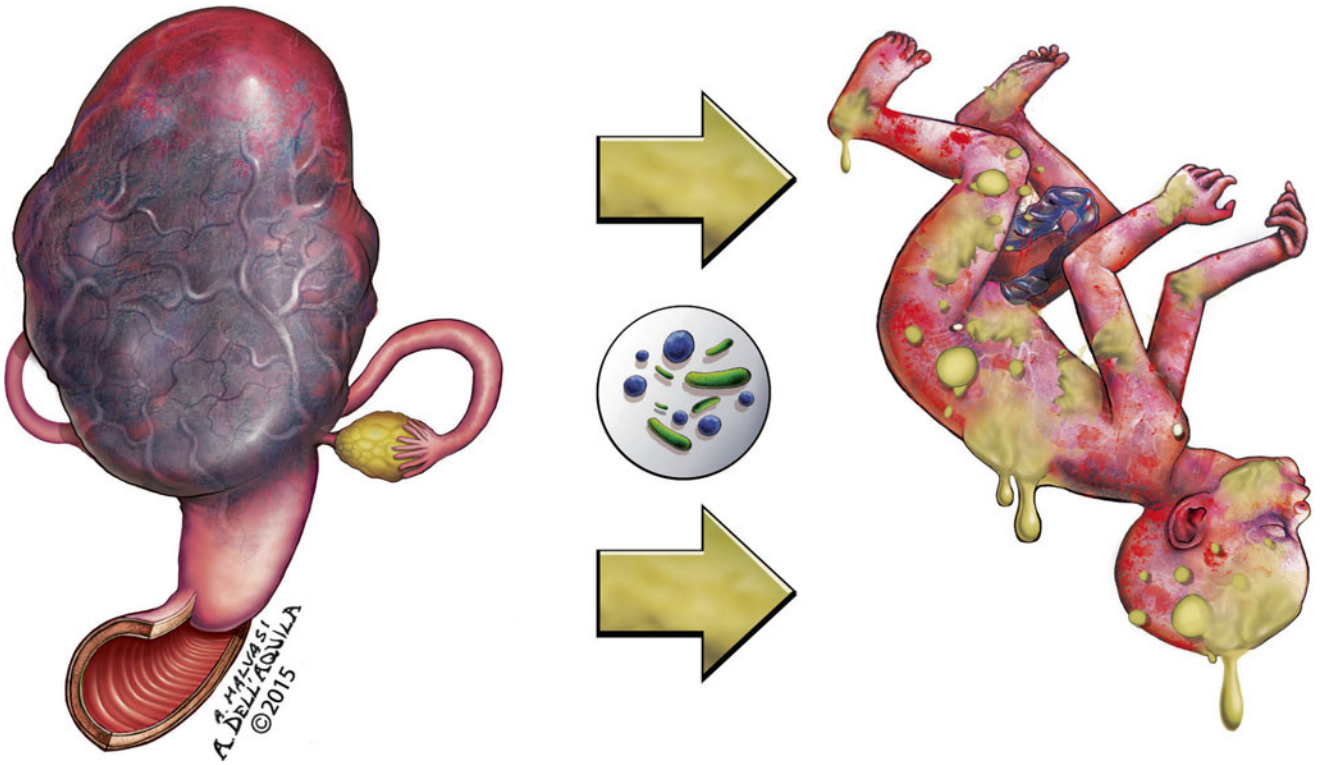
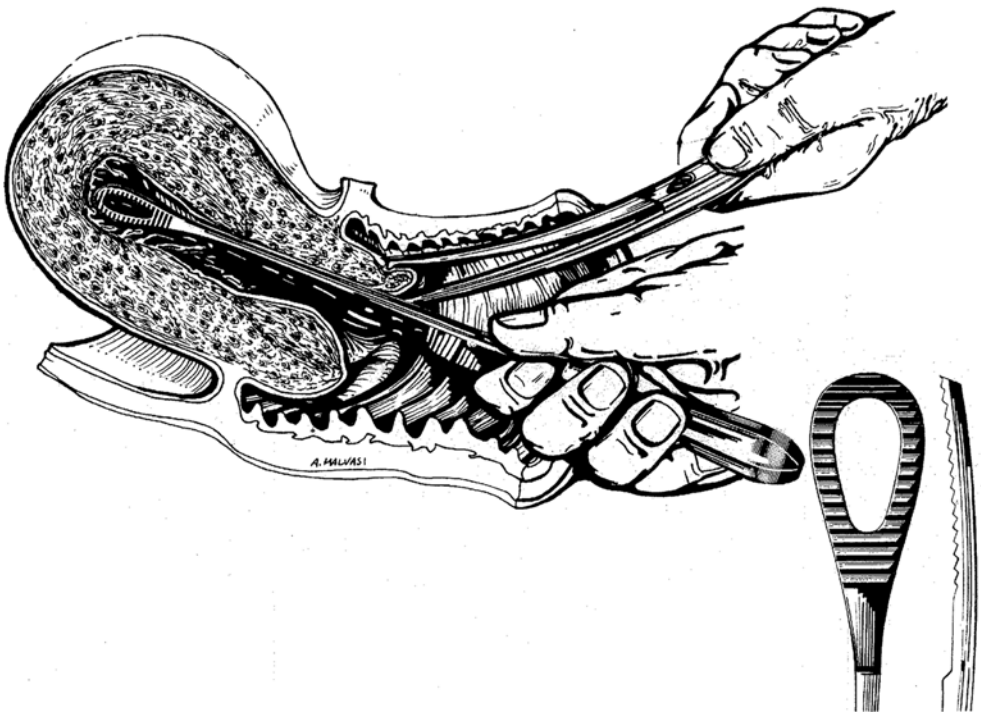


Fig. 2.5 A septic abortion

Fig. 2.6 Uterine curettage



(Fig. 2.9) or curette (Fig. 2.10) or forceps (Fig. 2.11) or Karman cannula (Fig. 2.12) [19]. An analysis of 67,175 curettage abortions performed at 13 institutions in the United States from 1975 to 1978 showed that if curettage were performed by an attending physician, the risk of uterine perforation was considerably lowered (Fig. 2.13). There are also many possibilities to perforate uterine cavity during a surgical abortion removal, while clinician measures by hysterometer the uterine length. It can be linked to uterine fibroids (Fig. 2.14), malformations, and post-cesarean section scar, with stenotic inner uterine orifice, uterine deep retroversion (Fig. 2.15), adhesions (Fig. 2.16), and the uterine niche (Fig. 2.17).

Dilatation of the cervix by laminaria also has a protective effect in preventing perforation, but the trend was not statistically significant (RR, 0.17; 95 % CI, 0.02–1.2) [20]. Darney et al. [18] have reviewed 15 cases of uterine perforations during second-trimester dilatation and evacuation (D&E). Two thirds of patients suffered concomitant bowel injuries and two patients required hysterectomy. These cases were characterized by errors in estimation of gestational age, failure to use sonography for dating, and inadequate cervical dilatation (Fig. 2.18) [21]. Traditionally, complications of uterine perforation were treated with laparotomy. However, today, with improved expertise in endoscopy, laparoscopy has been reported as a safe and effective option for treating these complications [22]. If perforation occurs prior to completing uterine evacuation, evacuation can be completed transcervically under direct visualization of the perforation site using laparotomy or laparoscopy [23].

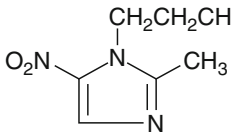


Fig. 2.7 The metronidazole chemical formulation

2.3.1.1 Failure to Diagnose Uterine Perforation

Some believe that perforation may be more common than diagnosed and that many patients may go undiagnosed without sequela. Perforation should be suspected if the instrument is passed to a greater depth than the measured

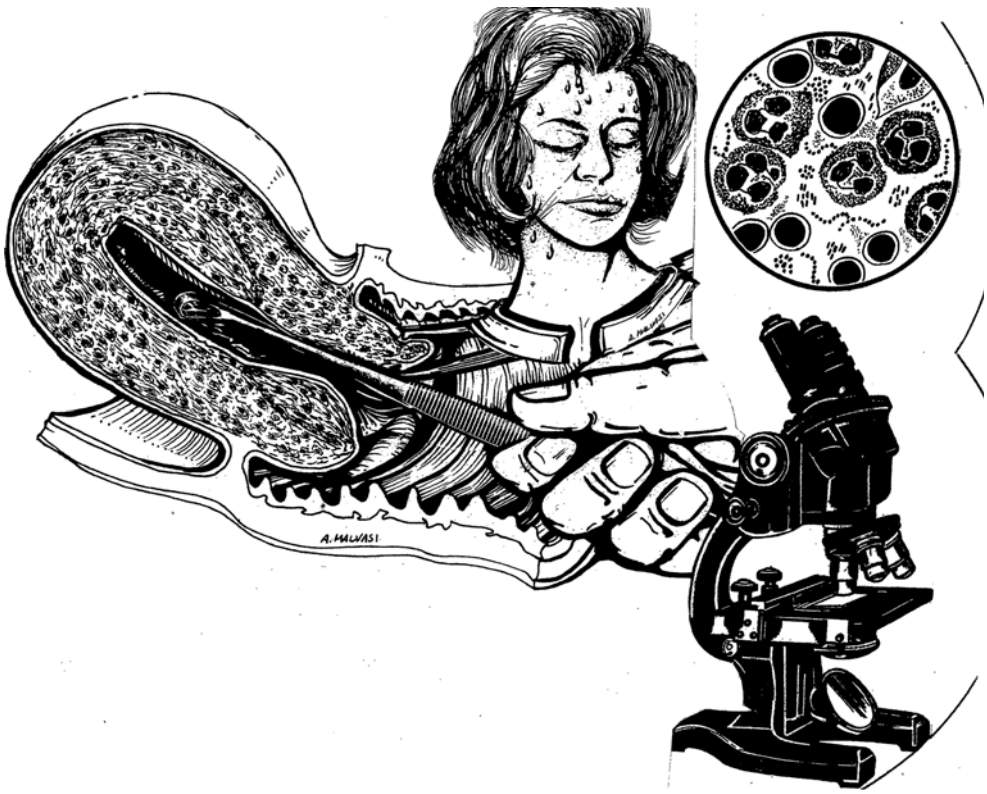


Fig. 2.8 The risk of septic abortion using nonsterile instrument

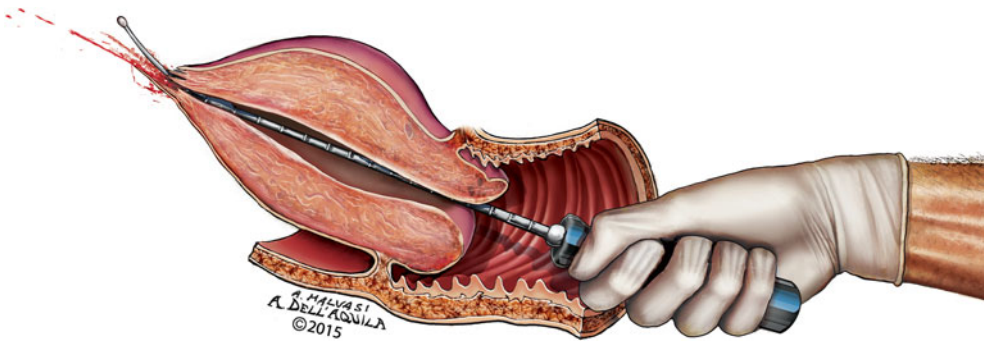


Fig. 2.9 The figure shows a uterine perforation by hysterometer in a complete abortion during excessive and wrong hysterometry

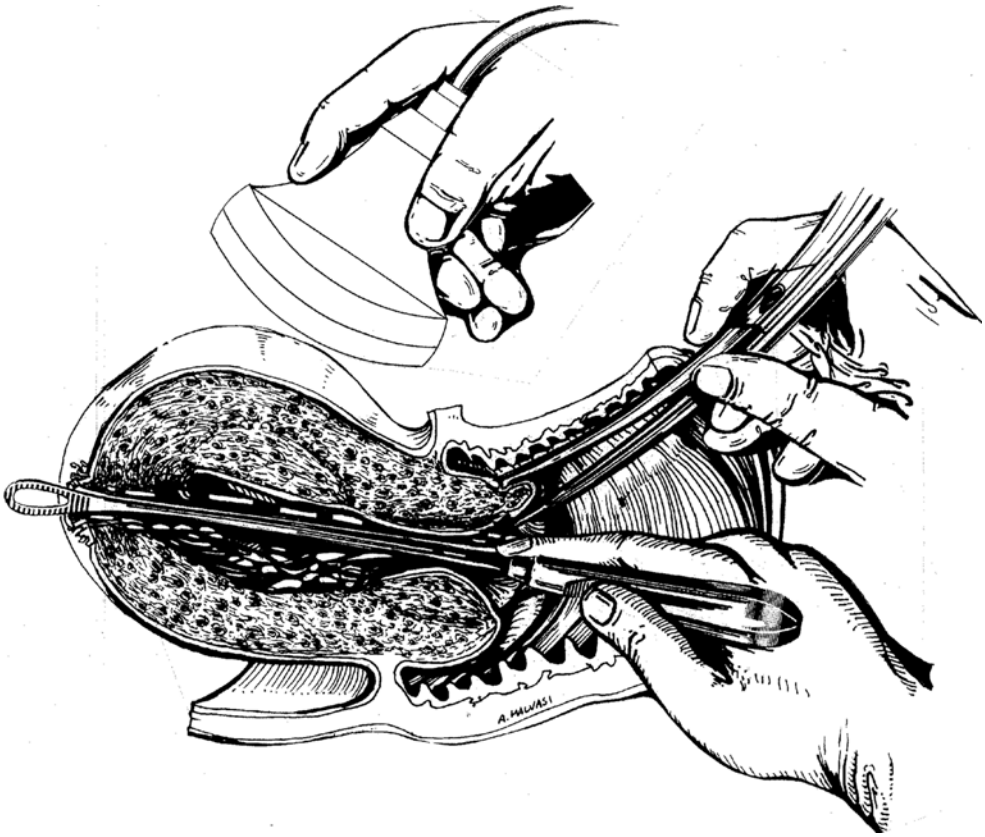


Fig. 2.10 Uterine fundal perforation by curette

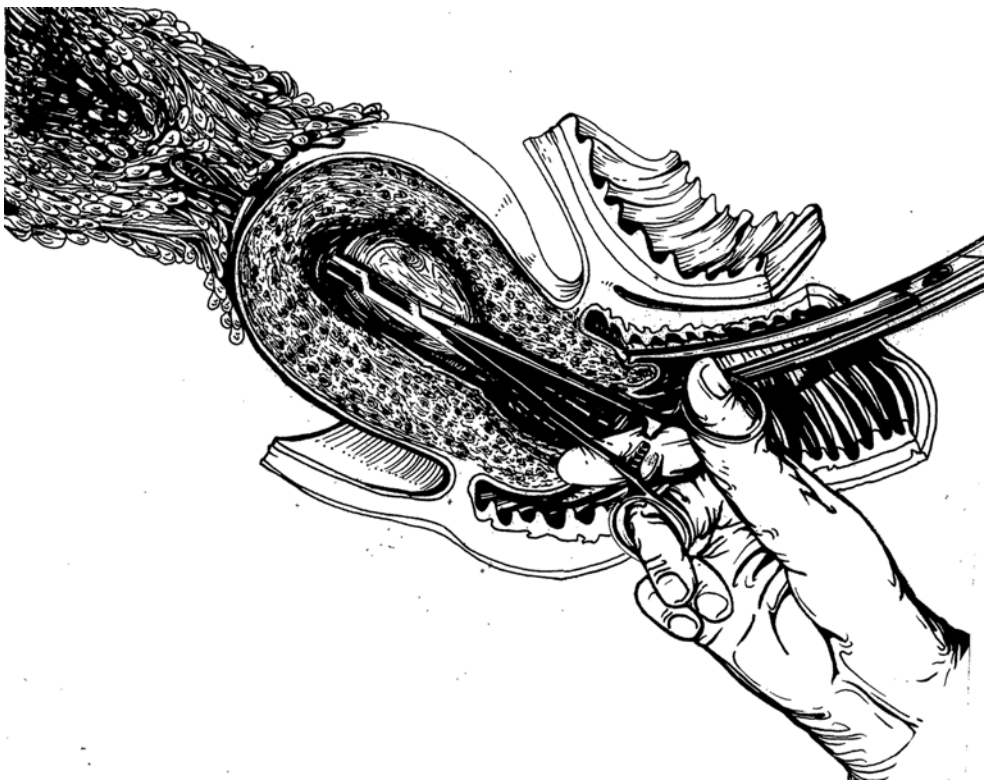


Fig. 2.11 Uterine fundal perforation by forceps, complicated by omental clamping

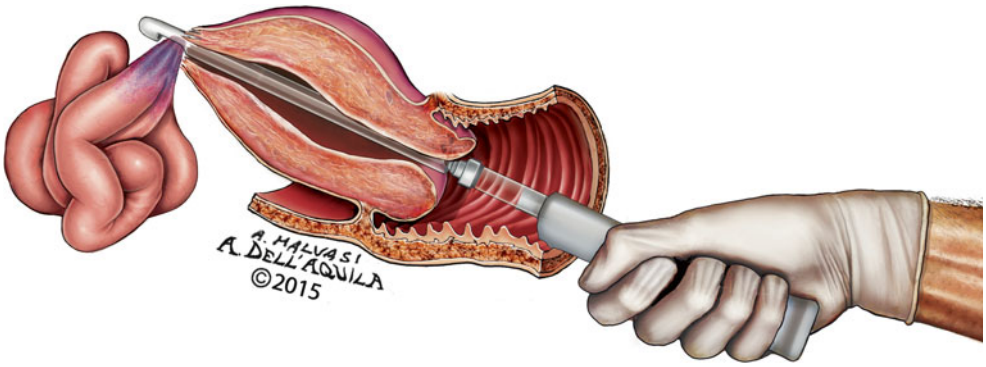


Fig. 2.12 Uterine fundal perforation by Karman cannula, complicated by bowel clamping

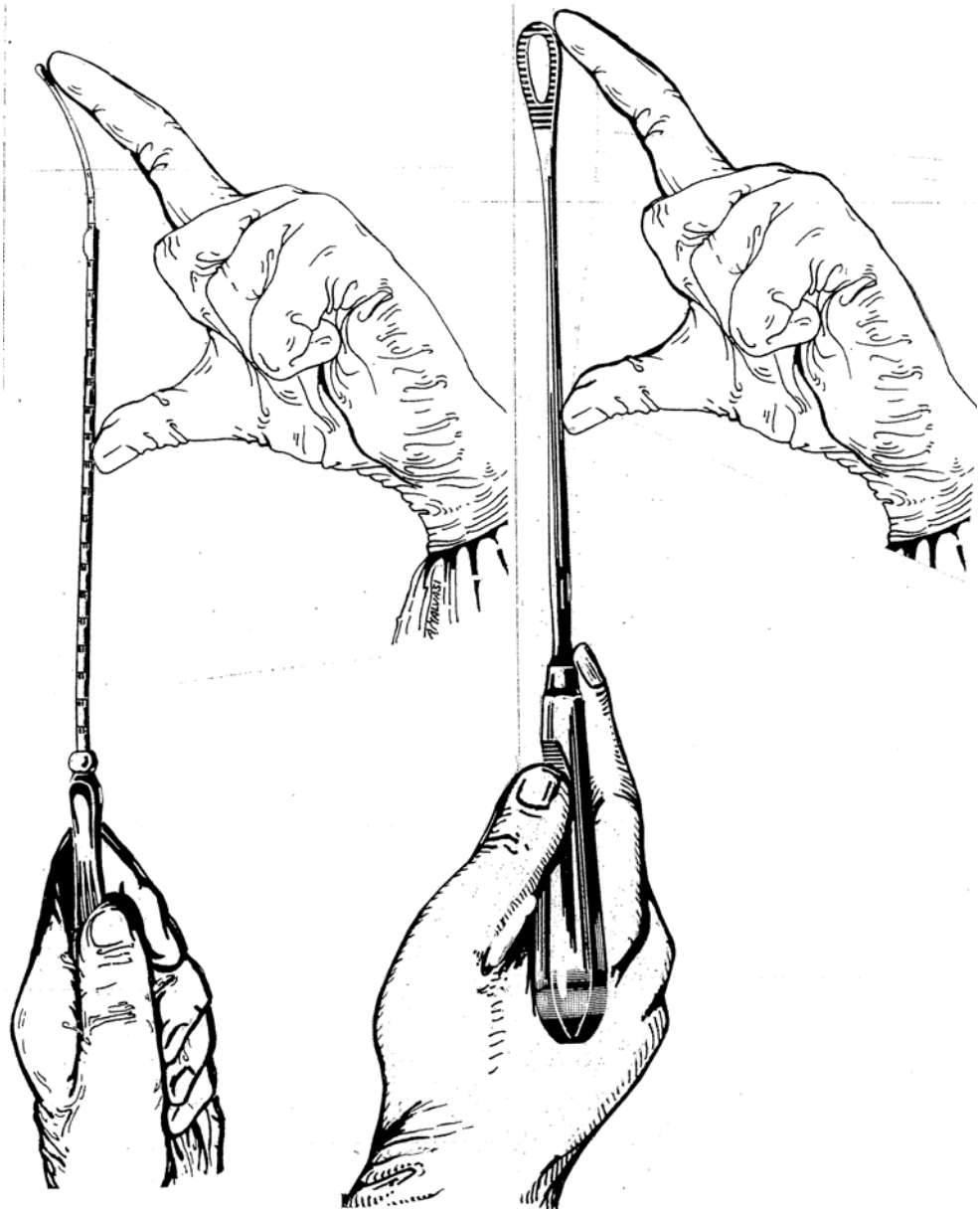


Fig. 2.13 Prior to cervical dilatation or curettage, it is mandatory to carefully measure the uterine length by hysterometry, and to compare it to the curette length, especially in cases of second-trimester abortion

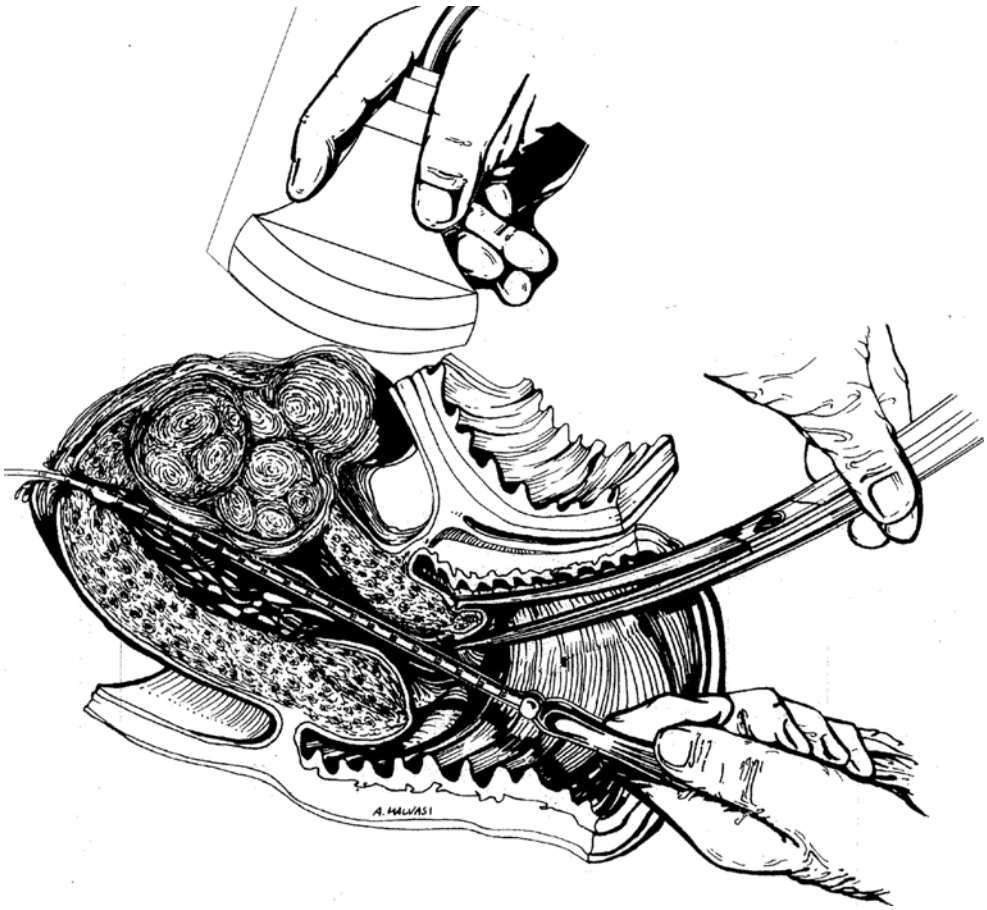


Fig. 2.14 Uterine fundal perforation by hysterometer in incomplete abortion for intramural anterior multiple fibroids

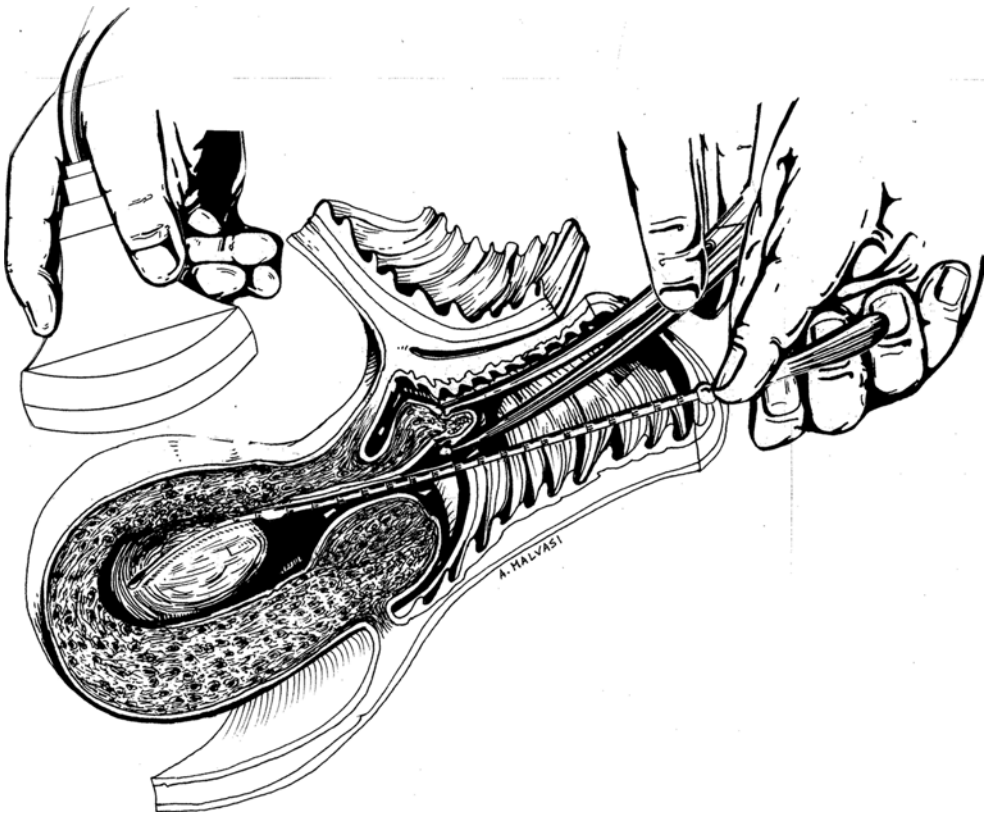


Fig. 2.15 Maneuver to avoid uterine perforation: uterus is clamped and pulled by clinicians and checked by ultrasonography during hysterometry (echo-guided abortion removal)

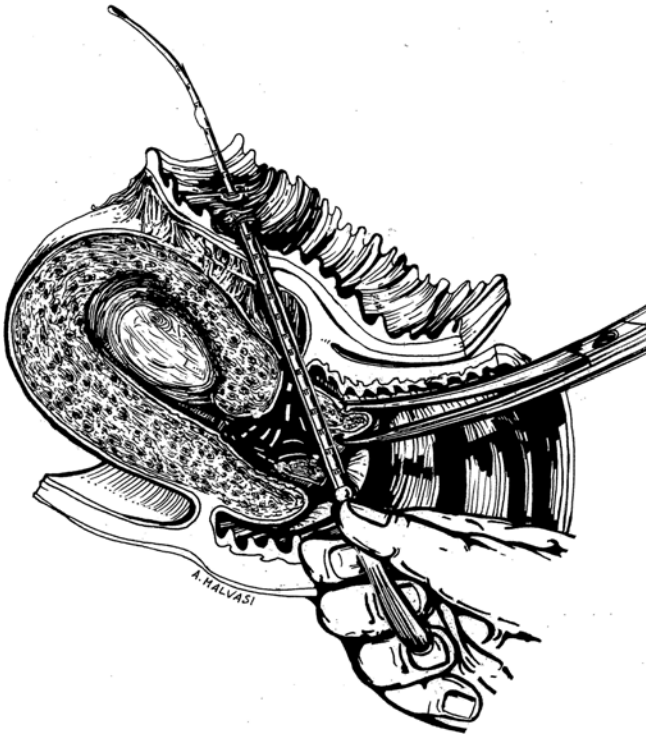


Fig. 2.16 A fixed uterus for deep and strong adhesions, perforated by hysterometer that penetrates into the bladder

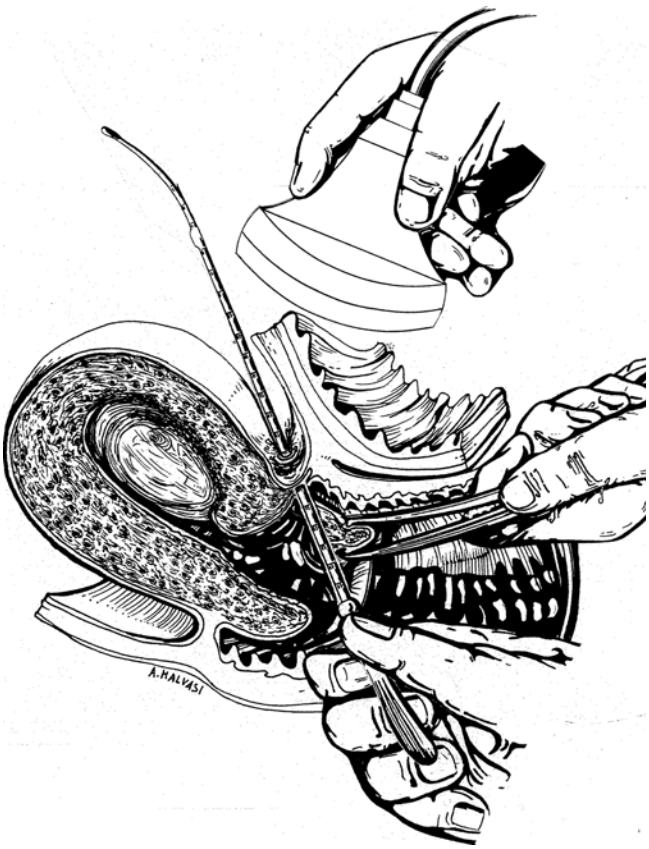


Fig. 2.17 Uterine perforation through the niche by hysterometer

size of the uterine cavity. If the perforation is not diagnosed, the patient may complain of excessive pain on awakening. There may be bleeding from the perforation site which may present as hemorrhage (Fig. 2.19). However, hemorrhage may not be apparent if bleeding occurs into the abdominal cavity or into the broad ligament in the case of a lateral perforation. Sometimes the perforation could be in the posterior part of the cervix (Fig. 2.20), without passing through the uterine cavity. Therefore, the vital signs should be monitored if perforation is suspected. The question arises as to when further intervention such as laparoscopy is indicated (Fig. 2.21). If fat or other extrauterine tissue is removed, it is our opinion that exploratory laparoscopy is mandatory. Laparoscopy is also indicated if the patient becomes hemodynamically unstable. If perforation is diagnosed prior to completion of curettage, the procedure can be completed either under laparoscopic or ultrasound control (Fig. 2.22). If there are no complications of perforation, the patient can be discharged home after 24–48 h. If there is organ damage (Fig. 2.23), this should be repaired appropriately. In cases of broad ligament hematoma, ultrasound should be used to demarcate the size of the hematoma and subsequent resolution.

Failure to diagnose uterine perforation either during or after the uterine revision, it can lead to further complications (Fig. 2.24). Su et al. described a 31-year-old woman with the ovary incarcerated into the uterine perforation [24], while Shulman et al. described incarcerated small bowel inside the uterus following uterine perforation [25] (Fig. 2.25).

2.3.2 Cervical Lacerations and Future Cervical Incompetence

Although cervical lacerations can occur during the spontaneous expulsion of gestational products at abortion, most lacerations arise during dilatation and curettage (D&C) or dilatation and evacuation (D&E). Lacerations can be due to the traction applied to the cervix with a tenaculum (Fig. 2.26), from trauma during dilatation of the cervix (Fig. 2.27) or from trauma during the curettage itself.

Cervical injury can be significantly reduced with the use of osmotic dilators such as *Laminaria japonica* and Dilapan-S [26] or cervical softening with misoprostol (Fig. 2.28) [27].

A large, retrospective study, analyzing 15,438 suction curettage procedures carried out at 12 or less gestational weeks, demonstrated that the use of laminaria had a strong protective effect on cervical injury compared to rigid dilators (RR = 0.19 CI 0.07–0.52), whereas if the operator was a resident rather than an attending physician, the RR was 2.0 (CI 1.3–2.9). It is interesting that the use of general rather

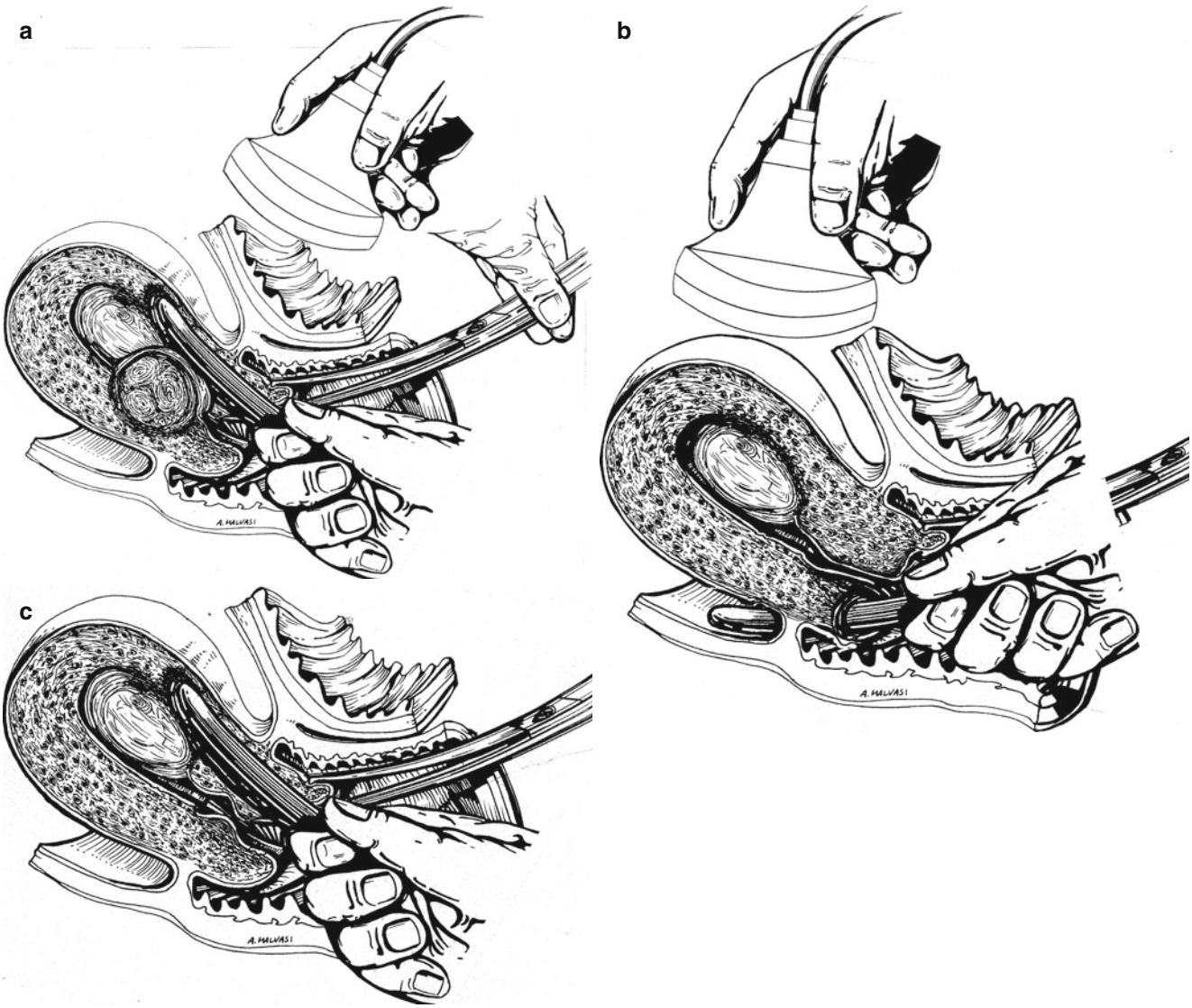


Fig. 2.18 Uterine perforation for inadequate cervical dilatation with Hegar dilator: (**a**) uterus with a large posterior myoma deforming the uterine cavity, (**b**) uterus in hyperanteversion, (**c**) uterus with anterior perforation

than local anesthesia had a detrimental effect on the occurrence of cervical injury (RR = 2.6 CI 1.8–3.9). The use of laminaria, local anesthesia, and performance by experienced physicians showed a 27-fold protective effect [26].

Bleeding from cervical lacerations can be managed with direct pressure or cautery to the bleeding site and in some cases suturing. An important long-term consequence of cervical injury during dilatation and curettage is cervical incompetence leading to subsequent late miscarriage, premature rupture of the membranes, and preterm birth. It has been shown that women with a history of termination of pregnancy have a significantly greater risk for preterm birth, and the risk increases as the number of terminations of pregnancy increases. However, other mechanisms may contribute to the increase in preterm births in women undergoing termination of pregnancy in addition to cervical injury, such as uterine scarring, that can lead to faulty placental implantation and socioeconomic status [28].

2.3.3 Cervical Stenosis and Hematometra

Hematometra also known as uterine distension syndrome usually presents immediately or soon after surgical evacuation of the uterus (Fig. 2.29). The classic presentation is pain without vaginal bleeding. The condition is caused by accumulation of blood within the uterus and lack of drainage through the cervix. An ultrasound examination will demonstrate the blood accumulated inside the uterine cavity (Fig. 2.30). The condition can be alleviated by passing a

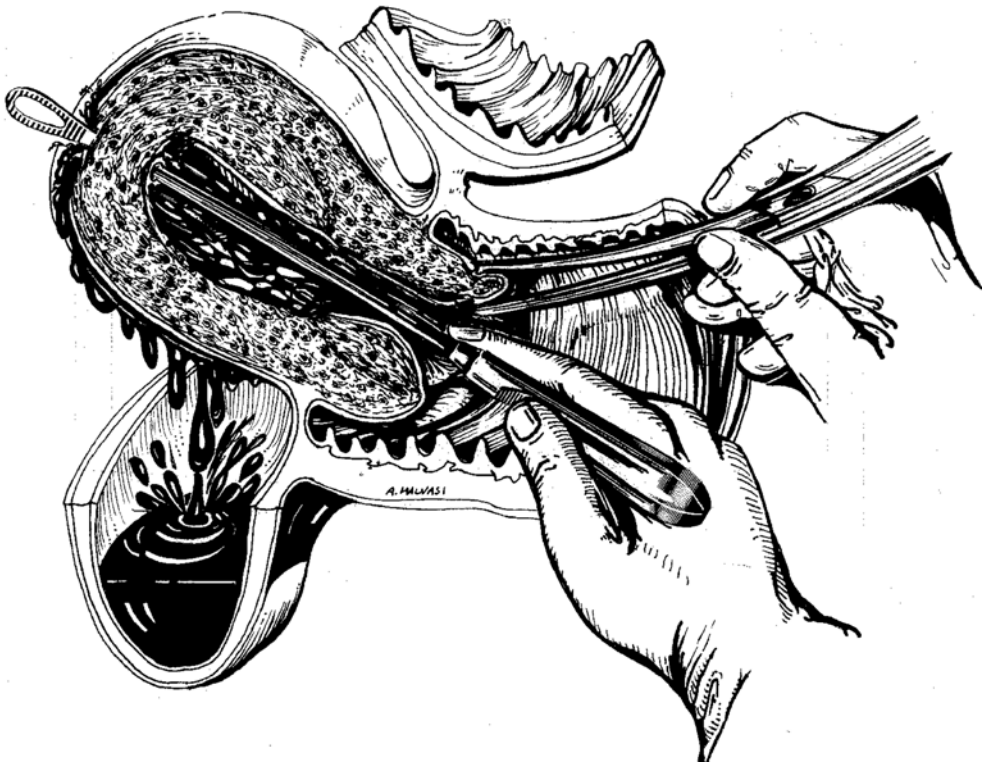


Fig. 2.19 Uterine perforation by a curette, suspected since the instrument passed to a greater depth than the measured size of the uterine cavity; it caused uterine bleeding in the Douglas pouch

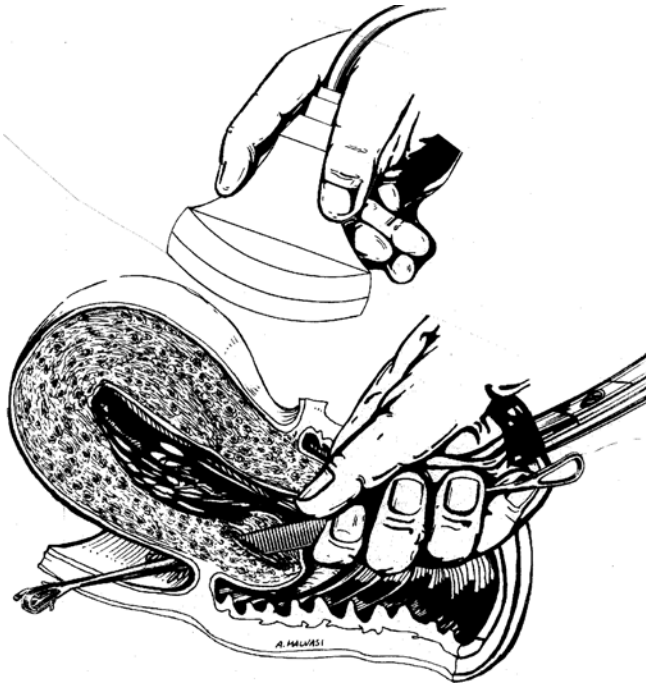


Fig. 2.20 Uterine perforation could be in the posterior part of the cervix

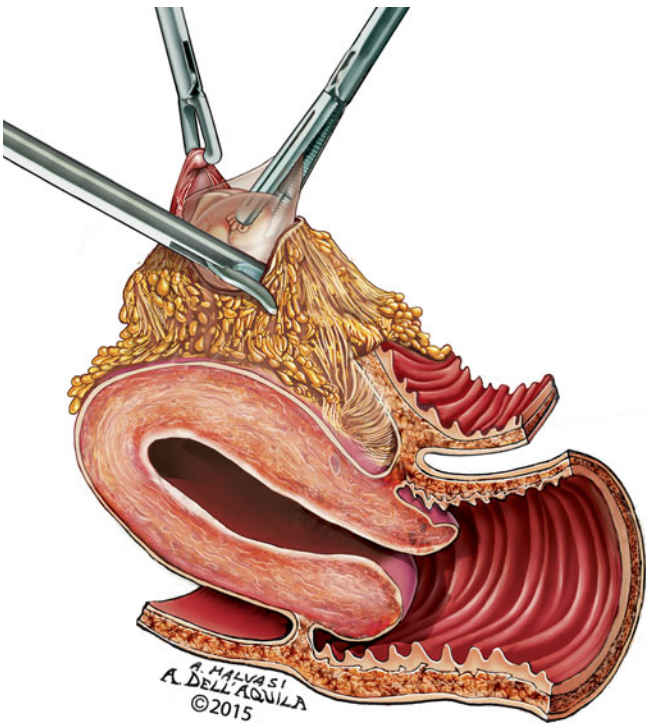


Fig. 2.21 Laparoscopic extraction of an embryo sac through the omentum attached to anterior uterine body, after uterine perforation

uterine sound through the cervix in order to release the blood. Another alternative is to use a curette (Fig. 2.31), or a pipette, and aspirate the blood. However, pipette aspiration is often painful. The use of methylergonovine maleate given either intramuscularly or orally may assist by contracting the uterus. However, neither aspiration nor uterine stimulants will prevent cervical stenosis. If there is stenosis, hematometra may reoccur at subsequent menstruation. Adequate cervical dilatation usually overcomes the problem of cervical stenosis (Fig. 2.32) and prevents further stenosis.

2.3.4 Anesthesia

Numerous anesthetic agents can be used for D&C: general, neuraxial (spinal or epidural), or local (paracervical block) which is usually combined with intravenous sedation. In cases of excessive blood loss, neuraxial anesthesia is contraindicated due to the risk of worsening hypotension. General anesthesia is preferred if the patient is emotionally upset or the gestational age is 13 weeks or above [29]. If local anesthesia is used, vasovagal syncope may occur (known as "cervical shock"). Cervical shock is self-limiting and can be treated or prevented with the use of atropine.

The complications of neuraxial anesthesia can be immediate, intermediate, or long term.

Immediate sequela includes high or prolonged blockade, motor blockade, and seizures after unintentional intravenous injection of local anesthetic. Intermediate complications include epidural hematoma and infection such as epidural abscess and meningitis [29]. The long-term neurologic sequela is clearly of most importance but is beyond the scope of this chapter. Grimes et al. [30] compared the safety of local versus general anesthesia. Local anesthesia was associated with higher rates of febrile and convulsive morbidity, while general anesthesia was associated with higher rates of hemorrhage, uterine perforation, and cervical injury. The authors concluded that both techniques appear to be safe although each is associated with a different spectrum of complications [30]. However, it should be noted that as the rate or abortion-related mortality decreases, the percentage of death related to general anesthesia increases. Using CDC data, it has been shown that the death-to-case rate for abortions at less than or equal to 12 weeks' gestation associated with general anesthesia was 0.37/100,000 – more than twice the rate with local anesthesia was 0.15/100,000 [31].

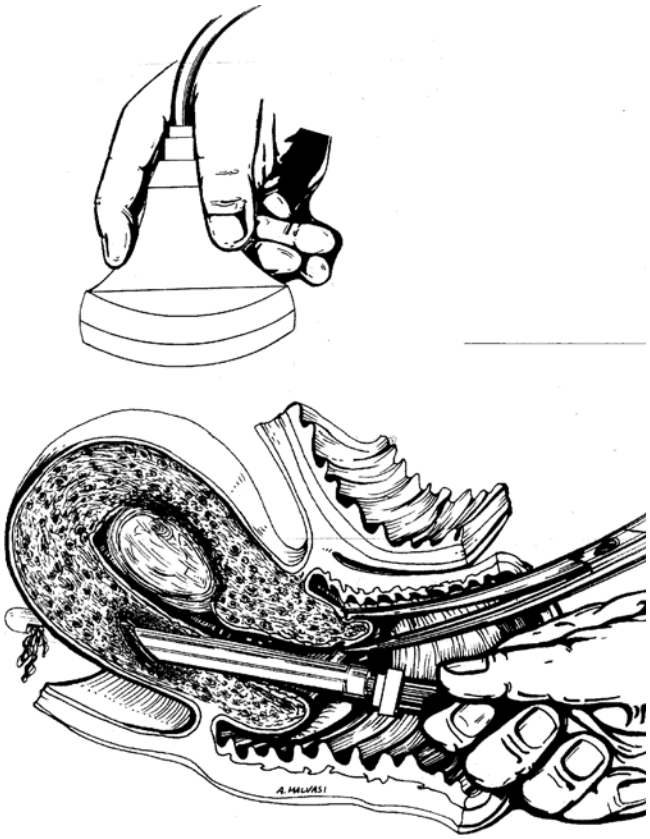


Fig. 2.22 A posterior uterine body perforation by Karman cannula: clinician checks by transabdominal ultrasound the gestational sac and the posterior perforation

2.4 Late Complications

2.4.1 Pain and Bleeding

Pain and cramps may persist in some women for the first few days or even weeks after miscarriage. Additionally vaginal bleeding may be normal in the first few weeks after miscarriage and is usually heavier and of longer duration after medical treatment with misoprostol than curettage

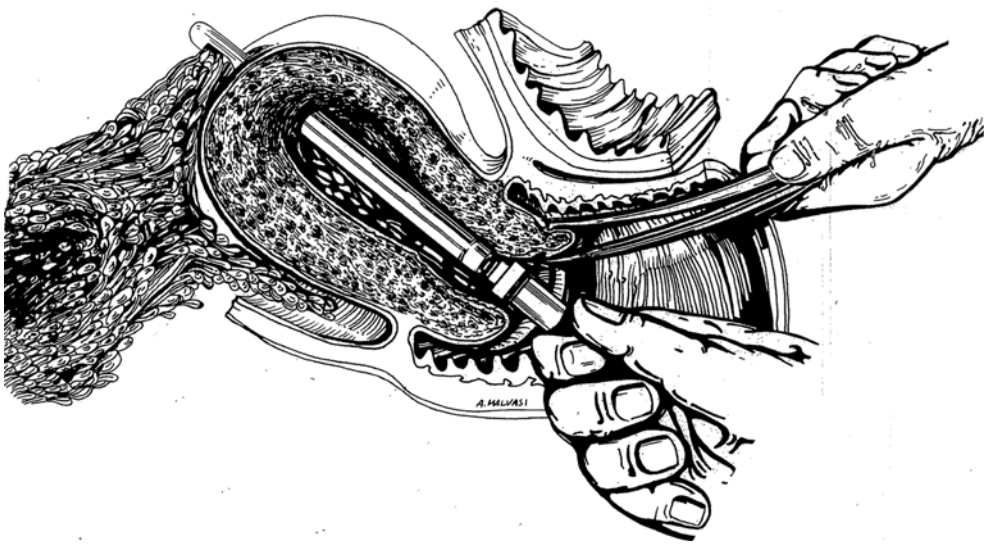


Fig. 2.23 Uterine perforation by Karman cannula and omental stripping

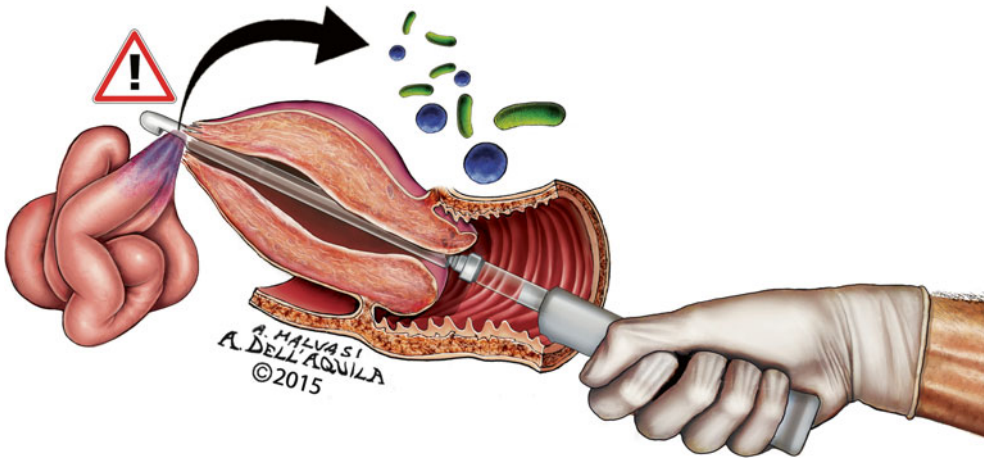


Fig. 2.24 Uterine perforation by Karman cannula and bowel clamping with enterobacteria release in the abdominal cavity (high risk of successive peritonitis)

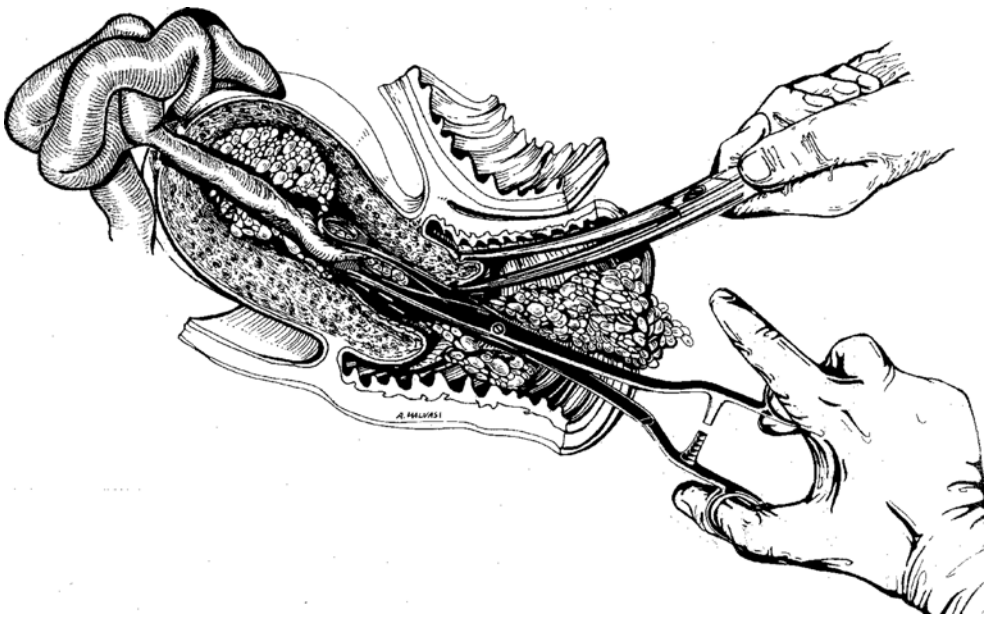


Fig. 2.25 An incarcerated small bowel inside the uterus following uterine perforation

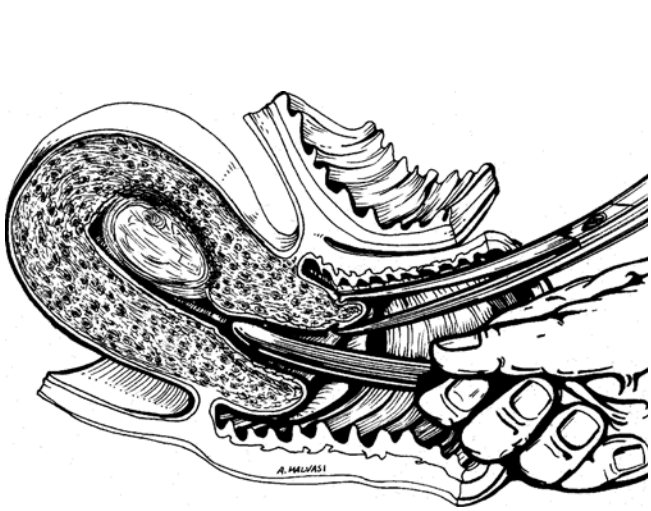


Fig. 2.26 Care should be taken not to traumatise the cervix with excessive dilatation due to the risk of subsequent cervical incompetence. Cervical dilatation can be facilitated with prior preparation with misoprostol or laminaria

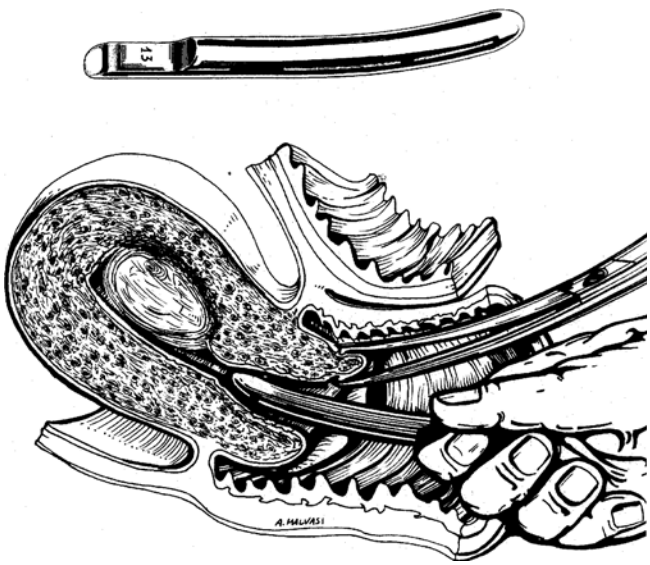


Fig. 2.27 A cervical trauma for excessive dilatation of the cervix with Hegar dilator n° 13

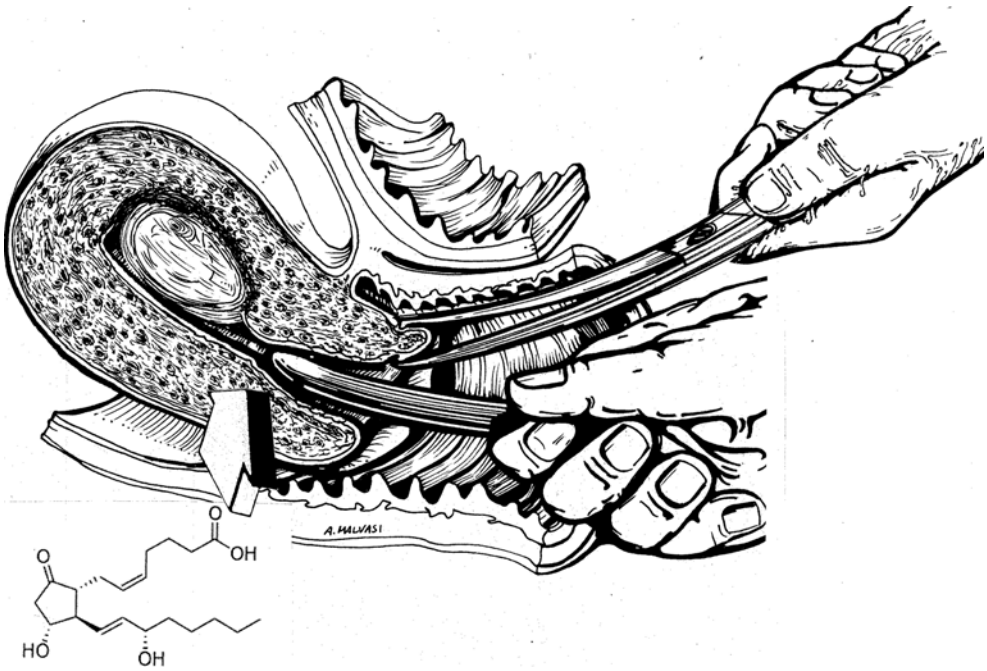


Fig. 2.28 Cervical dilatation after prostaglandin administration

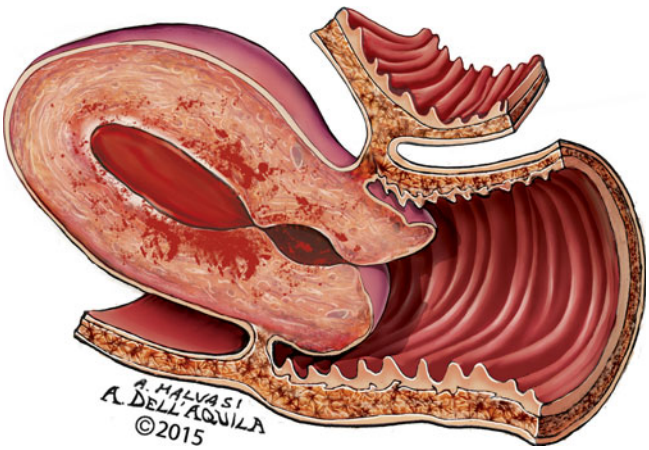


Fig. 2.29 Hematometra is accumulation of blood in the uterine cavity, causing distension immediately or soon after surgical evacuation of the uterus

[32]. The clinical challenge is to identify the women that require further investigation. Clearly worsening or heavy bleeding and worsening pain or additional symptoms such as fever should alert the physician to search for the complications described in this chapter such as retained products of conception and endometritis.

2.4.2 Retained Products of Conception (RPOC)

The clinical presentation of retained products of conception may include irregular uterine bleeding, pelvic pain, uterine tenderness, and fever. The ultrasound findings indicative of RPOC are a hyperechoic endometrial thickness combined with abundant low-resistance flow in the myometrium or just beneath the endometrium. Diagnostic confirmation may be necessary depending on the expertise of the ultrasonographer. Repeat curettage, suction evacuation, removal by clamp ring (Fig. 2.33), or hysteroscopic resection can be employed. Hysteroscopic excision is probably the treatment of choice as hysteroscopic excision allows the retained placental products to be excised under direct vision, possibly leading to fewer uterine adhesions and avoidance of incomplete evacuation [33]. Women preferring to avoid surgical intervention can be treated with misoprostol (Fig. 2.34) in order to induce uterine contractions. Complete evacuation rates have been reported to lie between 53 and 87 % [34]. It has been suggested that the progesterone receptor modulator mifepristone should be added to misoprostol in order to enhance the effect. However there is insufficient evidence to draw firm conclusion about the added value of mifepristone [35]. In our clinical experience, the efficacy of misoprostol in leading to evacuation of the uterus decreases as the time from the primary abortion increases.

2.4.3 Asherman Syndrome

Asherman originally defined the syndrome bearing his name as intrauterine adhesions accompanied by amenorrhea or infertility [36]. The condition is mainly caused by intrauterine trauma associated with surgical procedures, especially curettage after missed abortion or puerperal curettage (Fig. 2.35) [37]. If excessive pressure is applied at curettage,

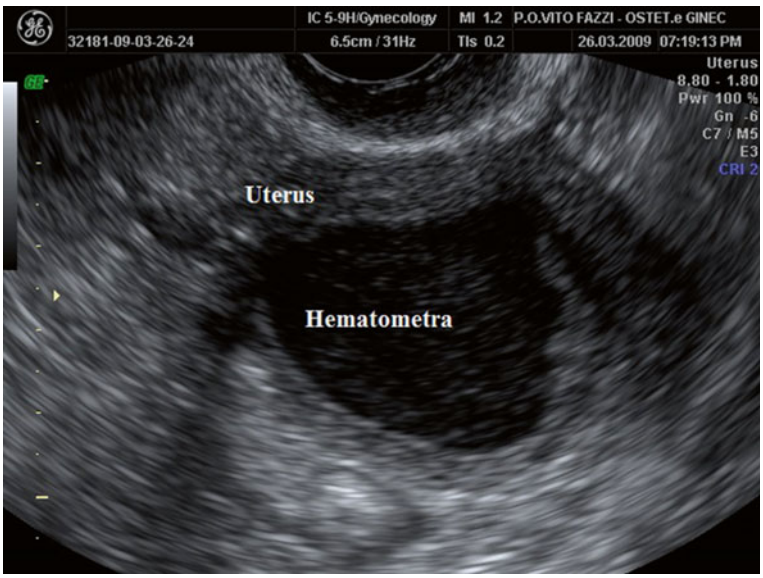


Fig. 2.30 Ultrasound image showing blood retained within the uterine cavity

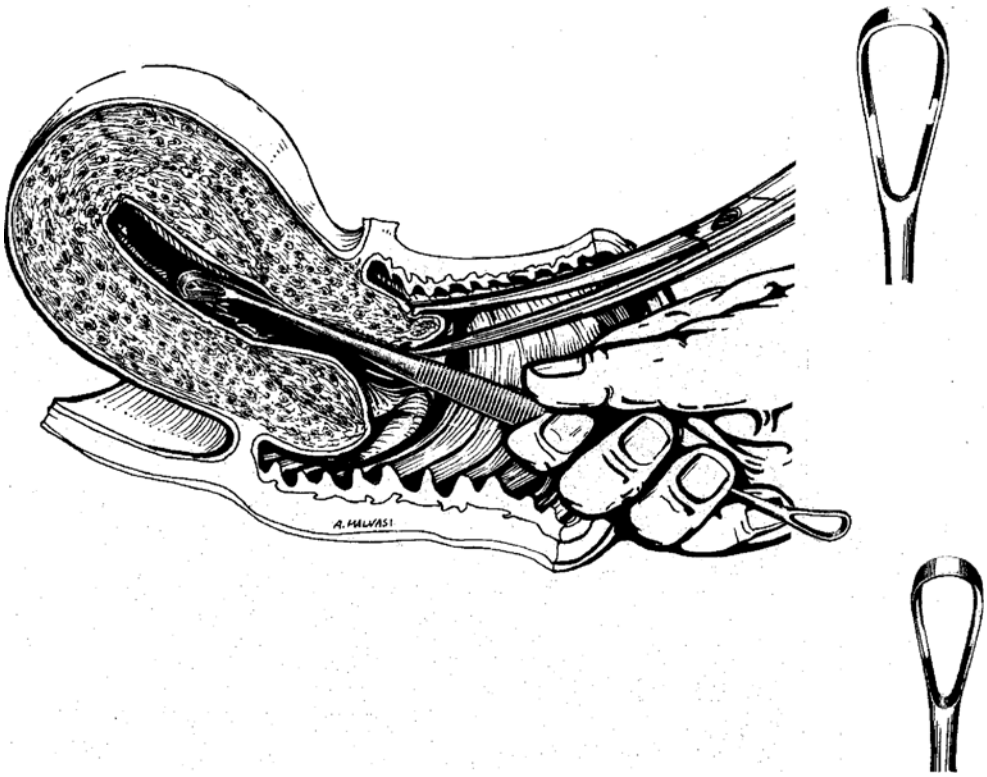


Fig. 2.31 Hematometra can be evacuated by curettage, or by suction applied through a pipelle of small diameter feeding tube. Feeding tube is illustrated

the stratum basale and even the myometrium may be excised, leaving a raw area, and denudation of the endometrium may adhere. Infection may also have a role in the pathogenesis, but the role of infection is controversial. Sometimes Asherman syndrome was suspected in patient treated by Foley catheter insertion after uterine cavity revision for abortion and massive bleeding (Fig. 2.36a, b).

Polishuk et al. [38] found no difference in the occurrence of intrauterine adhesions between patients who developed endometritis (Fig. 2.37) when compared to a control group of women that did not develop infection.

Asherman syndrome can be prevented by minimizing the trauma to the uterus, by avoiding postpartum or postabortion, and by repeat curettage for residual placental tissue. Suction curettage is probably much less traumatic than sharp curettage, as the suction curette does not allow excess pressure to be applied. The treatment of choice for removing residual placental tissue is probable hysteroscopic excision [39]. Hysteroscopy

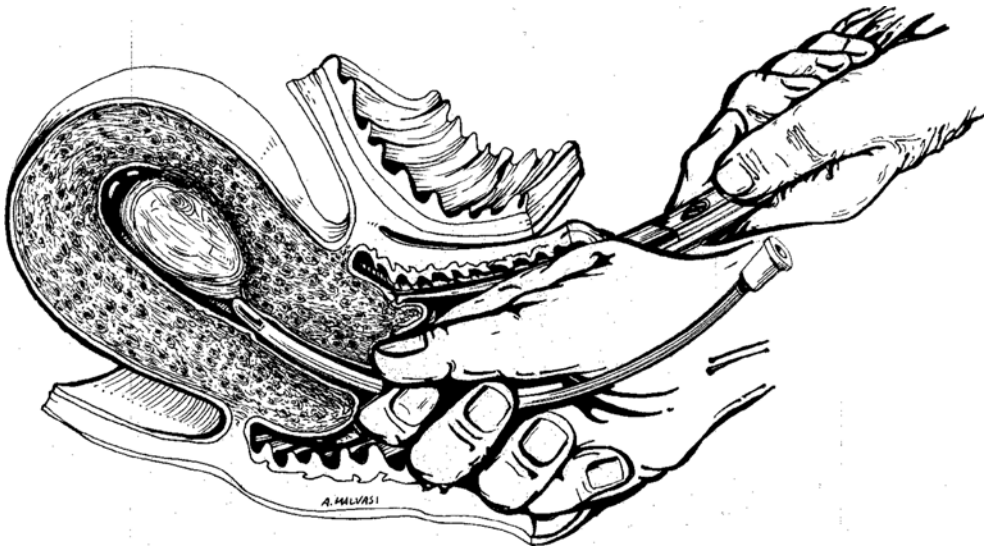


Fig. 2.32 Cervical stenosis at the level of the canal or internal os. Dilatation can be performed by passing a Foley catheter, inflating the balloon, and applying gentle traction

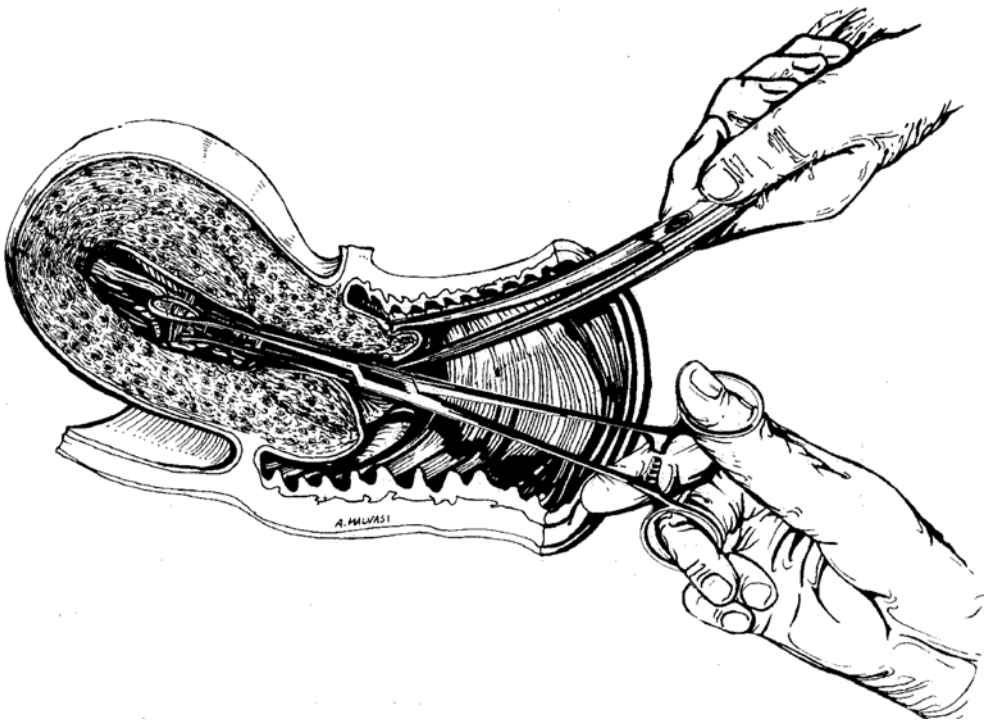


Fig. 2.33 Removal of retained products of conception in the uterus using a clamp ring

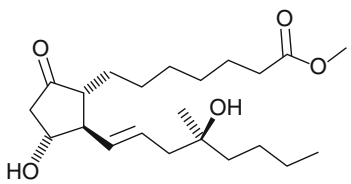


Fig. 2.34 Misoprostol

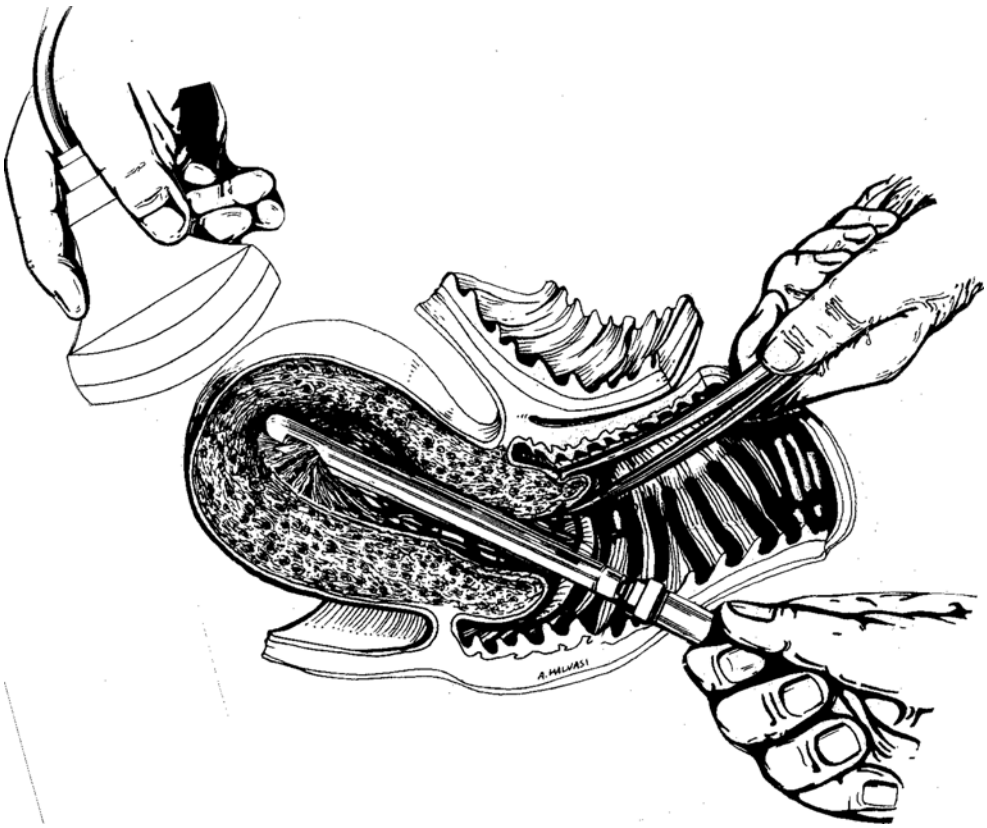


Fig. 2.35 Uterine cavity revision by Karman curette. Some operators prefer the Karman curette, as it is flexible, and my carry less risk of perforation, than a hard metal instrument

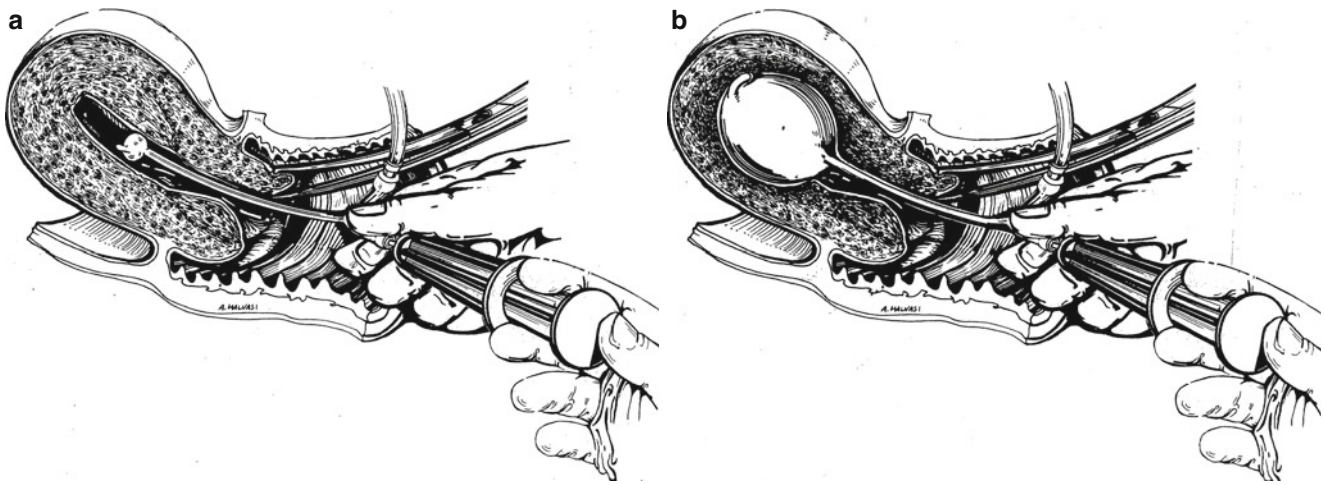


Fig. 2.36 Foley catheter insertion in the uterine cavity after uterine cavity suction (**a**) and balloon insufflation (**b**)

allows direct vision of Asherman syndrome (Fig. 2.3a, b) and of residual tissue and shows the plane of demarcation between the placental tissue and endometrium. A diathermy loop can then be used to excise the retained products of conception under direct vision (without using diathermy).

Subsequent pregnancy after Asherman syndrome is at a higher risk for spontaneous abortion, intrauterine growth restriction, preterm delivery, placenta previa or accreta, and even uterine rupture [36].

2.4.4 Rhesus (Rh) Alloimmunization

Rh-D-negative women who are pregnant with an Rh-D-positive fetus and who are exposed to fetal blood cells are at risk of developing anti-D antibodies. In a subsequent pregnancy, if the fetus is Rh-D positive, maternal antibodies may cross the placenta causing hydrops fetalis and hemolytic disease of the fetus and newborn (HDN). HDN can be associated with severe morbidity and mortality. Alloimmunization can be prevented

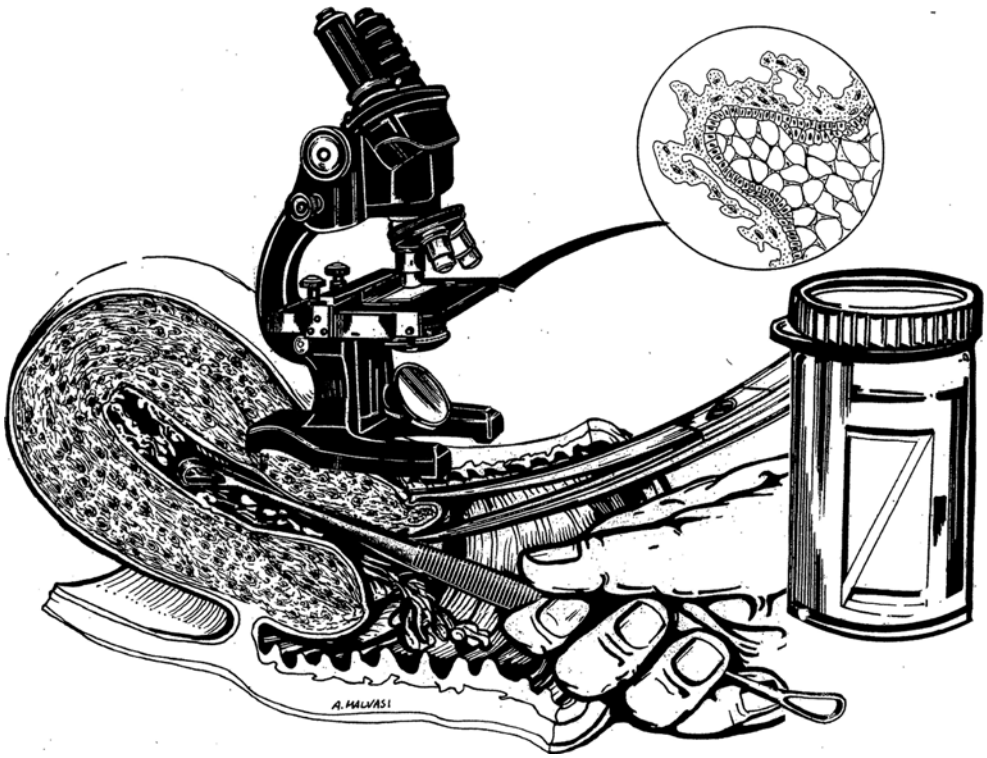


Fig. 2.37 Uterine cavity revision by curette in a patient with puerperal endometritis

by administration of anti-D immune globulin within 72 h of suspected maternal exposure to fetal blood cells. The Rh-D antigen has been detected in embryos from 38 days of gestation [40]. Spontaneous abortions are associated with a 1.5 % risk of alloimmunization. This risk rises up to 5 % if a D&C is required [41]. Because the red cell mass of the first-trimester fetus is small, the dose of anti-D administered can be adjusted, and 50 μg (microgram) is adequate for first-trimester abortions. Spontaneous or induced abortion in the second trimester onward requires the standard 300 μg dose [41].

2.4.5 Recurrent Miscarriage

Recurrent miscarriage is defined in North America as two or more miscarriages, but in Europe as three or more consecutive miscarriages. If the incidence of miscarriage is 15 % of all pregnancies, three losses would be expected to occur in 0.03 % of women. In fact the incidence of three consecutive miscarriages is 1 % [42], which suggests an underlying recurrent cause rather than a repetition of chance events. Additionally the cause of miscarriage is chromosomal rearrangements in approximately 60–70 % of cases (such as 16 trisomy, triploidy, monosomy X, etc.) [43]. There is at present no known cause of recurrent aneuploidy. However, recurrent aneuploidy is known to exist in approximately 15 % of women with recurrent miscarriage due to fetal aneuploidy [44, 45]. Hence there is little reason to consider recurrent miscarriage as a complication of spontaneous miscarriage.

2.4.6 Psychological Complications

The reaction to miscarriage varies greatly among different couples: some exhibit little or no reaction, whereas others show a significant decline in their coping ability [46, 47]. There may be feelings of emptiness and guilt, increased anxiety, and depressive symptoms [47, 48]. These depressive symptoms can include staying in bed and doing nothing, difficulty in performing daily tasks, and a feeling of a physical illness. One month after miscarriage, approximately half of the women are still depressed, and for some depression may persist up to half a year after the miscarriage [48].

Many couples experiencing a miscarriage undergo a process of grieving [46]. They mourn the lost child and their unaccomplished parenthood. Unfortunately, these couples do not generally receive social support, particularly if the miscarriage occurs before the couple share the news of the pregnancy. It is crucial to understand that even if the embryo was lost at a very early gestational week, many couples already regard their embryo as a baby, name or nickname him, talk to him, ascribe him with a specific personality, and imagine his future. However, the psychological consequences of pregnancy loss are usually reversible. While psychological treatment is not necessary for all women after miscarriage, an empathetic and respectful attitude of all medical teams is associated with better psychological experience and outcomes [49]. In some couples, however, psychological support may be helpful. Psychological support can take

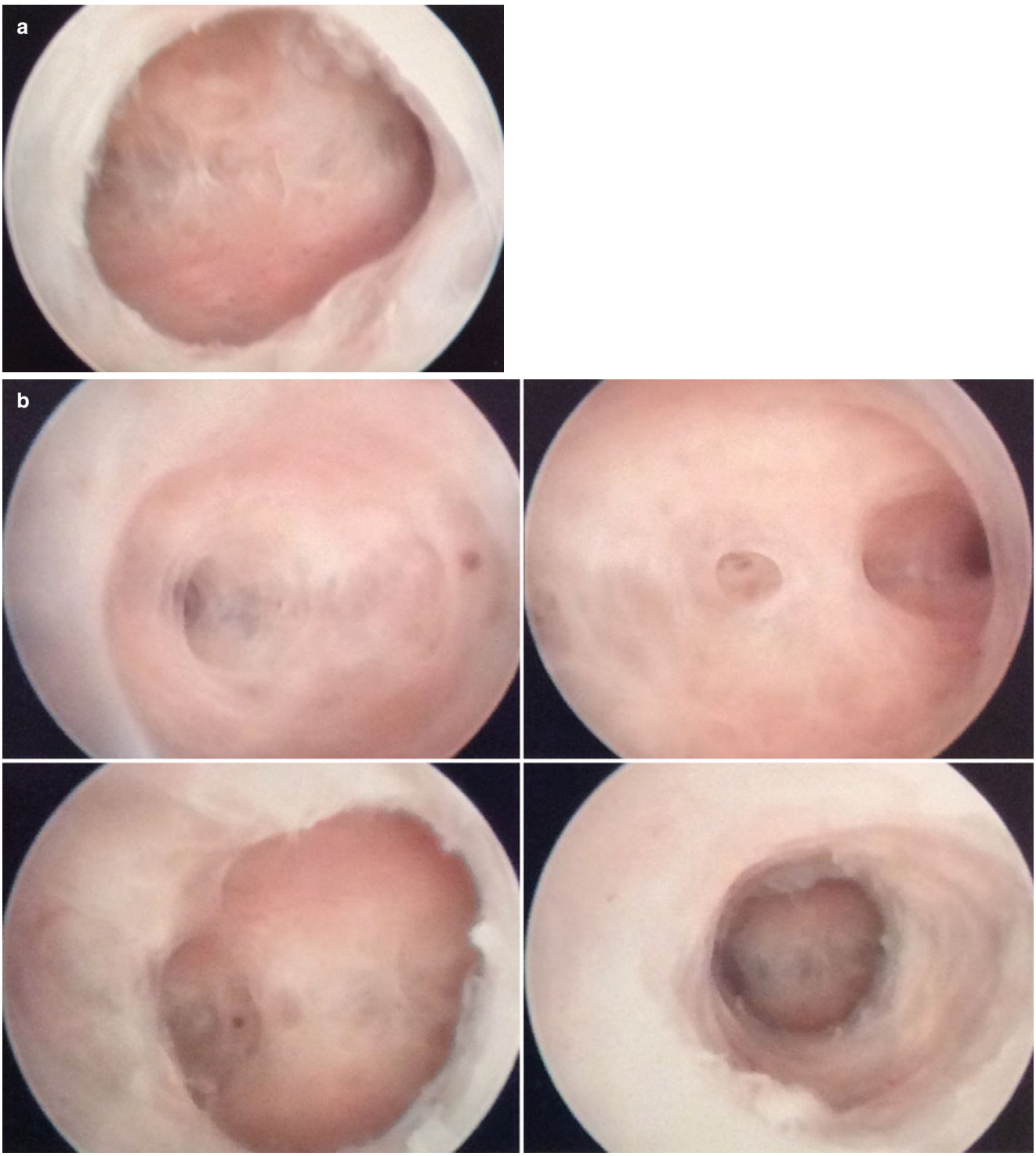


Fig. 2.38 (**a**, **b**) Typical hysteroscopic image of the uterine cavity with Asherman syndrome (**a**) and other four hysteroscopic images of Asherman syndrome (**b**)

numerous forms including group therapy, which allows couples to share their experience of pregnancy loss; educating couples about the grieving process, so that they understand that grieving is one of the normal coping mechanisms; and reducing anxiety with physical activity, art, meditation yoga, etc., all of which are not specific and are dependent on the patients particular interests and cognitive restructuring (Fig. 2.38).

Acknowledgment Text contributed by Abraham Tzur and Howard Carp. Illustrations contributed by Antonio Malvasi and Ughetta Vergari.

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Pathological Diagnosis of Abortions

3

Ezio Fulcheri, Maria Pia Brisigotti, and Leonardo Resta

3.1 Introduction

A miscarriage can be defined as a pregnancy that ends spontaneously before the foetus has reached a viable gestational age [26]. The term miscarriage is often utilised for both a clinical and a biochemical pregnancy loss. Clinical pregnancies are the ones that can be identified by ultrasound or histological evidence, while biochemical pregnancies occur earlier and can only be identified by a raised bHCG. In practice, the majority of biochemical pregnancy losses may go unnoticed. In fact, evidence suggests that the actual biochemical loss rate in the general population may even reach 60 % [3].

A miscarriage can be *sporadic* if there is only a single occurrence within the reproductive life of the woman, but if there are two miscarriages, it is *repeated*; however, if there are three or more, it is defined as *recurrent miscarriage* (or habitual) by most clinicians [10].

Though miscarriage is a rather common event, it is not easy to determine the true incidence due to impossibility of correctly evaluating signs and symptoms. Miscarriages, according to the *American College of Obstetricians and Gynecologists*, are the most frequent type of interruption of the pregnancy, reporting that miscarriages after artificial insemination are about 50 % of the total. The overall risk of miscarriage is estimated to be from 10 to 25 % and it increases with age. For women over age 35, the probability is 15 %, while from age 35–45 the risk is much higher being from 20 to 35 %. However, for women over age 45, the probability of a miscarriage reaches about 50 %. In the case of women who have already experienced a sporadic miscarriage, the probability of a second event is around 20 %, which in fact is not that much different from women who have not miscarried [20, 28]. If biochemical pregnancy loss were fully taken into consideration, the rate of spontaneous recurrent miscarriage would reach 20 %.

Miscarriage can be separated into early pregnancy loss (EPL) and late pregnancy loss (LPL) but not only because of when the miscarriage occurs but also because of its cause. EPL is defined as in the period from conception to the tenth conception week (12th gestation week) so including the blastogenesis and organogenesis phases and also the initial period of xenogenesis. From the 12th gestational week to the 22nd week, a miscarriage is classed as a LPL. In a late pregnancy loss, the cause is almost always to be found in some type of infection, while in early loss, for the majority of events, there is some structural alteration of the villi due to karyotype anomalies.

3.2 Histopathological Diagnostics of Early Pregnancy Loss

The histopathological diagnostics of EPL as part of the pathology of human reproduction has today become even more important than before because of the radical changes which have taken place in the last 30 years concerning the conditions leading to EPL. These can be defined as intrinsic (those pathological conditions of the mother and of the embryo/foetus and its placenta) and extrinsic (those environmental conditions from the artificial environment created by humans). Within intrinsic causes we find the mother's age, dyslipidaemias and autoimmunity while within extrinsic causes we can list increases in radiation, pollution, chemicals found in soils or in industrial processes

E. Fulcheri, MD, PhD (✉)
Division of Anatomic Pathology, Departement of Surgical and Diagnostic Science, University of Genoa, Genoa, Italy

UOSD Feto-perinatal Pathology, IRCCS Istituto Giannina Gaslini, University of Genoa, Largo G.Gaslini 5, Genoa 16147, Italy
e-mail: ezio.fulcheri@unige.it

M.P. Brisigotti, MD
Ph.D course in Paediatric Science, Fetal-Perinatal and Paediatric Pathology, University of Genoa, Genoa, Italy

UOSD Feto-perinatal Pathology, IRCCS Istituto Giannina Gaslini, Genova, Largo G.Gaslini 5, Genoa 16147, Italy

L. Resta, MD, PhD
Section of Pathological Anatomy, Department of Emergency and Organ Transplantation (DETO), University of Bari, Bari, Italy
e-mail: leonardo.resta@uniba.it

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_3

and of course medicinal drugs whether administered voluntarily or involuntarily as in adulterated or contaminated foodstuffs.

Today we must be even more aware of the anthropological and psychological aspects of miscarriage as a pregnancy is sought for and programmed and nonsuccess is not part of the programme, especially if this lack of success is repeated. The emotional impact can be damaging to the extent in which a person believes that disease and death can be beaten back and no longer accepts defeat. Every miscarriage must be seen as an event for grieving, an event which can undermine not only the psychological and behavioural equilibrium of the mother but also the equilibrium and future of the parents' relationship.

People look more and more to histopathological diagnostics to find more precise answers to the question of how much risk there is of a recurrence of the event in future pregnancies or if the mother has a latent pathology.

3.3 The Diagnostic Approach

The diagnostics of EPL cannot have the same criteria as those of "surgical pathology". The approach must be broad and open-minded with all the characteristics of a postmortem examination of an adult. Today the autopsy of the embryo requires all the aspects of a complex and multispecialist diagnostic approach. Only such an approach allows a global vision of the pathology of the pregnancy which includes the conditions of the mother and of the foetus, the normal or pathological conditions of the foetal adnexa, including the gestational sac and the placenta and the even more delicate relationships in the interactions with the decidua implantation site [9].

This all-round approach permits the making of diagnoses not only speculatively useful in the determination of the cause of the miscarriage (post hoc) but above all useful for the discovery of any possible latent maternal pathologies, parental genetic anomalies or even extrinsic natural/unnatural environmental conditions (human–nature relationship).

3.4 The Thanatology of the Embryo and Its Adnexa

Determining the time of arrest in the development of the embryo is extremely important not only for diagnosis but also for the clinical anamnestic aspects of the case management [35].

In the large majority of cases, the moment of arrest of development (the death of the embryo) is different to the moment of expulsion from the gestational sac or what remains of it.

This discrepancy is important to be able to correctly interpret the autolytic phenomena which have taken place in the embryo but more crucially in the amniochorial structures necessary for a correct differential diagnosis with morphological or structural anomalies as the cause of the miscarriage.

With this operational method, it is in fact possible to identify four major conditions:

1. The death of the embryo coincides with the moment of expulsion with there being the retention of the embryo after death and there being no suffering prior to death.
2. The death of the embryo coincides with the moment of expulsion; however, this is preceded by a prior state of suffering and late development.
3. After death there is a period of retention of varying length in the uterus before the expulsion of the embryo, without a prior state of suffering.
4. After death there is a period of retention of varying length in the uterus before the expulsion of the embryo; however, this is preceded by a prior state of suffering and late development.

3.5 The Morphological Definition of the Gestational Sac

The second most important diagnostic aspect is the morphological definition of the gestational sac. In the literature we find different classifications [22, 36], some of which are now historic, but it seems there is neither a universally accepted valid classification system nor one which reflects actual clinical needs.

It needs to be said that all the diagnostics of EPL are not an exercise in virtuosity for the pathologist but in fact an important tool in the management of the infertile parents and especially of the woman.

Many classification systems are based almost exclusively on the macroscopic aspects of the expelled material, but without knowledge of the diagnostic procedure, it is difficult for them to be validated. Before taking up this theme, a few words are needed on how the material is collected.

3.6 Procedure for the Collection of the Material

The aspects of the material that reaches the pathologist have been influenced by the situations outlined above and especially by the method of expulsion (spontaneous or pharmacologically induced or via suction or scraping).

In a miscarriage with spontaneous expulsion, a large quantity of blood clots is usually present and not infrequently

all of the uterine mucosa (decidua) detached in one piece. Such an event allows a complete examination of the gestational sac to be carried out together with a precise analysis of the implantation site. It must be remembered that the material could be from a second expulsion of the decidua and remaining parts of the chorial structure after a spontaneous miscarriage which is often unrecognised by the patient.

In a pharmacologically induced expulsion of the foetus through the use of prostaglandin, there will be much material complete of all structures. However, the alterations such as the oedema of the mucosa and the congestion of the blood vessels of the decidua are directly correlated with the effect of the drugs and they must not be considered in the report.

In a surgically induced evacuation of the products of conception, we must distinguish between the material obtained by suction and that obtained by scraping. In the first case, all the villous structures will be distorted and twisted, and the embryo, if developed beyond the 18th week, will necessarily be fragmented and lacerated. In the second case, the material will be characterised by a large quantity of blood clots and often the edges of the decidua will be lacerated and delaminated in a mix with the chorial tissue.

It is evident that any macroscopic classification of the gestational sac will initially be affected by the method of collection and by the thanatologic chronology.

The listed above procedures were stated by [8].

3.7 The Main Classifications

The main classifications for early pregnancy loss had the first of them originally defined in 1966 followed by others but without any of them ever having a significant impact on the diagnostics. A brief analysis of these will be useful before we propose a new classification system.

The Fujikura classification [7] is based on the integrity of the gestational sac, on the presence or absence of the embryo and on the characteristics of this, if it is amorphous, cylindrical or stunted; the completeness or incompleteness of the material which reaches the pathologist is emphasised together with the integrity or not of the gestational sac.

The Poland classification [24] concentrates on the examination of the embryo, completely ignoring the characteristics of the gestational sac; embryos are divided into three categories, stunted (dimensions between 1 and 4 mm), cylindrical (dimensions less than 10 mm) and if the embryo has a perfect correlation between the cranium-caudal length and the stage and if there are abnormal pathologies present in the embryo. Differently to Fujikura's scheme, the three types of embryo are defined based on both the macroscopic and microscopic aspects, including some parts of the details of Carnegie's classification [21] and part of the characteristics of the adnexa (yolk sac and amniotic sac).

Great weight is given to the gestational sac if it is found to be intact and empty.

Later, a classification by Mall condensed and simplified various features of Poland's classification. Rushton proposed a fourth classification [31] based principally on the morphological and histological aspects of the placenta. Three categories were identified, the first relative to the early phases of conception, the second to the presence of a macerated foetus and the third with a non-macerated foetus. The third category is primarily interested in late pregnancy loss, while the second focuses on the diagnostics of early pregnancy loss at the end of the phase of embryonal development.

3.8 Normal Histology of the Gestational Sac and the Embryonic Adnexa

Before talking about the histopathological picture of EPLs, it is necessary to define the important aspects of a normal histological picture.

The decidua is composed of the decidua basalis, the implantation site, the parietalis and the capsularis.

The *decidua basalis* is characterised (and recognisable) for the thick fibrinoid streak above it. It is composed of markedly modified stromal cells thanks to the effects of progesterone (physiological hyperprogesteronism). The cells have a pale cytoplasm slightly distant between themselves in a loose interstitial matrix. We find modified endometrial glands lined by a simple cuboidal epithelium, while the vessels have walls of irregular thickness, maintained by infrequent smooth muscle cells (IICH positive for smooth muscle actin) [2]. The wall, like the endometrial modified stroma (decidua cells), is infiltrated by a proliferation of extravillous intermediate trophoblasts (EVIT) which have a discretely enlarged roundish nucleus with an abundant eosinophilic cytoplasm. These elements (IICH – positive for CD 146 and CK 19) infiltrate the vessel walls substituting the normal constituents and not infrequently they are found in clumps inside the vessels [6, 17, 23].

Other EVIT colonise the decidua stroma arranging themselves in band-shaped clumps. In this situation it is not possible to find a tissue-type structure as the cells remain isolated and disaggregated like "flocks of birds".

There are also loci relatively limited by fibrinoid necroses of the endometrial stroma with an inflammatory infiltrate principally made up of lymphocytes. Such loci can be compared to the normal mechanism of expansion of the placenta bed and not infrequently they are characterised peripherally by a valley of ischaemic necrosis which involves both the stroma cells and the EVIT that colonised the sector.

The *decidua capsularis* lacks the fibrinoid streak while there is the presence of scattered villi, without a trophoblast layer and with unrecognisable vessels. The villous stroma

which makes up the majority of the structure is compact and slightly basophilic. The endometrial stroma is also compact with rare small vessels and sparse EVIT cells.

The *decidua parietalis* is sometimes the larger part of the abortive material. It is a thick endometrium, completely decidualised with dilated glands, lined with simple cuboidal epithelium, often separated. The endometrial vessels are modified, with normal or apparently thickened walls by a contraction of the smooth muscle cells. The endothelium is always integral and well preserved.

EVIT cells are few and sparse. Some elements have a hyperchromatic nucleus which is slightly irregular or pyknotic, a sign of a cell in functional exhaustion.

During the phase of what is known as the Arias Stella reaction, the endometrium is characterised by lushness and crowded secretory glands with a sinuous lumen which has a ragged profile, all due to the hyperprogesteronism, causing hyperplastic and secretory modifications of the glands further from the implantation site. The cells are enlarged with an abundant clear cytoplasm of the secretory type, and they jut out into the lumen in tufts. Atypical cytology is common enough to have a situation known as an atypical Arias Stella phenomenon.

The gestational sac gives us the chorionic plate with branching villi, the amniochorial membranes and the funiculus and very rarely the yolk sac.

The chorion has two distinct parts:

The *chorion laeve* is made up of a layer of fibrinoid and a chorionic plate from which short irregular shaped villi branch off, principally attributable to intermediate or prestem elements. The stroma of the villi is characterised by a considerable level of degeneration. The trophoblast lining is irregular if not completely absent. Commonly, especially in the weeks after the fifth week, the villi are walled inside the aforesaid fibrinoid layer. The decidua capsularis which lines the chorion laeve is thin, a modified stroma for the most part without glands but with a complete blood vessel network.

The *chorion frondosum* is made up for the most part of villi that will go on to create the chorionic plate; only from the 12° gestational week can we talk about a chorionic plate and therefore a placenta.

The villi are crowded but branch regularly and will eventually form the stem villi and the intermediate type. They exhibit a bilayer epithelium of cytotrophoblasts and syncytiotrophoblasts, the former being positive for the stain IIC with p63 while the latter being positive for HCG and PLAP. The villous stroma is a reticular fibrous network of cells with a small nucleus with interspaces in which Hofbauer cells are suspended, them being typical. Blood vessels are generally without walls, with a regular and slightly prominent endothelium (positive for IIC per CD 31).

At the superior part of the immature intermediate villi, we find buds of intermediate trophoblasts which are strongly positive for Ki67 e per CD 146 [11].

The *amniochorial membranes* are difficult to identify as the free membranes are strongly influenced by the presence of *chorion laeve* in which numerous chorial villi still remain, while the membranes which line the *chorion frondosum* are not yet well anchored to the villous part which will later go on to form the chorionic plate as an integral part of the completed placenta structure. Therefore, in the expelled material, we can find ribbons of amniotic epithelia sustained by homogeneous sub-amniotic connective tissue which is lightly coloured. The amniotic epithelium is simple, cylindrical and cuboidal.

The *funiculus* is distinguishable only from Carnegie stage ten. Prior to this we find the body stalk in which we can find two arteries and a vein. Occasionally there are reports of a second vein in involution or parts of a vessel in the Wharton jelly.

Remains of the allantois and the ductus omphaloentericus are very rarely found because they are not still functionally active.

The *yolk sac* is the part of the embryo adnexa which is the most important in the diagnostics of early pregnancy loss. Responsible for the production of red blood cells, it has a honeycomb structure that is an anastomosed network with small sacs and lacunae wherein we find the immature elements of erythropoietic production (foetal erythroblasts). The foetal erythroblasts are released together with the mature erythrocytes in a percentage which varies from week to week. The major peak is at the seventh gestational week (fifth conception week, Carnegie stage 13) which sees the progressive expansion of the amniotic sac inside the chorionic sac with the initial fusion of the two elements. At the eighth gestational week, the nucleated erythrocytes are 75 % of the total erythrocytes in circulation; this percentage goes down to 50 % at the ninth week, 20 % at the tenth week and 10 % at the 11th week. In the placenta, in its definite form at the 12th week, nucleated erythrocytes are only 1 % of the total population.

3.9 Interpretative Errors: Main Pitfalls to Avoid on Normal Examples

For the decidua:

1. The normal inflammatory reaction around the loci of necrobiosis, which is one of the mechanisms of growth for the chorionic plate, must not be interpreted as villitis.
2. The vessels of the decidua parietalis must not be evaluated to establish their normality or pathological modification.

For the chorial structures:

1. The folds of the sub-amnion chorionic layer (future chorionic plate on the foetal side) must not be seen as large hydropic villi or as stromal cisterns.
2. The main stem villi of loose stroma must not be seen as oedematous.
3. The villi retained in the uterus, due to the collapse of the vascular structures owing to lack of embryonic circulation, must not be seen as villi without vascularisation.

3.9.1 The Embryo

For a morphological description of the embryo, see the classification of the Carnegie Institute of Embryology [21].

3.10 The Type of Material

Before taking up the argument of the diagnostics of EPL, it is necessary to draw a conclusion on what has been said so far.

3.11 Criteria and Diagnostic Elements

The famous classifications utilised for the definition of miscarriage essentially refer to a macroscopic evaluation of the expelled tissues.

In the case of massive expulsion of the integral gestational sac complete with the endometrial layer, we are in the ideal conditions to carry out a detailed assessment of all the components of the mother–embryo complex. Only in this case can we diagnose a "blighted ovum", an early arrest of the development of the embryo, anomalies of development and formation of the embryo and more generally all the conditions of the large and complex chapter of embryo pathology.

In the case of expulsion with lacerations of the gestational sac (as in the case of haemorrhage of a prior pregnancy loss or in the case of a cleaning out of the cavity), the material is not really representative of all the constituents and even less representative of the embryo or what remains of it due to autolytic activity. The absence of the embryo does not permit a complete diagnosis to be carried out.

The histopathological diagnostics is therefore based on expelled material or that collected from scraping in a very altered and fragmented condition from which it is often difficult to identify the topographical anatomical relationships of individual components, and so the reconstruction of the histo-architecture of the various tissues becomes difficult.

All the anatomic parts making up the mother–embryo complex, even if fragmented, incomplete and mixed together, are essential to define the adequacy or not of the material; in the absence of one or more parts, the diagnosis will necessarily be only partial and incomplete, less comprehensive or even only approximate [8].

This distinction must be kept to the forefront whenever one speaks of diagnostic criteria and must of course be mentioned in the diagnostic report.

3.12 The Classification of the Principal Histopathological Features

A basic classification of the principal histopathologic categories identifies eight principal groups of lesions.

3.12.1 Histo-architectural Alterations Indicative of Karyotype Anomalies

This category is the most important in miscarriages in the first trimester of gestation [16, 29, 34].

3.12.1.1 Clinical Findings

The incidence of major chromosomopathy in miscarriage varies between 40 and 60 %. The distribution of said anomalies sees in the first place autosomal trisomies (52 % approx.) followed by 19 % of a missing X chromosome (45,X0), 22 % of polyploidy (of which 16 % is triploidy), 7 % of structural aberrations and 8 % of mosaicism or autosomal monosomy. The clinical meaning of the chromosomic aberrations of number is only relative in that there is a low recurrence in successive pregnancies. There are however families with a significant recurrence of aneuploidy: in these cases the genetic mechanisms are suspect, but they are difficult to evaluate clinically as they are such as disjunction defects and germinal mosaicism. Fifty percent of the structural aberrations are inherited from a parent carrier of balanced structural rearrangement. In couples with recurrent miscarriage, the prevalence of a parent carrier of balanced structural rearrangement (reciprocal and robertsonian translocations, inversion) is estimated to be at about 5 % with a direct and apparently significant proportionality between the number of miscarriages and the frequency of parental chromosome rearrangements. The constant progress in molecular genetics can open a new chapter in aetiopathogeneses of miscarriage, particularly in recurrent miscarriage. We still do not have definite data, but mechanisms such as uniparental disomy, genomic imprinting, monogenic anomalies and the alterations of random X chromosome inactivation will probably assume an important role in the aetiopathogenetic definition of a still unexplained quota of recurrent unsuccessful pregnancies.

3.12.1.2 Principal Macroscopic Morphological Characteristics

Usually there is abundant material, with the chorionic component being predominant and formed of oedematous villous structures which give a swollen aspect to the tissue. Readily identifiable pale and translucent villous groups can be seen; however, this cannot be used diagnostically as it is well known that in some karyotype anomalies, villi are fibrotic, thin and compact.

Consideration must be given to the extraction method because in the case of suction, the macroscopic chorionic component is severely altered, but with little change to the decidua.

3.12.1.3 Principal Microscopic Morphological Characteristics

Chorionic villi have an irregular pattern of growth and branching, characteristically having large and swollen alternating with smaller villi (Figs. 3.1 and 3.2). There is no unique pattern, there being an extreme variety of shapes including some that seem bizarre and others that seem more shapeless but with deep indentations. The trophoblastic layer loses its regular linearity of the two types of trophoblasts though not in a circumferential way but from a focal point and so presents a hyperplasia of the trophoblast even with macro-nucleated forms or with vacuoles in the cytoplasm. Some hyperplastic aspects, with high-eosinophil cytoplasm cells, are ascribable to the intermediate villous trophoblast. The stroma is loose, with reduced cellularity, or frankly oedematous with small aggregates of cells of a histiocytic macrophagic nature. Degenerative phenomena consist mainly of basophil degeneration and of the mineralisation of the basal membrane of the trophoblast covering.

Characteristic and pathognomonic are the inclusion of trophoblasts (determined by the intersection of a cut line with a deep invagination) (Fig. 3.3). The vessels are irregularly distributed and it is difficult to recognise the affluent vascular structure within the main branches of the villi, precursors of the stem villi. Some of the villi are hypovascularised or with an extremely irregular or reduced vascularisation (differential diagnosis in a complete mole). If

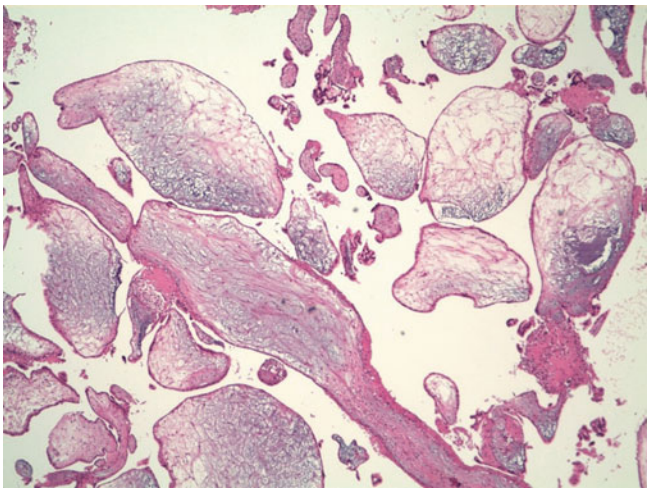

Fig. 3.2 Chorionic villi in an abortive pregnancy with anomalous karyotype of the embryo. The stroma is oedematous and shows a basophilic degeneration. Small collapsed vessels are evident in the sub-trophoblastic area. The trophoblast shows a minimal and focal hyperplasia: this aspect is different from the circumferential proliferation present in the hydatidiform mole

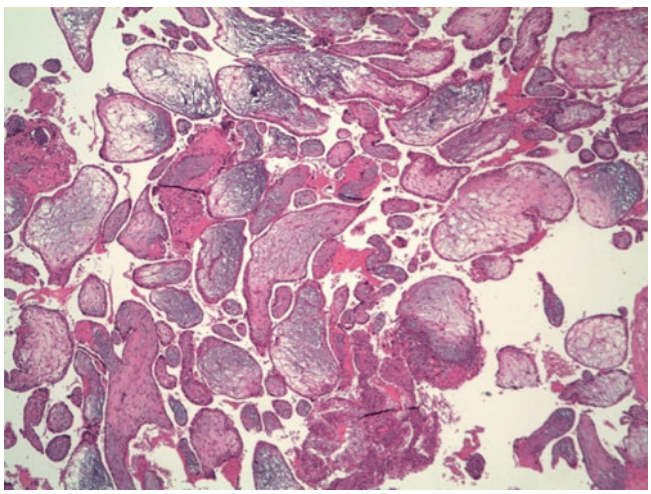

Fig. 3.1 Picture of a group of crowded chorionic villi with evident histo-architectural alterations. The villar profile is irregular. Bizarre forms and different size of villi are present. A small amount of fibrinoid may be observed in the intervillar space. These characteristics are referred to a genetic disease of the embryo

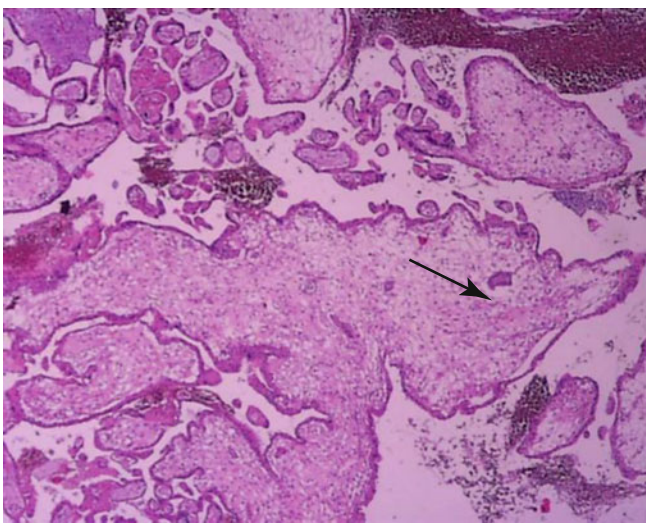

Fig. 3.3 In this particularly we observe a scalloped villus with marked irregularity of the profile and pseudo-inclusion of the syncytio-trophoblast (*arrows*)

present, the erythrocytes in circulation do not correspond to the gestational period (ratio between erythroblasts and erythrocytes).

3.12.1.4 Differential Diagnosis

The most basic differential diagnosis is the hydropic abortus in which the proliferative aspects of the trophoblast are missing and above all there is the irregular profile of the villi with fiord-like indentations. However, the main differential diagnosis is that of molar degeneration, both total (hydatidiform) and partial (triploidy) [4, 5].

3.12.2 Infarcted Haemorrhagic Lesions Responsible for the Separation of the Gestational Sac

3.12.2.1 Clinical Findings

This category of miscarriage includes numerous pathologies such as diabetes, gestational and essential hypertension and even genetic factors which seem to play an important role (genes Stox1, COMT and CORIN). These pathologies can have diverse symptoms and have a varying impact on the pregnancy. From recent studies, smoking also has an important role in this problem.

3.12.2.2 Principal Macroscopic Morphological Characteristics

The material contains a large quantity of blood and blood clots either recent or stratified with fibrin; often the chorionic villi are bathed in clotted blood and the decidua material, which has a wine-red colour and is more abundant than the chorionic material. The quantity and the characteristics of the blood clots vary depending on whether the material comes from a complete and sudden separation of the gestational sac or from a separation in steps over time.

3.12.2.3 Principal Microscopic Morphological Characteristics

The main histological alterations affect the decidua. In the decidua basalis, we find haemorrhages (Fig. 3.4) which are recent or mixed over time accompanied by thrombi of the decidua lacunae or of the modified spiral arteries. In some cases, it is possible to see the breakage of the vessel walls with haemorrhagic apoplectic type expansion which disassociates the cells from the cytogen stroma.

A second characteristic element is the haemorrhagic flooding of the inert glandular structure. There is also an accompanying inflammatory infiltrate which is more marked when there have been a series of haemorrhagic events over time before the final event of the complete separation. In this case we observe (a) blood clotting or fresh thrombi alternating with reabsorbed clotting which leave traces in the histiocytic

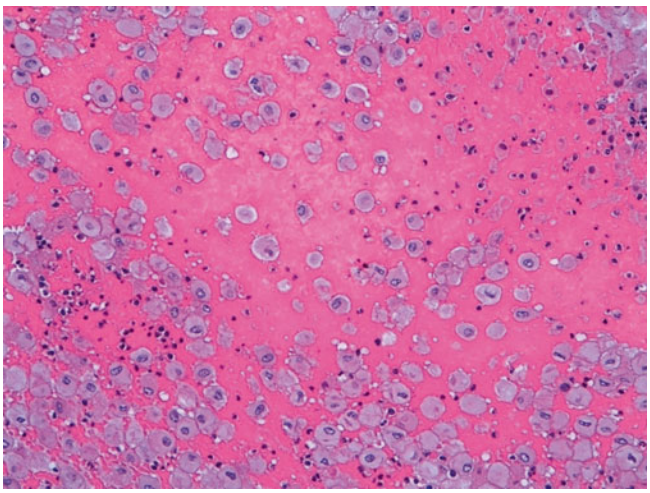

Fig. 3.4 Decidua with recent haemorrhages

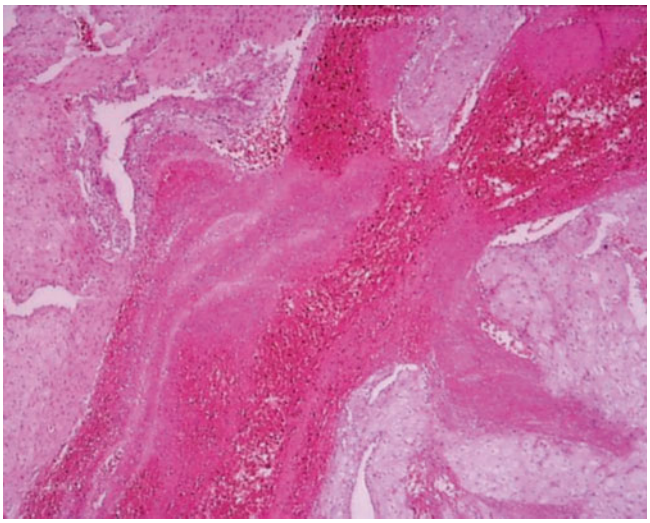

Fig. 3.5 Case of miscarriage due to abruption of the ovular sac. The picture shows in the decidua a large haemorrhagic focus, partially organised, for several repetitive and more serious events

haemosiderophagic elements (Fig. 3.5) and (b) recent thrombi alternating with completely organised thrombi (Fig. 3.6).

In the decidua parietalis, we find interstitial oedema and haemorrhagic vessel outflows. The decidua vessels far from the implantation site can be normal or have thickened walls because of hyperplasia of the smooth muscle cells or for hyalinosis of the media. The complete separation of the gestational sac can be due to varying causes including maternal circulatory pathologies such as thrombophilia and all of the maternal hypertensive states. This can determine both a haemorrhage behind the plate with successive miscarriage and a state of hypoxic hypo-perfusive suffering which provokes villous lesions due to the hypoxia or even ischaemic infarction.

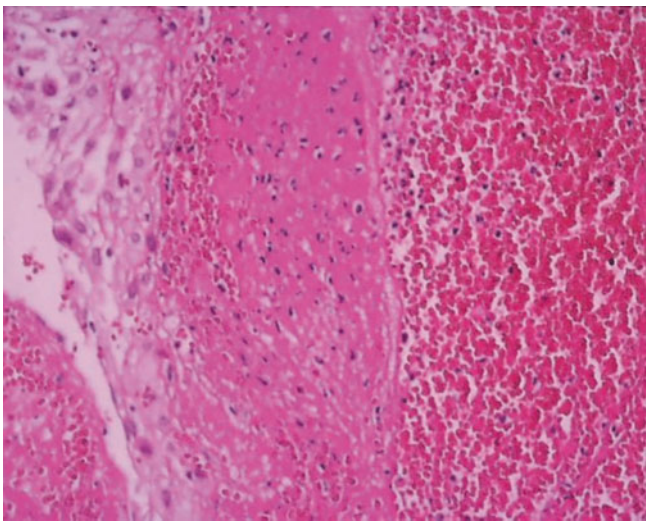

Fig. 3.6 Decidual haemorrhage with a partially organised thrombus and reactive inflammatory infiltrate. The pattern is characteristics of the subacute and repetitive haemorrhagic events. A differential diagnosis with several types of maternal thrombophilia or coagulative disorders is necessary

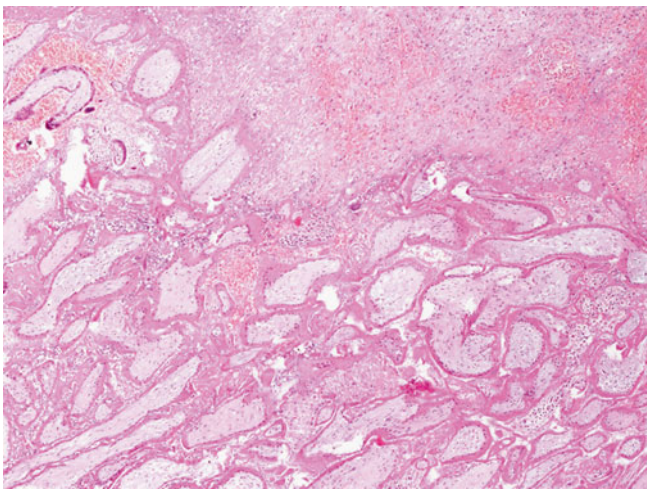

Fig. 3.7 Old ischaemic infarctual lesion characterised by collapsed villi, with interposition of a minimal amount of fibrinoid material, is present in a decidual sheet. A necrotic and haemorrhagic band with a reactive inflammatory infiltrate is interposed between the lesion and the endometrium

The chorial components include more or less normal villi in the case of massive recent separation or, depending on the type and on the chronology of the haemorrhagic events, three main alterations. In case of a recent massive membrane separation, the villi are normal. A recent but not massive separation shows swollen oedematous villi, while in cases with a series of partial separations which have been long time, we find villi with fibrotic stroma with a slight hyperplasia of the syncytiotrophoblast even in syncytial knot shapes. These findings are consequent to the hypo-perfusive state determined in the chorionic plate by the disconnection between the chorionic structure and the maternal vascular bed caused by the interposition of the clots. In these conditions there is an increase in the intervillous fibrin with moderate inflammatory lymphoplasmacellular infiltrate.

3.12.2.4 Differential Diagnosis

The differential diagnosis comes from the haemorrhage consequent to the endometritis or to the vasculitis of whatever origin or aetiology, considering that the relationship between haemorrhage and inflammation is always a consequence and rarely they do manifest themselves in isolation or in a pure form.

3.12.3 Decidua Vascular Lesions or Primitive Maternal Systemic Lesions Responsible for Hypo-perfusion and Hypo-oxygenation of the Chorionic Plate

Such conditions form in a maternal pre-existing hypertensive state, of maternal degenerative vasculopathies, especially atheromatous, or from smoking. Particular attention should be given to smoking as a cause of increased risk to vascular pathologies especially in young women and those with a genetic predisposition to heart problems [15, 27]. The damage to placental vessels is antecedent to the pregnancy and to the fertilisation.

3.12.3.1 Principal Macroscopic Morphological Characteristics

As the concluding event of the miscarriage is usually a haemorrhage with separation of the gestational sac, the macroscopic view is not much different from that of decidua haemorrhage. In this case the villous component is normally present and the villi appear thin and often compacted in clumps of fibrin.

3.12.3.2 Principal Microscopic Morphological Characteristics

In the decidua basalis we find recent haemorrhages cause a terminal separation of the gestational sac (Fig. 3.7); the decidua arteries appear normally modified by the proliferation of extravillous intermediate trophoblasts with a loss of the smooth muscle component of the walls. In the most striking cases, we can find a vascular dilation with fibrinoid deposits in the intima. There is also a minimum infiltration of foamy histiocytes [12] accompanied by rare lymphocytes which dissect the sub-intimal portion of the vessels among the remains of the rare smooth muscle cells. The decidualisation of the endometrial stroma appears normal as is the proliferation of the extravillous intermediate trophoblasts.

For the decidua parietalis, the most relevant finding is the already reported hyperplasia and hypertrophy of the tunica

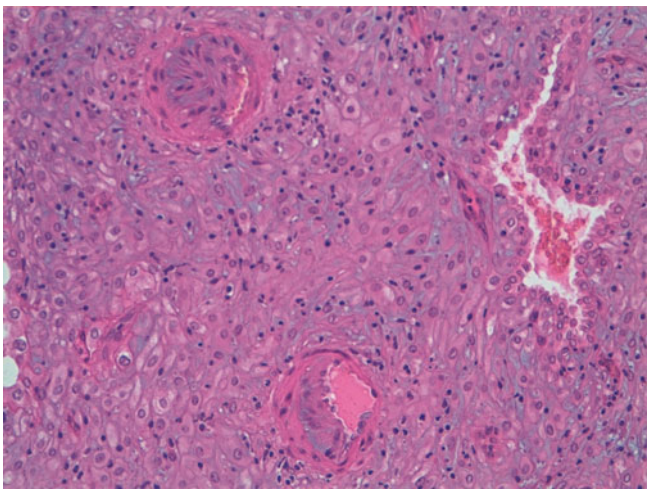

Fig. 3.8 Histological picture of a fragment of decidua parietalis in which the spiral arteries are not modified by the trophoblast, as in the normal pregnancy. The arterial lumen is reduced and/or obliterated by a cell proliferation in the intima and the sclerosis of the media layer. This aspect is typical of the endometrial arteriopathies correlated with the maternal older age, hypertension or smoking abuse

media accompanied by a reactive thickening of the intima itself (Fig. 3.8). The lumen is restricted if not virtual while the thickening by both a hyperplasia of the smooth muscle cells and a fibro-sclerosis of the wall itself.

The most characteristic lesions are from the chorionic component. The villi appear hyper-mature and hyper-branched, having stem villi (normally present in the third trimester) that are completely out of sync even if the miscarriage takes place slightly later (9–10 weeks). The villi have buds and syncytial knots while the stromal support has a lightly diffused fibrosis. The excessive branching is supported by a proliferation of capillaries and pre-capillaries which are dilated especially in the peripheral parts.

In the case of a hypoxic ischaemic suffering which persists in the embryo or in the case of arrested development or a protracted retention, the vessels appear in a collapsed state with a virtual lumen. Usually the circulating foetal erythrocytes in the ratio of erythroblasts/erythrocytes are not congruent with the gestational time.

3.12.3.3 Differential Diagnosis

The differential diagnosis is found in all the defects of superficial implantation either due to an inadequate proliferation of extravillous intermediate trophoblasts or due to inadequate and insufficient implantation because of an incomplete decidualisation of the endometrium mainly caused by luteal deficits. The histology is complicated and complex and involves the decidua basalis which presents arteries at the implantation site which are unmodified or only a little modified, or there is a scarce decidualisation of the stromal cells in which elements of the endometrial stroma can still be seen.

At the chorionic level, the villi are thin, little branched, far apart and with a fibrous stroma. The only element common to the damage by hypo-perfusion is found in the presence of the syncytial knots, in the terminal parts of the villi and along the length of the stem villi.

3.12.4 Histo-architectural Alterations Indicative of Inadequate and Insufficient Implantation

These conditions include:

(a) Luteal deficit with inadequate decidualisation of the endometrial stroma, both of the decidua parietalis and, above all, of the decidua basalis [25]
(b) Inadequate proliferation of the extravillous trophoblast and therefore lack of expansion of the interface maternal chorionic area that is the implantation site with a consequential inadequate modification of the wall with the spiral arteries

3.12.4.1 Clinical Findings

A lutein insufficiency, otherwise known as corpus luteum deficiency, is a defect found in 4–5 % of women with unexplainable infertility or recurrent miscarriage. They often suffer from problems with the rhythm of the menstrual cycle with a shorter progestin phase.

3.12.4.2 Principal Macroscopic Morphological Characteristics

There are no particular macroscopic aspects. There is an average quantity of material, haemorrhagic in part due to the separation or how the material was obtained.

3.12.4.3 Principal Microscopic Morphological Characteristics

As was said in the introduction, there are two distinct situations: the first mainly due to a maternal alteration (luteal phase defect) and the second mainly due to an alteration in the gestational sac.

(a) The decidua basalis is found with an endometrial stroma little modified by the action of progesterone and small cells similar to the morphology of the non-decidual stroma alternate with large cells with abundant clear cytoplasm. The inert glandular structures present an epithelium which is still relatively expansive, and there is a hint of branching. The spiral arteries open into the lacunae but a muscle wall persists which is resistant to the aggression of the extravillous intermediate tropho-

blasts. Loci of necrobiosis with an inflammatory reaction are few and far between in the expansion phase of the chorionic bed. The fibrinous streak is present though thinner. Even the extravillous intermediate trophoblast is almost lacking, misaligned and irregularly distributed in the little modified decidua stroma. The decidua parietalis presents analogous characteristics even more accented by the lack of trophoblastic proliferation at the implantation site. The alterations to the villi are principally fibrous villi hypo-branching from the stromal support axis and hypo-vascularisation. Syncytial buds are common as are false syncytial buds created by a focal hyperplasia of cytotrophoblast. There is little intervillous fibrin and the degenerative hydropic phenomenon of the villi is almost absent.

(b) While the histopathological characteristics are the same as what we described above, the main differences are to be found in the decidua basalis. The only differential element is the scarceness of the accumulated clumps of villous intermediate trophoblasts from the invasive villi. The decidua basalis is characterised by a normal decidualisation of the stroma, by a normal involution of the glandular component and by a moderate interstitial oedema. The main differences are found in the vessels (spiral arteries) (Fig. 3.9) which are little modified by the extravillous intermediate trophoblast and the muscle wall persisting with uniform circumferential smooth muscle cells (Fig. 3.10), while only peripherally they do seem to have been invaded by elements of the extravillous intermediate trophoblast that anyway are not able to reach the lumen and substitute the endothelium lining of the intima (Fig. 3.11). The extravillous intermediate trophoblast in the stroma appears disorganised without the traditional columns for deep invasion.

3.12.4.4 Differential Diagnosis

The differential diagnosis does not treat the different situations which cause the miscarriage but treat the two different categories described in this paragraph or the hypo-perfusion states described previously (Figs. 3.12 and 3.13). What is essential is the evaluation of the vascular wall by immunohistochemical staining with antibody anti-smooth muscle

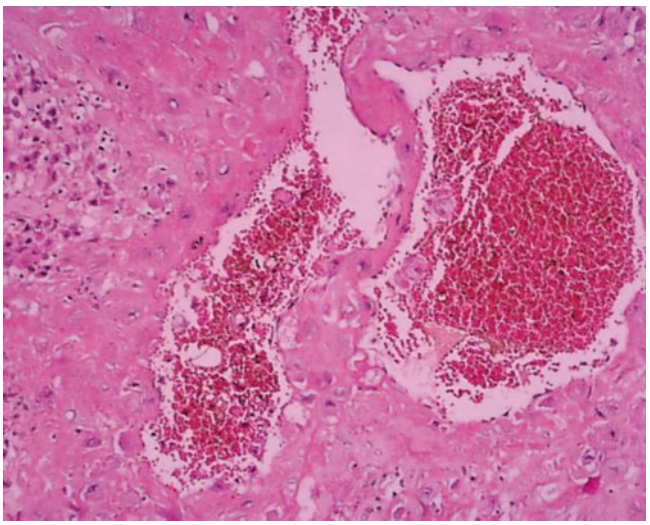

Fig. 3.9 Picture of the implantation site with partially modified spiral arteries. The presence of the extravillous intermediate trophoblast is low and the endovascular infiltration lacks. This pattern is present either in cases of luteal defect or in cases of primary deficiency of the extravillous trophoblast

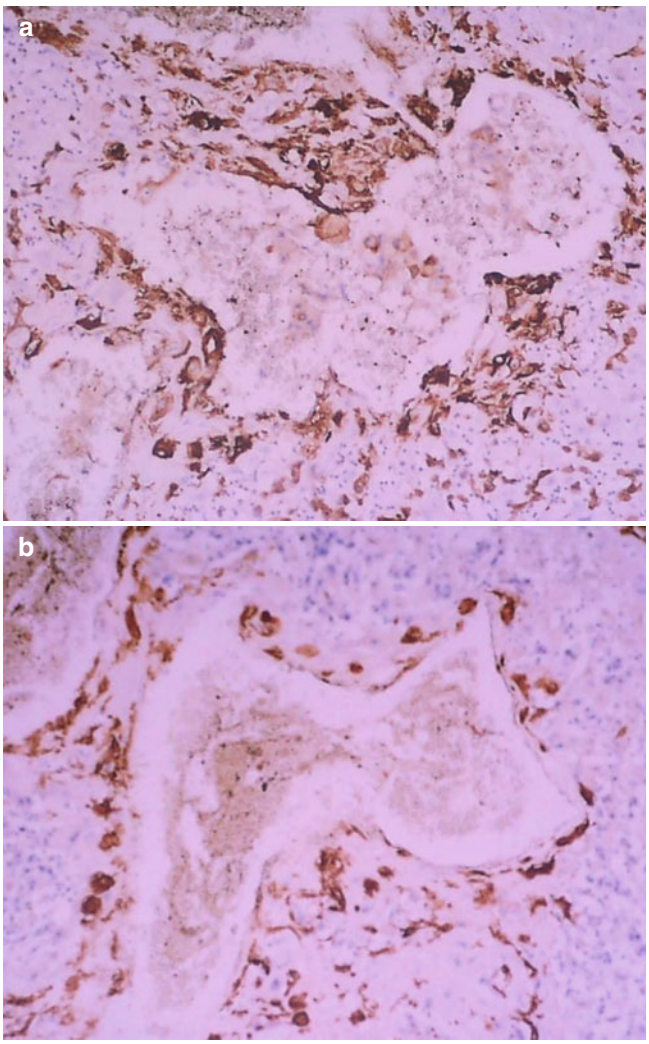

Fig. 3.10 Case of the decidua with partially modified spiral arteries: (**a**) the immunohistochemical reaction for the cytokeratin 18 witnesses the low presence of the extravillous intermediate trophoblast; (**b**) the persistence of smooth muscle cells in the spiral arteries is demonstrated by immunohistochemical reaction for smooth muscle actin

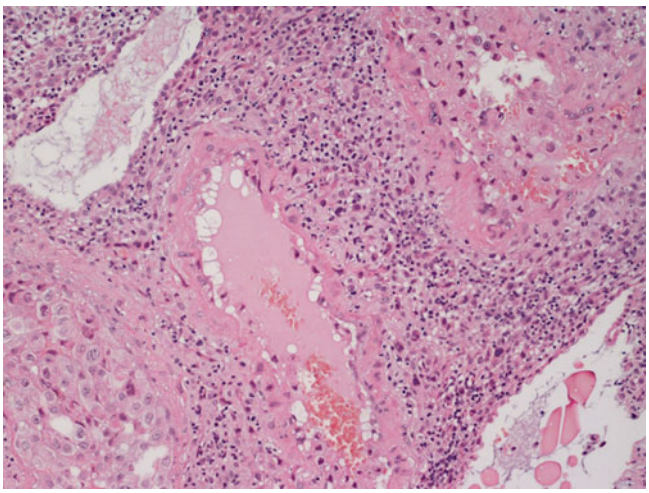

Fig. 3.11 High magnification of endometrial vessels in the decidua basalis, with a permanent muscular wall. The picture has to be differentiated from a miscarriage due to an endometritis, in which an important inflammatory infiltrate is present around the arteries and well modified by the intermediate extravillous trophoblast

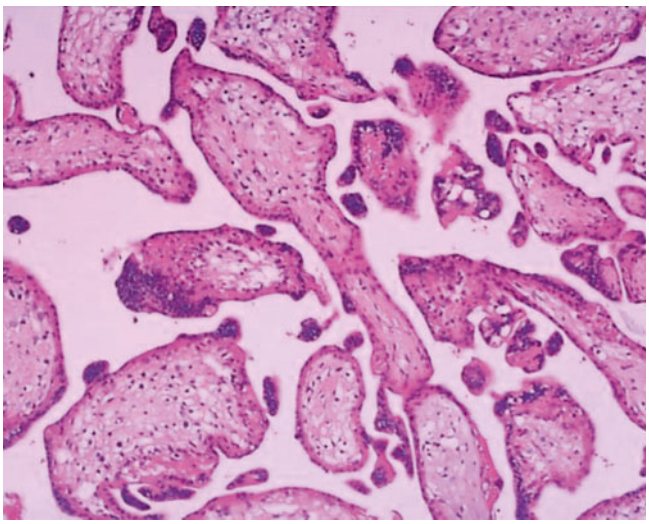

Fig. 3.12 Miscarriage for insufficient and inadequate implantation. The villi are hypo-branching with syncytial knots

actin and desmin and by typing the extravillous intermediate trophoblast with antibody anti-CD 146.

The defect in trophoblast proliferation can also be correlated with a misreactive state or autoimmunity of the mother that in fact reduces the growth and organisation of the trophoblasts especially that part destined to invade and modify the maternal vessel network. Each form of misreactivity is able to interfere in the relationship between maternal immunology and foetal immunology, modifying their interactions and the subsequent morphological expression of their interface.

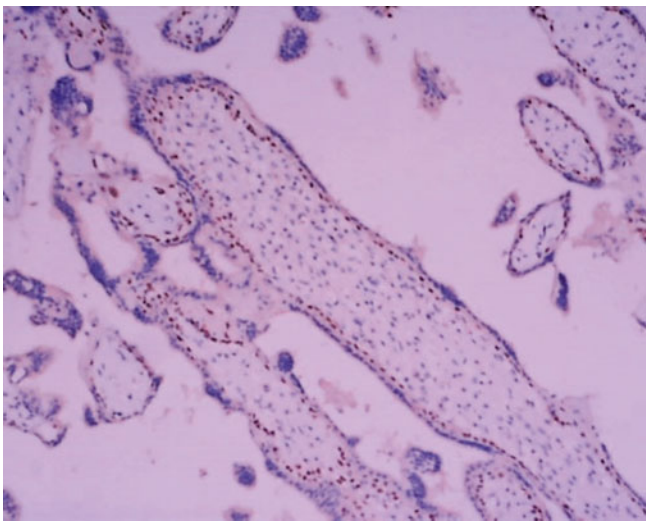

Fig. 3.13 Miscarriage for insufficient and inadequate implantation. The villi are hypo- branching with syncytial knots. The figure shows a thin and elongated villus in which the immunohistochemical reaction for p63 demonstrates the regular presence of cytotrophoblast cells. The regularity of the cytotrophoblast layer excludes an anomalous karyotype and witnesses a regular even if hypo-perfusion inhibited development of the villi

We must remember that a raw defect in the proliferation of the extravillous trophoblast causes damage exclusively to the gestational sac. This situation opens an important chapter linked to the intrinsic characteristics of the embryo and of its own pathologies. The examination of the embryo will not be dealt with here as embryo pathology deserves a chapter to itself.

3.12.5 Infective States

3.12.5.1 Clinical Findings

These situations are extremely serious and devastating and so it is often very difficult to identify the pathogen. Microbiology and virology can lead to a sure aetiologic diagnosis. However, a precise diagnosis of the pathogen involved is not very useful in a context of the pathology of reproduction and rarely is it identified.

The signs and symptoms of miscarriages caused by infections are properly those of the infection (shivering, fever, septicaemia, peritonitis) and of the threat of miscarriage or incomplete miscarriage. There is a leucocytosis (WBC 16,000–22,000/ml). Those severely ill patients can show signs of septic or endotoxin shock with vasomotor collapse, hypothermia, oliguria or anuria and respiratory failure. The causes include *Escherichia coli*, *Enterobacter aerogenes*, *Streptococcus haemolyticus*, staphylococci and some anaerobic microorganisms like *Clostridium perfringens*. If the sepsis is due to *C. perfringens*, an intravascular haemolysis is possible.

3.12.5.2 Principal Macroscopic Morphological Characteristics

Material is abundant and the decidua material is pale and spongy, while the chorionic component is normal or swollen.

3.12.5.3 Principal Microscopic Morphological Characteristics

These can be divided into two principal categories:

(a) Acute inflammation: with a large quantity of lymphocytes and granulocytes, mainly neutrophils, both in the decidua basalis and decidua parietalis. In the decidua parietalis, the absence of modifications in the implantation permits seeing the evident inflammatory infiltrate which is often distributed in large areas in the endometrial stroma (Fig. 3.14).

In these cases, the decidual vessels (spiral arteries and lacunar vessels) are spared (Fig. 3.15).

The villi present normal branching and a normal trophoblast but can suffer serious reactive alterations such as oedema of the stroma or basophil degeneration. Inflammatory infiltrates to the chorionic structures are few while intervillous fibrinoid deposits are absent or nearly absent.

(b) Chronic or persistent inflammation: an often only moderate inflammatory state which involves the decidua basalis, the decidua parietalis and the villous structures. The first two are often involved in an inflammatory lymphoplasmacellular process which affects the decidual arterioles.

The villi are normally shaped, often with a hint of stromal fibrosis and sometimes a slight hyperplasia of the trophoblast.

The principal morphological characteristics of some specific infections are:

1. In CMV, clumps of abundant cytoplasm eosinophilic cells with a hyperchromatic nucleus are found mixed with cellular detritus and micro-deposits of fibrinoid and lysed erythrocytes. The loci are found in an eccentric position on the outermost part of the surface of the villi.
2. In the case of parvovirus or herpes villitis, what's distinctive is the low level of the inflammatory reaction and the presence of typical cytopathic effects evident in the stroma cells. The cells contain large round hyperchromatic nuclei in the case of parvovirus while in a HSV infection, we find the typical syncytial elements.
3. In the case of bacterial infections, a special mention must be given to *Listeria*. On the amnion that is on the inside of the membrane, and more rarely on the villi, small clumps of bacteria can be observed which are strongly stained by haematoxylin.

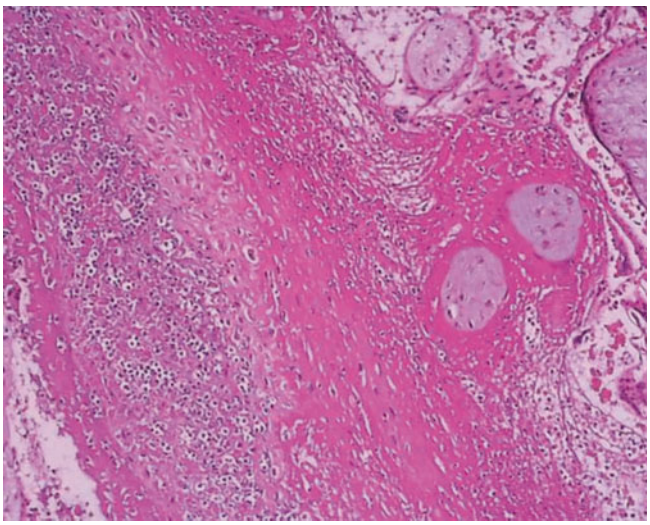

Fig. 3.14 Miscarriage due to a diffuse endometritis. The decidua capsularis is largely infiltrated by lymphocytes, plasma cells and granulocytes

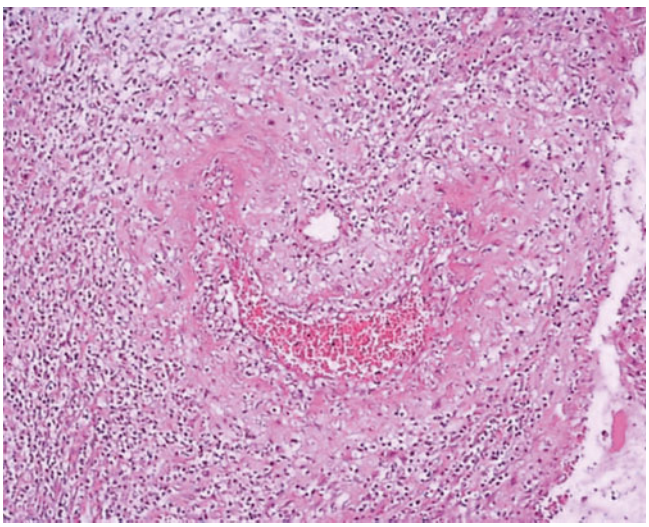

Fig. 3.15 Miscarriage due to a diffuse endometritis particularly of the decidua basalis with a diffuse and perivascular inflammatory infiltration. Note the regular modifications of the spiral artery in the site of implantation

There is a separate chapter for chronic histiocytic intervillites. The main histological findings are from the chorionic components where there are very close villi with interposed thin filaments of fibrin-containing histiocytes in their network, and these histiocytes have an abundant cytoplasm that is well stained by immunohistochemical anti-CD 68. Chronic histiocytic intervillositis (CHI or CHIV) has recently been isolated from the plate infections also in nonspecific forms to be collocated in the chapter on maternal misreactive states (Fig. 3.16). There is more and more evidence emerging showing its correlation with recurrent miscarriage.

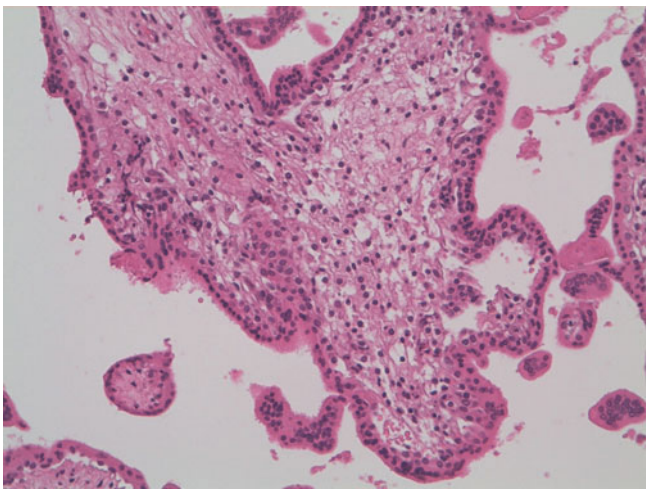

Fig. 3.16 Miscarriage due to a persistent villitis. The villi show an inflammatory infiltration of the stroma and a mild hyperplasia of the trophoblast

3.12.5.4 Differential Diagnosis

The differential diagnosis is the exaggerated inflammatory and necrobiotic reaction at the implantation site that is at times particularly marked and characterised by scarce necrotic tissue. In this case the material from the decidua parietalis is spared by the inflammatory infiltrate.

Particular attention must be paid to those low-level non-specific inflammatory states that can easily be present in miscarriages long believed to be either reactive to structural alterations or dystrophic in the chorionic components.

3.12.6 Autoimmune Disorders

Pregnancy in itself is a pro-inflammatory state and produces a protracted hypercoagulatory state [13, 30] and so can activate a latent immunitary defect or modulate an already known autoimmune disease. The most common acquired thrombophilia [1] in cases of recurrent miscarriage that needs to be considered is antiphospholipid syndrome (APS). The diagnosis of APS requires at least one of the clinical criteria and one of the laboratory criteria. Laboratory criteria must be positive on two or more occasions, at least 12 weeks apart. In a large meta-study on couples with RM, the incidence of APS was 15–20 % compared to 5 % in nonpregnant women without a history of obstetric complications. In particular, the antiphospholipids (aPL) are being intensively researched as the mechanisms leading to miscarriage are not well known. Though aPLs are associated with thrombosis, these events cannot explain all the aPL-related miscarriages. There is in vitro evidence of a direct link between aPLs on the trophoblast which provokes a reduction in cell proliferation, in the release of human chorionic gonadotropin, in the invasiveness of the trophoblasts and in the expression of adhesion molecules. It also induces an increase in apoptosis. The damage caused by the aPL seems to be mediated by the beta2 glycoprotein I (ß2GPI) which acts as a cofactor in the bonding of circulating antibodies. An ulterior effect of the bonding of the anti-ß2GPI antibodies is given by the induction of a pro-inflammatory phenotype at the level of decidua, so fostering the activation of the complement and the local secretion of pro-inflammatory cytokines/chemokines [14].

The autoimmune state of the mother can play an important role in miscarriages of the first trimester. Even if we still cannot define a correlation with the individual autoimmune diseases, their effects are sufficiently clear to permit their inclusion in a nosographic work. In this way the doctor can examine such problems and at the same time avoid wasting time and energy in exploring all the possible causes of the miscarriage. For this reason, each and every diagnostic effort must be made with the aim of characterising the condition. It is worth repeating that the expulsion event is often only the result of a pre-existing disease condition that had determined the failure of the pregnancy and more that sudden dramatic events like endometritis or acute villitis can establish themselves more easily in a compromised autoimmune mother. Finally, even in the case of the identification of the cause of the miscarriage which seems unrelated to the autoimmune field, for example, a structural anomaly in the villi or an alteration in karyotype, it is still necessary to be able to exclude a coexisting autoimmune disorder which could again provoke other future miscarriages.

3.12.6.1 Principal Macroscopic Morphological Characteristics

There are no particular macroscopic aspects. There is an average quantity of material, haemorrhagic in part due to the separation or how the material was obtained.

3.12.6.2 Principal Microscopic Morphological Characteristics [18, 32, 33]

The basal layer of the endometrium appears normally decidualised and the spiral arteries are also normally modified while the proliferation of the extravillous trophoblast is only moderate. We find inflammatory infiltrates characteristically in loci and even more so in the decidua parietalis where small aggregates of lymphocytes crowd the non-modified vessel walls (Figs. 3.17 and 3.18). Some arterioles present thickened intima with hyperplasia of the endothelium and this finding is relatively more evident in the states of transition from decidua basalis to decidua parietalis where you can find larger calibre vessels not yet modified by trophoblastic proliferation. In the chorionic plate, abundant fibrinoid deposits englobe small groups of villi or individual villi (Fig. 3.19). There is also a slight inflammatory infiltrate in the stroma of the villi, while the

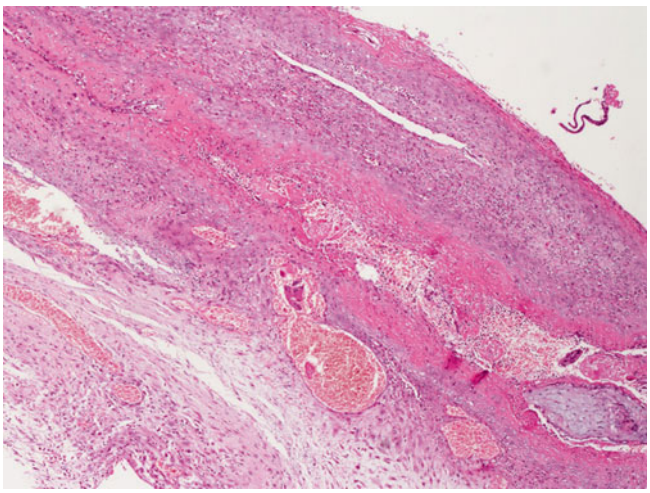

Fig. 3.17 Miscarriage due to a maternal autoimmune pathology. The decidua shows partially modified spiral arteries and focal inflammatory infiltration. In the borderline between the decidua basalis and parietalis, some more large vessels are not still modified by the trophoblast proliferation. The pattern is very complex with ambiguous findings: the lesions of an inadequate implantation (low or inadequate modification of the arterial wall) are prevalent. On the other hand, the inflammatory reaction and the lesions of the vessel intima suggest a disreactive maternal disease which could be the reason of all the described modifications

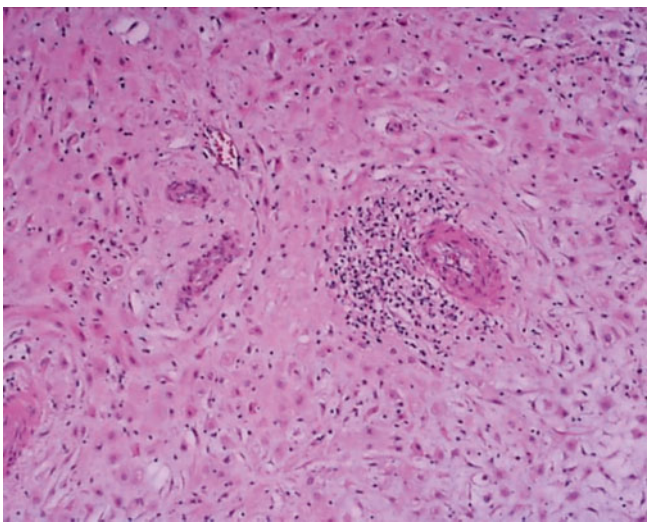

Fig. 3.18 Miscarriage due to an autoimmune maternal disease. The small arteries of the decidua parietalis are characterised by a thick intimal layer and some perivascular aggregation of inflammatory infiltrate. The endometrial stroma is very oedematous

characteristic histo-architecture of all the chorionic villi is particularly normal components. Only the major vascular branches of the amnio-chorionic network can show alterations in the intima with hyperplasia and endothelium proliferation determining a sub-stenosis of the lumen or a complete vascular occlusion actioned by recent or organised parietal microthrombi.

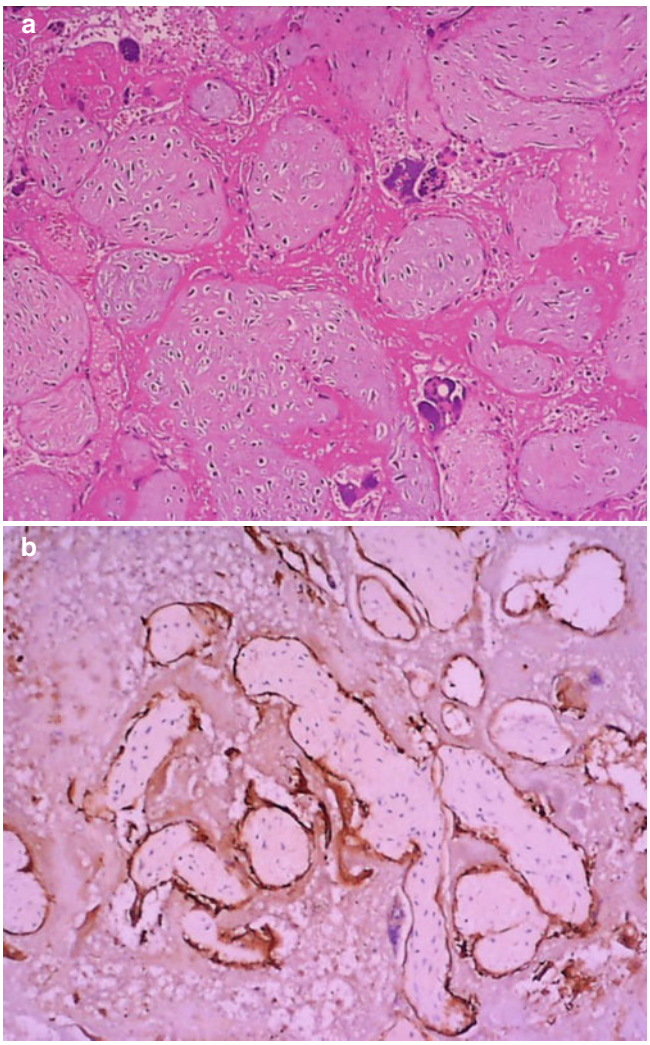

Fig. 3.19 (**a**) Miscarriage due to an autoimmune maternal disease. In the chorionic disc, a large amount of fibrinoid circumscribes the villi (the s. c. fibrinoid pseudo-infarcts). The trophoblast aggregates and small calcifications are present. (**b**) Another field of the same case: the picture shows the villi embedded in the fibrinoid material. The immunohistochemical reaction for ck 18 (expressed by the trophoblast) designs the villar contour

3.12.6.3 Differential Diagnosis

The differential diagnosis is the inadequate and insufficient implantations that coexist and are mixed with the misreactive and autoimmune states of the mother and which not infrequently are the effect of the latter. We should always remember that the extravillous trophoblast proliferation is orthologic and efficient only when guaranteed by a normal reactive maternal immune system.

3.12.7 Pathology of the Embryonic Adnexa

The pathology of the adnexa is principally that of the yolk sac (Fig. 3.20) [19].

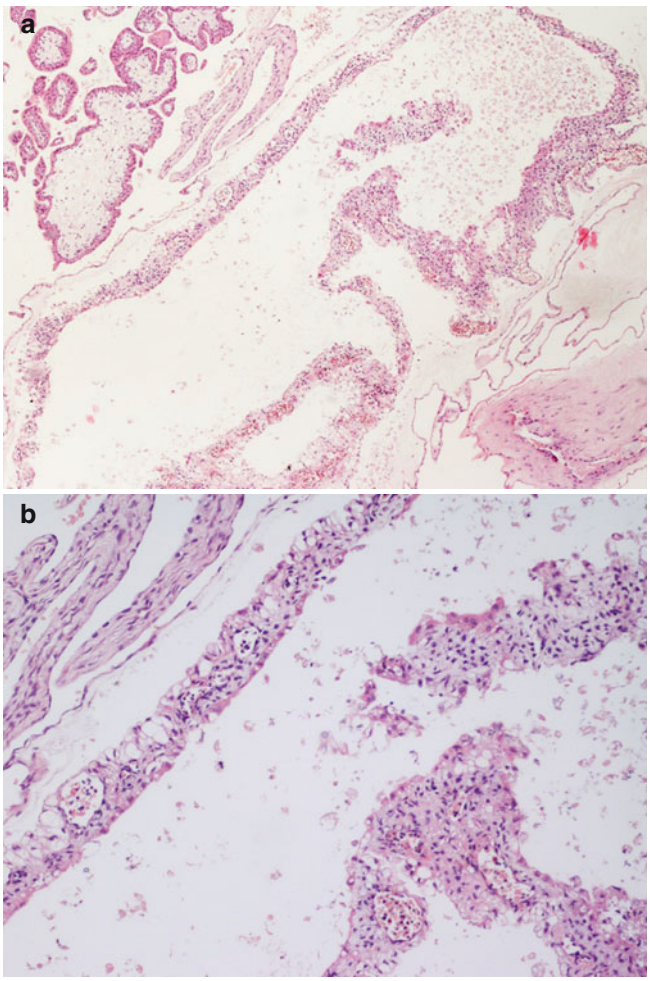

Fig. 3.20 (**a**) Yolk sac. In this figure the characteristic structure of the yolk sac (organ of the primary haemopoiesis) is evident. Its wall is thick for the presence of a rich network of sacs and lacunae, often lacking of red blood cells. Note in the *top left* some normal villi and in the *bottom right* a sheet of amniotic membrane. (**b**) Yolk sac. A particular area of the structure of the yolk sac with an evidence of the network of lacunae and sacs in which the immature haemopoietic cells are evident. A minimal inflammatory infiltrate and signs of fibrosis evoke an initial involution of this foetal organ

In the embryonic period between the Carnegie stages 13–22, early involutions of the umbilical vesicle can occur so causing a reduction in erythropoiesis that is critical for the embryo. The involutions are normally determined by moderate and subclinical inflammatory states which are insufficient to provoke an immediate miscarriage.

The opposite situation is created when for pathological reasons of the embryo or mostly for genetic anomalies, there is an early arrest in development of the embryo and only the umbilical vesicle remains. This can occur between the Carnegie stages four to ten (period of blastogenesis, second/third conception week). For a long time, this was confused with a blighted ovum and only a meticulous examination technique of an integral and closed gestational sac permits an incisive differential diagnosis. With the yolk sac remaining, the presence of the embryo is indirectly documented even if there is an early arrest in development.

3.12.8 Pathology of the Embryo

Leaving aside the classifications of Poland, Mall and Rushton that refer only to the macroscopic aspects of the embryo after being deformed by the autolytic processes with its retention in the uterus, this is not the place to embark on an analysis of the pathologies of the embryo which should be treated exhaustively and comprehensively in another place. Embryo and foetal pathology is a study which requires high levels of competence and above all good technique and diagnostic methodologies. Therefore, to fulfil the obligations of the present work, we define the following diagnostic categories as basic and important:

(a) Whether the embryo is present.
(b) If the embryo has been altered by post-death autolytic phenomena consequent to a protracted retention in the uterus.
(c) If the embryo is recognisable as normally developed for its gestation time. The application of the classification criteria of the Carnegie Institute is sufficient to define the embryo's development stage without entering into any analysis or description of anomalies, malformations or pathological lesions.

3.13 Closing Considerations

The pathologist's activities are more and more important in the diagnosis of miscarriage and abortion and also in the field of infertility to which it is often linked. Socio-anthropological change in recent decades has changed the characteristics of the female population, and we are also seeing significant ethnic changes in both urban and rural areas. The most obvious changes in procreation are the increasing age of women when deciding to become a mother and the decision to have only one child at a determined time, while the new immigrants have desires and needs both in maternity and fertility which are different to the local population of today and of yesterday.

Evidently, a general diagnostic formulation carried out on abortive material is no longer sufficient, but it is also evident that a timely and correct diagnosis can be made only in optimal conditions and with the support of cytogenetic examinations and clinic-anamnestic information.

Therefore, taking into account the abovementioned conditions and the fact that in the case of an occasional miscarriage there is no possibility of gathering all the information necessary, we are led to consider the problem from another viewpoint.

There are four different situations:

1. A first miscarriage in a patient with a blank patient history, and in this case we know only the date of the last menstruation and few other data for the pathologist.
2. A first miscarriage in a patient in treatment for infertility or another maternal pathology, and in this case the clinical data should be rich and full.
3. A recurrent miscarriage, and in this case also the clinical data should be rich and full.
4. In a case of a recurrent miscarriage, the revision and reformulation of the diagnosis on previous abortive material could be made as this material is often available within the same clinic or perhaps another, though unfortunately this is not always possible as material from the first miscarriage is not always sent to the pathologist.

It remains to ask, with the whys and wherefores of these situations, what can be the minimum or maximum diagnostic level and the most correct type of finding. A diagnosis which is certain, exhaustive and complete is rare as is almost as rare a diagnosis with a high probability of being correct as can be seen from the reviews available. Then there are the diagnoses which are indicative and which have a high value in the delicate fields of infertility and recurrent miscarriages. In no field except this one does the indicative diagnosis become so important in the anatomo-clinical dialogue and in consultations on the pathologies of human reproduction. There remain the diagnoses of exclusion which are still very useful in evaluating the problems of recurrent miscarriage.

In following this scale of diagnostic complexity, the ability to interpret the signs of the gestational sac and of the membranes is paramount, but first it is necessary to exactly establish the adequateness of the material to study in the histological examination:

(a) Is the ovum–decidua material complete and integral?
(b) Is the ovum–decidua material complete and fragmented?
(c) Is the ovum–decidua material incomplete (that is only from the endometrium or only from the gestational sac)? In this case the diagnosis can only refer and be limited to the material under examination. For example, a miscarriage with a massive expulsion of the endometrium can occur without the gestational sac which was expelled previously without the woman being aware of it. A diagnosis of "massive separation" of the gestational sac in fact indicates only the mode of expulsion and the cause is not determined.

The basic difference between cause and effect must be clear in the generic diagnostic definition of separation of the gestational sac. In fact, the separation that always follows any type of abortion can in some cases be its own cause, as *abruptio placentae*, while in other cases it is the normal consequence of a defunct gestational sac.

In conclusion it is worthwhile to summarise and underline the most important aspects.

- Anatomo-clinical integrated diagnostics with the histological examination of the abortive product is a determining moment in the management of spontaneous miscarriage in the first trimester whether it is sporadic or recurrent.
- Missing the diagnostic moment makes it impossible to treat not only the woman but also, in the widest sense, the couple.
- In a spontaneous miscarriage, as in all diagnostic activities in infertility of the couple, current or retrospective investigation on recovered biological material is significant for the health of the mother, becoming a real tool in preventive medicine for those diseases present at the start of the pregnancy (diabetes and hypertension) though latent or not recognised by the woman.
- The reduction to the minimum or the abolition of anatomo-pathologic diagnostic activity has been transformed into an exorbitant increase in costs for nonspecific examinations that could be avoided instead of specific focused investigations.

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Tubal Pregnancy

4

Jun Kumakiri, Rie Ozaki, Satoru Takeda, Antonio Malvasi, and Andrea Tinelli

4.1 Introduction

Ectopic pregnancy is defined as a pregnancy in which the fertilized ovum is implanted outside the endometrial cavity. Ectopic pregnancy is one of the leading causes of maternal death during the first trimester of pregnancy, and it is related to 10 % of all maternal deaths [1]. However, in recent years, since the development of high-resolution ultrasonography and the availability of techniques for the rapid measurement of serum human chorionic gonadotropin (hCG) concentrations has improved early detection of tubal pregnancy, ectopic pregnancy-related deaths have decreased. Most (93–98 %) ectopic pregnancies are located within the fallopian tube (Fig. 4.1). Of these, 13 % are isthmic, 75 % ampullary, and 12 % fimbrial [2]. Major risk factors of tubal pregnancy include previous chlamydia infection, adnexal adhesions owing to previous surgery, and smoking. In addition, ectopic pregnancy including tubal pregnancy has increased because of the recent technical progress and prevalence of artificial reproductive technology.

Some investigators postulate that the etiology is likely to be a combination of impaired embryo-tubal transport and alterations in the tubal environment allowing early implantation [3]. While the characteristics of ectopic pregnancy in humans are well known, they are not yet understood in animals. Because tubal pregnancy does not occur in laboratory, domestic, or farm animals but is limited to primates, no animal model of the condition exists [4]. Several factors related to ovum implantation are reported as being different between humans and animals. For example, it was suggested that a mechanism in rabbits that prevents oviductal implantation is lacking in human fallopian tubes [5].

Ectopic pregnancy is potentially life threatening. If the fallopian tube ruptures before the woman is diagnosed and treated, massive intra-abdominal hemorrhage can occur (Fig. 4.2), leading to death. We summarize here the clinical presentation, diagnosis, and surgical and medical treatments of ectopic pregnancy.

4.2 Epidemiology

Ectopic pregnancy has increased in recent decades, with the rate of diagnosis increasing sixfold between 1970 and 1992 in the United States [6–9], although it seemed to be stabilizing in the late 1990s [10]. The reason for this increase is the increased prevalence of risk factors of ectopic pregnancy. For example, sexually transmitted disease, mainly chlamydia infection, has been spreading worldwide.

J. Kumakiri, MD, PhD (✉) • R. Ozaki, MD • S. Takeda, MD
Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
e-mail: junkumakiri@gmail.com; rieozaki@juntendo.ac.jp; staked@juntendo.ac.jp

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_4

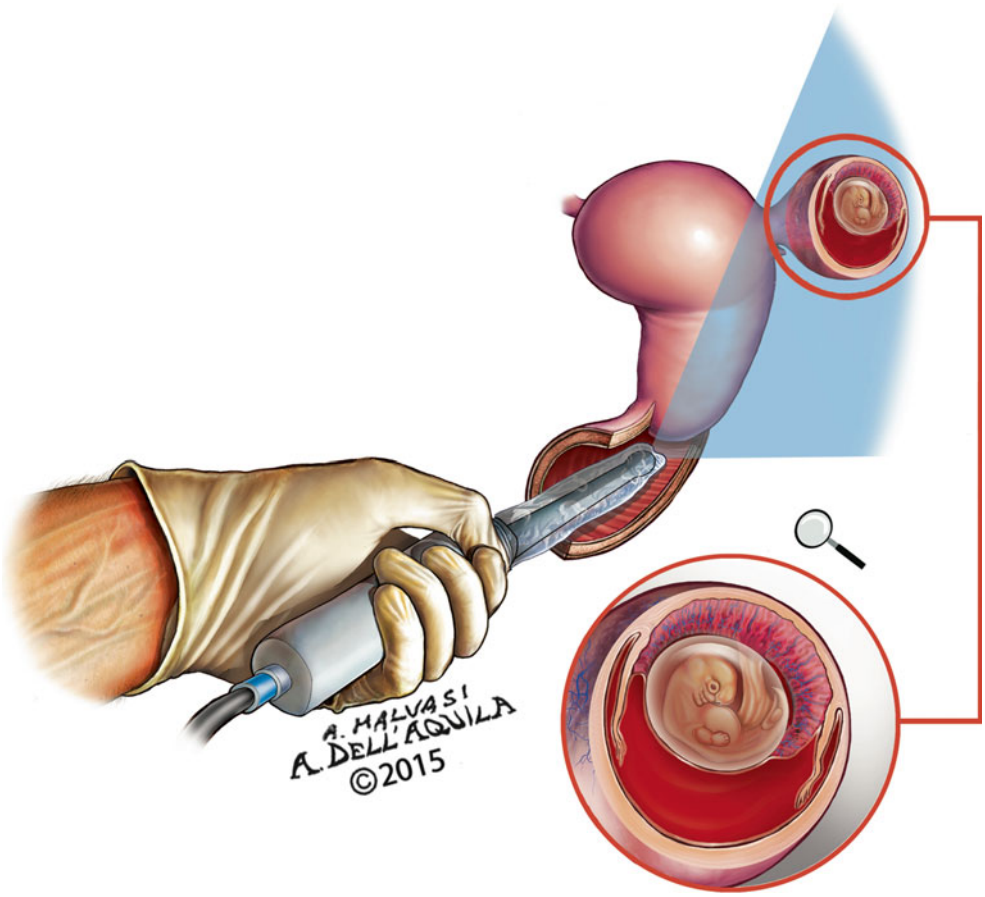


Fig. 4.1 A transvaginal pelvic ultrasonographic scanning of a left tubal pregnancy

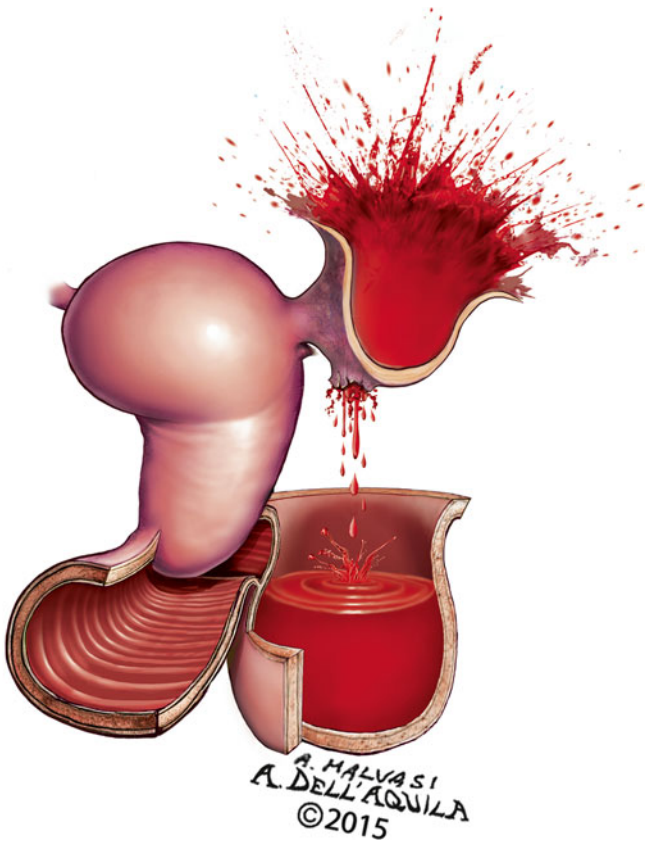


Fig. 4.2 The image represents a fallopian tube rupture with a massive hemorrhage collecting in the Douglas pouch

The increasing prevalence of assisted reproductive technology also accounts for some of the increase in ectopic pregnancies. Epidemiologic data vary depending on the country studied. Approximately 2 % of all pregnancies in Europe and the United States are ectopic [1, 11]. Investigators have reported annual ectopic pregnancy rates of 20.70 per 1000 reported pregnancies and 1.03 per 1000 women aged 15–44 years [11]. The incidence of ectopic pregnancy in the United Kingdom was reported as 11.1 per 1000 pregnancies [7], which is similar to that in other countries, including Norway (14.9 per 1000) [12] and Australia (16.2 per 1000) in 1994 [13], while that in California was 11.2 per 1000 pregnancies during 1991–2000 [14]. The data from 1991 to 1999 in the United States estimated an ectopic pregnancy mortality rate of 31.9 per 100,000 ectopic pregnancies [15]. However, the mortality rate of ectopic pregnancy has decreased annually. In the United States, 876 deaths in the United States were attributed to ectopic pregnancy between 1980 and 2007. The mortality rate decreased from 1.15 to 0.50 deaths per 100,000 live births between 1980–1984 and 2003–2007 [16]. In addition, during 2003–2007, the mortality rate was 6.8 times higher for African Americans than for whites and 3.5 times higher for women older than 35 years than for those younger than 25 years. The majority of ectopic pregnancies occur in the fallopian tube, with 40–80 % of these occurring in the ampulla,

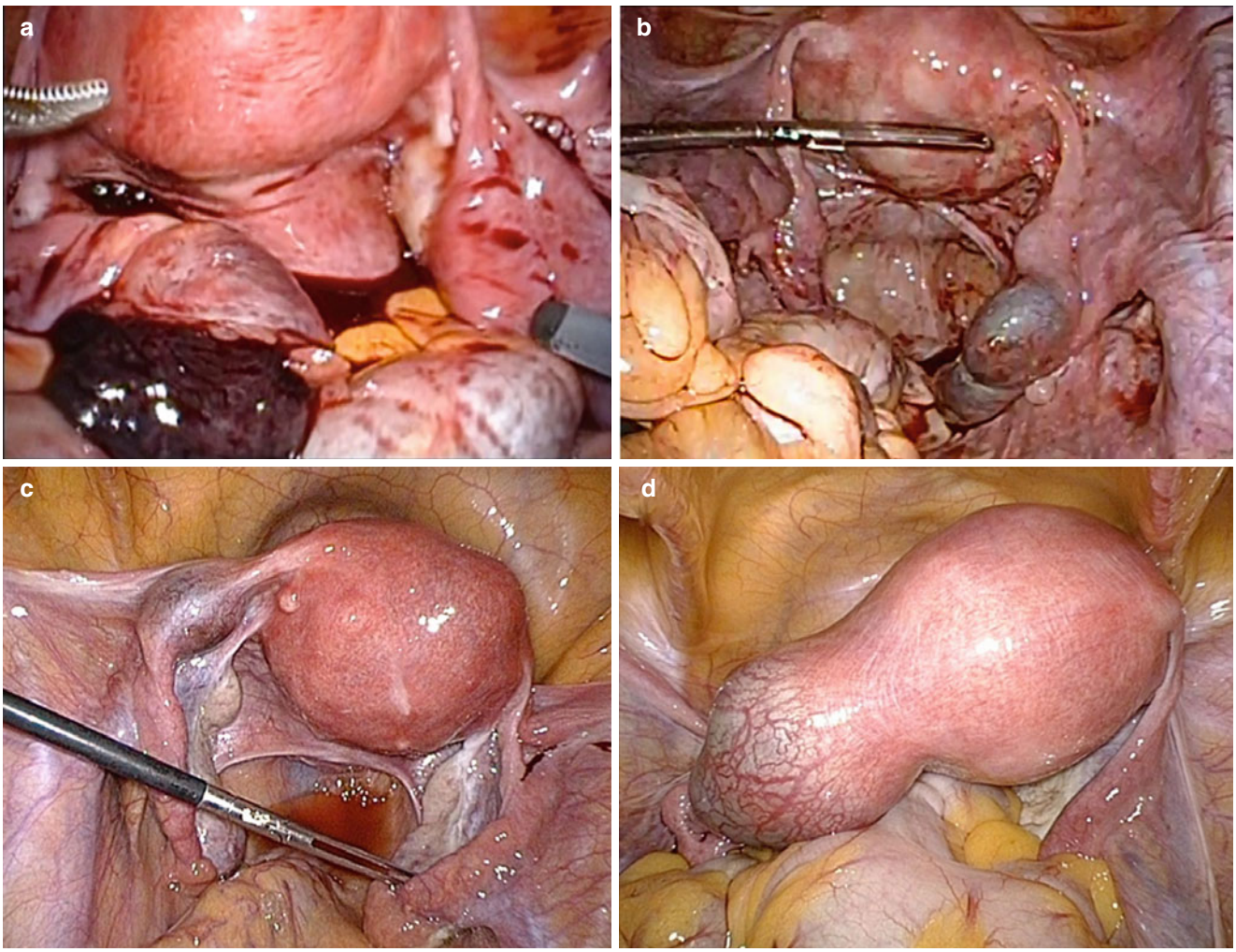


Fig. 4.3 Locations of tubal pregnancies. (**a**) Fimbria, (**b**) ampulla, (**c**) isthmus, (**d**) interstitial portion

10–28 % in the isthmus, 7–17.4 % in the fimbriae, and 2–13 % in the interstitial (cornual) region [2, 17, 18] (Fig. 4.3).

4.3 Etiology

The exact etiology of tubal pregnancy is unclear. However, it is hypothesized that tubal pregnancy is caused by a combination of the embryo remaining in the fallopian tube (Fig. 4.4) owing to an impaired embryo-tubal transport system and alterations in the tubal environment that allow early implantation [19]. The contraction of the smooth muscle of the fallopian tube plays a key role in the embryo transport system [3, 20] and is modulated by several factors, including adrenergic neurons [21], sex steroid hormones, prostaglandins [22–24], nitric oxide [25, 26], prostacyclin [27], and cAMP [28]. A tubal pregnancy may occur when the embryo transport system is impaired for any reason. Another key factor is activity of the cilia within the fallopian tube dominantly influences embryo-tubal transport [28], which is impaired in tubal pregnancy, as evidenced by a large reduction in the number of ciliated cells [29].

The etiology of tubal pregnancy has been studied from the viewpoint of molecular mechanisms, and several proteins have been implicated in its development. Sex steroid hormone receptors play a key role in the activity of the fallopian tubes, and progesterone receptor levels are significantly reduced and estrogen receptor α is absent in the fallopian tubes of women with tubal pregnancies [30–32]. Leukemia inhibitory factor (LIF), which has roles in extravillous trophoblast adhesion and invasion and which is present in ectopic implantation sites, may be associated with the development of tubal pregnancy: LIF-stimulated blastocyst adhesion to fallopian tube epithelial cells was significantly reduced after LIF inhibitor treatment, and LIF promoted placental explant outgrowth, whereas co-treatment with LIF inhibitor blocked such outgrowth [33]. The interleukins (ILs), which are dominant inflammatory proteins, are also implicated. A study using quantitative competitive polymerase chain reaction (PCR) to analyze segments of fallopian tube adjacent to an ectopic pregnancy and from women

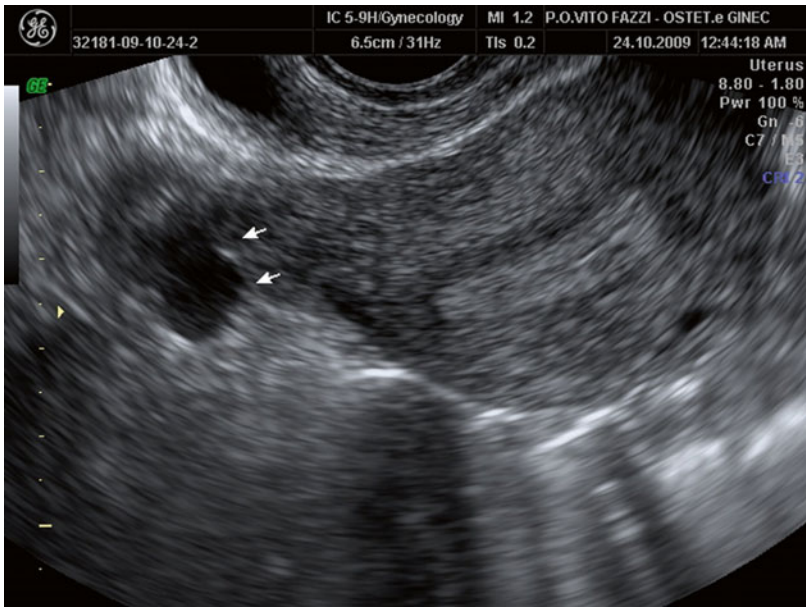


Fig. 4.4 A transvaginal pelvic section of extrauterine right tubal pregnancy at 5 weeks, showing a small anechoic round image

undergoing tubal ligation as controls demonstrated that IL-1β mRNA expression was decreased and IL-1 receptor antagonist (IL-1ra) and IL-1 receptor type 1 mRNA expression was increased in the fallopian tubes with ectopic pregnancies in comparison with the control tubes [34]. The authors concluded that a lower IL-1β to IL-1ra ratio and a higher expression of the IL-1 receptor in the fallopian tubes may be associated with tubal pregnancy. An immunohistochemistry study revealed that the expression levels of IL-6 and IL-8 were significantly upregulated, particularly near the implantation site, in fallopian tubes with tubal gestation [35]. Vascular endothelial growth factor (VEGF), which is a key generator of angiogenesis, contributes to the establishment of a viable pregnancy and participates in the processes of implantation. In the fallopian tube, VEGF is localized in the epithelial cells, smooth muscle cells, and blood vessel cells in a region-specific manner [36, 37]. The VEGF-A and VEGF receptor mRNAs are significantly increased in the implantation site compared with non-implantation sites of fallopian tubes [38] and are associated with trophoblastic invasion into the tubal wall [39]. Indeed, circulating levels of VEGF-A have been found to increase in women with an ectopic pregnancy [40].

4.4 Risk Factors

Risk factors for ectopic pregnancy include pelvic inflammatory disease (Fig. 4.5a), previous surgery, age over 35 years, in vitro fertilization, and smoking. A matched case–control study conducted in women with planned pregnancies including 900 women diagnosed with ectopic pregnancy and 889 women with intrauterine pregnancy as the control group found a significant positive risk of ectopic pregnancy for previous adnexal surgery [odds ratio (OR) = 3.99], uncertainty of previous pelvic inflammatory disease (OR = 6.8), a history of infertility including tubal infertility (OR = 3.62), non-tubal infertility (OR = 3.34), and in vitro fertilization treatment (OR = 5.96). In contrast, previous use of condoms was a negatively significantly associated with ectopic pregnancy (OR = 0.27) [41]. Knowledge of risk factors for tubal pregnancy could be helpful for an early and accurate diagnosis, resulting in appropriate and immediate management including surgery and medical therapy. Table 4.1 shows risk factors of tubal pregnancy.

4.5 Chlamydia Infection

Chlamydia trachomatis is the most common bacterial sexually transmitted infection throughout the world. The infection rate estimated to be 89 million cases per year worldwide [42]. Untreated urogenital *Chlamydia trachomatis* infection may give rise to complications including pelvic inflammatory disease (Fig. 4.5b), ectopic pregnancy (Fig. 4.5c), and tubal pathology [43, 44]. Furthermore, tubal pregnancy is more common in women who have experienced pelvic inflammatory disease. Although the exact mechanism by which *C. trachomatis* infection leads to tubal pregnancy remains unknown, the chlamydial heat shock protein is associated with arrest of the chlamydial developmental cycle and persistence of infection. The antigens, a group of highly conserved membrane proteins found in both prokaryotes and eukaryotes, cause a tubal inflammatory response leading to tubal blockage or a predisposition to tubal implantation [45]. Repeated infections with *C. trachomatis* are thought to increase tubal damage [46].

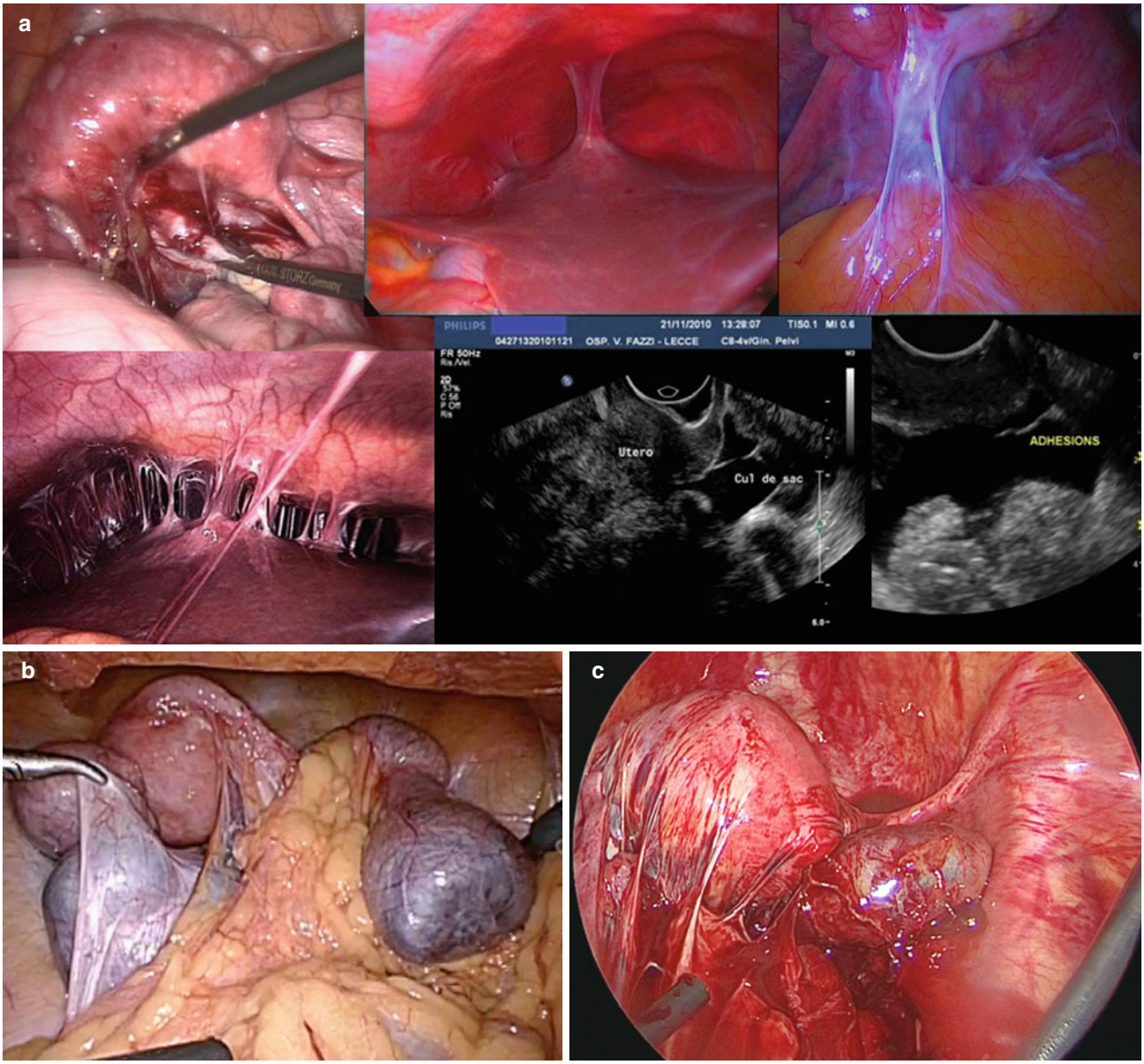


Fig. 4.5 (**a**) The image collects aspects of pelvic inflammatory disease (PID), showed by diffuse adhesions in the Douglas pouch, between uterus, bowel, adnexa, and large ligaments, by Fitz-Hugh-Curtis syndrome (adhesions between the liver and diaphragm) and by ultrasonographic images of pelvis with free fluid in the Douglas pouch and adhesions. (**b**) Bilateral hydrosalpinx caused by previous *Chlamydia trachomatis* infection. (**c**) Right tubal ampullary pregnancy with adhesions caused by *Chlamydia trachomatis* infection

4.6 History of Surgery

Prior tubal surgery (Fig. 4.6) (salpingostomy, neosalpingostomy, fimbrioplasty, tubal reanastomosis, and lysis of periadnexal adhesions) increases the risk for developing a tubal pregnancy, which depends on the degree of damage and the extent of anatomic alteration [47]. A retrospective cohort study carried out between January 2003 and September 2011 of 618 patients admitted to a hospital with tubal pregnancy and who had received surgical treatment reported 2-year cumulative recurrent tubal pregnancy rates of 8.1 % for salpingectomy, 6.3 % for salpingostomy, and 16.7 % for tubal anastomosis. Taking the patients who underwent salpingectomy as the reference group, the patients who underwent tubal anastomosis had a significantly higher risk of recurrent tubal pregnancy (hazard ratio = 2.280; 95 % confidence interval [CI], 1.121–4.636) in univariate analysis [48]. The perforation that complicates appendicitis can lead to

Table 4.1 Risk factors for ectopic pregnancy

Risk levels	Risk factors
High	Previous ectopic pregnancy
	Previous tubal surgery (including female sterilization)
	Genital infection and pelvic inflammatory disease (caused by *Chlamydia trachomatis* and gonorrhea)
	Assisted reproductive technology
Moderate	Infertility (tubal disease, unexplained infertility)
	Intrauterine contraceptive device
	Multiple sexual partners
	Smoking (including past exposure)
	Increasing age
Low	Progestogen-only contraception
	Pelvic surgery (including ovarian cystectomy and caesarian section)
	Abdominal surgery (including appendectomy and bowel surgery)
	Vaginal douching
	Early age of intercourse (<18 years)

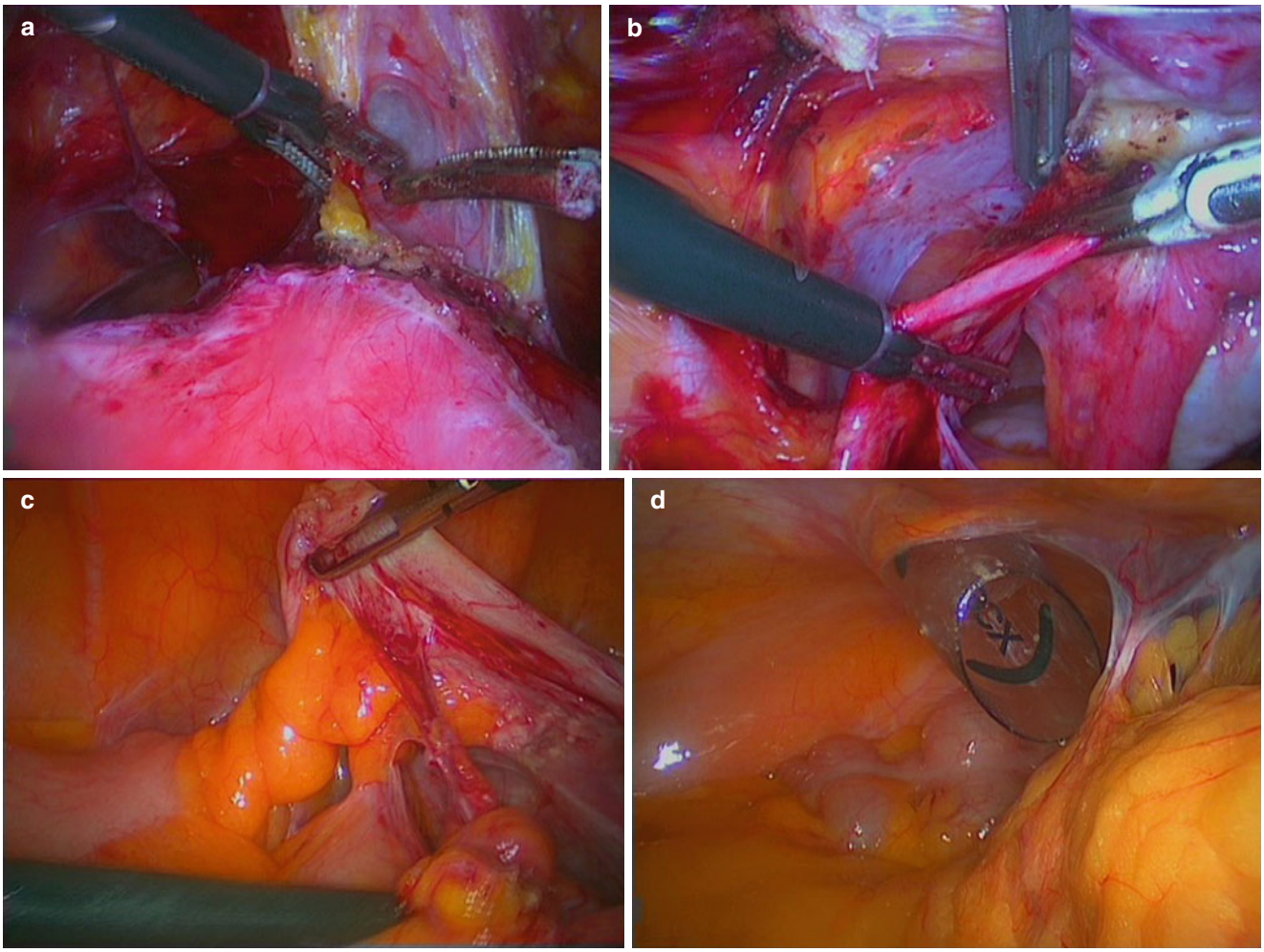


Fig. 4.6 Laparoscopic images of prior pelvic peri-tubal surgery, with lysis of peri-adnexal adhesions

intra-abdominal infection and scarring, which can secondarily result in obstruction of the fallopian tubes and subsequent infertility [49]. A meta-analysis revealed a significant effect of appendectomy on ectopic pregnancy based on a pooled estimate from four studies (OR = 1.78, $p < 0.0001$) [50].

4.7 Age

Advanced maternal age is one of the risk factors of tubal pregnancy, with the incidence of increasing from 1.4 % of all pregnancies in women aged 21 years to 6.9 % in women aged ≥44 years [51, 52]. A physiologic explanation for the association of tubal pregnancy and advanced maternal age at conception remains unclear, but hypotheses include an increase in chromosomal abnormalities in trophoblastic tissue and age-related changes in tubal function that delay ovum transport, resulting in tubal implantation [19].

4.8 Assisted Reproductive Technology

Assisted reproductive technology (ART) is suggested to increase the risk of tubal pregnancy (Fig. 4.7). The rate of tubal pregnancy following in vitro fertilization (IVF)–embryo transfer (ET) is three- to five-fold higher than that in the general population [53]. The prevalence of ectopic pregnancy following ART ranges between 2.1 and 8.6 % of all pregnancies and can reach up to 11 % in female patients with a history of tubal factor infertility [54]. The risk of tubal pregnancy following IVF-ET suggests that tubal damage has a predominant role in the same pathogenesis of naturally occurring tubal pregnancies (Fig. 4.8) [55]. E-cadherin is a useful marker of endometrial receptivity; a study demonstrated strong immunochemical staining for E-cadherin in cytotrophoblast cells of chorionic villi in post-IVF tubal pregnancies but negative or weak staining in spontaneous tubal pregnancies. The authors hypothesized that the differential expression of E-cadherin, a potent adhesion molecule, resulted in tubal pregnancy owing to less than optimal, temporal, and spatial conditions during the IVF cycle [56]. Furthermore, the technique of ET itself may be a potential cause, as the number of embryos that are transferred during IVF treatment has been reported as a risk of tubal pregnancy [57].

4.9 Smoking

Multiple studies have demonstrated a strong association between cigarette smoking and ectopic pregnancy. A French population-based study [58] showed a significant positive association of smoking with ectopic pregnancy in women who smoked compared with those who had never smoked (adjusted OR = 3.9), and the risk associated with smoking increased in a dose-dependent manner (adjusted OR = 5.9 for >20 cigarettes/day). Smoking increases transcription of prokineticin receptor 1 (PROKR1), a G-protein-coupled receptor [59] that is known for its angiogenic properties, control of smooth muscle contractility, and regulation of genes important for intrauterine implantation. Its expression is altered in fallopian tubes from women with tubal pregnancy, where implantation has already occurred. An in vitro study analyzed changes in gene expression using the Illumina Human HT-12 array in an oviductal epithelial cell line (OE-E6/E7) and in explants of human fallopian tubes from nonpregnant women exposed to physiologically relevant concentrations of cotinine, the principle metabolite of nicotine [60]. Cotinine-sensitive genes identified through this process were

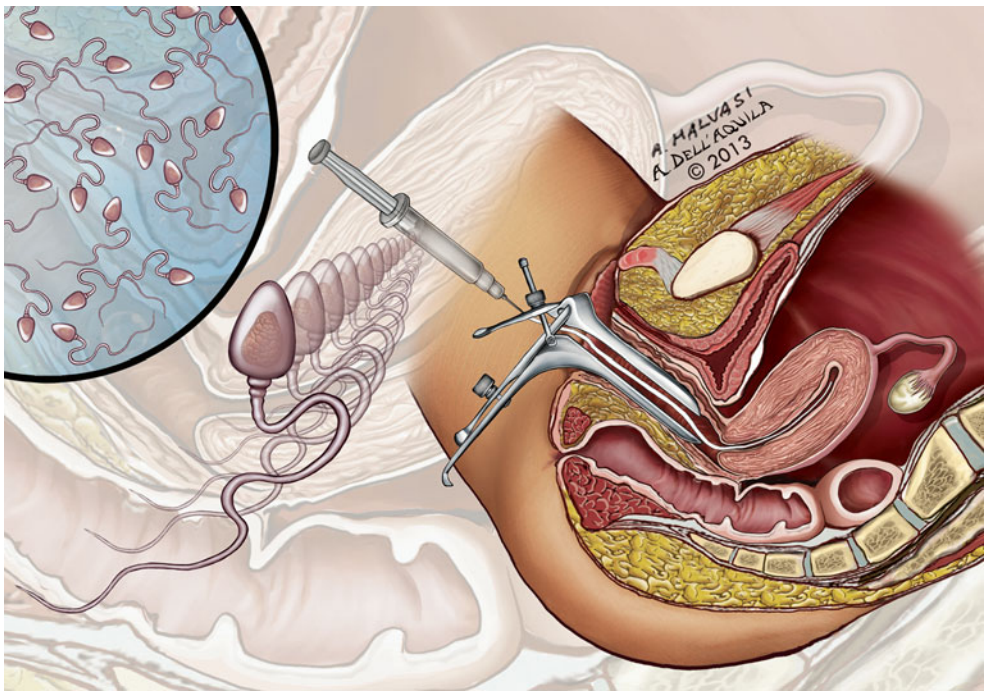


Fig. 4.7 The figure represents an intrauterine insemination

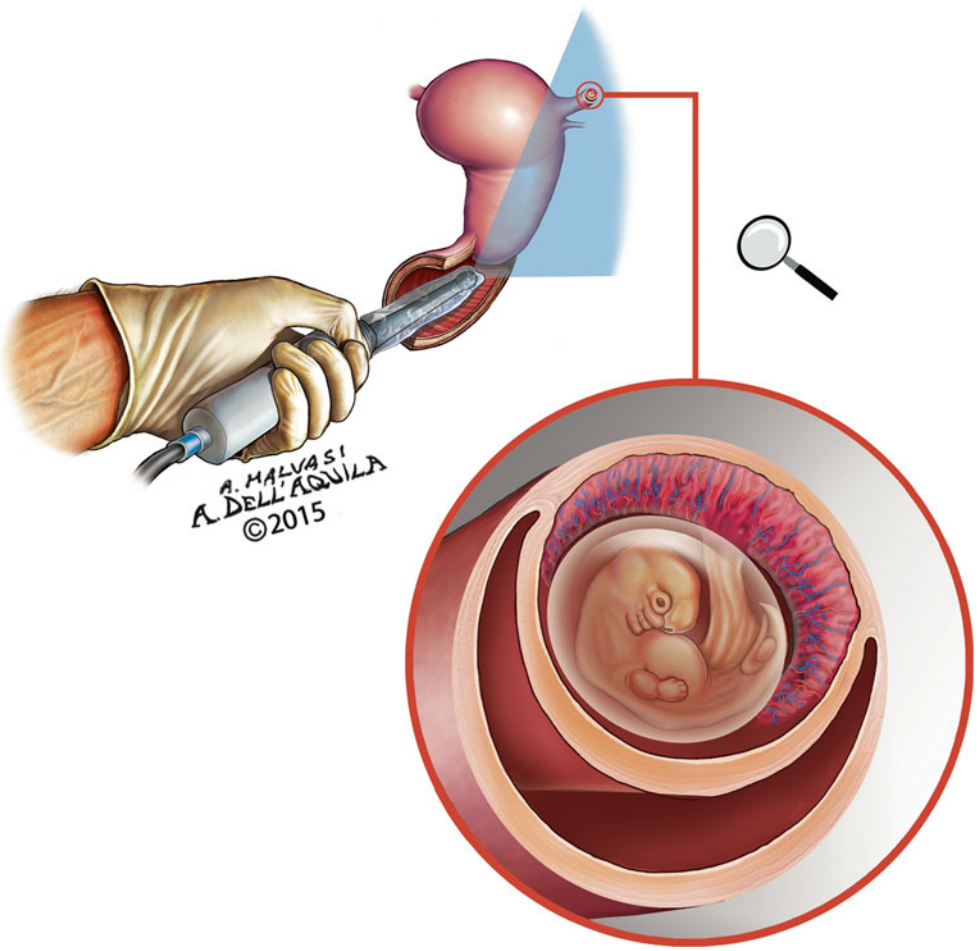


Fig. 4.8 An early tubal pregnancy following IVF-ET at 4 weeks detected by transvaginal pelvic scanning

then localized and quantified in fallopian tube biopsies from nonpregnant smokers and nonsmokers using immunohistochemistry and TaqMan reverse transcription–PCR. The principal cotinine-induced change in gene expression detected by the array analysis in both explants and the cell line was significant downregulation of the proapoptotic gene *BAD*. Consistent with the array data, smoking was associated with decreased levels of *BAD* transcript and increased levels of *BCL2* transcript ($p<0.05$) in fallopian tube biopsies. The authors suggested that smoking may alter tubal epithelial cell turnover and is associated with structural as well as functional changes that may contribute to the development of ectopic pregnancy.

4.10 Other Risk Factors

The use of an intrauterine device (IUD) (Fig. 4.9) is known to increase the risk of tubal pregnancy. A retrospective nested case–control study [61] showed a significant positive association of IUD use with tubal pregnancy (OR = 4.39). Another study reported that previous use of IUDs was associated with a slight risk of ectopic pregnancy and the risk increased with the duration of previous use [62]. The adjusted risk of ectopic pregnancy of prior spontaneous abortions was particularly high in women with three or more previous spontaneous abortions. In addition, there was an association between previous induced abortions and ectopic pregnancy, with an adjusted OR of 1.9 for women with two or more prior induced abortions [58]. A study evaluating the association between the risk of ectopic pregnancy and the use of common contraceptives during the previous and current conception showed that the incidence of ectopic pregnancy may be higher in women using a contraceptive method that failed than in those not using a contraceptive [62]. Endometriosis and its treatment (Fig. 4.10) have also been correlated to the development of tubal pregnancy [41, 55, 63]. The formation of pelvic and tubal adhesions caused by endometriosis could result in abnormal tubal function.

4.11 Clinical Presentation

Early in gestation (approximately 5 weeks), women with ectopic pregnancy are usually asymptomatic. With advancing gestation (>6 weeks), atypical symptoms, including genital

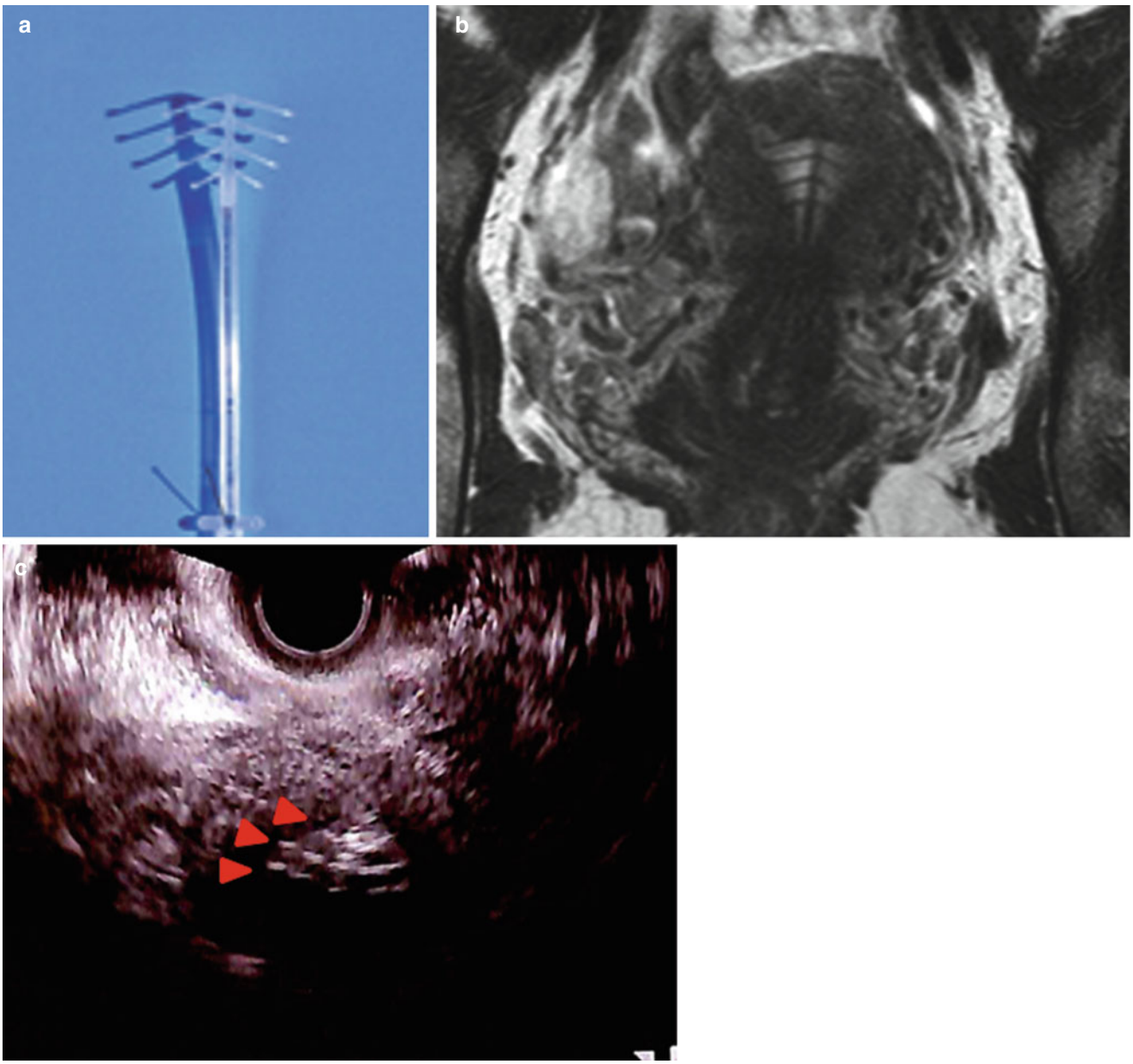


Fig. 4.9 Ultrasound image of the intrauterine device. The FD-1 (Fuji Latex Co., Ltd., Tokyo, Japan) is a commonly used intrauterine device in Japan (**a**). A coronal T2-weighted image reveals the FD-1 inserted in the uterine corpus (**b**). Axial transvaginal ultrasonography shows the hyperechoic shadow (*arrowheads*) of the FD-1 within the uterine corpus (**c**)

bleeding and abdominal pain, may be present. Although more than 50 % of women with tubal pregnancy may present with vaginal bleeding, the symptom is not considered typical and the amount of genital bleeding is usually small. Vaginal bleeding is sometimes mistaken for normal menstrual bleeding or earlier chemical miscarriage. The genital bleeding results from the decidualization of thickened endometrium that is not stabilized owing to an inadequate amount of progesterone from the corpus luteum. Abdominal pain associated with tubal pregnancy ranges from mild to severe, according to the condition of the ectopic mass. The pain is related to tubal distention (Fig. 4.11) caused by the proliferating chorionic villi and hemorrhage into the lumen. When the abortion of the ectopic mass occurs in the fallopian tube, moderate to severe abdominal pain may be present owing to peritoneal irritation caused by hemoperitoneum. On pelvic examination, adnexal tenderness at the concurrent location of a unilateral tubal mass is often noted; however, the tubal mass is rarely palpable. In addition, bimanual examination should be done carefully and gently because manual pressure occasionally results in rupture of the fragile ectopic mass (Fig. 4.12). In contrast, although clinical symptoms are useful

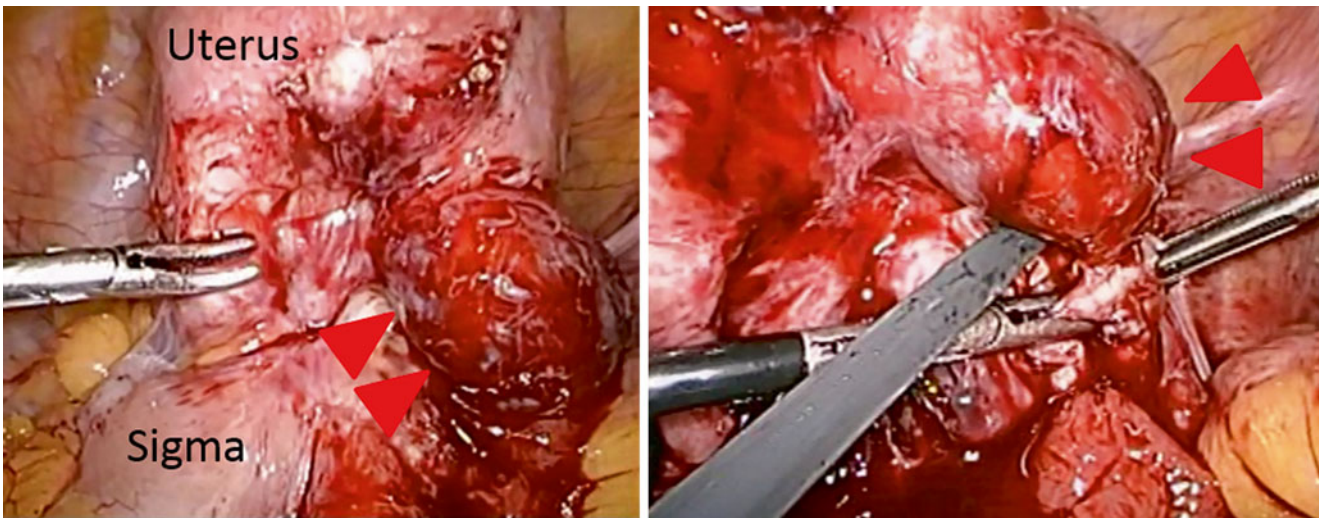
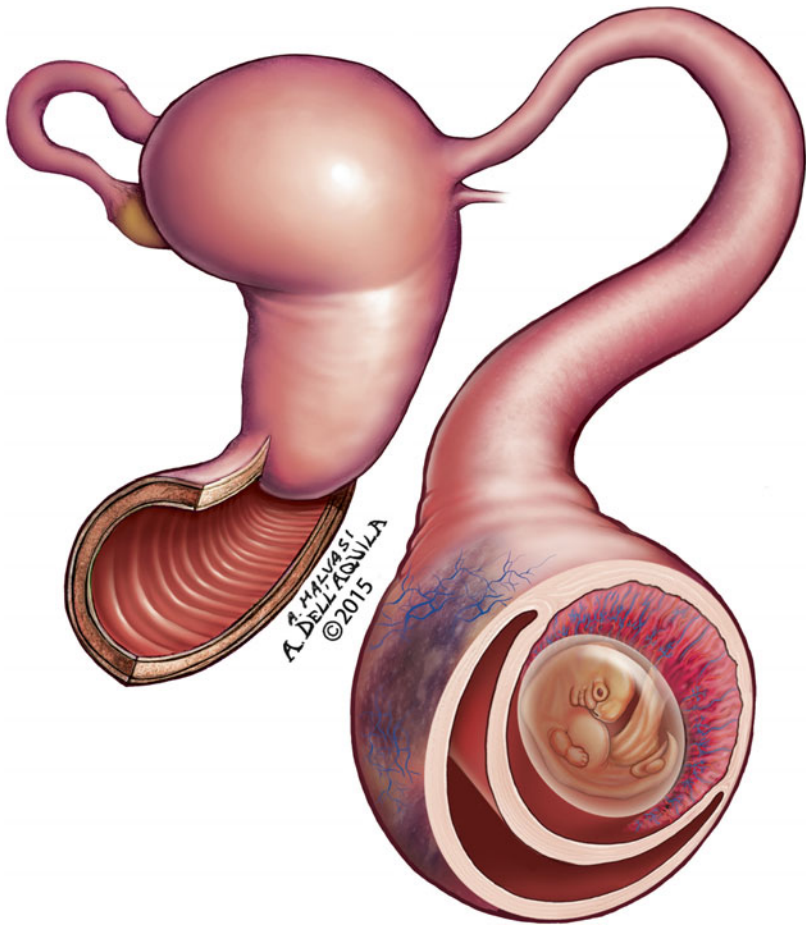


Fig. 4.10 Right tubal ampullary pregnancies (*arrowheads*) with severe adhesions caused by pelvic endometriosis

Fig. 4.11 The figure represents an overdistention of left unruptured tubal pregnancy evoking abdominal pain, ranging from mild to severe



for an earlier auxiliary diagnosis, a recent study reported that one-third of women with ectopic pregnancy have no clinical signs and 9% have no symptoms [64, 65]. The tubal mass sometimes, but not always, ruptures during the clinical course, usually after 7 weeks of gestation (Fig. 4.13). The rupture may occur because of the limitations of the growing ectopic mass imposed by the tubal lumen. When a rupture is present, severe abdominal distention and marked tenderness may be present due to peritoneal irritation caused by massive hemoperitoneum (Fig. 4.14). When these physical signs are

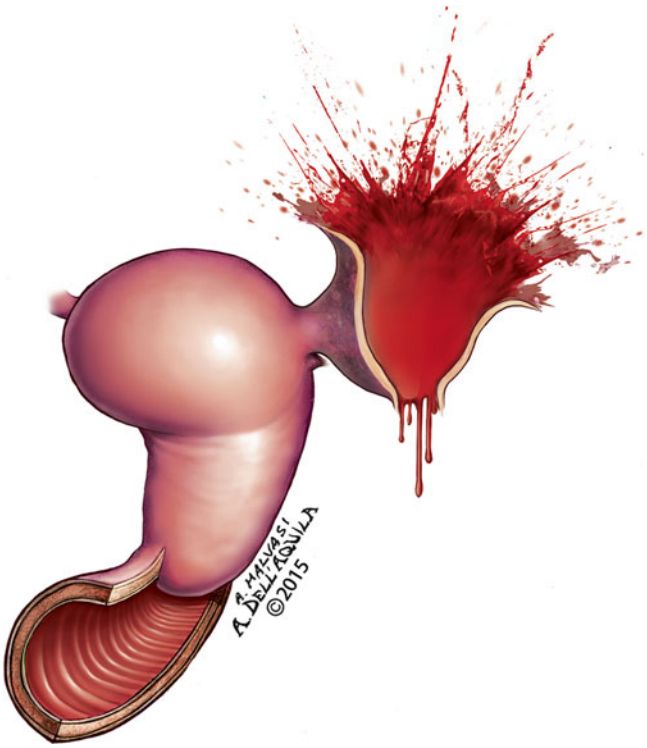


Fig. 4.12 The image shows a tubal rupture of the fragile ectopic mass with massive bleeding

obvious and the woman has a tendency of hypotension and tachycardia, immediate fluid reinfusion should be selected for maintaining a sufficient volume flow through the circulation and surgical management to arrest the hemorrhage.

4.12 Diagnosis

The accuracy of diagnosing tubal pregnancy has been greatly improved by technical advances in diagnostic tools and techniques. However, discriminating earlier spontaneous pregnancy is inevitable. Differentiating spontaneous abortion from tubal pregnancy is also necessary. In addition, early diagnosis of tubal pregnancy is important to prevent maternal mortality due to massive hemorrhage of a ruptured tubal pregnancy.

4.12.1 Ultrasonography

Ultrasonography is the first diagnostic tool used when a tubal pregnancy is suspected. Ultrasonography technology has been markedly advanced in recent years, and high-resolution images can help in earlier detection of ectopic masses (Fig. 4.15). Transvaginal ultrasonography (TVS) for diagnosis of tubal pregnancy is considered superior (Fig. 4.16) to transabdominal ultrasonography (TAS). The first step in diagnosing tubal pregnancy is differentiating it from spontaneous pregnancy and miscarriage by visibility and viability of an intrauterine gestational sac using TVS (Fig. 4.17). If the gestational sac is not visible on TVS after 5 weeks of gestation, other findings should be carefully evaluated when a tubal pregnancy is suspected. However, in some cases of tubal pregnancy, a pseudo-sac appears in the intrauterine cavity, leading to a misdiagnosis of spontaneous pregnancy on TVS [66, 67]. In addition, although spontaneous heterotopic pregnancy is considered very rare with an incidence of 1 in 30,000 pregnancies, the incidence of heterotopic pregnancy following ART is increased and has been reported to occur in approximately 0.8 % of pregnancies following infertility treatment (Fig. 4.18) [68]. It is known that previous surgery is one of the risk factors of heterotopic tubal pregnancy. A literature review estimated by 80 women with heterotopic pregnancy demonstrated that 51 women (63.8 %) had the previous surgery including salpingectomy for previous tubal pregnancy (Fig. 4.19) [69]. An anechoic free fluid in the pouch of Douglas on TVS (Fig. 4.20) is generally detected in not only intrauterine but also ectopic gestations [70]. The presence of echogenic fluid has been found in 28–56 % of women with tubal pregnancy [70, 71]. The echogenic appearance reflects the condition of tubal pregnancy and correlates well with the surgical findings of hemoperitoneum [72]. The presence of fluid in the Morrison's pouch observed via TAS indicates that severe hemoperitoneum may have occurred by rupture of the tubal pregnancy (Fig. 4.21). The most common finding of adnexal ectopic mass is visible as an inhomogeneous or a non-cystic adnexal mass (Fig. 4.22) sometimes known as the blob sign in approximately 60 % of cases [73]. A prospective study on over 5000 consecutive women including 120 tubal pregnancies demonstrated that 73.9 % of tubal masses were visualized on TVS when the patient first attended the clinic [74]. A meta-analysis

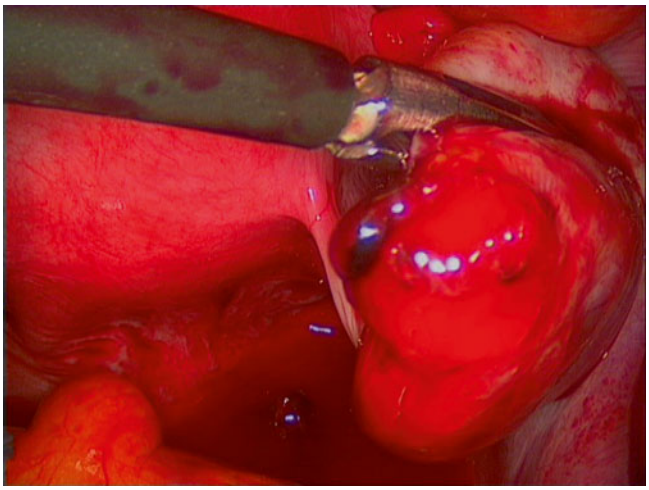


Fig. 4.13 A laparoscopic image showing a tubal rupture of an ectopic mass at 7 weeks of pregnancy, with blood collection into the Douglas pouch

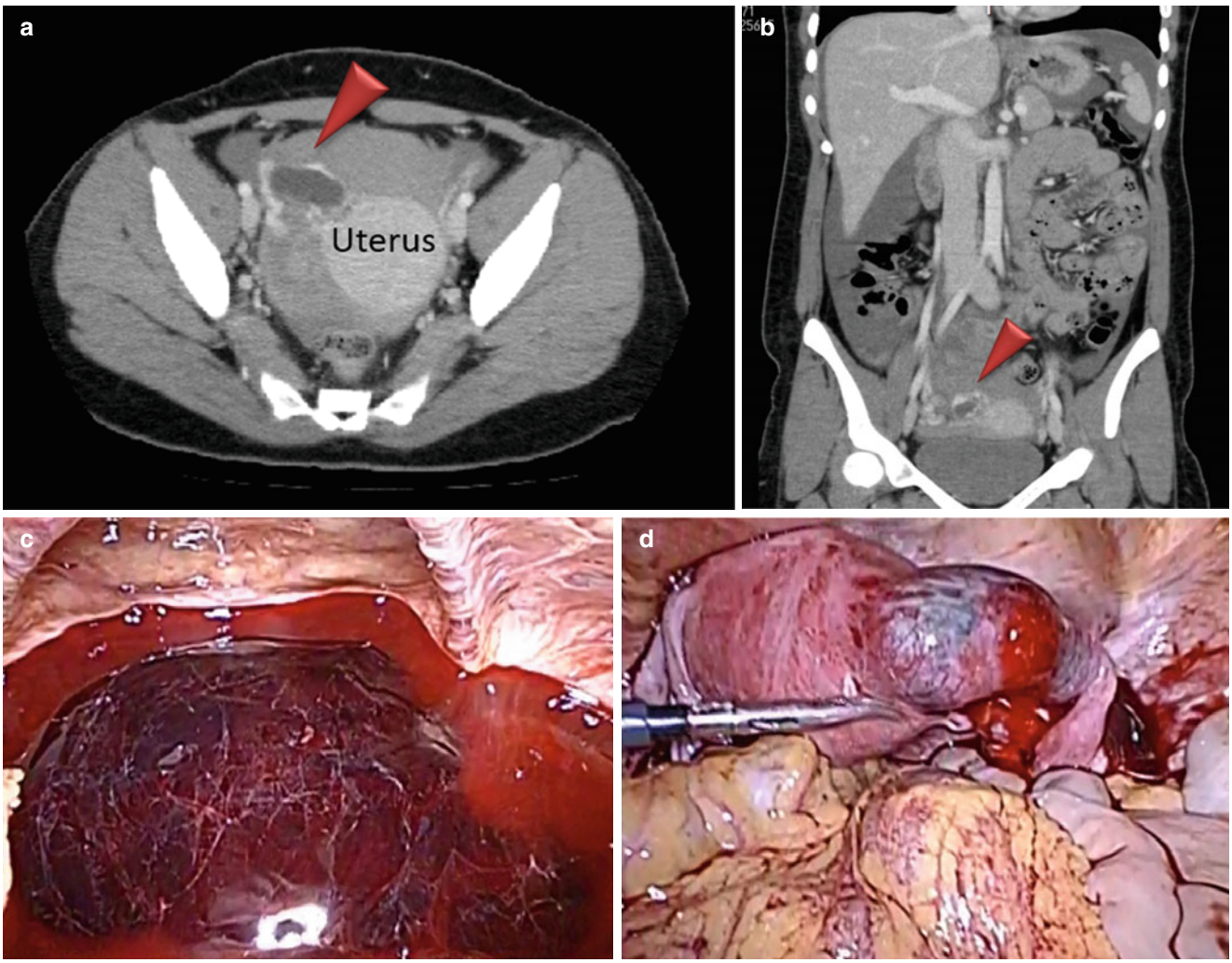


Fig. 4.14 Patient with ruptured tubal pregnancy. Computed tomography revealing isodense areas of severe hemoperitoneum around the uterus (**a**) and the spleen and liver (**b**). The dilated left tubal isthmus (*arrowheads*) can be seen (**a**, **b**). Laparoscopy revealing massive hemoperitoneum in the pelvis (**c**) and continuous bleeding from ruptured tubal isthmus (**d**)

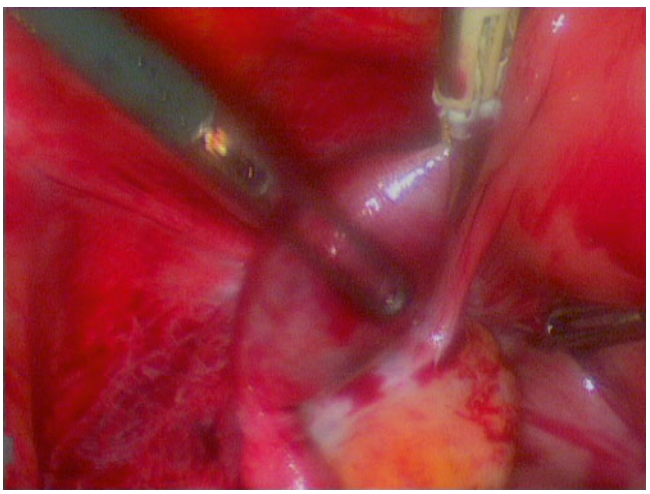


Fig. 4.15 A laparoscopic earlier detection of a right tubal ectopic pregnancy

of 10 studies showed TVS could be used to detect the mass of a tubal pregnancy with a specificity, positive predictive value, sensitivity, and negative predictive value of 98.9 %, 96.3 %, 84.4 %, and 94.8 %, respectively [75].

4.12.2 Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a useful marker for diagnosing tubal pregnancy. The quantitative measurement of hCG is accurately correlated to TVS findings [76]. Serial hCG measurements are also useful for pregnancy of unknown location (PUL) when an intrauterine gestational sac cannot be visualized using ultrasonography, e.g., earlier stage of pregnancy, spontaneous abortion, or ectopic pregnancy. Many physicians consider that a slower rise in hCG indicates an abnormal pregnancy [77]. Silva et al. [78] reported that the

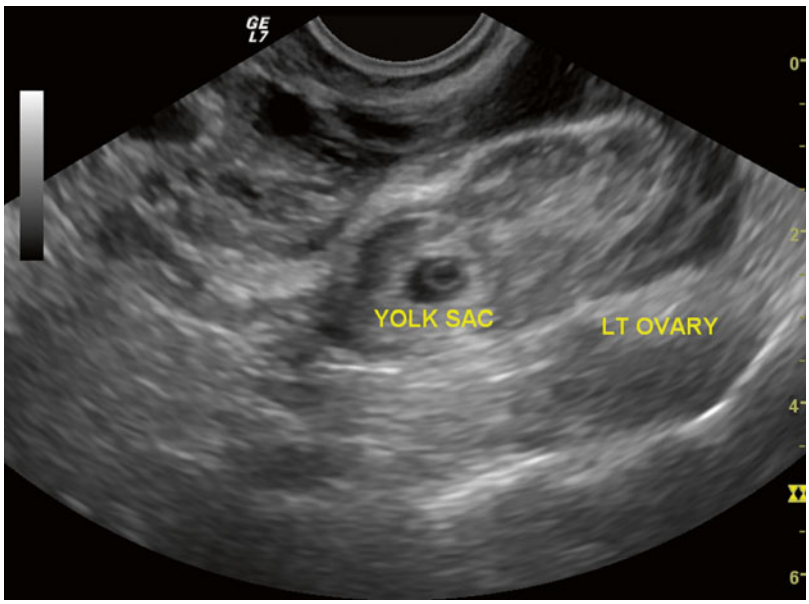


Fig. 4.16 A transvaginal pelvic ultrasonography diagnosing an early left tubal pregnancy, at 5 weeks of pregnancy

initial rise of hCG among 200 women with an ectopic pregnancy was slower (75 % increase in 2 days) than that reported for women with a viable intrauterine pregnancy. In addition, the authors found that the initial decline in hCG was slower (27 % decline in 2 days) than the mean reported for completed spontaneous abortion. Doubling of hCG concentration over 2 days is often used to predict a normal pregnancy [79, 80]. Seeber [77] considered that a miscarriage or ectopic pregnancy is not in doubt in cases of PUL in which the hCG concentrations do not rise at least 53 % within 2 days after the initial measurements, based on the studies of Barnhart et al. [76, 81]. The reason the author adopted the predictable limit of the subsequent hCG rise was that the limit with a 99 % CI intends that <1 % of viable pregnancies indicated an hCG rise even slower than that. However, clinicians need to know that the hCG concentrations of some women with ectopic pregnancy behave irregularly. Silva et al. [78] reported that 20.8 % of women with an ectopic pregnancy presented with a rise in hCG concentrations similar to the minimal rise for women with an intrauterine pregnancy and 8 % of women presented with a fall in hCG values similar to women with a spontaneous abortion. Therefore, although measuring hCG concentrations for a suspected tubal pregnancy is essential, a comprehensive diagnosis in combination with assessment of clinical presentations and appearance of ultrasonography should be conducted. It was reported that the combination of hCG measurement and TVS could detect ectopic pregnancy with 97 % sensitivity and 95 % specificity, avoiding the need for further invasive tests including a dilatation and curettage [81]. It is suggested that a definition of a discriminatory zone to identify the optimal hCG concentration at which a normal pregnancy can be visible on ultrasound is important for individual institutions or clinicians. When the hCG concentration exceeds the discriminatory zone and an intrauterine pregnancy is not confirmed by ultrasonography, the pregnancy is not viable but is a suspected PUL including ectopic pregnancy. It is important to be careful in setting the range of discriminatory zone, because setting it too high or too low may lead to delayed diagnosis of ectopic pregnancy or excessive and unnecessary interventions for a normal pregnancy. The discriminatory zone ranges between 1500 and 2000 mIU/mL according to guidelines from the American College of Obstetricians and Gynecologists (ACOG) [82]. Detection of discriminatory zone may differ according to the type of hCG immunoassay method. Desai et al. [83] studied how a lack of hCG assay harmonization may affect the interpretation of serum hCG concentrations with respect to the discriminatory zone. They used seven hCG reagent platforms to evaluate 80 serum samples containing various concentrations of hCG. They concluded that the hCG concentration within a discriminatory zone of 1500–3500 IU/L can be used for all but one commonly used hCG reagent platform.

4.12.3 Other Serum Markers

The markers are classified with respect to the biological conditions of ectopic pregnancy, including endometrial function and angiogenesis for implantation and corpus luteum function and trophoblast functions for embryonic viability [84–86]. Serum progesterone concentrations are stable at 8–10 weeks of gestation [87]. Serum progesterone has been widely studied as a marker of viability of early pregnancy. However, a meta-analysis evaluated 26 studies concluded that though less than 5 ng/mL of serum progesterone concentration had good prediction for non-viability of PUL, it has no ability to

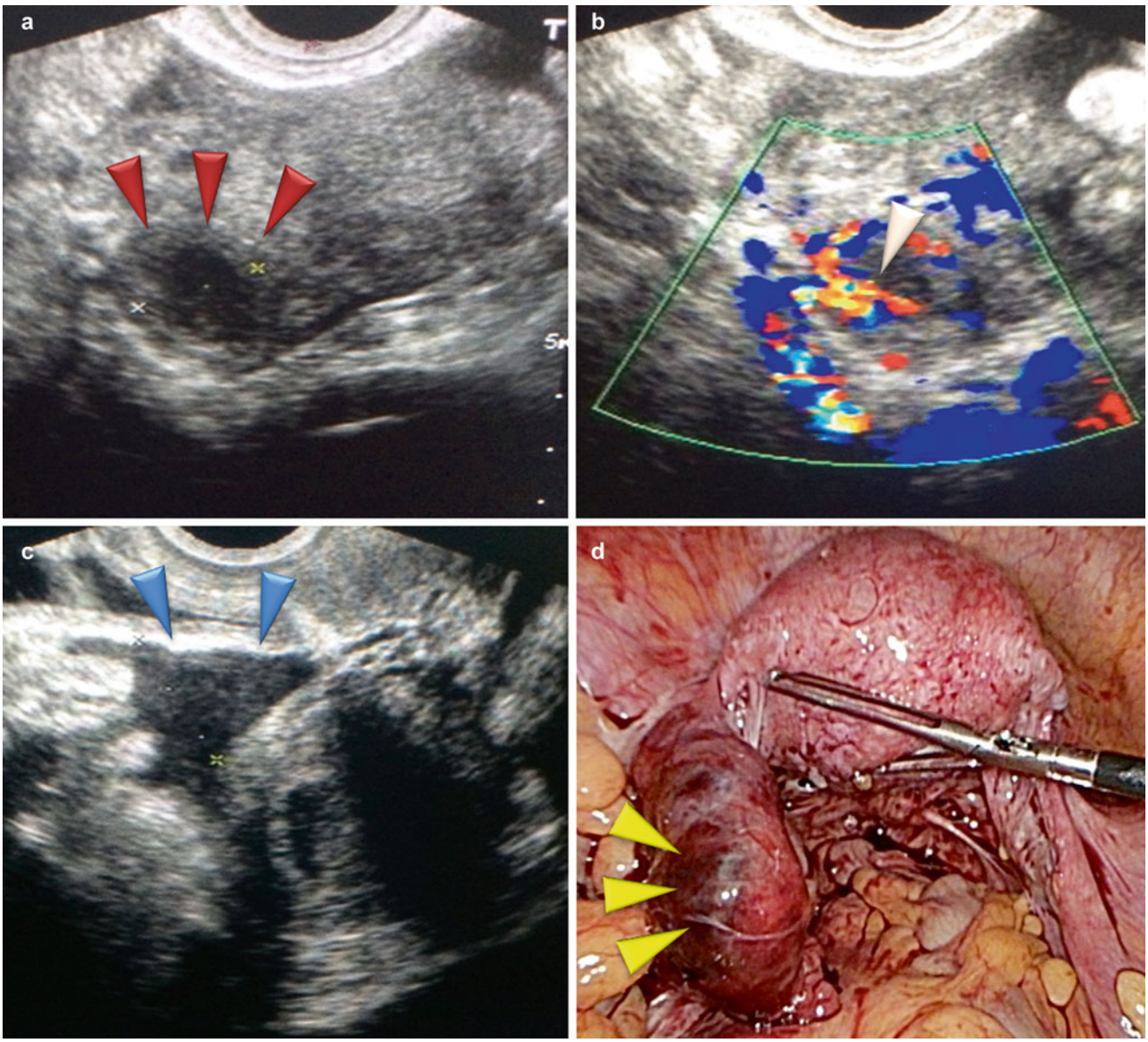


Fig. 4.17 Left tubal ampullary pregnancy. Ultrasonography revealing a low echoic cystic mass (*red arrowheads*) on left adnexal area (**a**). Color Doppler ultrasonography revealing blood flows (*white arrowhead*) in a fetus-like lesion inside the cystic mass (**b**). Echo-free space (*blue arrowheads*) detected around the uterus caused by hemoperitoneum (**c**). Laparoscopic image of the left tubal ampullary pregnancy (*yellow arrowheads*) confirmed by ultrasound imaging (**d**)

discriminate tubal pregnancy from PUL [88]. It is suggested that a single serum progesterone concentration could be used only to assess the risk of ectopic pregnancy in a PUL but not to differentiate ectopic pregnancy from spontaneous abortion. However, the measurement of serum progesterone concentrations combined with other serum markers may be occasionally helpful for the discrimination between tubal pregnancy and spontaneous abortion. In a retrospective case–control study including 50 of women with ectopic pregnancy and 50 of women with abortion, serum progesterone and anti-angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1) serum levels were measured. Although the area under curves for progesterone and sFlt-1 was low at 0.756 (cutoff point; 6 ng/mL, sensitivity = 60 %, specificity = 72.7 %) and 0.842 (cutoff point; 93 pg/mL, sensitivity = 84.5 %, specificity = 86.3 %), the combination of both markers allowed us to increase the AUC to 0.910 [89]. Table 4.2 shows other diagnostic serum markers for tubal pregnancy.

A prospective study assessing the association between ultrasound images and serum concentrations of VEGF in tubal ampullary pregnancies in 55 patients demonstrated, via multiple logistic regression analysis, a significant association

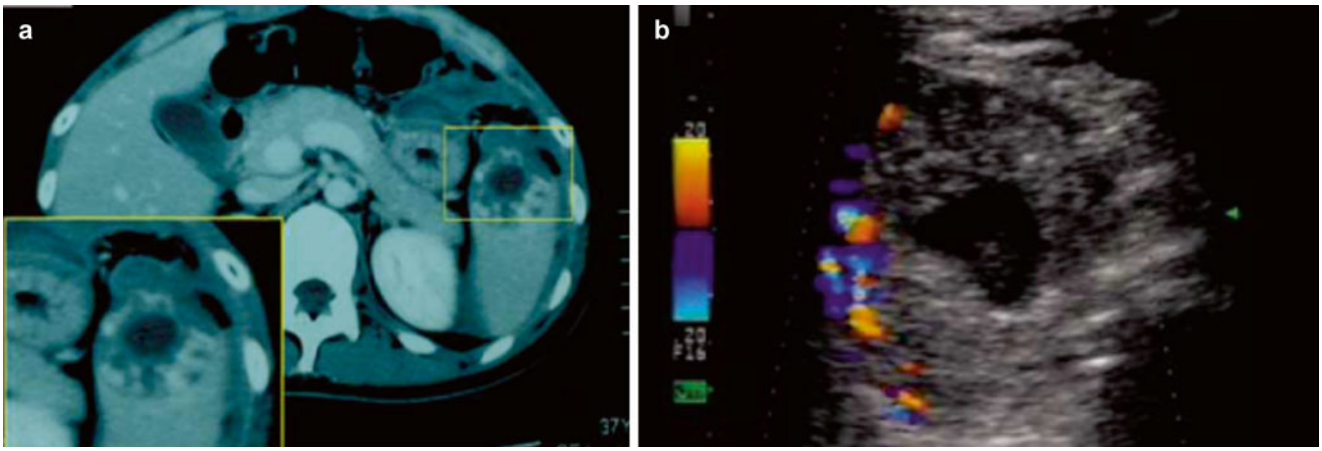


Fig. 4.18 Simultaneous tubal-splenic pregnancy after assisted reproductive technology. Although the pregnancy was found in the right tubal ampulla after salpingectomy at 6 weeks of gestation, the patient serum human chorionic gonadotropin level increased at 8 weeks of gestation. Upper abdominal computed tomography revealing a cystic lesion accompanied by edema at the inferior pole of the spleen (**a**). Ultrasonography revealing a gestational sac and fetus with a beating heart in the inferior pole within the spleen (**b**) (See Refaat et al. [68])

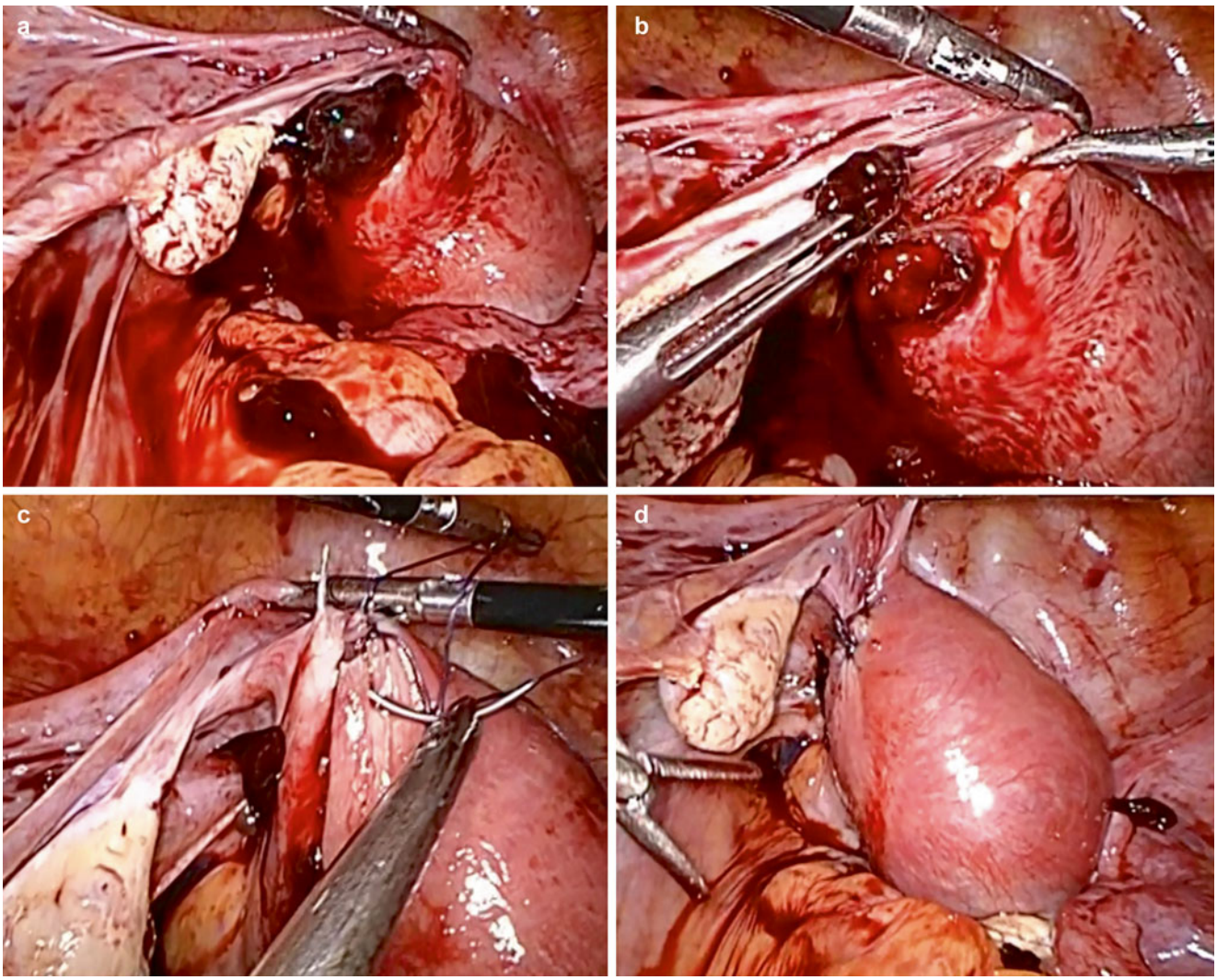


Fig. 4.19 Heterotopic pregnancy after assisted reproductive technology. Laparoscopy showing the heterotopic pregnancy with a ruptured ectopic mass, located in the stump of the ipsilateral tube, persisted after a previous salpingectomy (**a**, **b**). After the removal of ectopic tissue, the stump was closed using absorbable strings (**c**, **d**)

between ultrasound images of an ectopic gestational sac in the ampulla containing an embryo or fetus with fetal heartbeat and serum VEGF values [90]. The authors suggested that serum VEGF facilitates a deeper invasion of trophoblastic tissue into the tubal wall and is related to embryonic cardiac activity.

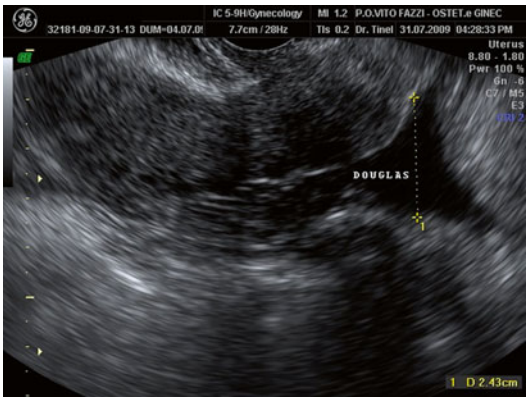


Fig. 4.20 An ultrasonographic transvaginal scan showing an anechoic free fluid in the pouch of Douglas generally detected in not only intrauterine but also ectopic gestations

MicroRNAs (miRNAs) are non-coding RNA molecules that regulate gene expression at the posttranscriptional level. Although miRNAs have been discovered only recently, they play a key role in diverse biological processes, including development, cell proliferation, differentiation, and apoptosis. Approximately 3% of human genes encode miRNAs, and miRNAs fine-tune the expression of as much as 30% of human protein-coding genes [91]. Recently, miRNAs have been scrutinized as candidates for diagnostic and prognostic biomarkers and predictors of drug response because they have also been implicated in a number of diseases. Pregnancy-associated circulating miRNAs have been proposed as potential biomarkers for the diagnosis of pregnancy-associated complications as well as ectopic pregnancy [92–95]. In a retrospective case–control analysis of 89 women with a diagnosis of viable intrauterine pregnancy, spontaneous abortion, or ectopic pregnancy [96], concentrations of serum hCG, progesterone, miR-517a,

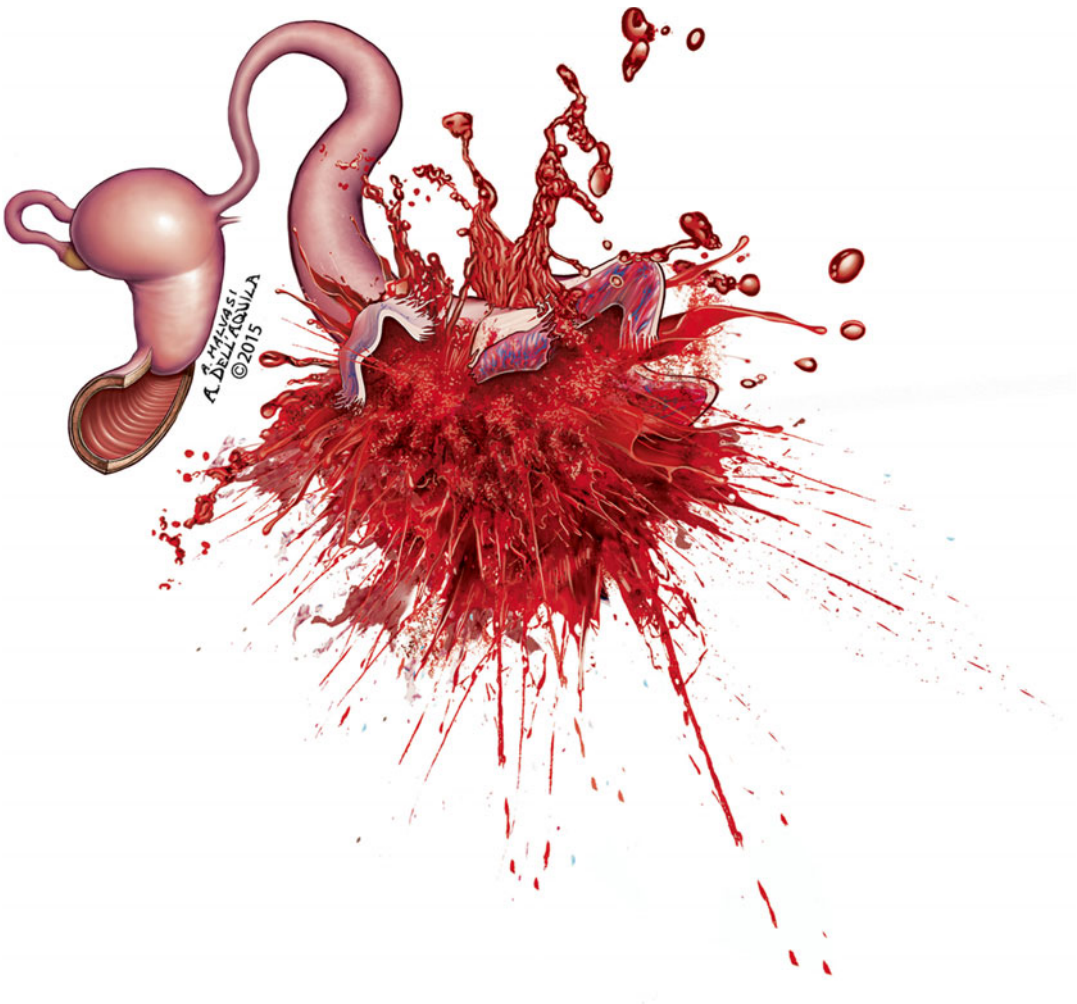


Fig. 4.21 The figure represents a sudden rupture of the tubal pregnancy; it is usually cause of severe hemoperitoneum

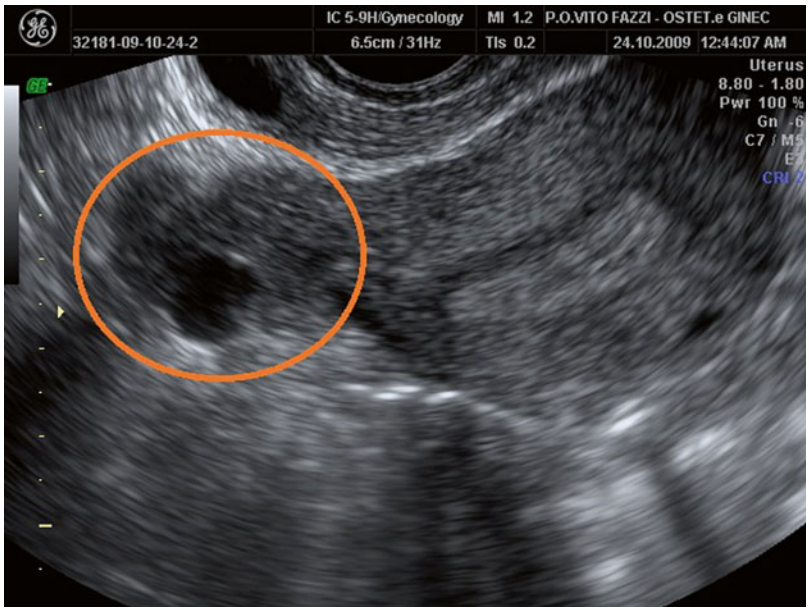


Fig. 4.22 A ultrasonographic transvaginal scanning showing the most common finding of adnexal ectopic mass: an inhomogeneous or a non-cystic adnexal mass (in the *orange ring*). The patient had a right early tubal pregnancy

Table 4.2 Serum biomarkers of tubal ectopic pregnancy

Major classifications	Biological functions	Markers
Related to embryo	*Trophoblast function*	hCG
		Hyperglycosylated hCG
		Activin A
		PAPP-A
		SP1
		hPL
		ADAM-12
		Placental mRNAs
		Placental micro RNAs
		Follistatin
		AFP
		Cell free fetal DNA
	Corpus luteal function	Progesterone
		Inhibin A
		Estradiol
		Relaxin and renin
	Angiogenesis	VEGF
		PlGF
		Angiopoietins
Related to implantation	*Endometrial function*	LIF
		Glycogen
		Muc-1
		Adrenomedullin
		Actin B
	Other tissue function	CK
		Smooth muscle heavy-chain myosin and myoglobin
		Cytokines
		CA125

hCG human chorionic gonadotropin, *PAPP-A* pregnancy-associated plasma protein-A, *SP1* pregnancy-specific beta glycoprotein-1, *hPL* human placental lactogen, *ADAM-12* a disintegrin and metalloprotease-12, *AFP* alpha-fetoprotein, *VEGF* vascular endothelial growth factor, *PIGF* placental-like growth factor, *LIF* leukemia inhibitory factor, *Muc-1* mucin-1, *CK* creatine kinase

miR-519d, and miR-525-3p were significantly lower in women with ectopic pregnancy and spontaneous abortion than in women with viable intrauterine pregnancy. In contrast, the concentration of miR-323-3p was significantly increased in women with ectopic pregnancy in comparison with women with viable intrauterine pregnancy and spontaneous abortion. A stepwise analysis that used hCG first, added progesterone, and then added miR-323-3p revealed a 96.3 % sensitivity and a 72.6 % specificity for the diagnosis of ectopic pregnancy.

4.12.4 Other Diagnostic Managements

If serum hCG concentrations do not rise normally and women are diagnosed with a PUL, endometrial curettage is recommended [1]. Determining the presence or absence of chorionic villi by endometrial curettage is helpful to distinguish between spontaneous abortion and tubal pregnancy. Women whose hCG concentrations do not decrease by at least 15 % in the 12 h after curettage or whose samples do not include chorionic villi are diagnosed with ectopic pregnancy [97]. However, the absence of chorionic villi does not definitively indicate an ectopic pregnancy, because chorionic villi will also be absent in patients with complete spontaneous miscarriage of an intrauterine pregnancy [98]. In addition, dilatation and curettage for diagnosing ectopic pregnancy is an invasive technique with a risk of adverse events [1].

Pelvic magnetic resonance imaging (MRI) can be helpful for detecting tubal pregnancy (Fig. 4.23). MRI is an excellent procedure to confirm or better define suspected tubal pregnancy when TVS fails to reveal the focus of adnexal abnormal implantation or to distinguish ectopic pregnancy from incomplete miscarriage. The advantage of MRI for diagnosing tubal pregnancy is an identifiability of fresh blood owing to its excellent tissue contrast as well as accurate localization of the abnormal implantation site [99]. A retrospective study evaluating characteristics obtained by pelvic MRI demonstrated that a well-demarcated and thick-walled cystic mass presumed

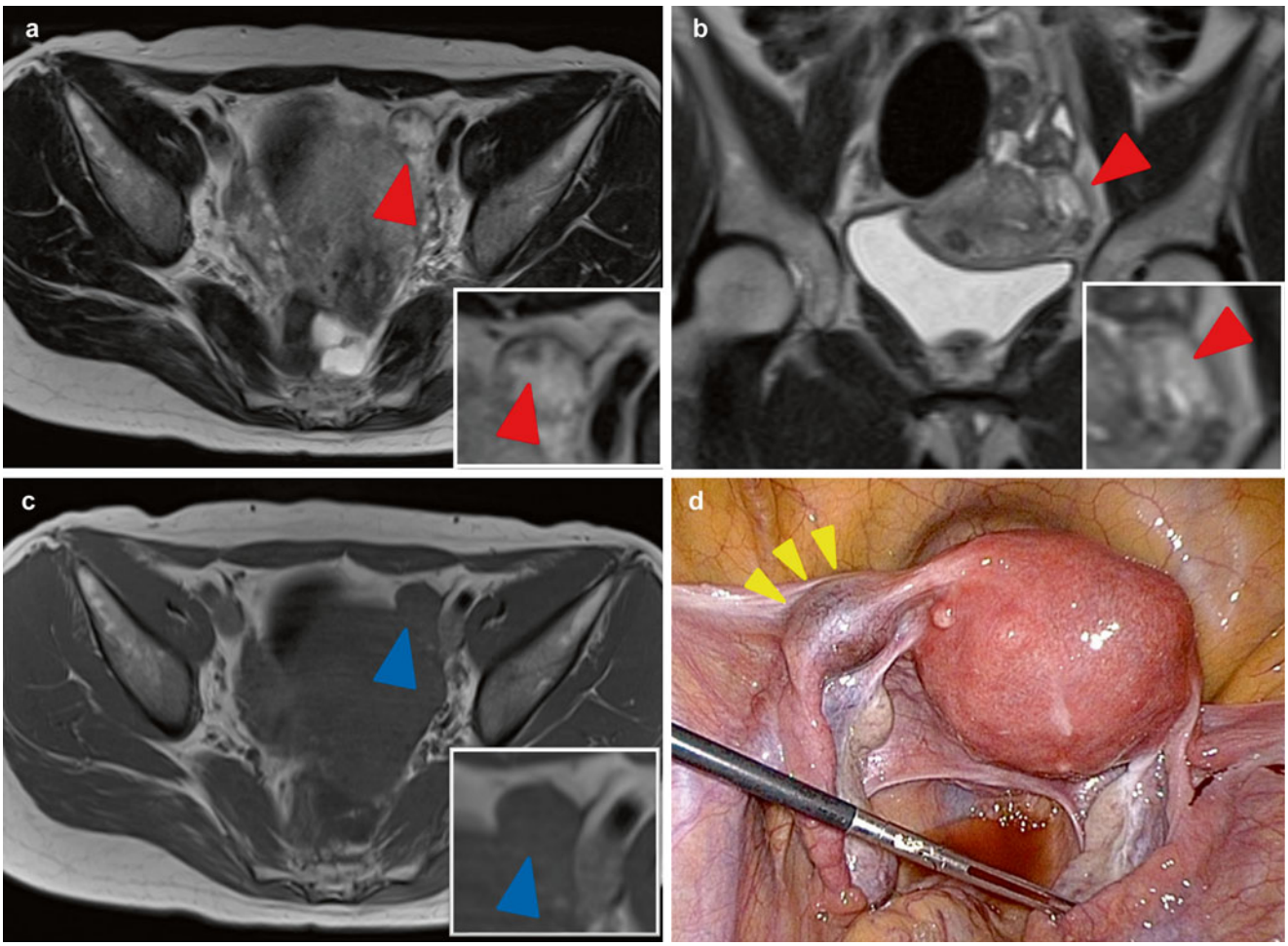


Fig. 4.23 Magnetic resonance imaging (MRI) of left tubal isthmus pregnancy at 5 weeks of gestation. A cystic gestational sac-like mass on the left side of the uterus shown on axial (**a**) and coronal (**b**) T2-weighted images as high-intensity areas (*red arrowheads*). The low-intensity area of the T1-weighted image indicates nonhemorrhagic content in the cystic mass (*blue arrowheads*) (**c**). Laparoscopic appearance of the tubal isthmus pregnancy (*yellow arrowheads*) detected by the MRI (**d**)

to be a gestational sac lateral or adjacent to the uterus could be detected in all 27 patients with tubal pregnancy [100]. The contents of the gestational sac-like structures in the 27 cases could be divided into three types: 26% of cases (7/27) exhibited nonspecific liquid with a hypointense signal on T1-weighted images (WIs) and a hyperintense signal on T2-WIs with no enhanced solid components, 56% of cases (15/27) exhibited papillary solid components representing embryo tissues with an isointense signal on T2-WI and marked enhancement, and 19% of cases (5/27) exhibited hyperintense signal on both T1- and T2-WIs, indicating fresh blood or a fluid–fluid level resulting from blood degradation without a visible solid component. In addition, the study demonstrated that MRI features, including dilatation of the affected fallopian tube associated with a hyperintense clot and hemoperitoneum associated with signal intensities higher than that of urine in the bladder on T1-WIs or clear fluid with hypointense signal on T1-WIs and hyperintense signal on T2-WIs in the pelvic cavity, were useful for diagnosing tubal pregnancy.

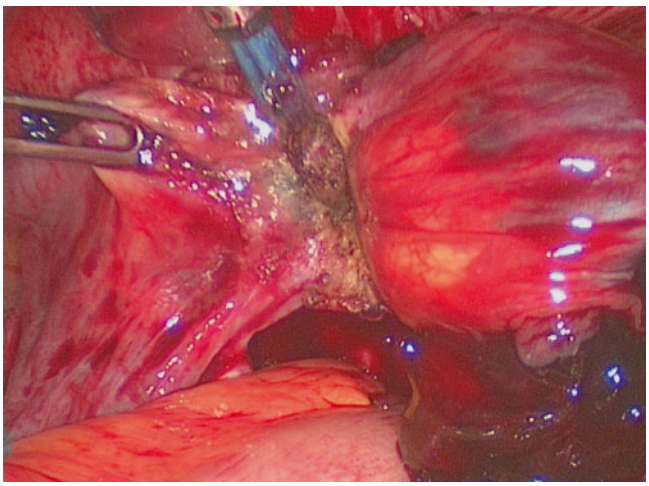


Fig. 4.24 A laparoscopic left salpingectomy chosen as a radical surgery for ruptured tubal pregnancy and hemoperitoneum

4.13 Treatments

Recently, the outcomes of tubal pregnancy, which had been a fatal condition in the first quarter of the twentieth century, have been dramatically improved by the developments of not only early diagnostic methods but also medical treatments. Both surgical and medication therapy are used. Salpingectomy is chosen as a radical surgery for tubal pregnancy (Figs. 4.24 and 4.25), and salpingostomy when the patient desires fertility-sparing surgery. In addition, laparoscopic surgery is

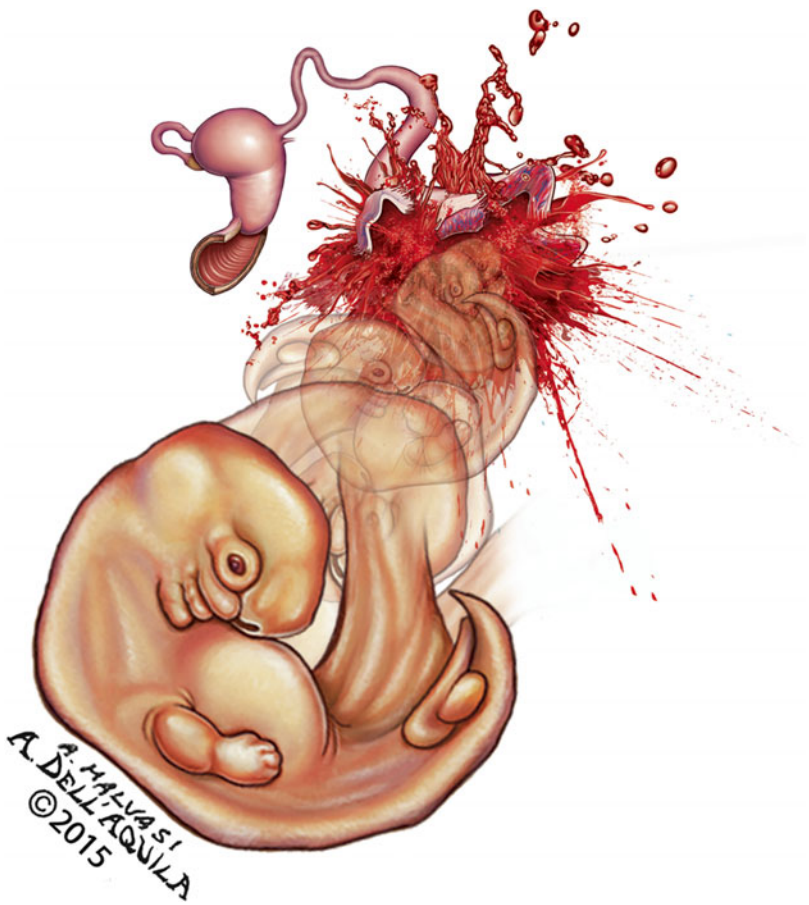


Fig. 4.25 The figure represents a dramatic rupture of right tubal pregnancy with embryo expulsion in the pelvis

the gold-standard surgical approach because it is less invasive than laparotomy. Medical treatment using methotrexate is used in some women with tubal pregnancy. A high recovery rate after methotrexate therapy can be predicted for selected women.

4.14 Expectant Management

Expectant management is occasionally applicable for symptomatic and clinically stable women with tubal pregnancy. Women with early tubal pregnancies with lower hCG levels are the best candidates for observation. Approximately 20–30 % of ectopic pregnancies are associated with decreasing hCG levels at the time of presentation [101]. According to ACOG guidelines, if the initial hCG level is <200 mU/mL, 88 % of patients experience spontaneous resolution, and lower spontaneous resolution rates can be anticipated with higher hCG levels [82]. In 107 women with tubal pregnancies, success was achieved in 75 women (70 %) undergoing expectant management [102]. The success of expectant management was 96 % (32/33 cases) in women with initial serum β-hCG ≤175 IU/L, 66 % (40/60) in women with β-hCG 175–1500 IU/L, and only 21 % (3/14) in women with β-hCG >1500 IU/L. The study also demonstrated that the success rate of expectant management was associated with low progesterone levels (<10 nmol/L), gestational age ≤42 days, and pregnancy measuring >15 mm in diameter. A prospective observational study was carried out to validate the efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with tubal pregnancy [103]. Selection criteria for expectant management were clinical stability with no or minimal abdominal pain, no evidence of significant hemoperitoneum on ultrasonography, ectopic pregnancy measuring <30 mm in mean diameter with no evidence of embryonic cardiac activity, serum β-hCG < 1500 IU/L, and the woman's consent. Of 146 women with tubal pregnancies who received expectant management, 104 (71.2 %) resolved spontaneously and two (1.4 %) were lost to follow-up; in the remaining 40 (27.4 %), expectant management was unsuccessful. In another study conducted to establish clearance curves for serum hCG levels, 161 women diagnosed with a nonviable tubal pregnancy underwent successful expectant management [104]. The study reported a mean initial serum hCG level of 488 (range 41–4883) IU/L and a median serum β-hCG clearance time of 19 (range 5–582) days. The average half-life of β-hCG was 82.5 h in patients with steadily declining serum hCG levels compared with 106.7 h in patients with primarily plateauing hCG levels in the declining phase. A recent multicenter randomized controlled trial [105] found that expectant management for women that are hemodynamically stable, with an ectopic pregnancy visible on transvaginal sonography, and with a plateauing serum hCG concentration <1500 IU/L or with a PUL and a plateauing serum hCG concentration <2000 IU/L, is an alternative to medical treatment with single-dose methotrexate treatment. The study demonstrated that there was no significant difference in primary treatment success rate of single-dose MTX versus expectant management, 31/41 (76 %) and 19/32 (59 %), respectively (relative risk;1.3, 95 % confidence interval; 0.9–1.8).

4.15 Surgical Management

4.15.1 Laparoscopic Approach

Laparoscopic surgery is the best possible treatment for tubal pregnancy (Fig. 4.26), and the laparoscopic approach has already been standardized. Laparoscopic surgery is minimally invasive, resulting in a shorter duration of hospital stay, lower blood loss, and lower pain after surgery. Two randomized studies comparing outcomes between laparotomy and laparoscopic surgery in the 1990s showed that laparoscopic surgery was superior to laparotomy [106, 107]. In addition, there was no significant difference in the tubal patency and intrauterine pregnancy or incidence of repeat tubal pregnancy after surgery. A randomized controlled study compared adhesion formation between salpingostomy via laparoscopy and laparotomy for ectopic pregnancy [108]. The study demonstrated that women who underwent laparotomy developed significantly more adhesions on the operated side than did women who underwent laparoscopy. Another advantage of laparoscopic surgery is that the abdominal appearance can be minutely inspected via a closed laparoscopic view. The first abdominal incision for a

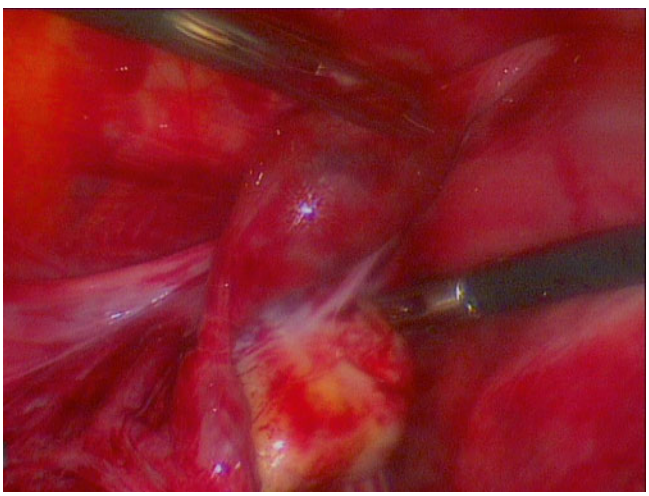


Fig. 4.26 A laparoscopic conservative management of an early left tubal pregnancy

laparoscopic approach is usually made at the umbilicus, and two to three additional incisions are made for intra-abdominal manipulations. In recent years, the invasiveness of the laparoscopic approach for tubal pregnancy has decreased with the use of reduced port surgery [109–114], including single-port laparoscopic surgery (Fig. 4.27); however, the duration of the procedures tends to be longer. Therefore, further randomized studies comparing these procedures should be conducted to confirm their benefits.

4.16 Surgical Procedures

4.16.1 Salpingectomy

Salpingectomy is a radical surgery for tubal pregnancy involving complete, or sometimes partial, resection of the fallopian tube containing an ectopic mass. Indications for salpingectomy include a ruptured ectopic pregnancy, a tubal ectopic mass diameter >5 cm, and a repeat tubal pregnancy after conservative management. The resection of an affected fallopian tube starts with an incision from the mesosalpinx between the fimbria and ovary using a monopolar or bipolar power device, and the tube is finally detached by cutting the uterine attachment site. Laparoscopic loop ligation was used as a classical procedure because of the convenience. However, the persisting remnant interstitial or fimbrial portions may result in an ipsilateral ectopic pregnancy [115–117]. Therefore, the fallopian tube should be completely resected all the way around. Recently, vessel-sealing devices (Fig. 4.27b), which can reduce blood loss and shorten the surgery duration, have been used instead of mono- and bipolar power devices for resection of the affected fallopian tube (Fig. 4.28). A laparoscopic disposable bag is useful to extracorporeally remove the resected fallopian tube to prevent residency of the ectopic tissue in the abdominal cavity.

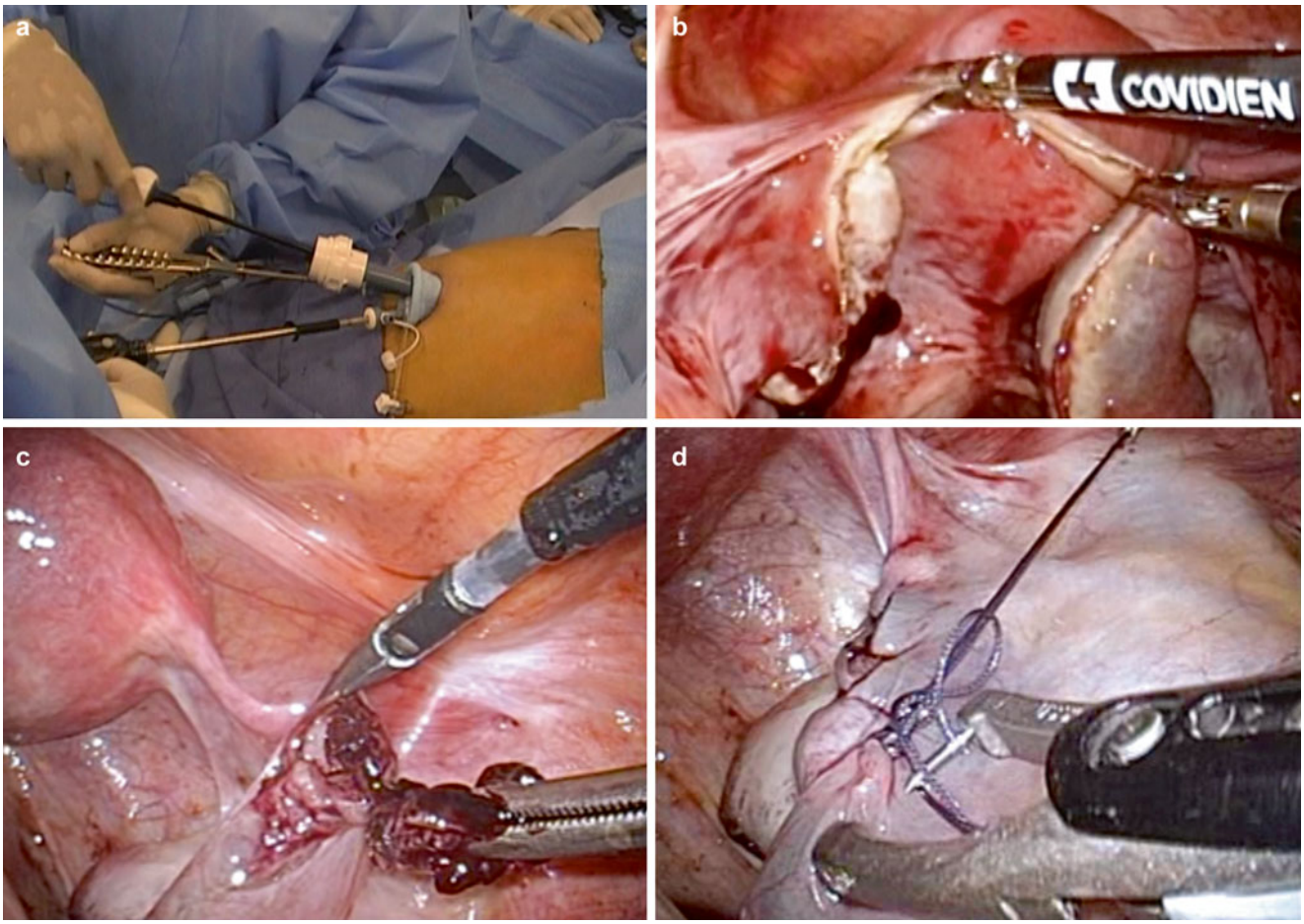


Fig. 4.27 Single-incision laparoscopic surgery for tubal pregnancy. Multiple devices for laparoscopic surgery are inserted through a single umbilical incision using SILS-port™ (Covidien, MA, USA) (**a**). A left fallopian tube with an ectopic mass is removed using a vessel-sealing device during single-incision laparoscopic salpingectomy (**b**). The ectopic mass is gently removed from the tubal lumen using forceps via a linear incision during single-incision laparoscopic salpingostomy (**c**). The tubal mucosa and serosa are closed by sutures using SILS-stitch™ (Covidien) during single-incision laparoscopic salpingostomy (**d**)

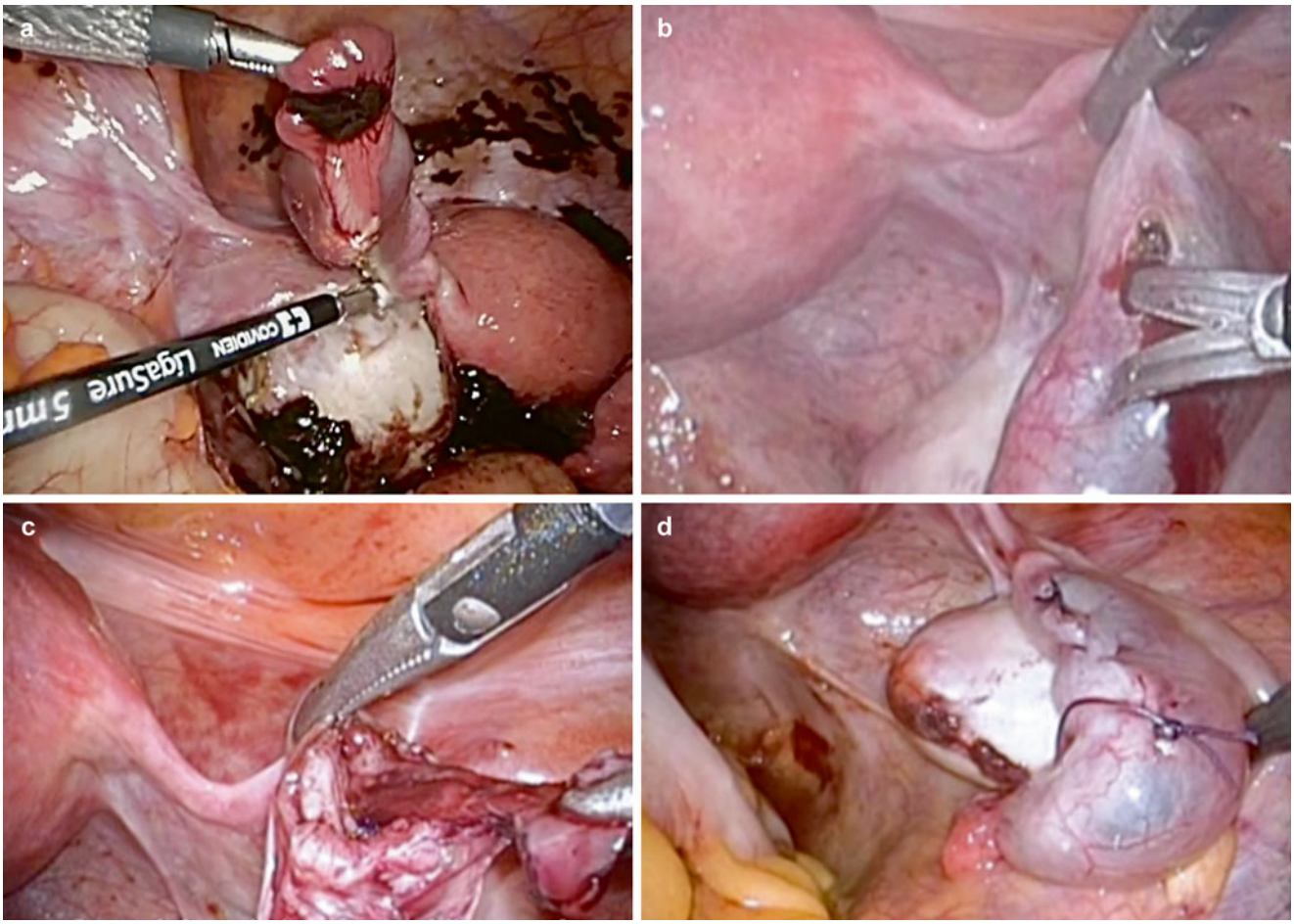


Fig. 4.28 Laparoscopic procedures for tubal pregnancy. (**a**) Using vessel-sealing device for salpingectomy. (**b**) Incision on the tubal serosa using laparoscopic scissors during salpingostomy. (**c**) Removal of intra-tubal ectopic tissue using a forceps. (**d**) Closing by suture on tubal serosa

4.16.2 Salpingostomy

Salpingostomy for tubal pregnancy is chosen for women who wish to retain fertility after the surgery. Injection of 2–4 IU vasopressin (diluted 1:100 in saline) into the mesosalpinx around the affected tube can reduce blood loss and prevent thermal damage caused by extensive coagulation during surgery. The tubal serosa of the superior edge of the mass is gently grasped, and an incision point is made on the tubal serosa using a monopolar needle or laparoscopic scissors (Fig. 4.29). Subsequently, 3–4 cm of tubal serosa and muscle are sharply and linearly dissected along the long axis of the tube using scissors. After complete fenestration of the tubal lumen, intra-tubal ectopic tissue is carefully removed using a forceps (Fig. 4.30). The most important issue in performing salpingostomy is to prevent the risk of persistent ectopic pregnancy. Therefore, the ectopic mass containing trophoblast tissue should be completely extracted from the fallopian tube. After the mass is removed from the fallopian tube, the inner lumen of the tube must be adequately irrigated with saline, and the milking of the fallopian tube should be performed with minimal tubal trauma to protect the salpingian mucosa. In a comparative observational study conducted on 102 patients with ampullary tubal pregnancy, stripping was performed in 56 women using unique fallopian tube stripping forceps devised for tubal milking, and salpingostomy was performed in 46 women. Although there was no significant difference in bleeding, surgical duration, or persistent ectopic pregnancy rate, the persistent ectopic pregnancy rate tended to be lower in women who underwent the stripping performed using the unique fallopian tube stripping forceps [118]. The cleavage site of the tubal muscular layer is confirmed by chromotubation with indigo carmine dye injected through the uterine manipulator (Fig. 4.30). Closing by suture is preferred because this may prevent postsurgical adhesion formation (Fig. 4.30); however, whether to suture the tubal incised serosa after tissue removal is controversial [119, 120]. A randomized study comparing outcomes between women who underwent salpingostomy without and with suturing showed, respectively, a 90 and 94% tubal

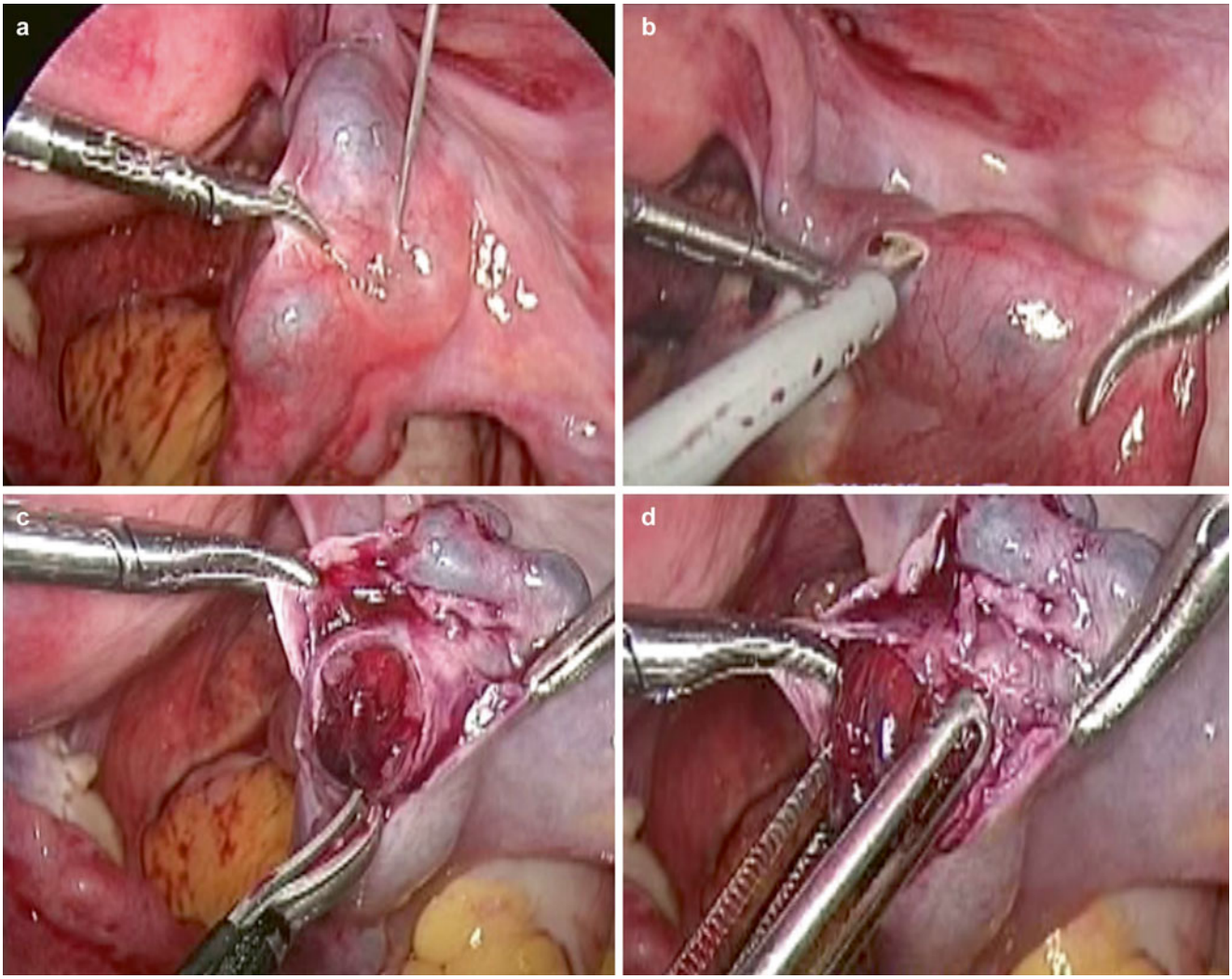


Fig. 4.29 Laparoscopic salpingostomy for tubal pregnancy. Vasopressin diluted in saline is injected into the mesosalpinx around the affected tube (**a**). An incision point is made on the tubal serosa using a monopolar needle (**b**). The tubal serosa and muscle are sharply and linearly dissected along the long axis of the tube using scissors (**c**). Intra-tubal ectopic tissue is carefully removed using forceps (**d**)

patency rate of the treated side, and evaluation of second-look laparoscopy 3 months after the initial surgery revealed peritubal adhesions in 33 % of the women without suturing and in 29 % of the women with suturing [119]. In addition, there was no significant difference in the incidence of tubal fistula or cumulative pregnancy rate after surgery between the two groups. The patency of the treated tube was favorable in approximately 90 % of women who underwent salpingostomy for tubal pregnancy [121].

4.16.3 Persistent Ectopic Pregnancy

The incidence of persistent ectopic pregnancy after salpingostomy is reported as 5–20 % [122]. It has been reported that a postoperative day 1 hCG decrease of <50 % from the initial preoperative hCG level was significantly associated with the development of persistent ectopic pregnancy after conservative surgical management for tubal pregnancy (Fig. 4.31) (relative risk = 3.51) [123]. In addition, no case of persistent ectopic pregnancy developed when the postoperative day 1 hCG declined more than 76 %. Two randomized controlled trials have shown that the risk of persistent trophoblastic tissue is higher after laparoscopy than after laparotomy [124, 125]. However, a recent retrospective cohort study has shown that only nine of 334 patients (2.7 %) who underwent laparoscopic salpingostomy developed persistent ectopic pregnancy and were treated with systemic methotrexate after surgery [126]. An observational study evaluating 46 women with tubal pregnancy showed that only one women (2.1 %) developed persistent ectopic pregnancy after laparoscopic salpingostomy [118]. These results indicated that advances in laparoscopic techniques may decrease the incidence of persistent ectopic pregnancy. It is suggested

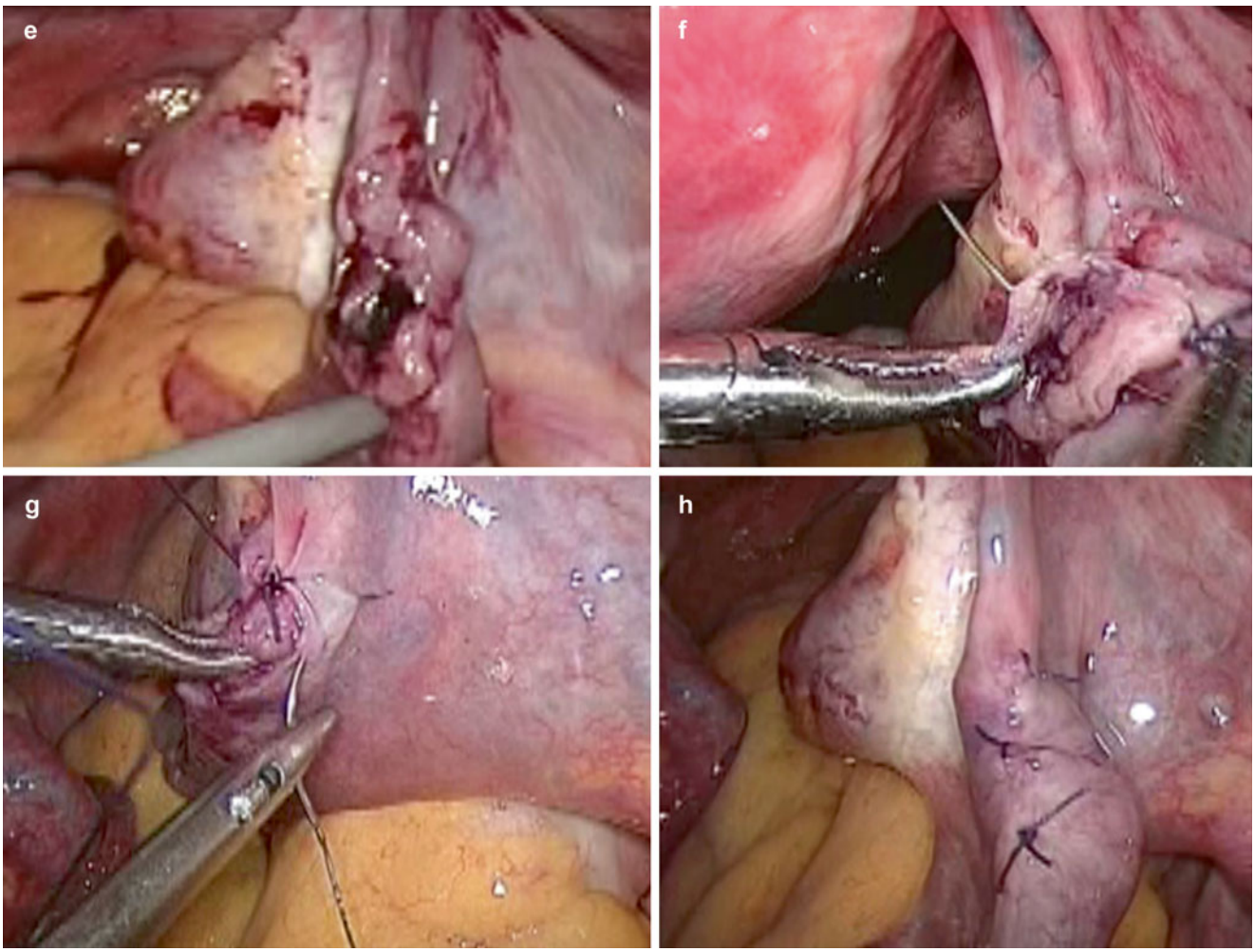


Fig. 4.30 Laparoscopic salpingostomy for tubal pregnancy. The cleavage site of the tubal muscular layer is confirmed by chromopertubation using indigo carmine dye (**e**). The tubal muscular and serosal layers are closed by continuous suture using 3-0 absorbable strings (**f**–**h**)

that several factors may increase the risk of persistent ectopic pregnancy after conservative surgery, including preoperative high hCG level, treatment for a ruptured tube, extraction of tissue containing a fetal heartbeat, an isthmus pregnancy, and the diameter of the tubal ectopic mass. A retrospective cohort study [127] demonstrated that among 1306 women with an ectopic pregnancy managed exclusively by means of laparoscopic conservative surgery, 86 (6.6 %) required further treatment for persistent ectopic pregnancy. The study found a statistically significant risk of failure in patients with preoperative serum hCG levels ≥1960 IU/L (OR = 1.8; 95 % CI, 1.1–2.8, $p = 0.02$). In another study [128], 47 of 134 women (35.9 %) who underwent successful linear salpingostomy developed persistent ectopic pregnancy after the initial surgery and 18 of 134 women had no patency in the treated tube evaluated by hysterosalpingography or second-look laparotomy. The study demonstrated that the serum hCG level in women who underwent unsuccessful procedures was significantly higher than that of the women whose procedures were successful, and the procedures in all women with serum hCG >10,000 IU/L failed; salpingostomy may also fail for women with a fetal heartbeat in the ectopic mass because these women had higher preoperative hCG levels. Some authors recommended that laparoscopic salpingostomy should not be attempted when the maximum diameter of the ectopic pregnancy lesion is more than 4–6 cm [128–130]. It was reported that the use of prophylactic methotrexate during or after surgery decreases the risk of persistent ectopic pregnancy. A randomized study evaluated the incidence of persistent ectopic pregnancy in women who underwent linear salpingostomy in comparison with women who received a single injected dose of methotrexate after surgery [131]. The study revealed that the incidence of persistent ectopic pregnancy was significantly lower in women injected with methotrexate after surgery (1.9 %) than in women without injection (14.5 %). In addition, the relative risk of developing persistent ectopic pregnancy after prophylactic methotrexate was 0.13. An observational study evaluating the incidence of

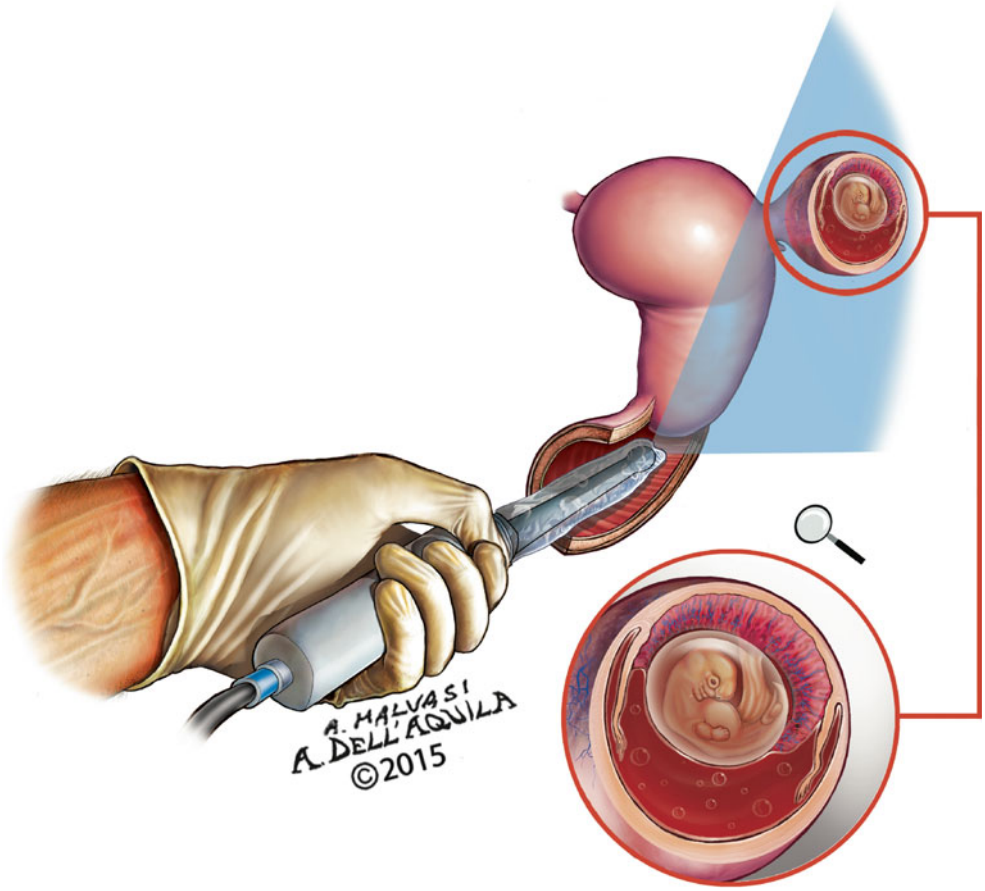


Fig. 4.31 A transvaginal pelvic scan detecting a persistent ectopic pregnancy after laparoscopic salpingostomy

persistent ectopic pregnancy in women who had 50 mg methotrexate locally injected into the tubal wall immediately following laparoscopic linear salpingostomy for tubal pregnancy [132]; none of the women who received a local methotrexate injection developed persistent ectopic pregnancy, but 17.5 % of the women in the control group did.

4.16.4 Salpingectomy Versus Salpingostomy

If the tube is ruptured or appears extensively damaged, salpingectomy may be preferred. However, there is debate over whether surgical treatment for tubal pregnancy should be a conservative salpingostomy or radical salpingectomy in women who desire a future pregnancy. Table 4.3 shows recent studies comparing outcomes of salpingostomy with salpingectomy [133–135]. An observational population-based study [133] assessed reproductive outcomes after an ectopic pregnancy based on the type of treatment used and reported that the 24-month cumulative rate of intrauterine pregnancy was 67 % after salpingectomy, 76 % after salpingostomy, and 76 % after medical treatment. In multivariate analysis, the intrauterine pregnancy rate was significantly higher after conservative treatment compared with that after salpingectomy (hazard ratio 0.784). However, two recent multicenter randomized studies denied the superiority of fertility outcomes after salpingostomy [134, 135]. The European Surgery in Ectopic Pregnancy (ESEP) study group [135] reported no significant difference in the cumulative pregnancy rate after salpingostomy (60.7 %) and after salpingectomy (56.2 %), and persistent ectopic pregnancy occurred more frequently in the salpingostomy group (7 %) than in the salpingectomy group (<1 %) (relative risk 15.0). In contrast, there was no significant difference in the incidence of repeat ectopic pregnancy between the two groups (8 % vs. 5 %). However, if a woman who has undergone salpingectomy due to previous tubal pregnancy would be occurred repeat contralateral pregnancy, the choice of salpingectomy for residual tube is not exactly for the feasibility of her future fertility. Therefore, further studies concerning to betterment of surgical treatment for fertility for women with repeat tubal pregnancy should be conducted.

4.16.5 Medication Therapy with Methotrexate

Methotrexate has been used as a unique medication therapy for tubal pregnancy, and its safety and efficacy for this

Table 4.3 Recent studies comparing salpingostomy to salpingectomy for tubal ectopic pregnancy

Authors	Study design	No. of patients	Surgical inclusion criteria	Persistent tubal pregnancy	Repeat tubal pregnancy	Cumulative pregnancy rate
de Bennetot et al. [133]	Observational population based-study	1064 salpingostomy, 646; salpingectomy, 299; Medical treatment, 119	Including symptomatic patients, ruptured tube and hCG >5000 IU/L	NA	Salpingotomy and salpingectomy, 18.5 %; medical treatment, 25.5 %	At 24 months salpingostomy, 76 %; salpingectomy, 67 %; medical treatment, 76 % $p=0.74$
Fernandez et al. [134] (The DEMETER study)	RCT	129 salpingostomy + MTX, 66; salpingectomy, 63	With hemodynamically stable, unrupured tube, and healthy contralateral tube	NA	Salpingostomy + MTX, 4 (8 %); salpingectomy, 6 (12 %) $p=0.96$	At 24 months salpingostomy + MTX, 70 %; salpingectomy, 64 % $p=0.77$, HR; 1.06, 95 % CI; 0.69–1.63
Mol et al. [135] (The ESEP study)	RCT	446 salpingotomy, 215; salpingectomy, 231	With hemodynamically stable, unrupured tube, and healthy contralateral tube	Salpingotomy, 14 (7 %); salpingectomy, 1 (<1 %), $p=0.01$	Salpingotomy, 18 (8 %); salpingectomy, 12 (5 %), $p=0.19$	At 36 months salpingotomy, 62.3 %; salpingectomy, 56.2 %, $p=0.49$, HR; 1.10, 95 % CI; 0.83–1.46

NA not applicable, *RCT* randomized controlled trial, *MTX* methotrexate, *HR* hazard ratio, *CI* confidence interval

purpose have already been proven. The use of methotrexate therapy was established in the late 1980s and has become widely accepted as a primary treatment for ectopic pregnancy, especially when an early diagnosis is made. In addition, methotrexate administration is often useful to prevent persistent ectopic pregnancy after surgery.

4.17 Mechanism of Action

Methotrexate, a folic acid antagonist that binds to the catalytic site of dihydrofolate reductase (DHFR), was the first agent to produce remission in leukemia and the first to result in the cure of a solid tumor, specifically choriocarcinoma. Folic acid is an essential component in the synthesis of DNA precursors such as purines and thymidylate [136]. Methotrexate and other folate analogs inactivate the enzyme DHFR, which leads to the depletion of tetrahydrofolate cofactors, which are required for DNA and RNA synthesis. In order to trap the folic acid analogs intracellularly, folylpolyglutamate synthetase adds extra glutamate residues onto the molecule. These residues do not cross cell membranes easily, and as such, this mechanism is efficient in increasing the intracellular concentration of the drug, thus prolonging the action of the medication within the cells. It is likely that this mechanism accounts for the feasibility of single-dose administration of the drug. Folate is reduced to tetrahydrofolate by DHFR by the addition of single-carbon groups, which are then subsequently transferred in the synthesis of DNA and RNA. Tetrahydrofolate is converted to dihydrofolate when it donates a methyl group to dUMP in the production of thymidylate. In order to keep the reaction propagating, dihydrofolate must again be reduced by DHFR to tetrahydrofolate in order to continue donating methyl groups for subsequent reactions. When DHFR is inhibited by folic acid analogs, the dihydrofolate polyglutamates build up in the cell and act as toxic substrates. When this occurs, the one-carbon transfer reactions are halted, as is the synthesis of DNA and RNA.

Folinic acid, the 5-formyl derivative of tetrahydrofolic acid, is readily metabolized in vitro by tetrahydrofolic acid and, like folic acid, also functions as a vitamin. It activates regardless of the action of DHFR and thus resolves the reduction of DHFR action caused by methotrexate, but the mechanism of this action remains unclear. Therefore, folinic acid (leucovorin) prevents some otherwise prohibitive side effects and allows for the administration of higher or multiple methotrexate doses for tubal pregnancy (leucovorin rescue). Methotrexate is rapidly cleared from the body by the kidneys, with 90 % of an intravenous dose excreted unchanged within 24 h.

4.18 Preparation of Methotrexate Treatment

Methotrexate should be administered only when a definitive pretreatment diagnosis of tubal pregnancy has been made lest women with undiagnosed miscarriage experience unnecessary side effects and costs. In addition, methotrexate carries a risk of congenital anomalies if it is administered during the first trimester of gestation. Administration of methotrexate is an option for women who do not have a ruptured tube, are hemodynamically stable, have no severe abdominal pain or signs of massive hemoperitoneum, and are reliable for continuation of follow-up until the resolution of the condition. Contraindications for methotrexate treatment are postulated by the ACOG guidelines [82]. Before treatment, adequate medical history and blood tests are essential to exclude absolute contraindications. Because methotrexate is hepatotoxic and is filtered by the kidneys, it should not be administered to women with liver or kidney disease. Patients should not be treated with methotrexate when laboratory data, such as liver transaminase levels, are outside of the normal range; other absolute contraindications include anemia, a creatinine level greater than 1.3–1.5 mg/dL, a white blood cell count <3000/μL, or a platelet count <100,000/μL [137]. Folic acid intake interferes with methotrexate efficacy and should be avoided [138]. A chest radiograph is needed to rule out pulmonary disease because methotrexate has been implicated as a cause of serious lung toxicity [139]. Relative contraindications are proposed by clinical failure of methotrexate treatment. The practice Committee of the American Society for Reproductive Medicine [140] suggested that predictive factors related to treatment failure are identified before treatment, including the presence of an ectopic mass >4 cm in diameter, visible fetal cardiac motion on ultrasound, and a serum hCG level >5000 mIU/mL, as relative contraindications. It was reported that women treated with a single-dose regimen for tubal pregnancy with an initial hCG concentration >5000 mIU/mL had a higher failure rate than did women with a lower hCG concentration (OR = 5.5; 95 % CI, 3.0–9.8) [141]. An ectopic mass with a diameter <3–4 cm by ultrasound is also commonly used as a patient selection criterion, although this has not been fully agreed on by some clinicians as a predictor of successful treatment. In addition, pregnancy after administration of methotrexate should be avoided for more than 3 months [138].

4.19 Protocols of Methotrexate Treatment

The two methotrexate protocols commonly used for ectopic pregnancy are multiple-dose and single-dose administrations. The multiple-dose protocol, which originates from early experience with methotrexate treatment for

trophoblastic disease, was first used to treat ectopic pregnancy [142]. For the multiple-dose protocol, methotrexate is intramuscularly administered at a dose of 1 mg/kg per day on days 1, 3, 5, and 7 of treatment [143]. Leucovorin is given at a dose of 0.1 mg/kg intramuscularly on days 2, 4, 6, and 8 to prevent cell toxicity from an overdose of methotrexate. Women receive up to four doses until their serum hCG level decreases by at least 15 % on two consecutive measurements, 2 days apart. All women need to be followed up until their hCG level is no longer detectable in serum. If the hCG level is confirmed to be increased or plateaued after four doses administered on day 7, an additional dose can be given 2 days later. However, surgical management may be preferable for such a condition.

Under the single-dose protocol, methotrexate is intramuscularly administered at a dose of 50 mg/m^2 body surface area [144]. Leucovorin rescue is not required because of the low dose. The advantage of this protocol is the simplified administration and less need for follow-up. However, if hCG values do not decrease by at least 15 % from the initial value between days 4 and 7 after initial administration, a second dose is administered after 1 week. Similar to the multiple-dose protocol, women are followed up until their hCG level is no longer detectable in serum.

Figures 4.32 and 4.33 show schemes of the two regimens.

4.20 Clinical Course and Side Effects of Methotrexate Treatment

Awareness of the clinical course after methotrexate treatment for ectopic pregnancy is indispensable for clinicians to immediately manage treatment failure and tubal rupture. Transient pain, the so-called separate pain, may occur between 3 and 7 days after treatment begins in some patients [145], but it normally is relieved within 4–12 h of onset. When severe and persistent pain is confirmed, surgical management should be considered with suspected rupture of the tubal ectopic mass. Signs suggesting treatment failure or possible rupture include hemodynamic instability, increasing abdominal pain regardless of trends in hCG levels, and rapidly increasing hCG concentrations (>53 % over 2 days) after four doses in the multiple-dose regimen or after two doses in the single-dose regimen [146]. Although methotrexate-related toxicity may include leukopenia, thrombocytopenia, pancytopenia, nausea, vomiting, stomatitis, mucositis, and liver and lung toxicity, these side effects are very uncommon. A previous retrospective study demonstrated that 2 % of 50 patients developed stomatitis, all of which resolved spontaneously [144]. In addition, a literature review showed that the single-dose regimen was associated with fewer side effects (OR = 0.44) compared with the multiple-dose regimen [147].

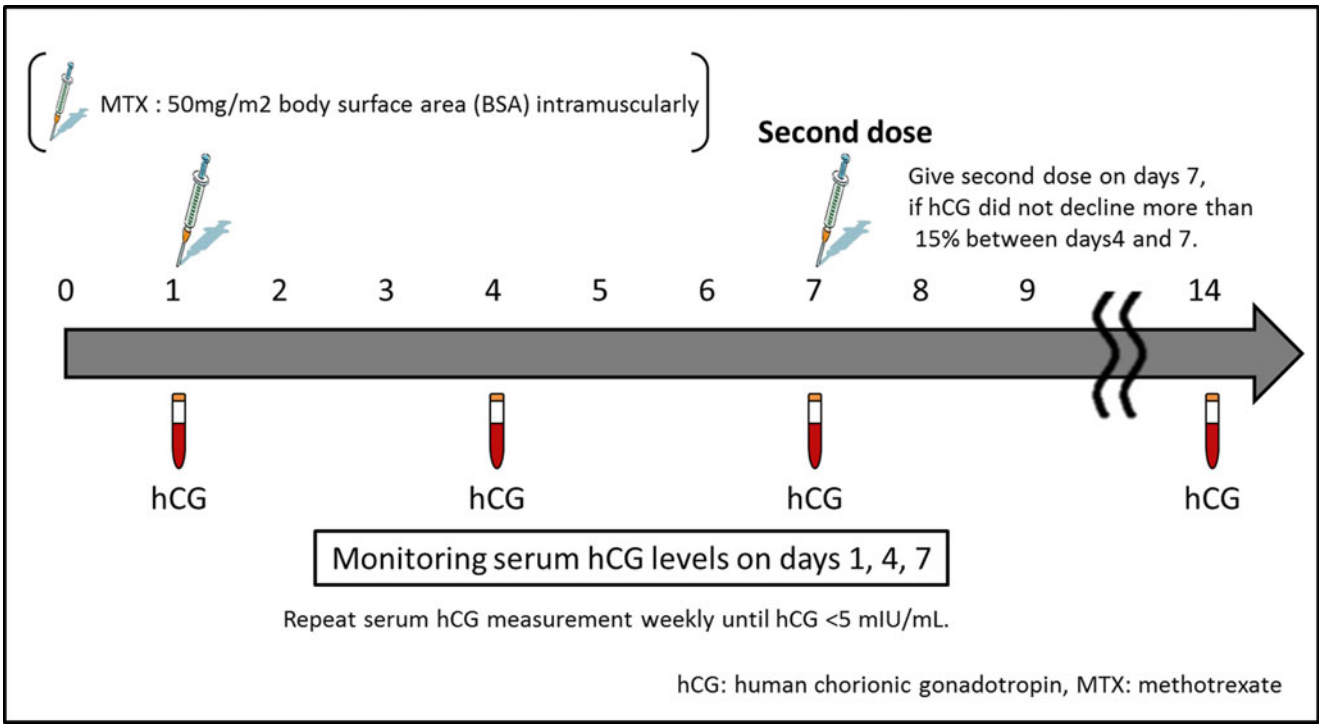


Fig. 4.32 The methotrexate protocol commonly used for ectopic pregnancy by single-dose administration. *hCG* human chorionic gonadotropin, *MTX* methotrexate

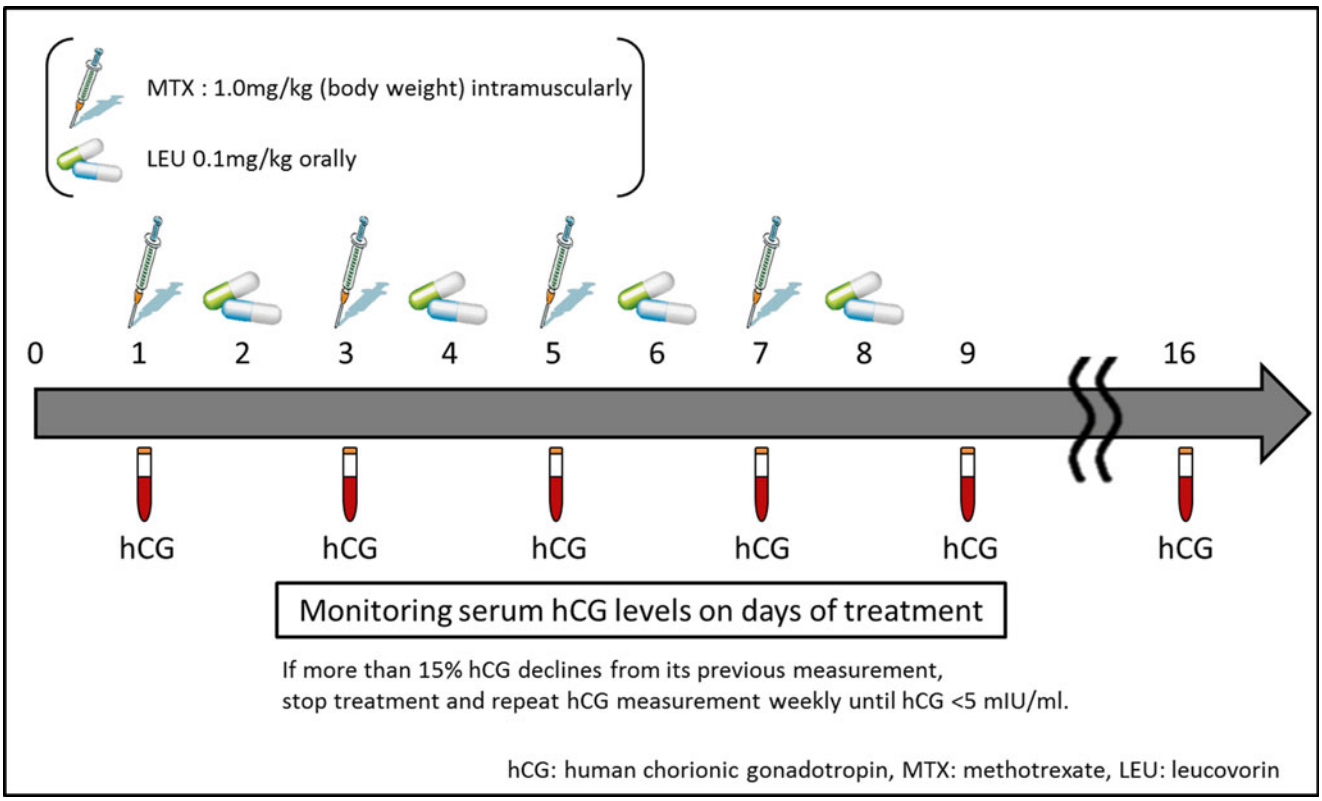


Fig. 4.33 The methotrexate protocol used for ectopic pregnancy by multiple-dose administrations. *hCG* human chorionic gonadotropin, *MTX* methotrexate, *LEU* leucovorin

4.21 Clinical Efficacy of Methotrexate Treatment

Table 4.4 shows recent studies comparing single-dose with multidose regimen [147–150]. A meta-analysis [147] of 26 articles including 1327 cases of women diagnosed with ectopic pregnancy treated with methotrexate reported an overall success rate of 89 % for women treated with methotrexate for an ectopic pregnancy, including single-dose and multiple-dose regimens. The presence of embryonic cardiac activity noted on ultrasound was significantly associated with treatment failure (OR 9.09; 95 % CI, 3.76–21.95). A total of 36.2 % of women experienced side effects, including nausea, diarrhea, mouth sores, or an increase in liver transaminases. The presence of abdominal pain was reported in 28.3 % of women. The overall success rate in 1067 women managed with the single-dose regimen was 88.1 % and that in the 260 women managed with the multiple-dose regimen was 92.7 %. Of the women who received the single-dose regimen, 14.5 % received more than one dose of methotrexate and 1 % received three or more doses. Of the women treated with the multiple-dose regimen, 53.5 % received four or more doses and 6.8 % received more than five doses. The single-dose regimen for ectopic pregnancy was significantly associated with a higher failure rate compared with the multiple-dose regimen; however, women treated with the single-dose regimen had significantly fewer side effects. Two randomized studies demonstrated that the success rate of the single-dose regimen was the same as that of the multiple-dose regimen [149, 150]. Another randomized study compared the success rate of the single-dose regimen with that of the multiple-dose regimen in 108 patients presenting with unruptured ectopic pregnancies with hemodynamic stability, tubal mass <3.5 cm in diameter, absence of fetal cardiac activity, and hCG <15,000 mIU/mL and found no significant difference between the two groups (88.9 % vs. 92.6 %) [149]. Although the number of doses of methotrexate in the multiple-dose group was higher, no significant difference between the two groups was found in the incidence of complications. Another randomized study evaluated 120 women with unruptured tubal pregnancy who met the criteria for hemodynamic stability, serum hCG levels reaching a plateau or increasing by <50 % in 48-h intervals, and an adnexal mass ≤3.5 cm in diameter and found no significant difference in the success rates between the single-dose and multiple-dose regimens (80.6 % vs. 89.7 %, $p = 0.21$) [150]. The mean number of days until the hCG level dropped <5 mU/mL was significantly longer in the single-dose group than in the multiple-dose group (22.3 ± 7.6 vs. 18.3 ± 10.7 days, $p = 0.03$). However, the incidence of side effects was signifi-

Table 4.4 Studies compared single-dose with multidose regimen for tubal ectopic pregnancy

Authors	Study design	No. of patients	Inclusion criteria	Success rate
Barnhart et al. [147]	Meta-analysis	Single-dose regimen, 1067; multidose regime, 260	NA	Single-dose, 88.1 %; multidose, 92.7 % $p=0.035$
Lipscomb et al. [148]	Retrospective cohort study	Single-dose regimen, 546; multidose regimen, 97	Ectopic mass, < 3.5–4 cm; absence of fetal cardiac activity	Single-dose, 90 %; multidose, 95 % $p=0.18$
Alleyassin et al. [149]	RCT	Single-dose regimen, 54; multidose regimen, 54	Ectopic mass, < 3.5 cm; absence of fetal cardiac activity serum hCG < 15,000 mIU/mL	Single-dose, 88.9 %; multidose, 92.6 % $p=0.07$, OR; 0.64, 95 % CI; 0.17–2.4
Guvendag Guven et al. [150]	RCT	Single-dose regimen, 62; multidose regimen, 58	Hemodynamically stable ectopic mass, <3.5 cm; absence of fetal cardiac activity serum hCG with plateau or increasing ≦50 % in 48-h interval	Single-dose, 80.6 %; multidose, 89.7 % $p=0.21$, OR; 0.90, 95 % CI; 0.77–1.05

NA not applicable, *RCT* randomized controlled trial, *OR* odds ratio, *CI* confidence interval

cantly higher in the multiple-dose group (48.3 % vs. 27.7 %, $p=0.02$). The authors concluded that the multiple-dose methotrexate regimen for unruptured tubal pregnancy is not more effective than a single-dose regimen.

4.22 Efficacy of Local Injection of Methotrexate

Although the population in studies of local injection is limited, some clinicians described that local injection of methotrexate is acceptable for women who have a tubal pregnancy with a high serum hCG concentration, large conceptus size, and the presence of fetal cardiac activity. A retrospective study including 12 women with ectopic pregnancy and fetal cardiac activity treated by combined local and systemic injection of methotrexate reported a success rate of 91.6 % [151]. A study evaluating the efficacy of a systemic multiple-dose regimen combined with ultrasound-guided local injection of methotrexate in 82 women with tubal pregnancies showed that the success rate in women who received combined therapy was higher than that in women who received only systemic treatment (93.3 % vs. 73.0 %, $p=0$ .05) [152]. The proportion of women in the systemic treatment group who received more than two injections of methotrexate was significantly greater than that in the combination treatment group (48.6 % vs. 15.6 %, $p=0.002$). The local injection of methotrexate is sometimes useful for women relative contraindications for methotrexate treatment; however, technical difficulties with this technique remain.

4.23 Surgery Versus Methotrexate Treatment

Several randomized controlled studies comparing methotrexate treatment with laparoscopic surgery for tubal pregnancy [153–157] demonstrated that methotrexate treatment is equal to laparoscopic surgery in selected women. In addition, it has also been reported that fertility after both treatments does not differ. A randomized controlled trial of comparison 34 women who received systemic methotrexate with 40 who underwent laparoscopic salpingostomy found that the cumulative spontaneous intrauterine pregnancy rates at 18 months were with not significantly different: 36 % and 43 %, respectively [155]. A recent randomized study comparing outcomes of single-dose methotrexate treatment for tubal pregnancy with laparoscopic surgery in 106 women with hemodynamic stability, a gestational sac diameter <3.6 cm, and plasma hCG <2000 IU/L [156] found no significant difference in the success rates and subsequent spontaneous intrauterine pregnancy rate between the two groups (74 % with methotrexate treatment vs. 87 % after surgery and 73 % with methotrexate treatment vs. 62 % after surgery, respectively). In contrast, systemic methotrexate therapy was reported to have a more negative impact on patients' health-related quality of life than laparoscopic surgery. A randomized controlled trial including 79 hemodynamically stable women with unruptured tubal pregnancy without signs of active bleeding compared patients' health-related quality of life after systemic methotrexate therapy and after laparoscopic salpingostomy [157]. The authors found that health-related quality of life, assessed using the Medical Outcomes Study Short-Form 20, was more severely impaired after methotrexate treatment than after laparoscopic salpingostomy. Physical functioning, role functioning, social functioning, mental health, health perceptions, and pain were all worse in the methotrexate treatment group than in the surgery group.

4.24 Summary

Although tubal pregnancy is a common gynecologic condition and the risk factors have been evaluated, the specific etiology is not yet fully clear. Therefore, further study is needed

Fig. 4.34 Schematic laparoscopic treatment of a tubal pregnancy. First step: tubal incision by monopolar instrument (croquet needle)

Fig. 4.35 Schematic laparoscopic treatment of a tubal pregnancy. Second step: extrauterine pregnancy removal

to elucidate the etiology of tubal pregnancy for better prevention and for the development of novel diagnostic procedures and therapy. Accurate earlier diagnosis for tubal pregnancy is mandatory to facilitate prompt management to prevent maternal fatal outcomes.

At present, although it seems that surgical and medical treatments have already been established, it is suggested that more minimally invasive (Figs. 4.34, 4.35, 4.36, and 4.37), as well as cost-effective, therapies and treatments could be developed in an effort to avoid deterioration in the health-related quality of life of patients.

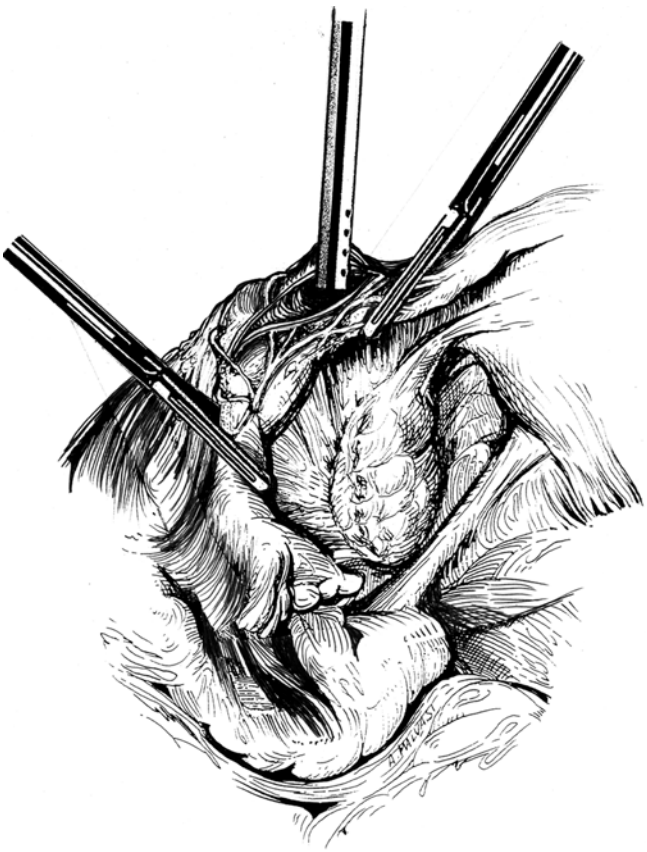


Fig. 4.36 Schematic laparoscopic treatment of a tubal pregnancy. Third step: intra-tubarian suction of residual fragments of extrauterine pregnancy

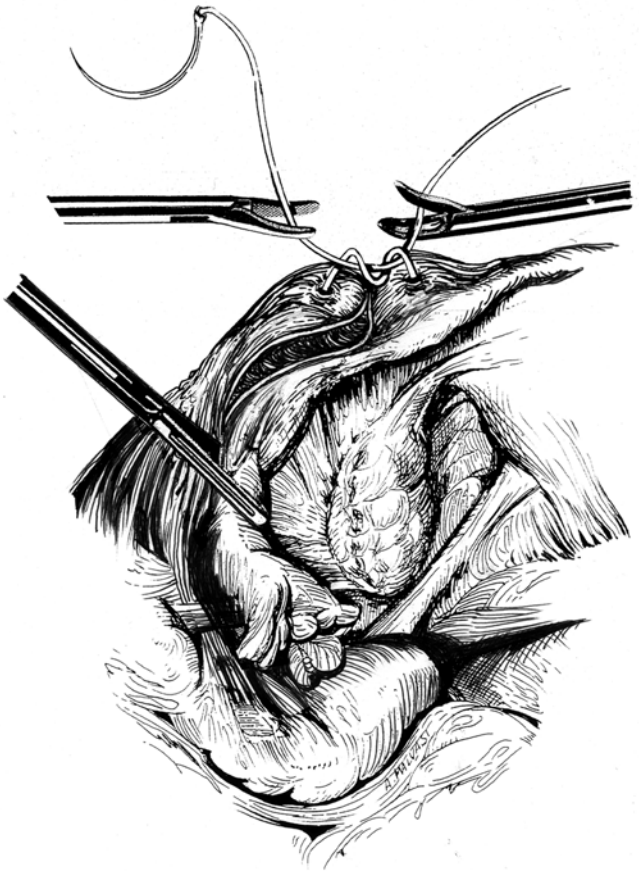


Fig. 4.37 Schematic laparoscopic treatment of a tubal pregnancy. Fourth step: anastomotic and hemostatic suturing of the incised fallopian tube

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Non-tubal Ectopic Pregnancies: Diagnosis and Management

5

Louise P. King, Jessica Kuperstock, Leonardo Resta, Andrea Tinelli, and Camran Nezhat

5.1 Diagnosis and Management

5.1.1 Incidence

Non-tubal ectopic pregnancies include those pregnancies occurring outside the uterus and tubes. Up to 98 % of ectopic pregnancies occur in the fallopian tubes. By contrast, non-tubal ectopic pregnancies occur with the following frequencies: 2.4 % interstitial, 12 % isthmic, 70 % ampullary, 11.1 % fimbrial, 3.2 % ovarian, and 1.3 % abdominal [1].

5.1.2 Definitions

There is some confusion regarding terminology when discussing non-tubal pregnancy [2]. The terms "interstitial" and "cornual" pregnancy are frequently used synonymously. Additionally, the term "cornual" pregnancy is sometimes used to described pregnancies in bicornuate or septate uteri, while *Williams Obstetrics* defines a cornual pregnancy as one occurring in the upper and lateral uterine cavity of an anatomically normal uterus [2, 3] (Fig. 5.1).

Angular pregnancy is a term not frequently used but defines a pregnancy just medial to the uterotubal junction, in the lateral angle of the uterine cavity, displacing the round ligament upward and outward [2]. An angular pregnancy can migrate to become a normal intrauterine pregnancy (Fig. 5.2).

By contrast, an interstitial pregnancy is found lateral to the round ligament [2] (Fig. 5.3).

An abdominal pregnancy is defined by lack of myometrium around the outside of the gestational sac or its location remote from the uterus (Fig. 5.4).

Using correct and clear terminology is becoming increasingly important. Traditionally, laparoscopy was the gold standard for the diagnosis of an ectopic pregnancy. However, increasingly, the use of imaging and serum assays has made laparoscopy for the purpose of diagnosis less important [2]. For this chapter, we will use the following definitions. Interstitial will refer to a pregnancy implanted within the proximal portion of the fallopian tube embedded within the muscular wall of the uterus. Cornual will refer to a pregnancy in a bicornuate or septate uterus. Angular will refer to an intrauterine pregnancy implanted medial to the uterotubal junction. Ovarian will refer to a pregnancy occurring within the ovary itself. Abdominal will refer to pregnancies occurring on the peritoneal surface or abdominal viscera.

L.P. King, MD, JD (✉)
Department of Obstetrics and Gynecology,
Beth Israel Deaconess Medical Center,
Harvard Medical School and Center for Bioethics,
Boston, MA, USA
e-mail: lpking@bidmc.harvard.edu

J. Kuperstock, MD
Department of Obstetrics and Gynecology,
Beth Israel Deaconess Medical Center, Harvard Medical School,
Boston, MA, USA

L. Resta, MD
Section of Pathological Anatomy,
Department of Emergency and Organ Transplantation (DETO),
University of Bari, Bari, Italy
e-mail: leonardo.resta@uniba.it

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital,
Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny,
Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

C. Nezhat, MD
Center for Special Minimally Invasive Surgery,
Stanford Medical Center, Palo Alto, CA, USA
e-mail: nezhatinstitute@gmail.com

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_5

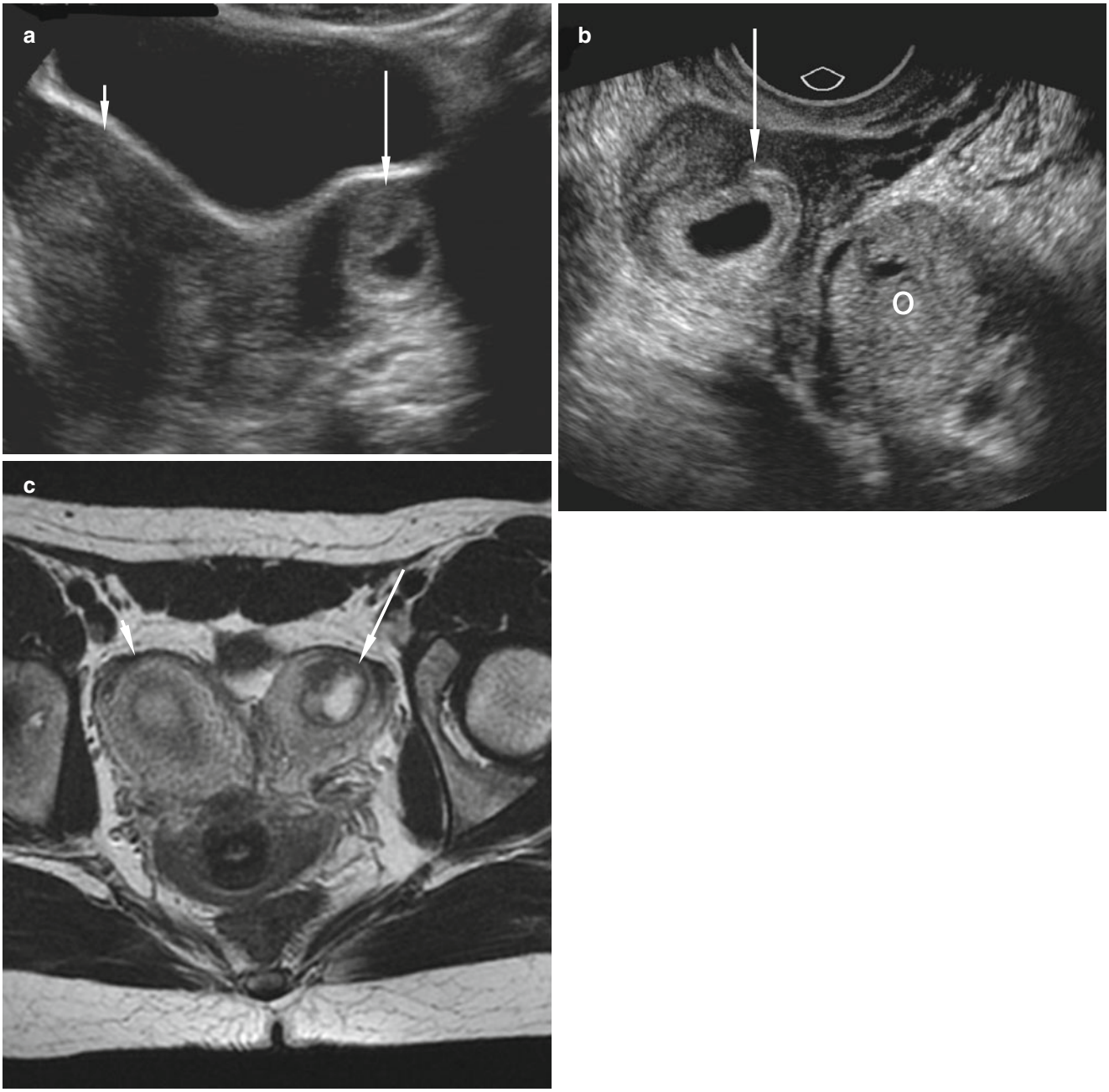


Fig. 5.1 Three images of cornual ectopic (Courtesy of Dr. Deborah Levine, MD, Boston, Massachusetts). (**a**) Transverse transabdominal sonogram shows a right horn (*short arrow*) and smaller left horn (*long arrow*) with the gestational sac. (**b**) Transvaginal sonogram shows the pregnancy in the left horn (*arrow*) adjacent to the ovary (*O*). Note how the myometrium is very thin posterior to the gestational sac. (**c**) Slightly angled axial T2-weighted MR image shows the right horn of the uterus (*short arrow*) and left horn with the gestational sac (*long arrow*). On other images, the left horn was seen to be atrophic and did not communicate with the cervix

5.1.3 Risk Factors

The risks factors for non-tubal ectopic pregnancy are the same as for tubal ectopics. They are addressed in detail in prior chapters. In short, prior history of medically treated ectopic and disruption of tubal or pelvic anatomy from infection, prior surgery, or endometriosis are the major risk factors. Cervical and interstitial pregnancies are also encountered more frequently following in vitro fertilization at a rate of 1.6 % as compared to 19 per 1000 in the general population [4].

5.1.4 Diagnosis by Imaging and Serum Testing

The diagnosis of an ectopic pregnancy is made using a combination of serum human chorionic gonadotropin (hCG) and

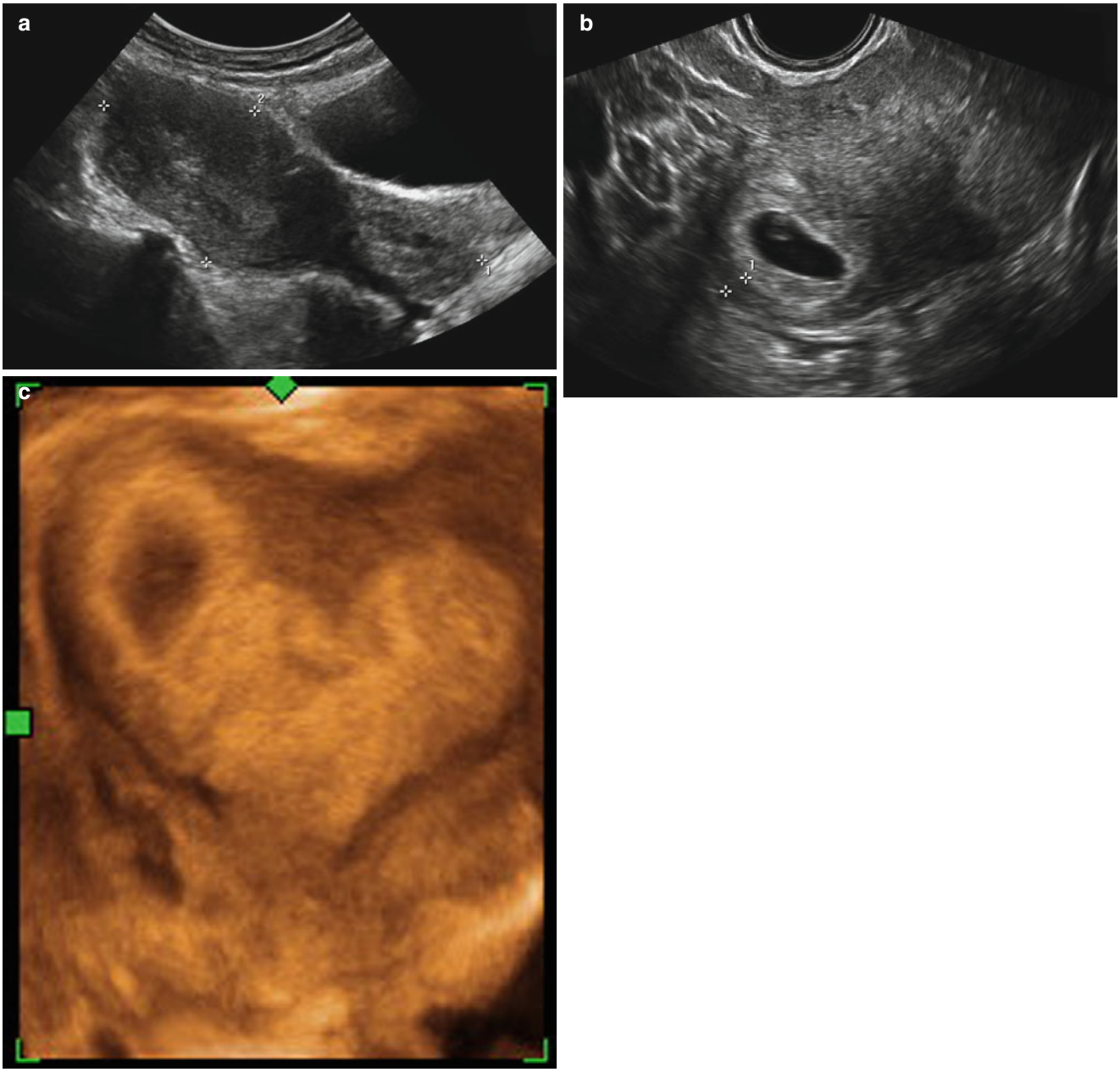


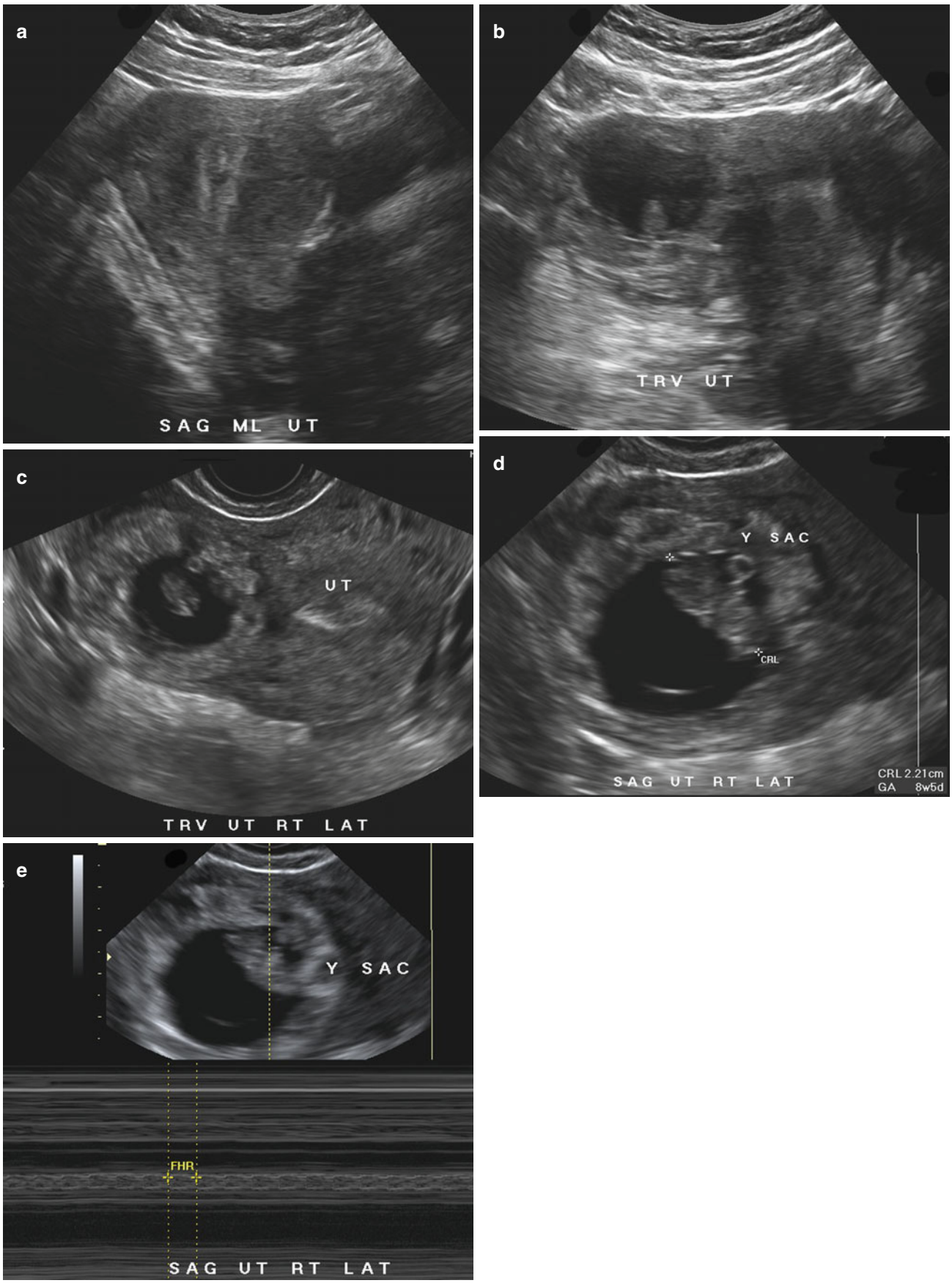
Fig. 5.2 Three images of angular pregnancy (Courtesy of Dr. Deborah Levine, MD, Boston, Massachusetts). (**a**) Transabdominal image of the uterus in a patient 6 weeks and 5 days pregnant by dates shows the endometrial cavity to appear normal without a gestational sac in the midline. (**b**) Transvaginal image angled to the right shows that the gestational sac is high and on the right. There is only 4 mm of myometrium (calipers) between the sac and the uterine serosa (not shown is the yolk sac and 3 mm embryo). (**c**) Coronal reconstructed image shows that the gestational sac is high on the right but does communicate with the endometrial cavity. The patient was closely followed. Two weeks later the sac was still in a high position with only 3 mm of myometrium around it on the right. By 9 weeks the concerning appearance had resolved and the gestational sac was centrally located in the uterus. The pregnancy was delivered at term

findings on transvaginal ultrasound. Discussion of diagnosis of specific non-tubal ectopic pregnancies can be found in the following sections. The most common presentation remains first trimester vaginal bleeding with or without abdominal pain [5]. Multiple algorithms exist to guide testing for suspected ectopic pregnancy and have been reviewed in depth elsewhere [6].

5.2 Interstitial Ectopic Pregnancy

5.2.1 Incidence and Diagnosis

Interstitial pregnancies are rare, accounting for only 2–4 % of tubal pregnancies [7]. However, because these pregnancies implant in a portion of the fallopian tube that traverses


a
SAG ML UT
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d
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CRL 2.21cm
GA 8w5d
e
Y SAC
FHR
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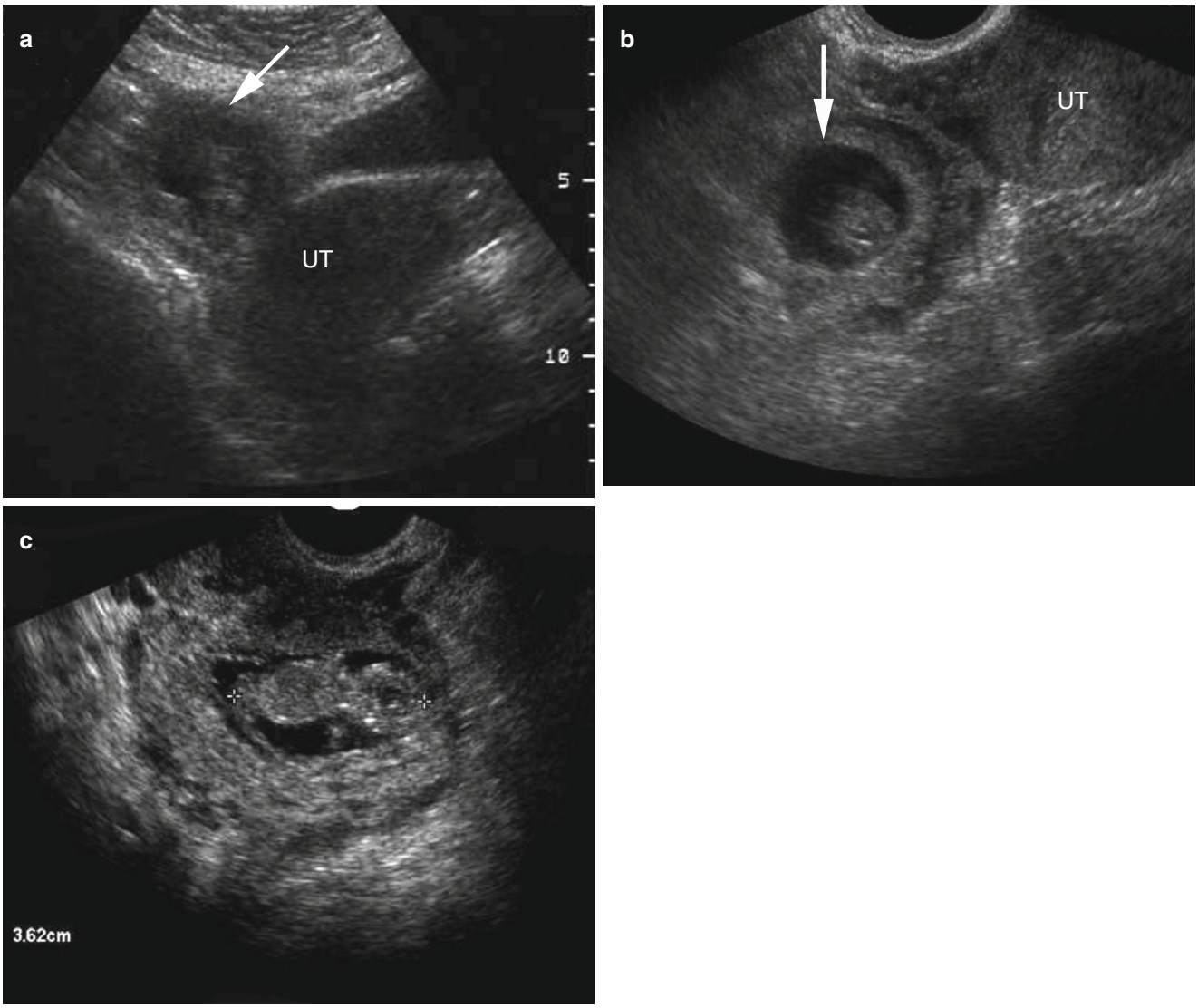

Fig. 5.4 Three images of abdominal pregnancy (Courtesy of Dr. Deborah Levine, MD, Boston, Massachusetts). (**a**) Transabdominal image shows a retroflexed uterus (*UT*) and mass/ectopic pregnancy (*arrow*) above it. (**b**) Transvaginal image shows the gestational sac (*arrow*) to be completely outside of the uterus. (**c**) Crown rump length of 3.3 cm in the live ectopic. Note that there is no myometrium around the outside of the gestational sac

Fig. 5.3 Five images of interstitial pregnancy (Courtesy of Dr. Deborah Levine, MD, Boston, Massachusetts). (**a**) Transabdominal sagittal image of the uterus shows empty endometrial cavity. (**b**) Transabdominal transverse image of the uterus shows empty endometrial cavity and the gestational sac off to the right, separate from the endometrial cavity. (**c**) Transvaginal image shows a gestational sac on the right, without endometrium surrounding it laterally compatible with interstitial ectopic pregnancy. (**d**) Transvaginal image shows a CRL in the ectopic pregnancy of 22 mm corresponding to 8 weeks and 5 days, which is almost 4 weeks greater than age by dates of 5 weeks and 1 day. (**e**) M-mode shows live ectopic pregnancy with a heart rate of 178 beats per minute

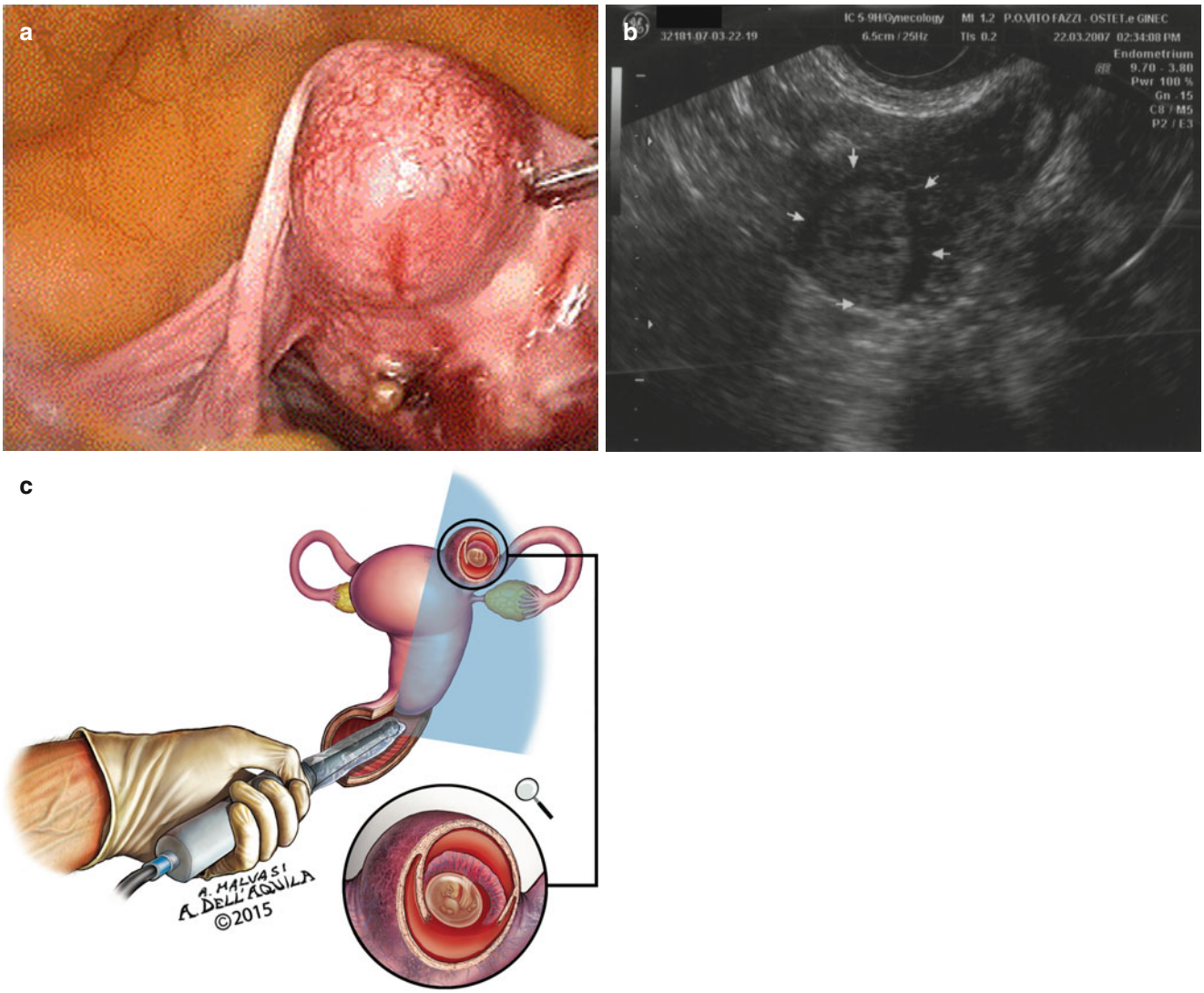

Fig. 5.5 (**a**) Laparoscopic image of interstitial pregnancy at 6 weeks. (**b**) Ultrasonographic transvaginal uterine section of an interstitial pregnancy, with a chorionic sac greater than 1 cm separate from the lateral edge of the uterine cavity with a thin myometrial layer. (**c**) A figure representing an interstitial pregnancy at 6 weeks

the muscular wall of the uterus, they are surrounded by thicker tissue with a great capacity to expand (Fig. 5.5a) [2, 7]. Thus, interstitial pregnancies may remain asymptomatic for longer than those found in other portions of the fallopian tube as the muscular wall expands to accommodate. Interstitial pregnancies are less likely to present with vaginal bleeding. Rupture later in pregnancy, as late as 7–16 weeks, can result in catastrophic hemorrhage given the abundant vascular supply in this area of the uterus fed by both the uterine and ovarian arteries [7].

As mentioned above, interstitial, cornual, and angular pregnancies can be managed very differently. Both cornual and angular pregnancies can potentially be viable intrauterine pregnancies. Thus, it is important to ensure that communication with your radiologist is clear and the diagnosis is established appropriately with high-resolution ultrasound or diagnostic laparoscopy if necessary.

Ultrasound findings will include an empty uterine cavity and a chorionic sac greater than one centimeter separated from the lateral edge of the uterine cavity with a thin myometrial layer (Fig. 5.5b, c) [8]. 3D ultrasound or MRI will allow for more accurate diagnosis if interstitial pregnancy is suspected and the patient is stable [9]. Findings on MRI will include a heterogenous mass with intermediate/high T2 hyperintensity surrounded by myometrium which is T2 hypodense or an intact junctional zone which is hypodense, adjacent to T2 bright endometrium. There should be an "interstitial line sign" or echogenic line in the corneal region bordering the midportion of the sac found in both ultrasound and MRI [7, 9]. In between 56 and 71%, diagnosis can be reliably made ahead of surgery [7].

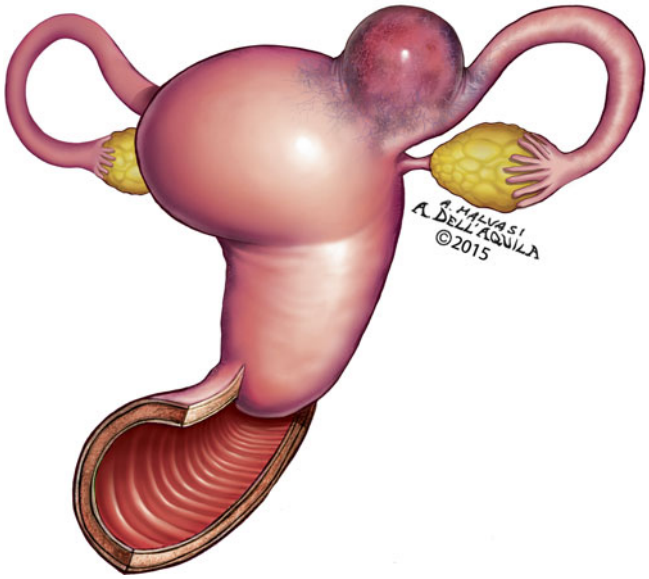

Fig. 5.6 Interstitial pregnancy

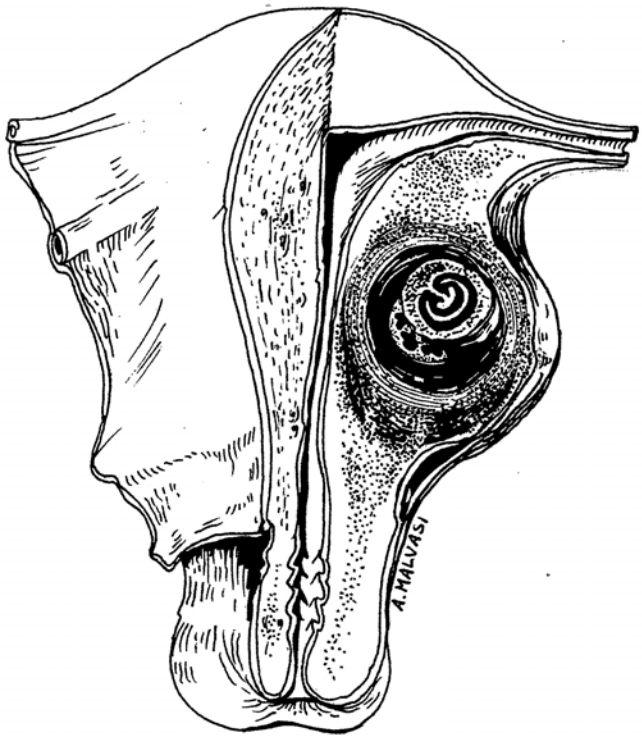

Fig. 5.7 Interstitial pregnancy to treat by wedge resection, involving removal of the pregnancy and surrounding myometrium

Assuming a conclusive diagnosis is not made by imaging, at laparoscopy an angular pregnancy will appear as an asymptomatic bulge deflecting the round ligament laterally (Fig. 5.6), while an interstitial pregnancy will appear lateral to the round ligament [7].

5.2.2 Risk Factors

Risk factors for interstitial pregnancy include in vitro fertilization, ovulation induction, uterine anomalies, prior salpingectomy, history of prior ectopic pregnancy, and history of prior infection [10].

5.2.3 Treatment

5.2.3.1 Surgical Treatment

In the past, interstitial pregnancy was treated with exploratory laparotomy and wedge resection. Wedge resection involved removal of the pregnancy and surrounding myometrium (Fig. 5.7). Given the highly vascular nature of this area of the uterus, total abdominal hysterectomy was sometimes required (Fig. 5.8a, b) [7].

5.2.3.2 Laparoscopy

Laparoscopic wedge resection is now possible especially earlier in gestation (Fig. 5.9a, b). The area around the ectopic should be injected with a solution of vasopressin ahead of resection. Resection can be accomplished with cold scissors or an energy source such as the harmonic scalpel or LigaSure.

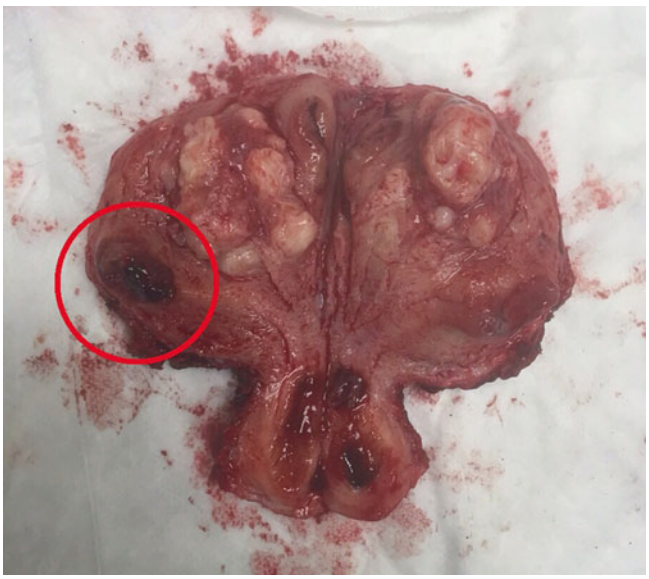

Fig. 5.8 Total abdominal hysterectomy for an interstitial pregnancy (*highlighted in the red ring*); (**a**) uterus in two midsections, with multiple intramural fibroids

The fallopian tubes and mesosalpinx can be removed if necessary during the resection. The defect is usually closed in a manner similar to that used during myomectomy with layering of suture to achieve hemostasis and restore anatomy [7].

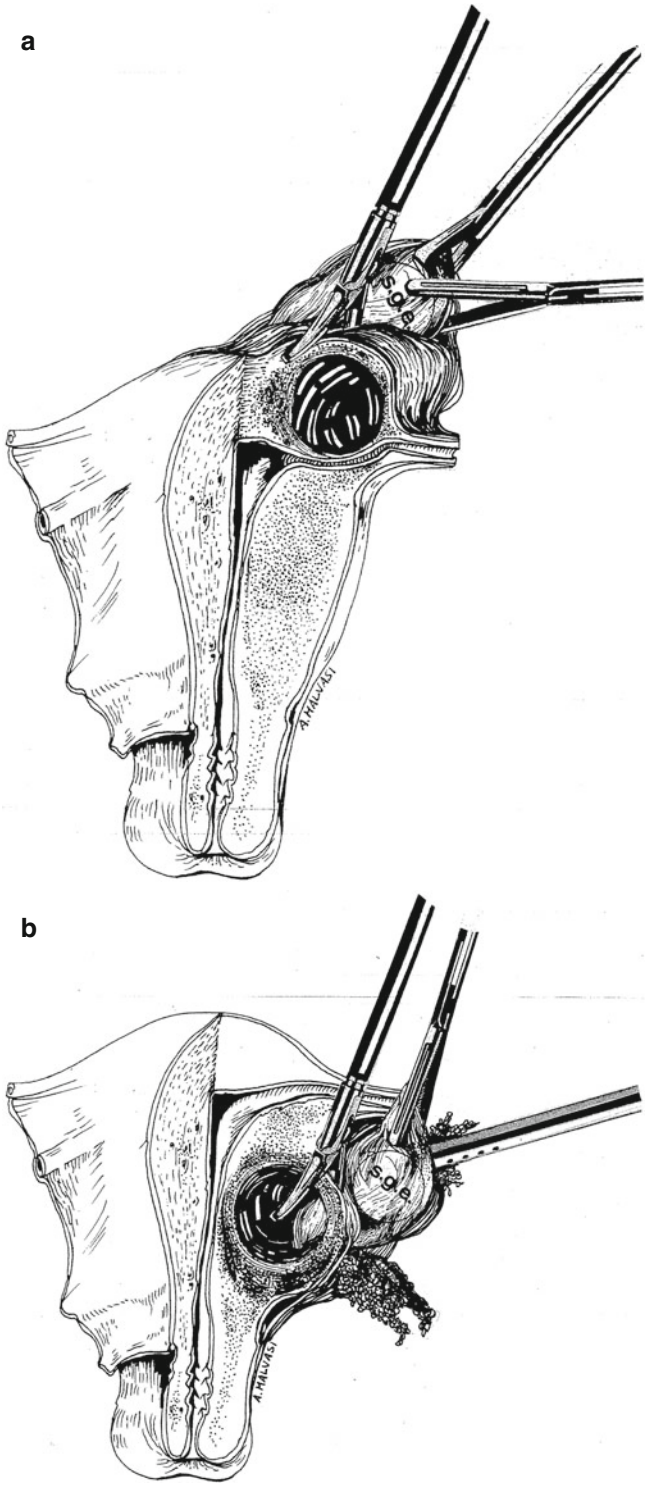

Fig. 5.9 (**a**) Ectopic pregnancy resection can be accomplished by cold scissors. (**b**) The ectopic pregnancy is laparoscopically completely removed

A minicornual excision or cornuotomy (Fig. 5.10a) can be undertaken during which an elliptical incision is made along the long axis of the pregnancy after vasopressin is injected. The area is "de-roofed" by excising the myometrial layer. The pregnancy is shelled out (Fig. 5.10b) and judicious cautery or suturing is used (Fig. 5.10c) to control bleeding, thus preserving to some extent the myometrium and vascular supply [7, 9, 11]. The risk taken when performing a salpingotomy or cornuotomy is that the cornual area will become weak and allow for future rupture.

5.2.3.3 Hysteroscopy

Successful hysteroscopic resection has been described. Using atraumatic graspers from a laparoscopic approach, the interstitium is pushed into the cavity allowing hysteroscopic resection using a 90° loop and electrocautery [12, 13].

Thus, multiple approaches have been described to surgical treatment of interstitial ectopic pregnancies but the optimal surgical treatment has yet to be established. Further study is warranted.

5.2.3.4 Management of Potential Hemorrhage

The key to any successful surgical treatment of interstitial pregnancy is to minimize blood loss. Given the highly vascular nature of these lesions, significant hemorrhage can occur quickly. Multiple methods to decrease blood loss have been described. Vasopressin solutions can be injected into the myometrium at the base of lesion ahead of dissection. One suggested dose of vasopressin is 10 units diluted in 10–100 ml of normal saline solution. As with myomectomy, the total dose used should not exceed 4 units to avoid risk of bradycardia, cardiovascular collapse, and death [14, 15]. Vasopressin should not be used in women with contraindications such as cardiovascular, vascular, or renal disease. Care should be taken to avoid intravascular injection.

The ascending branch of uterine artery can be occluded by suture ligation or electrocautery ahead of dissection with suture. Sutures can be placed under the pregnancy ahead of dissection [7]. However, this technique as with suture closure of the defect can result in anatomic distortion and tubal occlusion. Patients should be informed of this possibility ahead of surgery.

5.2.3.5 Ancillary Treatments

A variety of ancillary techniques have also been described in the literature. In 2015, Takeda et al. described diagnosis of an unruptured interstitial pregnancy by MRI that was treated by initial devascularization with transcatheter arterial chemoembolization. Thereafter, the interstitial gestational products were removed hysteroscopically under laparoscopic guidance. The patient subsequently had a successful pregnancy delivered by cesarean section and the authors noted that the interstitial portion of her uterine wall was well preserved [8].

In their review, Fornazari et al. describe various interventional radiology procedures that can assist or fully treat non-tubal ectopic pregnancies [16]. Methotrexate can be directly injected into the gestational sac, ensuring high local concentrations and

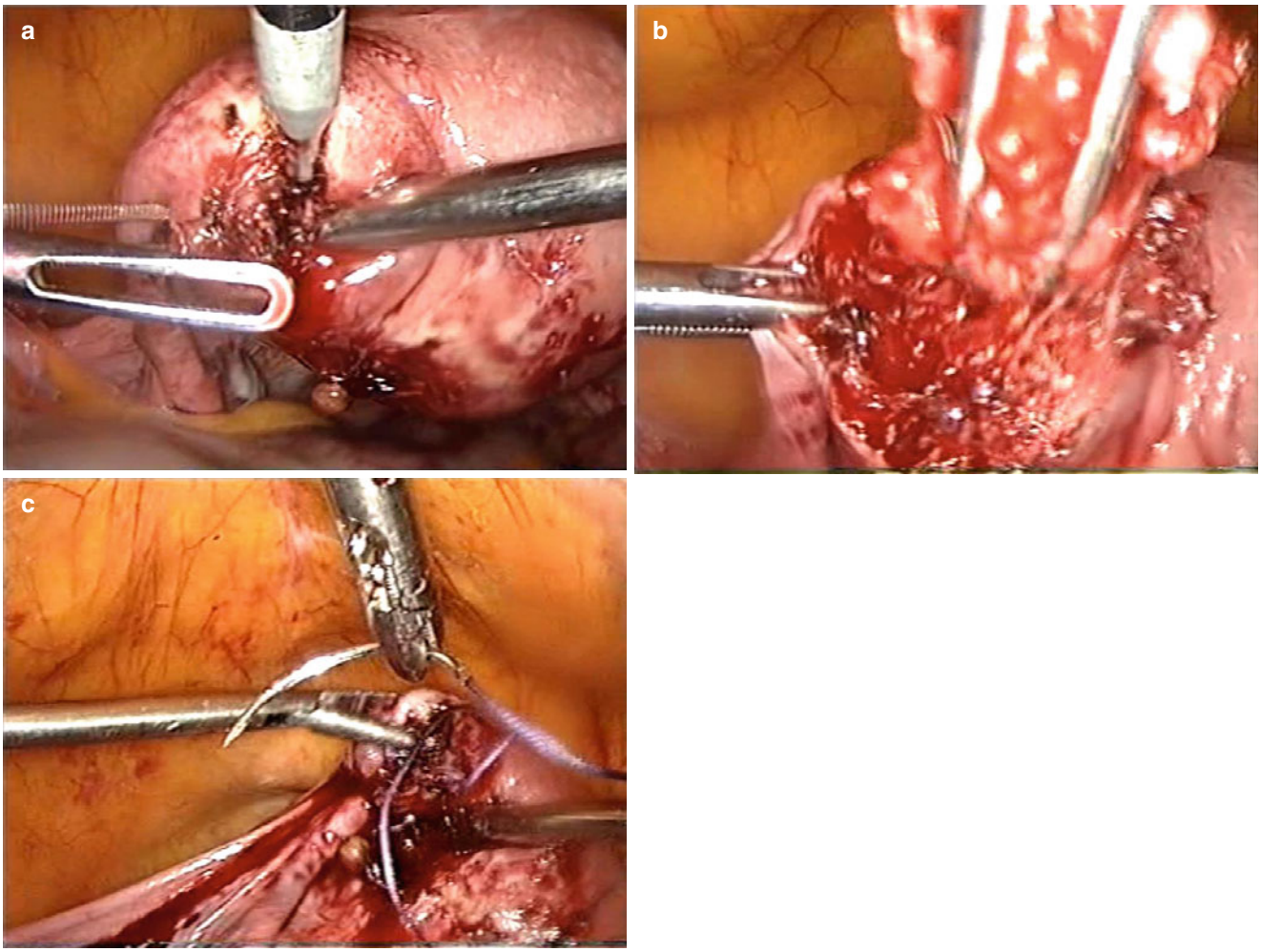

Fig. 5.10 (**a**) Cornuotomy by a laparoscopic monopolar croquet needle. (**b**) Laparoscopic pregnancy is shelled out by Johannes clamps. (**c**) Laparoscopic suturing of the cornual edges

lowering the risk of systemic toxicity. In the presence of contraindications to methotrexate (liver disease, severe pulmonary disease, blood dyscrasia, or others), potassium chloride and hyperosmolar glucose can be injected. Alternatively, methotrexate can be infused into the uterine arteries followed by microsphere embolization. This would ensure direct exposure of the embryo to a high dose of methotrexate, consequently, greater ischemia and trophoblastic degeneration, and reduction of side effects. Neither of these techniques has been studied rigorously to date and further study is warranted.

5.2.3.6 Medical Treatment

Experience with systemic medical treatment of interstitial ectopic pregnancy has been described in the literature although case reports are limited. Success rates have been reported as high as 83 % for systemic combined with local treatment [17]. By contrast, a retrospective study of 31 patients with ultrasound-guided local injection and systemic methotrexate for viable unruptured interstitial pregnancies noted a success rate of only 66.7 % [18]. As up to 30 % of patients may require urgent surgery posttreatment, patients must be watched closely should they opt for medical management. Other agents used for medical therapy have very limited evidence (KCl, etoposide, and actinomycin). Further study is warranted.

5.3 Angular Pregnancies

As described earlier in this chapter, angular pregnancy is a term not commonly used. There are minimal case reports in the literature. Expectant management while likely not appropriate for interstitial pregnancy given the risk of catastrophic rupture is potentially appropriate for angular pregnancy (Fig. 5.11). Angular pregnancies can proceed forward to intrauterine pregnancies that may end in miscarriage or potentially term gestation. Thus, accurate diagnosis by high-level imaging is essential (Fig. 5.12). Case reports have

described multiple treatment modalities including suction curettage under laparoscopic guidance [19], hysteroscopic resection [20], diagnostic hysteroscopy and laparoscopy with salpingectomy and cornuostomy and subsequent adjuvant methotrexate [21], and methotrexate alone [22]. Some of these case reports likely address interstitial pregnancies. Careful use of terminology should be encouraged to avoid confusion in the literature.

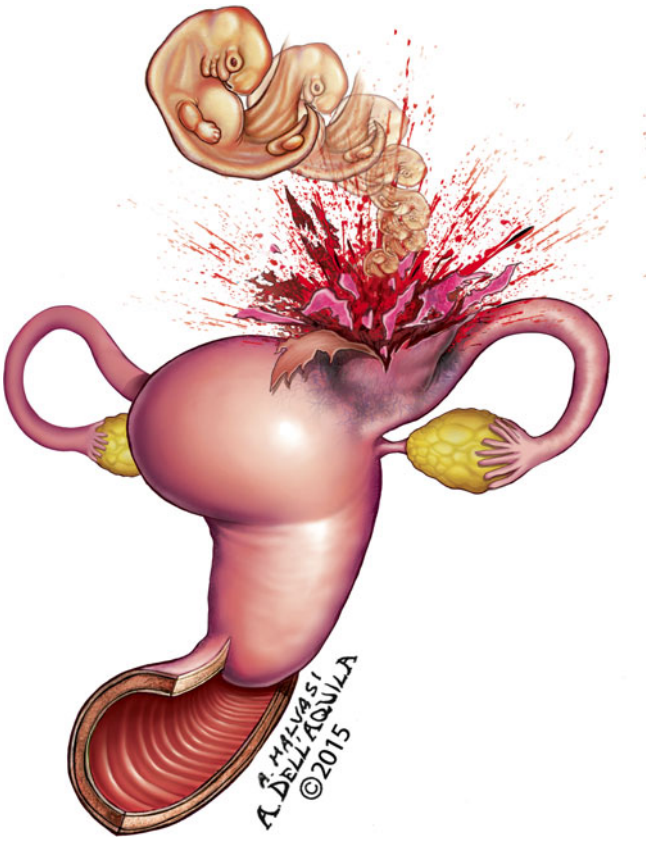

Fig. 5.11 Interstitial pregnancy with its catastrophic rupture and embryo expulsion of pregnancy

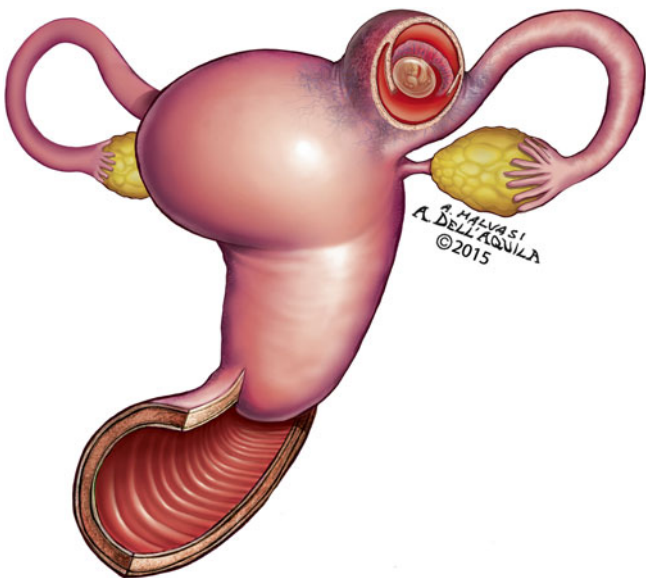

Fig. 5.12 Figure shows an interstitial pregnancy with the embryo inside

5.4 Cornual Ectopic Pregnancy

5.4.1 Diagnosis

The classic definition of cornual ectopic pregnancy is one that arises in one horn of a bicornuate or septate uterus (Fig. 5.13) [2]. Others, including *Williams Obstetrics*, would define a corneal pregnancy as one arising in the cornual region of a normal uterus (Fig. 5.14), aka upper and lateral uterine cavity, while still others would define this entity as one in the rudimentary horn of a unicornuate uterus [23]. Given this confusion in definitions, review of the literature surrounding this type of ectopic is difficult. It can be treated laparoscopically.

5.4.2 Treatment

In 2009, Chetty described treatment of a pregnancy in a rudimentary horn by either laparotomy or laparoscopic excision of the rudimentary horn [23]. A small review is available describing medical treatment in 27 cases of unusual ectopics including six cornual ectopics treated with KCl injection. Three were treated with transvaginal ultrasound guidance; three were treated with transabdominal ultrasound guidance. Five of the six resolved over a course of between 1 and 5 months of treatment. The final case was heterotopic. She underwent a D&C for an intrauterine pregnancy yet unfortunately she subsequently suffered a cornual rupture [24].

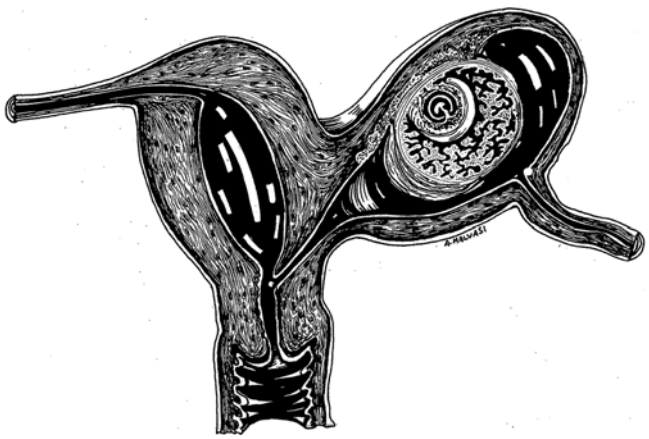

Fig. 5.13 Cornual ectopic pregnancy arises in one horn of a bicornuate or septate uterus

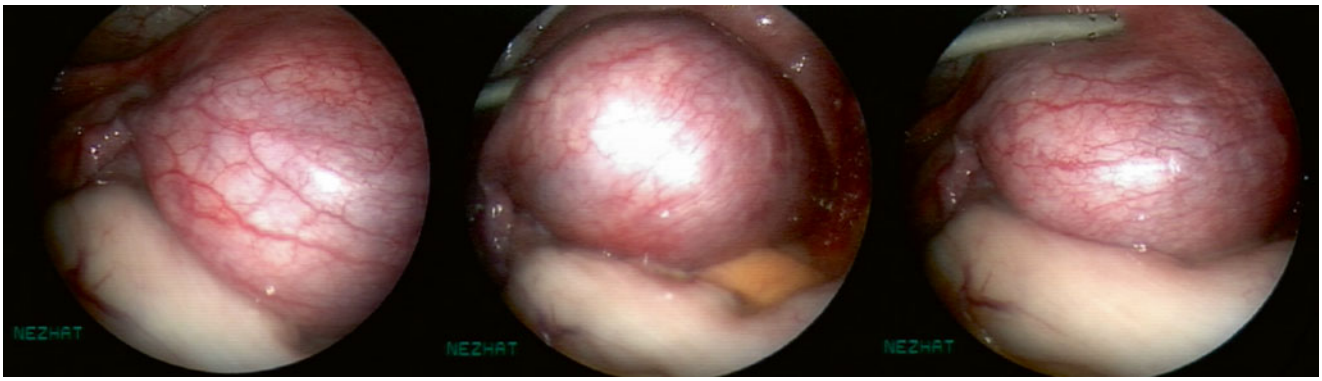

Fig. 5.14 Cornual ectopic pregnancy at laparoscopy (Courtesy of Dr. Ceana Nezhat, Atlanta, Georgia)

Clearly, further study is warranted using agreed-upon universal definitions to define the appropriate treatment in suspect cornual ectopic pregnancies. The need for intervention is likely driven by the underlying anatomy of the patient in question. While a pregnancy in a bicornuate uterus can potentially proceed with expectant management, a pregnancy in a rudimentary horn may require urgent or semi-urgent surgical evaluation. Mullerian anomalies can present along a spectrum between a true bicornuate and a rudimentary horn; thus the ultimate treatment for any particular patient will depend greatly on the judgment of the surgeon. Consultation with radiologists and surgeons familiar with this entity and with experience in management is encouraged.

5.5 Ovarian Ectopic Pregnancy

5.5.1 Incidence and Diagnosis

Diagnosis of ovarian ectopic pregnancy is made by ultrasound findings including a normal and intact ipsilateral tube with a gestational sac located in the area of the ovary (Fig. 5.15). The ovary and the gestational sac are usually found to be connected to a uterine ovarian ligament. After surgical excision, histology will confirm the presence of placental tissue mixed with the ovarian cortex [23, 25].

The risk exists that this entity on ultrasound will be confused with a luteal cyst, thus leading to a delay in diagnosis and the potential for catastrophic rupture. Preoperative diagnosis is correct less than 30 % of the time and it is mainly by ultrasounds (Fig. 5.16) [26]. Laparoscopy is thus more frequently required for diagnosis and subsequent treatment in ovarian ectopic pregnancy (Fig. 5.17a–c) [27]. When doubt exists, consultation with radiologists and surgeons familiar with this entity and with experience in management is encouraged if possible.

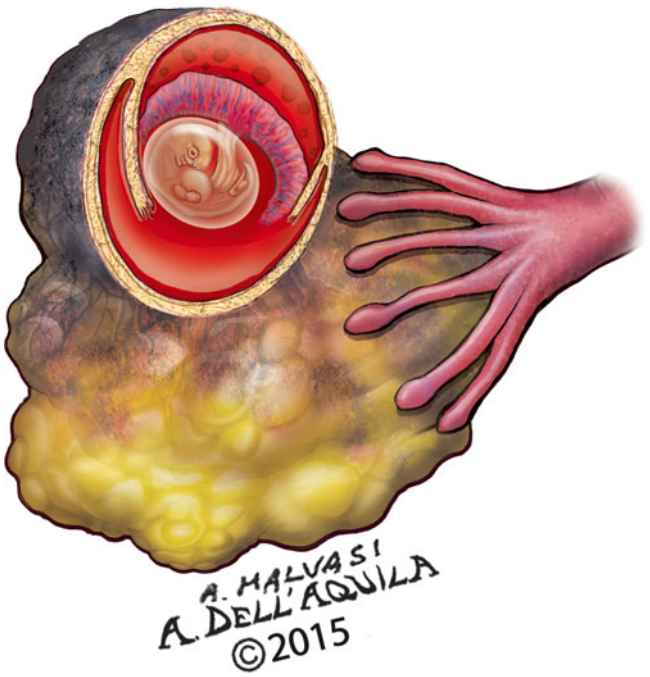

Fig. 5.15 Image shows an ovarian pregnancy with a normal and intact ipsilateral tube with a gestational sac located in the area of the ovary

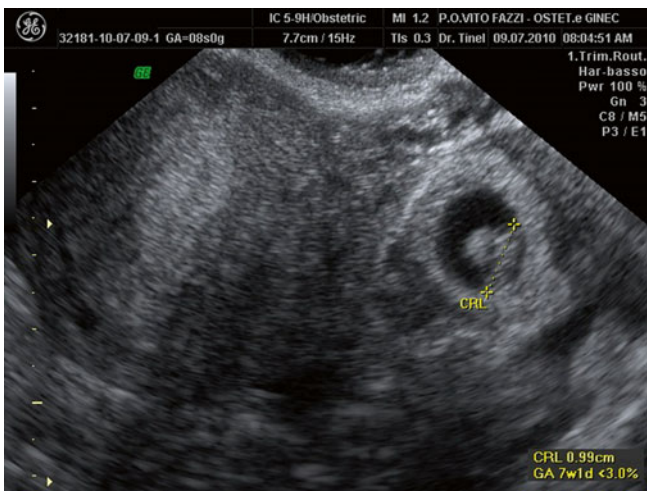

Fig. 5.16 Left ovarian ectopic pregnancy at 7 weeks of gestation with a well-detected embryo

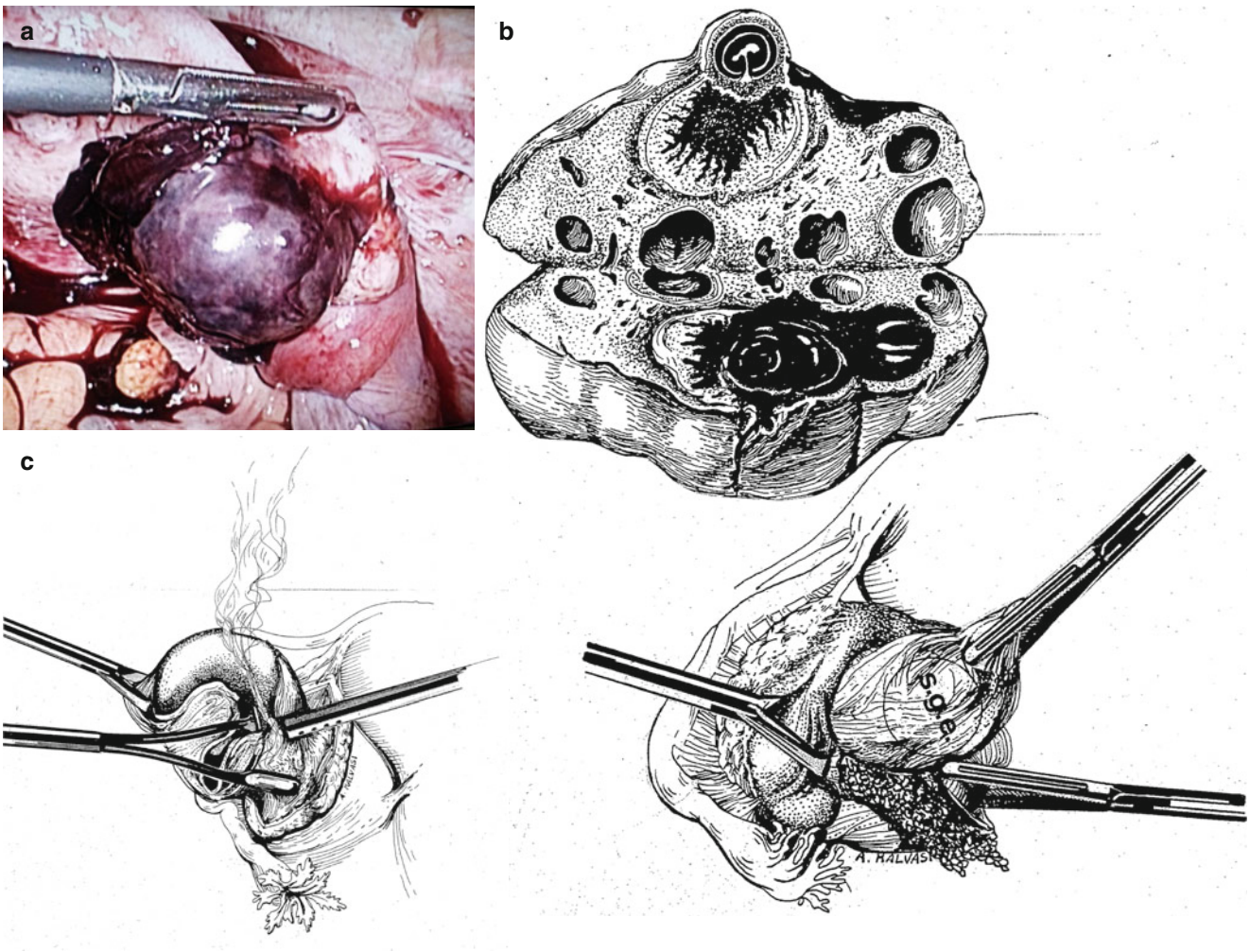

Fig. 5.17 (a) Laparoscopic treatment of a right ovarian pregnancy; (**b**) schematic representation of ovarian pregnancy (*upper part of the figure*) and its removal from the ovary (*the lower part of the figure*); (**c**) hemostatic coagulation of the edges of the ovary where it was placed in the ovarian pregnancy

5.5.2 Risk Factors

Risk factors for ovarian ectopic pregnancy include the presence of an IUD, exposure to assisted reproductive technology, a history of endometriosis, pelvic inflammatory disease, and prior surgery [10].

5.5.3 Treatment

Surgical treatment is the method of choice for ovarian ectopic pregnancy. Typically, in early gestations, ovarian wedge resection is possible so as to preserve ovarian tissue for future pregnancies and hormonal function. Various reports have described laparoscopic techniques to proceed with resection. Use of electrocautery or cold dissection with scissors and subsequently bipolar cautery to achieve hemostasis is reasonable [25, 28]. Oophorectomy is advised and likely required for safe management of advanced gestations.

One case report exists of systemic methotrexate treatment of unruptured ovarian ectopic diagnosed at laparoscopy. However, given the risk of rupture and significant hemorrhage from this potentially highly vascular entity, this is not a common practice [29].

5.6 Abdominal Ectopic Pregnancy

5.6.1 Incidence

Abdominal ectopic pregnancy represents 1–4 % of all ectopic pregnancies [10]. Symptoms include lower abdominal pain, possibly localized pain to the site of implantation, and occasionally palpable fetal parts [10]. Secondary

implantation of a ruptured tubal ectopic is a more common etiology for an abdominal ectopic pregnancy as compared to primary implantation in the abdomen [30].

Major complications of abdominal ectopic pregnancy are common and include massive hemorrhage, DIC, ARDS, pulmonary edema or embolism, sepsis, potential perforation into the bowel with intestinal obstruction, fistula formation, and potential perforation of the bladder, vagina, or abdominal wall [31]. The maternal mortality rate for abdominal ectopic pregnancy is eight times higher than for any other ectopic [32, 33]. Fetal survival is reported to be only 20–40 % in advanced cases, while perinatal mortality approaches 95 % in some series (Fig. 5.18) [31].

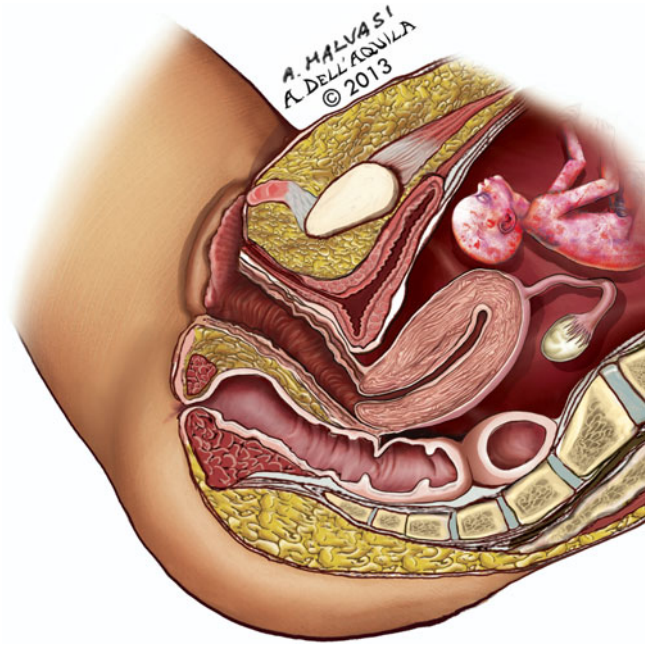

Fig. 5.18 atypical presentation of abdominal pregnancy, with a dead fetus in the second trimester

5.6.2 Diagnosis

Diagnostic criteria by imaging include: (1) bilaterally normal tubes and ovaries with no evidence of recent rupture, (2) no uteroperitoneal fistula, and (3) early pregnancy (less than 12 weeks) with trophoblastic attachments solely to the peritoneal surface [30]. Imaging can be by ultrasound (Fig. 5.19) but frequently MRI is required to establish diagnosis. Characteristic ultrasound features of abdominal ectopic pregnancy are an empty uterus adjacent to the bladder, absence of any myometrium surrounding the fetus, a poorly visualized placenta, an unusual fetal lie, relative oligohydramnios, fetal parts found adjacent to maternal abdominal contents, and an extrauterine placenta [10]. Up to 50 % of cases will be missed antenatally contributing to the high maternal and perinatal mortality.

Frequently, the diagnosis is not made preoperatively and surgeons must maintain a high index of suspicion at time of laparoscopy. In a retrospective review of abdominal ectopic pregnancies, none of 11 abdominal ectopics were diagnosed preoperatively [34]. A separate case report noted an abdominal wall ectopic pregnancy was initially misdiagnosed as endometriosis at the time of diagnostic laparoscopy and later found appropriately diagnosed upon repeat laparoscopy [35]. Our colleague, Prof. Leonardo Resta, reports two rare cases

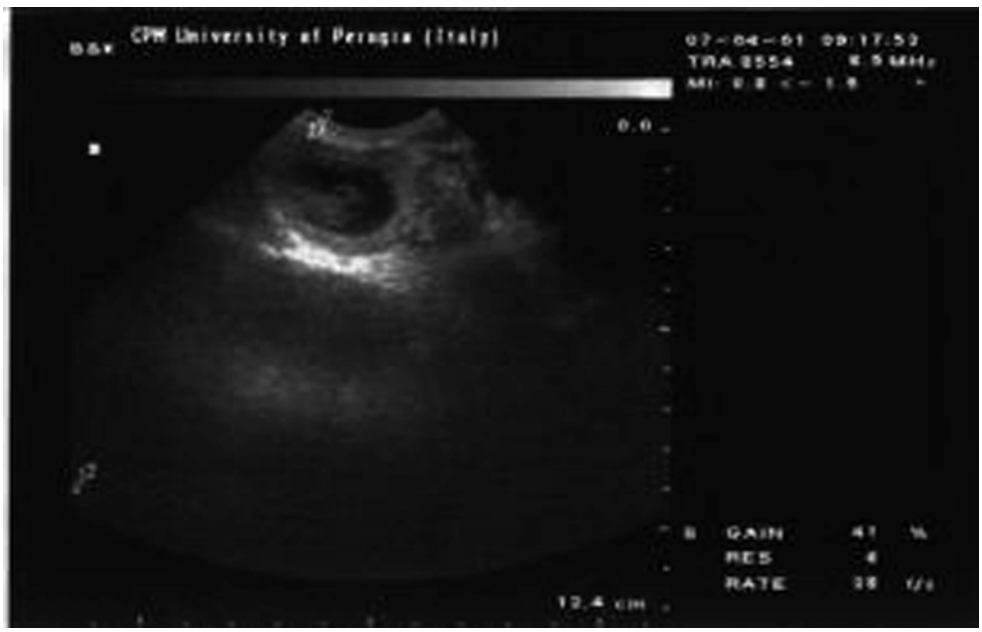

Fig. 5.19 Abdominal gestational sac revealed during transvaginal ultrasound. The unusual location of the pregnancy was particularly evident in the dynamic modality of the ultrasonographic examination (Courtesy of Dr. Sandro Gerli, Department of Obstetrics and Gynecology, University of Perugia, Italy)

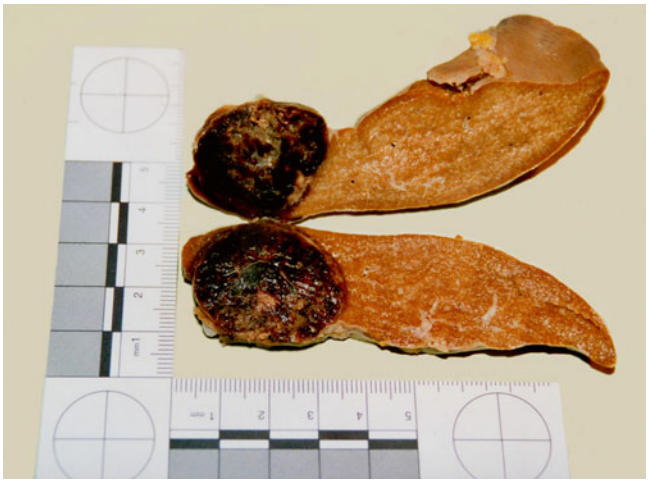

Fig. 5.20 Thirty-eight-year-old woman with an intrauterine device (IUD) since 10 years. She underwent surgical treatment for abdominal pain and hemoperitoneum. Macroscopic view of the hemorrhagic focus (3.5 cm) in the lower pole of the spleen

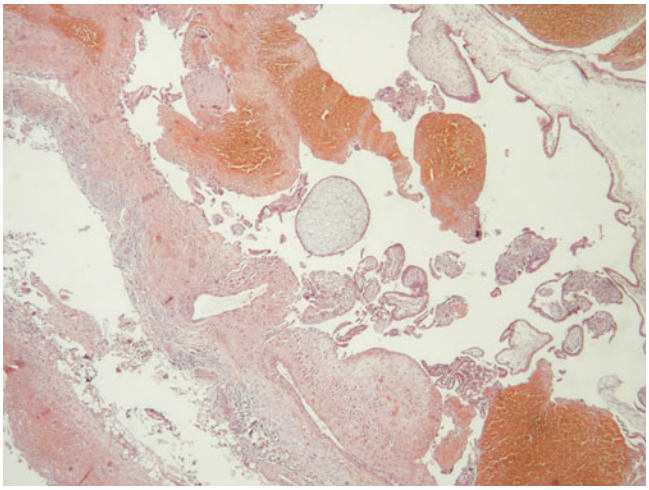

Fig. 5.22 Area of the spleen implantation of chorionic villi. The different sizes and histological aspects of the villi are related to the insufficient arterial modification, the consequent low amount of maternal blood to the placenta, and the precocious loss of the embryo

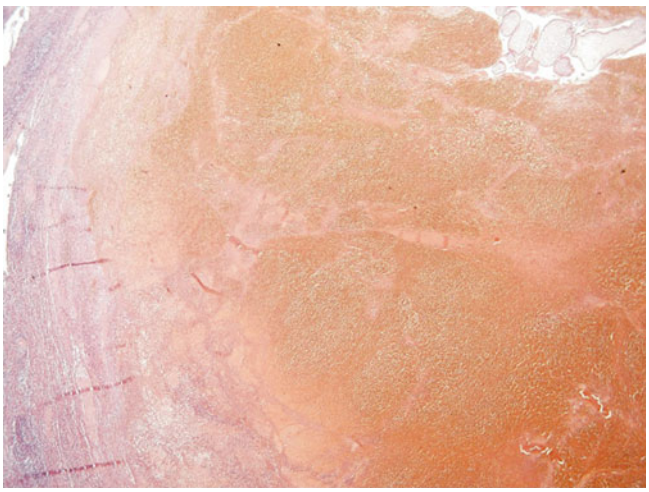

Fig. 5.21 General histological view of the hemorrhagic focus in the spleen

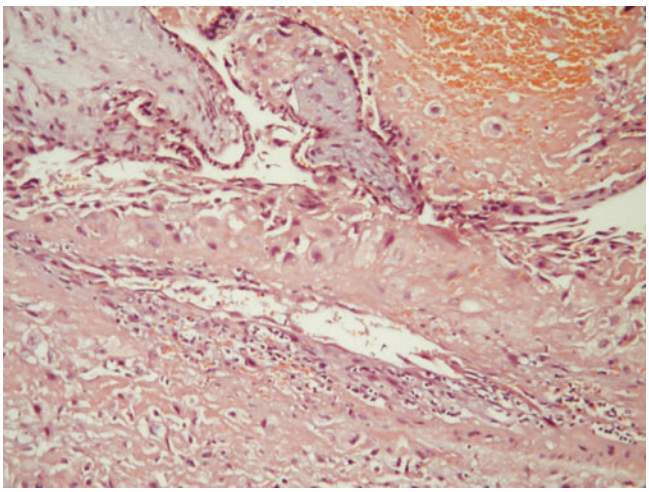

Fig. 5.23 Evident partial invasion of the arterial wall by the extravillar trophoblastic cells in the bed of the spleen pregnancy

of spleen pregnancy (Figs. 5.20, 5.21, 5.22 and 5.23) and omental pregnancy (Figs. 5.24, 5.25 and 5.26), documented by histological samples.

5.6.3 Risk Factors

No studies have clearly defined the risk factors for abdominal ectopic pregnancies other than those for other ectopic pregnancies. Thus, risk factors include prior history of a medically treated ectopic, and disruption of tubal or pelvic anatomy from infection, prior surgery, or endometriosis is the major risk factor. Abdominal ectopic pregnancies have been described after ART, specifically after IUI [36], after IVF [37], and after Clomid [38].

5.6.4 Surgical Treatment

Laparoscopic treatment of abdominal ectopic pregnancy is generally feasible and safe given the appropriate level of skill. Advanced gestations or ectopic pregnancies that have implanted in highly vascular or anatomically difficult areas may require laparotomy for treatment.

A retrospective review describes surgical treatment of eleven abdominal ectopic pregnancies. Five were treated laparoscopically and six were treated by laparotomy. Laparoscopy was associated with less operative time, blood loss, and hospital stay [34].

An operative technique will again depend upon the presentation and anatomical location of the lesion. Various

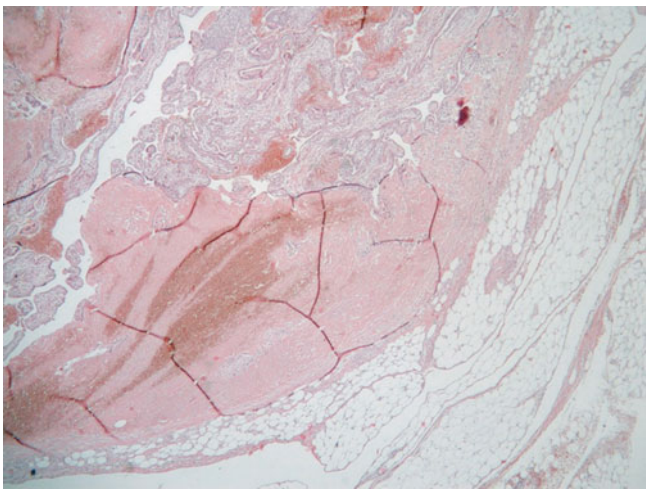

Fig. 5.24 Thirty-year-old woman, previously treated with a bilateral salpingo-oophorectomy for subsequent tubal pregnancies, was submitted to a medically assisted insemination. At 10 weeks ultrasonography revealed a normal intrauterine pregnancy and a second pregnancy in the omentum. An omentectomy was performed. The large section of the omentum reveals the hemorrhagic pattern of the omental localization

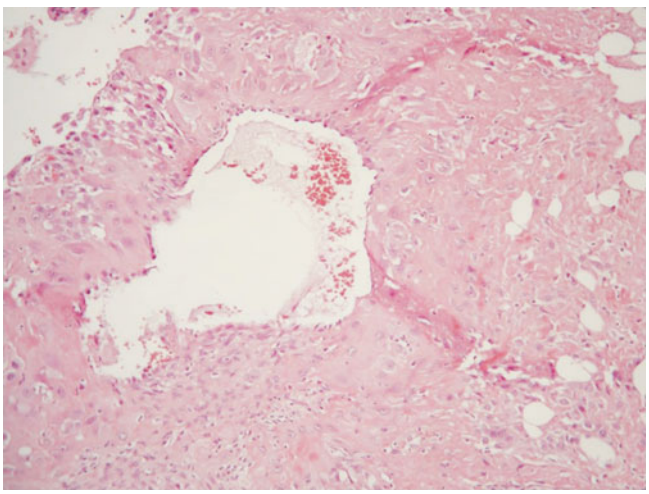

Fig. 5.25 This picture witnesses the deficient modification of the omental arteries in the bed of the pregnancy by the extravillar trophoblastic cells. A part of the arterial muscle cells is conserved and the trophoblastic cells are absent in the arterial lumen

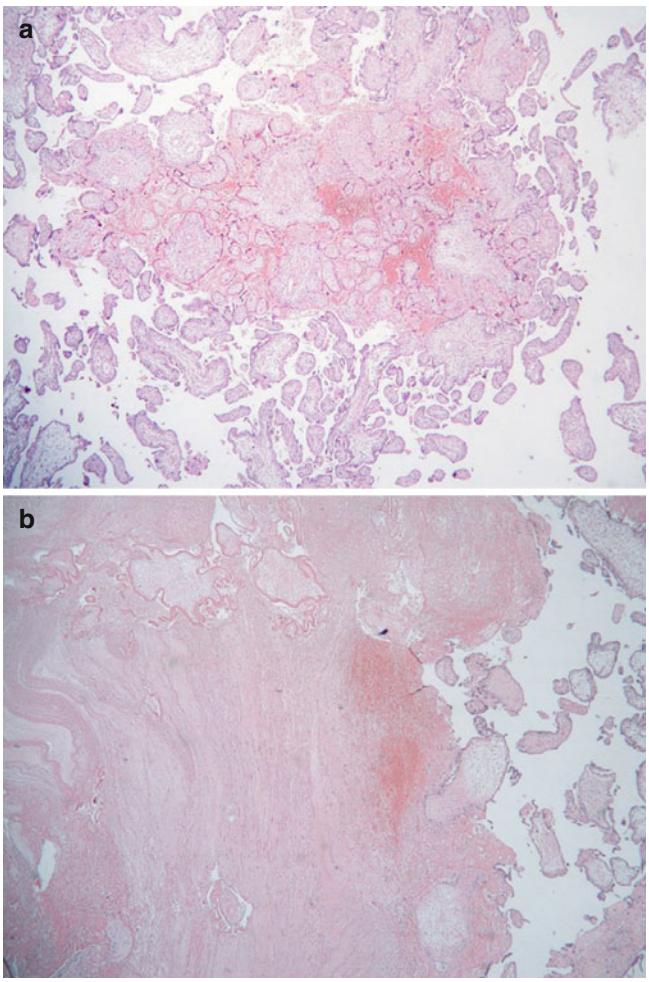

Fig. 5.26 Consequence of the deficient arterial modification is documented by the presence of (**a**) ischemic villi and (**b**) hemorrhagic foci

reports have described the use of hydrodissection [39], electrocautery, and single-site surgery [40].

Case reports do exist of laparoscopic treatment of advanced gestations. Rahaman and colleagues described a 21-week gestation abdominal ectopic pregnancy that was initially treated with preoperative uterine artery embolization. Thereafter the group proceeded with laparoscopically assisted delivery through a 6 cm midline incision. The placenta was left in situ. The patient was treated with postoperative methotrexate 50 mg/m^2×4 doses at an interval of every 3 weeks [31].

Rahaman and colleagues addressed the controversial issue of management of the placenta in these cases [31]. Complete removal is clearly preferred if possible. However, given likely vascularization this may lead to catastrophic hemorrhage. Alternatives to removal include ligating the cord close to the placenta and allowing resorption; however, this process can take years. The risks of leaving the placenta in situ include secondary hemorrhage, abscess formation, peritonitis, intestinal obstruction, wound dehiscence, and amniotic fluid cyst formation. The retained placenta can provide an excellent nexus for infection. In a review of five abdominal ectopic pregnancies with placentas left in situ and treated with methotrexate, all developed intra-abdominal infections. Further study is warranted to determine the optimal course in these cases with regard to the placenta [41, 42].

As with interstitial ectopic pregnancies, control of blood loss is essential to successful treatment. Meticulous control of blood supply recruited by the ectopic pregnancy and placenta is paramount. Case reports have described use of FloSeal to control bleeding after partial omentectomy [43] as

well as use of the PlasmaJet to vaporize residual tissue and achieve hemostasis [35]. Uterine artery embolization is a reasonable first step ahead of surgery, depending on anatomical location of the abdominal ectopic pregnancy [44].

Expectant management is not advised although case reports exist including one abdominal ectopic diagnosed at the time of cesarean section for breech [34, 45].

Various authors have described failed attempts at medical management including failure of methotrexate [46, 47]. However, Cobellis and colleagues have described three cases of abdominal ectopic pregnancy diagnosed laparoscopically and thereafter successfully treated with intravenous methotrexate [48].

In short, the optimal mode of treatment for abdominal ectopic pregnancy, a fairly heterogenous condition that can affect multiple organs in the abdominal cavity, is not yet known. Consultation with experienced surgeons is recommended especially in later gestations. Further study is warranted.

Conclusion

Non-tubal ectopic pregnancies are rare but can be dangerous. Although a few review articles exist, our comprehensive review of the literature noted a significant number of case reports available in the literature. Thus, although rare, experience with this entity exists.

To determine the optimal mode of treatment and assess the use of adjuvant and ancillary modalities including the ones from our colleagues in interventional radiology, further study or a registry is warranted.

A first step toward achieving protocols for treatment in these rare presentations would be to establish a common nomenclature as proposed by Arleo and colleagues [2].

Given the dangers inherent in treatment of interstitial, some cornual, and abdominal ectopic pregnancies, consultation with experts in radiology, surgery, and potentially interventional radiology is highly encouraged, especially when confronted with later gestations.

Acknowledgment The authors wish to thank Prof. Leonardo Resta, Department of Emergency and Organ Transplantation (DETO), Section of Pathological Anatomy, University of Bari, Italy (e-mail: leonardo.resta@uniba.it).

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Adnexal Pathology in Pregnancy

6

Maria Andrikopoulou, Anthony M. Vintzileos, Andrea Tinelli, and Farr R. Nezhat

6.1 Introduction

The increasing use of antenatal ultrasound and screening during the first trimester of pregnancy has led to an increased incidence of adnexal pathology diagnosis. Even though adnexal pathology is most commonly associated with masses of ovarian origin (Fig. 6.1), it can also include causes of tubal and paratubal pathology (Fig. 6.2) as well as pedunculated fibroids (Fig. 6.3), which in imaging may appear to be extrauterine. The incidence of an adnexal mass in pregnancy ranges from 1 to 10 % depending on the population studied, the frequency of ultrasound use, and the gestational age at the time of the ultrasound exam [1–3]. The incidence of adnexal masses is higher in the first trimester (Fig. 6.4) because most of them are of benign cystic ovarian origin and approximately two thirds will resolve spontaneously later in pregnancy [3]. The risk of malignancy of an adnexal mass is very low. A population-based study of more than 4 million obstetrical patients has reported that the incidence of ovarian cancer is as low as 0.93 % [4]. Another report of 130 cases of adnexal masses, which were managed surgically, has estimated a higher risk of malignancy or borderline malignancy at 6.1 % [5]. Other risks associated with adnexal masses during pregnancy that contribute to maternal morbidity include torsion, rupture, bleeding, infection, and labor obstruction (Fig. 6.5) [3]. It should be noted that the overwhelming majority of patients are asymptomatic at the time that an adnexal mass is discovered by ultrasound (Fig. 6.6). However, in some cases, it presents with abdominal pain secondary to rupture, torsion, infection, or bleeding [6–9].

Most first-trimester cystic adnexal masses will resolve spontaneously during the second trimester. However, controversy exists regarding the diagnosis and management of a persistent adnexal mass since the risks and benefits of certain diagnostic and surgical options should be carefully balanced.

M. Andrikopoulou, MD, PhD (✉) • A.M. Vintzileos, MD
Department of Obstetrics and Gynecology,
Winthrop-University Hospital, Mineola, NY, USA
e-mail: maria_andrik@hotmail.com

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy

F.R. Nezhat, MD
Department of Obstetrics and Gynecology,
Winthrop-University Hospital, Mineola, NY, USA

Department of Obstetrics and Gynecology,
New York-Presbyterian/Weill Cornell, New York, NY, USA

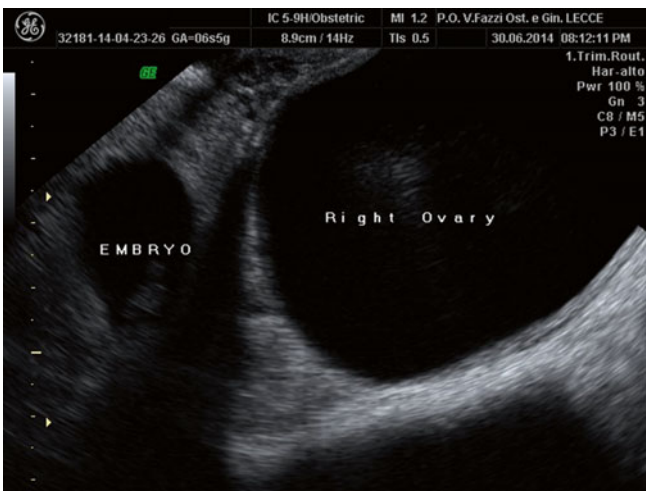

Fig. 6.1 Ultrasonographic image showing a right ovarian cyst at 6 weeks and 5 days of pregnancy

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_6

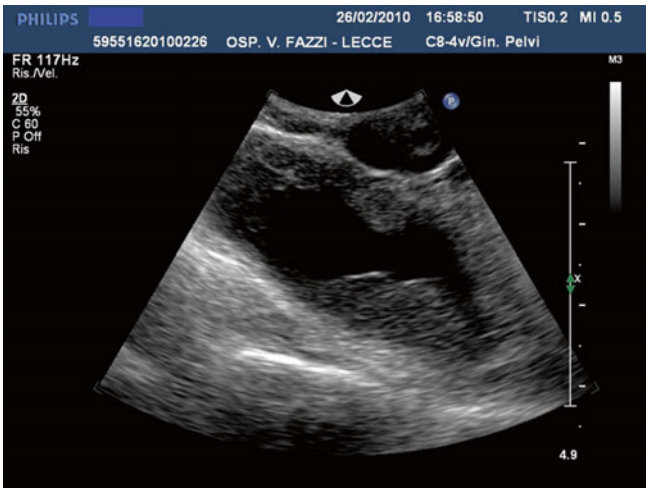

Fig. 6.2 Ultrasonographic image showing a left sactosalpingitis in early pregnancy

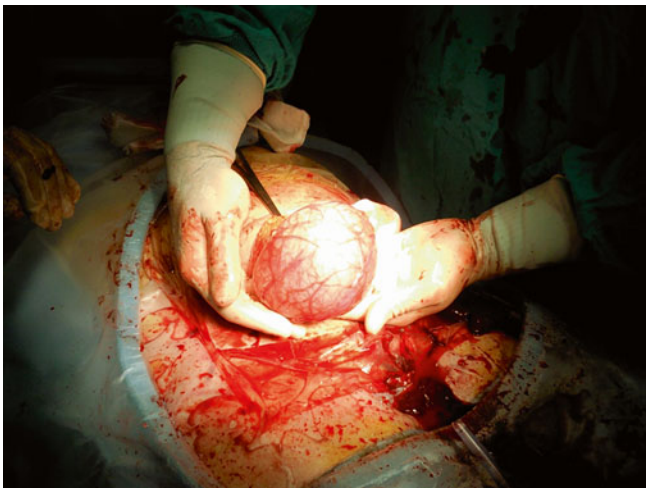

Fig. 6.5 A left ovarian mucinous cystadenoma removed during cesarean section, causing labor obstruction

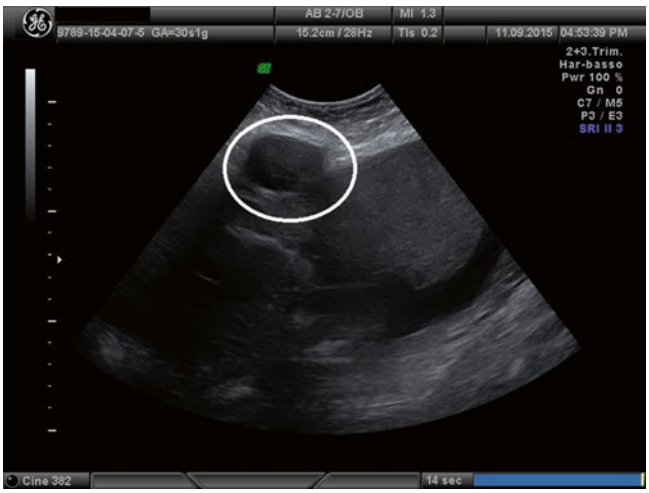

Fig. 6.3 Ultrasonographic image showing a pedunculated anterior fibroid of 4 cm in diameter (*in the with ring*), at 30 weeks of pregnancy

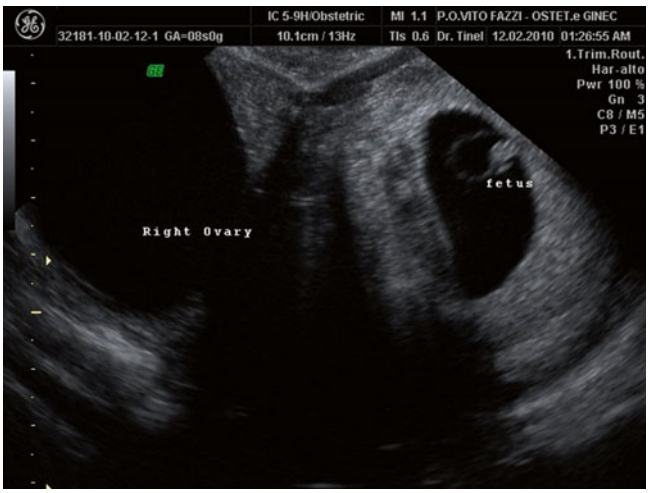

Fig. 6.6 A right serous adnexal cyst discovered occasionally during a first-trimester scanning

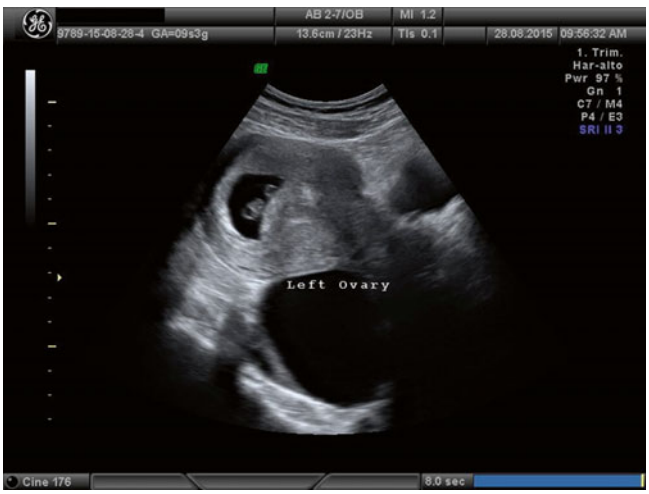

Fig. 6.4 Ultrasonographic image showing a left ovarian cyst at 9 weeks of pregnancy

6.2 Causes of Adnexal Pathology in Pregnancy

The most common causes of adnexal pathology in pregnancy are functional or hemorrhagic cysts (Fig. 6.7), which usually resolve later in pregnancy (Fig. 6.8). However, the differential diagnosis should also include benign ovarian masses such as dermoids (Fig. 6.9), serous and mucinous cystadenomas, endometriomas, fibroids, and adenofibromas (Fig. 6.10) [5, 10]. Adnexal masses specific to pregnancy include luteomas, hyperreactio luteinalis, and theca lutein cysts, especially in the presence of a molar pregnancy or hyperstimulation (Fig. 6.11) secondary to infertility treatment [11]. Tubal pathology includes heterotopic pregnancy (Fig. 6.12a, b), tubo-ovarian abscess, hydrosalpinx, and paratubal cysts. Uterine fibroids can also appear as adnexal masses in

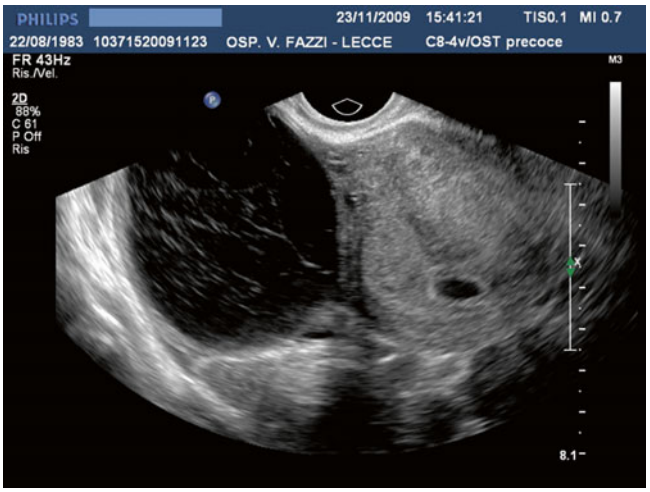

Fig. 6.7 A left hemorrhagic cyst detected in the first trimester of pregnancy

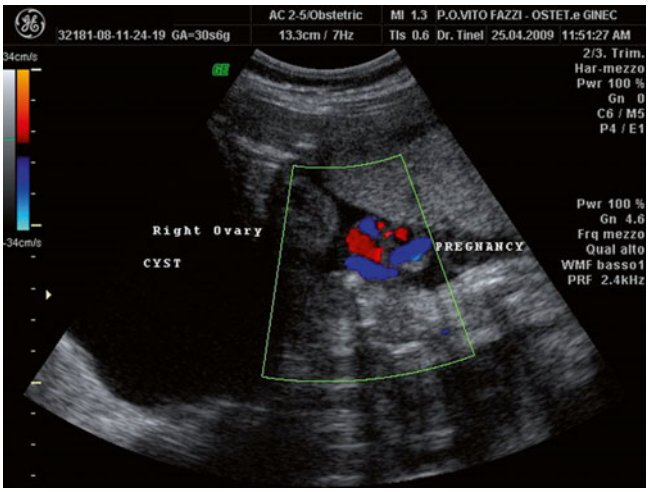

Fig. 6.8 Right functional cyst reducing in diameter at 30 weeks of pregnancy (disappeared at the term of pregnancy)

imaging. Even though the incidence of malignancy is low, epithelial tumors, germ cell tumors, and sex stromal tumors should be included in the differential diagnosis. A study of Leiserowitz et al., which examined pathologically cases of ovarian cancer in pregnancy in a large cohort of obstetrical population, showed that the majority of cases were epithelial, both malignant and borderline (51 %) [4]. Germ cell tumors were the second most common malignancy, with predominance of dysgerminomas and malignant teratomas.

6.2.1 Ovarian Pathology

6.2.1.1 Simple and Hemorrhagic Cysts

Simple and corpus luteum hemorrhagic cysts account for the majority of adnexal masses in pregnancy, and usually they regress spontaneously in the second trimester [12].

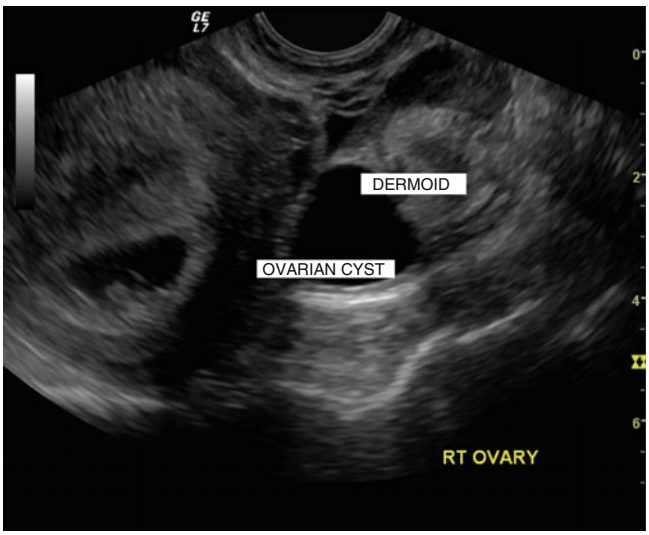

Fig. 6.9 A right ovarian cyst in pregnancy, with a dermoid mass inside

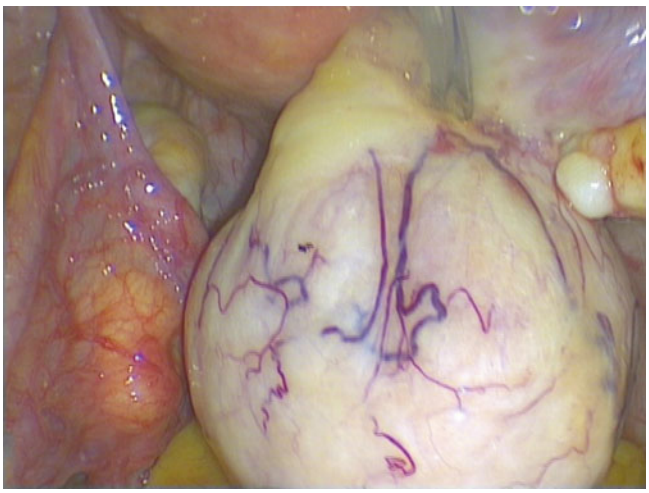

Fig. 6.10 A laparoscopic image of a right-twisted ovarian adenofibroma at 9 weeks of pregnancy

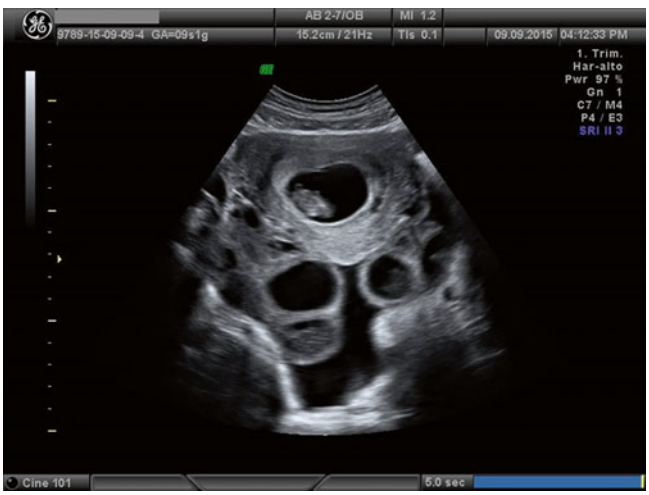

Fig. 6.11 An ovarian hyperstimulation at 9 weeks of pregnancy

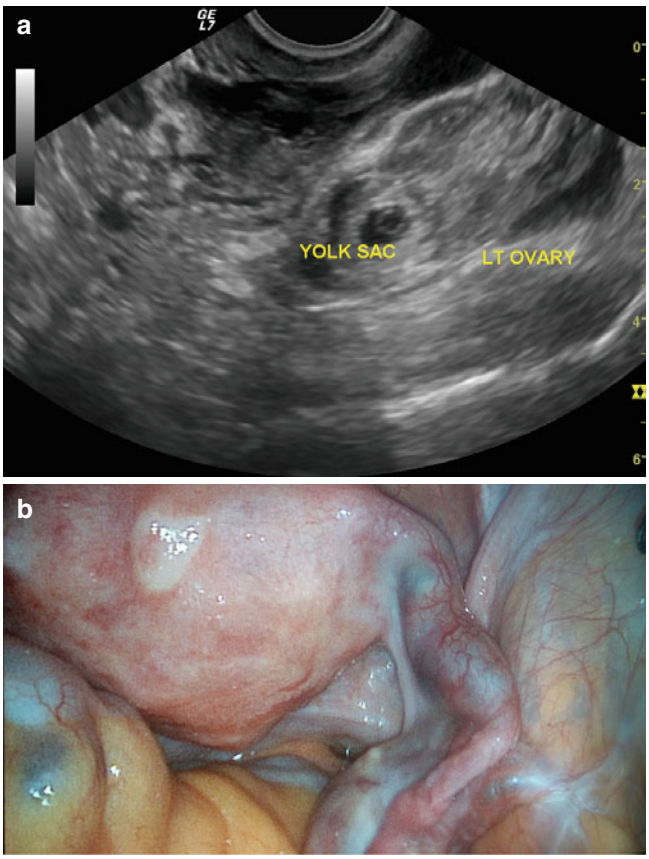

Fig. 6.12 (**a**) An ultrasonographic image showing a left heterotopic tubal pregnancy and (**b**) a laparoscopic image of a right tubal pregnancy

A simple ovarian cyst usually presents as a simple anechoic adnexal mass, whereas a hemorrhagic corpus luteum cyst presents as a complex mass with diffusely thick wall and peripheral vascularity. The best predictors for the persistence of these masses are complex appearance on sonography and the size of the mass [13]. Masses with diameter larger than 5 cm have higher likelihood to persist during pregnancy.

6.2.1.2 Endometriomas

An endometrioma is a rare entity in pregnancy (Fig. 6.13) [14, 15]. It usually presents as a unilocular cyst with diffuse homogeneous ground-glass echoes. Complications during pregnancy, such as rupture, have been reported in the literature [16]. However, it is not clear whether endometriomas in general are associated with adverse obstetrical outcomes. Some studies have suggested that the presence of endometriomas during pregnancy is associated with complications such as preterm birth, antepartum hemorrhage, and preeclampsia [17, 18], whereas other investigations have failed to show increased risk for obstetrical complications [19].

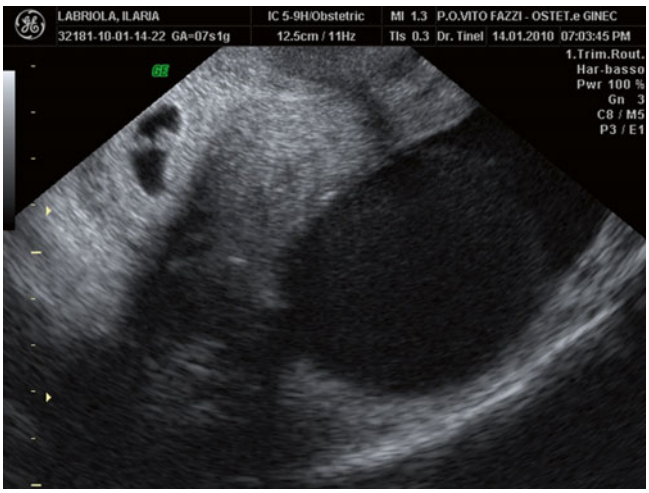

Fig. 6.13 A small right ovarian endometrioma in a pregnant at 7 weeks

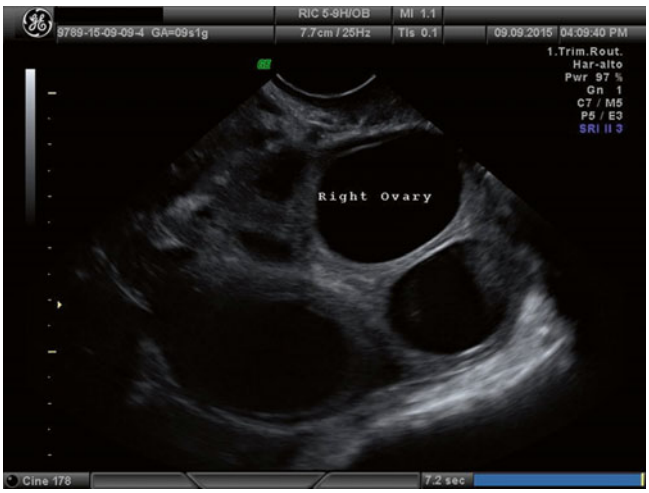

Fig. 6.14 A right enlarged ovary hyperstimulated, with multiple peripherally located cysts

6.2.1.3 Ovarian Hyperstimulation

Ovarian hyperstimulation during in vitro fertilization-embryo transfer is a risk factor for developing adnexal torsion in pregnancy. The syndrome presents with enlarged ovaries with multiple peripherally located cysts (Fig. 6.14) and in the majority of the cases is self-limited. However, there have been reports in the literature of adnexal complications during pregnancy such as hemorrhage and torsion [11, 20, 21].

6.2.1.4 Leiomyomas

Uterine fibroids are very common findings in women of reproductive age. In pregnancy, solid adnexal masses very commonly present as subserous (Fig. 6.15), intramural (Fig. 6.16), pedunculated fibroids or fibroids located in broad ligament. Approximately one third will increase in size, whereas a small percentage will undergo red/carneous

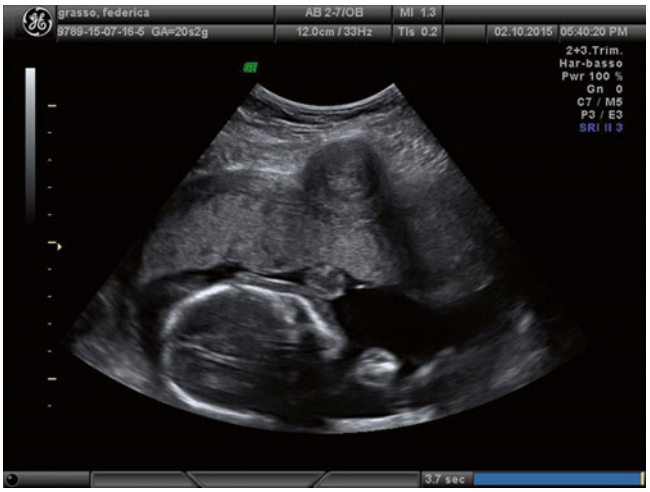

Fig. 6.15 An anterior subserous uterine body fibroid at 20 weeks of pregnancy

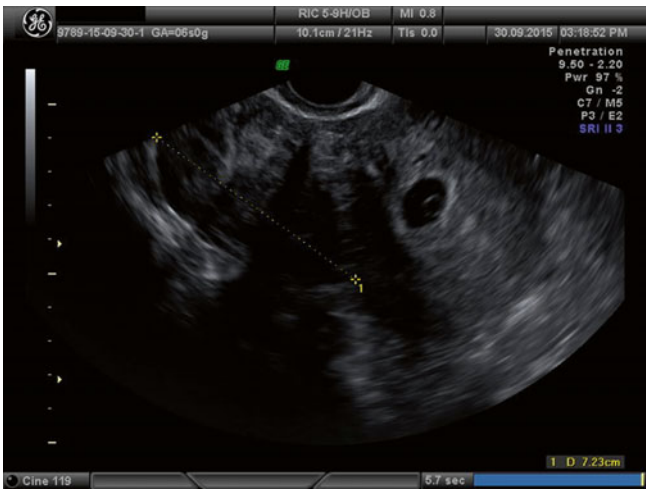

Fig. 6.16 A left transmural uterine fibroid of 7 cm of diameter at 6 weeks of pregnancy

degeneration secondary to hemorrhagic infarction with subsequent acute abdominal pain [22].

6.2.1.5 Luteoma

Luteomas constitute rare adnexal masses specific to pregnancy which usually regress in the postpartum period and can be hormonally active. Luteomas most commonly present in the second half of pregnancy as bilateral solid or mixed ovarian masses associated with elevated testosterone levels [23, 24]. They can also be found in normal pregnancy. They are usually asymptomatic, but they may present with signs and symptoms of virilization of the mother or infant or with complications such as torsion. Due to the commonly seen solid nature of this entity, the differentiation from an ovarian neoplasm can be challenging.

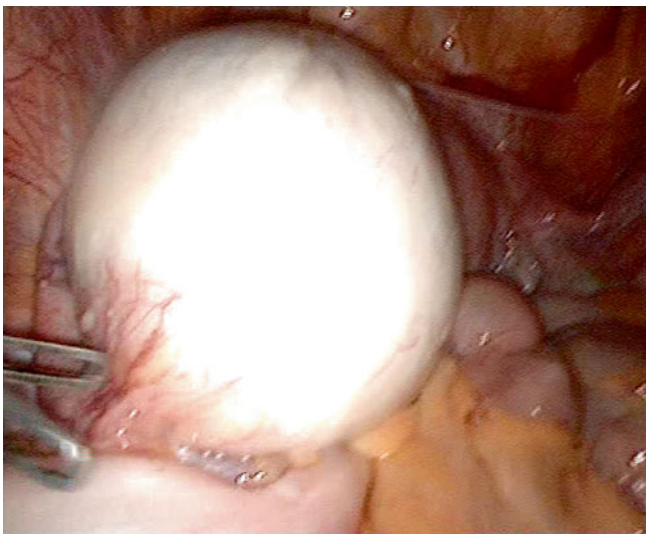

Fig. 6.17 A laparoscopic image of torsed left solid and cystic ovarian dermoid at 9 weeks of pregnancy

6.2.1.6 Hyperreactio Luteinalis

Hyperreactio luteinalis is a rare entity usually associated with trophoblastic disease, high-order multiple pregnancy, and fertility treatment. It is caused by increased levels of β-hCG and is usually asymptomatic or presents with abdominal pain or signs and symptoms of torsion. In one fourth of the cases, it can be associated with hyperandrogenism. Large adnexal masses consisting of many thin-walled small cysts can be seen in ultrasound similar to ovarian hyperstimulation syndrome. The majority of these lesions resolve spontaneously after delivery [25].

6.2.1.7 Theca Lutein Cysts

Theca lutein cysts are associated with gestational trophoblastic disease (complete molar pregnancy) and are considered to be secondary to excessive amounts of circulating gonadotrophins. They usually present bilaterally with thin walls and a solid component and are associated with increased risk of post-molar trophoblastic disease [26].

6.2.1.8 Dermoid Cysts

Dermoid cysts constitute the most common diagnosis of surgically removed adnexal masses in pregnancy (Fig. 6.9) [27]. Sonographic findings of dermoid cysts may include a cystic or a combined cystic and solid component. Some mature teratomas (10–20 %) are cystic in nature, and they may be indistinguishable from other cystic masses. However, the most common ultrasound appearance is combined both solid and cystic (Fig. 6.17) with the following characteristics: (a) a solid spherical component, representing the hair and sebum, may occupy part of the cyst; (b) echogenic lines and dots, representing floating hair, dispersed throughout the cyst; and (c) shadowing from the echogenic portion of the tumor due to bone

calcifications or adipose tissue. Many studies in the literature have reported complications secondary to rupture, torsion, or labor dystocia of dermoid cysts in pregnancy [28, 29]. However, a study by Caspi et al. has demonstrated that ovarian dermoid cysts <6 cm are not expected to grow or to cause complications during pregnancy or labor [30].

6.2.1.9 Cystadenomas

Cystadenomas are benign tumors and constitute the most common ovarian neoplasms. There have been many reports in the literature of both serous (Fig. 6.18) and mucinous (Fig. 6.19) cystadenomas in pregnancy [31, 32]. In the cohort of Goh et al. which included patients with persistent ovarian masses during pregnancy that underwent surgical treatment, almost one third of the cases were serous and mucinous cystadenomas [27]. In the retrospective study by Gordon et al., benign cystadenomas comprised one fifth of all surgically resected ovarian neoplasms [33]. During ultrasonography they present as simple cysts or they may contain septations. Mucinous cystadenomas tend to be larger at presentation compared to serous. The presence of irregular septations and nodules increases the risk of malignancy.

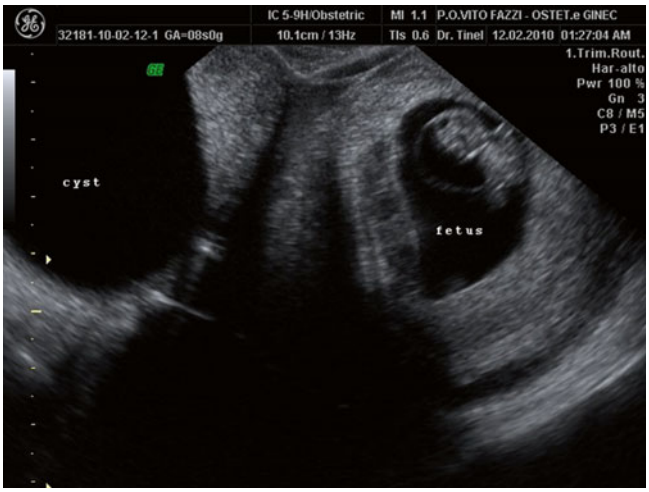

Fig. 6.18 An ovarian left serous cystadenomas at 8 weeks of pregnancy

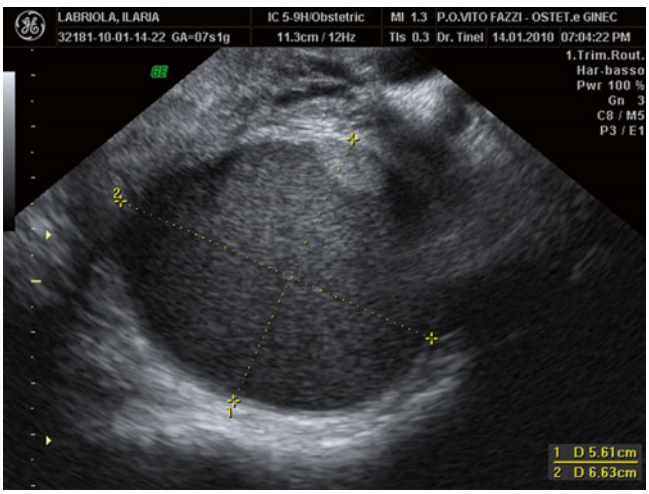

Fig. 6.19 A right ovarian mucinous cystadenomas at 7 weeks of pregnancy

6.2.1.10 Ovarian Malignancy

The incidence of ovarian malignancy during pregnancy is very low. Sonographic features suggestive of malignancy include a complex cyst with thickened walls, septations, papillary solid components, and increased blood flow detected by color Doppler. Most of the ovarian cancers diagnosed during pregnancy are epithelial and low-malignant-potential tumors. Most malignancies are diagnosed at earlier stages [34]. This can be explained by the younger age of pregnant women. For the same reason, it appears that there is an increased incidence of germ cell tumors during pregnancy.

6.2.1.11 Tubal Pathology

Tubal pathology can present during pregnancy as hydrosalpinx, tubo-ovarian abscess (TOA), or heterotopic pregnancy. Hydrosalpinx commonly associated with pelvic inflammatory disease (PID) appears at sonographic imaging as an anechoic tubular or elongated fluid-filled structure, and its morphology remains unchanged during pregnancy. Tubo-ovarian abscess (Fig. 6.20) is a very uncommon entity in pregnancy and most often arises as a consequence of PID. However, TOA can be also associated with recent pelvic surgery of intra-abdominal infectious process such as appendicitis. Also, there have been case reports of TOA in pregnancy after oocyte retrievals in women with preexisting endometriomas [35]. TOAs usually present with signs and symptoms of pelvic infection and in ultrasound imaging as one or more multilocular complex cysts. Heterotopic pregnancy, even though extremely rare, should be included in the differential

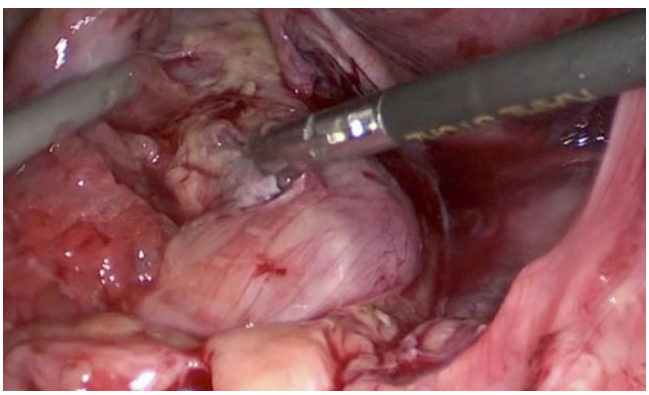

Fig. 6.20 A laparoscopic image of a tubo-ovarian abscess in pregnancy

diagnosis especially in patients with history of IVF or ovulation induction [36]. The ultrasound may reveal features of concomitant ectopic and intrauterine pregnancy.

6.3 Diagnosis

6.3.1 Ultrasound

Most of the adnexal masses in pregnancy are incidental findings during antenatal ultrasound evaluation. If a mass is clinically palpated during pregnancy, ultrasonography is the initial imaging modality of choice because of its low cost, safety, high resolution, and noninvasive nature. Features suggestive of malignancy include a solid component within a cystic mass papillary projections, excrescences, vegetation, and nodules. Septations in a cystic ovarian mass may indicate the presence of a malignant neoplasm especially if greater than 2–3 mm in thickness; other ultrasound signs suggestive of malignancy include ascites, increased thickness of the cyst wall, and a very large size of the mass [13, 37]. Conventional ultrasonography has been shown in many studies to be helpful in characterizing the nature of adnexal lesions and identifying the cases with possible malignancy [5, 10, 38, 39]. Although the accuracy of conventional ultrasound in differentiating malignant from benign neoplasms has been questioned and color Doppler has been suggested as a means to improve the accuracy of diagnosis, the high incidence of false-positive results up to 49 % provided by color Doppler makes unclear at this time if it adds any further information to the conventional sonogram [37, 40].

6.3.2 MRI

Many studies have evaluated the role of MRI in the diagnosis of adnexal masses in pregnant populations as it is generally considered a safe modality during pregnancy. MRI is a useful adjunct when sonography is inconclusive and can be used to guide management of adnexal masses especially due to its ability to evaluate tissue contrast [41]. MRI may help the physician differentiate whether the adnexal mass originates from the uterus, the ovary, or the tube and also identify specific characteristics of the morphology of the mass such as leiomyoma degeneration (Fig. 6.21), decidualization of endometrioma, and the presence of massive ovarian edema [42]. Additionally, in cases of malignancy, the MRI can define the extent of the disease and possible metastases [43].

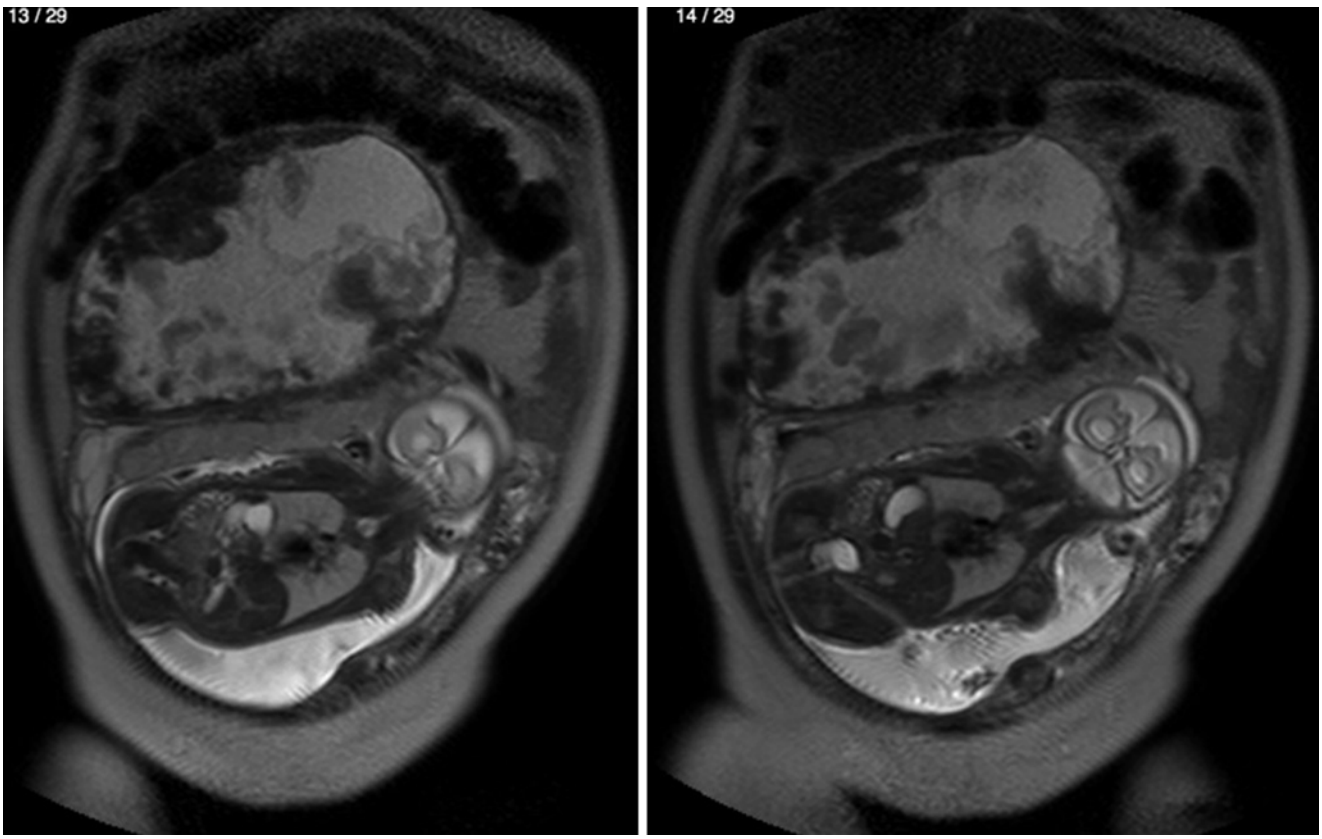

Fig. 6.21 A MRI coronal scan showing a huge subserous leiomyoma in degeneration in a pregnant at 25 weeks

6.3.3 CT Scan

CT scan of the abdomen and pelvis is another imaging modality that can be used in the evaluation of maternal adnexal masses. Even though CT scanning is considered relatively safe during pregnancy since the typical fetal radiation dose for a routine CT of the abdomen and pelvis is only 25 mGy [44], it should be kept in mind that the contrast material, if needed, can cross the placenta. CT scan is also very useful in identifying other intra-abdominal pathology in a pregnant woman such as appendicitis or diverticulitis.

6.3.4 Tumor Markers

The interpretation of tumor markers during pregnancy can be very challenging.

CA 125 is a glycoprotein which holds an important role in monitoring patients with ovarian cancer. However, its levels can be elevated in early pregnancy and during the early postpartum period, thus making its interpretation very difficult in the presence of suspicious adnexal masses [45]. AFP (a fetoprotein) which is typically used as part of antenatal screening can be elevated in endodermal sinus tumors, and elevated lactate dehydrogenase levels may be associated with dysgerminomas. However, the levels of these tumor markers can vary in pregnancy, thus limiting their use; additionally, normal levels of tumor markers cannot exclude malignancy. As a result, the decision to pursue surgical versus conservative management should be in general based on the symptomatology, physical examination, and imaging findings rather than the level of the tumor markers.

6.3.5 Management of Adnexal Mass in Pregnancy: Observation Versus Surgery

Controversy exists regarding the management of adnexal mass in pregnancy. Some studies recommend conservative management and observation, whereas other investigations favor surgical intervention [10, 46]. The majority of simple cysts that are less than 5 cm in diameter will resolve spontaneously during the course of pregnancy [13]. Thus, many observational studies support close monitoring during pregnancy in selected cases as an alternative to antepartum surgery [10, 47]. Surgical management is warranted when the patient is symptomatic and when complications such as adnexal torsion, rupture, or enlargement enough to cause possible labor obstruction occur. If an adnexal mass is suspicious of malignancy with sonographic evidence of solid component(s), nodules, thick septations, and size greater than 5 cm, surgical management should be strongly considered, ideally during the second trimester of pregnancy (Fig. 6.22) [34, 48].

Studies in the literature have shown the advantages of surgical management during the second trimester of pregnancy. The intervention at this time of pregnancy is associated with reduction of obstetrical complications such as miscarriage and preterm labor or birth with the absolute risk being very small. The theory behind this recommendation is that the developing pregnancy is dependent on the corpus luteum during the first trimester and much less in the second trimester [49].

The surgical approach for the management of adnexal mass during pregnancy can be via a laparotomy or laparoscopy. Even though until the 1990s, pregnancy had been considered a contraindication to the use of laparoscopy, many observational studies have shown that laparoscopy in the second trimester for the management of adnexal mass can be safe and technically feasible in the hands of a skilled laparoscopic surgeon [50–53]. The frequency of obstetric complications, such as low birth weight, preterm delivery, the use of tocolytics for preterm labor, low Apgar score, and fetal anomaly, is quite acceptable [53].

Laparoscopy in pregnancy can provide accurate diagnosis, faster recovery, minimal risk for thromboembolic disease, less fetal depression secondary to decreased narcotic use, fewer incisional hernias, and fewer postoperative adhesions. However, the risks related to pregnancy should always be taken into account [54, 55]. The trocar placement can lead to uterine injuries due to the enlarged uterine size; therefore, trocar placement under direct visualization, rather than insufflation with Veress needle, or open laparoscopic approach using the Hasson cannula is suggested. An additional concern is that increased intra-abdominal pressure can decrease cardiac output in pregnancy; thus, left lateral position of the mother is of utmost importance. Finally, the potential risk of hypercarbia and acidosis can be decreased by maintaining the intra-abdominal pressure less than 20 mmHg.

Even though observational studies have provided overwhelming evidence for the safety of laparoscopy and the advantages in postoperative course during the second trimester of pregnancy, the decision regarding laparotomy versus laparoscopic approach should be tailored on each case individually based on the preference and experience of the surgeon.

Adnexal mass can be detected for the first time during cesarean section in 0.3–0.5 % of cases, and up to 5 % can be bilateral [56, 57]. The options include conservative management for simple small cysts and excision for larger heterogenous complex cysts so that further surgical intervention after cesarean section is avoided and malignancy is excluded [1, 43, 49, 56].

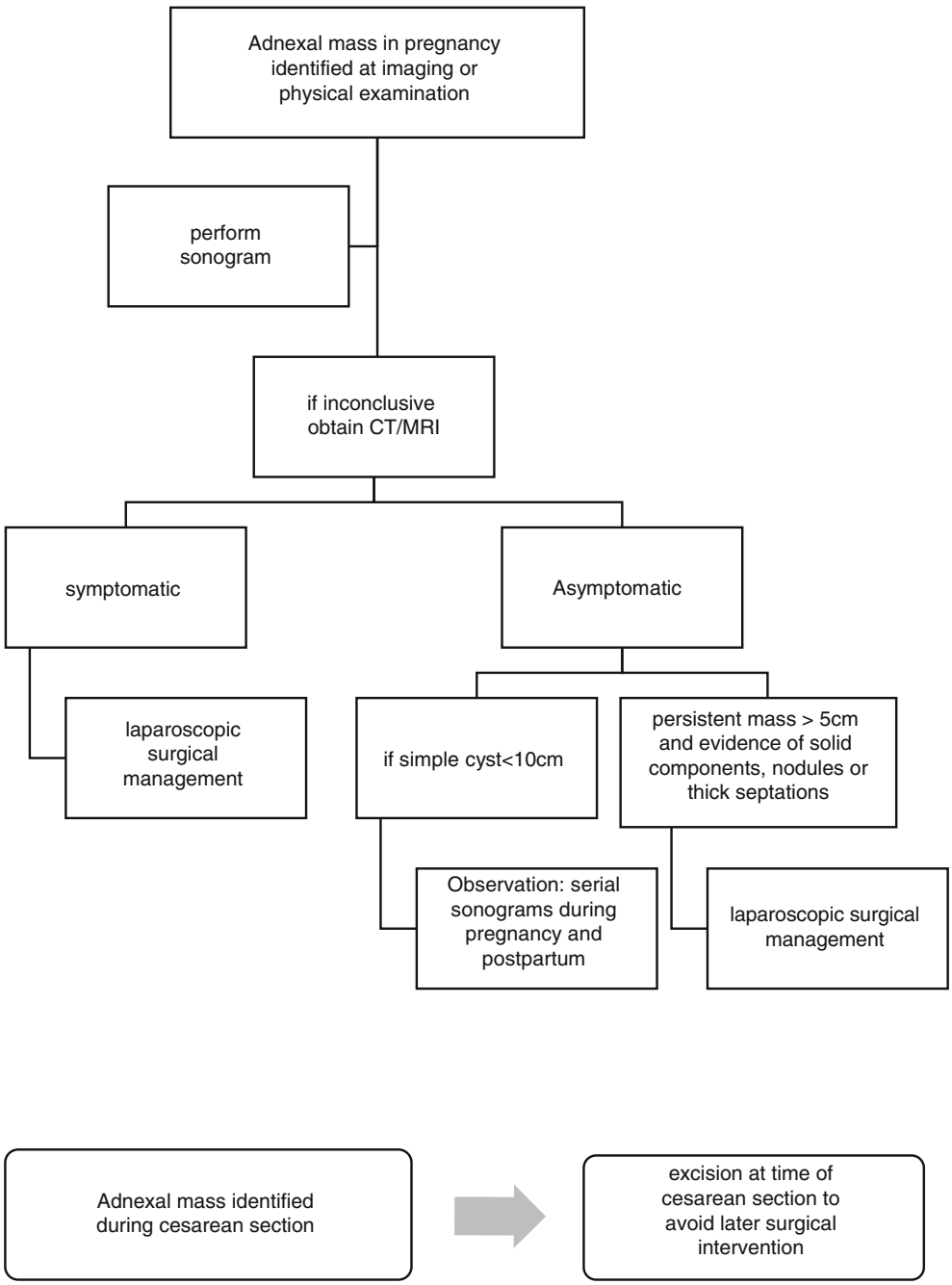

Fig. 6.22 Management of adnexal mass in pregnancy

Conclusion

The extensive use of ultrasound for antenatal screening has led to an increased frequency of incidental adnexal mass diagnosis during pregnancy. Thus, it is of utmost importance that the physician is familiar with the modes of accurate diagnosis and management of this entity. Other than ultrasound, MRI and CT scan can be employed for better characterization of the morphology of the mass and for evaluation of other intra-abdominal pathologies. In terms of management of adnexal mass in pregnancy, observation can be a viable option in cases of small masses with no signs of possible malignancy. Surgical intervention is recommended for larger persistent complex masses as the risk of complications such as torsion or rupture and malignancy are increased. Given the benefits of laparoscopy versus laparotomy, laparoscopy should be preferred as a surgical option in the hands of a skilled laparoscopic surgeon.

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Fibroid Complications in Pregnancy

7

Bradley S. Hurst, Andrea Tinelli, Antonio Malvasi, and William H. Parker

7.1 Introduction

Uterine fibroids can be identified by first-trimester ultrasound in approximately 8–20 % of women (Fig. 7.1). Most women with uterine fibroids can expect to have a normal pregnancy and delivery. However, complications from fibroids may occur during pregnancy depending on the size, number, and location of fibroids, and preconception treatment of fibroids may also pose risks to the pregnant woman and her fetus.

B.S. Hurst, M.D (✉)
Reproductive Endocrinology and Infertility, Carolinas HealthCare System, 1025 Morehead Medical Drive, Suite 500, Charlotte, NC 28204, USA
e-mail: bhurst@carolinas.org

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

W.H. Parker, MD
Minimally Invasive Gynecologic Surgery, UCLA Medical Center, Santa Monica, CA 90401, USA

Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, CA 90401-2831, USA

Very rarely does the presence of a fibroid during pregnancy lead to an unfavorable outcome. Submucous fibroids can prevent implantation and cause infertility and can increase the risk of first- and second-trimester miscarriage. During delivery, fibroids may rarely obstruct the normal passageway for delivery (Fig. 7.2a, b) and, when cesarean section is needed, can increase the complexity and risks associated with the procedure (Fig. 7.3). Uterine fibroids can increase postpartum bleeding, sometimes requiring transfusion and occasionally leading to life-threatening bleeding. Finally, in the postpartum interval, uterine fibroids may limit contraceptive options or reduce the efficacy of contraception.

Treatment of fibroids before conception is also associated with risks to the pregnant patient and her fetus, beyond the risks of surgery, anesthesia, adhesions, and possible decreased fertility and the discomfort and time away from work and family. For women who have undergone myomectomy, there may be an increased risk of dehiscence of the myomectomy incisions during pregnancy or delivery (Fig. 7.4), and hysteroscopic or laparoscopic myomectomy may increase the incidence of placental abnormalities such as placenta accreta. Pregnancy is usually not recommended after uterine artery embolization, magnetic resonance-guided focused ultrasound-directed surgery, or myolysis due to the uterine abnormalities that persist after these procedures, possibly associated with myometrial abnormalities.

In this chapter, we will review the pathophysiology of uterine fibroids and discuss the consequences and management of uterine fibroids during pregnancy.

7.2 Background

7.2.1 Epidemiology and Pathophysiology

Uterine fibroids can be identified in approximately 70–80 % of women (Fig. 7.5) by the time they reach menopause, although most are asymptomatic [1]. Most of these benign tumors develop independently. Growth is stimulated by

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_7

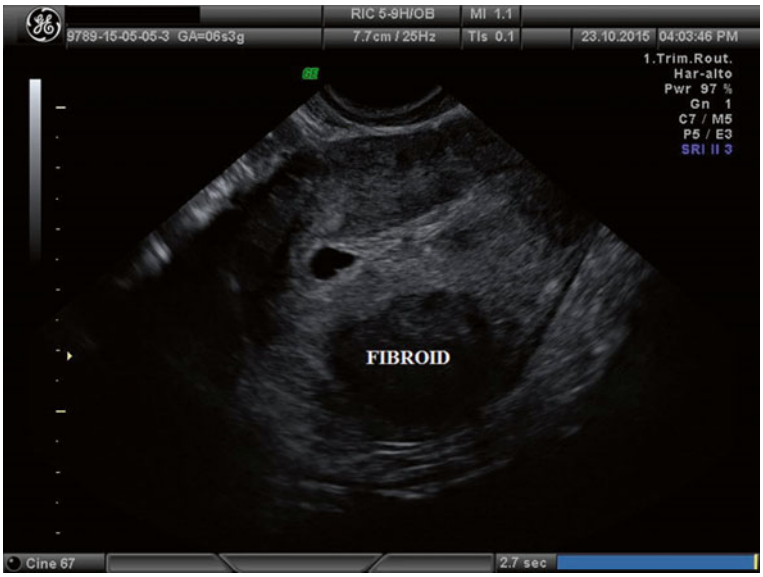

Fig. 7.1 A sagittal section of a pregnant uterus at 6 weeks with a posterior intramural fibroid of 3 cm in diameter

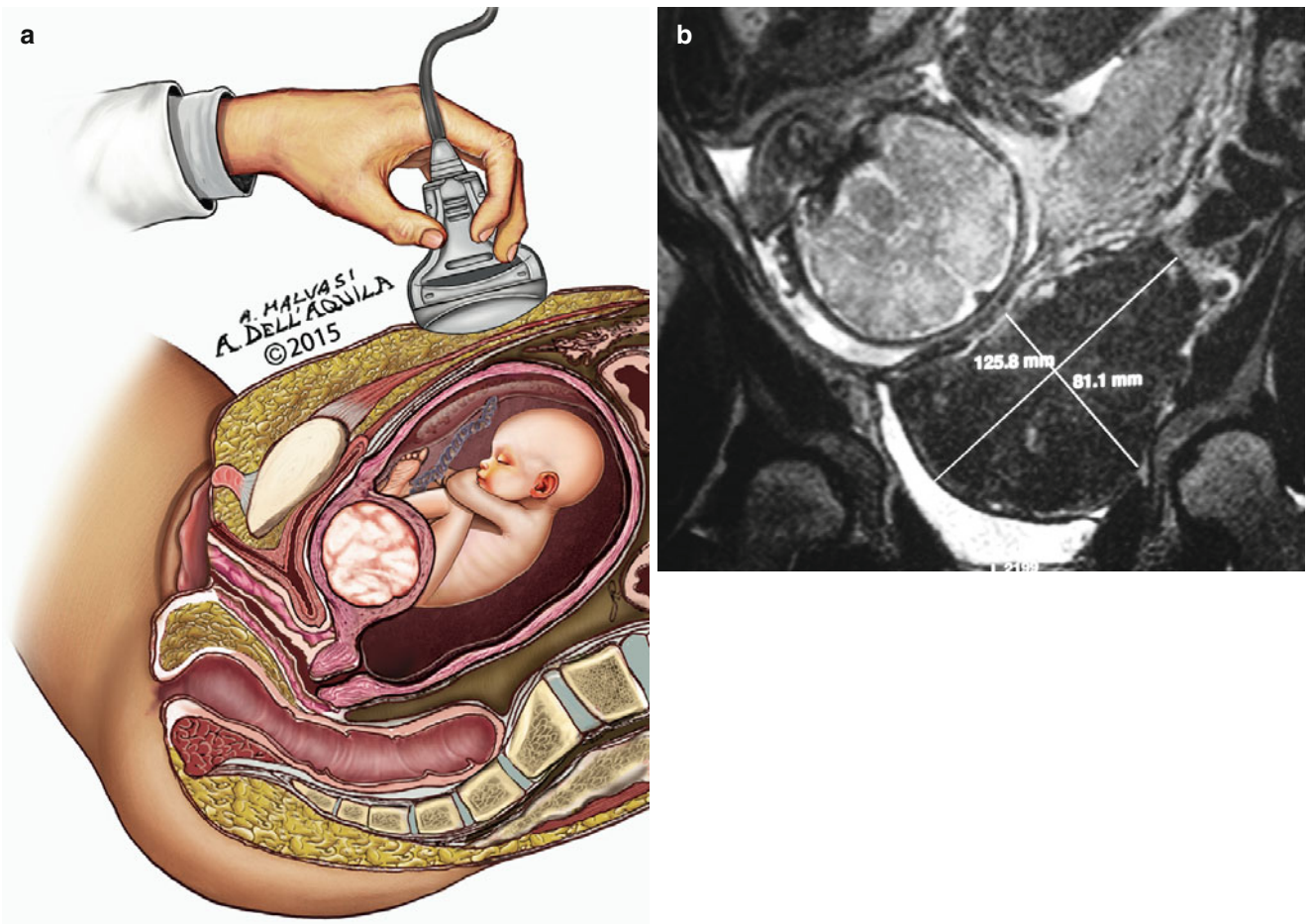

Fig. 7.2 (**a**) A draft of ultrasonographic scan of a cervical anterior fibroid, at the beginning of pregnancy. (**b**) MRI image of a larger cervical fibroid obstructing the normal passageway for delivery (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

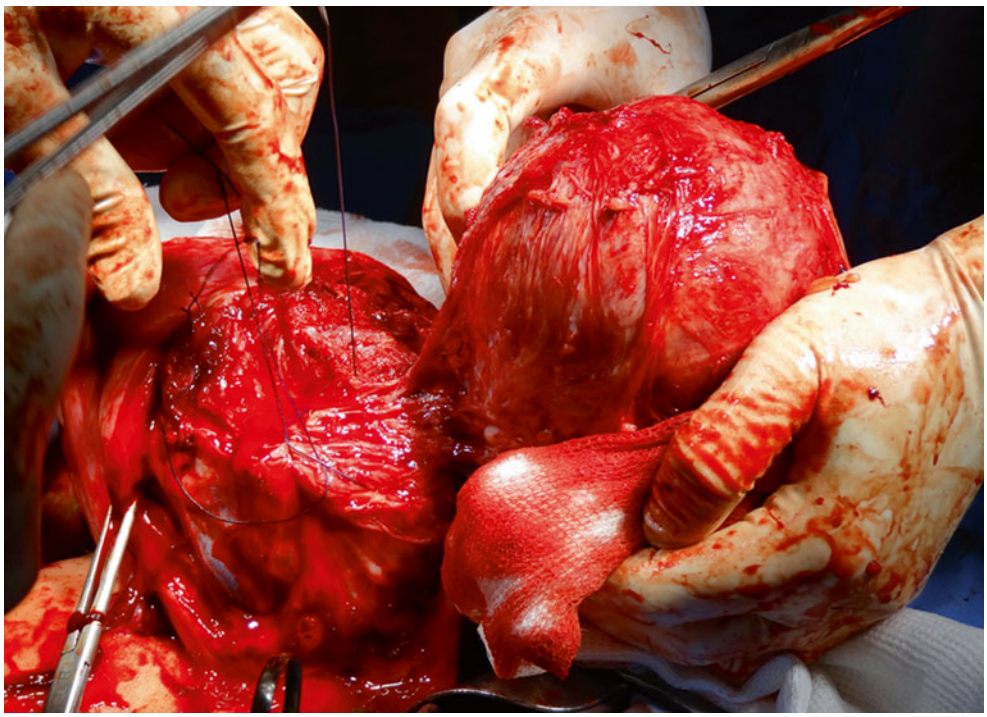

Fig. 7.3 A large anterior fibroid enucleated during cesarean section, after delivery of the newborn (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

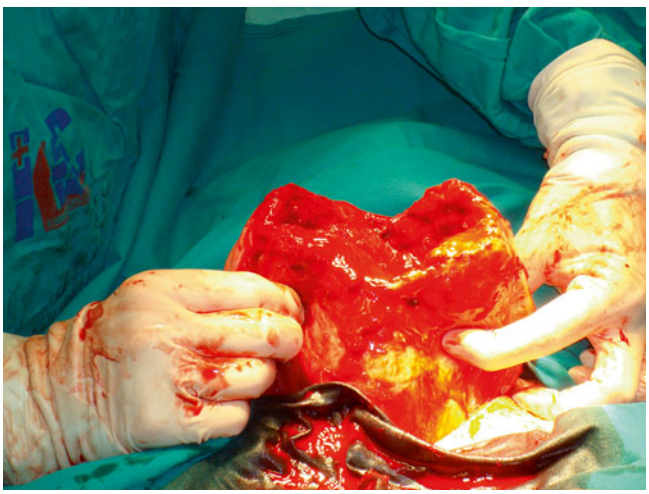

Fig. 7.4 A dehiscence of uterine scar after myomectomy during pregnancy, at 25 weeks (Courtesy of Dr. Radmila Sparic)

estradiol, progesterone, and local growth factors and promoted by angiogenesis. Because of stimulation by estrogen and progesterone, the peak prevalence of fibroids occurs during the 40s. Many fibroids have chromosomal abnormalities including translocations, aneuploidy, gene mutations, deletions, inactivation, or overexpression [2]. Vitamin D deficiency is likely to play a role in the development of uterine fibroids, as vitamin D3 reduces fibroid cell proliferation in vitro and fibroid tumor growth in animal models [3]. It has been suggested that vitamin D deficiency may be a factor to explain why women of African descent have a higher incidence and a greater number of uterine fibroids than other ethnic groups. There is also familial tendency to develop these tumors between first-degree relatives and twins [4].

About 40% of fibroids grow during pregnancy (Fig. 7.6), and most of the growth takes place during the first trimester (Fig. 7.7). During pregnancy, uterine fibroids are exposed to high levels of estrogen and progesterone. Estrogen produced by the ovary and the placenta, as well as additional growth factors, stimulates the growth of fibroids. Additionally, local conversion of androgens to estrogens by aromatase occurs within the tumors [5]. The primary action of estrogen and the estrogen receptor α (ERα) appears to be mediated by induction of progesterone receptors (PRs), which makes the tumor responsive to progesterone. Progesterone stimulates the growth of the fibroid through genes that regulate both apoptosis and cell proliferation.

Since fibroid growth is stimulated by estrogen and progesterone and both of these hormones are elevated during pregnancy, it is reasonable to expect growth of these masses during pregnancy. Although the growth or degeneration of a fibroid is not linear throughout the course of pregnancy, there is remarkable growth during the early pregnancy. This was shown in a prospective case-controlled study of women with fibroids undergoing IVF, in which fibroids were serially

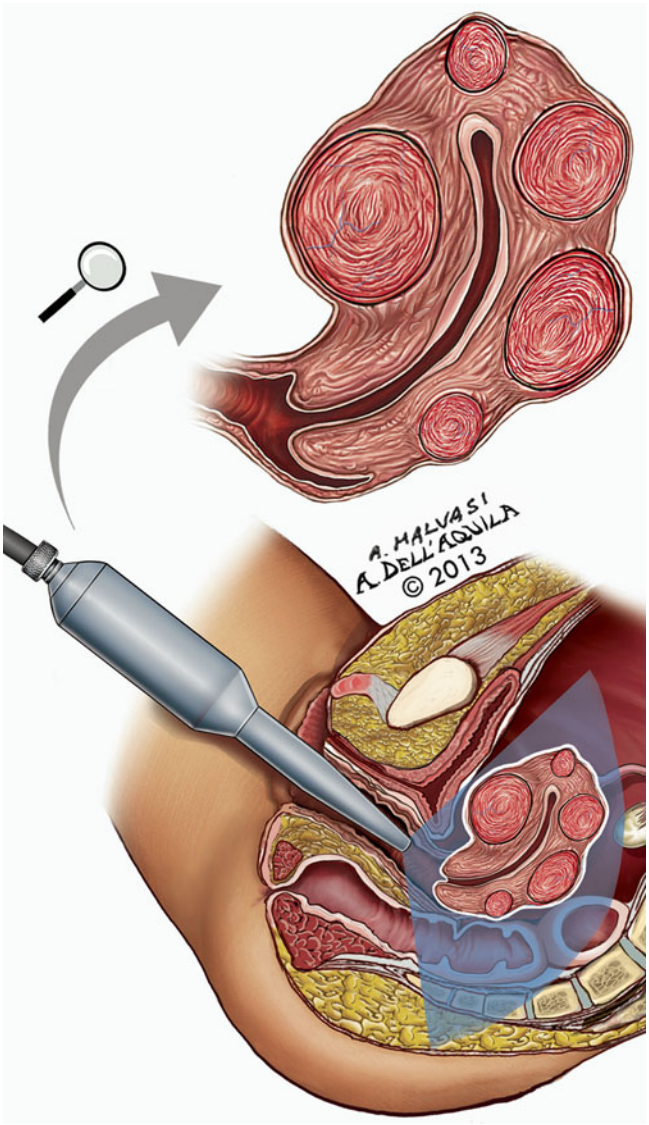

Fig. 7.5 A transvaginal sagittal uterine scanning with multiple fibroids

measured by ultrasound in 25 women who became pregnant and in 25 who failed to conceive [6]. A significant 34 % increase in the mean diameter of fibroids was found in early pregnancy, compared to a 2 % increase in those who failed to conceive. There was no correlation between ovarian responsiveness and fibroid growth; therefore the changes were attributed solely to pregnancy-associated factors. The observation that fibroids grow in diameter by approximately 30–35 % during the early pregnancy is concerning, as it is possible that an asymptomatic or seemingly "innocent" fibroid near the endometrium could enlarge and lead to unexpected problems during pregnancy. However, it is important to consider that there is no evidence that "prophylactic surgical treatment" is beneficial.

The fibroid is surrounded by a "pseudocapsule" (Fig. 7.8), and recent studies have demonstrated the importance of the pseudocapsule. The pseudocapsule is a fibro-neurovascular structure surrounding a fibroid (Fig. 7.9), separating it from normal peripheral myometrium (Fig. 7.10). The fibroid pseudocapsule is composed of a neurovascular network rich in neurofibers and contains neurotensin, neuropeptide tyrosine, and protein gene product 9.5, as well as substance P and vasoactive intestinal polypeptide [6]. There is a significant increase in endoglin expression level in the pseudocapsule compared to the myometrium or the uterine fibroid, indicating that an active neoangiogenesis is present in pseudocapsule, whereas angiogenic factors including von Willebrand factor (vWF) and vascular endothelial growth factor A (VEGF-A) seem to have little influence on the pseudocapsule angiogenesis. Endoglin is preferentially expressed in proliferating endothelial cells, whereas the vWF and VEGF-A are preferentially expressed in preexisting endothelial cells [7]. Combined, these important findings suggest healing after myomectomy is likely promoted by preservation of the pseudocapsule.

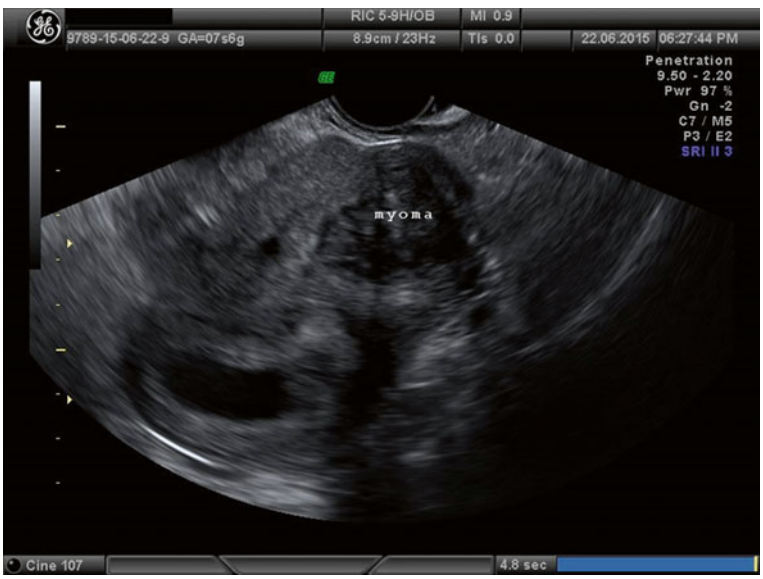

Fig. 7.6 An ultrasonographic transvaginal uterine section showing an anterior isthmic fibroid of 3.5 cm in diameter in a pregnant at 7 weeks

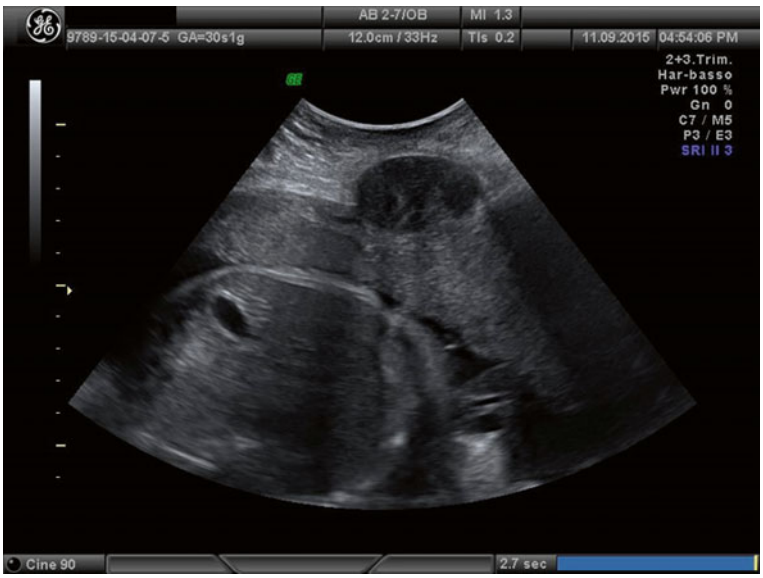

Fig. 7.7 A transabdominal uterine scanning of a patient at 29 weeks with an anterior subserosal fibroid of 4.5 cm in diameter

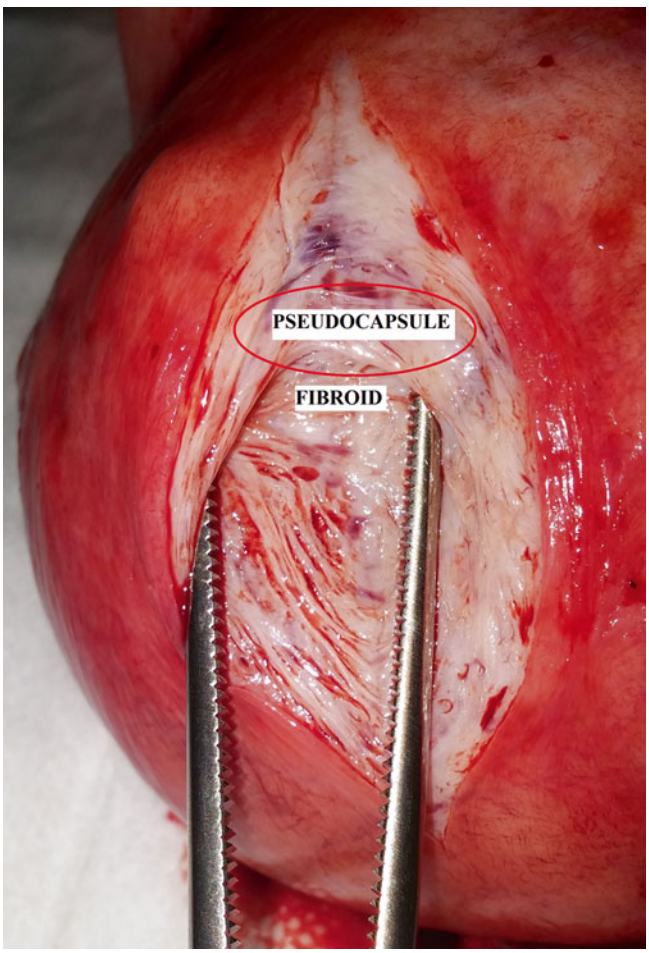

Fig. 7.8 A macroscopic image of a uterine fibroid and its surrounding pseudocapsule in the *red ring*

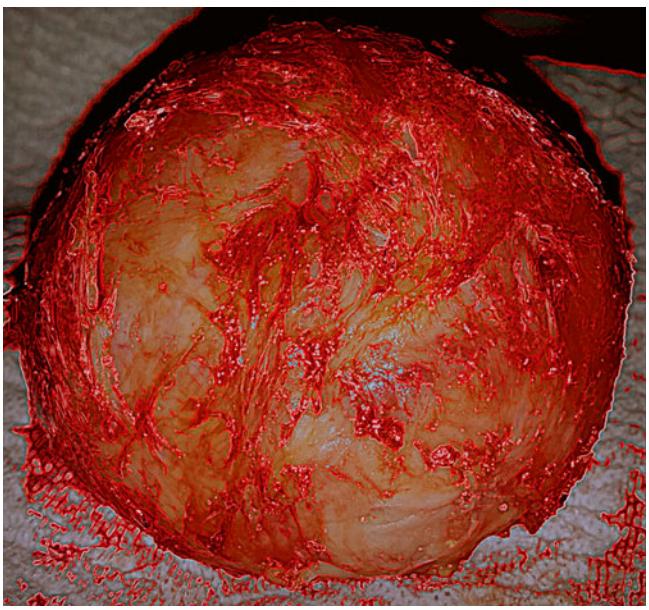

Fig. 7.9 A *white* fibroid surrounded by its branches of pseudocapsule, enhanced in *red*

7.2.2 Clinical Presentation in Nonpregnant Women

Most women with uterine fibroids are asymptomatic. In these women, fibroids may be diagnosed during a pelvic examination or when a pelvic ultrasound is performed (Fig. 7.11). When symptomatic, uterine fibroids cause morbidity corresponding to the size, number, and location of

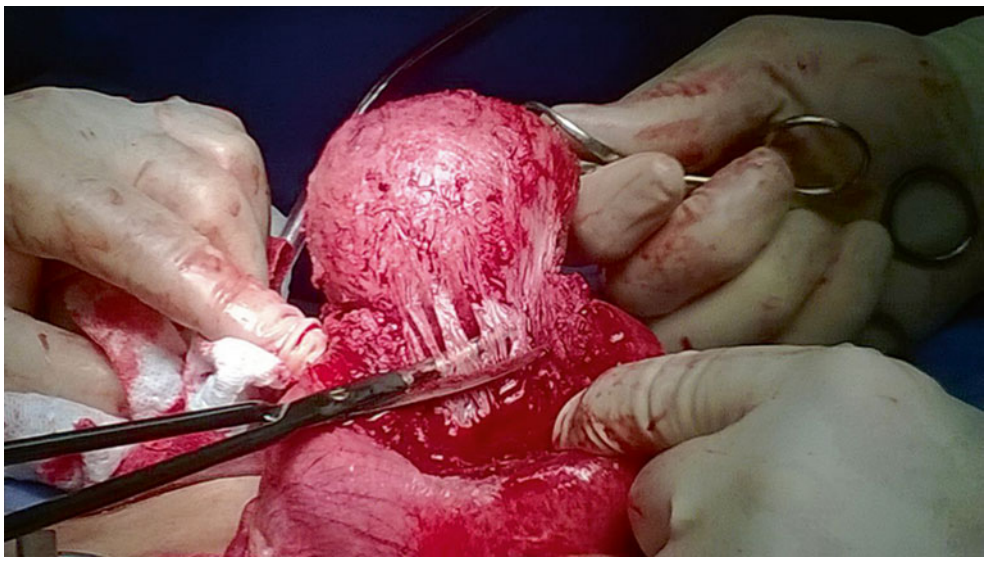

Fig. 7.10 A laparotomic image showing the fibroid pseudocapsule detached from fibroid by surgical scissor

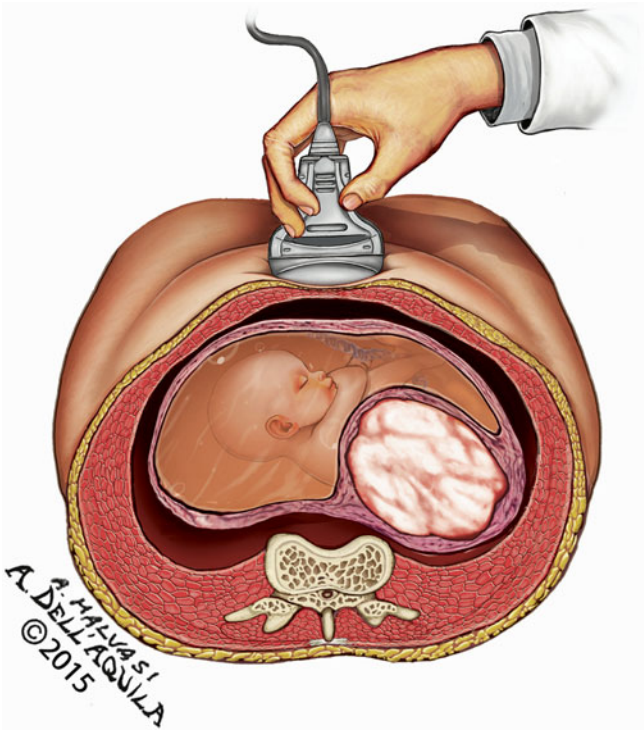

Fig. 7.11 A transabdominal ultrasonographic scanning showing a posterior uterine fibroid

the masses (Fig. 7.12). Common symptoms in the nonpregnant woman related to a submucous fibroid include heavy menstrual bleeding or intermenstrual bleeding, pain, pressure, and infertility. Bulk symptoms may be present, based on size and location of the fibroids, typically occurring with large subserosal or intramural fibroids (Fig. 7.13). These tumors may also cause urinary frequency if they compress the bladder, dyspareunia if the mass distorts the posterior cul-de-sac or cervical position, or difficulty with defecation for a posterior fibroid (Fig. 7.14).

While the most common reasons women seek treatment for uterine fibroids are bleeding and pressure, fertility and obstetric issues play a role as well. There is a clear cause and effect for submucosal tumors affecting fertility (Fig. 7.15). Pregnancy outcomes improve after removal of submucous fibroids. There is a general consensus that subserosal fibroids do not cause infertility (Fig. 7.16). There is more controversy regarding intramural fibroids on fertility (Fig. 7.17). However, in some women with otherwise unexplained infertility, myomectomy may improve pregnancy outcomes [8].

7.2.3 Treatment of Fibroids in Nonpregnant Women

Treatment of fibroids in a nonpregnant woman is important since all treatments can have important implications during pregnancy and in the peripartum interval. Management options include medical therapy; primarily gonadotropin-releasing hormone agonists (GnRHas) and progesterone antagonists; surgery including hysteroscopic myomectomy (Fig. 7.18), laparoscopic myomectomy (Fig. 7.19), or abdominal myomectomy (Fig. 7.20); radiologic interventions including uterine artery embolization (UAE) and magnetic resonance-guided focused ultrasound surgery (MRgFUS); and myolysis procedures.

Medical treatments such as combined oral contraceptive pills or continuous progestin pills have limited evidence for efficacy, especially in women with distortion of the uterine cavity from fibroids, and are primarily considered as temporizing measures [9]. GnRHa may be used to decrease menorrhagia, especially in preparation for surgery, to allow for

recovery of anemia, thin the endometrial lining, and facilitate hysteroscopic resection of a submucous fibroid. GnRHa reduces the diameter and volume of fibroids while the patient is hypoestrogenic, but rapid regrowth of fibroids occurs when the medication is discontinued. GnRHa should generally be avoided prior to a myomectomy as it can make the procedure more difficult, and administration before myomectomy increases the likelihood of persistent or recurrent fibroids [8]. Cost and side effects of these medications limit their long-term use and many women go on to other forms of treatment.

Ulipristal acetate (Fig. 7.21) is a selective progesterone receptor modulator that is approved for treatment of symptomatic uterine fibroids in Europe and Canada. Approximately 62 and 73 % of women become amenorrheic during treatment, and bleeding is controlled in over 80 % of women with abnormal bleeding due to fibroids [10]. Menstruation resumes after each treatment course and is diminished compared with the baseline. When a second treatment course is administered, fibroid volume is reduced approximately 55 % compared to the baseline, and pain and quality-of-life measures improve. Since repeated courses may reduce the need for surgery for some women with fibroids, conception without further intervention may occur.

Pregnancy outcome data is limited after treatment with ulipristal. One study reported that 15 of 21 women who attempted to conceive were successful after participating in one of the ulipristal clinical trials [11]. Among the 18 pregnancies in these women, 12 resulted in births of healthy babies and six ended in early miscarriage. No further growth of fibroids was found during pregnancy. While this early observation is encouraging, it is too soon to determine if this medication will be a good option for women with symptomatic fibroids who wish to avoid surgery.

7.2.4 Surgery

Surgical management of uterine fibroids is appropriate in the following situations (1): abnormal uterine bleeding not responding to conservative treatments (2), high level of suspicion of pelvic malignancy (3), growth after menopause (4), infertility when there is distortion of the endometrial cavity or tubal obstruction (5), recurrent pregnancy loss (with distortion of the endometrial cavity) (6), pain or pressure symptoms (that interfere with quality of life) (7), urinary tract symptoms (frequency and/or obstruction), and (8) iron-deficiency anemia secondary to chronic blood loss [12].

Myomectomy refers to the excision of one or more uterine fibroids. It is considered the best option for young women with symptomatic fibroids who desire preservation of fertility. The benefit of myomectomy in infertile women is difficult to assess since the incidence of fibroids increases with age as does the incidence of infertility. The route of myomectomy, including hysteroscopy, laparoscopy, or open myomectomy, is chosen based on patient symptoms and the size, number, and location of the fibroids.

7.2.5 Hysteroscopic Myomectomy

Transcervical hysteroscopic myomectomy (Fig. 7.22) is appropriate for women with a symptomatic submucous fibroid and a desire for childbearing or uterine preservation. Following hysteroscopic myomectomy, the risk of early miscarriage is significantly reduced, and there is a corresponding increase in viable term deliveries [13]. When needed, hysteroscopic myomectomy can be performed concurrently with abdominal or laparoscopic myomectomy to reduce bulk symptoms. During hysteroscopy, the uterine cavity is filled with distention media, and the fibroid is resected with scissors, with monopolar or bipolar cautery, or with a hysteroscopic morcellator [14]. Typically hysteroscopic resection of fibroids is appropriate for tumors 6 cm or less, while larger masses may require a two-step surgery [15]. The surgical technique used during hysteroscopic myomectomy may be important for women as it relates to rates of conception, spontaneous abortion, and pregnancy outcomes. Some methods may be more likely than others to damage the endometrium, some procedures and techniques may allow for a greater percentage of complete removal of the submucous fibroid, and some approaches could damage the myometrium. Data to recommend one procedure over another, however, is lacking at present.

Pregnancy outcomes are favorable after hysteroscopic myomectomy. In one study, 86 % of women conceived after hysteroscopic myomectomy, and there was no difference in outcomes for fibroids that were completely, mostly, or partially intracavitary [16]. Pregnancy and birth rates were not related to the number, localization, or diameter of the fibroids. Miscarriage was more likely to occur when the fibroid was resected in the anterior uterine wall, and preterm delivery was more common when a fundal fibroid was removed. It is reasonable to monitor women carefully for miscarriage and preterm labor after undergoing hysteroscopic myomectomy.

7.2.6 Abdominal Myomectomy

In 1845, Washington Atlee reported his experience performing a successful abdominal myomectomy in the *American Journal of the Medical Sciences* [17]. Mortality associated with this procedure was high until Victor Bonney mastered the techniques of myomectomy, inspired by his nulligravida wife's emotionally devastating hysterectomy for a submucous fibroid in 1908. Bonney introduced many surgical techniques still used today, including compression of the uterine arteries

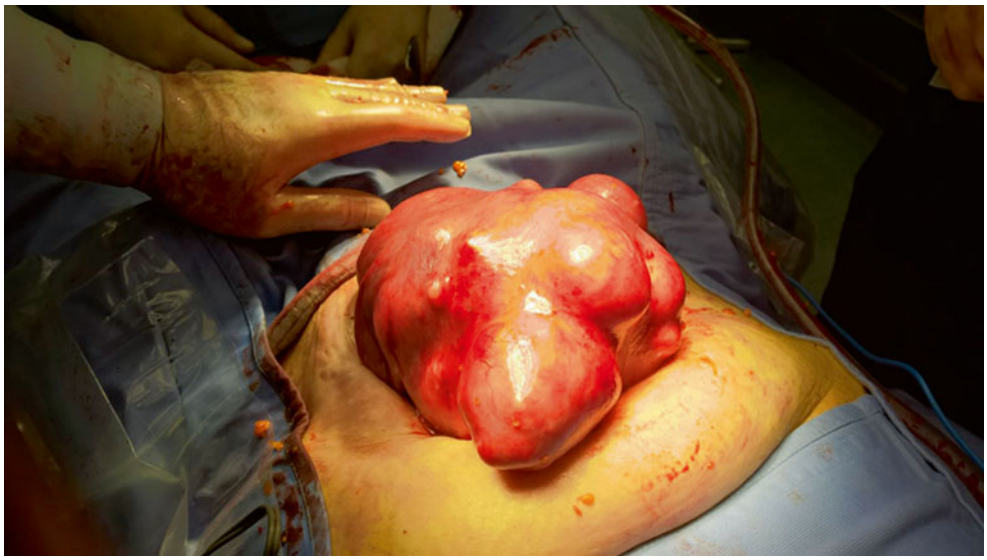

Fig. 7.12 A giant uterus with multiple fibroids causing compressive symptoms and massive bleeding during menses

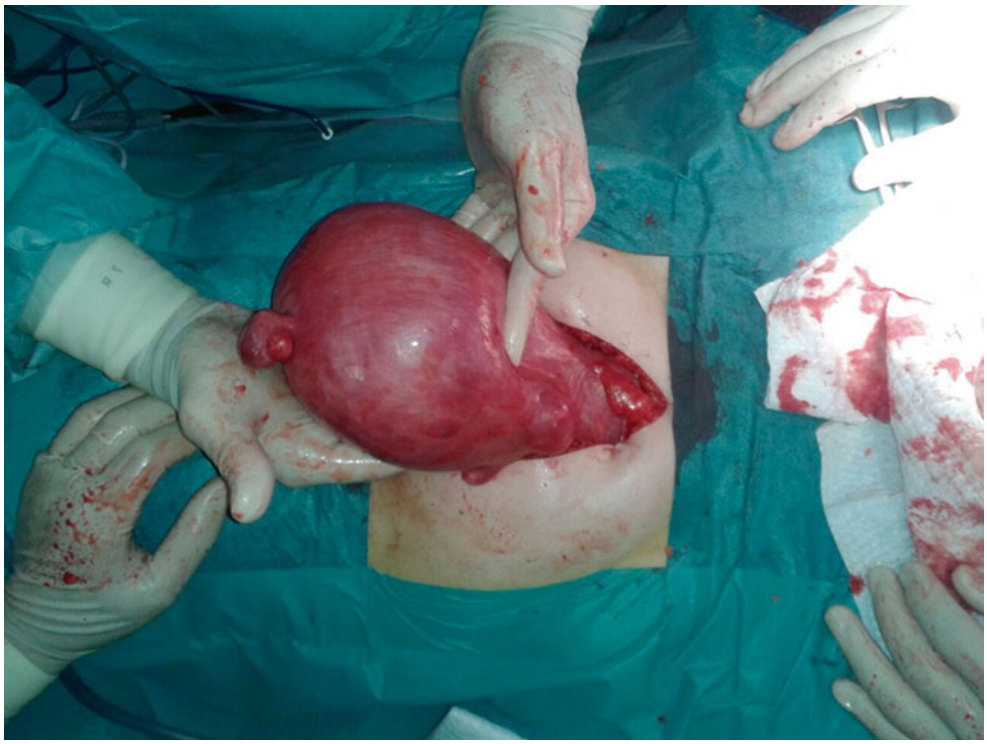

Fig. 7.13 A large subserosal/intramural fibroid, whose upper limit reaches the liver

with a clamp, now referred to as a "Bonney clamp," to reduce bleeding and elevate the uterus to improve exposure during myomectomy. He recognized the problem caused by dead space from the myoma bed and described a technique to obliterate the cavity by under-sewing the deeper layers. Bonney eventually performed over 700 myomectomies, and his mortality rate was only 1.1 %, remarkable in an era before blood transfusion and antibiotics were available. By the 1930s, Bonney advocated abdominal myomectomy for any woman with fibroids wishing to have children under the age of 41.

Recently, Tinelli and colleagues have emphasized the importance of surgical technique to preserve the fibroid pseudocapsule during myomectomy (Fig. 7.23a, b), to reduce intraoperative bleeding, promote postoperative healing, and preserve function of the uterus [18]. Since a "classical" myomectomy technique was not used for controls, the findings should be interpreted with caution. However, myomectomy with preservation of the pseudocapsule resulted in a reduction of the uterine healing area from 78 % of the previous fibroid size on the first day to <4 % on the 45th day after surgery [19].

Long-term outcomes following abdominal myomectomy are typically good and patient satisfaction is high, but adhesions and recurrent fibroids may compromise the results in some individuals. Myomectomy often reduces bleeding and improves fertility

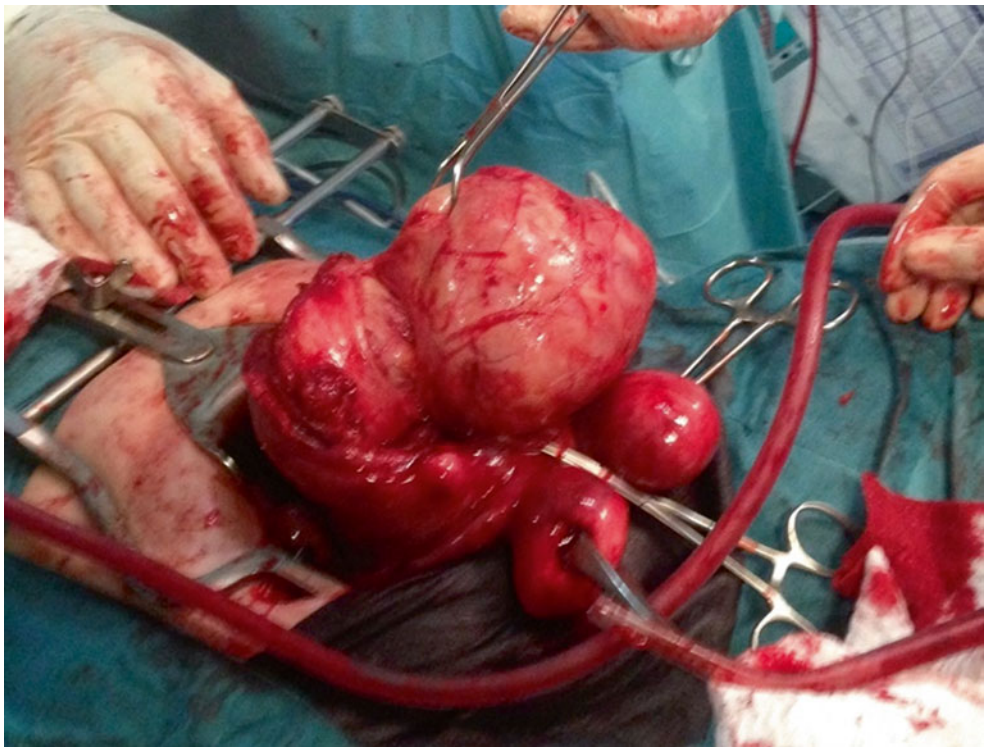

Fig. 7.14 A uterus with visceral anatomy subverted by multiple fibroids of different diameters (from 4 to 18 cm), aspect (intramural, subserosal, and pedunculated), and location (anterior, posterior, fundal) contemporary causing urinary frequency, dyspareunia, and difficulty with defecation for a posterior fibroid

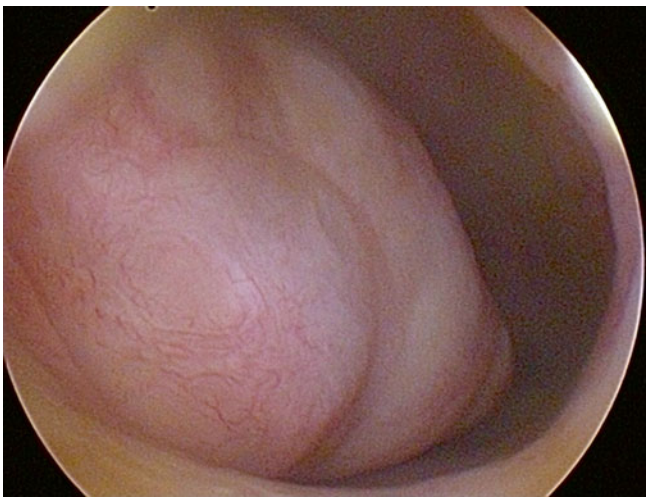

Fig. 7.15 A left submucous fibroid of 3 cm in diameter largely occupying uterine cavity

in women with excessive bleeding or infertility primarily caused by endometrial distortion from submucous myomas or large intramural myomas. Slightly more than 50% of women conceive after open myomectomy [20]. Adhesions form in more than 90% of abdominal myomectomies, with the incidence highest (94%) with posterior incisions and lower (56%) with fundal or anterior uterine incisions [21]. When severe, adhesions can result in bowel obstruction and require additional intervention. Adhesions can also increase the complexity of cesarean delivery. For this reason, adhesion barriers are recommended to minimize the extent of adhesions. Seprafilm and Interceed (Fig. 7.24) both have been shown to reduce the extent and severity of post-myomectomy adhesions [22, 23]. Growth of new fibroids is not uncommon after myomectomy, but additional surgery is required in a minority of patients.

7.2.7 Laparoscopic Myomectomy

Laparoscopic myomectomy was first described in the 1970s. Advances in instruments and surgical knowledge have progressed so that laparoscopic myomectomy is considered preferable to abdominal myomectomy when feasible. Laparoscopic myomectomy provides some obvious advantages compared to abdominal myomectomy. Decreased postoperative pain, shorter recovery time, reduced febrile morbidity, decreased blood loss, and decreased adhesion formation are the clear advantages seen in the minimally invasive approach. The risk of recurrence of fibroids and pregnancy outcomes are comparable after resection of fibroids from abdominal versus laparoscopic route [8]. In a study looking at intracapsular subserous and intramural myomectomy preserving the fibroid pseudocapsule (Fig. 7.25a, b), women who underwent the procedure for infertility (74%) eventually conceived [24]. To optimize laparoscopic myomectomy, it is important to properly select patients, place trocars to optimize visualization and prevent instrument collision, use the principles of traction and countertraction to the best advantage, and utilize appropriate instruments and suture material to better facilitate the case. The fibroid is enucleated from the surrounding pseudocap-

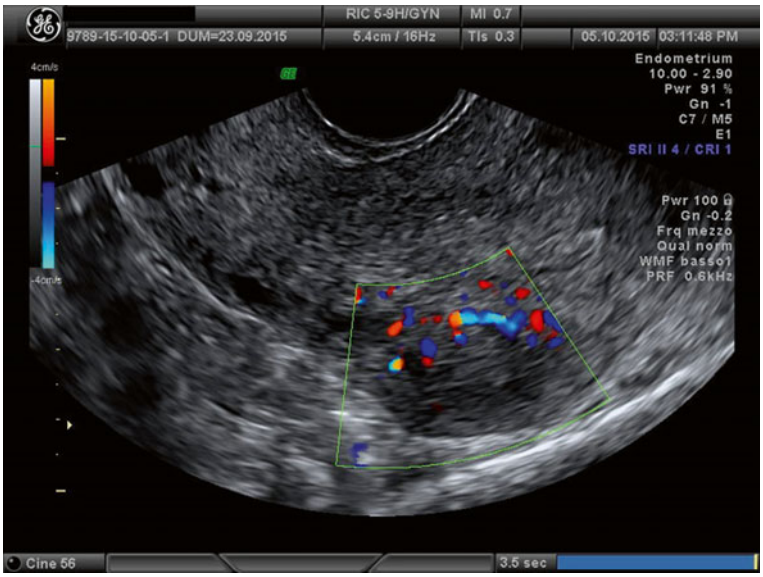

Fig. 7.16 An ultrasonographic sagittal scan of a retroverted uterus of a patient wishing pregnancy with a posterior subserosal fibroid

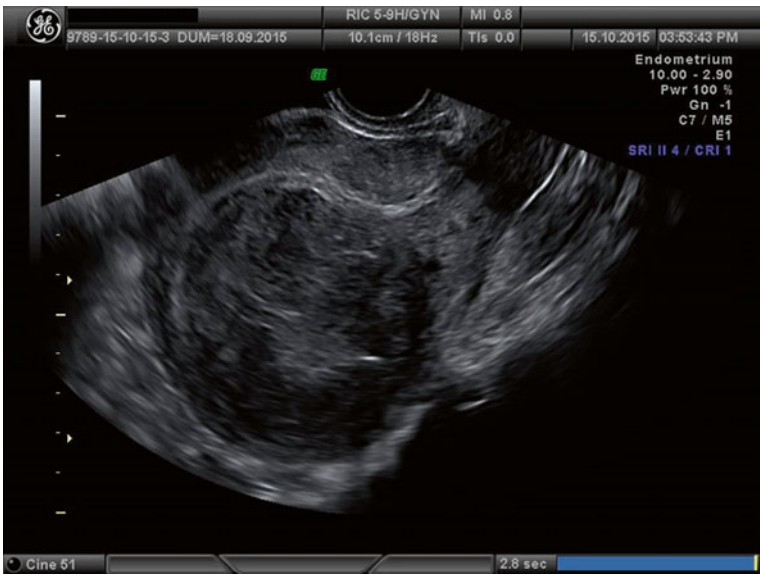

Fig. 7.17 A 30-year-old patient with an intramural fibroid in the posterior uterine body of 7 cm in diameter

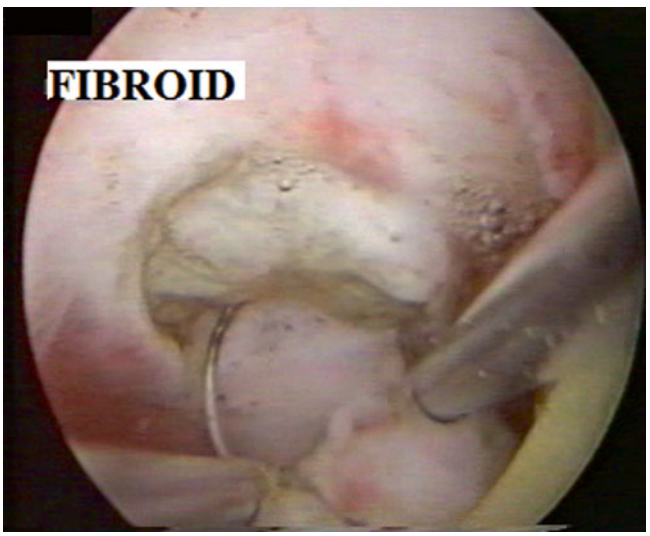

Fig. 7.18 A hysteroscopic myomectomy of anterior G2 fibroid

sule (Fig. 7.26) and the uterus repaired in single layer for subserosal fibroids (Fig. 7.27) and double layer for those extending into the myometrium (Fig. 7.28). Appropriate candidates for a laparoscopic myomectomy traditionally have less than three fibroids and size less than 8–10 cm. However, depending on individual surgical expertise, fibroids larger than this can be attempted, though typically with longer operating time and more anesthetic complications [25].

While there is a steep learning curve associated with the advanced laparoscopic techniques such as intracorporeal suturing, robotic-assisted laparoscopy allows for laparoscopic myomectomy in a wider scope of practice. Advantages include improved dexterity and three-dimensional view. While operative times tend to be longer in robotic-assisted cases than traditional laparoscopic, robotic-assisted laparoscopy has a shorter learning curve and does not add morbidity to the procedure. Pitfalls include loss of tactile sensation during surgery and increased cost [26]. Advanced laparo-

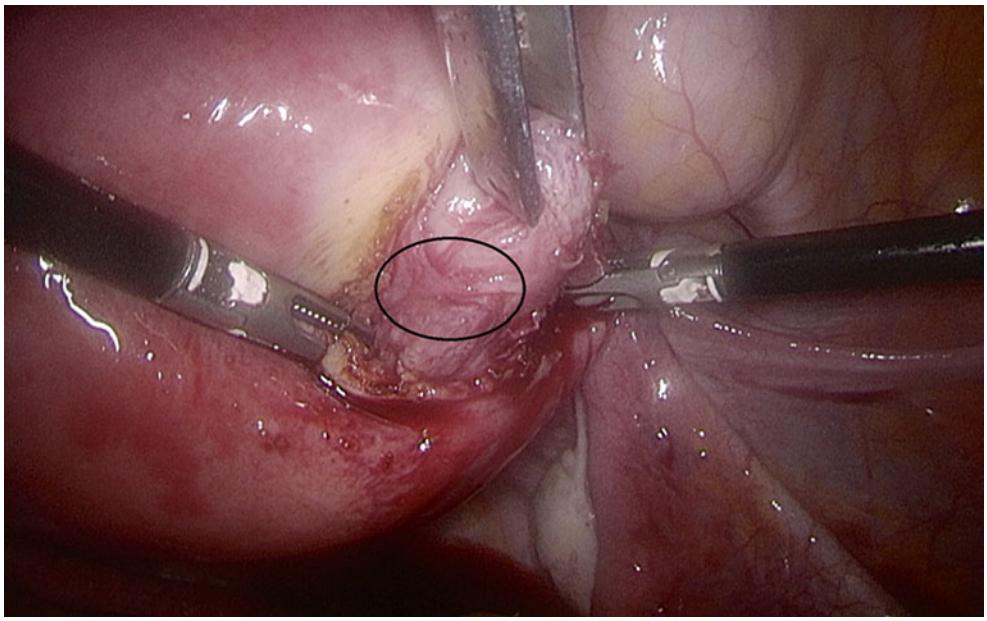

Fig. 7.19 A laparoscopic myomectomy; in the *black ring* the myoma pseudocapsule is highlighted

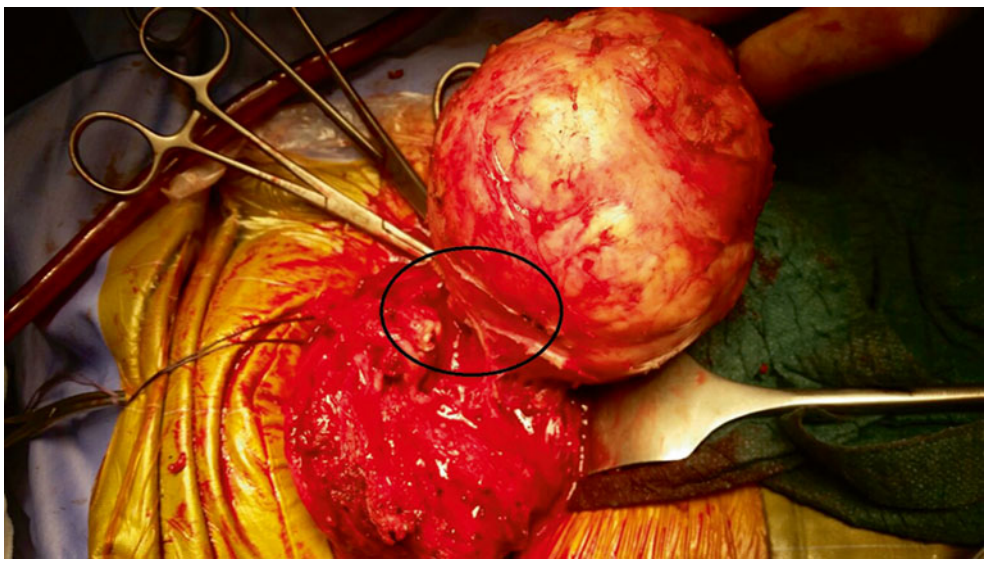

Fig. 7.20 A laparotomic myomectomy; in the *black ring* the myoma pseudocapsule is highlighted

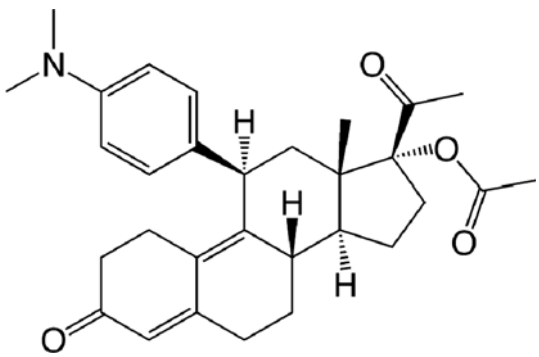

Fig. 7.21 Ulipristal acetate, a selective progesterone receptor modulator

scopic technique with the rise of single-port laparoscopic surgery to myomectomy presents a steep learning curve but has proposed benefits such as improved cosmetic outcome [27].

Surgical technique for any myomectomy is important in considering subsequent obstetric outcomes. Regardless of technique, it is important to recognize that a prior myomectomy increases the risk of uterine rupture. While this risk is less than 1 % when performed by a skilled surgeon [8], uterine rupture is important as rupture is an obstetrical emergency and can have catastrophic consequences for the mother and fetus (Fig. 7.29) [28]. The risk of uterine rupture is not known when the surgery is performed in most communities. The risk is likely higher when multiple large and deep uterine incisions are required to complete the myomectomy or suboptimal surgical techniques are used or if the myomectomy incision becomes infected postoperatively [29]. Although the risk of uterine dehiscence during pregnancy is low with proper myometrial closure, data are insufficient to determine if cesarean section should be routinely advised for delivery after resecting large, deep, or multiple fibroids (Fig. 7.30a, b).

7.2.8 Endometrial Ablation

Endometrial ablation can be performed after a hysteroscopic myomectomy for women with submucous fibroids who do not desire future fertility. However, ablation of the uterine cavity is not intended as a method of contraception, and some women have conceived, often with serious complications, after undergoing this procedure.

Since the endometrium is severely and irreversibly damaged by any endometrial ablation technique, it is not surprising that serious complications have been reported in women who died of a uterine rupture and massive internal bleeding at 24 weeks of gestation and a woman who required an emergency hysterectomy after a pregnancy termination was complicated by placenta increta [30]. Another report described a nonfatal uterine rupture that occurred at 26 5/7 weeks in a woman who conceived following ablation [31]. Because of the high morbidity associated with pregnancy after endometrial ablation, reliable contraception should be used. When pregnancy occurs, close monitoring for placental abnormalities, premature rupture of membranes, pregnancy distorted by uterine synechiae, or uterine abruption and the need for emergency hysterectomy may occur [32]. Even pregnancy termination should be considered to be a potentially high-risk procedure associated with complications including septic abortion and may necessitate hysterectomy [33]. Any pregnancy after endometrial ablation should be considered to be potentially dangerous, and the patient should be informed that hysterectomy may be needed if complications arise.

Several techniques and methods for endometrial ablation have been described since the procedure was introduced in the 1980s. Initially, ablation was performed using a rollerball, a resectoscope loop, or a contact laser. The technique requires technical expertise with operative hysteroscopy, and potential complications include uterine perforation and fluid overload. In the late 1990s and early twenty-first century, several ablation devices were introduced for endometrial ablation including a balloon system that heats the endometrium, a cryoablation

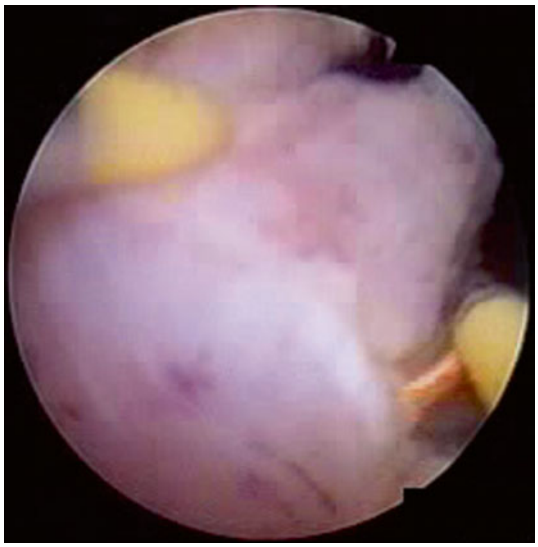

Fig. 7.22 Transcervical posterior hysteroscopic myomectomy, by a bipolar resector

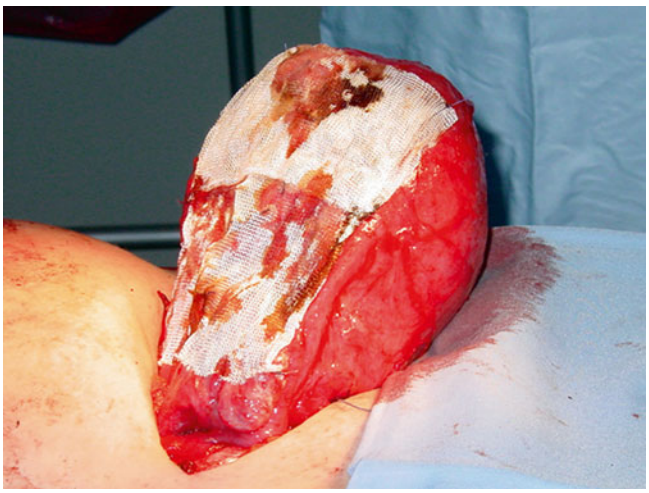

Fig. 7.24 An Interceed adhesion barrier applied on the uterine sutured surface after cesarean section, to minimize the extent of adhesions (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

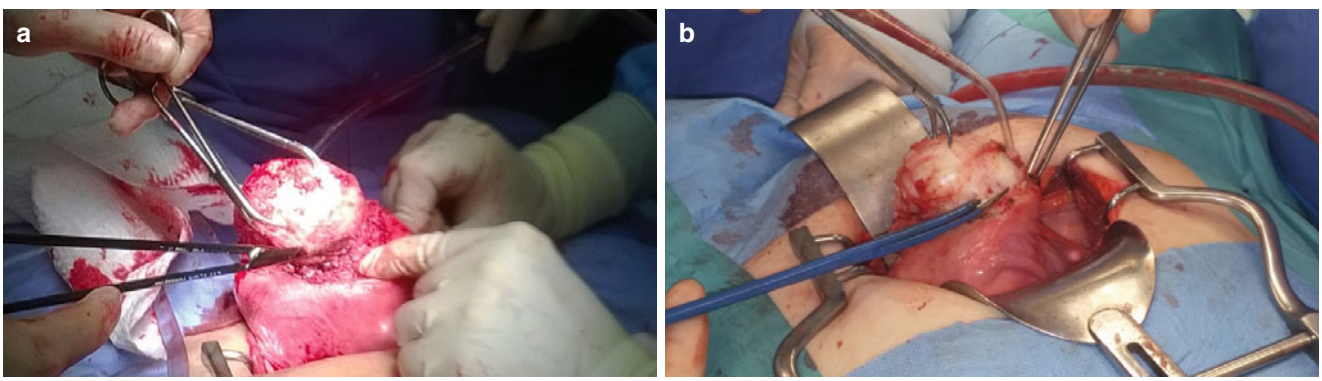

Fig. 7.23 Two laparotomic myomectomies (**a**, **b**) by intracapsular technique showing the surgical scissors cutting the pseudocapsule branches attaching myoma to the pseudocapsule

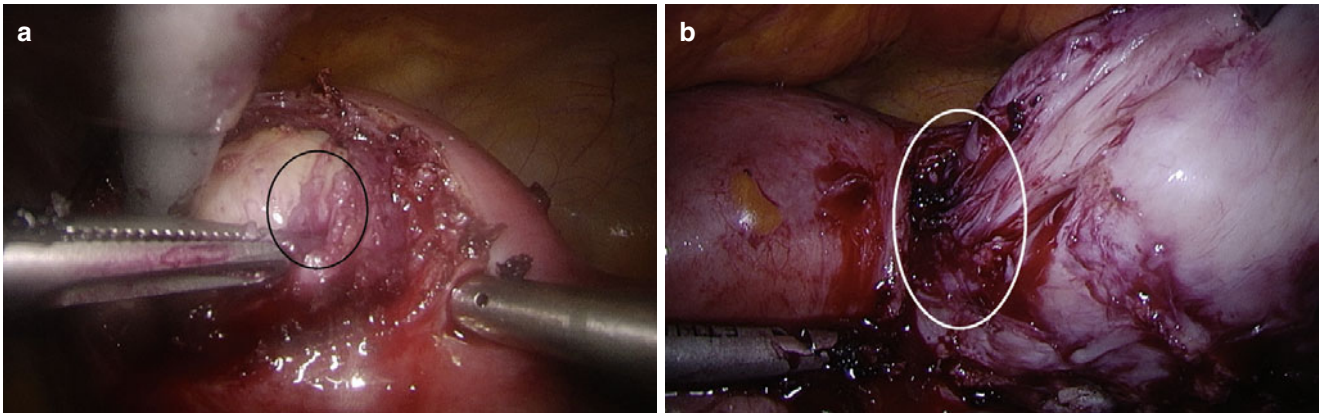

Fig. 7.25 Two laparoscopic myomectomies (**a**, **b**) by intracapsular technique showing, in the *black* (**a**) and *white* (**b**) ring, the pseudocapsule branches attaching myoma to the pseudocapsule

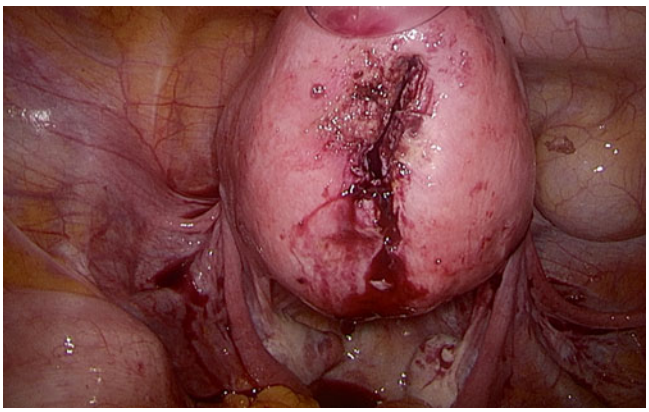

Fig. 7.26 The final result of laparoscopic intracapsular myomectomy, with intramural fibroid enucleated by uterus-sparing myoma pseudocapsule, with few bleeding from hysterotomy, before suturing

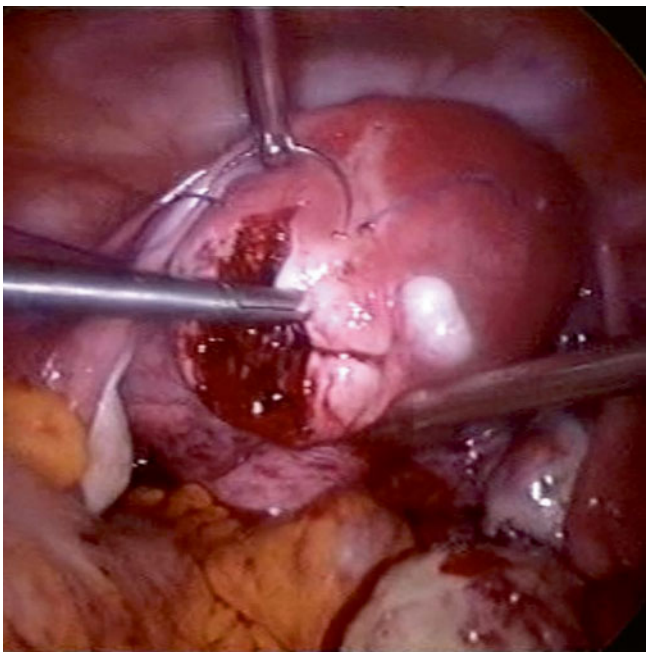

Fig. 7.27 A laparoscopic hysterorrhaphy by a single layer suturing after a subserosal fibroid enucleating

system under ultrasound guidance, and a system that delivers heated saline under hysteroscopic guidance. A microwave mesh system, NovaSure (Novacept, Palo Alto, CA), is performed by placing a triangular electrode in the uterus, and negative pressure pulls the endometrium into contact with the electrode. The NovaSure system is the only FDA-approved device to treat small (<2 cn) polyps, and it can be used to treat a fibroid uterus, as long as there is no distortion of the shape of the cavity. However, none of these devices is intended for endometrial distortion from uterine fibroids, so the utility for ablation with submucous fibroids is limited [34].

7.2.9 Uterine Artery Embolization

If future fertility is desired, myomectomy is preferred over embolization, as pregnancy outcomes are uncertain. Uterine artery embolization (UAE) is primarily performed by interventional radiologists by a catheterization of the femoral artery and bilateral occlusion of uterine arteries with substances such as polyvinyl foam particles. The selective perfusion of these vessels causes infarction and the fibroids decrease in volume by approximately 50 %. UAE is a reasonable alternative to hysterectomy and abdominal myomectomy with favorable short-term outcomes including improved bleeding, pain, and quality of life and similar long-term outcomes [35]. Uterine artery embolization is most appropriate for women with symptomatic fibroids who are past the childbearing years and poor surgical candidates or those who wish to avoid hysterectomy.

In one study, 14 of 23 women who desired pregnancy conceived, resulting in 13 uncomplicated term deliveries and two miscarriages at 12 and 16 weeks [36]. In another study, approximately 28 % of women who tried to conceive were successful after UAE, and only about 14 % had a live birth [37]. In another study, only 1 in 31 women who desired

fertility eventually conceived, and she experienced a first-trimester miscarriage [38].

Fibroids may degenerate but do not disappear after UAE; therefore the remaining fibroids may still compromise the gravid uterus. Furthermore, during embolization, the particles used to occlude the vascular flow of the fibroid also may occlude normal vessels of the myometrium and endometrium. Although the uterus receives flow from the cervical and ovarian arteries and blood flow is maintained to the uterus, the particles used for UAE are trapped within the small arterial branches, although they have not been shown to cause long-term effects. Therefore, it is not surprising that UAE results in infertility and more pregnancy complications such as spontaneous abortion, preterm delivery, malpresentation, abnormal placentation, and postpartum hemorrhage compared to myomectomy [39]. Reported pregnancy outcomes in women who have undergone UAE include first-trimester miscarriage [38], uterine rupture, and placenta increta [40]. Although the Society of Interventional Radiology Standards of Practice Committee states UAE may be preferred for women with prior myomectomy and that patient's preference for UAE as primary therapy for fibroids should be respected [41], currently, we do not recommend UAE for women who desire future fertility, and pregnancies

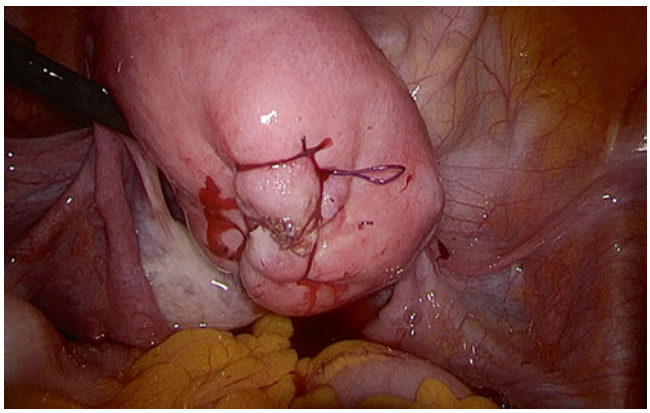

Fig. 7.28 The final result of a laparoscopic hysterorrhaphy by a double layer suturing after an intramural fibroid enucleating: the suture is always introflexing as a "basketball suture"

Fig. 7.29 Uterine rupture is an obstetrical emergency for massive bleeding and painful–hemorrhagic shock, with possible catastrophic consequences for the mother and fetus

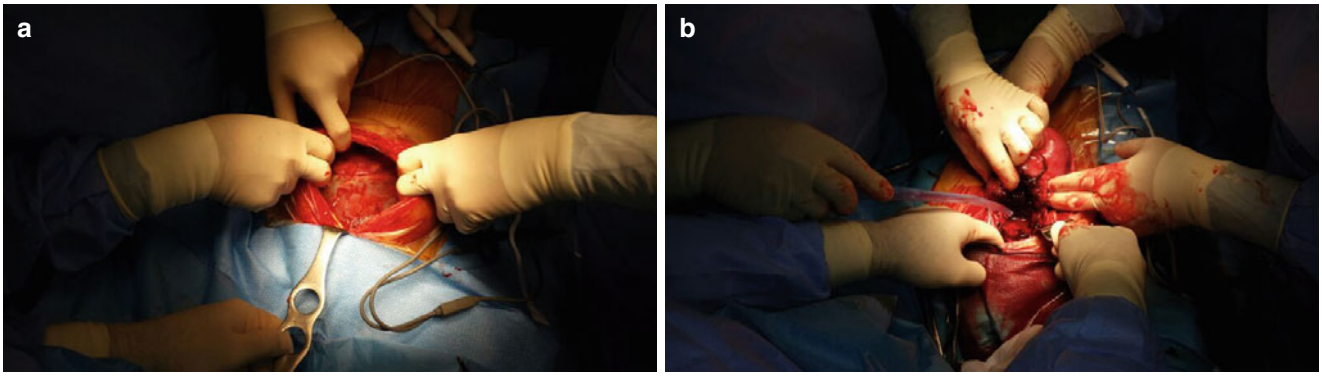

Fig. 7.30 Images of urgent longitudinal laparotomy at 23 weeks, in a patient with a previous laparotomic anterior isthmic myomectomy: (**a**) after the opening of abdominal cavity, the placenta appears completely free floating on the abdominal cavity; (**b**) after fetus and placental removal, surgeons show the uterine rupture on the previous uterine scar

that occur should be considered high risk for uterine or placental abnormalities.

7.2.10 MRgFUS

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a noninvasive approach to treat fibroids that utilizes magnetic resonance imaging (MRI) to visualize anatomy and monitor tissue temperature and thermal dose during delivery of focused ultrasound to the target tissue. The ExAblate system (InSightec, Haifa, Israel) was approved by the FDA in 2004 after initial clinical studies showed significant improvement in quality-of-life scores [42]. Fibroid volume is decreased approximately 29 % 6 months after treatment [43]. Reintervention rate after MRgFUS is approximately 13 %, after a mean follow-up of approximately 19 months [44].

Although the procedure is not recommended for women who desire future fertility, by 2010 there were 54 pregnancies reported in 51 women after MRgFUS treatment of fibroids, resulting in a 41 % live birth rate, a 20 % ongoing pregnancy rate beyond 20 weeks, a 28 % spontaneous abortion rate, and an 11 % pregnancy termination rate [45]. Although favorable pregnancy outcomes following MRgFUS have been reported, until more safety data is available, MRgFUS should not be chosen for women who desire future fertility, and pregnancies that occur should be monitored for uterine or placental abnormalities.

Appropriate candidates for MRgFUS include premenopausal women who have completed childbearing and have accessible MR-enhancing symptomatic uterine fibroids (i.e., not shielded by the bowel or bone) less than 24 weeks in size. Ineligible women include those who are pregnant and lactating, have active pelvic inflammatory disease or any active infection, and have chronic leg or lower back pain, severe claustrophobia precluding the use of MRI, weight that exceeds MR capability (approximately 113 kg), implanted materials or devices that are contraindicated for MR, extensive abdominal scarring in the ultrasound beam path that cannot be avoided, dermoid cyst in the beam path, intrauterine device, pedunculated fibroids, known or suspected hyperplasia or malignancy, and undiagnosed uterine bleeding. Overall, less than half of women are eligible for MRgFUS, with the most common exclusions being fibroid size, high cost, and desired fertility [46].

MRgFUS-related complications include skin and sciatic nerve injury, and there is a small risk of bowel and bladder injury. A study prospectively comparing MRgFUS and hysterectomy found fewer complications and faster recovery after MRgFUS but better quality-of-life scores 6 months after hysterectomy [47].

7.2.11 Myolysis

Electrical, thermal, and ultrasound energy sources have been used to coagulate and devascularize symptomatic myomas. Current methods of myolysis have achieved success in relieving symptoms relating to myoma volume, but little is known about its safety for women wishing pregnancy.

Myolysis involves placement of the ablation device using either ultrasound or directly inserted into the uterus during laparoscopy. Many types of ablation devices have been described, including monopolar electrical or radiofrequency devices, thermal devices, or laser probes. Older devices placed during laparoscopy often caused uterine serosal injury and induced dense pelvic adhesions [48]. Bipolar electrode probe myolysis reduced myoma volume by 89 % and had a 97 % patient satisfaction rate at 6 months from surgery [49]. In another case series, the addition of bipolar electrode probe myolysis to endometrial ablation reduced the need for repeat surgery by 66 % and increased the postsurgical amenorrhea rate from 37 to 57 % [50]. However, bipolar myolysis also

caused a high rate of dense adhesions. Fibroid volume reduction following laparoscopic cryomyolysis was only about 10 % in one study, and postoperative adhesion formation was high [51]. A different laparoscopic cryomyolysis study of 20 patients, however, produced fibroid volume reduction of 80 % and improved symptoms [52].

A newer form of myolysis, the Acessa procedure, has provided renewed interest in myolysis. The approach uses radiofrequency energy to a fibroid through a needle array during laparoscopy. A laparoscopic ultrasound determines the size and location of fibroids. The introducer is placed through the serosa into the fibroid, and the electrode array is placed with laparoscopic and ultrasound visualization [53]. In a study of 135 women undergoing this type of myolysis, menstrual blood loss was reduced by approximately 40 %, and fibroid volume decreased by 45 % by 12 months. By 36 months, the cumulative repeat intervention rate was 11 % [54]. A postmarketing study is under way to report pregnancy outcomes for women who conceive after treatment [55].

As is the case after UAE and MRgFUS, the fibroid size is reduced but still remains; therefore pregnancy outcomes could be compromised, at least compared to a woman without fibroids. It is possible that some techniques damage the myometrium and could increase the risk of uterine rupture during pregnancy and delivery. Furthermore, dense adhesions induced by laparoscopic techniques could increase the difficulty and complexity of cesarean delivery.

So far, there is limited data that describes pregnancy outcomes after myolysis. One report identified two women who delivered 15 and 18 months after undergoing ultrasound-directed transvaginal myolysis, and no complications arose during or after delivery [56]. However, another report identified three women who conceived soon after undergoing laparoscopic myolysis, and two experienced uterine rupture at 32 and 39 weeks, with death of the 32 week fetus [57]. The third delivered at the term. While it is possible that these pregnancy complications were related to expensive damage to the myometrium due to imprecise placement of the myolysis device during laparoscopy, pregnancy should be discourage for the woman who has undergone myolysis until more data are available.

7.3 Fibroids and Pregnancy

7.3.1 Incidence of Fibroids During Pregnancy

The prevalence of fibroids in pregnancy is 18 % in African-American, 8 % in white, and 10 % in Hispanic women, based on first-trimester sonography [58].

The mean size of the fibroids is approximately 2.5 cm. However, when ultrasound is delayed after first visit (Fig. 7.31), at 7–10 weeks, they may be more difficult to identify, as the fibroids are detected in only 3.2 % of pregnancies in the second trimester (Fig. 7.32) [59]. Clinical exam detects 42 % of fibroids larger than 5 cm during pregnancy, but only 12.5 % of those smaller than 5 cm [60].

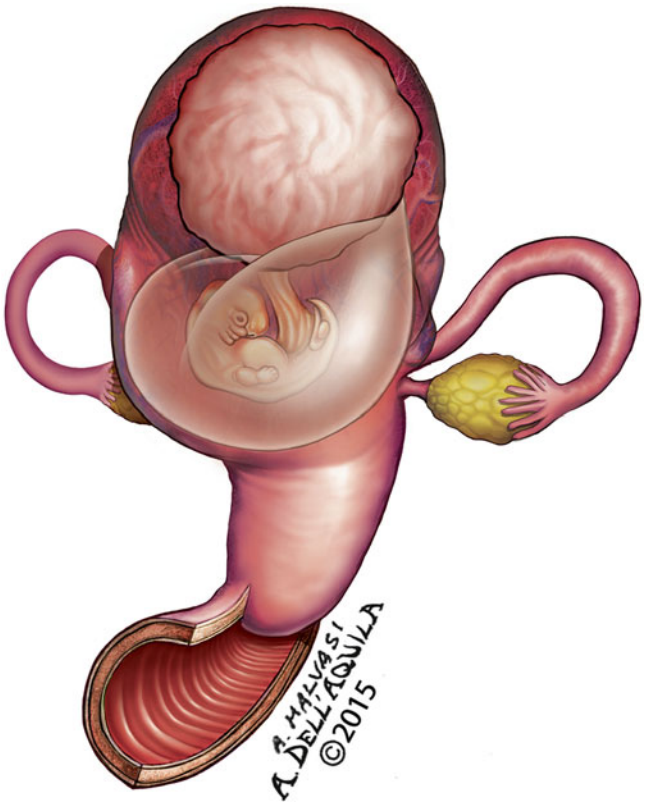

Fig. 7.31 An ultrasonographic scan of a fetus at 8 weeks with an overlying fundal fibroid

7.4 Effect of Pregnancy on Fibroids

Although fibroids grow during the first trimester, pregnancy has a variable and unpredictable effect on fibroid growth after the early pregnancy. One study found that fibroid size remains unchanged after it is first discovered by ultrasound during the first trimester in 69 % of women with a single fibroid (Fig. 7.33) [61]. In those who had enlargement of the fibroids, the greatest increase in size occurred before 10 weeks of gestation (Fig. 7.34). Fibroid growth was independent of the initial fibroid volume. After delivery, a reduction in fibroid size was noted.

7.5 Fibroid Degeneration During Pregnancy

Degeneration occurs in approximately 9 % of women with uterine fibroids during pregnancy, based on clinical symptoms and instrumental evidence (Fig. 7.35) [62]. Infarction of a fibroid may occur if the vascular supply is insufficient to keep up with fibroid growth. It may also occur if there is a

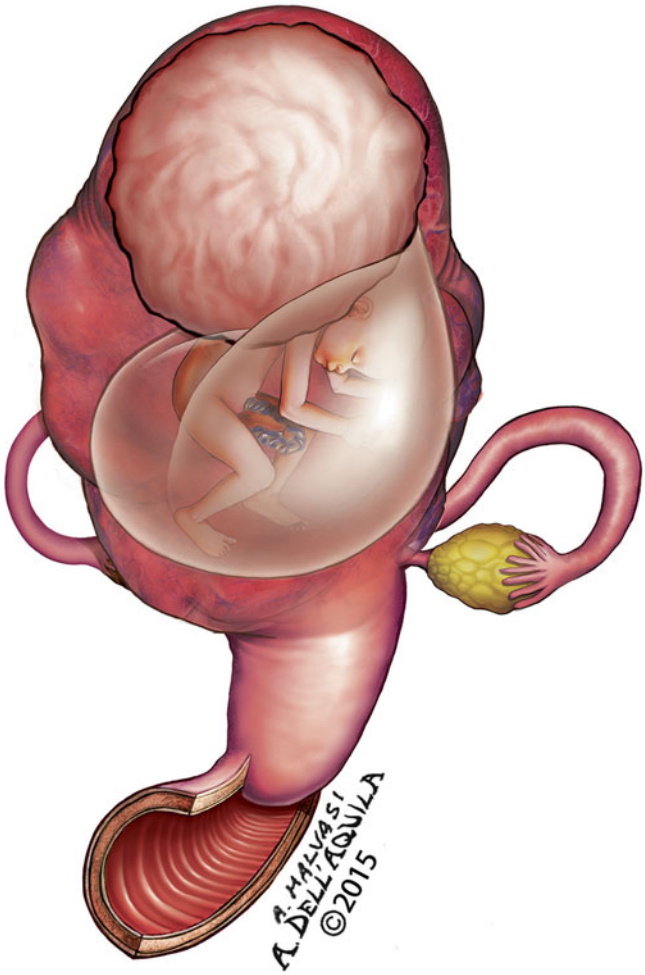

Fig. 7.32 An ultrasonographic scan of a fetus at 14 weeks with an overlying fundal fibroid

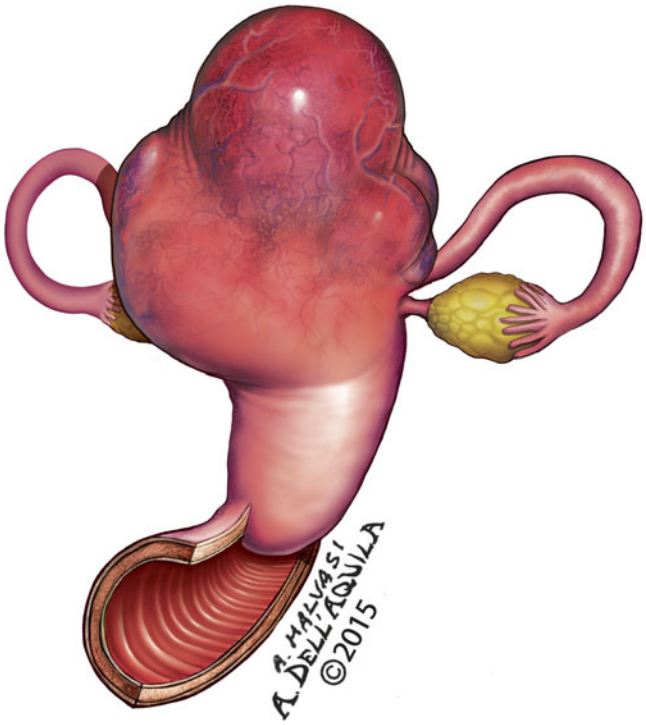

Fig. 7.33 A single fundal fibroid discovered during the first trimester of pregnancy

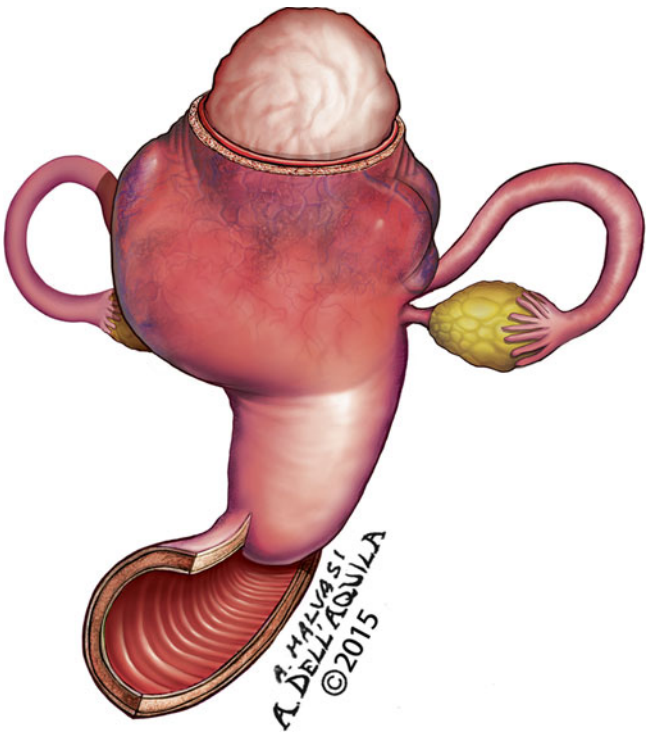

Fig. 7.34 A single fundal fibroid increasing in size before 10 weeks of gestation

sudden occlusion of the vascular flow to the fibroid, such as with torsion of a pedunculated tumor (Fig. 7.36), or sudden change in estradiol and progesterone levels, which may occur during miscarriage. Among 113 women followed during pregnancy with serial sonography, ten (9%) developed anechoic spaces or coarse heterogeneous patterns consistent with fibroid degeneration. Seven of ten women also had severe abdominal pain requiring hospitalization consistent with infarction and degeneration of the fibroids. No sonographic changes were observed in the other 103 women, of whom only 12% had similar pain. A small study found that ibuprofen shortened the hospital stay and decreased readmission [63].

On occasion, myomectomy has been required in cases of torsion of a pedunculated fibroid associated with intense pain (Fig. 7.37). In one case, a woman who presented with an acute abdomen at 11 weeks was found to have a normal pelvis with the exception of an 8 cm pedunculated fibroid [64]. Another case described a successful pregnancy after laparoscopic myomectomy for a woman who presented with an acute abdomen at 10 weeks [64]. In both cases, laparoscopic myomectomy resulted in rapid pain relief and term delivery of a healthy baby.

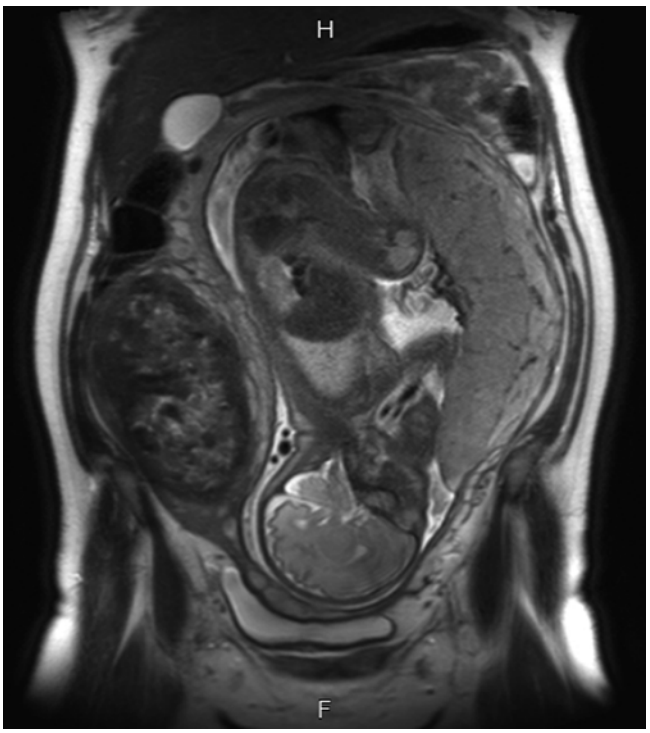

Fig. 7.35 MRI scan showing a fetus in longitudinal position at 34 weeks in a uterus with a fibroid of 12 cm in diameter in degeneration (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

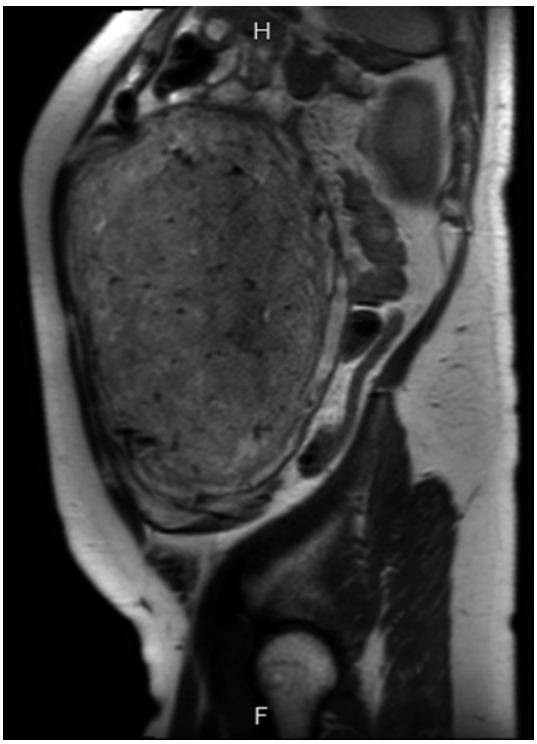

Fig. 7.37 A sagittal scan by MRI of a large pedunculated fibroid in an early pregnant women, with initial fibroid torsion on its axis (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

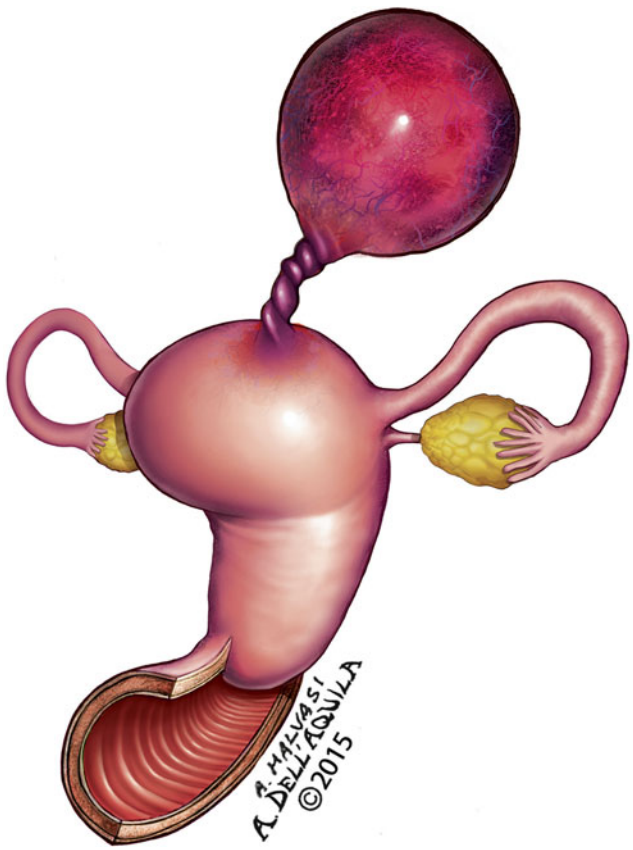

Fig. 7.36 A torsion of a pedunculated fibroid, with its degeneration

Uterine torsion, rotation of the uterus more than 45° along the long axis, can occur when the fibroid uterus is markedly enlarged. In one case, a 27-year-old woman presented at 15 week 3 day pregnancy in shock with an acute abdomen [65]. Laparotomy demonstrated complete axial torsion of the uterus due to a large fundal myoma and a massive abruption. When acute uterine torsion occurs near term, an emergency cesarean section can be performed, but may necessitate what is actually an anatomically posterior uterine incision [66]. A high index of suspicion is needed to rapidly diagnose and manage women with fibroids who present with an acute abdomen, and fibroid-related causes should be included in the differential diagnosis.

7.6 Influence of Fibroids on Pregnancy

Most women with uterine fibroids can expect to have a pregnancy without fibroid-related complications (Fig. 7.38). However, the incidence of complications has varied in different study groups.

In one study of 12,600 pregnant women, 167 were found to have uterine fibroids, and there was no difference in the incidence of preterm delivery, premature rupture of membranes, fetal growth restriction, placenta previa, placental abruption, postpartum hemorrhage, or retained placenta [67]. Only cesarean deliveries were more common among women with fibroids (23 % vs. 12 %).

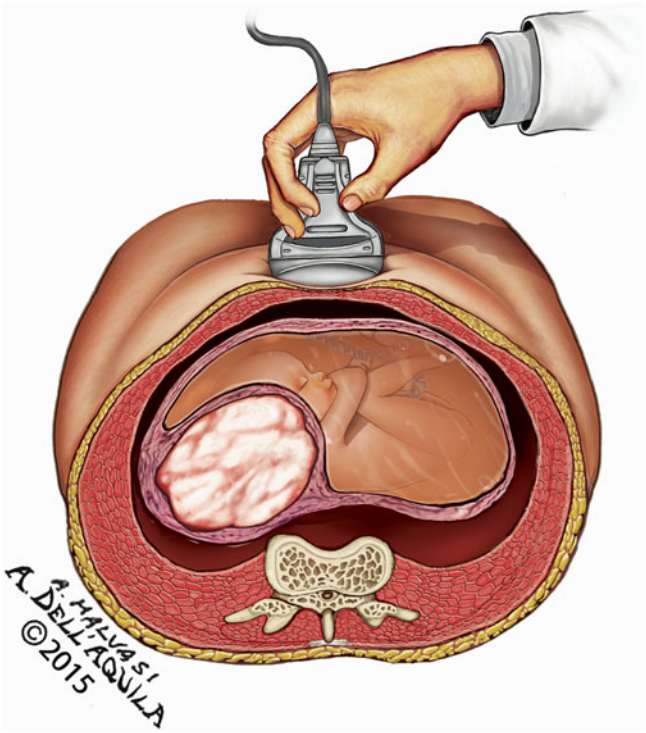

Fig. 7.38 A pregnant with a posterior uterine fibroid; she can even expect to have a pregnancy without fibroid-related complications

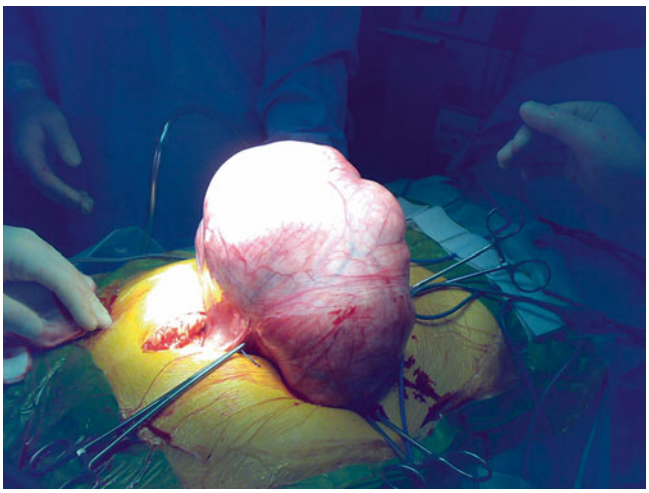

Fig. 7.39 A longitudinal laparotomy in a patient at 44 years old with a massive hemorrhage at 9 weeks from a giant uterus with multiple fibroids; such woman gives the consent to urgently remove the uterus as a life-treating therapy

In contrast to this relatively reassuring study, other investigators have found a higher incidence of fibroid-related complications during pregnancy (Fig. 7.39). In a retrospective study of 15,104 pregnancies that included 401 women diagnosed with fibroids by second-trimester ultrasound, there was no increase in premature rupture of membranes, operative vaginal delivery, chorioamnionitis, or endomyometritis [68]. However, compared to women without fibroids, there was a higher incidence of preterm delivery (19 % vs. 13 %), placenta previa (3.5 % vs. 1.8 %, a difference of 1.7 %), postpartum hemorrhage (8.3 % vs. 2.9 %), and cesarean delivery (49 % vs. 21 %). Other studies have found that women with untreated fibroids have an increased risk of poor obstetric outcomes including increased incidence of growth restriction, intrauterine fetal demise, placental abruption, placenta previa, preterm birth, breech presentation, premature rupture of membranes, blood transfusion, as well as an increased cesarean delivery rate [69]. Stout and colleagues found placenta previa in 1.4 % with fibroids compared with 0.5 % with no fibroids, a 0.9 % difference; placental abruption in 1.4 % with fibroids compared with 0.7 % with no fibroids, a 0.7 % difference; and preterm rupture of membranes in 3.3 % of fibroids compared to 2.4 % with no fibroids, a 1.1 % difference [59]. The preterm birth rate at 34–37 weeks was 15.1 % with fibroids compared with 10.5 % without, a 4.6 % difference, but the clinical significance of this is small since these babies do very well. The preterm birth rate less than 34 weeks was 3.9 % compared with 2.8 % without, a 1.1 % difference that was statistically significant.

The size of uterine fibroids is an important factor in determining prognosis and pregnancy-related complications [70]. In one study that compared women with no fibroids or small fibroids, women with fibroids larger than 5 cm (Fig. 7.40) delivered at a significantly earlier gestational age (38.6 vs. 38.4 vs. 36.5 weeks). The rates of preterm premature rupture of membranes and preterm delivery were significantly higher with large fibroids, and the prognosis was also related with the number of fibroids >5 cm in diameter (Fig. 7.41). Blood loss at delivery was significantly higher in the large fibroid group, and 12 % of women with large fibroids needed a postpartum blood transfusion.

The location of fibroids is another factor that contributes to pregnancy-related complications. Posterior fibroids that were 3 cm or larger (Fig. 7.42a, b) are associated with significantly more pelvic pain ($p = 0.001$) and a significantly higher miscarriage rate compared to those with anterior fibroids of comparable size [71]. However, no difference was observed between those with anterior or posterior fibroids related to the rates of preterm delivery, bleeding in early pregnancy, infants with small for gestational age, and hospitalization period during pregnancy. Women with posterior located myomas had significantly higher miscarriage rates.

Fetal injury attributed to mechanical compression by fibroids has been reported to occur very infrequently. A search of the PubMed database from 1980 to 2010 revealed one case of fetal head anomalies with fetal growth restriction [72], one case of a postural deformity [73], one case of a limb reduction [74], and one case of fetal head deformation with torticollis [75].

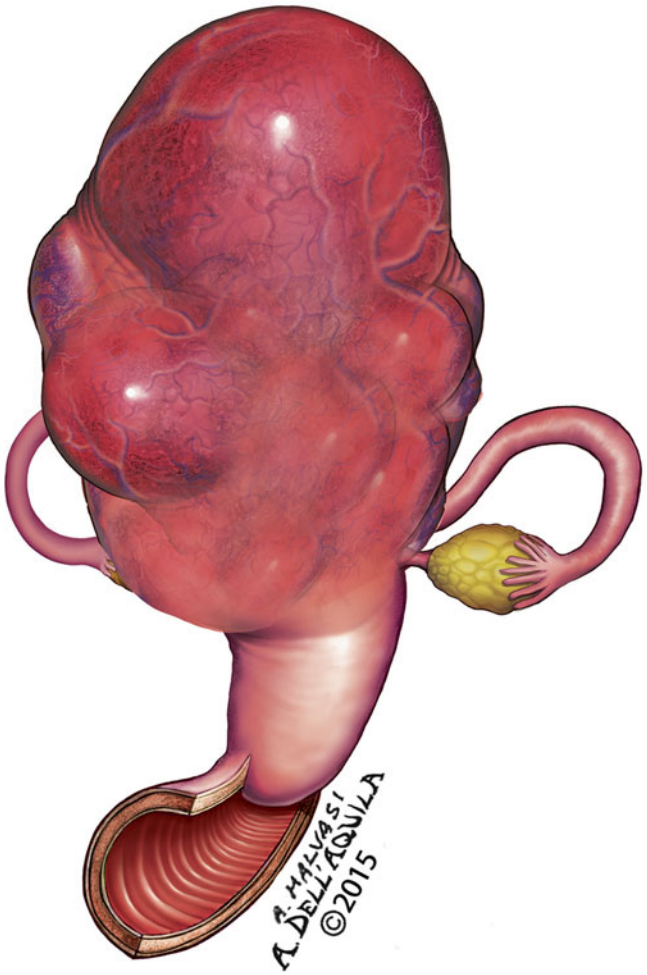

Fig. 7.40 A fundal fibroid of 6 cm in diameter in a uterus with multiple fibroids in pregnancy

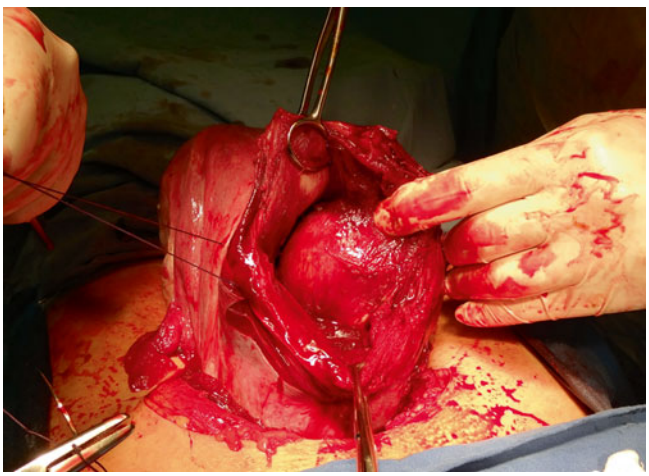

Fig. 7.41 A laparotomic image showing a large fibroid causing a premature rupture of membranes and preterm delivery by urgent cesarean section; the fibroid was enucleated after fetal delivery (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

It is clear that the incidence of cesarean delivery is increased in women with uterine fibroids, especially with fibroid 3 cm or larger [76]. In some cases, a fibroid located at or near the site of the preferred cesarean incision site (Fig. 7.43) can increase the complexity and complications of the procedure. In some cases, myomectomy during cesarean section (Fig. 7.44) may be appropriate, and in other cases it may be in the patient's interest to undergo myomectomy for large fibroids during cesarean delivery. However, when myomectomy is performed during cesarean section, it is important to observe meticulous surgical techniques (Fig. 7.45).

Tinelli and colleagues described a prospective case–control study of 68 women who underwent (Fig. 7.46), compared to a control group of 72 women who underwent cesarean delivery without myomectomy [77]. Most of the fibroids were subserosal or intramural, and 54 % were fundal, 32 % were in the body of the uterus, and 19 % were in the lower uterine segment. Surgical techniques including focal gentle hemostasis, sharp pseudocapsule dissection, careful approximation of the myometrial edges, and closure of dead space was performed with meticulous attention to prevent hematoma formation. Comparing the two groups, there was no difference in the duration of hospital stay or postoperative anemia. Another study compared myomectomy at cesarean section in 76 women with fibroids and 60 women who underwent cesarean delivery without myomectomy and demonstrated that myomectomy could be a safe option for some women with fibroids [78]. These studies demonstrated that myomectomy can safely be performed by experienced surgeons during cesarean delivery.

Conclusion

Because of the high incidence of uterine fibroids during the reproductive years, prepregnancy treatment for uterine fibroids and pregnancy with uterine fibroids is a common occurrence (Fig. 7.47). Sometimes fibroids in pregnancy lead to a complicated pregnancy (Fig. 7.48). Most women with asymptomatic fibroids experience a normal pregnancy and birth. When pregnancy is desired by a woman who has symptomatic fibroids, hysteroscopic myomectomy and laparoscopic or abdominal intracapsular myomectomy provide better outcomes than procedures that reduce the size of fibroids, including uterine artery embolization, magnetic resonance-guided focused ultrasound surgery, and myolysis. However, pregnancy-related complications can occur with all of these approaches. In women who conceive with uterine fibroids, the incidence of cesarean delivery is increased, also for contemporary cesarean myomectomy (Fig. 7.49). Maternal and fetal complication related to the size and location of fibroids may include growth

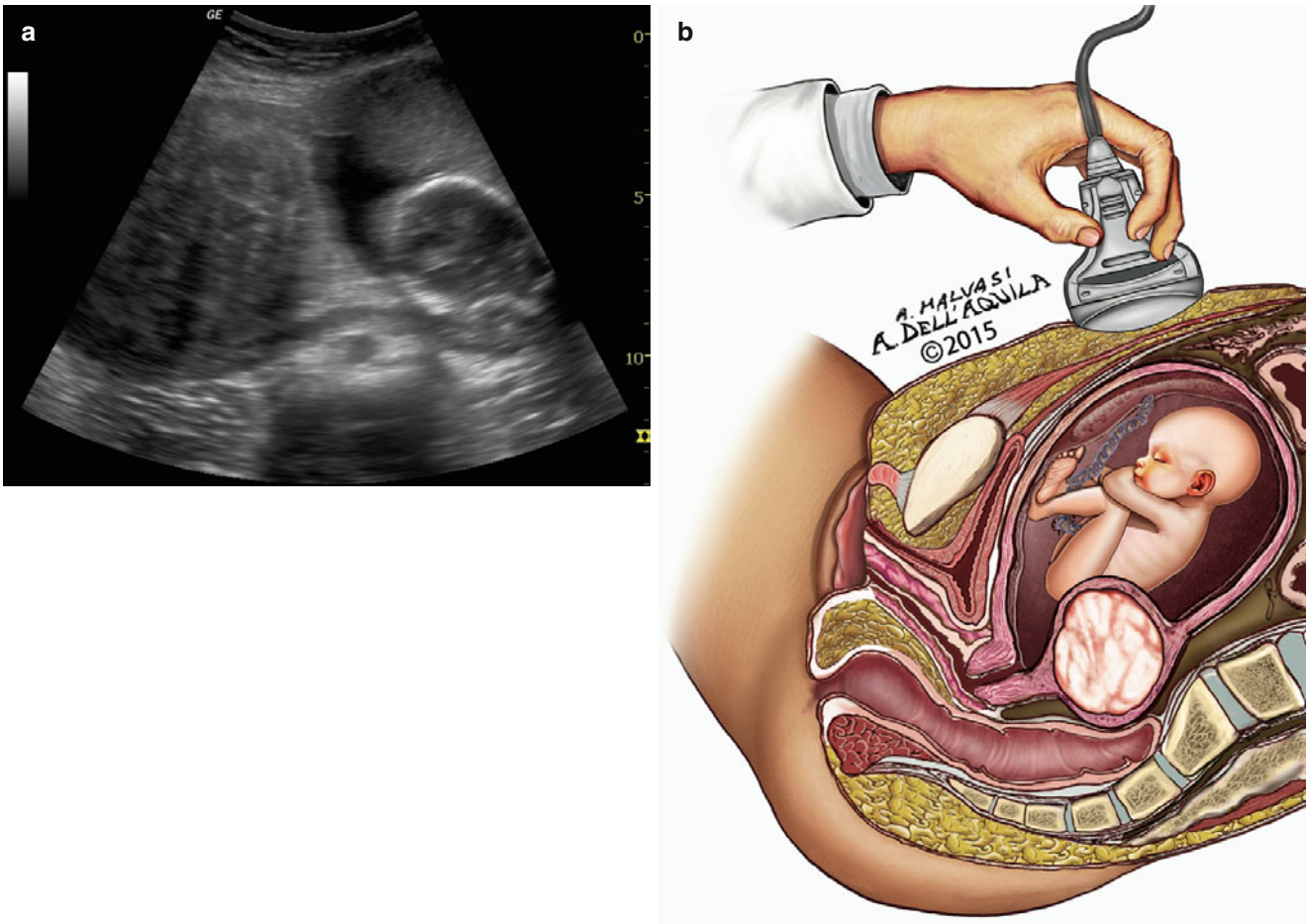

Fig. 7.42 An ultrasonographic scan showing a fetus at 18 weeks in a uterus with an anterior placenta and a posterior fibroid of 8 cm in diameter (**a**); the draft shows a fetus at 15 weeks in a uterus with anterior placenta and posterior uterine fibroid

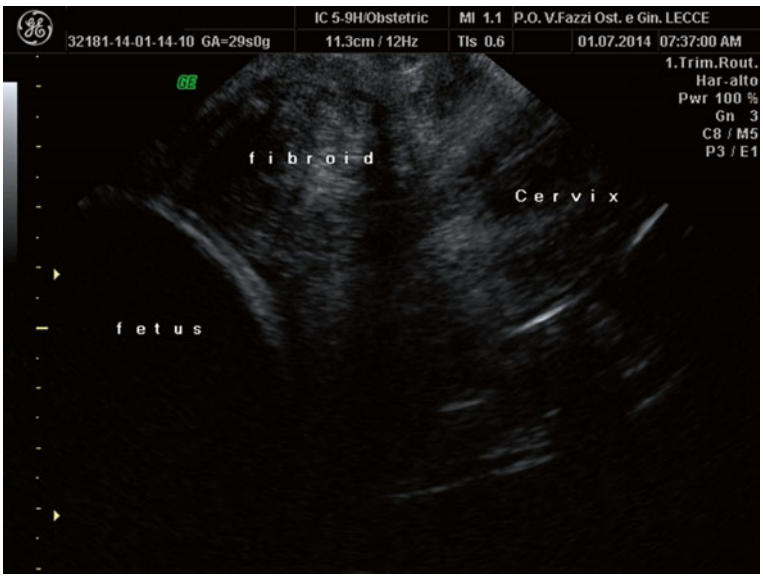

Fig. 7.43 An ultrasonographic scan showing an anterior fibroid located at or near the site of the preferred cesarean incision site

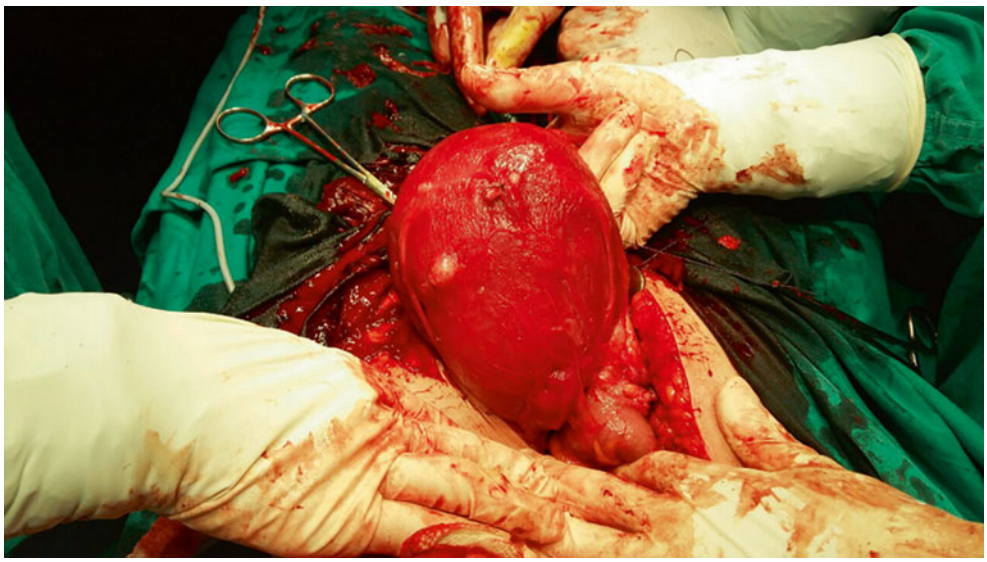

Fig. 7.44 A hysterorrhaphy after anterior myomectomy during cesarean section in a patient with multiple adhesions after a previous myomectomy

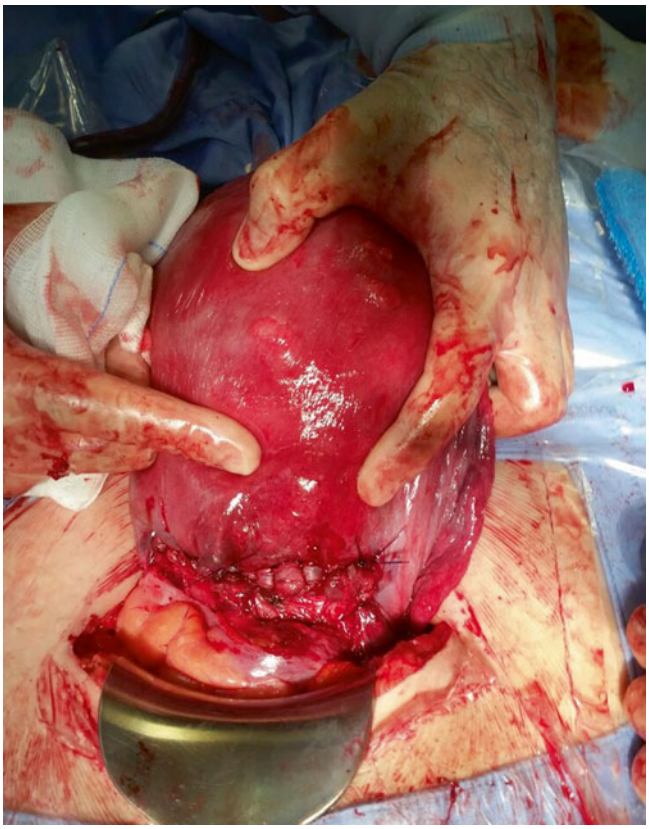

Fig. 7.45 The image shows a low uterine segment myomectomy performed during cesarean section; it is important to observe meticulous surgical techniques during fetal extraction and fibroid enucleating

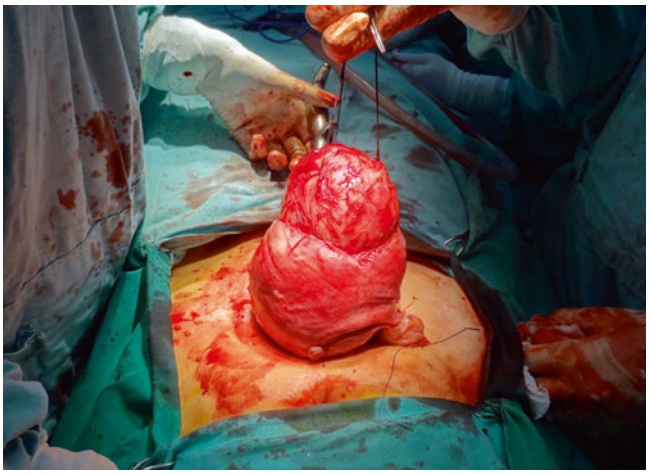

Fig. 7.46 An intracapsular cesarean myomectomy

restriction, placental abruption, placenta previa, preterm birth, breech presentation, premature rupture of membranes, and blood transfusion, in addition to an increased cesarean delivery rate and possibility of cesarean hysterectomy (Fig. 7.50). Because of the potential for these complications, all women who are pregnant and have been treated for fibroids or have fibroids identified before or during pregnancy should be followed closely to improve the likelihood of delivering a healthy baby at term.

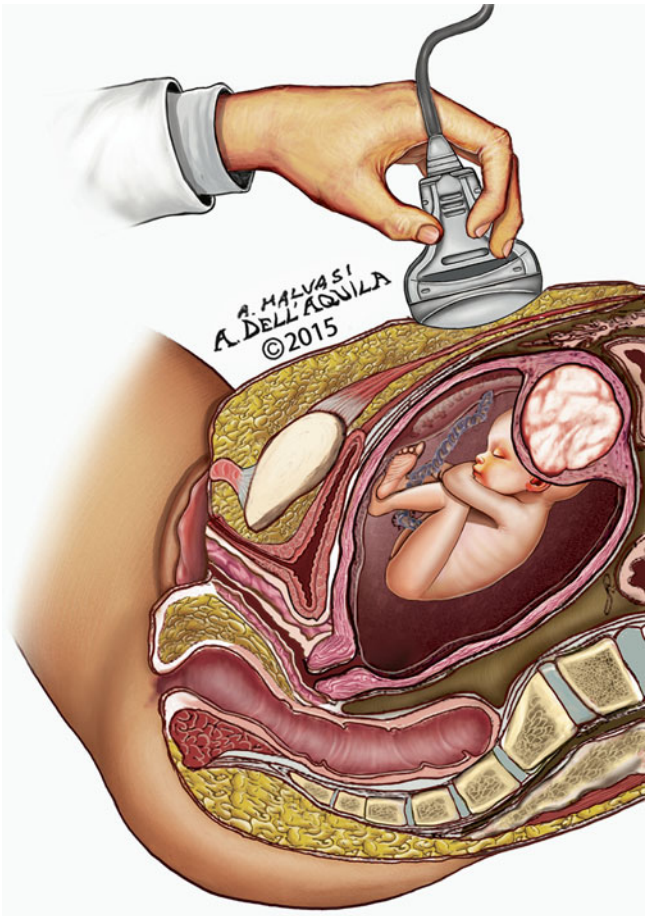

Fig. 7.47 A pregnant with a fetus at 15 weeks and a fundal uterine fibroid

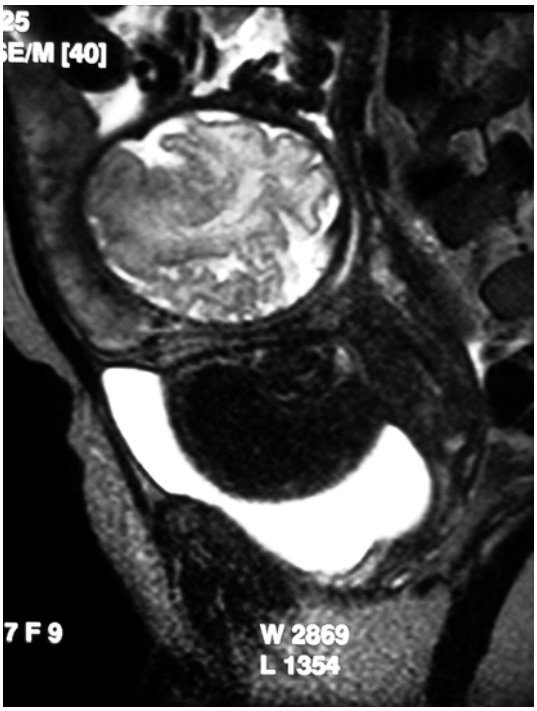

Fig. 7.48 A sagittal scan by MRI of a large symptomatic cervical fibroid in a pregnant woman at 19 weeks (Courtesy of Prof. Dr. Josè Palacios de Jaraquemada)

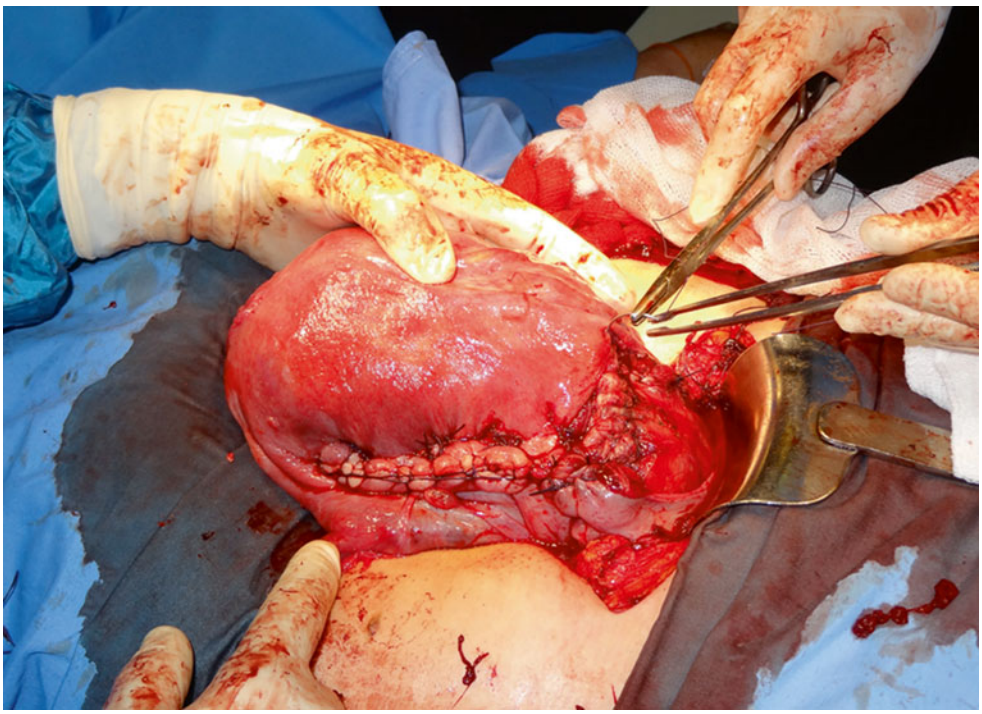

Fig. 7.49 A cesarean myomectomy result: after fetal delivery, the incision of low uterine segment had been prolonged on the right upper lateral anterior part of the uterine body, to remove large fibroid

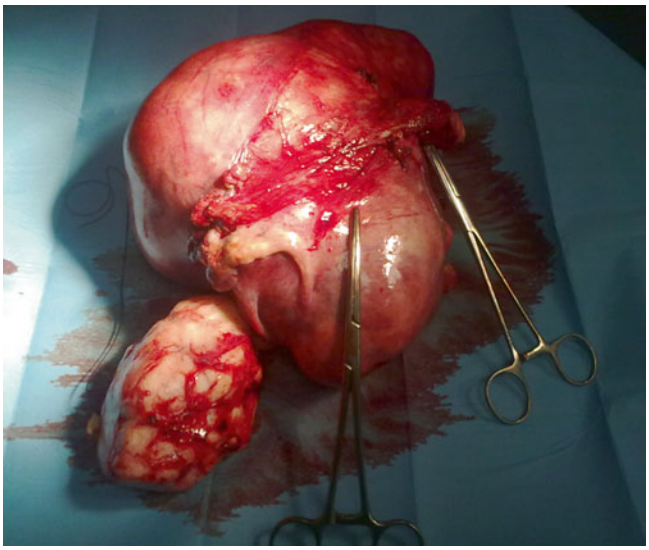

Fig. 7.50 A cesarean hysterectomy: the pregnant uterus, deformed by multiple large fibroids, was removed after the delivery of newborn

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Cervical Pregnancy

8

Togas Tulandi, Audrey Gilbert, Luis Alonso Pacheco, Andrea Tinelli, and Antonio Malvasi

8.1 Introduction

Cervical ectopic pregnancy is defined as implantation of a fertilized ovum in the endocervical canal (Fig. 8.1). The estimated incidence is 1 in 1000–18,000 pregnancies [1–5]. It represents less than 1 % of all ectopic pregnancies and constitutes the least common site of ectopic pregnancy. The classical clinical presentation of cervical pregnancy is painless first-trimester vaginal bleeding followed by massive hemorrhage, which could lead to life-threatening situations (Fig. 8.2) [6, 7]. In early reports, the mortality rate could be as high as 40–45 % [8] and the hysterectomy rate was up to 90 % of cases [9]. Today, hysterectomy might still be needed but death at least in developed countries is practically nil [10].

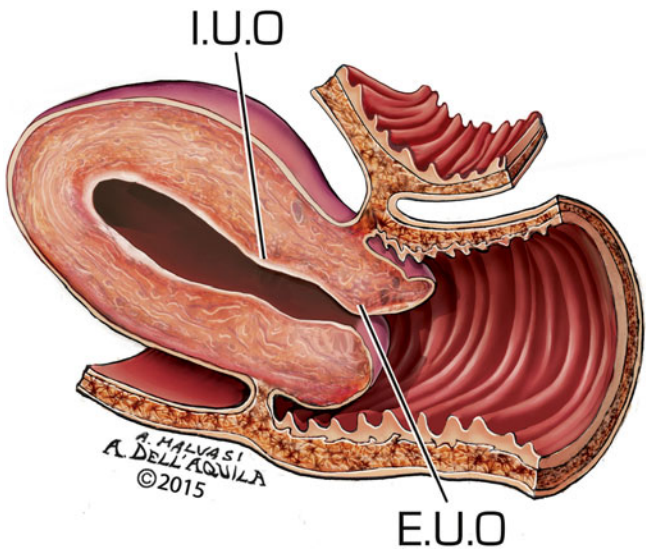


Fig. 8.1 Cervical ectopic pregnancy is defined as implantation of a fertilized ovum in the endocervical canal, located between external uterine orifice (EUO) and internal uterine orifice (IUO)

T. Tulandi (✉)
Reproductive Medicine, McGill University, Montréal, QC, Canada

Department of Obstetrics and Gynecology, McGill University Health Center, Montréal, QC, Canada
e-mail: togas.tulandi@mcgill.ca

A. Gilbert, MD, FRCSC
Department of Obstetrics and Gynecology, McGill University, Glen Site, 1001 boulevard Decarie Room D05-2570, Montréal, QC H4A 3J1, Canada
e-mail: audrey.gilbert@mail.mcgill.ca

L.A. Pacheco
Unidad Endoscopia, Centro Gutenberg, Malaga, Spain
e-mail: luisalonso2@gmail.com

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_8

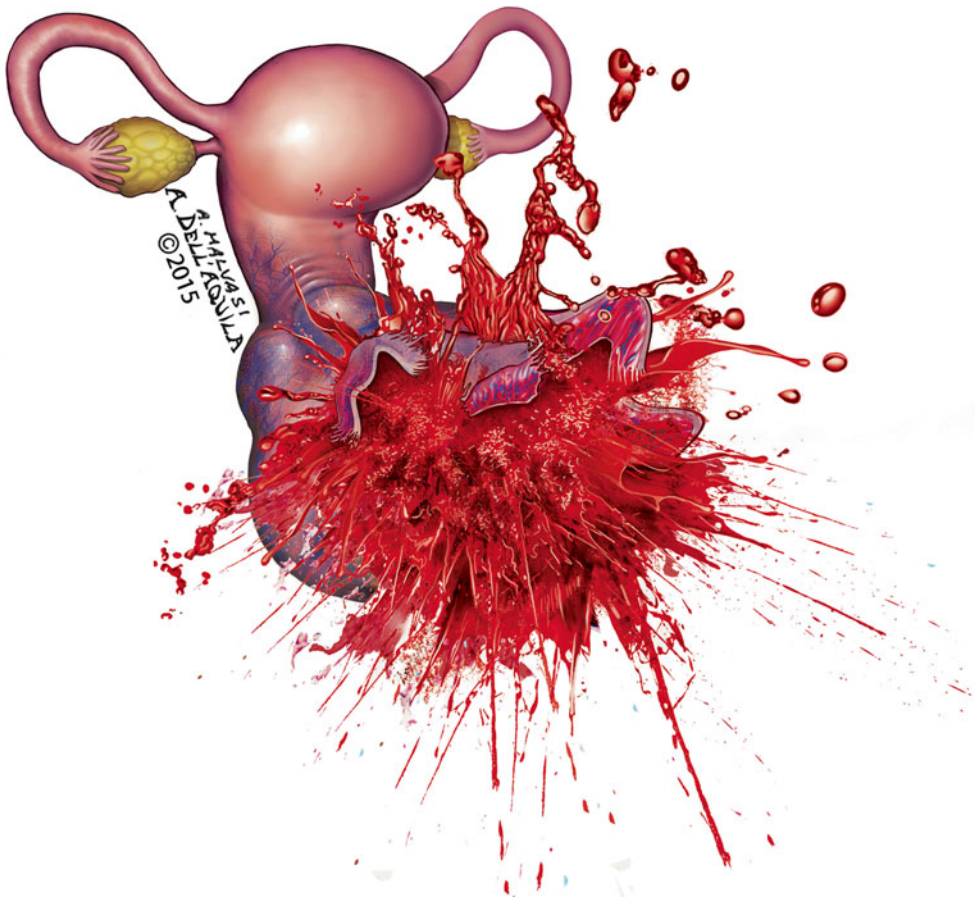


Fig. 8.2 The cervical pregnancy could lead to life-threatening situations for massive hemorrhage, usually without pain

Table 8.1 Risk factors for cervical pregnancy

1. Previous history of uterine curettage
2. Preceding instrumentation of endocervical canal
3. Presence of intrauterine device
4. Uterine fibroids
5. Cesarean scar and uterine surgery
6. Assisted reproduction techniques
7. Intrauterine adhesions (Asherman)
8. Atrophic endometrium and chronic endometritis
9. Uterine and cervical anomalies

8.2 Pathogenesis

There are two main theories to explain the occurrence of cervical pregnancy: accelerated transport of the blastocyst through the endometrium and delayed implantation and late fertilization of the ovum inside the cervical canal [11]. Risk factors for cervical pregnancy include current use of intrauterine device, history of uterine instrumentation such as curettage, previous cesarean deliveries, the presence of uterine myoma, and intrauterine adhesions [4, 7]. In vitro fertilization treatment also plays a role in the increased incidence of cervical pregnancies [1, 12]. Risk factors for cervical pregnancy are shown in Table 8.1 [13]. The main risk factor is previous history of uterine curettage that can be found in up to 70% of cases [2, 14].

8.3 Clinical Manifestations

The main clinical symptom of cervical pregnancy is painless vaginal bleeding usually during the first trimester, although there are some reports of bleeding in the second trimester. It can be mild bleeding or spotting or can be a massive life-threatening bleeding. Another symptom is abdominal cramps. In a series of 89 patients reported by Ushakov et al., vaginal bleeding was associated with abdominal cramps in 26% of cases [1].

8.4 Diagnosis

In the past, diagnosis was usually made by the pathology of surgical specimens after hysterectomy (Fig. 8.3) [15–19]. In 1911, Rubin established four diagnostic criteria for the diagnosis of cervical pregnancy; those criteria are still valid today (Table 8.2). In current clinical practice, ultrasound is the most important tool after history and physical examination (Fig. 8.4a, b). It allows early identification of cervical pregnancy even before it becomes symptomatic.

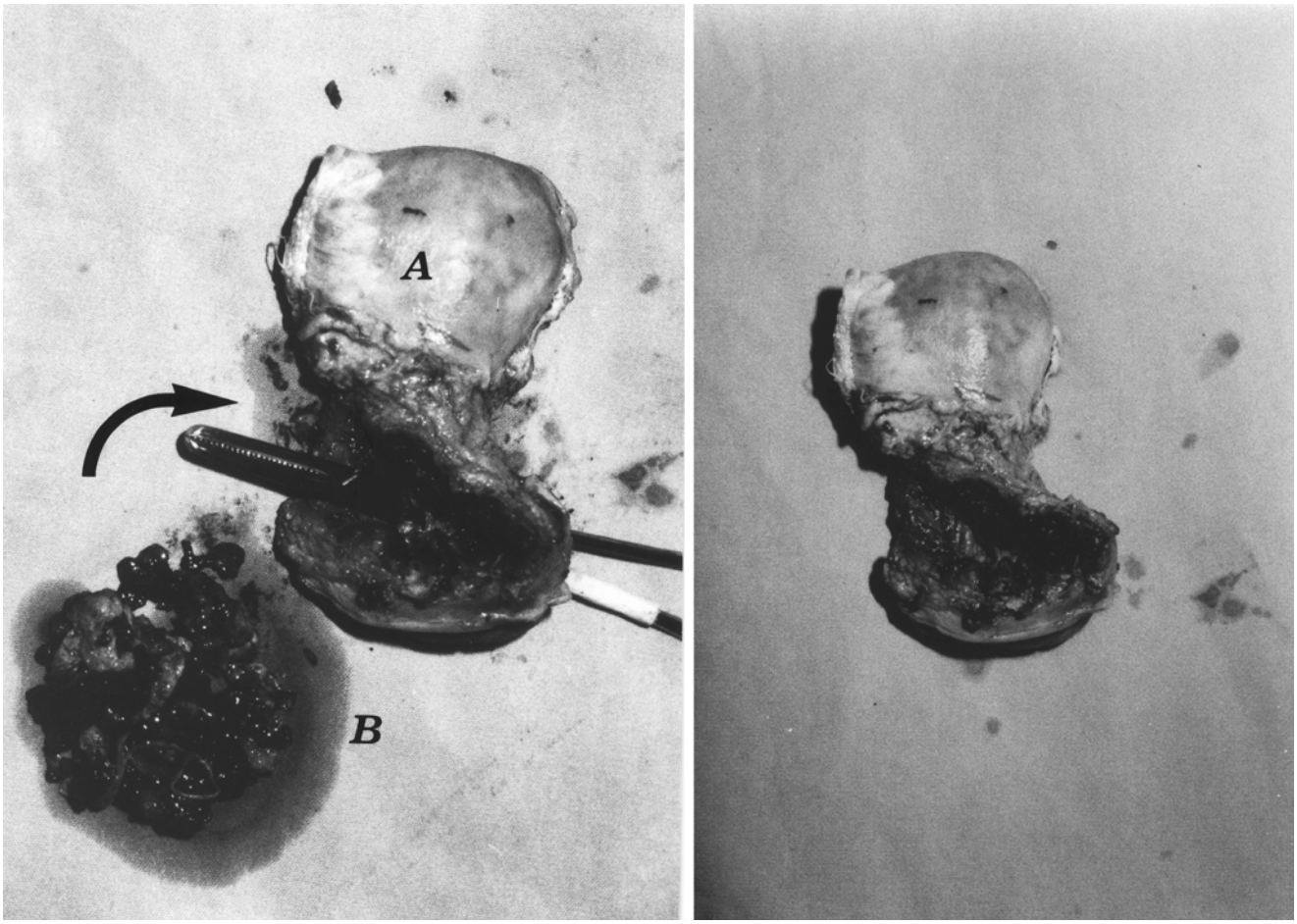


Fig. 8.3 On the *left* a uterus (*A*) post hysterectomy for complicated cervical pregnancy, with a Kocher forceps inside the perforated cervix and ectopic pregnancy (below) (*B*); on the *right*, a uterus after cervical pregnancy rupture, with a destroyed anterior cervical wall

Table 8.2 Diagnostic criteria for cervical pregnancy

1. Cervical glands must be present opposite the placental attachment
2. The attachment of the placenta to the cervix must be intimate
3. The placenta must be below the peritoneal reflection of the anterior and posterior surfaces of the uterus
4. Fetal elements must not be present within the uterine cavity

Paalman and Mc Elin described clinical criteria of cervical ectopic pregnancy [16]. They include painless vaginal bleeding after amenorrhea with closed or partially open external os and disproportionally enlarged cervix with products of conception entirely confined within the endocervix. Ultrasound criteria of cervical pregnancy include enlargement of the cervix, uterine enlargement, diffuse amorphous intrauterine echoes, and absence of intrauterine pregnancy (Fig. 8.5). Other ultrasound diagnostic criteria are location of the products of conception below the internal os and barrel-shaped and dilated cervical canal (Fig. 8.6). Jurkovic proposed two additional criteria to differentiate cervical pregnancy from spontaneous miscarriage. They are the "*sliding sign*" and the visualization of peritrophoblastic blood flow with the use of color Doppler (Fig. 8.7) [20]. The sac that slides with slight pressure of the ultrasound probe on the cervix suggests no intimate attachment between the cervix and the endocervical tissue; this is an abortion in progress. Table 8.3 demonstrates ultrasound criteria for the diagnosis of cervical pregnancy as published by Ushakov et al. Using those criteria, diagnosis of cervical ectopic pregnancy can be established in over 85 % of cases. 3D ultrasound can also be used to allow accurate view of the endometrial cavity and the cervix [21], and MRI can be considered in difficult cases. Jung reported a case series in which all patients with cervical pregnancy showed intracervical heterogeneous hemorrhagic mass with densely enhancing papillary solid components [22].

8.5 Differential Diagnosis

The differential diagnosis includes spontaneous abortion in progress at the level of the endocervical canal (Fig. 8.8), cervico-isthmic intrauterine pregnancy (Fig. 8.9), and cesarean scar pregnancy (Fig. 8.10). In cesarean scar pregnancy, the gestational sac is surrounded by the myometrium and/or fibrous scar tissue and completely separated from the uterine

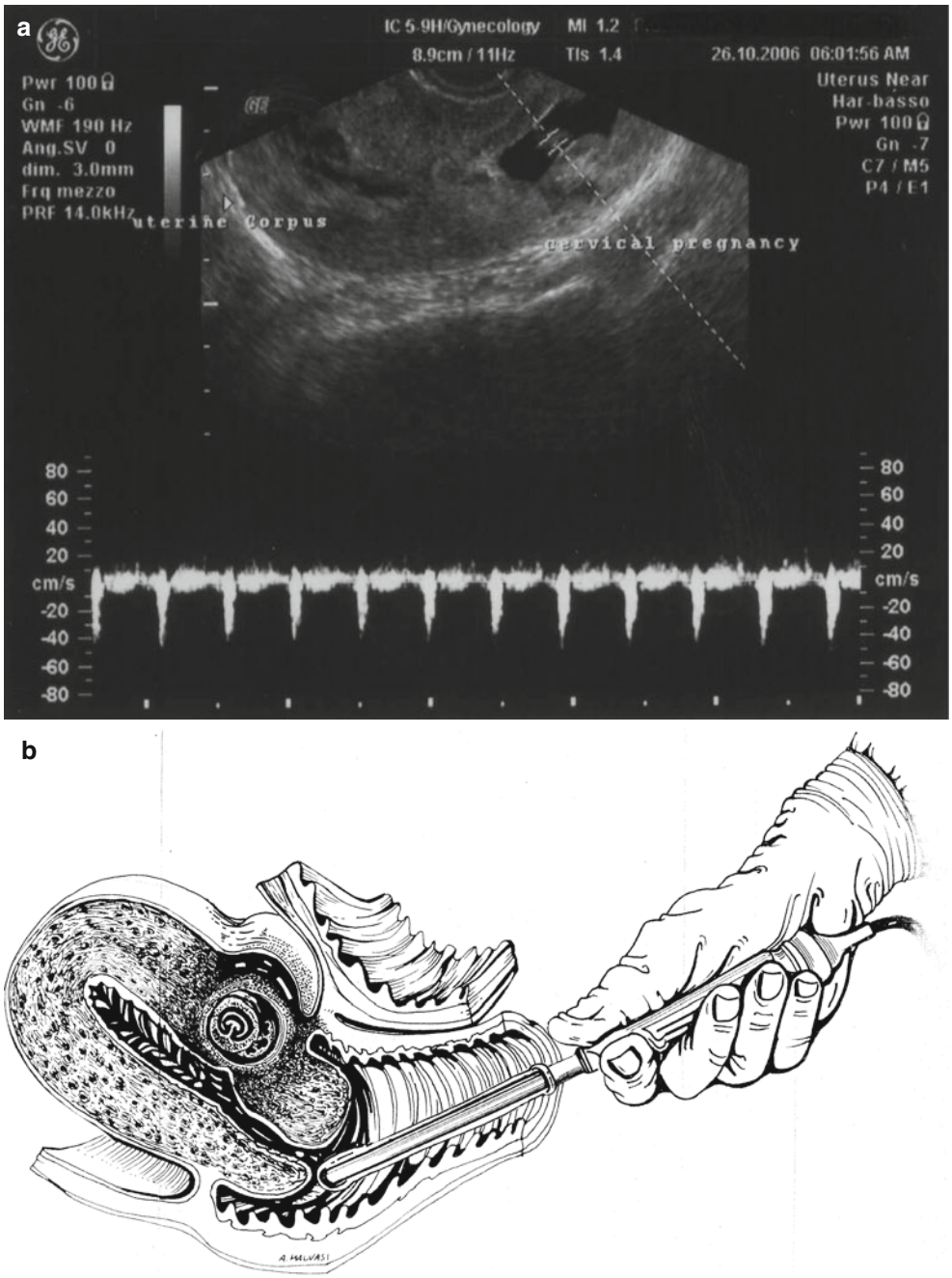


Fig. 8.4 (**a**) Ultrasonographic sagittal section of a uterus with a cervical pregnancy at 6 weeks gestation; it shows fetal cardiac activity; (**b**) a diagram of transvaginal ultrasonographic scan of a cervical pregnancy in the anterior cervical wall

cavity [23]. Sonographic criteria of cesarean scar pregnancy include an empty uterine cavity and endocervical canal, location of the gestational sac peripherally within the anterior portion of the lower uterine segment, deficient or absent myometrium between the gestational sac and the bladder, and complete encasement of the gestational sac by the myometrium and/or fibrous scar tissue [24]. It is important to note that the cesarean scar defect can be located at the cervico-isthmic junction. Gubbini et al. found that cesarean scar defect is present in the inferior third of the cervical canal in 21.9 % of patients [25]. The main point to differentiate between cervical and cervico-isthmic pregnancies is cervical dilatation and the location of the pregnancy in relation to the internal os. In cases of cervical pregnancy, the internal os is closed. It can be identified at the level of the insertion of the uterine arteries [26].

8.6 Management

Management of cervical pregnancy can be divided into conservative (with preservation of the uterus) or radical treatment. The conservative management includes medical,

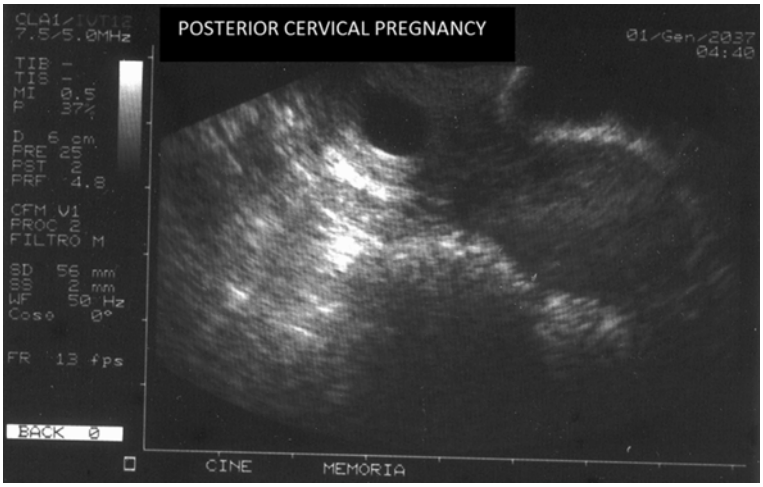


Fig. 8.5 An ultrasonographic sagittal scan of a posterior cervical pregnancy under the internal uterine orifice, according to Paalman and Mc Elin criteria; schematic representation of a posterior cervical pregnancy

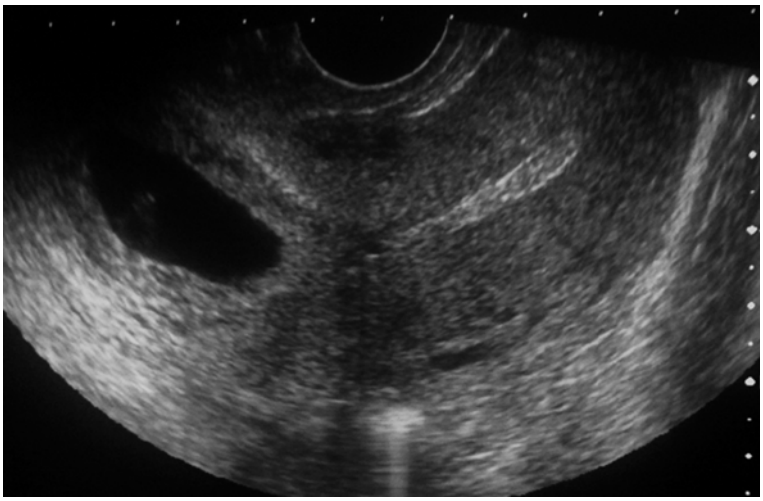


Fig. 8.6 A ultrasonographic sagittal scan showing location of the products of conception below the internal orifice

surgical, or combined treatment. The treatment depends on factors such as clinical hemodynamic condition, gestational age, available resources, and operator's experience. The two main objectives in the management of cervical pregnancy are to minimize the risk for massive bleeding and to avoid the need for hysterectomy. Nonsurgical treatments include systemic administration of methotrexate (MTX), intra-amniotic injections of MTX (Fig. 8.11) or potassium chloride (KCL), and uterine artery chemoembolization with MTX [27]. Surgical treatment includes curettage followed by Foley balloon tamponade (Fig. 8.12) or a gentle digital removal of products of conception followed by a gauze tamponade into the cervix (Fig. 8.13) and vaginal approach or hysteroscopic removal of the products of conception (Fig. 8.14). Table 8.4 shows different treatments of cervical ectopic pregnancy. Combined treatment has also been described with over 80 % success rate. Nonsurgical treatment should be considered as the first line of treatment (Fig. 8.15).

8.7 Medical Treatment

8.7.1 Methotrexate

Methotrexate treatment is the treatment of choice for most cervical pregnancies. It can be administered systemically or intra-amniotically. Systemic administration of MTX is effective in treating cervical ectopic pregnancies. Kung et al. estimated a 91 % probability to preserve the uterus with the use of systemic methotrexate in cervical pregnancies at a gestational age less than 12 weeks regardless of the presence of fetal heart activity [28]. Methotrexate can be used in a single-dose regimen (50 mg/m^2 intramuscular) or in a multiple-dose regimen (1 mg/kg body weight every other day) with folic acid rescue. However, experience with the use of MTX for treatment of cervical pregnancy is limited to case reports and small series.

The criteria for selecting appropriate candidates for medical treatment of cervical pregnancy are also unclear [29].

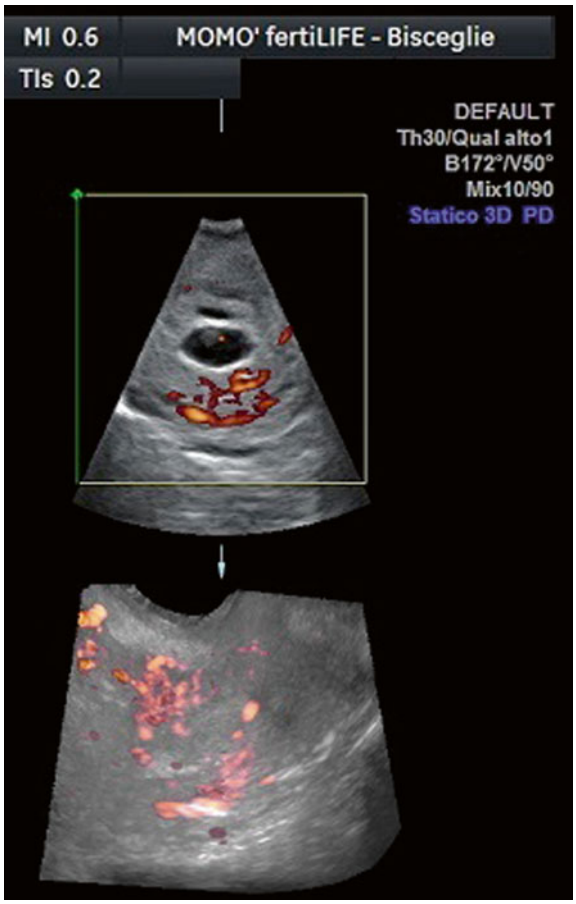


Fig. 8.7 The ultrasonographic image shows the peritrophoblastic blood flow with the use of color Doppler

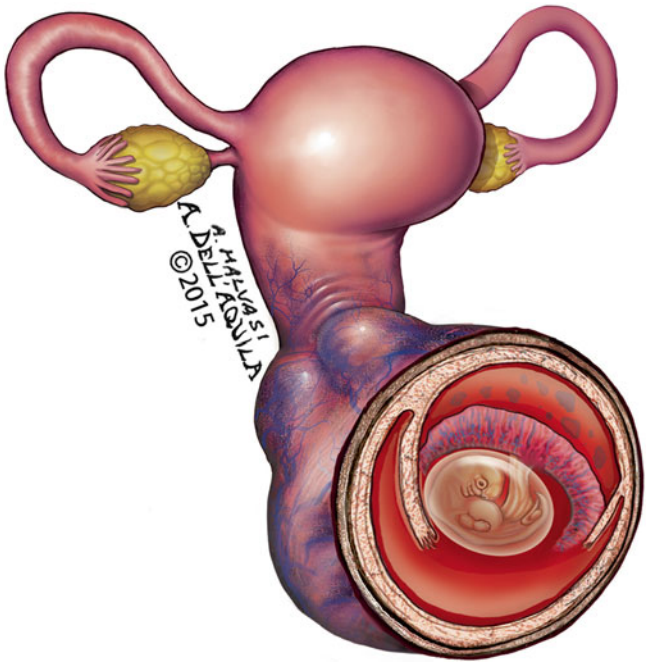


Fig. 8.8 The image shows a spontaneous abortion in progress at the level of the endocervical canal

Table 8.3 Ushakov's sonographic criteria for cervical pregnancy

1. Gestational sac situated in the endocervical canal
2. Presence of some intact cervical tissue between the GS and the internal orifice
3. Trophoblast invasion of the endocervical tissue
4. Embryonal or fetal structures, in particular pulsating heart, in the ectopic GS
5.Empty uterine cavity
6. Endometrial decidualization
7. Sand-glass shaped uterus
8. Doppler detection of peritrophoblast arterial flow

Yet, Hung et al. reported success with systemic methotrexate with high HCG levels of 125,000–135,000 mU/mL [10]. Methotrexate treatment is less effective when the following conditions are present: gestational age is greater than 9 weeks, beta-HCG level is more than 10,000 mIU/mL, fetal cardiac activity is present, and when the crown rump length is more than 10 mm [30]. Intra-amniotic administration of MTX with or without KCL has been shown to be effective in treating cervical pregnancy [31]. This procedure is performed under transvaginal ultrasound guidance. It is particularly useful in cases of heterotopic pregnancy where preservation of the intrauterine pregnancy is desired [30, 32]. Krissi et al. evaluated chemoembolization on 25 women with non-tubal ectopic pregnancies including ten cervical pregnancies. They administered multidose systemic methotrexate. The first methotrexate dose was administered by intra-arterial injection during catheterization prior to Gelfoam occlusion of the uterine arteries (Fig. 8.16). There were no failures in the cervical ectopic group with this technique. Mild side effects included abdominal discomfort, groin/leg pain, and puncture site infections. There were no serious complications and subsequent pregnancies were achieved in five women with cervical pregnancy [33]. Whether chemoembolization leads to a better outcome than multidose methotrexate alone is unclear. The side effects of methotrexate include gastrointestinal upset, stomatitis, elevated liver enzymes, thrombocytopenia, leukopenia, conjunctivitis, and fever [29]. Evidence of liver toxicity warrants cessation of the therapy [34, 35]. Live births after treatment of cervical pregnancy with systemic MTX treatment have been reported [16, 36].

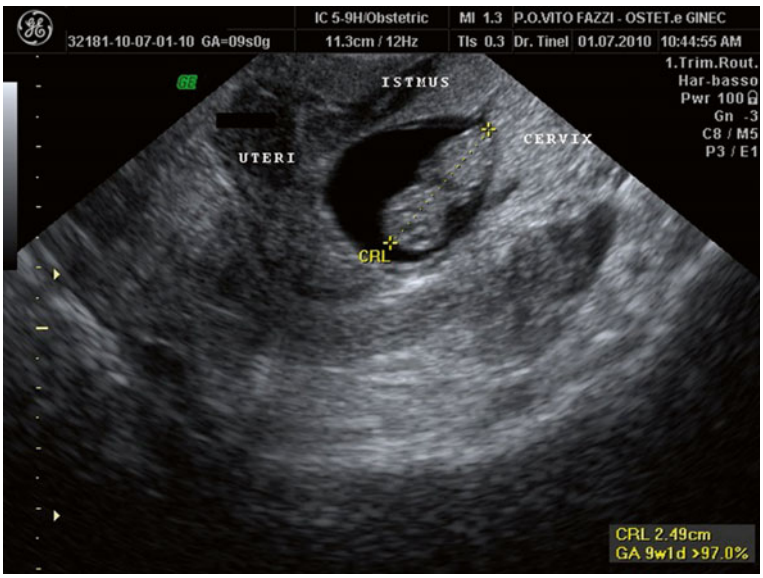


Fig. 8.9 The image shows a cervico-isthmic intrauterine pregnancy at 9 weeks

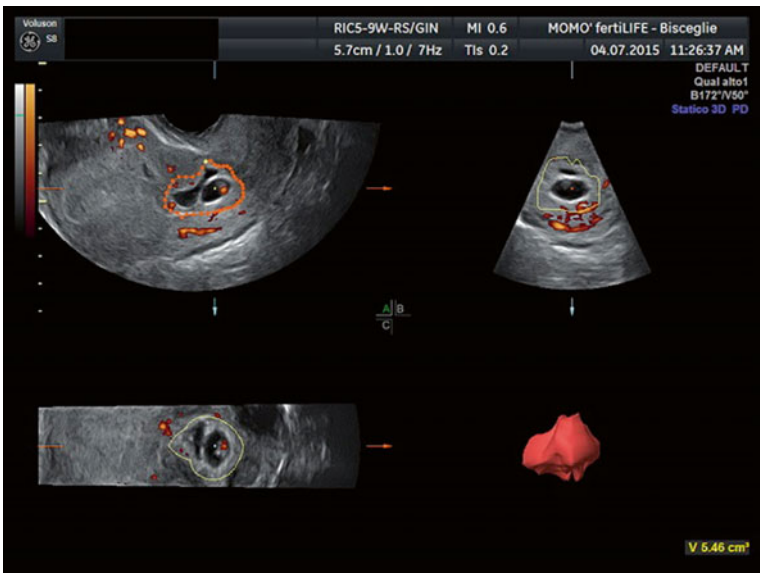


Fig. 8.10 The image shows a cesarean scar pregnancy at 5 weeks, with a 3D reconstruction of embryo

8.7.2 Potassium Chloride (KCl)

Direct injection of KCL (3–5 mL of 2 meq/mL) into the fetal heart under transvaginal ultrasound guidance is often used to induce fetal demise and was first described for this purpose in 1988 [37]. Direct intracardiac injection produces asystole in the fetus. It can be a valid option when the gestational age is more than 9 weeks and in cases of heterotopic pregnancy. The combination of KCl with methotrexate reduces the failure rate of medical treatment in cases with positive heartbeat [6].

8.7.3 Mifepristone

Mifepristone is a selective progesterone receptor modulator that has been used as an abortifacient. It induces decidual necrosis and leads to detachment of the products of conception. A combination of mifepristone with methotrexate improves the success rate of conservative treatment of ectopic pregnancies, reduces the dose of methotrexate, and decreases blood loss during curettage [38].

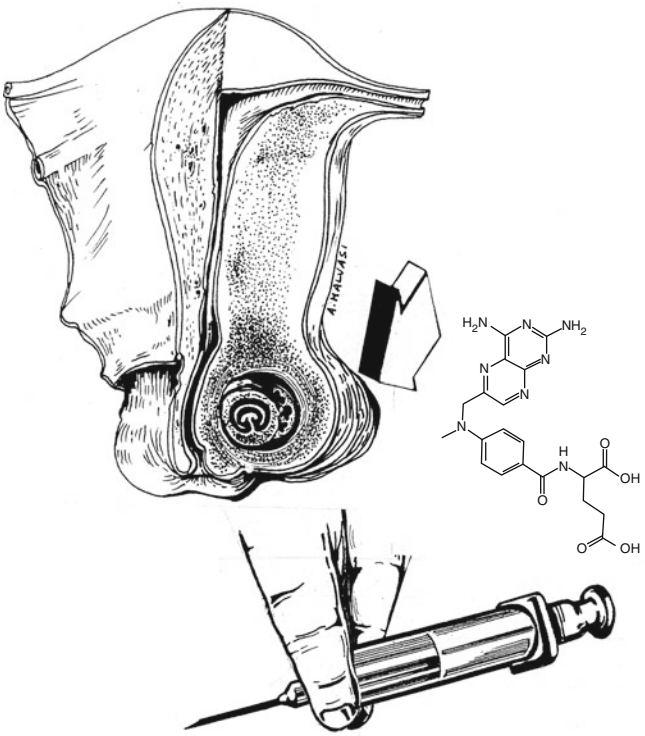


Fig. 8.11 Medical treatment of cervical pregnancy by methotrexate injection

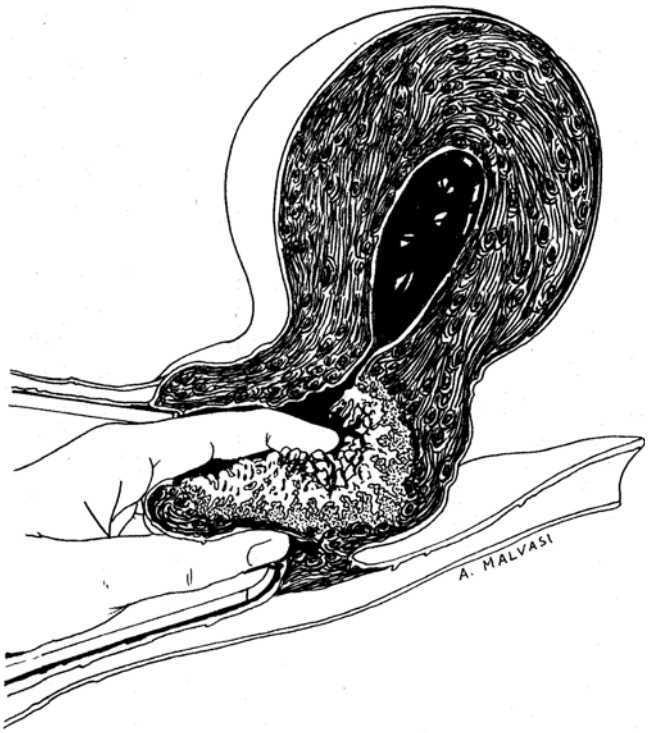


Fig. 8.13 Cervical pregnancy gently removed by digital maneuver

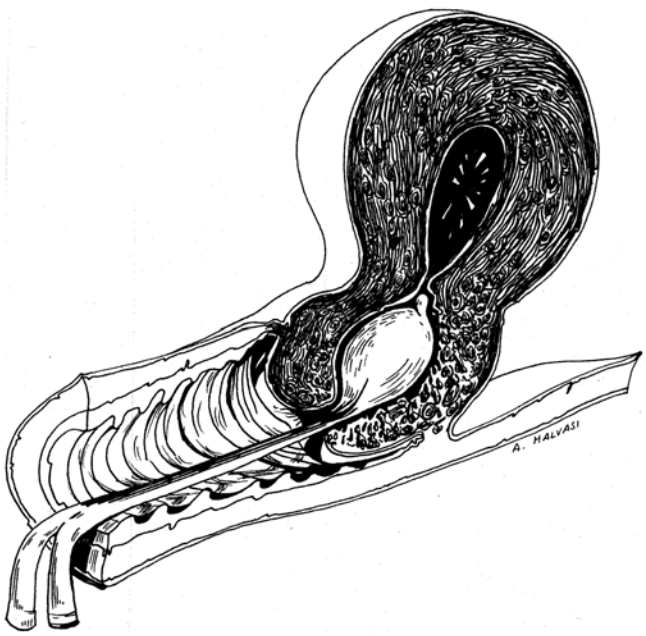


Fig. 8.12 The figure shows a Foley balloon tamponade after curettage for cervical pregnancy

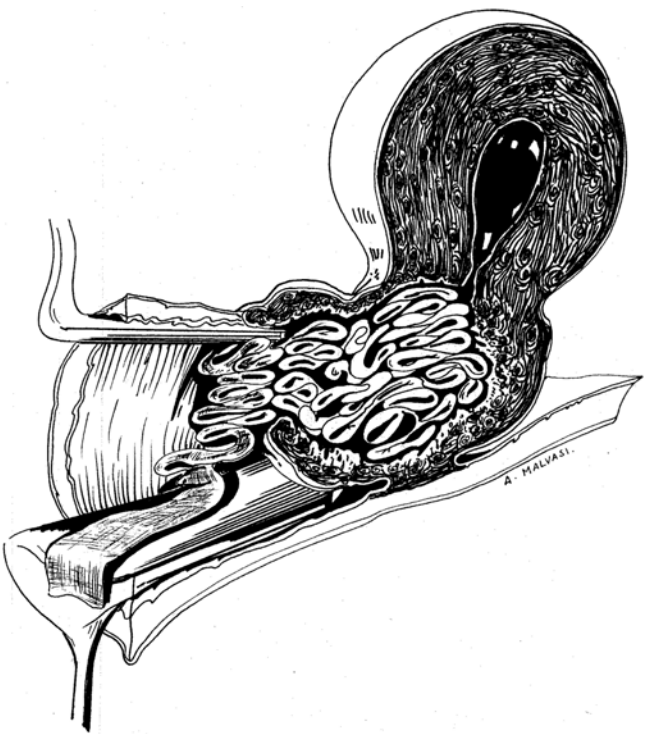


Fig. 8.14 After cervical pregnancy removal, clinicians can use a gauze tamponade intracervically for hemostasis

8.7.4 Intrauterine Irrigation with H_2O_2

Kim et al. reported a case series of ten patients with cervical pregnancy treated by hysteroscopy. They irrigated the uterine cavity with 3.5 % H_2O_2 to reduce bleeding during the procedure [39]. H_2O_2 produces cell death due to release of free oxygen and causes vasoconstriction resulting in atrophy of the embryonic gestational sac and trophoblastic cells.

Table 8.4 Treatment of cervical pregnancy

Conservative
Medical
Methotrexate
KCL
Mifepristone
H_2O_2 intrauterine
Surgical
Suction evacuation
Curettage
Hysteroscopy resection
Cerclage
Vaginal cervicotomy
Embolization
Tamponade
Laparoscospic assited
Radical
Partial trachelectomy
Hysterectomy

8.8 Surgical Treatment

8.8.1 Suction

Fylstra reported successful treatment of 13 cases of early cervical ectopic pregnancies [40]. He suggested that first-trimester cervical pregnancies, even in cases of heterotopic pregnancies, could be easily treated with suction curettage. The cervical stroma was first infiltrated with vasopressin and cerclage suture was placed high on the cervix. The efficacy and safety of this technique remain to be seen.

8.8.2 Curettage Followed by Foley Balloon Tamponade

The possibility of cervical bleeding can be minimized by ligation of the cervical branch of the uterine arteries, cervical cerclage, or uterine artery embolization. Before each surgical maneuver, the surgeon should well expose the cervix by a valve (Fig. 8.17) and then proceed by curettage (Fig. 8.18). It is advisable to administer vasopressin intracervical before conducting the curettage (Fig. 8.19): 20–30 mL of vasopressin (0.5 U/mL)

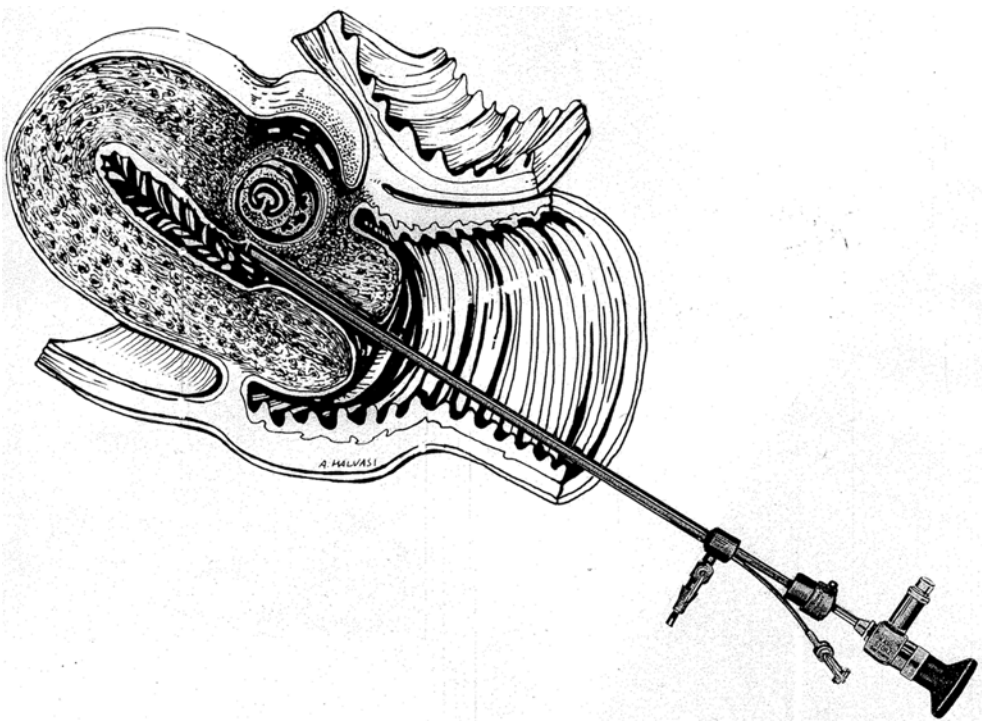


Fig. 8.15 The image shows hysteroscopic removal of cervical pregnancy

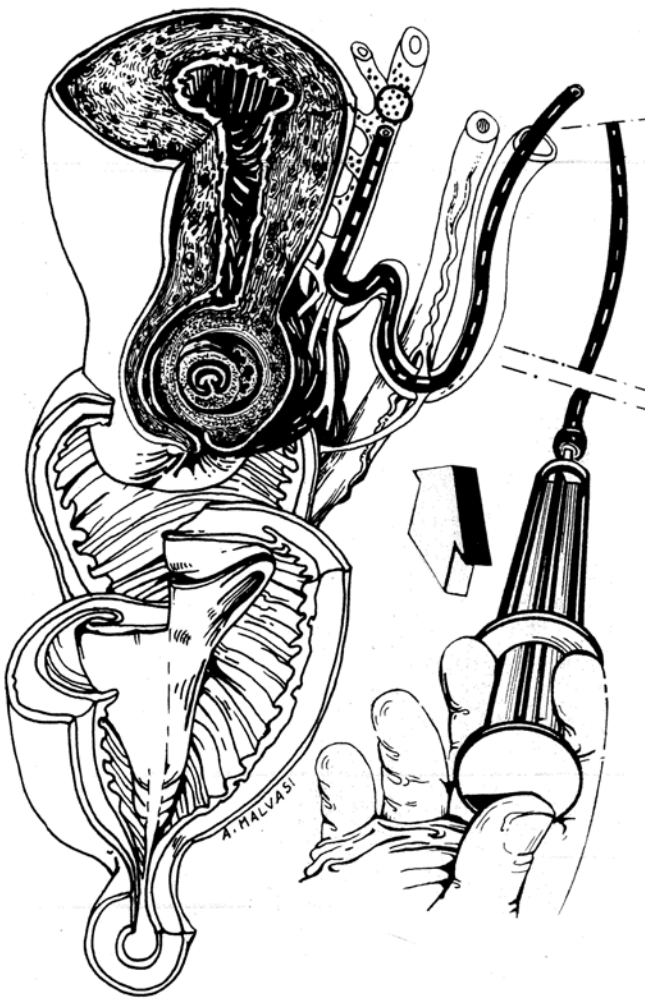
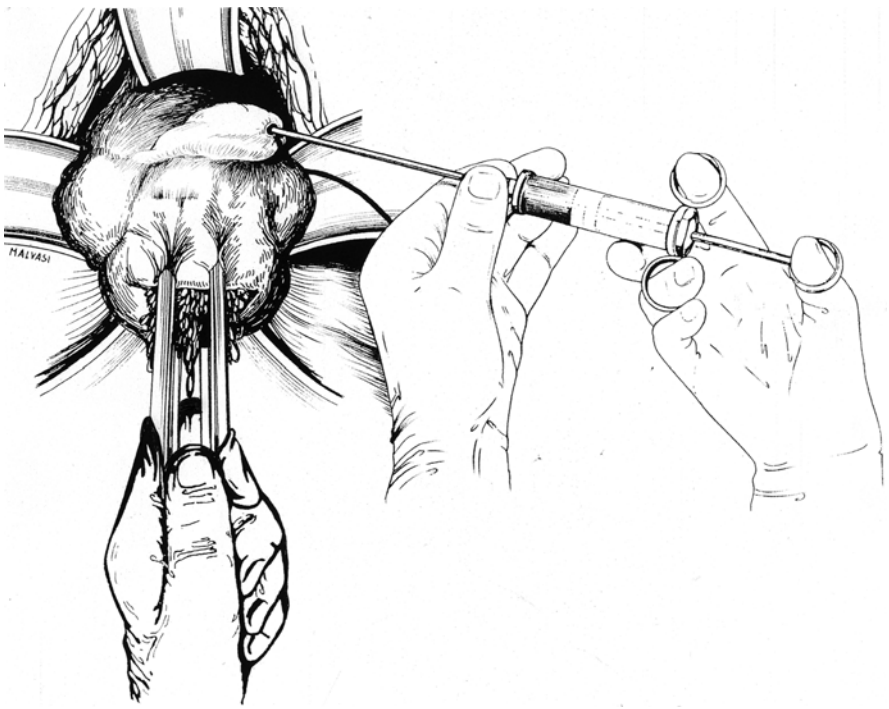


Fig. 8.16 An intrauterine arterial catheterization, with injection of Gelfoam for the occlusion of the uterine arteries

Fig. 8.17 Exposure of the cervix with vaginal retractors, as the first step of any surgical treatment

Fig. 8.18 Intracervical vasopressin injection before conducting the curettage of cervical pregnancy



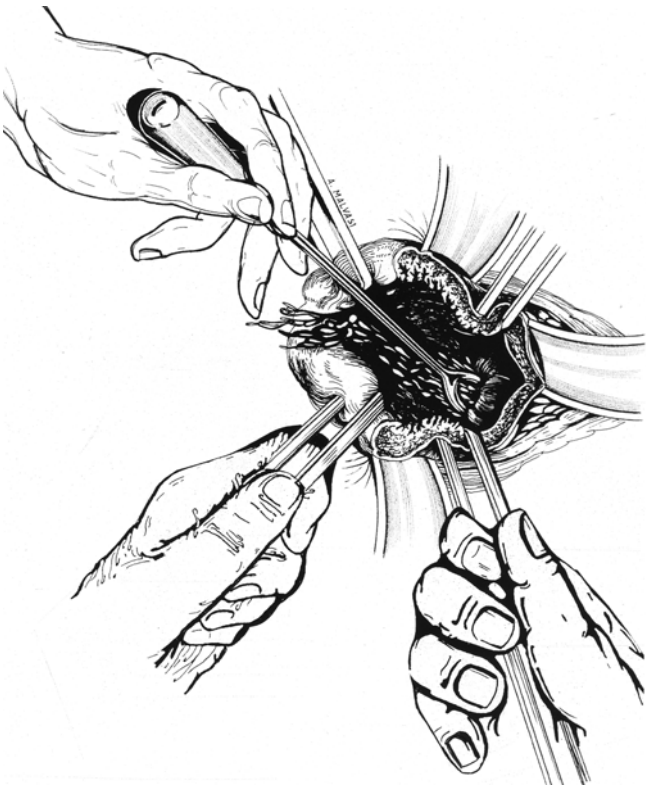


Fig. 8.19 Cervical gentle curettage of pregnancy

is injected with a 21 gauge needle circumferentially into the cervical stroma [20]. Bleeding could be controlled by inserting a Foley catheter with a 30 mL balloon into the dilated cervix for 24 h. In order to secure the catheter in place, a purse string suture is placed around the external cervical os.

8.8.3 Hysteroscopic Removal

Ash and Farrel first reported hysteroscopic management of cervical pregnancy [41]. The hysteroscopic approach allows a complete resection of the gestation under direct vision. This method can also be used for treatment of heterotopic pregnancy [42].

8.8.4 Cervical Cerclage

Scott first described this technique in 1978 [43]. Mashiach published a case series in which he performed a cerclage to treat the cervical ectopic pregnancy [44]. The cerclage technique selected was Shirodkar over McDonald due to its placement in a higher localization on the cervix (Fig. 8.20a, b). They argued some advantages of this method as better control of the massive bleeding, avoidance of systemic side effects of methotrexate, and possibility of use in cases of heterotopic pregnancy.

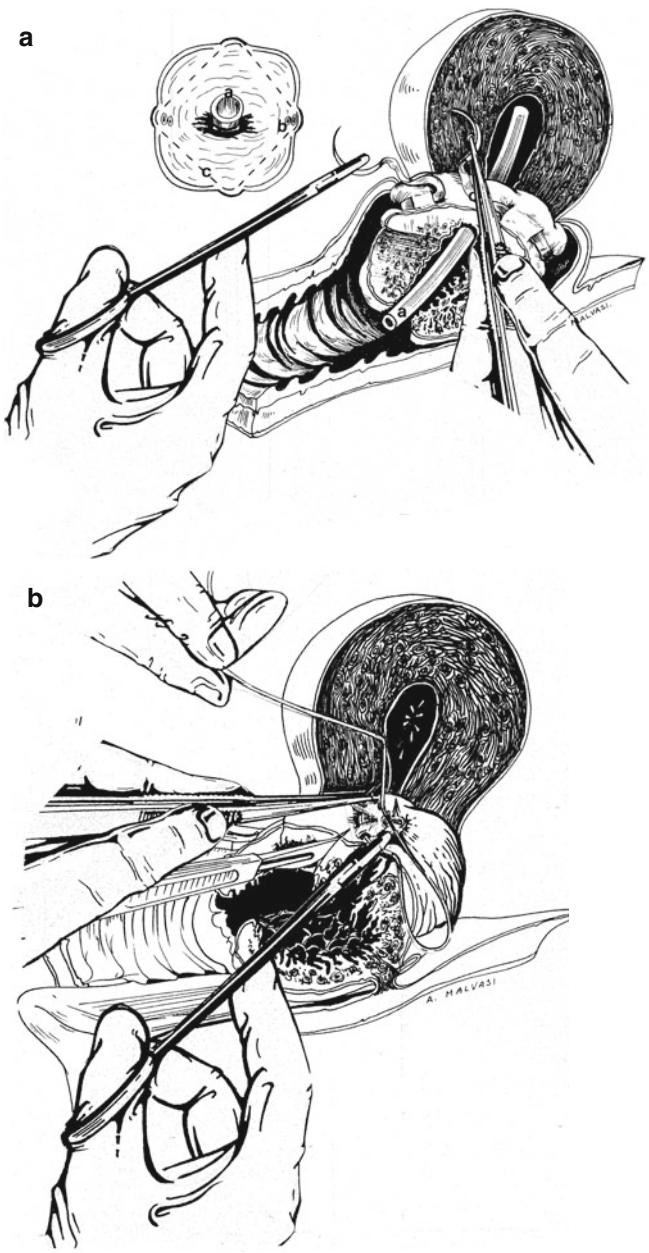


Fig. 8.20 (**a**, **b**) The cervical ectopic pregnancy treatment can be performed by a cerclage, the technique selected was Shirodkar (**a**), with a Hegar dilator put inside the cervix during surgery, and a cervicotomy (**b**) of the localized pregnancy into the cervix, prior to reconstitute the cervical integrity with cerclage

8.8.5 Vaginal Approach

The vaginal approach was first described by Matracaru [45]. With this technique, the bladder is first dissected off

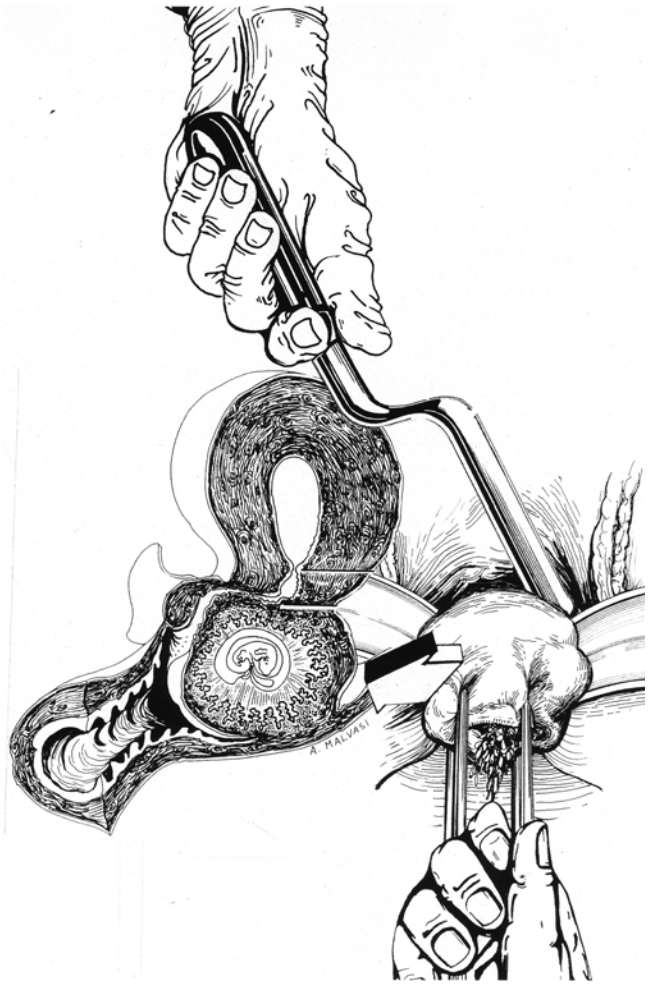


Fig. 8.21 Matracaru operation; first step is the exposure of the cervix with vaginal retractors

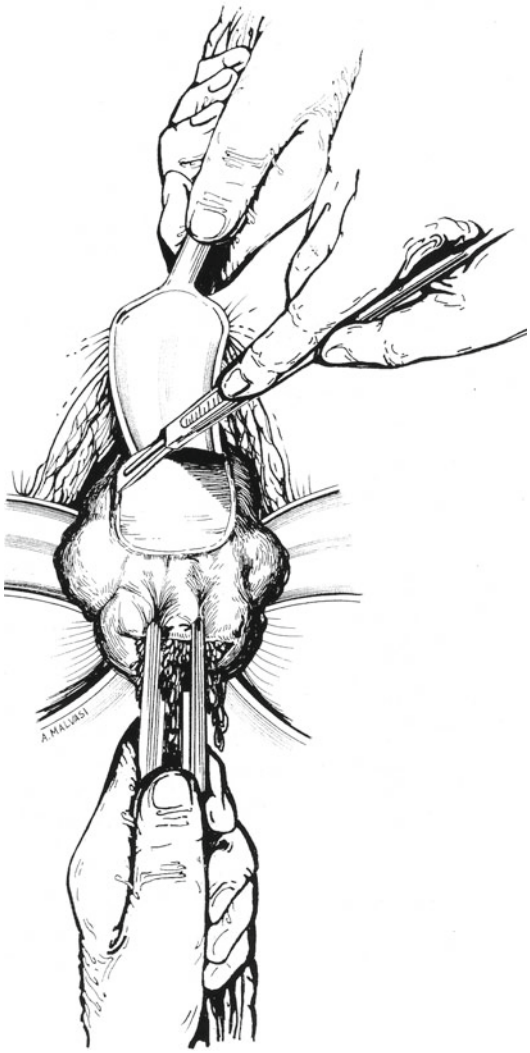


Fig. 8.22 Incision of the anterior cervical wall

the cervix, and blood vessels at each side are clamped. A longitudinal incision is made along the anterior cervical wall from external to internal os and the products of conception are removed, and then the surgery is completed by suturing the cervix and removing the clamps (Figs. 8.21, 8.22, 8.23, 8.24, 8.25, 8.26, 8.27, 8.28, 8.29, and 8.30). This technique was later modified later by Akutagawa [46] who ligated the descending branches of the uterine arteries with absorbable suture (Figs. 8.31, 8.32, 8.33, 8.34, 8.35, 8.36, and 8.37).

8.8.6 Uterine Artery Embolization

Lobel et al. first used uterine artery embolization to decrease the cervical blood supply [47]. This procedure is usually used in combination with curettage.

8.8.7 Tamponade

Cervical tamponade after removal of a cervical pregnancy has been a standard method to minimize massive vaginal bleeding. It can be achieved with insertion of Foley catheter balloon or a sterile gauze intracervically [48]. It is usually left intracervically for at least 24 h.

8.8.8 Laparoscopic-Assisted Treatment

A more invasive technique to reduce bleeding from a cervical pregnancy is laparoscopic occlusion of the uterine arteries [49, 50].

Fig. 8.23 Bipolar coagulation of the highly vascularized anterior cervical wall

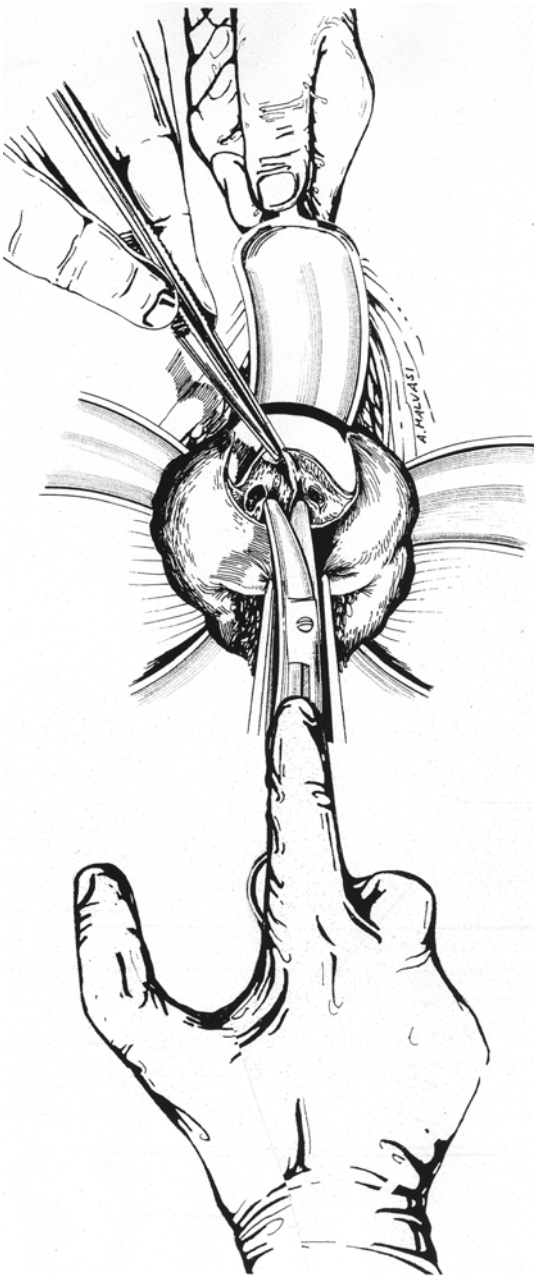


Fig. 8.24 The surgeon dissects by scissors, the anterior cervical wall to expose the cervical pregnancy

8.9 Radical Treatment

8.9.1 Trachelectomy

Kamoi et al. described surgical treatment of cervical pregnancy with "partial trachelectomy" [51]. The procedure is performed by ligating the descending branches of the uterine arteries, circumcision of the vaginal fornix and a partial resection of the cervical wall with the products of conception, and reconstruction of the cervix and vagina. Another option is abdominal trachelectomy [52].

8.9.2 Hysterectomy

After the laparoscopic removal of cervical pregnancy [53] (Fig. 8.38a, b), hysterectomy is the final measure to treat

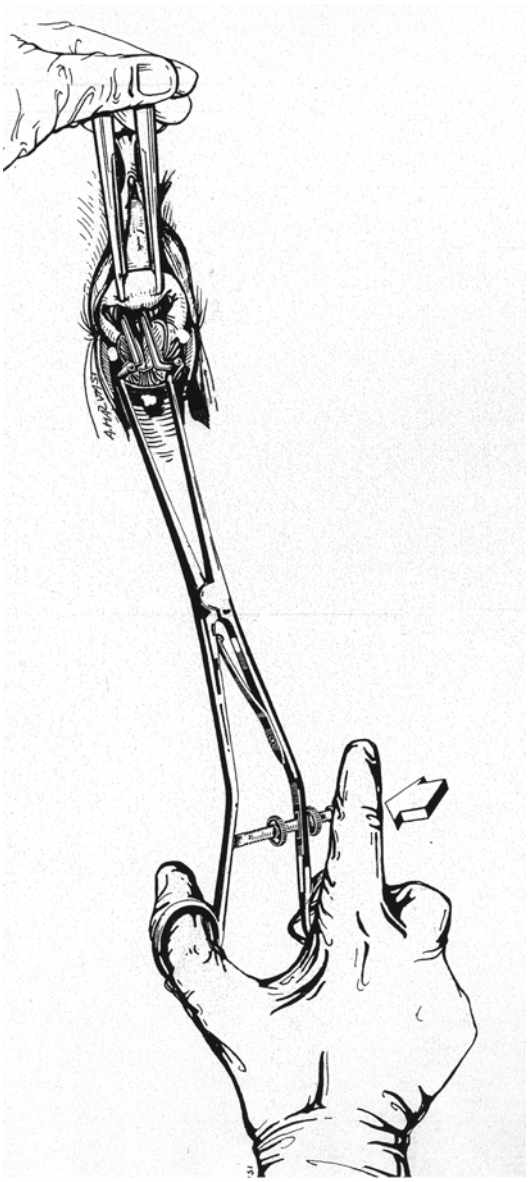


Fig. 8.25 Once the plane of dissection is reached, the surgeon performs the dissection of the pregnancy from the cervix by scissors

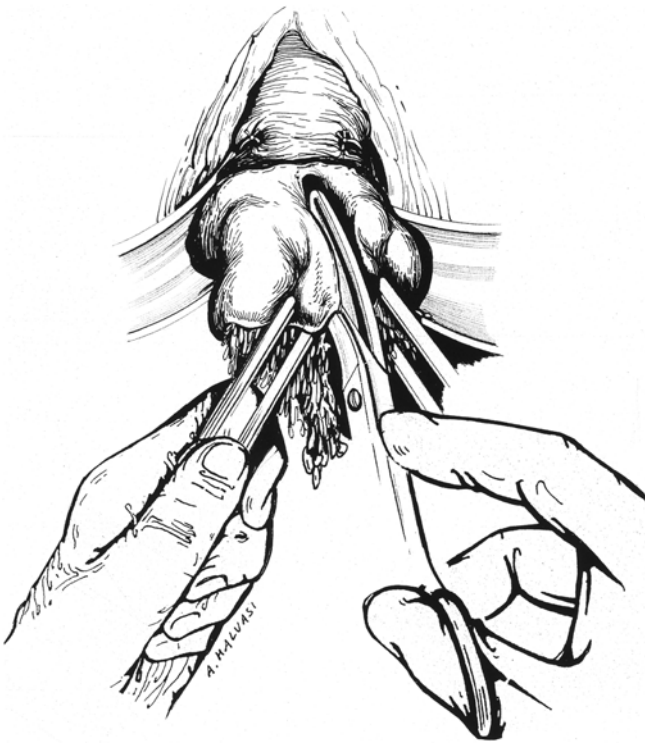


Fig. 8.26 The surgeon cuts the cervix over pregnancy, to better expose the ectopic gestational sac

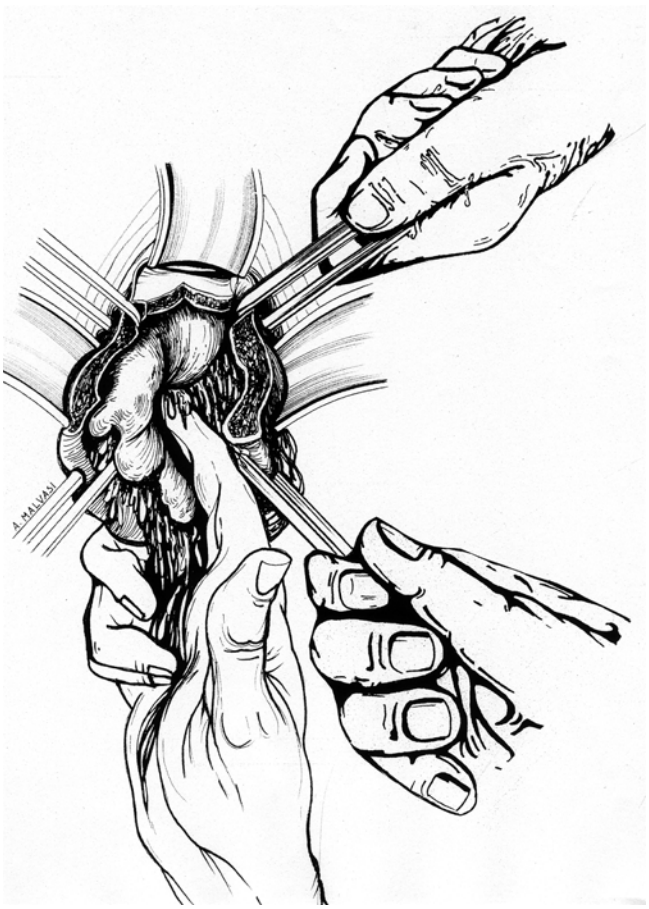


Fig. 8.27 The surgeon removes, the cervical pregnancy from the uterine cervix digitally

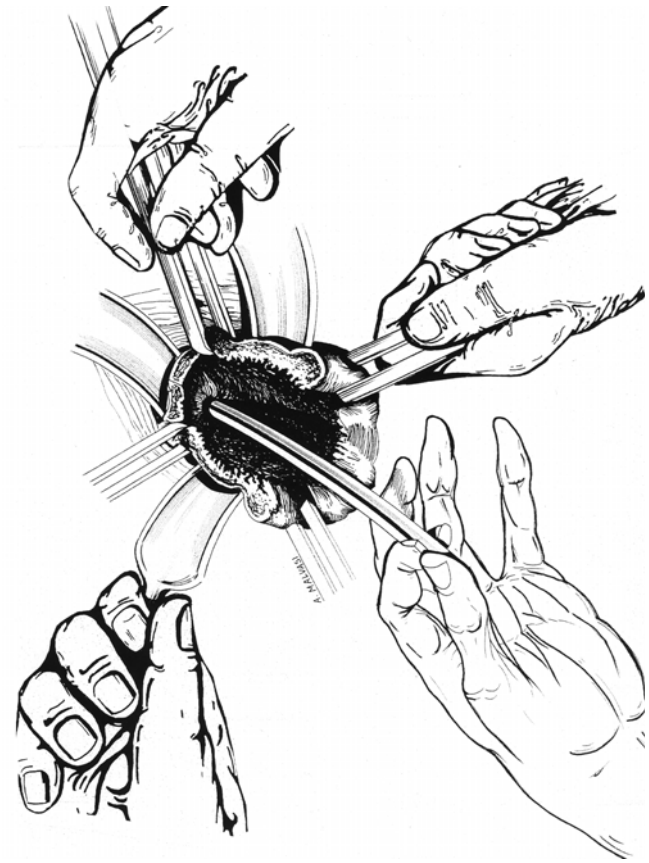


Fig. 8.28 Once pregnancy is removed, the cervix is exposed and ready to be reconstructed by suturing; the surgeon inserts a dilator into the cervix, as a guide to suture preserving cervical patency

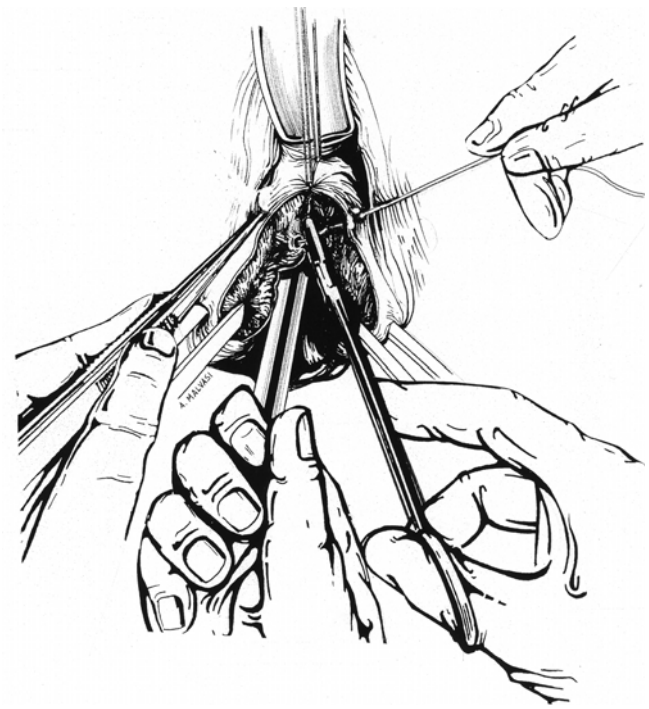


Fig. 8.29 Suturing of the cervix to reconstruct its anatomy

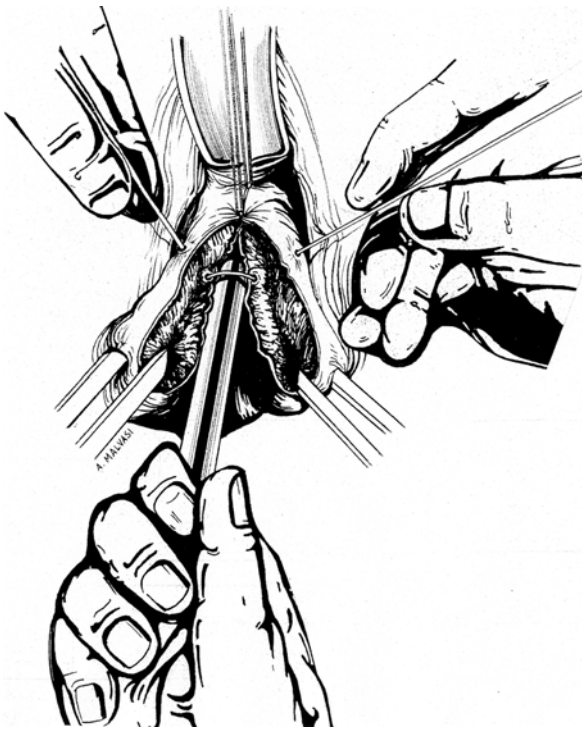


Fig. 8.30 Suturing with a dilator inside the cervical canal

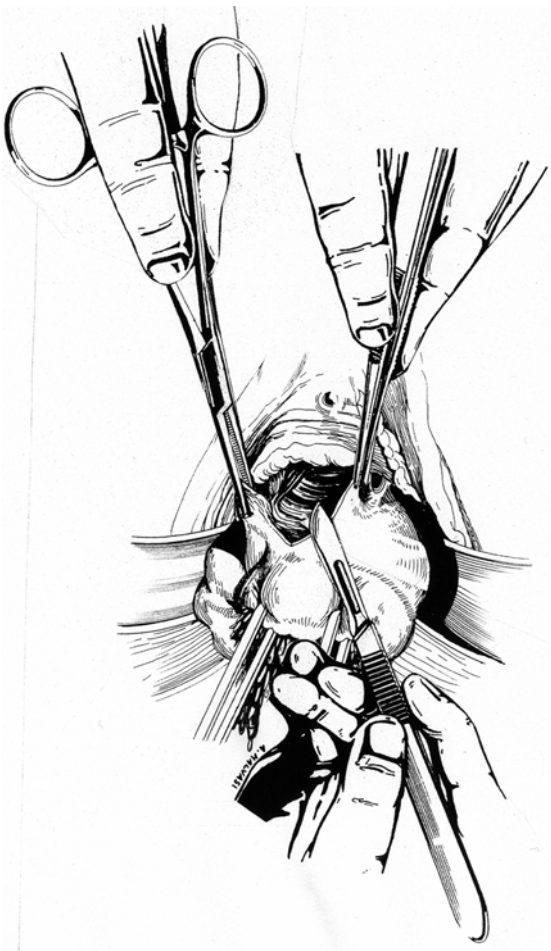


Fig. 8.31 Akutagawa operation: incision of the anterior cervix to create a cervical flap

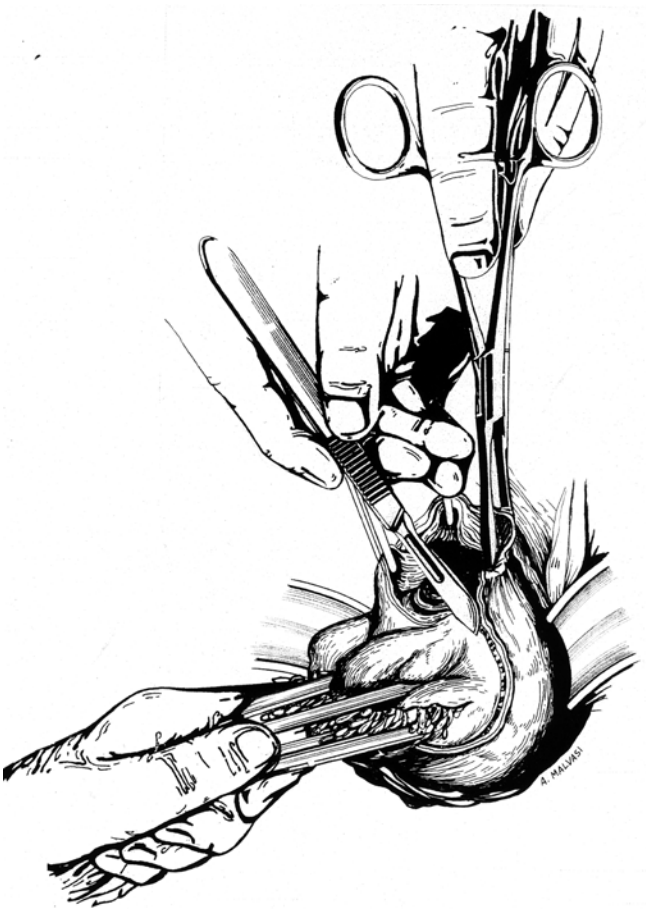


Fig. 8.32 Circular incision of the uterine cervix and exposure of the anterior cervical wall

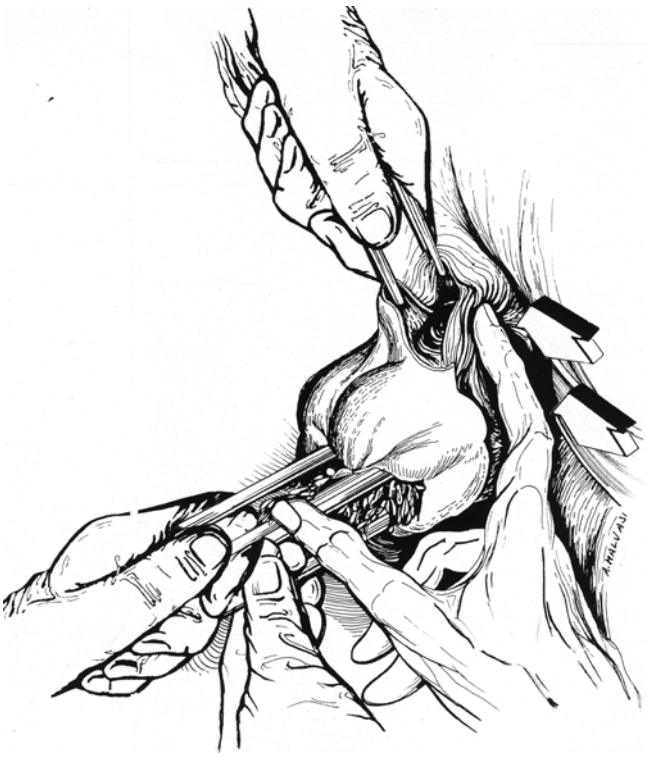


Fig. 8.33 The surgeon starts to dissect, digitally, the connective tissue over the descending branches of the uterine arteries

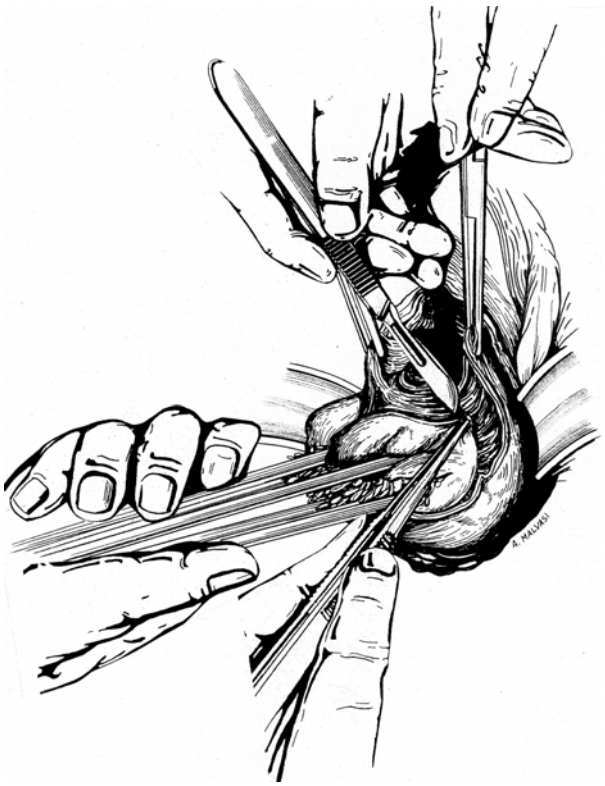


Fig. 8.34 The surgeon dissects with a scalpel the connective tissue of the anterior cervical wall, to expose the vascularized area over ectopic pregnancy

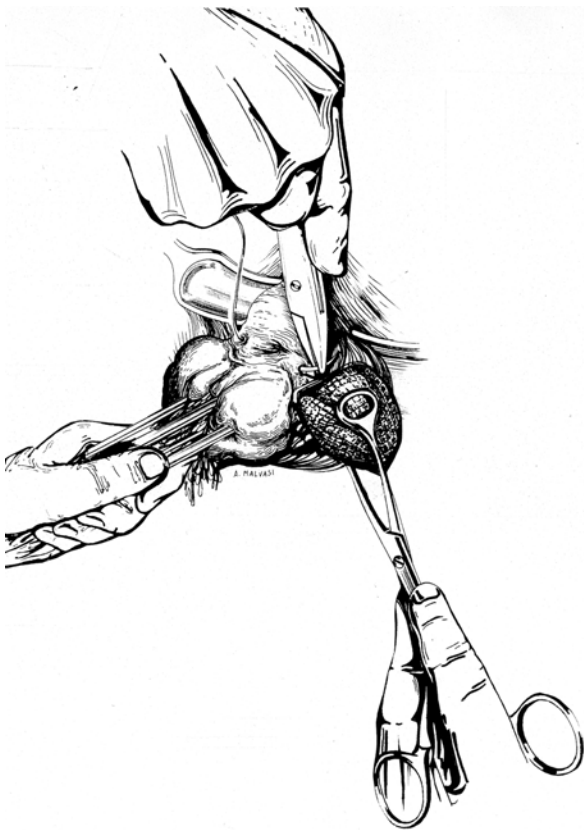


Fig. 8.35 The surgeon dissects using a gauze the connective tissue and exposes the descending branch of the uterine arteries

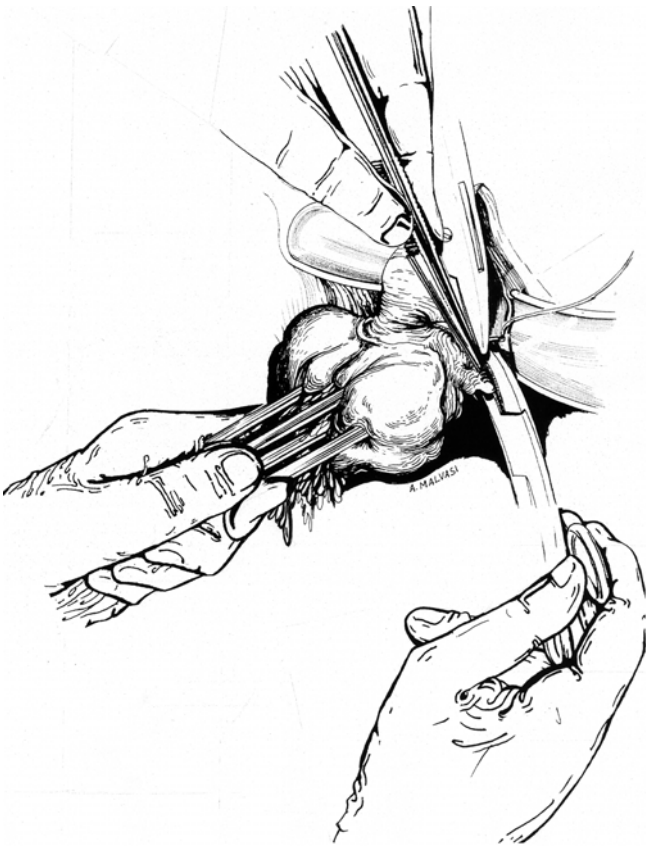


Fig. 8.36 The surgeon ligates the descending branches of the uterine arteries with absorbable suture

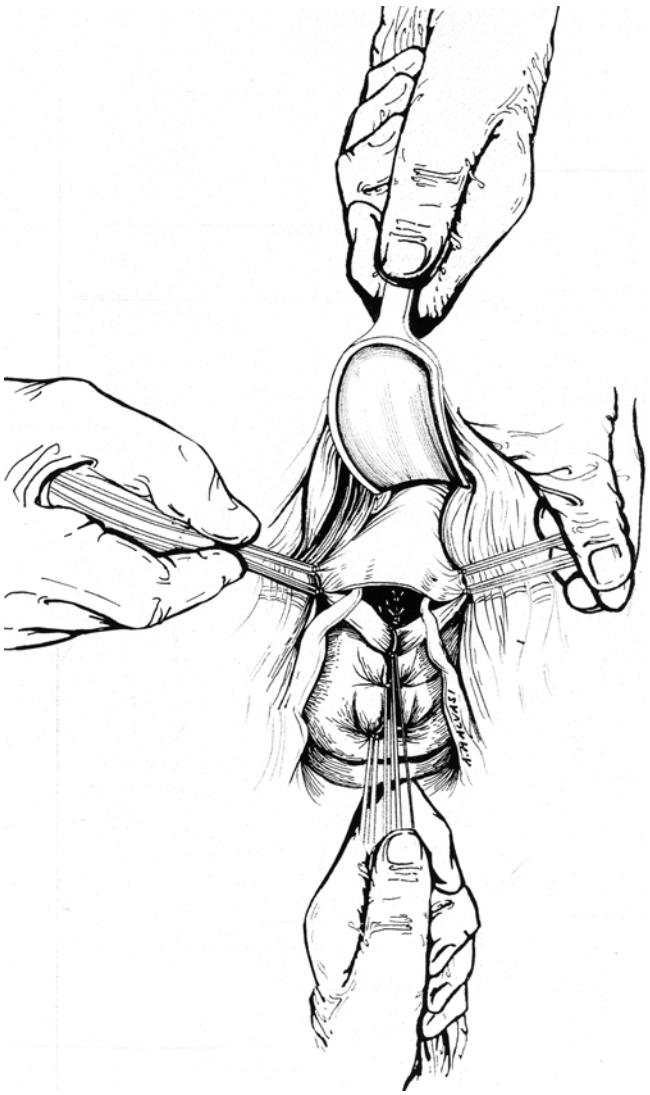


Fig. 8.37 At the end of the operation, before suturing the dissected tissue, a gauze is inserted into the dissected space anterior to the cervix to facilitate hemostasis (gauze to be removed before suturing)

patients with cervical pregnancy. Before the 1980s, the hysterectomy rate for cervical pregnancy was around 70 %. Today, only cases undetected until the second trimester might require a hysterectomy; yet the total rate of hysterectomy is only around 5 % [54].

8.9.3 Monitoring Results

Conservative treatment of cervical pregnancy should be followed by close follow-up with serial measurements of B-HCG levels and sonographic evaluation if needed. It is important to note that there is no direct correlation between the decrease of the HCG levels and the regression of the mass. If serum HCG levels decrease between 9 and 17 days, regression of the mass takes around 40 days [35].

8.9.4 Obstetric Outcomes After Cervical Pregnancy

Subsequent pregnancies after successful medical or surgical treatment of cervical ectopic pregnancy have been described [55]. The best interval of pregnancy after methotrexate treatment is still unclear [56]. Some studies reported that methotrexate can still be found in the cells for 8 months after being administered systemically [56]. In general, most clinicians advise the patient not to conceive only 3 months after methotrexate treatment.

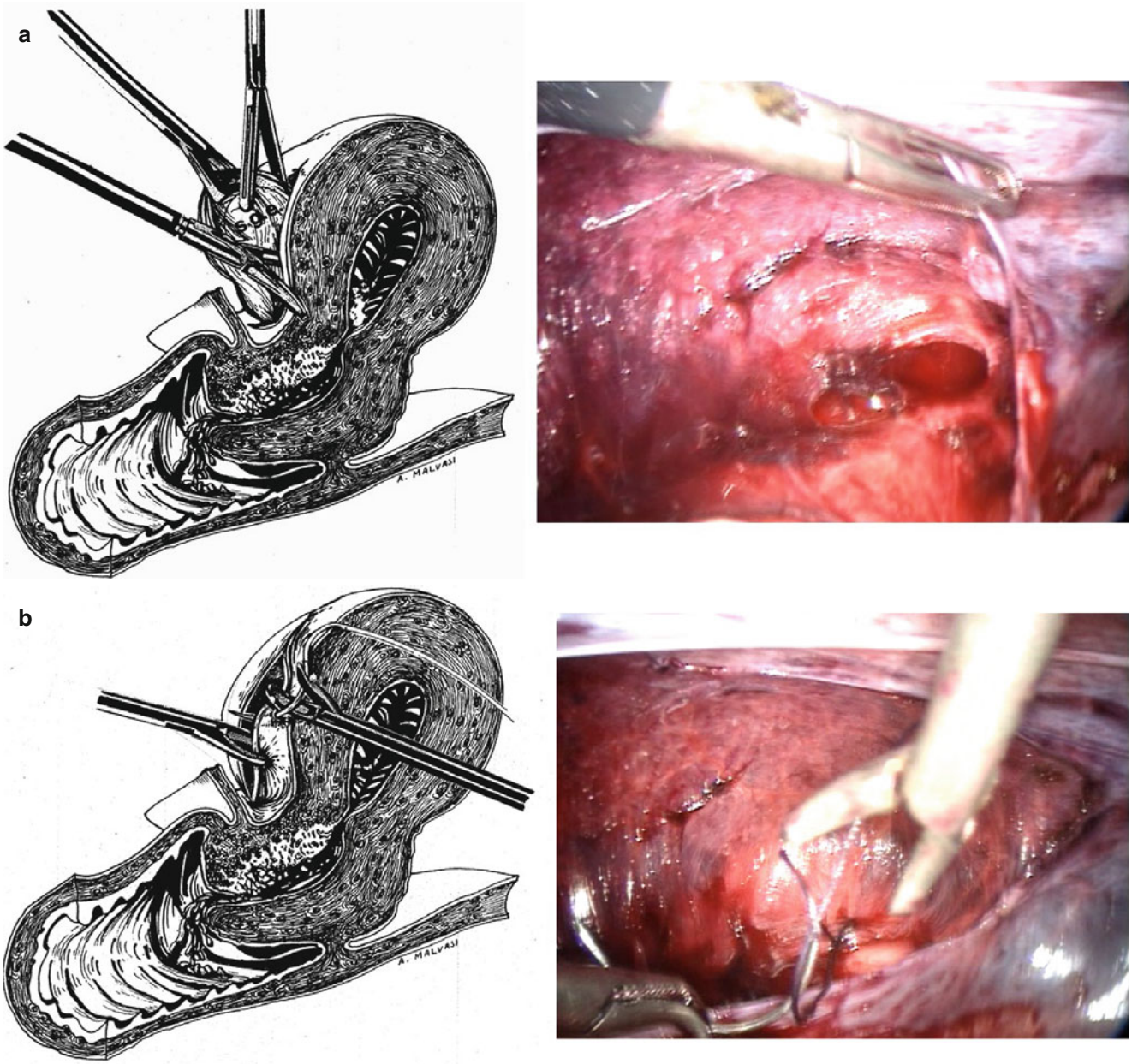


Fig. 8.38 (**a**, **b**) During the laparoscopic approach after dissection of the bladder flap, the surgeon incises the anterior cervical wall (**a**), to remove gestational tissue (**b**) and sutures the cervical edges to reconstruct the cervix

Conclusion

Cervical ectopic pregnancy is a rare event that can result in loss of fertility. However, today most cervical pregnancies can be diagnosed early allowing fertility-sparing treatments. Systemic methotrexate has resulted in high rates of successful treatment with no documented long-term effects on future fertility. Intra-amniotic injections, uterine artery embolization, curettage with Foley balloon tamponade, and hysteroscopic removal can be reserved for cases that have failed methotrexate or that have contraindications to its use.

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Molar and Trophoblastic Disease

9

Leonardo Resta, Antonio Malvasi, Ljiljana Mirković, and Radmila Sparić

9.1 Historical Overview

Gestational trophoblastic disease (GTD) has been known for over 2400 years and, in the last century, Dr. Ober was one of the first to compose a review of GTD history [1]. Hippocrates (460–370 AD) first described the hydatidiform mole as the "dropsy of the uterus." In 600 AD, Aetius of Armida (502–575 AD) described a uterus "filled with bladder-like objects," probably referring to a molar tissue. Velpeau and Boivin recognized hydatids as cystic dilations of chorionic villi in 1827. Marchand, in 1895, proved these tumors to be the sequelae of pregnancy, abortion, or hydatidiform mole and described the proliferation of the syncytium and cytotrophoblast [2]. Finally, Fels, Ernhart, Reossler, and Zondek proved the presence of high levels of gonadotropic hormone in the urine of patients with GTD [3].

L. Resta, MD
Section of Pathological Anatomy, Department of Emergency and Organ Transplantation (DETO), University of Bari, Bari, Italy
e-mail: leonardo.resta@uniba.it

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

L. Mirković, MD
Head of Obstetric Intensive Care Unit, Medical Faculty, University of Belgrade, Doktora Subotića 8, Belgrade 11000, Serbia

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Višegradska 26, Belgrade 11000, Serbia
e-mail: drljiljamirkovic@gmail.com

R. Sparić, MD (✉)
Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Višegradska 26, Belgrade 11000, Serbia

Medical Faculty, University of Belgrade, Doktora Subotića 8, Belgrade 11000, Serbia
e-mail: radmila@rcub.bg.ac.rs

9.2 Definition and Synonyms of Gestational Trophoblastic Disease

GTD is a spectrum of tumors differently aggressive and a high potential for metastasis. Its pathogenesis is unique because the maternal tumor arises from the gestational tissue [4]. GTD refers to both the benign and malignant entities.

One of the most important features of the trophoblast is its capacity of invasion. Luckily, in a healthy trophoblast, the malignant-like behavior is strictly controlled. The trophoblast of the human placenta differentiates into the villous and extravillous type during early placentation. The extravillous trophoblast in early pregnancies starts invading the maternal uterus to regulate adequate blood flow and nutrient supply to the growing fetus. The villous trophoblast provides the epithelial cover of the placental villous trees that are in direct contact with maternal blood, while the extravillous trophoblast invades maternal uterine tissues, thus directly contacting maternal stromal and immune cells. A unique set of events includes the plugging and remodeling of the maternal vessels. Inadequate remodeling of the spiral arteries can seriously complicate a pregnancy, threatening the well-being of both the mother and the developing fetus. The trophoblast can be detected by PCR in maternal circulation [5]. However, when the regulatory mechanisms fail, it can lead to different, highly invasive, metastatic, and very vascular entities.

The term "GTD" comprises a range of pregnancy-related disorders and refers to the group of tumors differentiated by abnormal trophoblast proliferation.

These are complete or partial hydatidiform moles, which are noninvasive and invasive moles, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, which are invasive and defined as gestational trophoblastic neoplasia (GTN).

The complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), and invasive moles (IM) are characterized by the presence of villi and are known as hydatidiform moles (HM). HM is edematous immature

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_9

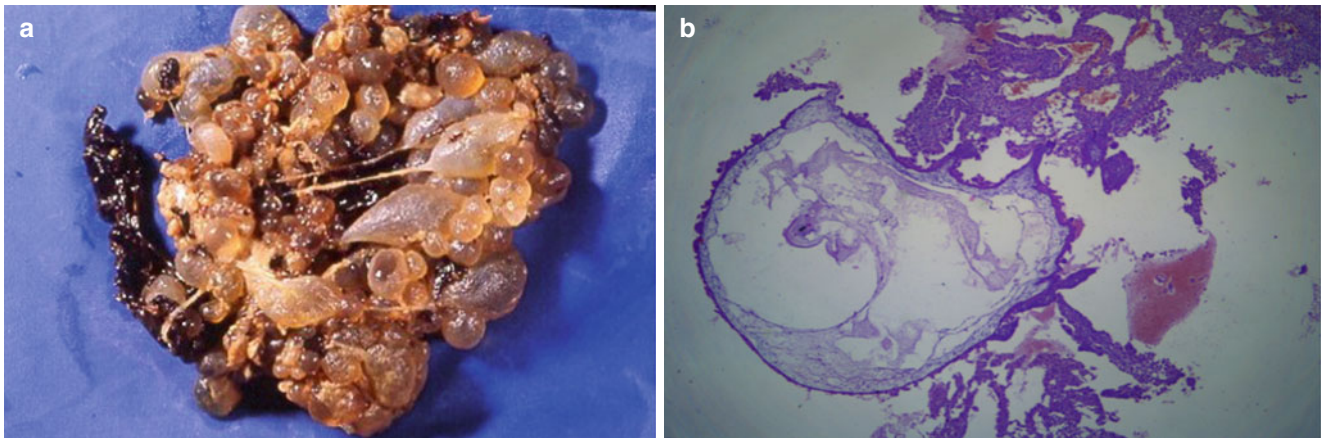

Fig. 9.1 (**a**) Macroscopic view of complete hydatidiform mole. The absence of an amnio-chorionic sac is evident. The villi are of giant size and show a form similar to a bunch of hydropic grapes. (**b**) Chorionic villi of complete moles exhibit hydropic swelling (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic)

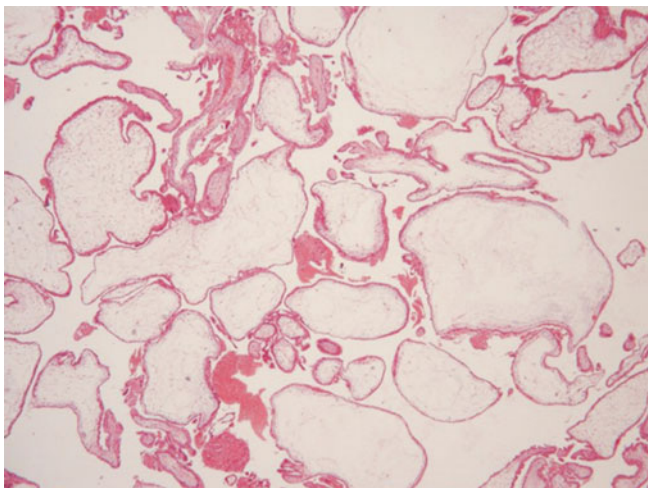

Fig. 9.2 General histological view of a complete hydatidiform mole. All villi are of large size. The stroma lacks vessels and contains a large amount of water

placenta [6]. By contrast, the lack of villi is a characteristic of choriocarcinoma (CC), placental site trophoblastic tumor (PSTT) (Figs. 9.1a, b and 9.2), and epithelioid trophoblastic tumor (ETT).

GTN develops for weeks or years following pregnancies or hydatidiform moles. Other terms used instead of GTN are persistent gestational trophoblastic disease and malignant gestational trophoblastic disease. The current WHO classification of GTD is as follows [7]:

1. Hydatidiform moles (HM)
   (a) Complete hydatidiform mole (CHM)
   (b) Partial hydatidiform mole (PHM)
2. Invasive hydatidiform mole
3. Gestational choriocarcinoma (CC)
4. Placental site trophoblastic tumor (PSTT)
5. Epithelioid trophoblastic tumor (ETT)
6. Tumor-like conditions
   (a) Exaggerated placental site reaction (EPS)
   (b) Placental site nodule (PSN)
7. Unclassified trophoblastic lesions

9.2.1 Epidemiology of Gestational Trophoblastic Disease

The rarity of GTD, inconsistencies in entity definitions, and lack of centralized databases are limited factors for accurate estimation of incidence. Still, it is clear that there is an ethnic predisposition to GTD. The highest incidence of the HM is among the African-Americans, American Indians, Eskimos, Hispanics and Asian populations [8]. The HM occurs with an incidence rate ranging from 2/1000 pregnancies in Japan and Southeast Asia [8] to 12/1000 pregnancies in Indonesia, India, and Turkey [9–11]. The incidence rates in Europe and America are approximately 0.57–1.1/1000 pregnancies [8]. CC affects 1 in 40,000 pregnancies in Europe and North America versus 9.2 in 40,000 pregnancies in Southeast Asia and Japan [3]. The incidence rate of CC is 1 in 50,000 deliveries in the UK in 2010, and PSTT accounted for about 0.2 % of the cases of GTD [3]. Worldwide, the incidence rates of both HM and CC have declined over the past decades [8].

There is substantial evidence showing an increased incidence of HM at the extremes of reproductive life. An increased risk of molar pregnancy is seen in the very young (<16 years), but is most associated with advanced maternal age (>45 years) [3].

In a study from Alaska [12], where the natives consume a high-protein diet consisting of fish, there is a higher incidence of HM compared to the Caucasian community. In another study from Mexico [13], the food histories of women

with HM and a control group of pregnant women were compared. No difference was detected in the intake of proteins, carbohydrates, and fats, excepting an inverse relationship between carotene and animal fat dietary intake [14, 15].

Women with a previous HM seem to be at a higher risk of having it again. The relative risk seems to be higher than that of the general population; however, it is even greater if a woman has had more than one mole [16]. The risk seems to decrease if there is one or more normal pregnancies following the HM. A recent study of subsequent pregnancies in 16,000 women confirms an increased recurrence risk of 1 % for a second molar pregnancy. This study has also revealed that this risk is associated with CHM rather than PHM [17].

In the last century, it has been recognized that among women with recurrent HM there is a number of women with familial recurrent hydatidiform mole (FRHM) – a rare autosomal recessive condition in which affected women have a predisposition to pregnancy losses, most of which are CM [18]. To date, mutations in two genes, NLRP7 (NLR family, pyrin domain containing seven) [19] and KHDC3L (KH domain containing 3-like, subcortical maternal complex member) [20], have been shown to be responsible for 75 and 5 % of the cases of FRHM, respectively. The data further indicate that the risk of a third HM is associated almost exclusively with CM, and this has led to the estimate that 1 in 640 women registered with a CM should have the FRHM [17].

There is little doubt that a previous HM is a predisposition for developing GTN. It is estimated that a malignant change will affect around 14 % CM and considerably higher than the 1 % for women with a PM [21]. The risk of GTN after HM has been estimated as 1000 times higher than after a term pregnancy [8]. However, a report from Japan has indicated that there has been a reduction in the incidence of HM from 4.9 to 1.9/1,000,000 of the population and of CC from 1.6 to 0.3/1,000,000 of the population [22]. The study by Eagles et al. [17] documented that there was no significant difference between the risk of developing GTN for typical sporadic CM and the diploid biparental CM associated with FRHM.

Women with blood type A or AB should have a higher risk of HM compared with women with a blood type B or O (with a relative risk of 0.9–4.8). The data also suggested a higher risk for persistent GTD and for CHM compared to PHM [23].

The use of oral contraceptives is generally associated with an increased risk of GTD and with relative risks ranging from 1.11 to 2.6 [23, 24]. There is insufficient information on other environmental and lifestyle factors or other possible etiological risk factors for GTD, such as smoking habits, alcohol consumption, socioeconomic status, and herbicide exposure [8, 9, 15, 23, 25].

9.2.2 Anatomo-Pathological Characteristics and Causes of GTD

The WHO classification of tumors of the female genital tract published in 2014 [26] has greatly modified the previous organization of gestational trophoblastic disease. Emphasis is given to lesions with aggressive behavior (choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor). These are followed by the nonneoplastic lesions (exaggerated placental site, placental site nodules, and plaques) and then by molar pregnancy or hydatidiform mole (complete, partial, and invasive), concluding with nonmolar abnormal villous lesions.

This classification, in its not truly academic peculiarity, mixes, without any discernible logical order, diseases with etiopathogenesis and evolutions which are too intricate to be able to easily distinguish and separate. It is difficult to see the link between malignant diseases and occasionally found nonneoplastic lesions, listing them before molar diseases which share a large part of their etiology with choriocarcinoma. Similarly, there is no doubt that an invasive mole belongs to the complete form, and it is not logical to insert the partial form between the two, especially as the partial form has a very different nosological meaning. No one felt the need to complicate the classification with the introduction of anomalous villous lesions which are nothing more than not yet completely absorbed villi. The desire to insert the old "trophoblastic diseases of undetermined significance," whose existence is not much believed in, is in fact a hindrance to the illumination of dubious lesions, which fortunately make up only a small amount of cases.

9.2.3 Complete Hydatidiform Mole

A CHM is a pathological condition wherein an anembryonic sac develops with the fertilization of an aneuploidic oocyte. This type of degenerative oocyte is frequent in women less than 15 years and more than 40 years, and it is fecundated by one or two sperms [27]. The embryo is precociously suppressed, and the extraembryonic portions (i.e., the villi with the trophoblastic epithelium) are present and proliferate. For these reasons the CHM have a diploid karyotype 46,XX. A rare condition of FRHM is composed by a biparental diploid tissue with karyotype 46,XY; the condition is due to a gene mutation (NLRP7) in the chromosomal region 19q13.4 [28].

Macroscopically (Fig. 9.1a), the chorionic plate is not recognizable as such, instead there being an unstructured mass of enlarged, edematous villi branching into cotyledon.

At histology (Figs. 9.1b and 9.2), the villi show very irregular branching, most being of an abnormal volume with circumferential hyperplasia and with variable degrees of trophoblastic proliferation. Particularly the syncytiotrophoblast

shows cytoplasm vacuoles and various degrees of nuclear atypia. The hyperplastic cytotrophoblast has a typically nuclear pleomorphism.

The stroma of the villi is edematous and hydropic with differing degrees of degenerative alteration, often displaying a central cavity known as a cistern. Vessels are absent.

Outside of the villi there is no sign of either the allantois or the yolk sac or of the embryo.

The trophoblast that lines the molar villi, the syncytiotrophoblast and the cytotrophoblast, is always negative for p57 (paternally imprinted maternally product of gene CDKN1C).

With respect to the early abortion, the differential diagnosis with the complete hydatidiform mole is based firstly on the presence of nonpolar trophoblastic proliferation in the neoplastic lesion (Fig. 9.3).

There is a general confusion in the definition of early CHM (first trimester). Typical signs are a basophilic stroma, immature vessels, and an irregular villous surface; however none of these is exclusive to early mole [29]. We are convinced that we can talk about a mole only when there is a documentable nonpolar trophoblast proliferation.

The extent of the trophoblastic hyperplasia and its atypical aspects are directly linked to the biological behavior of the lesion. The major risks consequent to the presence of a CM can be defined in three adverse events:

- Mole residues remain in the uterine cavity even after repeated scraping (*persistent mole*).
- Appearance of an invasive mole.
- Choriocarcinoma (more rarely).

The evolution to an invasive mole or a choriocarcinoma occurs in 8–30 % of complete mole cases.

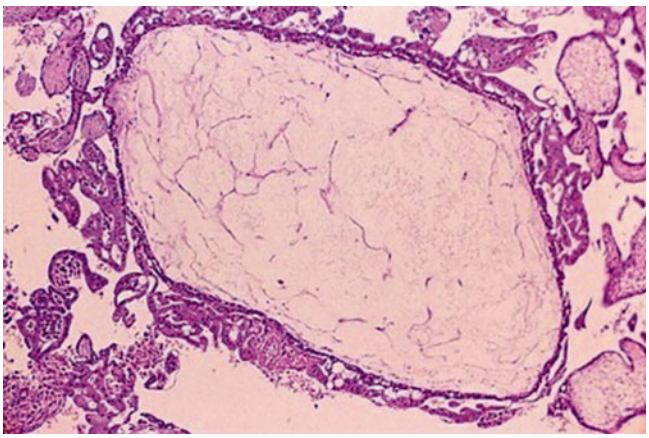

Fig. 9.3 Comparison between villi of a hydatidiform mole (**a**) and a spontaneous abortion (**b**). In molar villi the proliferative trophoblast involves a large part of (or the total) surface of the villus. In the normal placenta and in the spontaneous abortion, the trophoblastic proliferation is of polar type (the proliferation is functional to the creation of a mesenchymal villus from an immature intermediate villus), and it involves only one point of the surface

9.2.4 Partial Hydatidiform Mole

A PHM is a pathological condition wherein a gestational sac which can be anembryonic or embryonic can continue the pregnancy, with frequent development of the products of conception and of the amniochorial membrane. It was once thought that the incidence of PHM was less than that of CHM but they are comparable. In fact, the real incidence of PHM is more than likely underestimated because of the difficulty in diagnosing the digynic form [30].

The PHM is generally characterized by a triploid karyotype (more often 69,XXY; less frequently 69,XXX or 69,XYY). In the case of diandric triploidy, there is a greater proliferation of molar villi than in digynic triploidy where the villous anomalies are of a more modest extent and allow the survival of the fetus up to the 21st–22nd week of pregnancy.

Stereomicroscopic observation shows the presence of both normal and enlarged villi. This is a histological characteristic (Fig. 9.4), and the normal villi show a slight degree of stromal fibrosis, while the others are hydropic with a modest hyperplasia of the trophoblast which can be either circumferential or multipolar. Many of the villi have a large central cistern, while others are characterized by actual alterations of all the karyotype anomalies such as extreme and irregular scalloped contours and inclusions.

The cytotrophoblast that lines the molar villi is positive for p57. Staining with antibody anti-CD34 is useful to see the altered or collapsed vascular structures which are difficult to identify morphologically.

The evolution of the disease into an invasive form or in choriocarcinoma is very rare.

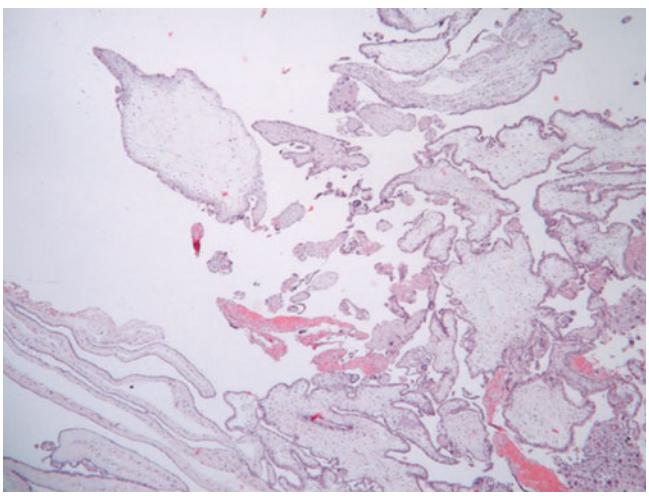

Fig. 9.4 Partial hydatidiform mole. The molar degeneration interests part of the villous tree. Part of the amnio-chorial membrane is evident in the *bottom left* of the picture

9.2.5 Invasive Mole

The invasive mole is characterized by the proliferation of molar villi with hyperplasia of the trophoblastic cells which not only penetrate the myometrium around the mole (Fig. 9.5) but can also (more rarely) invade the perimetrium and the hematic vessels, with distant diffusion in extrauterine sites (e.g., the lungs).

It can develop from a CHM, it rarely being of primitive form. It is the most common complication of GTD and occurs in about 16 % of all complete mole cases.

Lesions have a flaky appearance so hemorrhaging and drying the uterus wall and beyond, with clumps of enlarged edematous villi.

The histological diagnosis is based on finding molar villi and accompanying intermediate trophoblast outside of the endometrium.

Good practice usually determines a hysterectomy. Death, an exceptional occurrence, is generally linked to local phenomena such as perforation of the uterus. The progression of an invasive mole is to a choriocarcinoma, which however is an infrequent occurrence especially when there is a cytotoxic chemotherapy for the management of the lesion.

9.2.6 Choriocarcinoma

CC is a rare malignant neoplasia of a proliferation of cytotrophoblast and syncytiotrophoblast together, in the absence of chorial villi.

Any type of pregnancy can be affected by this disease, but in 50 % of cases it is preceded by a mole, in 25 % by an abortion, and in 22.5 % by a normal pregnancy. Onset in the third trimester of pregnancy of the intraplacental form is exceptional.

Macroscopically, a choriocarcinoma is an infiltrative lesion which destroys the myometrium and is flaky and hemorrhagic without defined borders. The surface can be polypoidal.

A histological examination shows the characteristic intimately related proliferation of atypical cytotrophoblast and syncytiotrophoblast. This proliferation has well-defined architectural characteristics (Fig. 9.6) of a central nucleus of cytotrophoblast nests surrounded by plurinucleate cells and maternal blood. Other characteristics are the lack of stroma or vessels and widespread but largely centralized hemorrhagic necrosis (Fig. 9.7).

All the neoplastic cells are intensely stained by immunohistochemical stain with antibody anti-keratin, in particular

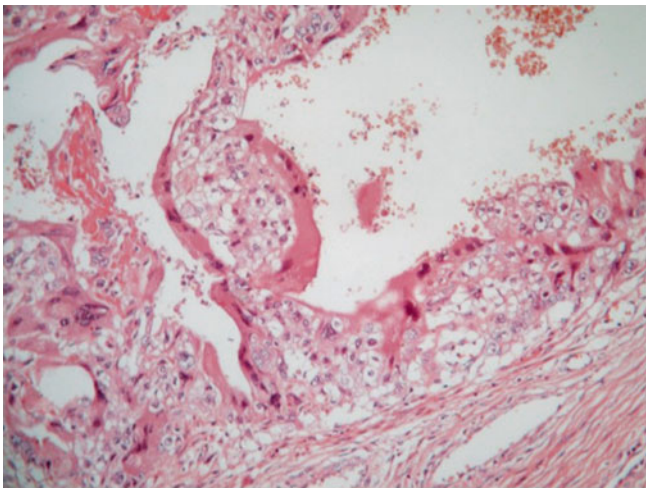

Fig. 9.6 Choriocarcinoma. Typical histological architecture of the tumor: the nucleus is composed of proliferative cytotrophoblast cells surrounded by syncytiotrophoblast. The maternal blood circulars in the neoplastic spaces

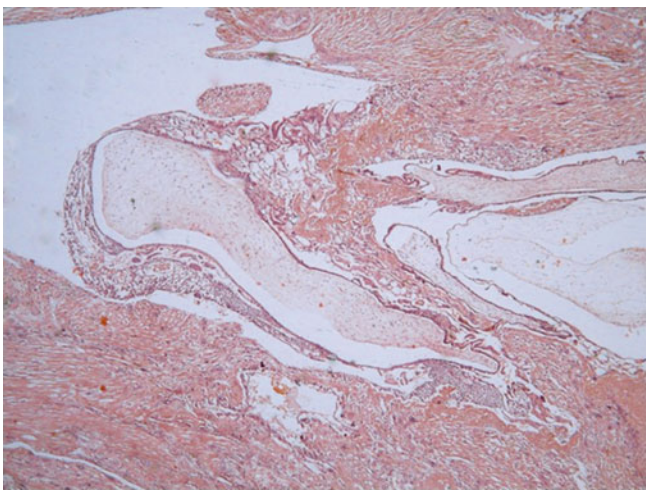

Fig. 9.5 Invasive mole. Some molar villi are present in the vascular spaces of the myometrium

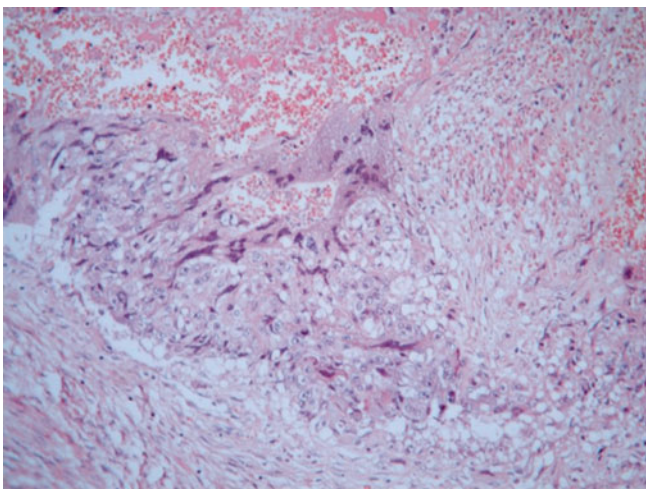

Fig. 9.7 Choriocarcinoma. Large foci of hemorrhage are constantly present in the tumor

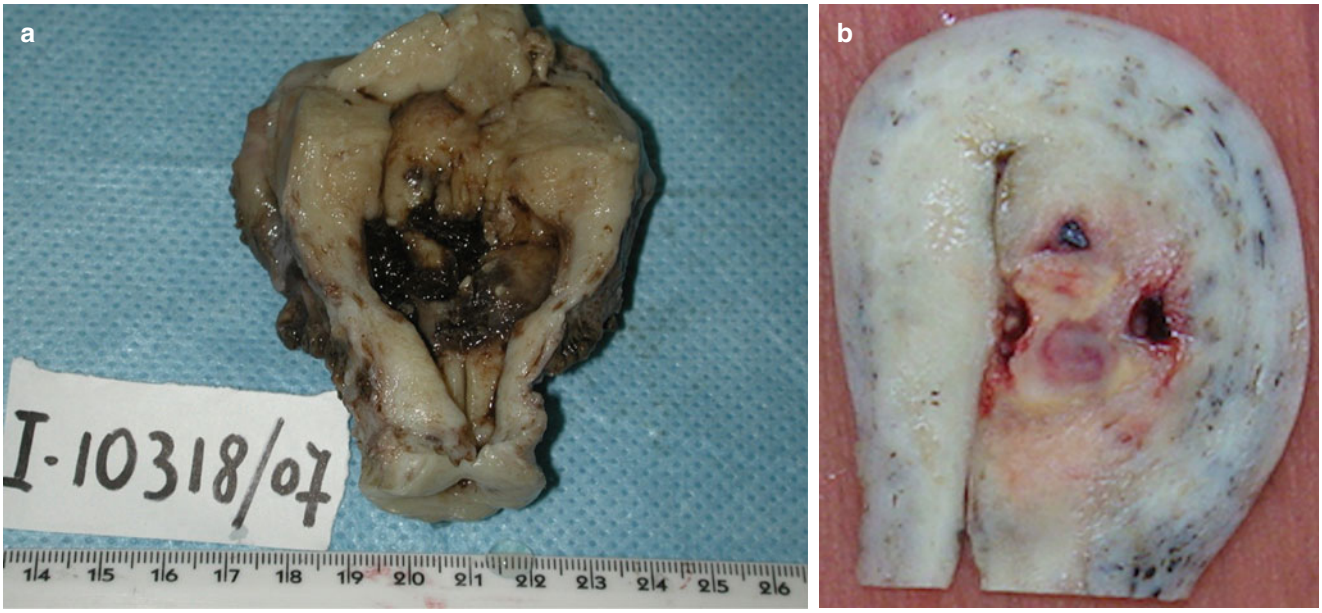

Fig. 9.8 (**a**) Placental site trophoblastic tumor. The macroscopic pattern of the lesion is characterized by a hemorrhagic mass infiltrating the uterine wall. This picture is not dissimilar of a choriocarcinoma. (**b**) Placental site trophoblastic tumor (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic)

by Cam 5.2. The part composing atypical syncytiotrophoblast is intensely positive for inhibin alpha and β-hCG; it is weakly positive for human placental lactogen (hPL), while the atypical cytotrophoblast is always negative for all stains.

The symptoms range from metrorrhagia to those linked to metastasis (more frequent in the lungs, liver, and SNC). Some patients with choriocarcinoma metastasis do not have a uterine neoplasia, probably due to regression of the primitive neoplasia. Elevated serum levels of β-hCG are constant, and this hormone together with the production of other hormones causes an ovaric reaction leading to a polycystic transformation, which can simulate a primitive ovaric neoplasia (hyperreactio luteinalis).

The neoplasia invades the myometrial vessels as well as the myometrium so explaining the ease of metastasis. The most common causes of death are therefore:

- Hemorrhage, especially in cerebral metastasis
- Respiratory failure in lung metastasis
- Complications from the therapy (cytotoxic polychemotherapy)

9.2.7 Placental Site Trophoblastic Tumor (PSTT)

PSTT is a neoplasia of uniquely intermediate trophoblastic cells important for implantation of the placenta. A PSTT can be preceded by a molar pregnancy, but the frequency is much less than for a choriocarcinoma. At gross examination we observe a hemorrhagic neoplasm not different from a choriocarcinoma or another malignant tumor of the uterine wall (Figs. 9.8a, b).

PSTT examination shows a proliferation of elements from extravillous mononuclear trophoblast cells or multinucleated cells mimicking syncytiotrophoblast. The cells can vary in size and appearance of the nucleus, but they show evident atypical characteristics (though variable from medium to serious) (Figs. 9.8a, b). Limited mitosis and fibrinoid material are found among groups of neoplastic cells and substitute the vessel structure. Vessel infiltrative images are common (Fig. 9.10), with the tumor growing substituting the vessel walls, as what happens in normal extravillous trophoblast proliferation at the placenta implantation site.

All the neoplastic cells are intensely stained by immunohistochemical stain with antibody anti-keratin (Fig. 9.11), in particular by Cam 5.2; the atypical extravillous trophoblast is weakly positive for β-hCG, while it is strongly positive for hPL. All the neoplastic elements, which have a proliferation index (Ki 67) of 15 %, are intensely positive in immunohistochemistry for Mel-CAM, inhibin A, and HLA-G.

The tumor is generally benign, but susceptible to becoming aggressive, and can appear a long time after a pregnancy.

In general (90 % of cases), it is self-limiting in its growth with a low mitotic index (≤5 mitosis/10 HPF); the neoplasia infiltrates the myometrium dissecting the single muscle fibers and penetrates the blood vessel walls in a way analogous to its behavior in a normal pregnancy.

In the other 10 % of cases, however, it can lead to death due to the perforation of the uterus following a transformation into a malignant form, with lung, liver, and brain metastasis; in these

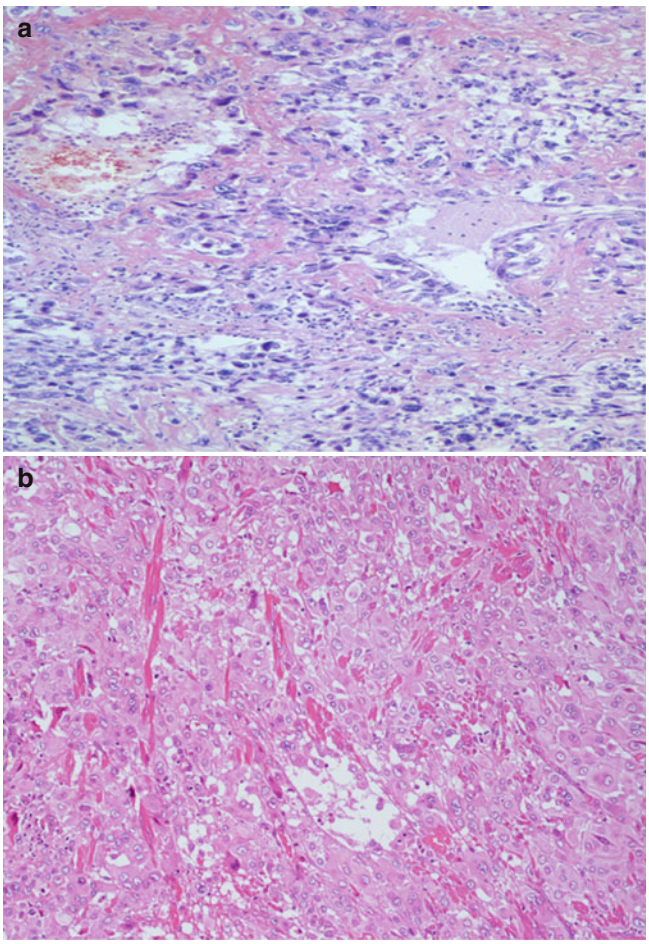

Fig. 9.9 (**a**) Histological microscopic images of placental site trophoblastic tumor (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic). (**b**) Placental site trophoblastic tumor. Histological view of large cells with clear nuclei and abundant eosinophilia infiltrating the myometrium

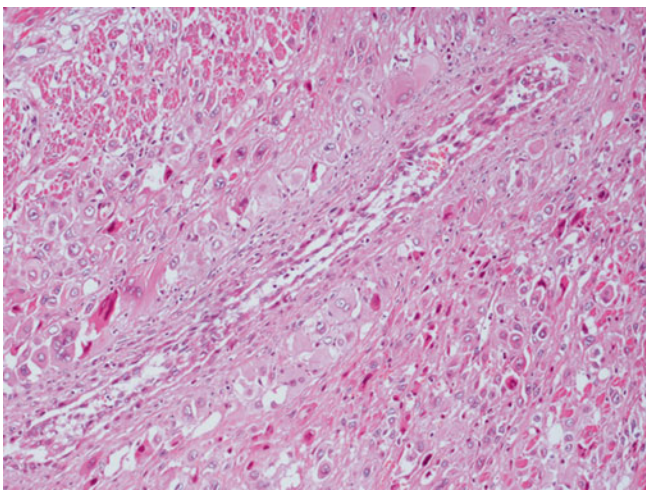

Fig. 9.10 Placental site trophoblastic tumor. Neoplastic cells are pleomorphic and some cells present numerous dark inactive nuclei. The maternal vessels are largely infiltrated by the neoplasia

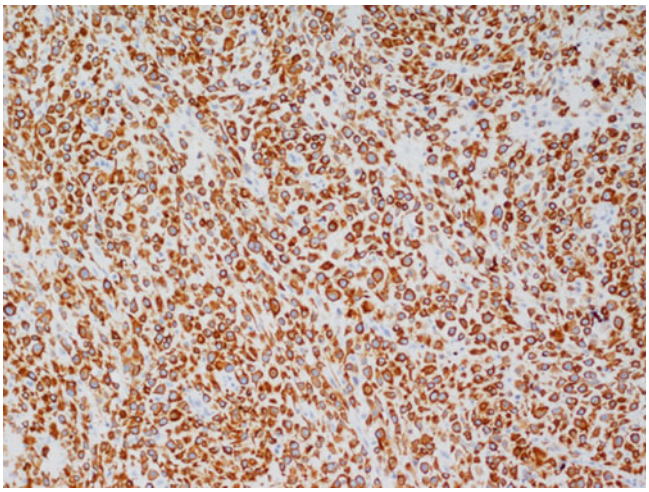

Fig. 9.11 Placental site trophoblastic tumor. The immunohistochemical reaction with antibodies against cytokeratins is strongly positive in the neoplastic cells. The reaction is very useful for the differential diagnosis with decidual cells or other uterine tumors

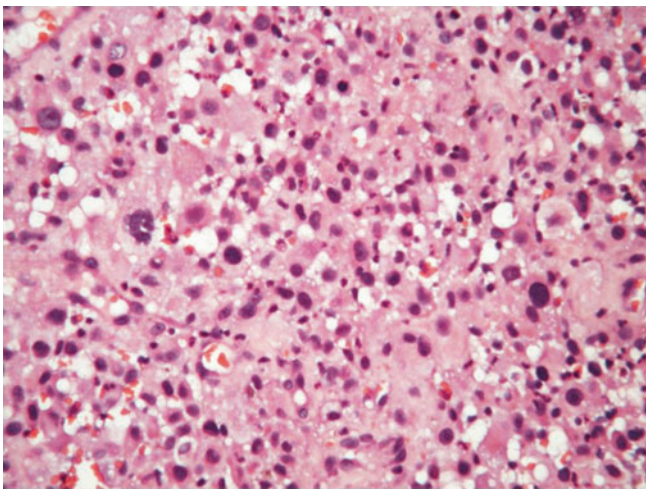

Fig. 9.12 Epithelioid trophoblastic tumor. With respect to the placental site trophoblastic tumor, the present tumor shows more monomorphic cells, necrosis, and diapedetic hemorrhages

cases the mitotic index is generally >5/10 HPF (1 HPF = 400 X). Serum levels of hCG are only moderately increased.

9.2.8 Epithelioid Trophoblastic Tumor

ETT is a neoplasia composed of a uniform population of intermediate trophoblastic cells similar to the trophoblastic cells in the chorion laeve, in consequence of the neoplastic transformation of villous intermediate trophoblastic cells (chorion membrane).

The lesion is ill defined and shows an increase in consistency due to a proliferation of epithelioid elements for the most part disassociated, of small size, monomorphic, and with rare mitosis (Fig. 9.12).

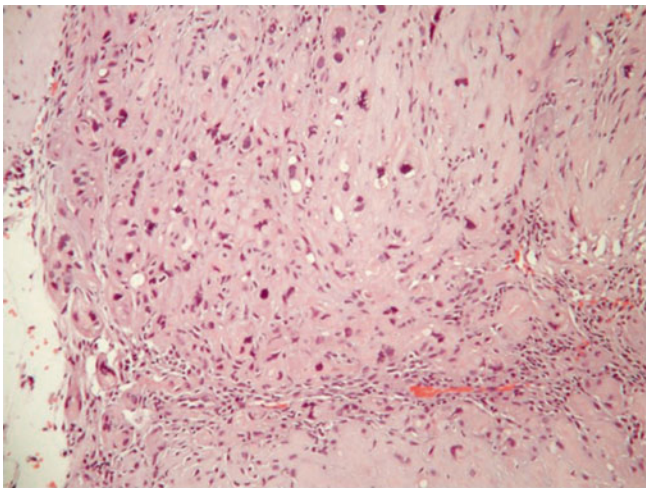

Fig. 9.13 Placental site nodule. The presence of pleomorphic cells in a contest of hyaline stroma in endometrium or endocervix may recall a residual sign of a previous pregnancy. The expression of cytokeratins is important to characterize the lesion

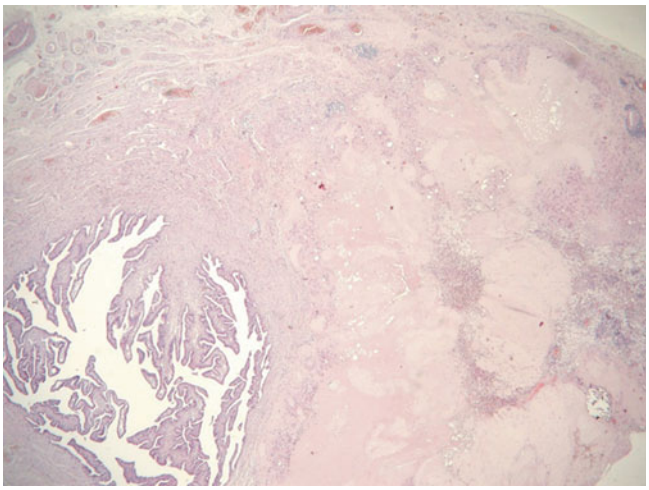

Fig. 9.14 This salpinx was removed in a menopausal woman with a diagnosis of tubal neoplasm. The histology reveals a large amount of hyaline stroma in the salpingeal wall

The behavior is of an expansive lesion, surrounded by lymphocytic infiltrate.

The cells of this neoplasia are strongly positive for placental alkaline phosphatase (PLAP) and for human placental lactogen (hPL), as they are for E-cadherin and for epidermal growth factor receptors (EGFR).

Being less aggressive than choriocarcinoma and more similar to PSTT, it can anyway relapse or metastasize, and it has a mortality of 10 % [31].

9.2.9 Exaggerated Placental Site Reaction

Exaggerated placental site reaction is a nonneoplastic lesion as an abnormal reaction of extravillous trophoblast following an inadequate or insufficient implantation, as frequent as in the implantation of chorial structures (chorion frondosum) with karyotype anomalies. It occurs in 2 % of normal pregnancies and early spontaneous abortions. There is a thickening of the decidua basalis with fibrinoid masses.

The lesion is characterized by an extensive infiltration of the implantation site (Fig. 9.13) by intermediate trophoblastic cells, sometimes also atypical, without significant replication activity.

Therapy is not required, and β-hCG administration is provided only in cases of a trophoblastic tumor not to be excluded in the implantation site.

9.2.10 Placental Site Nodule

A placental site nodule (PSN) is a remnant of the chorion from a previous pregnancy (from several months to years). Typically, it is found accidently in tissue obtained for other reasons, and therefore we cannot identify its rate of occurrence (Figs. 9.14 and 9.15). It is made up of cells similar to normal *chorion laeve* cells. No therapy is required.

In 2014, Kim [29] has proposed an interesting diagnosis path for uterine epithelioid lesions:

1. Uterine epithelioid smooth muscle neoplasm: SMA/desmin+
2. Squamous cell carcinoma: Ck 18−, p16/HPV+
3. Trophoblastic lesion: Ck 18+, p16/HPV−
   (a) Choriocarcinoma: dimorphic pattern/elevated serum β-hCG
   (b) Chorionic trophoblast proliferation: p63+; PLAP++; hPL±; CD 146−
      b.1 Placental site nodule: Ki67, 1–5 %
      b.2 Epithelioid trophoblastic tumor: Ki67 >10 %
   (c) Implantation site trophoblast proliferation: p63−; PLAP−; hPL+; CD 146+
      c.1 Exaggerated placental site: Ki67, 1–5 %
      c.2 Placental site trophoblastic tumor: Ki67 >10 %

9.2.11 Clinical Presentation of Gestational Trophoblastic Disease

Different types of GTD have different clinical presentation [31]. The clinical presentation of women with a molar pregnancy has changed notably over the past several decades [31–33]. The reasons for this are improvement of prenatal care and universally available sonography. As a result, most GTDs are detected when they are small, before any complications can develop [32, 33].

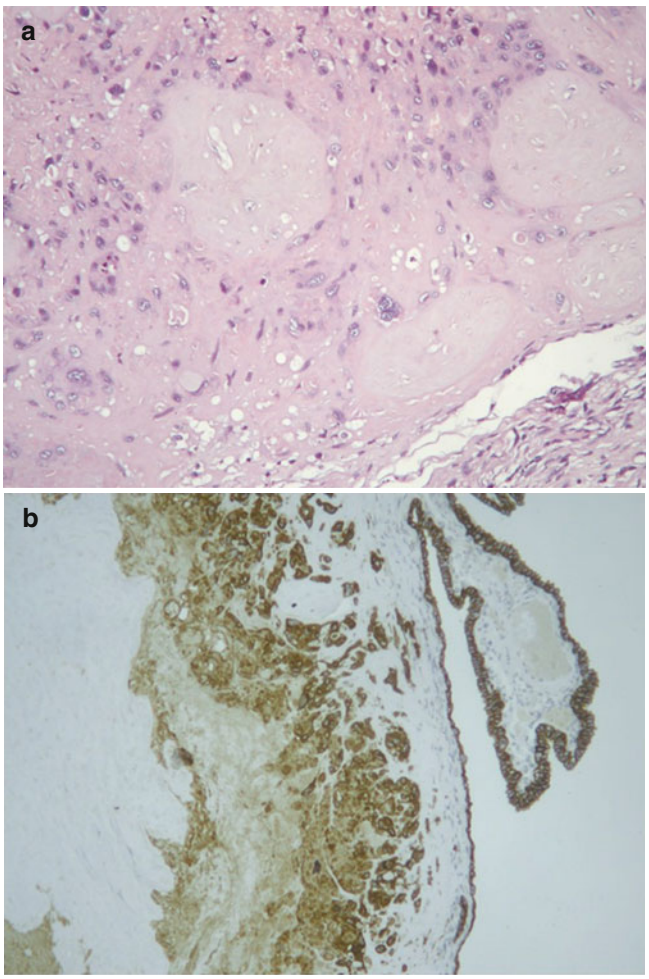

Fig. 9.15 Some case of the previous figure. At higher magnification (**a**) several cells with dark irregular nuclei are evident. These cells, in the tubal wall, were positive for the expression of cytokeratin (**b**). The present is an evident case of residuals of a previous unknown tubal pregnancy

9.2.12 Complete Hydatidiform Mole

The CHM is most commonly associated with vaginal bleeding, usually occurring at 6–16 weeks of gestation in 80–90 % of cases [8]. The other classic clinical signs and symptoms, such as uterine enlargement greater than expected for gestational dates, hyperemesis, and pregnancy-induced hypertension in the first or second trimester, occur less frequently in recent years due to earlier diagnosis and accurate hCG testing. Bilateral theca lutein cyst enlargement of the ovaries occurs in approximately 15 % of cases; hCG levels are often 100,000 mIU/mL, and fetal heart beats are absent [8, 31, 34].

9.2.13 Partial hydatiform mole

The PHM and complete mole are not characterized by the same features. More than 90 % of patients with PHM have symptoms of incomplete or missed abortion, and the diagnosis is usually given after a histological review of the curettage specimens. The main symptom is vaginal bleeding, which occurs in approximately 75 % of patients. Excessive uterine enlargement, hyperemesis, pregnancy-induced hypertension, hyperthyroidism, and theca lutein cysts rarely develop.

9.2.14 Gestational Trophoblastic Neoplasia

GTN has a varied presentation depending on the antecedent pregnancy event, the extent of the disease, and its histopathology. Postmolar GTN (invasive mole or choriocarcinoma) is usually associated with irregular bleeding after hydatidiform mole (HM) evacuation. Symptoms of postmolar GTN are an enlarged, irregular uterus and persistent bilateral ovarian enlargement. A metastatic vaginal lesion may occasionally be noted upon evacuation, which may cause uncontrolled bleeding. CC commonly preceded by non-molar gestation has no characteristic symptoms or signs and is mostly associated with tumor invasion of the uterus or with metastatic sites. The differential diagnostic code in patients with postpartum uterine bleeding and abnormal puerperal involution should consider GTN along with other possible causes, such as retained products of conception or endomyometritis, primary or metastatic tumors of other organ systems, or another pregnancy occurring shortly after the first. Bleeding resulting from uterine perforation or metastatic lesions may cause abdominal pain, hemoptysis, melena, symptoms of increased intracranial pressure from intracerebral hemorrhage or metastatic lesions [2, 35]. Patients may also have pulmonary symptoms, such as dyspnea, coughing, and chest pain, caused by extensive lung metastases. PSTTs and ETTs almost always cause irregular uterine bleeding, which usually occurs some time after a non-molar gestation; they rarely cause virilization or nephrotic syndrome as well. The uterus is usually symmetrically enlarged, and serum hCG levels are only slightly elevated [36, 37].

9.3 Diagnosis of Gestational Trophoblastic Disease

9.3.1 Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a placental heterodimeric glycoprotein composed of two dissimilar subunits (alpha, α, and beta, β) joined non-covalently. The alpha subunit resembles the pituitary glycoprotein hormones and the beta subunit is unique to trophoblast production. Regular hCG, hyperglycosylated hCG, and hyperglycosylated hCG-free β are widespread in GTD. These three molecules plus ten

degradation products constitute the 13 forms of hCG β-subunit present in the serum or urine samples. Ideally, total hCG tests should detect all of these hCG-related molecules to optimally monitor pregnancy, gestational trophoblastic diseases, and cancer cases. The hCG molecules in GTD are more heterogeneous and degraded than those in a normal pregnancy. Prospective studies in large patient cohorts are needed to define the role of hyperglycosylated hCG and hCG-free β in the management of gestational cancers. Automated radiolabeled monoclonal antibody sandwich assays measure different mixtures of hCG-related molecules [38]. They can detect hCG accurately at much lower concentrations by using modern automated tests and significant knowledge about hCG structure and its degradation process [39].

Hydatidiform moles (HM) are commonly associated with notably elevated hCG levels, above those of a normal pregnancy. Approximately 50 % of patients with a CHM have pre-evacuation hCG levels of 100,000 mIU/mL [2, 40]. PHM, however, are commonly not characterized by such elevated hCG levels, 100,000 mIU/mL in 10 % of patients [2].

Following the evacuation of a hydatidiform mole, a clinical diagnosis of postmolar GTN is often made based on the rising or plateauing hCG levels. CC is usually diagnosed by the finding of an elevated hCG level, usually together with the discovery of metastases following other pregnancy events. PSTT and ETT are commonly associated with slightly raised hCG levels.

Quiescent gestational trophoblastic disease is a term applied to a presumed inactive form of GTN, characterized by persistent, unchanging low levels (200 mIU/mL) of "real" hCG for at least 3 months. These are patients with a history of a hydatidiform mole, gestational trophoblastic neoplasm (GTN) or choriocarcinoma, or spontaneously aborting pregnancy but without a clinically manifested disease. In all cases, no disease is detectable either clinically or by sophisticated imaging. The hCG levels do not change with chemotherapy or surgery [41–47]. Yet, in most of the studied cases, the patient has been treated with a single-agent chemotherapy, when the hCG fails to decrease with polychemotherapy and/or hysterectomy or other surgery. The studies indicate that these patients have residual syncytiotrophoblast cells with no or very few invasive cytotrophoblast cells and, therefore, have an active disease [42, 43]. In 10–25 % of these quiescent GTD cases, the persistent hCG concentration changes and starts to elevate rapidly 5 months to 10 years after the finding of the persistent elevated hCG. In most of these cases, a tumor is later identified, with its pathology indicating CC or other GTN. This might suggest that quiescent GTD is a premalignant syndrome with malignant transformation occurring in a number of cases [43–46]. According to the International Society for the Study of Trophoblastic Disease in 2001, false-positive hCG resulting from heterophile antibodies or LH interference should be excluded in managing this condition. The patients should be thoroughly examined for disease symptoms; immediate chemotherapy or surgery should be avoided. They should be monitored over a longer period with hCG testing at regular intervals while avoiding pregnancy. Treatment should be undertaken only when there is a clearly clinically manifested disease or a sustained rise in hCG level [47]. The risk of GTN after the normalization of hCG was 0.34 % following an HM, 0 % after a partial PHM, and 0.36 % after a CHM [48].

9.3.2 Ultrasonography

Ultrasonography plays a significant role in detecting both complete and partial moles, particularly the transvaginal scan with the Doppler flow and three-dimension power Doppler imaging [49, 50]. A characteristic vesicular ultrasonographic pattern, consisting of multiple echoes (holes) within the placental mass and without fetus, can be observed because the chorionic villi of complete moles exhibit diffuse hydropic swelling.

A clinician skilled in ultrasound examinations is able to detect most first trimester complete moles (Fig. 9.16) [49]. An elevated hCG measurement at the time of sonography may help to differentiate an early CHM from a missed abortion [2]. Ultrasonography may also facilitate the early diagnosis of a PHM by showing focal cystic spaces within the placenta together with an increase in the transverse diameter of the gestational sac [2]. Changes in the shape of the gestational sac may be part of the embryopathy of triploidy. When both findings are present, the positive predictive value for PHM approaches 90 %. The ultrasound may also show the presence of a growth-retarded fetus with multiple congenital anomalies (Fig. 9.17) associated with a focally hydropic placenta [51].

9.3.3 Surgical Evacuation

Uterine cavity suction and curettage (Fig. 9.18), regardless of uterine size, is the most commonly opted method of evacuation in patients suspected of having an HM and wanting to preserve fertility [52, 53]. Women who are nulliparous should not be given prostanoids (Fig. 9.19) to ripen the cervix, since these drugs can induce excessive uterine contractions and might increase the risk of pulmonary embolization by trophoblast [54]. Hysterectomy is rarely recommended, but it might be considered for women who do not want to have more children or who have life-threatening hemorrhage (Fig. 9.20) [55]. Patients must be informed that although hysterectomy prevents the risk of local invasion, it does not

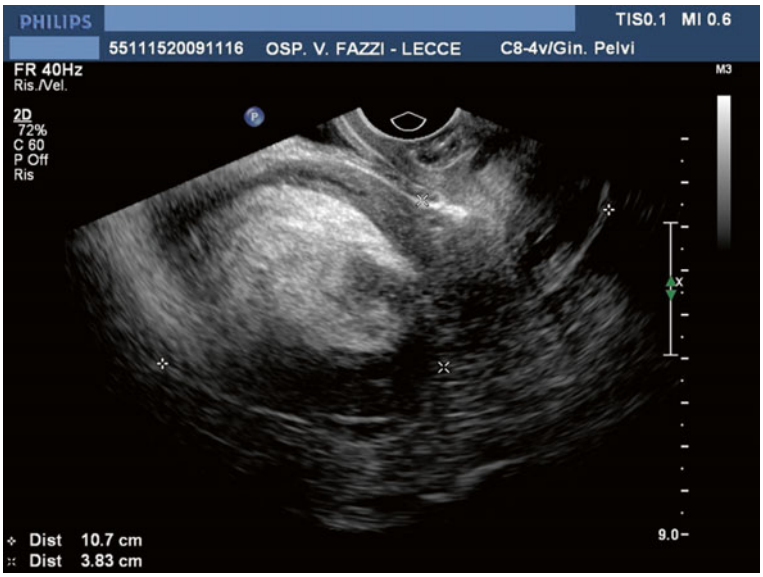

Fig. 9.16 A transvaginal uterine sagittal section of a pregnant uterus at 8 weeks with a completed mole, showed by a large hyperechoic area inside the uterus

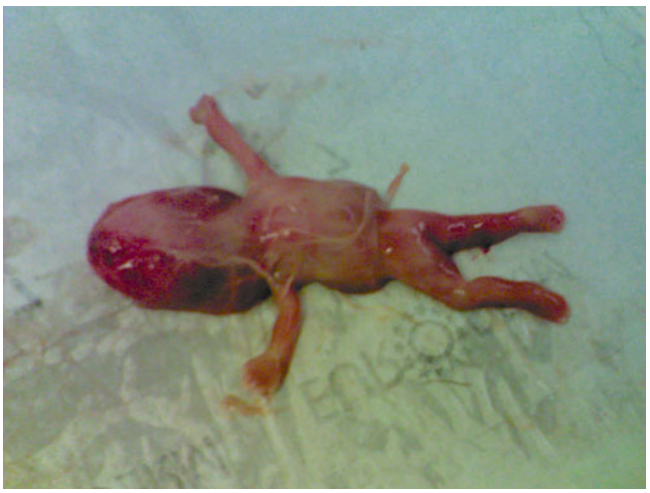

Fig. 9.17 A picture of a growth-retarded malformed fetus at 14 weeks in a pregnancy with a partial mole

eliminate potential need for chemotherapy and that the monitoring of hCG concentrations still needs to be done.

9.3.4 Gestational Trophoblastic Neoplasia Staging

Adequate staging and risk scoring systems are prerequisite for the proper treatment of patients with gestational trophoblastic neoplasia [56]. Staging and scoring systems are also important for comparing treatment results obtained from different centers, researching new chemotherapeutic drugs and treatment protocols, and assessing the prognosis, thus allowing multicenter comparisons and international trials. Such efforts would result in global improvement of both the survival rate and quality of life of the affected women.

9.3.5 Pretreatment Investigative Steps in Staging

Staging and scoring of a disease must be performed prior to GTN treatment [57]. This is essential for achieving optimal treatment results, as GTN is a highly curable disease even when widespread metastases are present [58, 59].

The basic checkup includes complete history and physical exam, pretreatment serum hCG testing, blood work including complete blood count and clotting function studies, and hepatic, renal, and thyroid function tests [57]. Pelvic examination is useful for identifying uterine enlargement and vaginal and pelvic metastases. Pelvic ultrasonography with a color Doppler can also be useful in identifying the site and size of the uterine tumor, the uterine wall involvement, and uterine volume. Furthermore, recent data suggest that Doppler measurements of the pulsatility index in the uterine arteries can predict the response to chemotherapy [7, 60]. Further investigation of metastasis includes a chest X-ray and abdominal ultrasonography [61].

Women who develop GTN following molar pregnancy are usually diagnosed early based on elevated hCG and do not require extensive investigation for staging [61]. In cases with elevated hCG following other types of pregnancy, a detailed investigation is required for staging purposes. Evaluation is performed by an abdominopelvic computerized tomography (CT) or magnetic resonance imaging (MRI) scans [61]. Approximately 40 % of patients with a negative chest X-ray have pulmonary micrometastases, which can be

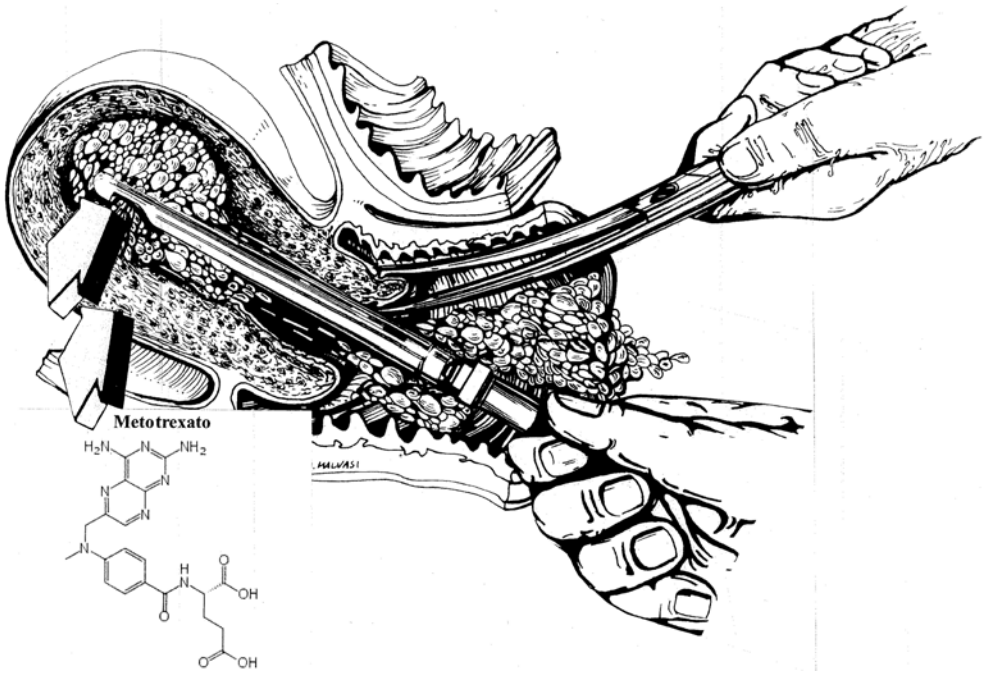

Fig. 9.18 The image represents a uterine cavity suction and its curettage, after MTX administration

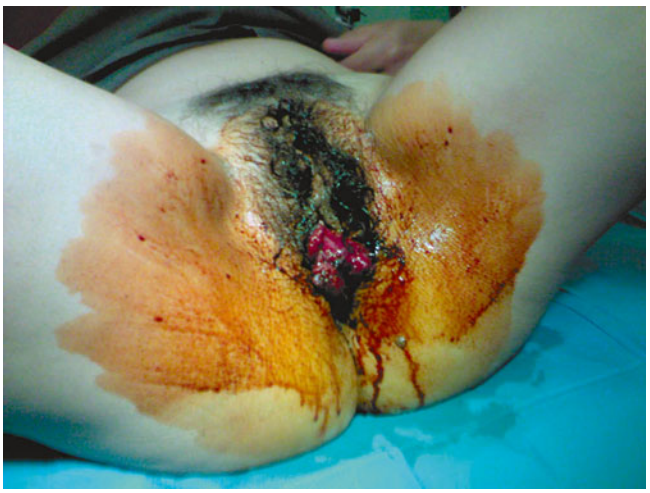

Fig. 9.19 A pregnant with two previous spontaneous deliveries who received prostanoids to stimulate spontaneous expulsion of a complete mole; she has been spontaneously ejecting the mole

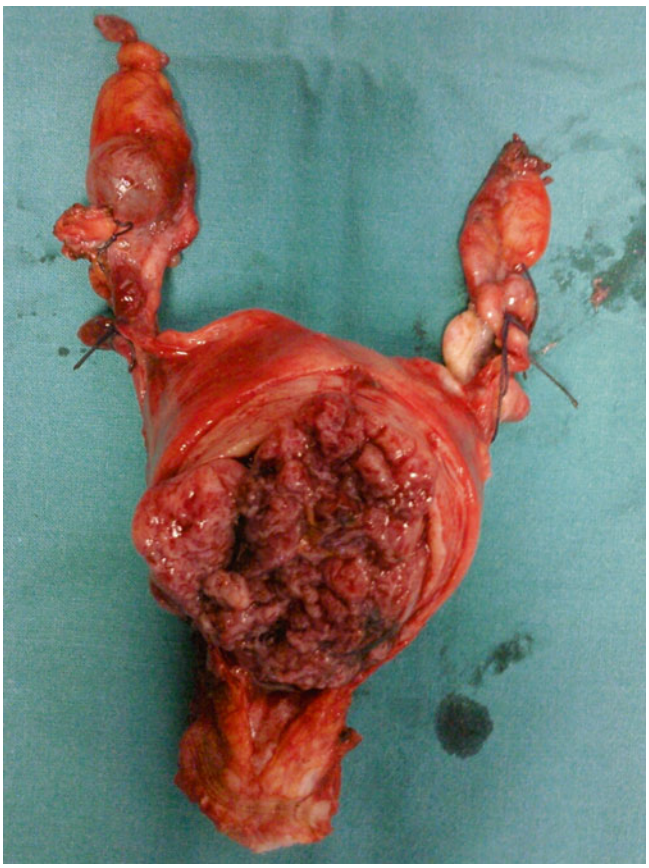

Fig. 9.20 A removed uterus with a complete mole at 9 weeks seen at longitudinal hysterotomy in a patient of 44 years with a familiar story of invasive cancers and personal history of ovarian borderline tumor

diagnosed with a chest CT scan, but its role in routine investigation is still debatable [3, 7]. When pulmonary and vaginal lesions and/or neurological symptoms are present, disseminated metastases can be expected, and this requires a brain MRI or a CT scan [7, 56]. Lumbar puncture and measuring hCG levels in the cerebrospinal fluid (CSF) can exclude cerebral metastases in patients with normal brain imaging, as the CSF/serum hCG ratio greater than 1:60 is indicative of a central nervous system (CNS) metastases [7]. The use of 18-fluorodeoxyglucose-positron emission

Table 9.1 The FIGO staging and risk factor scoring system for gestational trophoblastic neoplasia (GTN)

FIGO staging				
Stage I	Disease confined to the uterus			
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)			
Stage III	GTN extends to the lungs with or without genital organ involvement			
Stage IV	All other metastatic sites			
FIGO risk factor scoring				
FIGO risk factor scoring values	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy (months)	<4	4–<7	7–<13	≥13
Pretreatment serum HCG values (IU/L)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3–<5	≥5	–
Site of metastases	Lung	Spleen Kidney	Gastrointestinal tract	Liver Brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

tomography (18 FDG-PET) enables the identification of the active disease sites in cases of unexplained high hCG levels and determines the potential for tumor resection [7, 56, 62]. Furthermore, it can determine the viability of the persistent disease foci [56]. FDG-PET may be a useful tool in investigating the response to treatment in patients with recurrent or resistant GTN [62, 63]. Except in highly selected cases, biopsies of GTN lesions should be avoided because of pronounced risk of severe hemorrhage [3, 56].

9.3.6 GTN Stages and Scores

Following the investigation, it is possible to define the extent of the disease and the presence of risk scoring factors. In 1983, the World Health Organization (WHO) recommended a prognostic scoring system based on risk factors for treatment failure. The risk factors determining the prognosis are defined by numerical values [2]. The sum of these is used to determine each case, either as a low risk or high risk one. In 1982, the International Federation of Gynecology and Obstetrics (FIGO) introduced an anatomic staging system for GTN, classifying patients into four stages [2].

In 2000, FIGO adopted a revised GTN staging system together with the modified WHO's risk scoring system. It was officially published in 2002 [64]. Each patient's diagnosis is assigned to the stage representing the anatomic localization of the disease and to a risk factor score representing the sum of all the risk factors. The FIGO staging and risk factor scoring system for GTN is presented in Table 9.1. Thus, a Roman numeral for stage and an Arabic numeral for score are assigned to each patient. This system does not include hydatidiform moles, and the patients are staged only in cases of persistent hCG and GTN. The FIGO staging and risk scoring systems cannot be fully applied to PSTT and ETT [65, 66].

Patients with a score of 0–6 represent a low-risk group, while a high-risk group has a score of seven or higher [64]. Patients with stage I disease generally have a low-risk disease, while those with stage IV have a high-risk disease. Stage II and III patients are those in whom both high-risk and low-risk score distinction is applied.

9.4 Treatment of Gestational Trophoblastic Disease

9.4.1 Basic Principles

During the early 1970s, in the UK, three registration centers were established for patients with gestational trophoblastic disease (GTD) [3, 63, 67], resulting in the largest database worldwide. Due to disease rarity, such national centralization in pathology review, treatment, and monitoring of patients with GTD is advisable [3, 63]. In this manner, patients can be provided with adequate level of expertise and the best available treatment. Available treatment options for GTN are presented in Table 9.2.

9.4.2 Management of Complete or Partial Molar Pregnancy

In patients wanting to preserve fertility, dilatation and suction curettage (D&C) (Fig. 9.21), with fast fresh histopathological

Table 9.2 Available treatments for gestational trophoblastic neoplasia

Treatment	Definition
None	No treatment
Chemotherapy	Performed either as a prophylactic treatment or as primary treatment following D&C with residual disease (uterine or extrauterine)
Surgery alone	Only hysterectomy (because of GTN), with normalization of serum β-hCG levels, performed on patients who did not undergo chemotherapy before and/or after hysterectomy
Chemotherapy + surgery	Chemotherapy plus surgery (abdominal and/or pelvic surgery, craniotomy, lobectomy of the lung, etc.) with the intention to treat GTN. Chemotherapy can be given before and/or after surgery

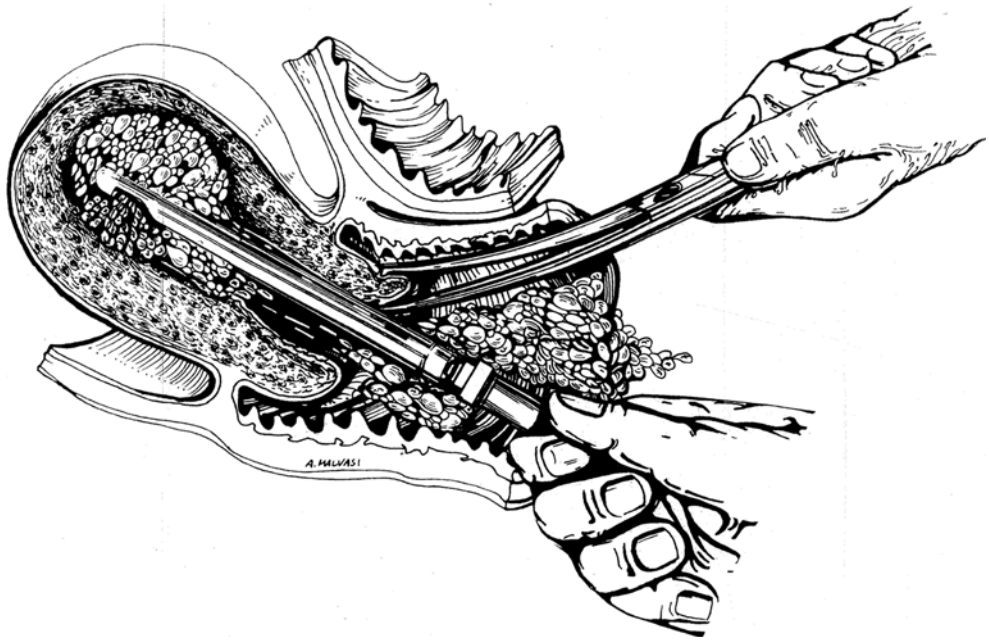

Fig. 9.21 A schematic representation of a dilatation and suction curettage (D&C) of a molar pregnancy by Karman cannula

examination of the specimens (Fig. 9.22), is the optimal method for evacuation [61]. The D&C preceded by the application of prostaglandins in the vagina (Fig. 9.23), better with ultrasound guidance, is the safest method of evacuating the uterine cavity, which minimizes the chances of uterine perforation [3]. Authors recommend more caution in this surgical procedure, as uterine perforation is always possible in every D&C procedure (Figs. 9.24 and 9.25). Sometimes, surgeons can remove directly molar pregnancy by using ring forceps and fingers (Figs. 9.26, 9.27 and 9.28). After D&C, the remaining residual trophoblastic tissue should be removed by gentle sharp curettage [8]. The use of oxytocin is advised in cases of severe bleeding [7]. Otherwise, its use is debatable, as oxytocin can raise intrauterine pressure, causing tumor embolism [61]. In Rh-negative women, Rh immune globulin should be administered at the time of suction [3]. Repeated D&C is not recommended due to risk of infection, hemorrhage, and uterine perforation [57, 63]; moreover, it will not eliminate the need for chemotherapy required because of myometrial invasion [3]. A second D&C may be needed only in selected cases when there is suspicion of a residual molar tissue after an ultrasound exam or due to vaginal bleeding. UK protocols recommend a second evacuation only in patients with a retained tissue when serum hCG is below 5000 mIU/mL [3, 7, 67]. Medical induction is optional in cases of a second trimester PHM, when surgical evacuation is technically not feasible. Otherwise, it is not recommended because of possible risks of trophoblastic tissue embolization, higher incidence of incomplete abortions, and increased likelihood for chemotherapy requirement [7, 68]. Hysterotomy is also not advisable, as it increases trophoblastic tissue dissemination and the development of postmolar GTN requiring chemotherapy, and it increases the cesarean section rate in subsequent pregnancies [8].

In women who do not wish to retain fertility, hysterectomy with the HM in situ is also an option, although it does not eliminate the need for chemotherapy [3]. Ovaries can be preserved following aspiration of the theca lutein cysts. In some cases, hysterectomy is required to control hemorrhage complications [68]. Women treated either way, including hysterectomy, need a serum hCG follow-up as the risk of postmolar GTN remains [8].

The issue of prophylactic chemotherapy with suction evacuation is debatable [8, 69, 70]. There are reports

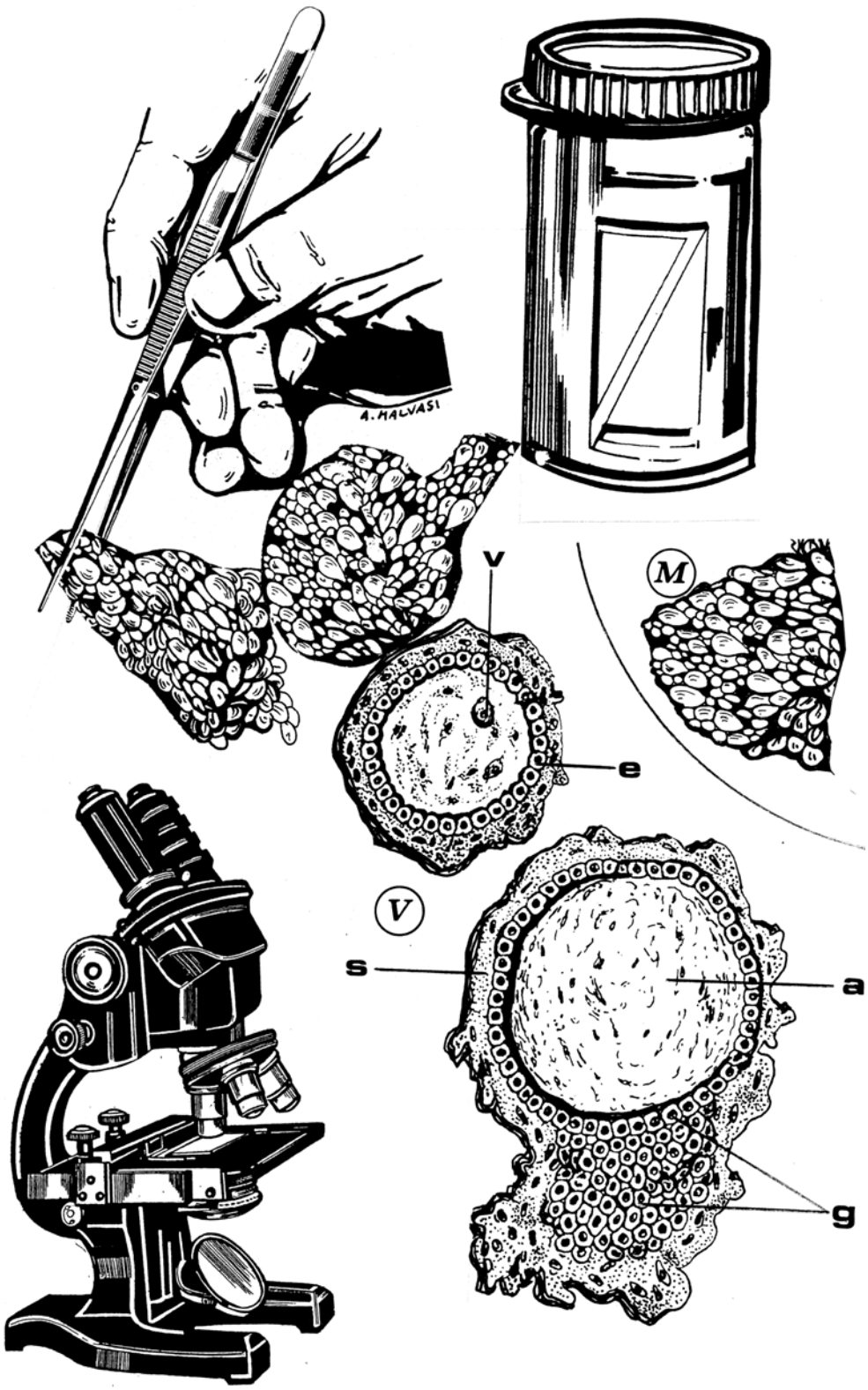

Fig. 9.22 A fresh histopathological examination of the specimens of a molar pregnancy, obtained by a D&C

indicating that chemoprophylaxis reduces the incidence of GTN from 3 to 8 % [8, 68]. However, Fu et al. [70] documented that patients who developed subsequent GTN are diagnosed later and require more chemotherapy cycles if they received prophylactic chemotherapy. Furthermore, such an approach would expose a large number of patients to cytotoxic chemotherapy, out of which a small number would develop GTN [61]. Hence, prophylactic chemotherapy is currently not recommended [70].

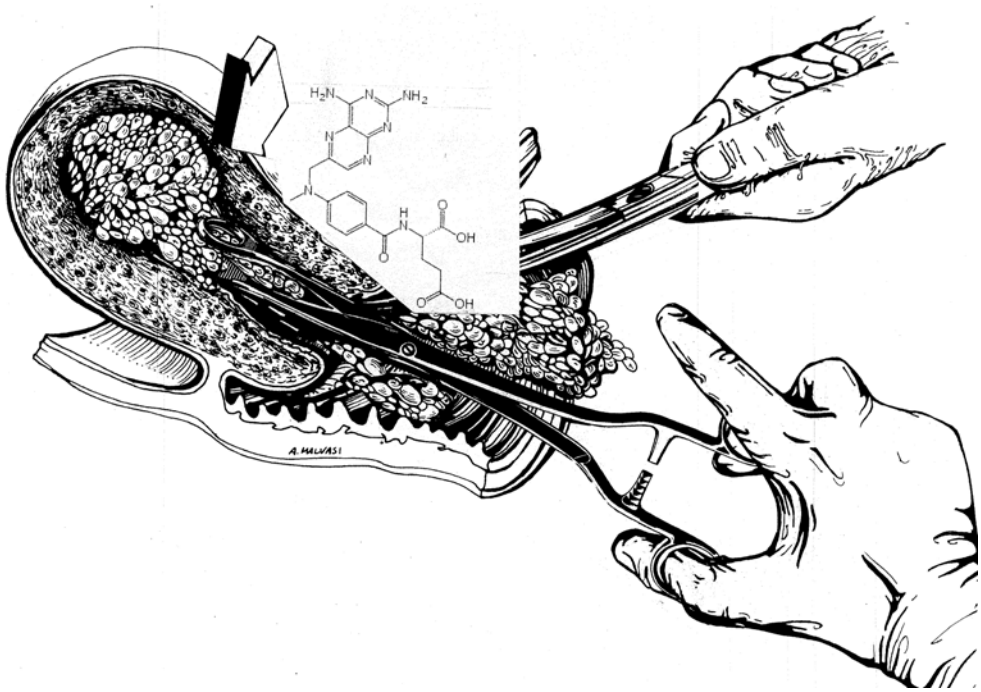

Fig. 9.23 A schematic representation of a molar pregnancy evacuated by Karman cannula introduced in the uterus after vaginal prostaglandin application

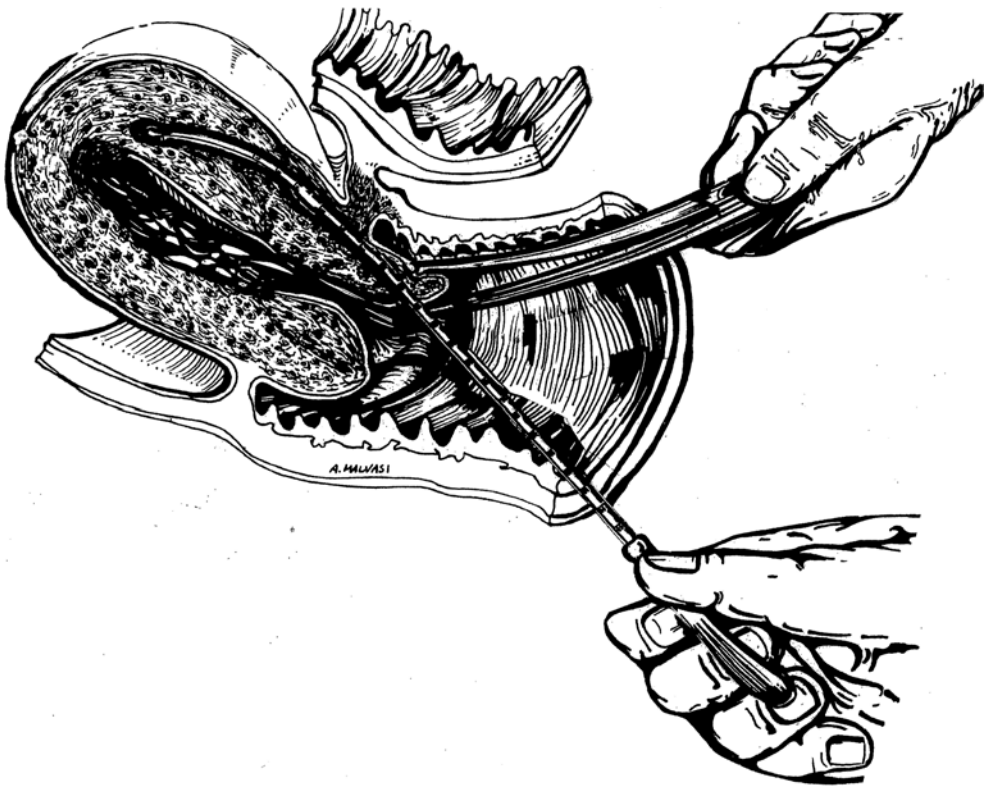

Fig. 9.24 A uterine perforation by hysterometer mistakenly introduced into the anterior uterine wall, in the myometrium, before a D&C

9.4.3 Management of Stage I GTN

The type of treatment in women with stage I GTN primarily depends on whether the patient desires future fertility. In patients who do not wish to retain fertility, hysterectomy with single-agent chemotherapy is a reasonable option, although it does not eliminate the need for chemotherapy [67]. Chemotherapy in such cases is useful for two reasons: the first being that it eliminates viable tumor cells that may have been disseminated during surgery and the other that it treats potentially present occult metastases. Literature data assert that chemotherapy is safe at the time of surgery and does not increase operative morbidity [56]. Fertility-sparing treatment implies local uterine resection with single-agent chemotherapy and can be applied in cases of well-circumscribed tumors.

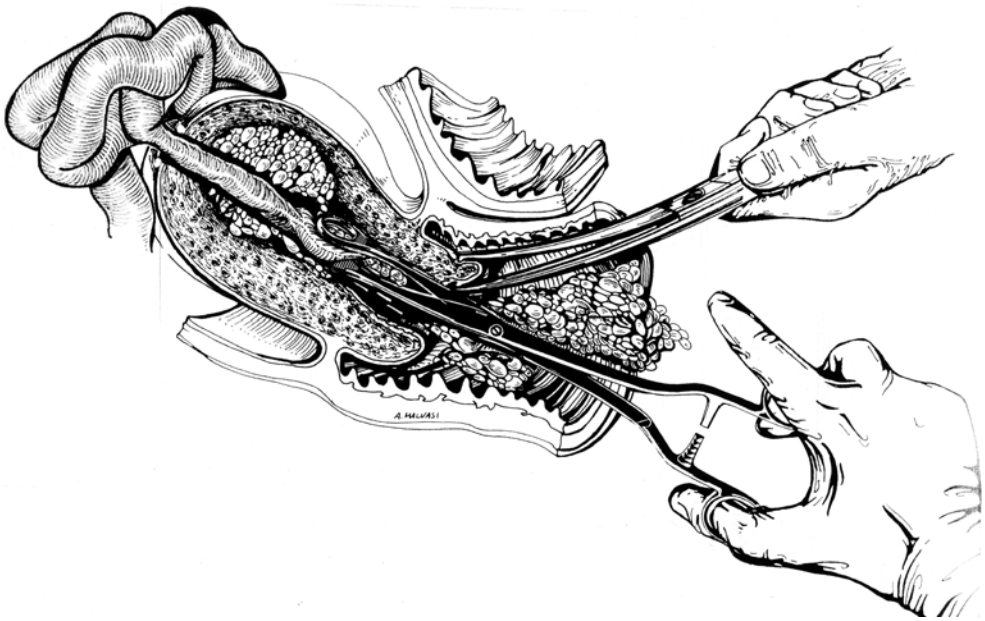

Fig. 9.25 Uterine perforation by ring forceps introduced in utero; the surgical forceps grasps the small bowel floating in the pelvis

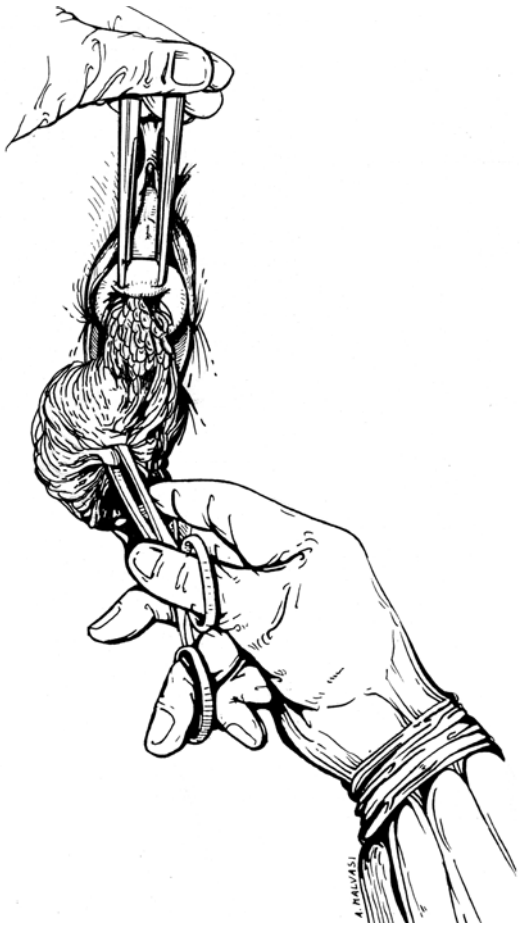

Fig. 9.26 The surgeon gently grabs, with the clamp ring, the molar pregnancy through the cervix, removing it by pulling it out of the uterus

9.4.4 Management of Stage II and III GTN

Depending of the risk scores, patients can be treated with single-agent chemotherapy in cases with low-risk scores or combination chemotherapy in cases with high-risk scores. Additional treatment options include hysterectomy, vaginal packing, arterial embolization, lung resection, and treatment of complications, mainly infection and hemorrhage [59, 61].

Hysterectomy is a reasonable option for reducing the uterine trophoblastic tumor load in patients with extensive uterine enlargement. Furthermore, it is necessary in patients with metastatic disease and complications, such as uterine perforation, hemorrhage, or infection [56]. Salpingo-oophorectomy is recommended in cases of theca lutein cyst complications [7]. Hysterectomy is also beneficial in patients with recurrent uterine disease. It also the treatment of chemoresistant tumors localized in the uterus, as well. In cases of a low-risk disease, hysterectomy can also contribute to the successful treatment with single-drug chemotherapy, as well as to fewer cycles and overall shorter duration of chemotherapy [56]. It proved to be safe both after and during the chemotherapy cycle, as it does not increase perioperative morbidity [56]. Furthermore, perioperative chemotherapy is useful for eradicating the possible dissemination of viable tumor cells during surgery [56].

In patients with vaginal metastases, profuse bleeding can be controlled by tamponade apposition [56]. When chemotherapy starts, lesions regress and bleeding is less likely. Hemostasis can be also achieved by angiographic embolization of the uterine or hypogastric arteries. This can only be performed in hemodynamically stable patients [7]. In settings where it is not possible, hysterectomy and arterial ligation are alternatives [61].

Lung resection is indicated in patients who are, overall, in good condition to sustain surgery, with single lung metastasis and no other metastatic sites and with controlled primary uterine malignancy and the hCG level below 1000 mIU/mL [56, 61, 71]. Such approach can improve remission rates. Thoracic surgery is also useful for curative resection of

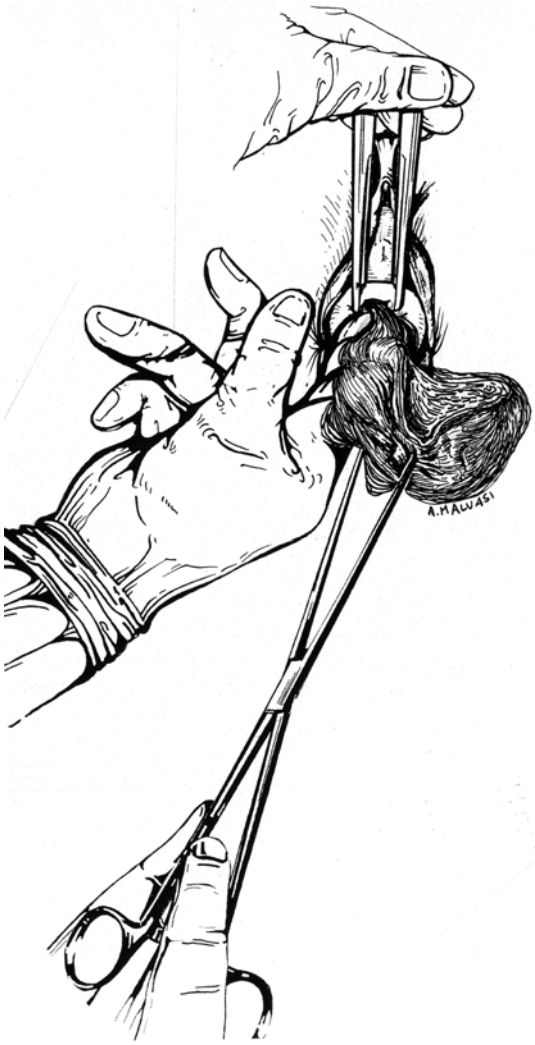

Fig. 9.27 The surgeon, keeping the molar pregnancy attached to the clamp ring, dilates the cervix by finger of the other hand, to facilitate the passage of molar pregnancy through the cervix

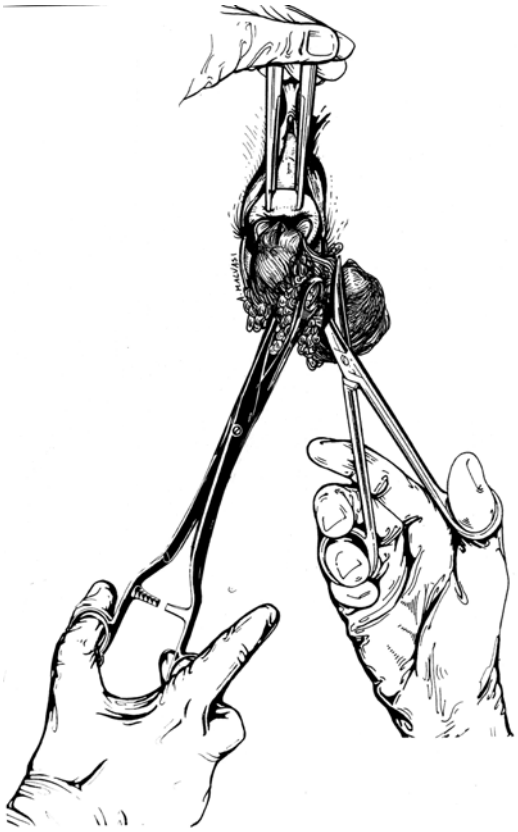

Fig. 9.28 During the removal of molar pregnancy through the cervix, the surgeon may also cut molar fragments as specimens for fresh histological analysis, by the pathologist

drug-resistant GTN foci [56, 67]. Nevertheless, the role of thoracotomy is limited, as most patients with lung metastases can be successfully treated with chemotherapy [56].

9.4.5 Management of the Stage IV GTN

These patients should be treated primarily with intensive polychemotherapy in combination with surgery and radiation therapy, if necessary. Unlike in cases with low-risk disease, hysterectomy does not improve the treatment outcome in patients with stage IV.

Optimal treatment for women with CNS involvement has yet to be established [35, 72]. Incidence of brain metastases ranges from 3 to 21.4 %, and these patients have low survival rates [72]. In cases with a disseminated disease, brain metastases are present in 90 % of patients [73]. CNS lesions can be treated by chemotherapy, either only by systemic chemotherapy or combined with intrathecal methotrexate (MTX) [72]. Apart from chemotherapy, brain metastases are treated with whole-brain irradiation or localized radiation, with metastasectomy and craniotomy to manage complications, such as hemorrhage and/or brain compression [7]. Irradiation has a dual role, both hemostatic and necrotic. In cases with multiple metastases, whole-brain irradiation is required, while solitary lesions can be treated locally. Metastasectomy is helpful in cases of superficial and solitary metastases and in cases resistant to chemotherapy [35]. Emergency craniotomy is necessary in cases with increased intracranial pressure caused by cerebral hemorrhage or edema [35, 72]. Cure rates reported in the literature for patients with cerebral metastases are 50–80 % [57]. Out of 101 patients treated in a single center over a 24-year period, 22 % had craniotomy which improved the prognosis [72]. The authors presented their experience in treating patients with brain metastases at Peking Union Medical College Hospital from 1990 to 2013. Patients with brain metastases were treated with polychemotherapy (fluorouracil/floxuridine, actinomycin D, etoposide, and vincristine). Their results assert that the disease can be cured and the patients have an overall 5-year survival rate of

Table 9.3 Indications for chemotherapy

Indications for chemotherapy	
hCG	Serum hCG levels above 20,000 IU/L more than 4 weeks after the evacuation
	Rising hCG levels
	hCG in body fluids >6 months after evacuation of molar tissue
Histology	Histological evidence of choriocarcinoma
Metastases	Evidence of brain, liver, or gastrointestinal tract metastases
	Radiological opacities >2 cm on chest X-ray
Hemorrhage	Long-lasting uterine hemorrhage following D&C
	Evidence of gastrointestinal or intraperitoneal hemorrhage

71.1 %, excluding early death cases. Prognosis is poor for those women with concomitant kidney metastasis and multiple site distant metastases and previous polychemotherapy failure history and who are over 40 years old with a FIGO score >12 [72].

Liver metastases are especially difficult to treat because of a pronounced risk of massive hemorrhage. In most cases, they can be successfully treated only by chemotherapy [56]. In highly selected cases, they are managed by hepatic resection and selective hepatic artery embolization [7, 56]. Seldom, liver metastases are simultaneously treated with radiotherapy and chemotherapy [7].

9.4.6 Principles of Chemotherapy

Chemotherapy is the first-line therapy for GTN [74]. Recommendations for its use are defined based on prognostic risk scores. According to the UK criteria, indications for chemotherapy are presented in Table 9.3 [67].

9.4.6.1 Low-Risk Disease

Low-risk GTN patients are those with stage I, II, and III cases with a FIGO score ≤6, and they usually respond well to single-agent chemotherapy [56]. Single-agent chemotherapy regimen applied in most GTN centers includes either methotrexate (MTX) or actinomycin D (ACTD) in various regimens [56, 57]. Most of the GTN treatment centers use MTX as the first line of therapy. In most patients with low-risk GTN, single-agent chemotherapy with MTX or ACTD is effective, well tolerated, and relatively safe and provides good results [63]. Literature data indicate that such an approach results in a remission rate of >90 % [57]. Those drugs are administered either at a fixed time interval or based on hCG regression curves [61]. Due to significantly higher toxicity, alternative drugs, such as etoposide and 5-fluorouracil, are rarely used as monochemotherapy in cases of low-risk GTN [7]. As ACTD is associated with much higher toxicity, most protocols include MTX with folinic acid (FA) rescue as the first line of therapy, with ACTD indicated only in patients who are not suitable for MTX, such as those with hepatic or renal dysfunction [56]. The most common side effects of MTX/FA include granulocytopenia, thrombocytopenia, rashes, stomatitis, and hepatotoxicity. According to the recent Cochrane review, ACTD treatment compared to MTX/FA has higher rates of primary cure and less treatment failure [75]. In patients with pleural effusions and large theca lutein cysts, it is also recommended to avoid MTX [57]. When patients become resistant to MTX/FA, they can be treated with ACTD, if hCG is less or equal to 100 mIU/mL, or with polychemotherapy if hCG is more than 100 mIU/mL [3]. In the UK, the cutoff level of hCG in such cases is 300 mIU/mL [3]. Polychemotherapy is advised for patients who develop a resistance to monochemotherapy. Approximately 20 % of low-risk patients will develop resistance to the initial chemotherapeutic drug [57]. Recent studies report that the uterine artery pulsatility index of ≤1 indicates an increased risk to MTX resistance in patients with low-risk GTN [60].

Patients with a recurrence of a low-risk disease, or MTX resistance, can be treated with ACTD or polychemotherapy, such as MAC (methotrexate, actinomycin D, and cyclophosphamide or chlorambucil) or EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine with folinic acid rescue) [7]. Etoposide is documented to increase the relative risk of later secondary malignancies [57]. Therefore, its use is reserved for cases with a high-risk metastatic disease, while in low-risk and nonmetastatic GTN patients, the MAC regimen is an acceptable option for polychemotherapy prior to regimens containing etoposide [61]. Approximately 10 % of low-risk patients will require polychemotherapy, with or without surgery, to achieve remission [57].

9.4.6.2 High-Risk Disease

Patients categorized as having high-risk GTN include those with stage II or III GTN and a FIGO prognostic score of ≥7 originally require treatment with polychemotherapy [56, 57]. There are various chemotherapy protocols used in treating a high-risk disease. However, accurate data on the efficacy and safety of these are still lacking [76]. In such patients, MAC protocol is insufficient, as cure rates are 63–71 % [56, 57]. In most centers, EMA-CO is the first-line regimen for the treatment of high-risk GTN due to its highest effectiveness-to-toxicity ratio [56, 63]. The documented side effects include mucositis, pleuritis, alopecia, liver damage, myelosuppression, and vincristine-associated peripheral neuropathy [7]. Still, 30–50 % of these patients develop resistance and require alternative treatments [61]. In such cases, it is crucial to recognize drug resistance, either by the plateauing or

rising hCG levels and/or by the appearance of new metastases. Other available protocols have also been recorded to be effective in GTN treatment [56]. Regardless of the chemotherapeutical agents used, it is essential to avoid treatment delays and dose reductions in order to reduce incidence of treatment failure and tumor resistance [56].

Both high-risk patients and those with resistant GTN requiring polychemotherapy must be treated with several cycles of chemotherapy to achieve remission. Response to chemotherapy is monitored by the serum levels of hCG [7]. Consolidation chemotherapy after hCG normalization is advisable in order to eradicate any residual disease foci [7]. It is advisable to administer two to four additional cycles of chemotherapy following three undetectable hCG levels [56]. Consolidation chemotherapy should be continued for 6 weeks after the normalization of hCG levels [3]. In patients with brain or liver metastases, therapy should be continued for 8 weeks [3].

Six weeks after the end of treatment, a detailed evaluation for persistent and recurrent GTN should be performed, and this should be repeated in 6 months [65]. Such evaluation includes a chest X-ray, a Doppler ultrasound of the pelvis, and either a CT or MRI imaging of all the disease sites. In cases of a recurrence in high-risk patients, aggressive polychemotherapy is recommended [58, 61].

Although the available agents have proven to be useful in GTN treatment, continuous scientific efforts are made in order to identify new drugs that would be active in cases when GTN becomes chemotherapy resistant.

9.4.7 Management of Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor

PSTT is a rare, slow-growing variant of trophoblastic tumor which imposes significant diagnostic and management difficulties. It was first described in 1976 [7]. Given the rarity of PSTT and its variable biological behavior, there are limited data regarding its optimal management and prognosis [77]. Most of the reported data are either case reports or small case series [65]. PSTT can present following any type of pregnancy with a long interval after an antecedent pregnancy [7]. Those tumors grow slowly, metastasize later, and produce less hCG. Tumors are commonly limited to the uterus, infiltrating the myometrium and spreading in the pelvis via lymphatics before systemic dissemination [7].

These tumors are relatively chemoresistant; therefore, surgery represents the most feasible treatment [63]. Hysterectomy, with or without ovarian conservation and pelvic and retroperitoneal lymph node dissection, plays a major role in PSTT treatment [63, 65]. A patient's age, family, and reproductive history influence the decision on oophorectomy [65]. The ovaries in premenopausal women can be preserved for possible future surrogate pregnancies, except in cases with ovarian involvement or in women with a family history of ovarian cancer [63]. Fertility-sparing options include focal resection of the affected part of the uterus in cases with limited myometrial involvement [7, 77]. Leiserowitz and Webb [78] presented a case of term live neonate cesarean delivery in a patient treated by local tumor excision and uterine reconstruction for anterior fundal tumor. On the other hand, Pfeffer et al. [79] documented the foci of PSTT in a hysterectomy specimen of a patient previously treated with fertility-sparing partial hysterectomy. The multifocal disease in their patient was missed by imaging, such as Doppler ultrasound, MRI, CT, and PET scan. In cases of incomplete resection due to multifocal microscopic uterine disease, hysterectomy and adjuvant chemotherapy are further treatment options [79].

Surgery alone is often effective for the treatment of stage I patients with PSTT [56]. There is no definite evidence regarding the benefits of chemotherapy in stage I and stage II patients [65]. Nevertheless, this combined treatment approach is recommended in the UK for patients with stage II disease [65]. In addition, it is recommended in cases with stage I disease, where there is the presence of risk factors for recurrence, such as a long interval after an antecedent pregnancy, vascular invasion, deep myometrial invasion, serosal involvement, high mitotic index, or the combination of these factors [65]. Surgery, if feasible, is also advised for a residual and metastatic disease, as well as for a recurrent disease [63, 65].

In cases of metastatic disease and in patients with positive hCG levels after surgery, polychemotherapy is necessary, either alone or in combination with surgery [77, 79]. Polychemotherapy protocols include EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), EP-EMA (etoposide, methotrexate, actinomycin D, cisplatin), and MAF (methotrexate, actinomycin D, etoposide) [65, 80]. It should be discontinued after 8 weeks of normal hCG [3, 63].

Patients diagnosed with PSTT should be exclusively managed in specialized centers with adequate level of expertise. Furthermore, such patients require a multidisciplinary treatment approach and teams of clinicians with expertise in managing GTN, consisting of gynecologists, medical oncologists, radiotherapists, and surgeons proficient in liver, brain, and thoracic surgery, as well as psychologists. The supportive care component must be included in the management of these women.

ETT was first described in 1998 [7]. It is the rarest type of GTN and reports are scarce [3, 56]. According to Davis et al. [81], the available data include a total of 108 reported cases, most of those being case reports. It is an extremely rare neoplasm derived from intermediate trophoblast and is frequently localized in the lower uterine segment or cervical canal [81, 82]. Its behavior is similar to PSTT [7]. Those

tumors are not chemosensitive and cornerstone treatment modality is surgery [7, 57, 82]. This is quite challenging, as those tumors are predominantly present in women of reproductive age [81]. Primary treatment modality for patients with intrauterine disease is hysterectomy [82]. If feasible, metastases are also treated surgically, by resection, i.e., lung resection and bowel resection [82].

9.4.8 Management of Chemoresistant and Recurrent GTN

Consolidation chemotherapy cycles are applied to avoid recurrence. Most recurrences happen in the first year of follow-up [63]. The risk of GTN recurrence is about 3 % in the first year after therapy completion, but later it is much lower [57]. Following initial chemotherapy, up to 25 % of GTN patients will develop resistance or recurrence, in which cases salvage chemotherapy, and in some instances, surgery is required [71, 83]. Reported recurrence rates range from 2.9 % for patients with stage I disease to 9.1 % for those with stage IV disease [56, 68]. Management of such patients requires a high level of expertise available in centers specialized for GTN treatment [57].

Risk factors for resistance and recurrence include advanced stage of the disease and high-risk score, an interval longer than 12 months between the antecedent pregnancy and the start of chemotherapy, high pretreatment hCG levels, histological diagnosis of choriocarcinoma, and undetectable serum β-hCG after seven cycles of chemotherapy and less than two cycles of consolidation chemotherapy [58, 71]. A significant risk factor for recurrence is also the patient's default from follow-up [58]. Recurrence after chemotherapy mostly occurs during the first 12 months of follow-up [67]. A great number of these patients can be cured with further chemotherapy [56].

Resistance to primary chemotherapy occurs in about 5 % of the patients with low-risk GTN without metastases and 10–15 % of those who have metastases [71]. For patients with a low risk of GTN, who become resistant to MTX, further treatment options include ACTD, followed by polychemotherapy with MAC or EMA-CO [71, 83]. ACTD is used in cases with low hCG levels (≤100 or ≤300 mIU/mL, depending of the institutional protocol), while in cases with higher levels polychemotherapy is used [71]. Due to increased risk of secondary malignancies in patients treated with etoposide, MAC is preferred over EMA-CO as the initial regimen [82].

Cases with high-risk GTN that develop resistance or recurrence are treated with various salvage polychemotherapy regimens, with or without surgery [71]. These chemotherapy protocols vary throughout the world [83]. These regimens mostly consist of etoposide or platinum in combination with bleomycin and isofosfamide [57, 58, 61]. In addition, surgery, when feasible, may also have an important role for these patients [2, 58, 61]. Both hysterectomy and focal uterine resection of the tumor mass are useful in cases of resistance [56]. Due to the heterogeneity of the cases, comparisons of these regimens in terms of efficacy and toxicity are difficult.

9.4.9 Psychological Counseling in Patients with Gestational Trophoblastic Disease

Women suffering from GTD are faced with significant psychological distress [56, 68]. However, data on health-related quality of life in those patients are limited [84]. The importance of psychological counseling is pronounced by high survival rates and overall excellent prognosis following chemotherapy. GTD jeopardizes both a woman's life and reproductive performance [85]. Forced delay in future pregnancies during the follow-up period potentially causes anxiety in these patients [85]. Marital and sexual problems could arise from the patient's perception of the nature of her disease inducing anger and guilt between patient and her partner. The negative impact of chemotherapy on these patients' sexual life is documented [84]. Furthermore, there is fear of possible side effects of chemotherapy, disease recurrence, infertility, and possible unfavorable outcome of a future pregnancy [84]. For all these reasons, approximately one-half of the affected women suffer from either physiological or sexual problems [68]. Hence, during therapy and follow-up, patients need emotional support from the medical staff and their family.

9.4.10 Follow-Up of Patients Treated for HM and GTN

Follow-up protocols vary depending on setting. Worldwide, different protocols for hCG surveillance are established with the same basic principles [63].

After the evacuation of molar pregnancy, remission is monitored with serial weekly hCG levels until non-detectable for 3 weeks. Further follow-up is performed with monthly investigation of hCG levels during a 6-month period [68]. During chemotherapy treatment, serum hCG concentrations are assessed twice a week, until hCG levels become normal [65]. Following normalization, hCG is measured once a week during consolidation chemotherapy cycles or at least once a week during 3 weeks [56, 74]. Further follow-up is conducted with monthly hCG assessment for 12 months, except in patients treated for stage IV disease, for whom this period is extended to 24 months [56]. In all stage patients, further checkups are advised every 6 months for the next 5 years [61]. Physical examinations are performed in

6–12-month intervals; other tests are rarely performed [57]. In the UK, follow-up with urine hCG assessments is continued for life [67].

After the normalization of hCG levels, women are advised not to get pregnant in order to allow efficient hCG follow-up. In cases of a molar pregnancy, this period is 6 months and in cases of GTD requires chemotherapy at least 12 months [65, 68]. During this period, reliable contraception including the use of low-dose oral contraceptives is strongly recommended [65]. The use of intrauterine devices is contraindicated, unless the hCG levels are normal [61]. Delayed conception allows the elimination of the mature ova that could have been damaged by exposure to chemotherapy [57]. In cases of pregnancies within 6 months after GTN treatment, the risk of miscarriage and stillbirths is increased [56].

The conception products of all future pregnancies should be histologically examined [61]. Following the completion of each future pregnancy, serum hCG level should be checked after 6 weeks and again after 10 weeks to exclude recurrence [63, 67].

9.4.11 Prognosis

In cases with CM, GTN may occur with a reported incidence ranging from 8 to 29 %, with an average of 15 % [58]. Following PM, 0.5–1 % of patients will develop GTN [3]. After D&C, hCG falls rapidly to normal levels in most patients with HM. In patients whose hCG levels become normal in up to 8 weeks following evacuation of the molar pregnancy, the occurrence of GTN is rare [8].

After a nonmetastatic and low-risk metastatic GTN treatment, the outcome is generally excellent. According to the FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer, the overall 5-year survival period of GTN patients is 97.3 % [64]. For stage IV disease, however, it is 62 % [64]. For the high-risk group of patients, the 5-year survival period is 79.5 %. It is important to underline that monitoring patients following a molar pregnancy would facilitate the diagnosis of GTN at an early stage, thus enabling prompt treatment and a survival rate of almost 100 % [64]. Stage IV disease is usually diagnosed in cases without a previous molar pregnancy, and it frequently is a choriocarcinoma. Therefore, choriocarcinoma should be considered in any women with symptoms of a metastatic disease of an unknown origin. This would facilitate a timely diagnosis in these patients.

The survival rate in patients with PSTT and ETT is approximately 100 % in women with nonmetastatic disease and 50–60 % in those with a metastatic disease [57]. Reliable data on optimum management, prognostic factors, and outcomes in women with PSTT are limited due to the rarity of the condition [65]. The overall prognosis is less favorable than in patients with other forms of GTN [65]. Patients with a recurrent disease have an unfavorable prognosis, with only 33 % achieving long-term remission [65].

Schmid et al. [65], in 2009, published the data on PSTT obtained in the UK. The study included 62 women treated over a 30-year period. Based on their findings, the overall 10-year survival period after the first treatment was 70 %, while recurrence-free survival was 73 %. Women with stage I disease had a 10-year overall survival rate of 90 %. The overall 10-year survival probability was 52 % for women with stage II disease and 49 % for stages III and IV. In cases with a recurrent or resistant disease, the prognosis was poor; approximately 22 % achieved a survival period beyond 60 months. The prognosis was worse for patients with a prolonged interval between the antecedent pregnancy and tumor development (over 48 months).

The data on survival and prognosis for patients diagnosed with ETT are mostly insufficient. The authors from the New England Trophoblastic Disease Center (NETDC) reviewed a case series of seven patients they treated for ETT [81]. They concluded that the most important factor for the poor prognosis is extrauterine disease. An interval greater than 4 years from an antecedent pregnancy is thought to be another possible marker for an unfavorable outcome. Conclusions on prognostic factors, treatment, follow-up protocols, survival rates, and incidence of recurrence are difficult to define due to insufficient data [81, 82].

The reported remission rates in women with chemoresistant and recurrent GTN are 52.6 % and 76.7 %, respectively [71]. The overall 5-year survival period for patients with GTN recurrence is 90 % [68]. In women with a recurrence of high-risk GTN, a 5-year survival rate is around 85 % [68].

Following treatment with etoposide-containing regimens, there is an increased risk of secondary malignancies, namely, acute myelogenous leukemia, colon cancer, melanoma, and breast cancer [57].

9.4.12 Fatal Outcomes

Although the overall survival of patients diagnosed with GTN is excellent, some of them die because of late presentation, complications, or drug resistance [3]. There are several risk factors associated with a fatal outcome of GTN. They include an antecedent non-molar pregnancy, high initial levels of hCG, choriocarcinoma, prolonged duration of the disease, multiple sites, and increased number of metastases and chemoresistance [66, 86, 87]. Causes of death described in the literature are hemorrhage, infection, multiorgan failure, or tumor lysis syndrome [66]. The incidence rate of early deaths, occurring within 4 weeks following the start of treatment, can be reduced with induction chemotherapy with a low dose of etoposide and cisplatin,

repeated weekly for one or two cycles in women with an extensive disease [66, 87].

Neubauer et al. [86] evaluated GTN with a fatal outcome at the Brewer Trophoblastic Disease Center in the USA. Out of a total of 443 women during the study period, 4 % with GTN died. Out of those, 95 % were treated for choriocarcinoma, while the remaining patients had PSTT. Non-molar index pregnancy was registered in 63 %. The causes of death included widespread chemoresistant disease, respiratory failure due to lung involvement, and fatal hemorrhage from the metastatic sites. The cited authors highlighted psychosocial factors as the contributing factors for unfavorable disease outcome, since 21 % of the women who died had delayed treatment due to psychosocial factors.

Lybol et al. [87] investigated 26 women who died from GTN over a period of four decades in the Netherlands. Early deaths occurred due to hemorrhage, sepsis, and pulmonary embolism. Patients who died after more than 4 weeks following the initiation of the treatment mostly died from metastases. Overall, 73.1 % of women died from metastatic disease. The most common cause of death was hemorrhage, either from the uterus or from metastases.

A recent analysis published by Bolze et al. [66] assessed the cases of fatal GTN from the French Center for Trophoblastic Diseases. The overall 5-year mortality rate after excluding PSTT and ETT cases in their series was 2 %. For PSTT and ETT, it was 7.6 %. A 5-year mortality rate in low-risk patients and high-risk patients was 0.3 % and 12 %, respectively. Women with a FIGO score of ≥13 represented 52 % of the fatal cases, and the 5-year mortality rate in those was 38.4 %. Therefore, they suggested a FIGO score of ≥13 as a criterion for defining the subgroup of GTN patients with increased risk of death. These patients should be managed in highly specialized centers capable of providing the necessary treatment and all the support measures, such as intensive care, interventional radiology, neurosurgery, and renal dialysis.

9.4.13 Persistent Gestational Trophoblastic Disease

Gestational trophoblastic tumors can develop after any type of antecedent pregnancy, most frequently after HM. Approximately 15 % of patients with complete HM and 0.5–1 % of patients with partial HM will exhibit persistent trophoblastic activity, which requires chemotherapy [61, 67]. This condition is defined as persistent gestational trophoblastic disease (PGTD) [67]. Most of these will have an invasive mole, while approximately 3 % will have choriocarcinoma or rarely PSTT or ETT [67]. The hCG regression curve serves as a reliable guide for chemotherapy administration, but can also be a means of identifying patients who are going to develop a persistent GTD [61].

Some patients develop PGTD after a non-molar pregnancy, i.e., non-molar abortions, ectopic pregnancies, or live births, and they account for approximately 17 % of the cases [58]. Differential diagnosis in these cases includes numerous primary non-gestational tumors with trophoblastic differentiation and hCG production, such as carcinomas of the bronchus, stomach, bladder, colon, etc. In these circumstances the genetic analysis of tumor origin is a valuable instrument for diagnosis, as the presence of paternal alleles reveal the gestational nature of the tumor [74, 88].

9.4.14 Management of Quiescent Gestational Trophoblastic Disease

Few GTD patients exhibit persistently low levels of hCG, without any clinical or imaging disease evidence [71]. They represent an entity called quiescent GTD [56, 71]. In these women, hCG levels are usually unchanged for at least 3 months, ranging from 50 to 100 mIU/mL [71]. Neither chemotherapy nor surgery leads to the normalization of hCG levels in such cases [71]. Patients with quiescent GTD can be identified by measuring hyperglycosylated hCG (hCG-H), which is present at very low levels or even undetectable [71]. Thus, it is a reliable tool for distinguishing GTN from quiescent GTD [71].

Patients with quiescent GTD and undetectable hCG-H should be monitored, and in most cases hCG levels will become normal within 6 months [71]. In 6–20 % of cases, over a period of several years, hCG levels will start rising, causing hCG-H to become detectable [56, 71]. When this occurs, chemotherapy will be required [71].

9.4.15 Twin Pregnancy with GTD

A healthy co-twin can develop alongside a complete or partial hydatidiform mole in 1 per 20,000–100,000 pregnancies [89]. In such cases, first a diagnosis by an ultrasound examination should be made. Amniocentesis is expected to aid the decision-making.

The complete hydatidiform mole with a coexisting fetus can be classified into three major types:

- Twin gestation, in which one twin is a normal diploid fetus with a normal placenta and the other twin is a complete hydatidiform mole without fetus
- Singleton gestation, consisting of a triploid fetus with partial hydatidiform mole placenta
- Twin gestation, in which one twin is a normal, diploid fetus with normal placenta and the other twin is a triploid fetus with partial hydatidiform mole placenta [90]

Categorization of the case is essential for proper management. The management of these pregnancies is difficult because they are usually associated with complications, such as fetal death, vaginal bleeding, preeclampsia, preterm delivery, and an increased risk of persistent GTD [91]. Some researchers recommended to terminate such pregnancies because of the low probability of a successful outcome and a high risk of developing a malignant disease [80, 91]. However, the results from a case series of 77 pregnancies suggest that about 40 % of women will deliver a healthy baby without an increased risk of malignant transformation of the complete hydatidiform mole [92].

Findings from a study of 2800 singleton molar pregnancies imply that late evacuation of complete hydatidiform mole is not associated with an increased rate of malignant disease [93].

Authors suggest that continuation of the pregnancy with complete hydatidiform mole and a coexisting fetus may be an acceptable option. Such pregnancies may continue until term if a normal anatomy is assured, and possible complications are under control. These patients require careful postpartum follow-up and any recurrent disease should be treated aggressively [94].

9.4.16 Risk of Repeat Gestational Trophoblastic Disease

Patients who had GTD are more at risk of having GTN after a subsequent normal pregnancy. Patients with previous GTD should undergo a detailed ultrasound exam in the first trimester of subsequent pregnancy to exclude a repeated molar pregnancy.

Eagles et al. [17] conducted a study of subsequent pregnancies in 16,000 women registered at Charring Cross Hospital in London during a 20-year period. Their results indicated that patients diagnosed with CM have a risk of repeated HM of 0.91 %, while those with PM have a lower risk of 0.28 %. In patients with CM, a second molar pregnancy was most likely to be the next one, while in those diagnosed with PM they found a history of live births and miscarriages before a second molar pregnancy. Out of 166 patients with a second HM, 22(13 %) had a third HM, most frequently CM. In this subgroup, FRHM was diagnosed in 11, which enabled the estimation that 1 in 640 of women diagnosed with CM has FRHM. FRHM is an autosomal recessive condition caused by mutation in either the NLRP7 or KHDC3L gene, predisposing women to molar pregnancies, although the absence of mutations in these genes does not exclude the diagnosis. Around 20 % of women affected with FRHM have possible mutations in some other genes that have yet to be identified [17]. These women, in order to achieve a normal pregnancy, should consider oocyte donation [17]. The presence of GTN requiring chemotherapy in this study was registered in 8.9 % of the patients following CM and 3.3 % of the patients diagnosed with PM.

9.4.17 Prognosis for Pregnancies After Molar Pregnancy and Gestational Trophoblast Neoplasia

It is generally accepted that patients with HM, either complete or partial, have later normal reproductive outcomes. Nevertheless, such patients are at increased risk of repeated molar pregnancy in future pregnancies [17]. After one molar pregnancy, the risk of developing HM in subsequent conception is 1–2 % [3, 67]. In patients who experienced two molar pregnancies, the risk is higher, and the reported incidence is 15–20 % [3, 67].

Most women affected with GTN are of reproductive age. Given the high overall current cure rate, fertility is an important issue for these women [57]. Approximately 7 % of the patients treated for GTN with chemotherapy will have secondary infertility [56]. In terms of subsequent pregnancies following GTN treatment, the prognosis is generally good, apart from the EMA-CO regimen bringing the menopause date forward by 3 years [3, 63]. Following chemotherapy, the overall pregnancy rate is more than 83 % [3], with term live birth rate over 70 % [68]. The incidence of congenital abnormalities is not higher [7]. There is no evidence showing the reactivation of the disease because of subsequent pregnancies [57].

Joneborg et al. [95] conducted a nationwide cohort study, including almost 3.7 million singleton births from the Swedish Medical Birth Register between 1973 and 2009. The authors investigated the risk of subsequent adverse maternal and neonatal outcome in women who had had HM. They did not find any association for pregnancy hypertension, placental abruption, and premature rupture of membrane (PROM). Surprisingly, women with a history of HM had a lower risk of preeclampsia. The same study found a minor but increased risk of low for gestational age (LGA) birth, preterm birth, and stillbirth.

Acknowledgment The authors thank Dr. Svetlana Milenkovic and Dr. Jasmina Atanackovic, histopathologists at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia, for their assistance in selecting photos.

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Assisted Reproductive Technique Complications in Pregnancy

10

Ioannis P. Kosmas, Constantina Tatsi, Stavros Sifakis, Avinoam Tzabari, Dimitrios Kiortsis, Ospan Mynbaev, Domenico Baldini, and Antonio Malvasi

10.1 Introduction

The sterility uses, currently, two techniques of treatment, the homologous insemination (Fig. 10.1) and intracytoplasmic sperm injection (ICSI) (Fig. 10.2). This chapter presents the complications of pregnancy after in vitro fertilization (IVF). These complications are presented as they arise during the process of ovarian stimulation (Fig. 10.3a, b). Mainly, meta-analytic studies have been used with priority, where available. The majority of complications during IVF or ICSI are presented as case reports. Differences have been observed in management options, especially the surgical management. Complications may be due to three main causes: pharmacologic stimulation, previous illnesses that complicate medical treatment, and surgical complications due to ovarian follicular pickup (Fig. 10.4). Pathophysiologic studies associated with these complications have been reported in a concise form.

10.2 Before IVF and During Patient Selection

10.2.1 Diseases That Pose Specific Risks in IVF Treatment

Severe mixed connective tissue disease (MCTD) mixes features of systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma) polymyositis, and a high titer of anti-ribonucleoprotein (RNP) antibody. Pregnancies of women with MCTD may be complicated by maternal disease flares, fetal loss, pregnancy-induced hypertension and preeclampsia, preterm delivery, and small-for-gestational-age babies with neonatal lupus. In case pulmonary hypertension (PH) develops, a significant cause of death in MCTD, it is an

In memory of Prof. Dimitrios Hassiakos, Aretaieion University Hospital, 1st Department of Obstetrics and Gynecology, Athens, Greece, a true inspirational leader in obstetrics and gynecology.

I.P. Kosmas, MD, MSc, PhD (✉)
Department of Obstetrics and Gynecology, Xatzikosta General Hospital, Ioannina, Greece

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia
e-mail: kosmasioannis@gmail.com

C. Tatsi, MD
Department of Obstetrics and Gynecology, Xatzikosta General Hospital, Ioannina, Greece
e-mail: con.tatsi@gmail.com

S. Sifakis, MD, PhD
Department of Obstetrics and Gynecology, University Hospital of Heraklion, Crete, Greece
e-mail: stavros.sifakis@yahoo.gr

A. Tzabari, MD, PhD
Department of Obstetrics and Gynecology, Medical Center Yoseftal Hospital, Eilat, Israel
e-mail: avinoamt@clalit.org.il

D. Kiortsis, MD, PhD
Department of Physiology, University of Ioannina Medical School, Ioannina, Greece
e-mail: dkiorts@cc.uoi.gr

O. Mynbaev, MD, MSc, PhD, ScD
Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia
e-mail: ospanmynbaev@crec.mipt.ru; ospanmynbaev@hotmail.com

D. Baldini, MD
Center for Medically Assisted Fertilization, MoMò Fertilife, Bisceglie, Italy
e-mail: dbaldini@libero.it

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_10

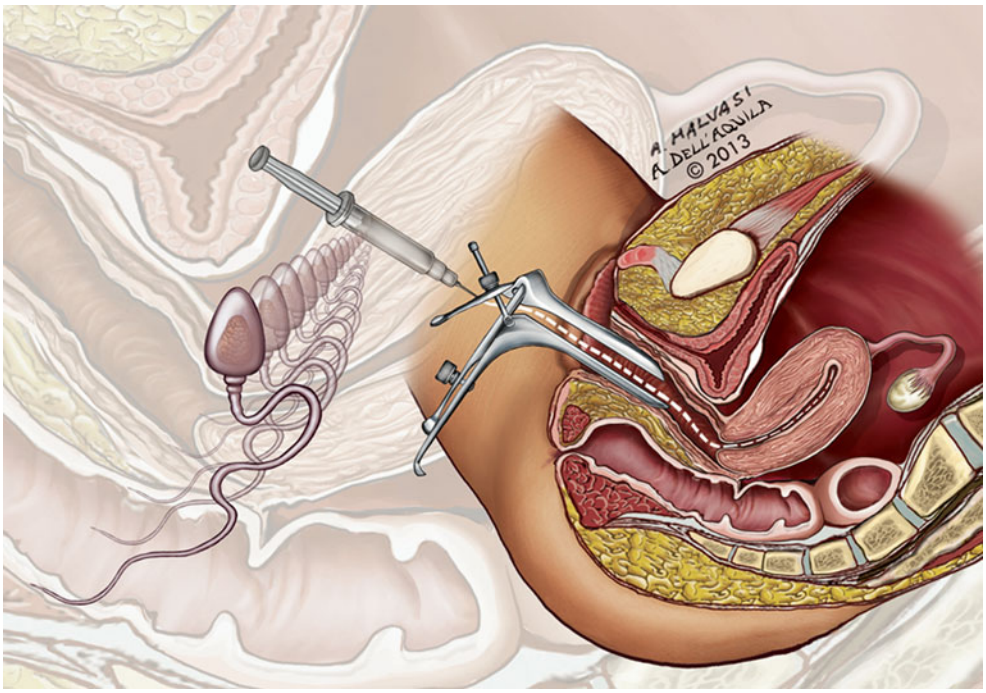

Fig. 10.1 The figure represents an intrauterine insemination

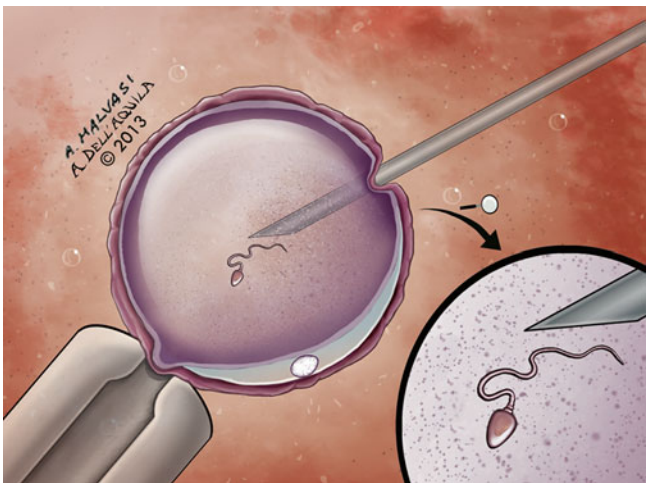

Fig. 10.2 The figure shows the intracytoplasmic sperm injection (ICSI) technique

absolute contraindication for carrying a pregnancy and in vitro fertilization and surrogacy are advised.

In a case, a 25-year-old woman referred to an IVF clinic underwent controlled ovarian hyperstimulation and embryo cryopreservation because she is planning autologous bone marrow transplantation. Her clinical situation was severe, with pulmonary hypertension and antiphospholipid antibody with a history of bilateral pulmonary embolism. She underwent mild ovarian hyperstimulation with a GnRH antagonist protocol and hCG trigger for final oocyte maturation. Two days after oocyte retrieval, she developed signs of infection, bibasilar atelectasia, and small pleural effusions. Obviously, in the pelvis, enlarged ovaries and moderate amounts of free fluid were observed. After 4 days, she developed hypoxia after multifocal pneumonia, hemoptysis, pulmonary hypertension, and fibrosis. Eventually, she developed ischemic colitis and left common femoral vein thrombosis. Because of prolonged respiratory failure, she had a tracheotomy. After 3 months of treatment, patient was discharged. The patient remained in stable condition for the next year and, at that time, had a spontaneous pregnancy that ended in miscarriage. After all these events, patient performed sterilization with laparoscopic bilateral tubal ligation and opted for a gestational carrier [1].

10.2.2 PCOS and Obstetric Complications After ART

Women with PCOS, after IVF, experience early pregnancy loss at a rate of 17 %, when compared with normally conceiving women at 15 %. Increased frequency of cervical incompetence has been found in pregnant PCOS women. In addition, PCOS women with CI were also more probable to have received gonadotrophin therapy, but it is still not recognized whether factors, like race and fertility drugs, play a part.

Likewise, women with PCOS, when pregnant, carry a significantly higher chance to develop gestational diabetes mellitus. A strong association between PCOS and preeclampsia has been established, and this is augmented by the fact that

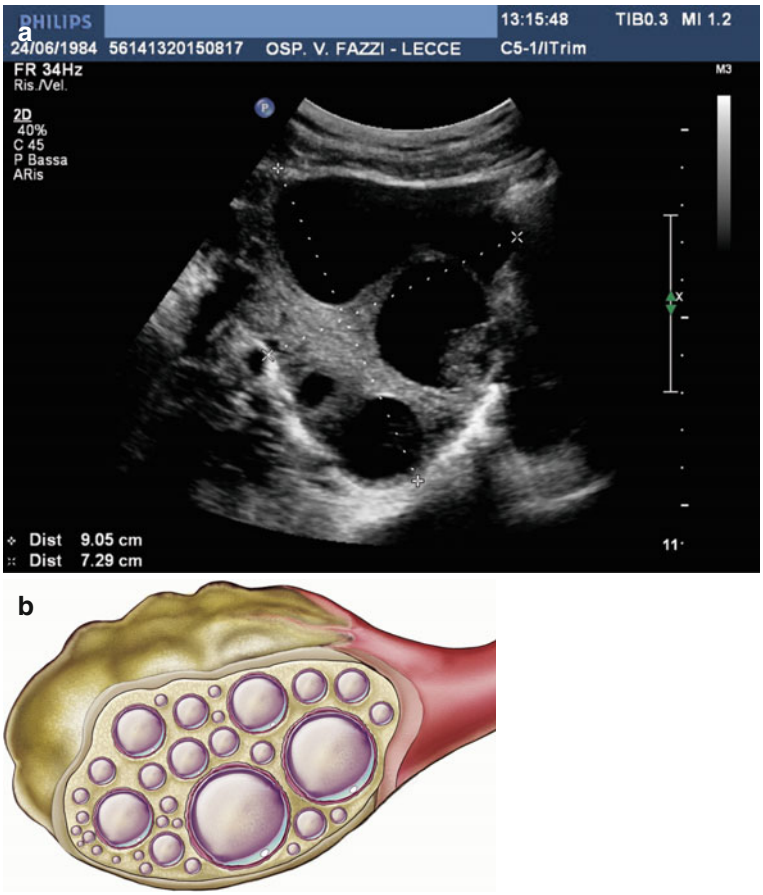

Fig. 10.3 (**a**, **b**) On the *left*, ultrasonographic transvaginal scan of an ovarian hyperstimulation; on the *right*, the corresponding draw

women undergoing ART have an increased risk of hypertensive disorders [2].

On the contrary, women on PCOS do not deliver small-for-gestational-age offspring, except secondary to pre-eclampsia. They usually deliver large-for-gestational-age babies, even in the absence of GDM.

Patients with the combination of PCOS and obesity have smaller oocytes [3]. Lean Chinese PCOS women present with higher clinical pregnancy rate after IVF than obese PCOS women of the same ethnicity [4]. Increased abdominal obesity is associated with increased lipid peroxide levels, and it is independent from PCOS but it is exacerbated by its presence [5].

10.2.3 Obesity and ART Pregnancy Complications

10.2.3.1 Maternal Obesity

Obese women are affected by metabolic syndrome (Fig. 10.5) and do not need higher FSH doses [6]. No significant difference has been found for euploid embryos, among overweight/obese women, when compared with normal weight women [7]. Also, pill administration for ovarian downregulation and follicle synchronization, in obese women, increases antral follicle count [8].

On the other hand, bariatric surgery that decreases BMI significantly reduces the amount of gonadotrophin needed; however, no other observed stimulation parameters change [9].

Overweight women with BMI between 25.0 and 29.9 kg/m^2 present with low offspring birthweight (<2500 g) [10]. Very early preterm birth is increased from maternal obesity [10]. The same applies for morbidly obese women (≥35.0 kg/m^2), both in singleton and twin pregnancies [11].

Obese poor responders, with BMI (≥30.0 kg/m^2), showed significantly lower fertilization and clinical pregnancy rates [12]. Metabolomic profiling from day 3 embryos culture media is different among obese and nonobese women [13]. In obese women, the number of COCs retrieved and MII oocytes are lower after IVF, but this does not apply to women with minimal stimulation [14]. It seems that oocyte mitochondria play a role [15] on obesity-related birth defects. With a mouse experimental model, fed with high-fat diet, maternal obesity is associated with oocyte meiotic aneuploidy and abnormal processes distinct from meiotic aneuploidy that both leads to early embryonic loss [16].

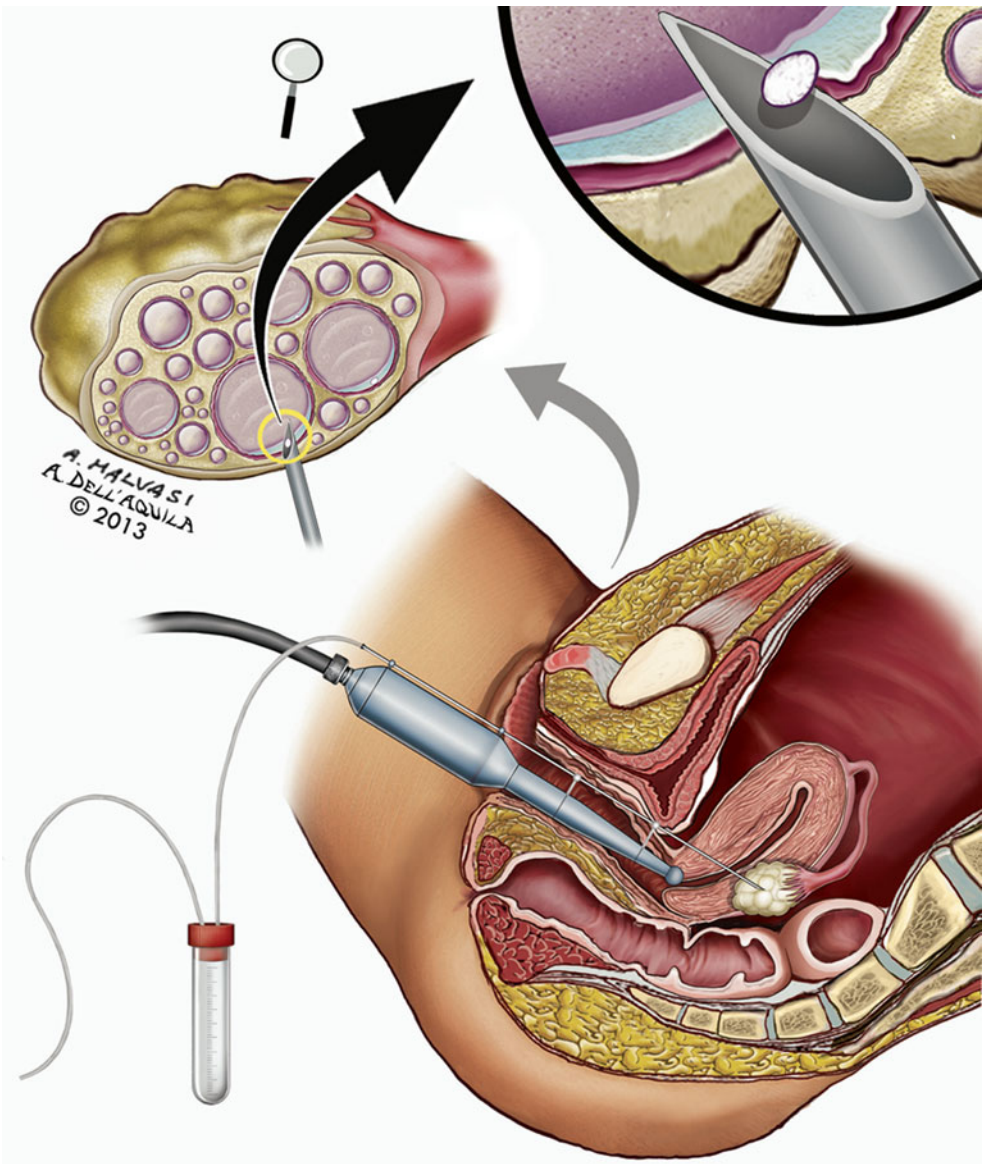

Fig. 10.4 An ovarian follicular pickup guided by transvaginal ultrasonography

10.2.3.2 Paternal Obesity

On the other hand, paternal obesity is associated with infertility (OR = 1.66, 95 % CI 1.53–1.79), reduced live birth per cycle (OR = 0.65, 95 % CI 0.44–0.97), and increased pregnancy embryo lethality [17]. Furthermore, offspring that came from high-fat diet mouse males and continues in the same diet shows a reduction in sperm motility, decreased sperm oocyte binding, and impaired overall parameters [18]. Preconception paternal obesity increases the incidence of metabolic disorders in offsprings [19]. Global methylation is significantly increased on female placentas that came from obese fathers [20], while preconception diet/exercise in these males normalizes sperm profile and metabolic status in female offspring [21]. Obviously, a lot more can be documented for obesity and IVF, but remains outside the scope of this chapter.

10.3 GnRH Downregulation and Ovarian Stimulation

10.3.1 Organ Dysfunction and Damage from GnRH Administration

10.3.1.1 Bowel Dysmotility

After GnRH analog downregulation, gastrointestinal complaints and bowel dysmotility have been described. In one study, the majority of patients experienced bowel dysmotility and suffered from endometriosis, while two patients have been homozygous for minor allele G, at the single nucleotide polymorphism. Another three patients expressed IGM antibodies against GnRH1 [22]. From animal studies, increased apoptosis of submucous and myenteric neurons in the fundus, ileum, and colon has been observed and possibly by

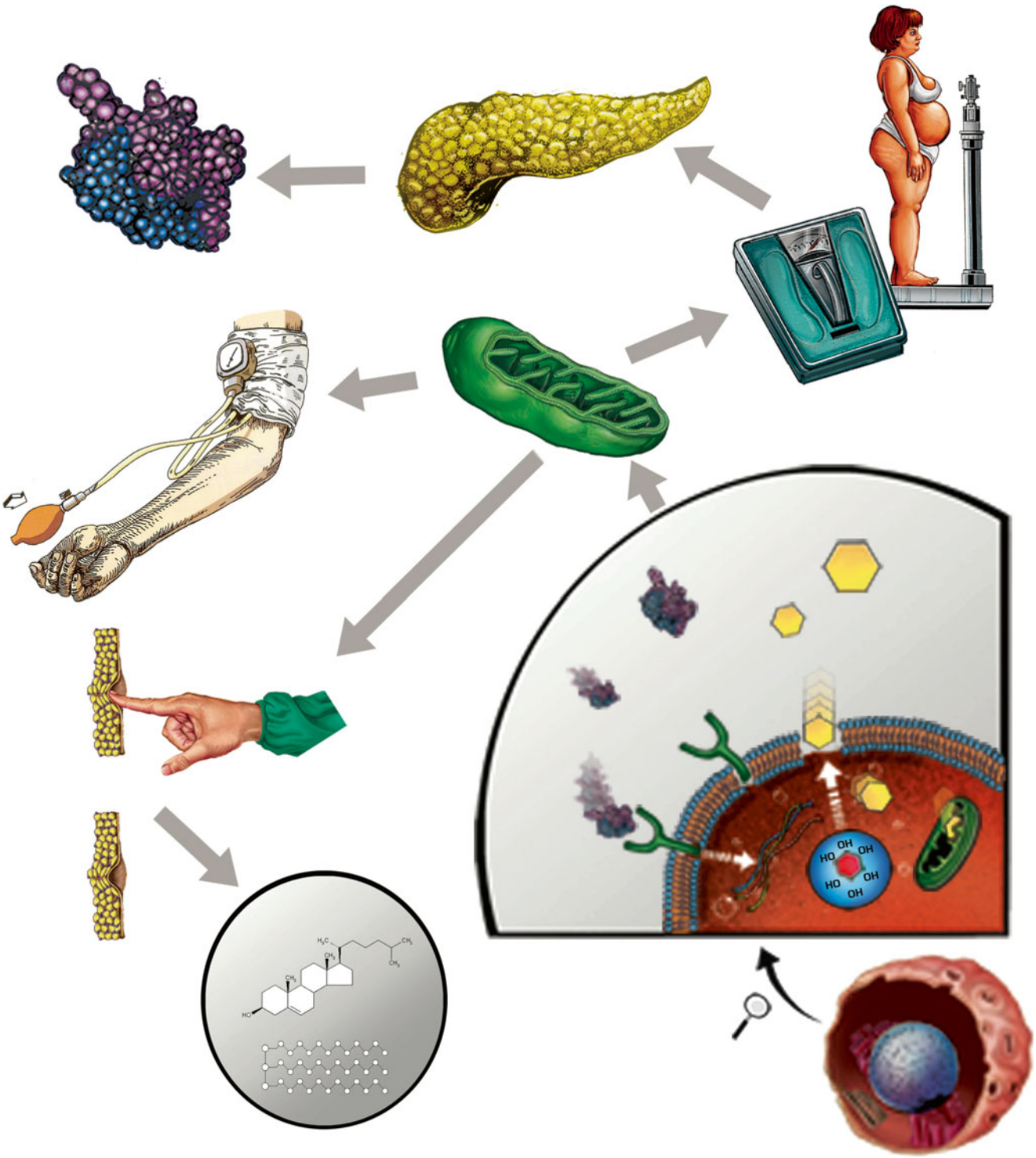

Fig. 10.5 Obesity is often associated with the metabolic syndrome: glucose intolerance, diabetes, hypertension, and dyslipidemia. Women with the metabolic syndrome to be submitted to ART are prepared with light therapy (inositol, secondary messenger of insulin)

neuron LH-receptor hyperactivation. These experimental data are associated with bowel dysmotility [23]. In humans, patients with dysmotility had depletion of gonadotrophin-releasing hormone (GnRH) receptors in the enteric nervous system (ENS) and serum antibodies against GnRH [24].

10.3.1.2 Bowel Obstruction

Small bowel obstruction, secondary to ovarian torsion after OHSS, has been observed at 12 weeks of gestation. Ovary was removed due to necrosis. Pregnancy viability was confirmed and patient discharged [25].

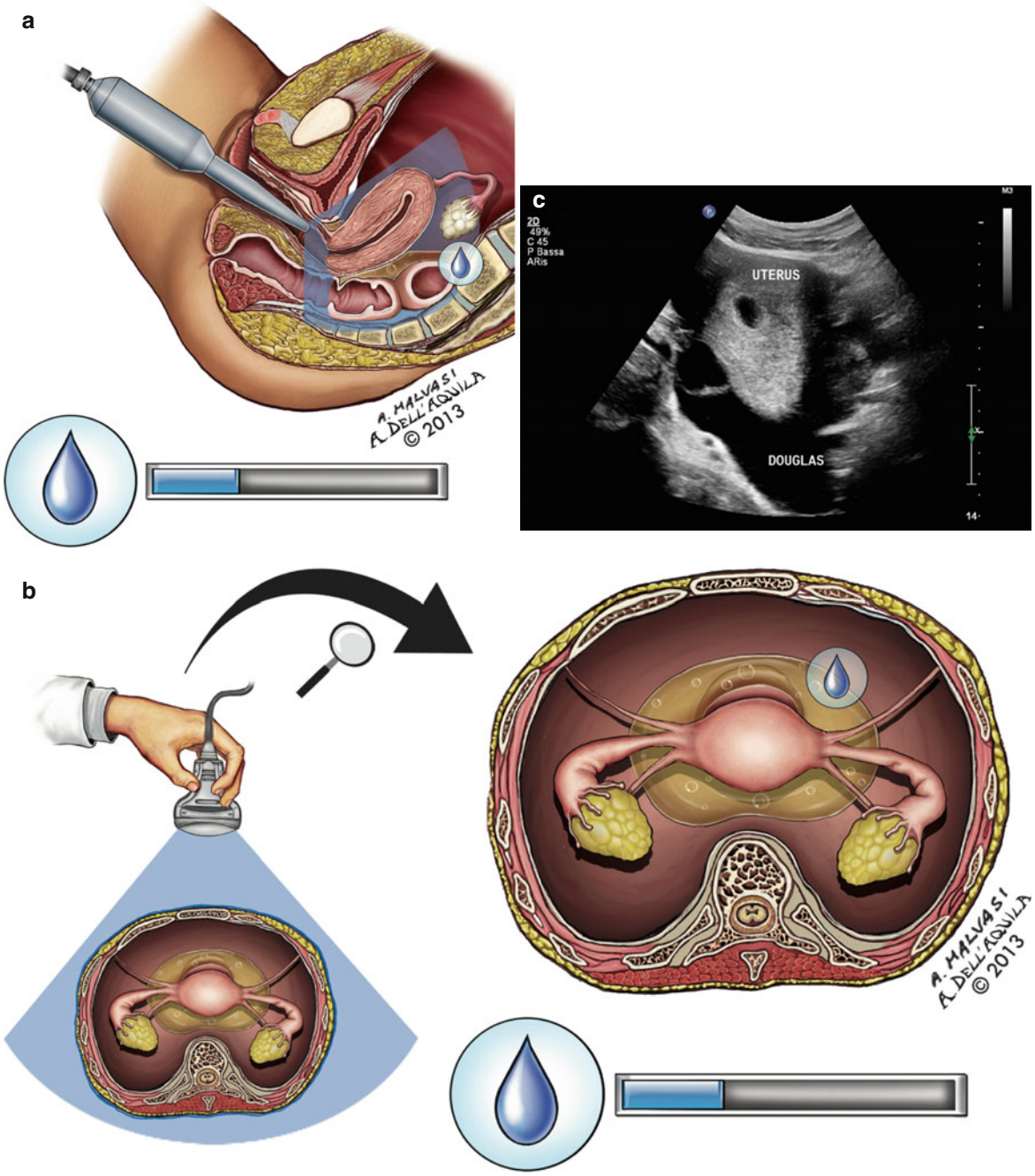

Fig. 10.6 (**a**, **b**) The mild ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

In another case, a 31-year-old woman after GnRH agonist administration and the flare-up effect revealed endometriosis recurrence from a deep endometriosis lesion, affecting the sigmoid and colorectal junction, eventually leading to bowel occlusion. Surgical resection of this laceration was necessary before treatment continuation [26]. A rare late complication from ileus has been reported after oocyte retrieval, at 28 weeks of gestation [27].

10.4 Ovarian Stimulation

The ovarian hyperstimulation syndrome (OHSS) is classified as mild, moderate, and severe, as American Fertility Society (AFS) reports:

1. Mild OHSS (Fig. 10.6a–c) is classified as follows:
Grade 1 – Abdominal distention and discomfort

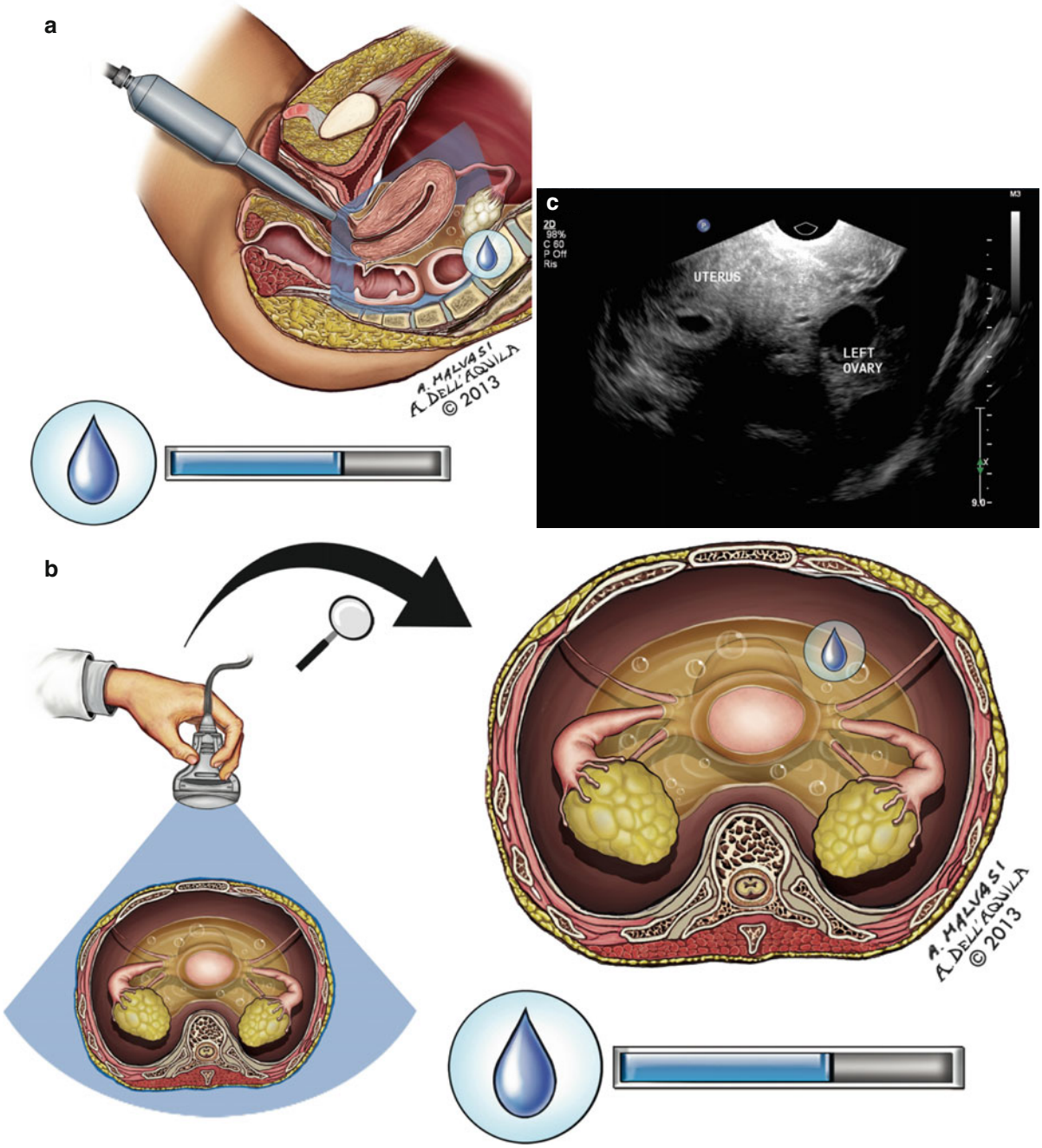

Fig. 10.7 (**a**, **b**) The moderate ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

Grade 2 – Grade 1 disease plus nausea, vomiting, and/or diarrhea, as well as ovarian enlargement of 5–12 cm

2. Moderate OHSS (Fig. 10.7a–c) is classified as follows:

Grade 3 – Features of mild OHSS plus ultrasonographic evidence of ascites

3. Severe OHSS (Fig. 10.8a–c) is classified as follows:

Grade 4 – Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties

Grade 5 – All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function

10.4.1 Ovarian Stimulation Neurological Symptoms

A 21-year-old woman underwent ovarian stimulation. The first day after oocyte retrieval, difficulty in speaking, mild disorientation, motor aphasia, and right-sided hypoesthesia

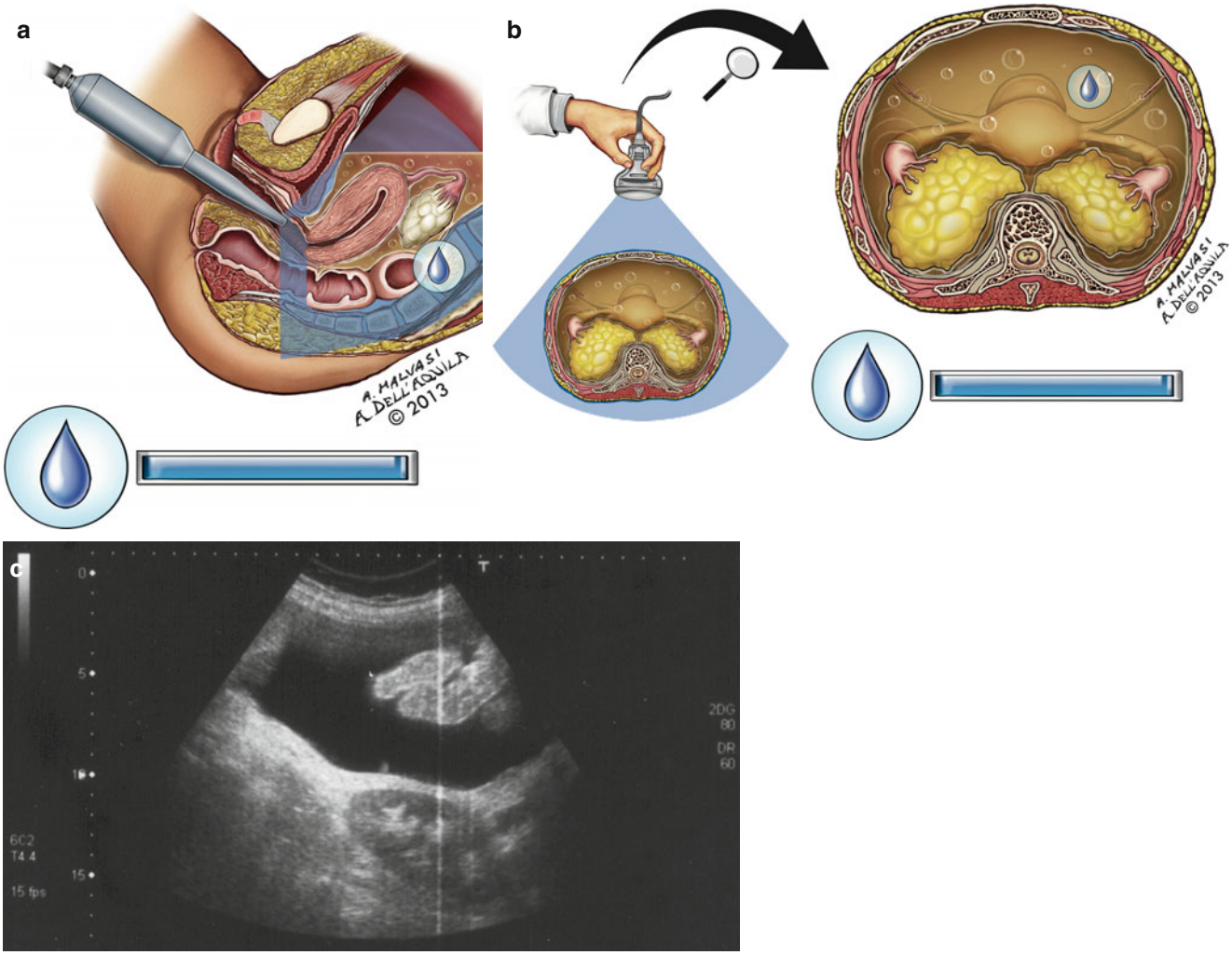

Fig. 10.8 (**a**– **c**) The severe ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

were noted. Brain-computed tomography scanning without contrast, magnetic resonance imaging (MRI), MRI angiography (MRA), and perfusion MRI were performed and showed left parietal lobe infarct with an infarct of the posterior division of the left middle cerebral artery (MCA). Patient recovered within 8 months and had a spontaneous pregnancy after 1 year. She had a vaginal delivery at 38 weeks of gestation. Ovarian hyperstimulation syndrome was not evident [28]. Another patient developed ischemic stroke after receiving clomiphene citrate and gonadotrophins [29].

More cases of thrombosis exist in the presence of ovarian hyperstimulation syndrome (OHSS). These case reports present with infarction as they have developed ovarian hyperstimulation syndrome. Main reason for arterial and venous occlusion is the hemoconcentration from the large fluid passage from the intravascular to the peritoneal cavity and subsequent increased blood viscosity.

In the first case, a female with OHSS presented with ischemic stroke due to right middle cerebral artery (MCA) occlusion. Eventually, left central hemiparesis occurred suddenly within a few days after the ET. She had magnetic resonance imaging diffusion-weighted images and a magnetic resonance angiography (MRA) that showed infarction in the right basal ganglia and revealed the occlusion of the M1 segment of the right MCA. She started the treatment, and 24 h after the stroke onset, MRA showed MCA recanalization. As a good prognosis patient, the neurological deficit resolved completely within 3 months. Eventually, she delivered two healthy infants at term [30].

The second case, after IVF, presented with sudden onset of left hemiplegia. CT scan showed a full thickness right MCA territory infarct, while a repeat MRI showed hemorrhagic conversion of infarct [31].

In the third case, a patient was already hospitalized, because she suffered from nausea and progressive abdominal distension, 8 days after ET, and all signs of ovarian hyperstimulation syndrome. She showed some improvement whereas she was treated with hypertonic solution, albumin

infusion, and paracentesis. Unfortunately, 11 days after ET and on the 4th day of hospitalization, she suddenly developed left hemiparesis, and dysarthria occurred. She progressed to complete hemiplegia within a few hours. Computed tomography and magnetic resonance angiography showed infarction of the right middle cerebral artery and occlusion of the main trunk of the right middle cerebral artery. Unfortunately, clinicians had to terminate the pregnancy because of progressive tachycardia, dyspnea, and increased abdominal girth despite supportive treatment. The neurologic deficits remained stationary at the time of discharge [32].

A 26 year old patient undergoing hMG/hCG therapy presented with multiple cerebral infarctions associated with ovarianhyperstimulation syndrome. She showed hemoconcentration, increased plasma levels of D-dimer and thrombin-antithrombin III complex, and decreased protein S activity, a hypercoagulable activity that is the base for thromboembolic events [33].

10.4.1.1 Early Diagnosis of Neurological Thromboembolic Events

Cerebral infarction associated with mild neurologic deficits may be overlooked in patients with ovarian hyperstimulation syndrome. Immediate recognition of neurologic symptoms will lead to treatment of thrombosis and brain damage minimization. On the other hand, clinicians should be aware that thrombosis may arise without ovarian hyperstimulation syndrome.

10.4.2 Ovarian Stimulation Psychiatric Symptoms

Psychotic symptoms have been described, after mild ovulation induction with clomiphene. Certain cases have been presented with transient psychosis after stimulation with a combination of clomiphene and bromocriptine [34]. The majority of them have a previous history of psychiatric disorders.

In a specific case, a 32-year-old woman developed symptoms 3 days after the start of the stimulation. On the next day, the patient had pronounced changes in her personality. Further, in the course of treatment, severe rational thought disturbances and perceptual and sensory deceptations arose. The patient was admitted to the psychiatric ward. From her medical history, it was evident that the patient had a history of psychic instability in stressful situations. After symptoms ceased after several weeks, treatment continued with human menopausal gonadotrophin plus hCG, without any psychiatric symptoms, at this time [35].

From the previous case reports, it is evident that previous psychiatric history should be taken into account, before starting ovarian hyperstimulation. In addition, rapid changes of estrogen levels due to clomiphene treatment may lead to an increased sensitivity of dopamine receptors [36].

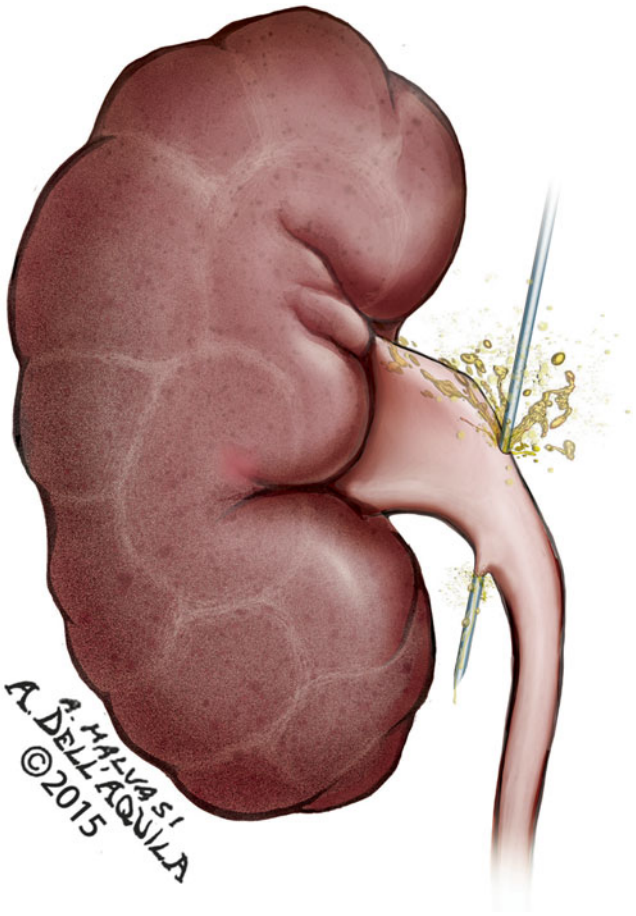

Fig. 10.9 The image shows a ureteral accidental injury during ovarian pickup

10.5 Oocyte Retrieval

10.5.1 Trauma During Oocyte Retrieval

10.5.1.1 Ureteral Injury

Ureteral injuries are rare (Fig. 10.9), but they are more possible in patients with ectopic kidney (Fig. 10.10a, b).

A 26-year-old patient presented, after oocyte retrieval, with acute pain and mild OHSS. Using computed tomography, it was found a right pelvic-ureter lesion. A right ureteral stent was placed. Patient delivers a healthy baby [37]. Another patient had a ureteric injury after OPU and treated also with ureteral stents. Stent was inserted in the next oocyte retrieval and better ureteral visualization was allowed, thus avoiding a repeat injury. A pregnancy occurred [38].

A 34-year-old patient received her second IVF attempt and 19 oocytes were retrieved after OPU. After 7 days, she presented with right lower quadrant pain. Using abdominal/pelvic computerized tomography, right hydronephrosis and mild hydroureter were found. Patient underwent cystoscopy and right ureteroscopy. Scope could not pass beyond 1 cm of the ureterovesical junction. A thrombus with underlying

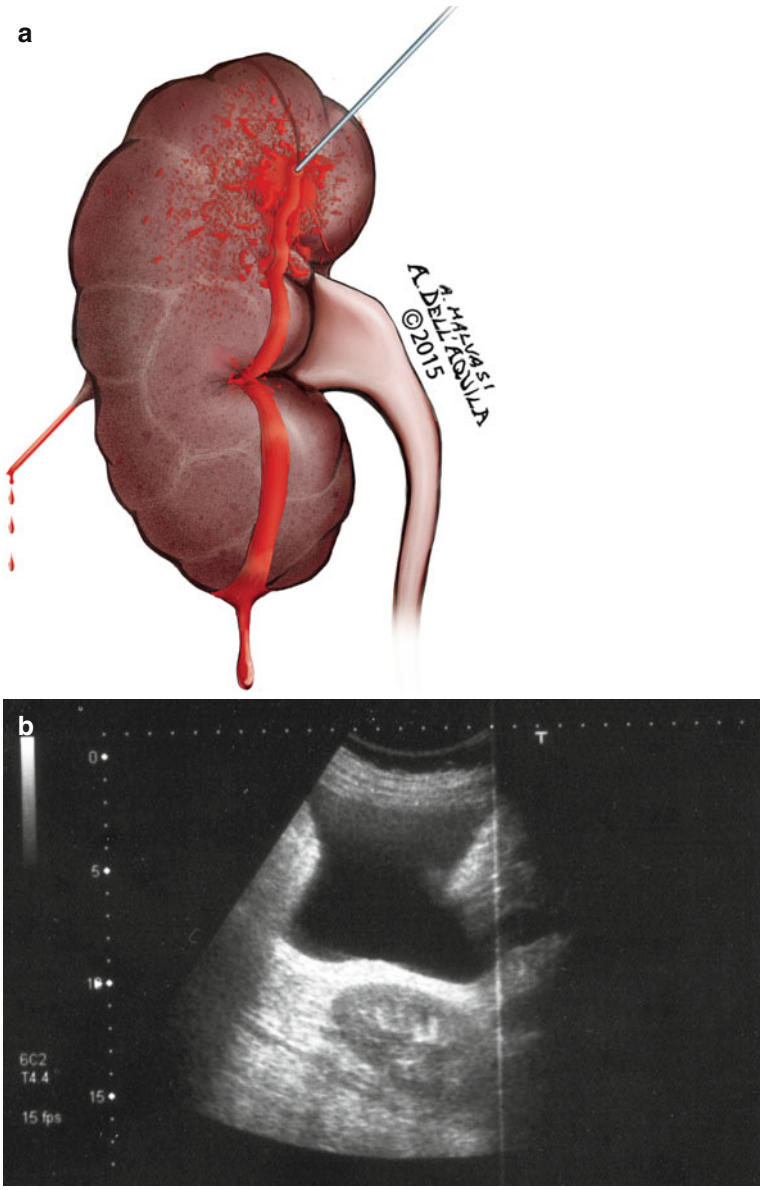

Fig. 10.10 (**a**, **b**) On the *left*, it is represented as an accidental puncture of the kidney; on the *right*, a transabdominal ultrasonographic image, showing an ectopic kidney in a patient with a severe OHSS

mucosal disruption was detected. A stent was placed and after symptoms resolved was removed with an office cystoscopy after 3 weeks. Unfortunately, this patient had a negative pregnancy test [39]. Another patient presented after OPU, with massive hematuria [40]. Immediate cystoscopy performed and revealed pseudoaneurysm. Consequent hemodynamic instability was stabilized with blood transfusion. Pseudoaneurysm was resected and cauterized.

Ureteric injuries are rare complications after OPU. Certain measures include the use of color Doppler technique to preview the needle path to avoid vessels [41] and maintain a needle lateral position than a anterior one. Have in mind that pelvic adhesions may exist due to endometriosis or pelvic infection and distort ureteric structures, ensuring that the aspiration needle do not pass through the ovary. Operators should know that symptom presentation may be early or late; they do present with compromised ureteral function. Differential diagnosis includes adnexal torsion, intraovarian hemorrhage or torsion, hematoma formation from pelvic blood vessels injury, and OHSS. Administration of antibiotics prevents infection. Stent insertion is the therapeutic solution. Stents should be inserted before repeat OPU also, to avoid another trauma.

During ovarian pickup, it is possible also to detect bladder lesions (Fig. 10.11a, b).

10.5.1.2 Vessel Injuries

Vessel punctures are possible during ovarian pickup (Fig. 10.12a, b). A patient presented with a pseudoaneurysm of left inferior pudendal artery. Diagnosis was set by US and angiography and treated with embolization. A cesarean section was performed at 32 weeks and a healthy infant was

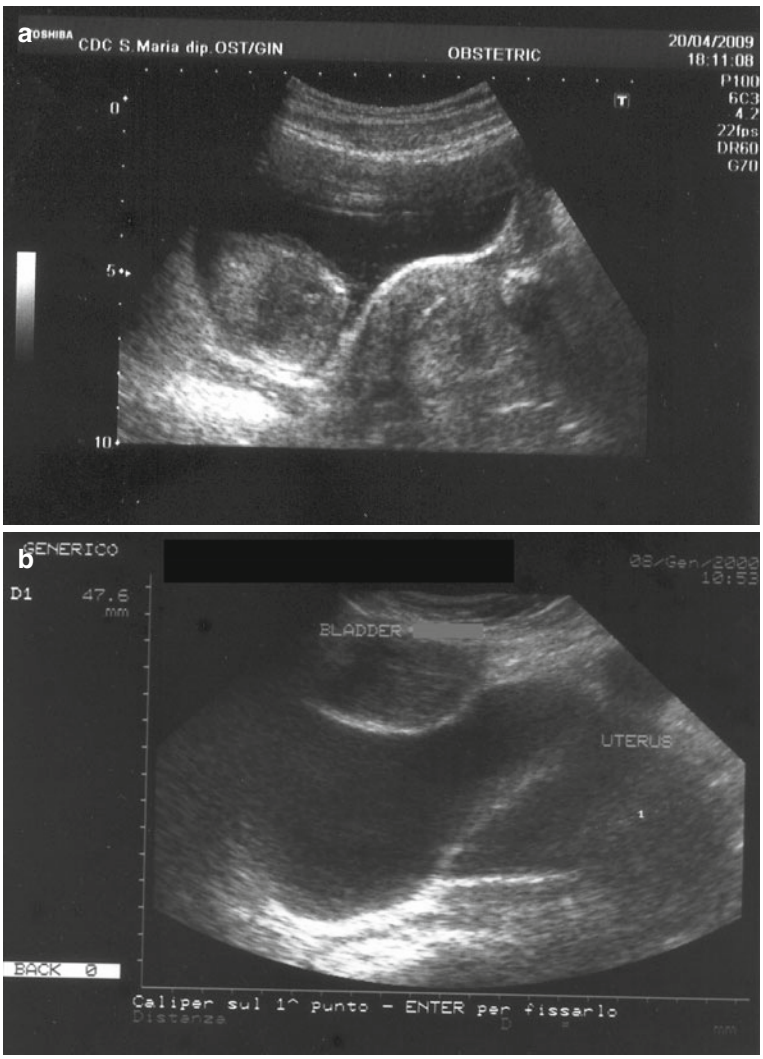

Fig. 10.11 (**a**, **b**) On the *left*, a transabdominal ultrasonographic scan showing coats into the bladder after an accidental puncture during an ovarian pickup; on the *right*, the image shows a hematoma of bladder dome, after an accidental puncture during ovarian pickup

delivered [42]. Late presentation takes place also. A pelvic pseudoaneurysm developed after an OPU 6 years earlier. It was treated by arterial embolization [43].

10.5.2 Specific Oocyte Retrieval (OPU)

10.5.2.1 OPU for In Vitro Maturation

Except oocyte retrieval of IVF, patients may undergo OPU for in vitro maturation. No serious complications have been seen for this technique. In a retrospective cohort study, 188 women underwent OPU for this reason. Only one patient presented with pelvic infection. Another patient had severe abdominal pain after retrieval. It seems that this technique is well tolerated although requires more punctures per ovary [44].

10.5.2.2 Transabdominal Oocyte Retrieval

When ovaries are not accessible through vaginal approach, then transabdominal retrieval should be undertaken. In a study [45], in 12 years, only one complication arose that needed hospitalization. Otherwise, this technique is safe and presents no statistical difference, with vaginal oocyte retrieval, between treatment parameters except the lower number of oocytes retrieved.

10.5.2.3 Hydrosalpinx Fluid Aspiration

In one of the first studies for hydrosalpinges ultrasound-guided aspiration [46], positive significant difference has been observed for clinical, ongoing pregnancy and the implantation rates, while patients with presence of hydrosalpinges had poor IVF outcomes.

In another study, aspiration took place after all oocyte retrieval, if hydrosalpinges are still present. Implantation and pregnancy rates are increased, if fluid reaccumulation takes place after the first 2 weeks of aspiration. This technique is simple safe and effective under ultrasound-guided aspiration [47].

Another clinical trial that tested aspiration of hydrosalpinx before oocyte collection found no difference in pregnancy rates between the two groups except biochemical pregnancy rate, favoring the aspiration group. Although the effectiveness of this technique is not established, on improving pregnancy rates, it is considered safe [48].

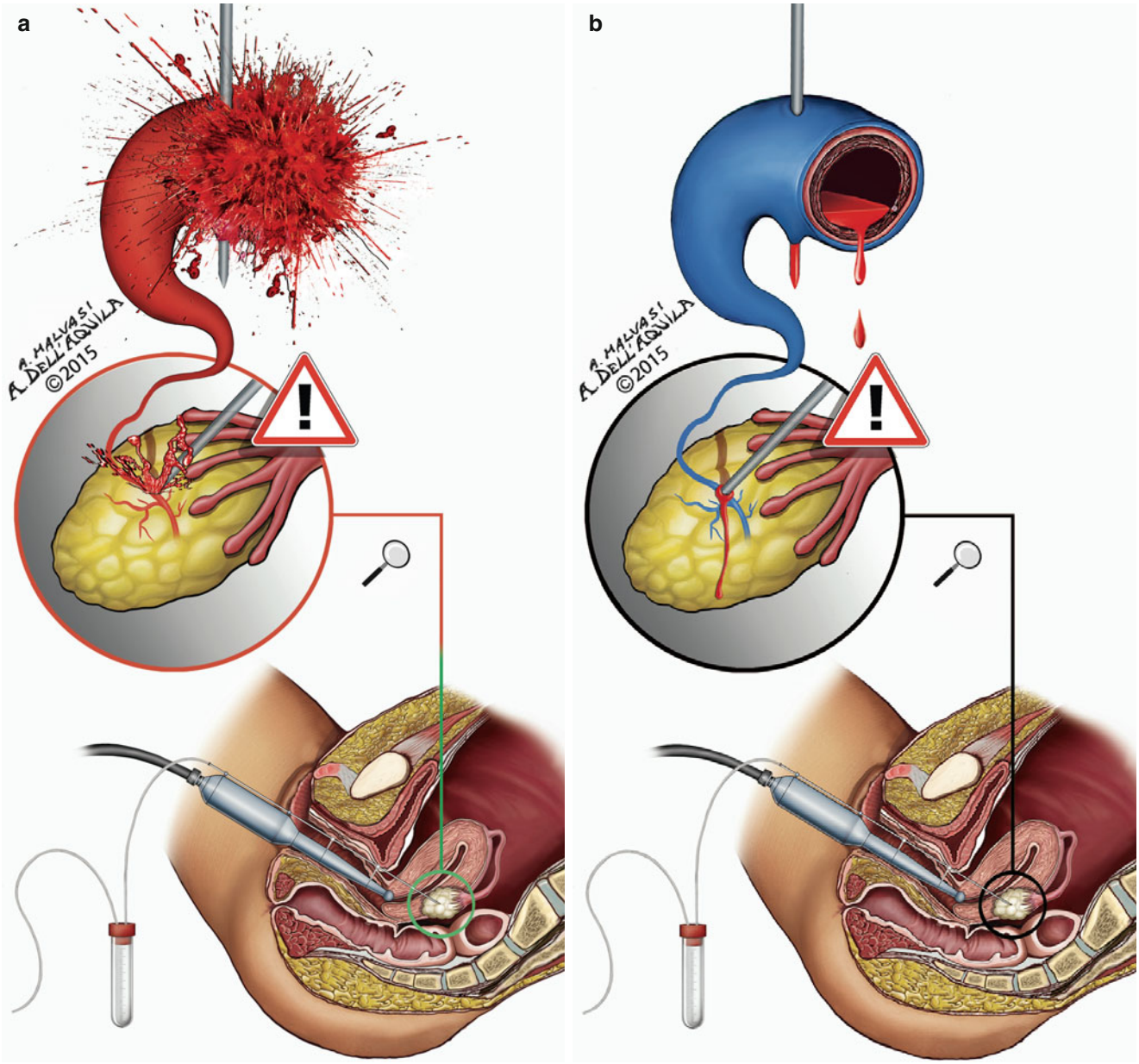

Fig. 10.12 (**a**, **b**) Accidental puncture of ovarian artery (requiring an urgent laparotomy), on the *left*, and ovarian vein (solving spontaneously, generally without problems), on the *right*

10.5.3 Strategies for OPU Injury

Although it was proposed as a method to reduce blood vessel injury risk, it is not entirely clear yet that transvaginal color Doppler ultrasound may achieve it. When it was routinely tested, it was found that it did not predict 45 % of moderate peritoneal bleeding [41]. Coagulation screening was proposed because of the risk of bleeding, after oocyte retrieval, for patients that plan an IVF cycle. The numbers needed to test to prevent one case of bleeding, associated with abnormal coagulation test, were 534 tests [49].

10.5.4 Infections After Oocyte Retrieval

10.5.4.1 Infection at Various Sites

Oocyte retrieval is considered a safe technique, but case reports associate this technique with various complications. In a case report, a 16-week pregnant woman that had undergone oocyte retrieval and ET had developed infectious spondylitis in the second and third lumbar vertebrae. Blood and spinal biopsies revealed *S. aureus*. The patient was treated with IV cefazolin (6.0 g/day) for 6 weeks. The patient delivered at 38 weeks and 4 days [50].

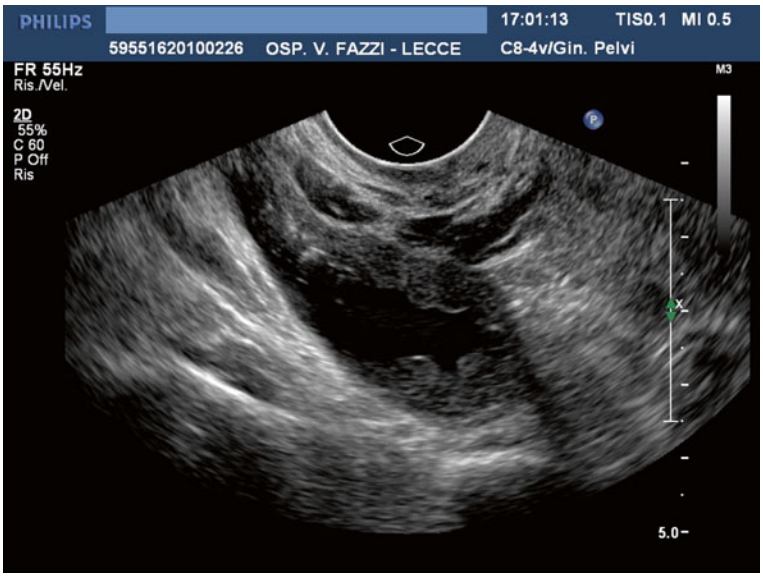

Fig. 10.13 An ultrasonographic transvaginal scan of a pyometra during first trimester after IVF

10.5.4.2 Pyometra

Two case reports of pyometra (Fig. 10.13) have been reported after oocyte retrieval. The first woman, 43 years old, presented with infection signs that eventually developed to septicemia. Pyometra was diagnosed and endometrial cavity biopsy showed vancomycin-resistant enterococci. The situation was partially resolved, and after infection recurrence, patient underwent hysterectomy. Autolyzed endometrium and subserosal and intramural abscesses have been found on the specimen [51].

The second case was detected during embryo transfer. At this patient, pyometra treatment was successful and was followed by a frozen embryo transfer. Authors conclude that the use of ultrasound during embryo transfer is essential for the diagnosis of pyometra and the change of treatment plan [52].

10.5.4.3 Ovarian Abscess

The ovarian abscess (Fig. 10.14) is a possible complication of ART. A 35-year-old woman developed pelvic infection, 16 days after oocyte retrieval. By transvaginal ultrasound, a solid mass was found between left ovary and the uterus. Both ovaries contained several follicles. The clinical situation was continuously deteriorating even with the administration of IV clindamycin and gentamicin. Consumption coagulopathy was developed. The patient underwent a midline laparotomy, and a large amount of pus was drained when incising the capsule of each ovary [53].

In a case series, three cases of tubo-ovarian abscess have been described after OPU. The first patient had a history of right ovarian cystectomy and bilateral ovarian endometriomas that were not punctured. The second one had a 3 cm ovarian endometrioma that was punctured and the third one with a history of right ovarian cystectomy for endometriosis. All three patients developed pelvic abscesses after OPU, even after antibiotic prophylaxis. Pelvic abscess had a size of 8–9 cm and the third one at 4 cm. All three cases required surgical drainage after antibiotic treatment, while the third one received right adnexectomy [54].

Rare Ovarian Abscesses

Bacteremia with *Actinomyces urogenitalis* has been described after oocyte retrieval, in parallel with tubo-ovarian abscess formation [55]. In another rare case, tuberculosis was diagnosed after histology of an ovarian abscess, after an unsuccessful IVF cycle. It is not clear whether this was initially infected or reactivated [56].

Ovarian Abscess and Pregnancy

A case of ovarian abscess that existed in parallel with the pregnancy is presented after a 35-year-old nulliparous woman underwent oocyte retrieval. Vaginal discharge was presented at a 13 weeks of pregnancy with no other symptoms. At 30 weeks of pregnancy, she developed an ovarian abscess, and for this reason, she was hospitalized and received broad-spectrum antibiotics. This woman delivered by cesarean section and at this time percutaneous drainage of abscess was performed [57].

Another case developed infection after oocyte retrieval. Although broad-spectrum antibiotics have been administered, an abscess was formed that needed transvaginal ultrasound-guided drainage after 9 days from OPU. In addition, posterior colpotomy and T-drain into the cul-de-sac was placed. Improvement was observed with a viable pregnancy. Drain was removed after 3 weeks. Eventually, patient had a successful completion of pregnancy and she delivered vaginally at 38 weeks of gestation [58].

Ovarian Abscess: Conclusion

Pelvic infections after OPU are rare. The percentage of tubo-ovarian abscess after OPU ranges from 0.6 % till 1.3 %. It is

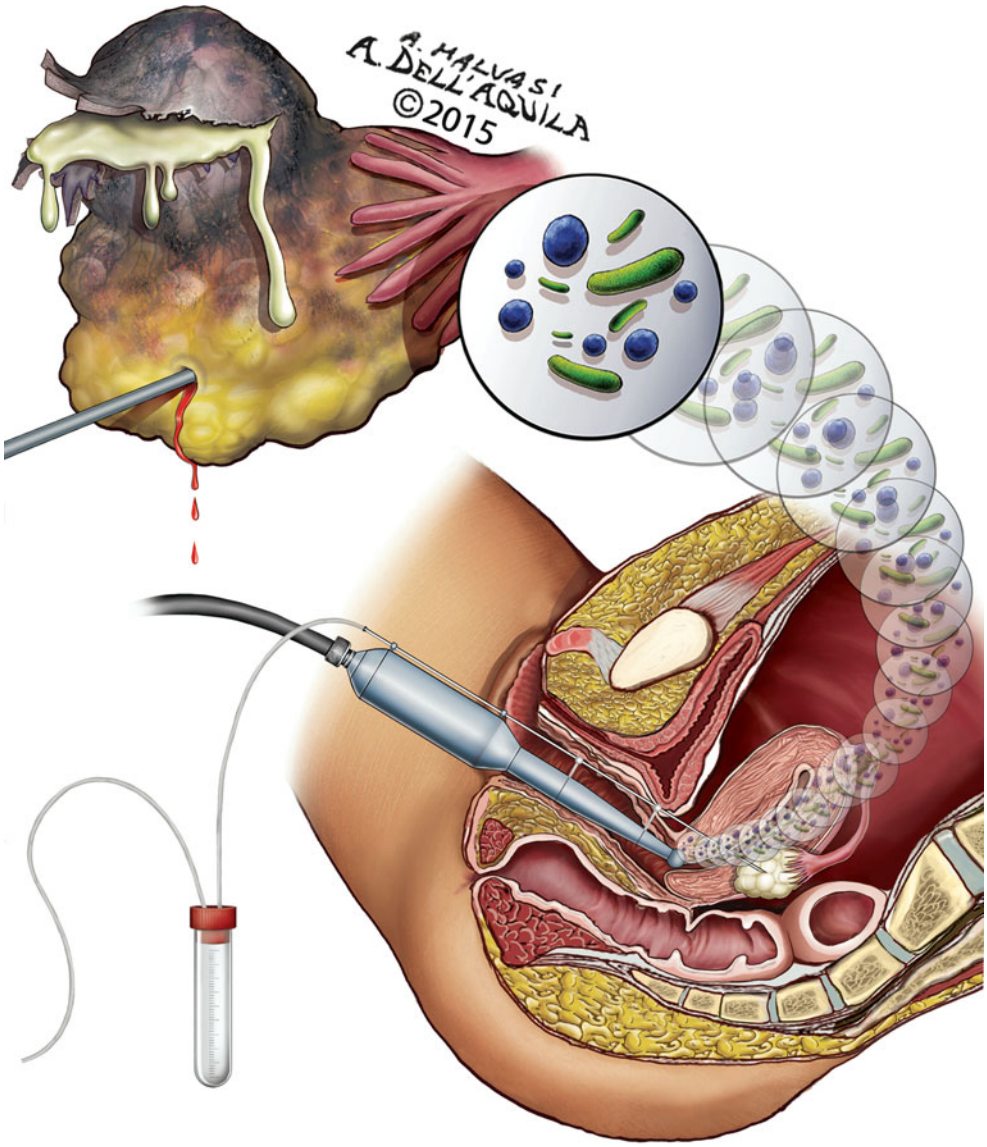

Fig. 10.14 The image shows an ovarian abscess after vaginal bacterial infection, during an ovarian pick up

not clear yet whether vagina cleaning with povidone iodine or chlorhexidine solution adds any real benefit. In addition, antibiotic prophylaxis remains controversial. Only for endometriosis patients, antibiotic prophylaxis is recommended during OPU, but this also remains controversial about its effectiveness [54]. From the other side, endometriosis is currently considered as a major risk factor for pelvic inflammation (33 %), especially after IVF but also a factor for higher percentage of antibiotic treatment failure (48 %) [59].

Pelvic infections after oocyte retrieval take place in patients with endometriosis, PID, pelvic adhesions, or pelvic surgery so these patients are recommended to receive prophylactic antibiotics.

Pelvic infection presentation takes place from a few hours to 56 days with the majority of cases to be presented within 3 weeks. Consumption coagulopathy may be developed and as such should be monitored. Increasing INR, APTT, D-dimers, and decreasing HB are the signs of it. Treatment may be medical alone (34–87, 5 % successful) or with a combination of surgical treatment (laparoscopically or by laparotomy). Incising the capsule of the ovary (if ovarian abscess), abscess drainage, and excision of infected tissue are performed. Severe pelvic adhesions are a limitation for laparoscopy.

Ultrasound-guided drainage of pelvic abscess has a value in the clinical setting. Residual abscess remains at 6.6 % and requires further surgery.

10.6 OHSS

10.6.1 OHSS: Clinical Symptoms

Ovarian hyperstimulation syndrome (OHSS) is observed with two distinct clinical presentations, the "early" and "late" forms (Fig. 10.15). "Early" OHSS takes place

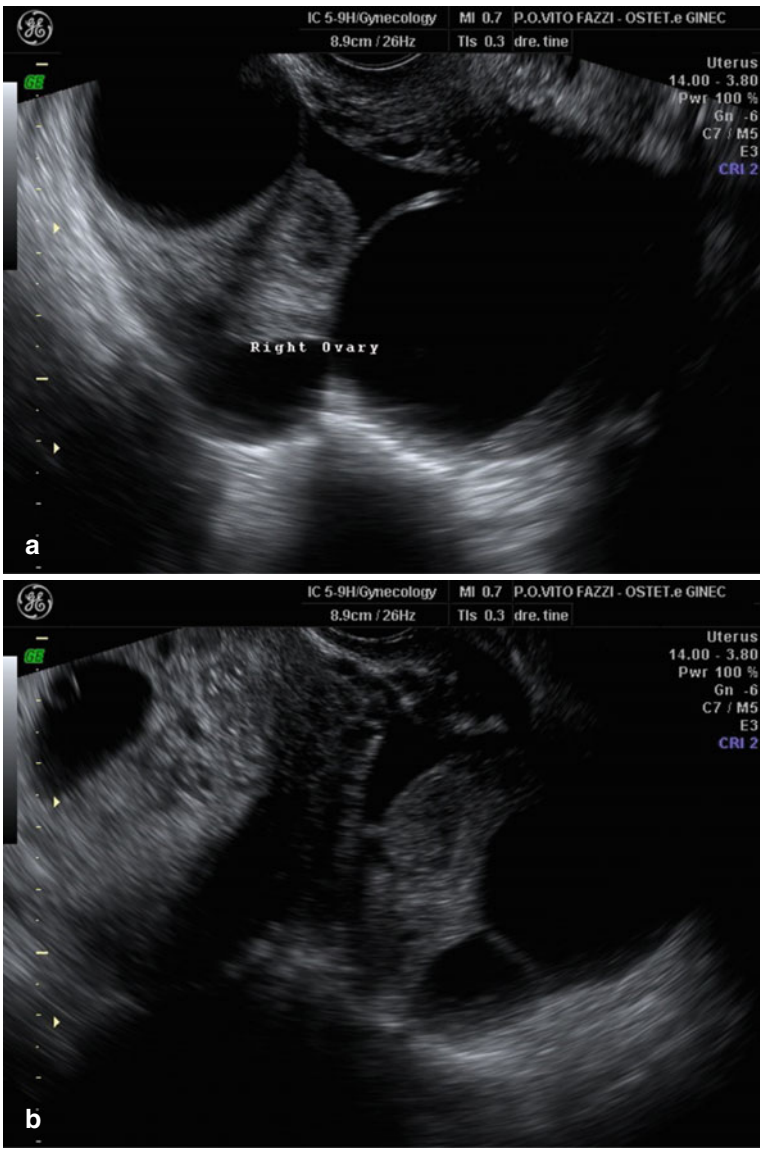

Fig. 10.15 (**a**, **b**) On the *left*, an ultrasonographic scan of "early" ovarian hyperstimulation (OHSS); on the *right*, a "late" OHSS

within 9 days of hCG administration while "late" OHSS presents more than 10 days after hCG. Obviously hCG plays an important role as it is recognized as a trigger for the syndrome. Pregnant patients produce high levels of hCG and take a longer time to recover [60]. OHSS is presented with enlarged ovaries, ascites, hemoconcentration and thrombosis, hypoalbuminemia and hypoproteinemia, electrolyte imbalances, and acute renal failure. Ascites may persist for a long time if not aspirated [61] and may extend to pleural effusion [62]. It may coexist with molar pregnancy [63, 64] with peritonitis due to perforation [62, 65], tuberculosis [66], ectopic pregnancy [67], and vulvar edema [68]. Hemoconcentration is produced from increased vessel permeability and hypovolemia. Disturbed balance between various clotting factors has been reported [69]. Thrombotic incidences and treatment have been reported previously.

10.6.2 OHSS: Prediction

Several efforts have been tried to associate various parameters of ovarian stimulation with OHSS, as measures of prediction for this. An antral follicle count (AFC) ≥ 24 seems to be to correlate with an increased risk of moderate to severe OHSS in comparison to an AFC < 24 (8.6 % versus 2.2 %) [70]. Other authors consider this is much lower at AFC (2–8 mm) ≥ 12. AMH > 0.47 pmol/L (3.36 ng/mL) shows a sensitivity of 90.5 % and specificity of 81.3 % predicting OHSS. Estradiol alone could not predict ovarian hyperstimulation, and various studies that tried to combine the number of follicles and estradiol levels on the day of hCG administration presented with low sensitivity and specificity. Young age and PCOS combined with low weight (thin PCOS) are important general factors predicting OHSS.

10.6.3 OHSS Treatment

The majority of efforts for OHSS prevention and treatment focus on the modification of protocols currently in use. None of these modified protocols have offered an entirely OHSS free practice, despite the claims of advocates of each protocol. Treatment remains largely empirical, although new medications like everolimus and kisspeptin offer possible future therapies. These modifications have been focused on the following:

10.6.3.1 OHSS: Treatment Before Ovarian Stimulation

Metformin, as adjuvant therapy has been used extensively to reduce the incidence of OHSS (OR 0.29; 95 % CI 0.18–0.49) [71]. No negative effect was observed in the number of oocytes yielded, serum estradiol levels, but reduced length of the stimulation and total amount of gonadotrophins have been used. Extensive use of metformin is needed for OHSS prevention (3–16 weeks at various doses) [72] and may be administered also during ovarian stimulation.

Pill pretreatment (OCP pretreatment) has been used in the past as a method to extensively downregulate the ovary for the 21 days before starting GnRH agonist. Sometimes it could be used both for overlapping each other. One of the benefits is that it homogenizes follicular development, so follicles develop in synchrony, without having a large number of small follicles. It is only used in the long GnRH agonist protocol. It is not clear yet whether pill pretreatment reduces pregnancy rates in GnRH antagonist cycles, so it is not used until now [73, 74].

10.6.3.2 OHSS: Treatment During Ovarian Stimulation

Low-dose hCG administration when combine with a GnRH antagonist protocol significantly reduces OHSS (OR 0.30; 95 % CI 0.09–0.96) [75]. Also observation of a steep rise of estradiol levels may incline the clinician to reduce gonadotrophin levels (step-down regimen). An extreme form of that is called coasting-withholding gonadotrophins, but it has adverse effects on pregnancy rates, if used for more than 4 days [76, 77].

Minimizing dose for hCG administration has been found to play a role. Doses at 5000 IU, 2500 [78] and 2000 IU [79] have been used without affecting the pregnancy outcomes.

Utilization of GnRH antagonist protocol has significantly reduced OHSS (OR 0.43, 95 % CI 0.33–0.57) [80]. In PCOS patients undergoing IVF, downregulation with GnRH antagonist reduces the risk of OHSS, when compared with long agonist (RR 0.60; 95 % CI 0.48–0.76) [81, 82]. The same applies for normal responders [83].

Long-acting and weekly administrated corifollitropin alfa, which is recombinant FSH (rFSH), is associated with increased ovarian response and risk of OHSS [84], so it needs to be administered with GnRH antagonist and not in good responders.

Coadministration of the dopamine agonist cabergoline has been found also to reduce the risk of moderate to severe ovarian hyperstimulation (RR 0.38, 95 % CI 0.29–0.51) [85] by inhibiting VEGF [86]. It may be better than the use of albumin infusion [87] and coasting [88].

Aromatase inhibitors may be used for two purposes. First, one is to reduce estradiol levels in breast cancer patients undergoing IVF before chemotherapy [89] and thus may be used for the same purpose in a hyperresponsive patient, although it is not clear yet the appropriate dose [90]. Second, to reduce total gonadotrophins administration, as long as they administered before cycle cancelation, is the last option, but with extensive psychological impact to the patient.

10.6.3.3 OHSS: Treatment During Oocyte Retrieval

Oocyte retrieval can be planned earlier when follicles are at 12–15 mm diameter and estradiol levels at ≥2500 pg/ml and mature in the laboratory, a technique that is called in vitro maturation. This is especially effective in PCOS, but it presents with lower pregnancy rates [91]. It is even more effective than GnRH antagonist protocol for preventing OHSS [92]. It may be combined with a freeze-all embryo strategy [93].

It is a promising technique under continuous development [94].

Albumin infusion (OR 0.67, 95 % CI 0.45–0.99) and hydroxyethyl starch infusion (OR 0.12, 95 % CI 0.04–0.40) are two methods of fluid replacement during OPU that seems to be effective preventing abdominal ascites [95]. For albumin infusion, opinions differ and certain authors speak about pregnancy rate reduction while in parallel does not reduce the incidence of OHSS [96, 97].

Given the possibility of viral transmission through albumin minimizes its use.

10.6.3.4 OHSS: Treatments for Oocyte Maturation

One method of OHSS prevention is to avoid hCG injection, but administering GnRH agonist for final oocyte maturation in GnRH antagonist cycles. Although there is a significant reduction of OHSS by GbRH agonist oocyte triggering in fresh (OR: 0.06; 95 % CI: 0.01–0.33) and donor cycles (OR: 0.06; 95 % CI: 0.01–0.27), there is a significant reduction in ongoing pregnancy rates in fresh autologous cycles (OR: 0.69; 95 % CI: 0.52–0.93), while no difference existed between the two regimens in oocyte donor cycles (OR: 0.91; 95 % CI: 0.59–1.40) [98].

10.6.3.5 OHSS: Treatment After Ovarian Stimulation

Transvaginal ascitic fluid aspiration has been proven effective to reduce further exacerbation of the symptoms. It may

take place one or more times in case of severe OHSS. It reduces the hospitalization time by dramatic symptom improvement, decreases abortion, and improves clinical pregnancy rates [99]. hCG as luteal phase support has long been abandoned with the use of progesterone. Obviously, it cannot be used in cases of ovarian hyperresponse.

It is not clear yet the role of embryo cryopreservation, alone, for avoiding OHSS. Embryos produce hCG and exacerbate OHSS phenomena. Issues like the pregnancy rates in a frozen-thawed cycle, the extensive storage capacity that is needed, and the labor-intensive use of embryo vitrification that is needed, mandate its use only within a GnRH antagonist protocol with agonist triggering.

10.6.4 OHSS: Pathophysiology

Ovarian hyperstimulation syndrome is associated with various genetic polymorphisms in AMH, AMHR2 [100], ESR1 AND 2 [101], VEGF receptors [102], and BMP15 [103]. It is not clear which pathways are involved in the syndrome presentation except that hCG activates P13K/mTOR signaling pathway and activates VEGF [104]. Till now VEGF-A is considered as the molecule that is responsible for OHSS, because it increases vascular permeability. From other studies, other pathways (mTOR) may be considered more effective because pathway inhibition has more effects on ovarian weight reduction and abdominal albumin concentration [105]. VEGF pathway inhibition has no effect in any of these parameters [106]. In parallel, calcium modulation is very effective in reducing abdominal fluid accumulation by either calcium pathway inhibition [106] or calcium infusion [107–109]. Also, kisspeptin-64 has been tested instead of hCG in oocyte maturation and it is very promising in reducing OHSS [110]. Overall, more research is needed to define the exact pathways responsible for the different phenotypes of OHSS.

10.7 Thrombosis

10.7.1 General

In a large cohort Swedish study of 964.532 deliveries, there was a 0, 2 % incidence of first trimester VTE in IVF patients compared with the normal population, while in IVF-OHSS patients, it showed a 100-fold increase of VTE. There was no increase in risk in frozen embryo transfer patients and after the first trimester of pregnancy [111].

In a retrospective study of [112] 65 patients with thrombosis after IVF, 10 had lower extremity thrombosis, 11 had upper extremity thrombosis,19 with neck thrombosis,18 with intracranial thrombosis, and 7 with thrombosis in other sites. In all cases, hematocrit rise >42 was in 62 % of the cases, estradiol rise >3000 pg/ml was at 54 % of the cases, and inherited thrombophilia existed in 23 % of the cases. Two deaths have been observed (both with intracranial thrombosis) and neurologic sequela was left at 18 % of the patients. Neurological sequelae included permanent hemiparesis (two patients) and impairment of daily activity (seven patients). Overall onset of the thrombotic event took place at 25.5 ± 20.1 days, while intracranial thrombosis took place at the earliest (10.2 ± 4.6 days) from all other cases [112].

Specific cases will be analyzed below.

10.7.1.1 Portal Vein Thrombosis

A 39-year-old woman, several days after oocyte retrieval, had an acute portal vein thrombosis with extension into the splenic and superior mesenteric veins. This was presented as a right upper quadrant pain [113].

10.7.1.2 Jugular Vein Thrombosis, Subclavian Vein, and the Right Brachiocephalic Vein Thrombosis

Nine days after the embryos were transferred, the patient had ascites, hydrothorax, and fluid of pelvic cavity accumulating. Her right neck had pain 43 days after the embryo transfer. B scan ultrasound showed jugular vein thrombosis, subclavian vein, and right brachiocephalic vein thrombosis [114].

Internal jugular vein thrombosis and subclavian vein thrombosis have been reported in a 26-year-old patient with OHSS. She was treated for OHSS, but after 2 days, she presented with left arm edema and neck pain. The abovementioned diagnosis was set up [115].

Right internal jugular vein may be presented as a neck lump [116], as a complication of OHSS [117, 118], in conjunction with a resistance to activated protein C (APC) or Dahlbäck disease [117] that usually is diagnosed later, even after low-dose heparin prophylaxis [118], and with factor V Leiden mutation (FVLM) either homozygous [119, 120] and the other heterozygous [120]. Also, infraction to the maternal side after an extensive placental infraction has been observed [120]. Two cases have been reported with internal jugular vein infraction and prothrombin 3 UTR mutations [119, 121], despite therapeutic anticoagulation.

Bilateral internal jugular vein thrombosis may take place after OHSS [122, 123], and without OHSS [124] may present at a rather late (8–9 weeks) pregnancy [124, 125], be evolved in pulmonary emboli [125], despite prophylactic albumin administration [123], negative thrombophilia screening [124], with twin pregnancies [126].

Subclavian vein thrombosis may be associated with OHSS [115, 127], may be presented at 7–10 weeks of gestation [128], and may already have received thromboprophylaxis [128].

In a patient with several risk factors (smoking, immobilization, a positive family history of thrombosis, protein S

deficiency, APC resistance), 5 weeks after IVF, complete obstruction of the subclavian and brachiocephalic vein on the right side and clots in the superior vena cava, left subclavian vein, bilateral internal jugular veins, and the right axillary vein, as revealed by magnetic resonance imaging (MRI), have been developed [129].

10.7.1.3 Cerebral Thrombosis

A 37-year-old woman presented to the emergency room with abdominal pain and tenderness. She had an IVF cycle 38 days ago. An ectopic pregnancy diagnosis and partial salpingectomy was performed. Two days after discharging from the hospital, she was presented with syncope and generalized tonic-clonic seizure. By cranial tomography, generalized edema and cerebral venous thrombosis were established [130].

In another case, a 30-year-old woman developed left middle cerebral thrombosis after IVF. Anticoagulation treatment was successful but patient left with neurologic sequelae [131].

A 38-year-old nulliparous woman on 7th day after OPU developed a severe headache and neck pain. Before 2 days, she had developed severe ovarian hyperstimulation syndrome, but was corrected. By MRI, extensive cortical vein and dural sinus thrombosis, including the superior sagittal sinus and transverse sinuses, were revealed. The thrombophilia test was negative. The patient was treated with low molecular weight heparin. She left the hospital 15 days after oocyte retrieval. After 2 months, a repeat MRI revealed patency in superior sagittal sinus and transverse sinuses and no evidence of flow obstruction while patient had no signs of neurological sequelae [132].

Another patient after her second cycle experienced ovarian hyperstimulation syndrome with progressive abdominal distention, 13 days after the embryo transfer. The next day, she developed mild difficulties in writing and generalized seizure. After MRI, a lesion found over the left high frontal lobe. Evidence of mild vasogenic edema at the brain white matter was found that pointed to small subacute hematoma. Eventually, diagnosis of cavernous angioma with hemorrhage was set up. The patient was set under observation while on treatment for neurological symptoms. After a positive pregnancy test, she had a paracentesis to improve symptoms. Unfortunately, after 1 week, the patient developed pain in left hip with mild edematous calf. A thrombus has been formed in the left common femoral vein extending into the left external iliac vein. Also, extensive venous thrombosis, up to the infrarenal portion of the inferior vena cava, was revealed. Both situations required a combined assessment, and decreased flow in the cortical vein was found that corresponds to the subacute hematoma previously mentioned. Termination of pregnancy was requested from the patient and eventually performed. Thrombophilia screen was negative, and no neurological sequelae were left. Complete solution of the intracerebral hemorrhage was established [133].

Two other cases have been presented. The first patient developed mild ovarian hyperstimulation 7 days after embryo transfer. The patient advised to monitor herself and return to hospital if symptoms worsen. Unfortunately, she presented with left hemiparesis, with loss of power in the left arm and leg. A hypodense cortical area was evident after computed axial tomography. After treatment, hemiparesis improved gradually in a week, but this patient did not get pregnant. She continued to improve her left motor weakness.

The second patient developed ovarian hyperstimulation 3 days after embryo transfer, with mild abdominal distension. During the admission to the hospital, she had a convulsive fit and left hemiparesis with motor power loss in both left arm and leg. A hypodense area was found in the left parieto-occipital lobe, both cortical and subcortical, and the diagnosis of acute infarction was made. After treatment, the situation improved in 36 h. On the third and fourth day, improvement continued and left leg and arm became normal. After 6 days, patient was discharged with no symptoms. Both patients have been normal for anticardiolipin IgG/IgM antibodies, protein C and S, and antithrombin III [134].

After OHSS, in parallel with cerebral infarction, myocardial infarction and death have been reported [135].

10.7.1.4 Carotid Thrombosis

It is a rare complication associated with OHSS. Three cases have been presented [136], associated with cardiovascular risk factors. In another case, in a 33-year-old patient, after OHSS, a floating thrombus located in the internal carotid artery has been found. The patient developed left hemiparesis and with open surgery avoided recurrent sequelae [137].

10.7.1.5 Mesenteric Vein Thrombosis

A 33-year-old patient developed abdominal pain after ET, and a CT scan showed a superior mesenteric vein thrombosis. The patient underwent therapeutic anticoagulation and finally the situation resolved [138].

A 39-year-old woman developed acute portal vein thrombosis with extension into the splenic and superior mesenteric veins, after oocyte retrieval. ET was postponed. Eventually, the situation was also partially resolved [113]. In another case [139], after mesenteric vein thrombosis, fatal outcome was reported.

10.7.2 Prevention and Treatment

Due to the life-threatening complications of jugular vein thrombosis, prevention and fast diagnosis are needed. Diagnosis is confirmed by Doppler ultrasound of the neck after symptom presentation. Prevention of ovarian hyperstimulation syndrome (OHSS) may reduce the incidence. Also increased APC resistance may contribute, but it is not clear

whether general screening for resistance to APC before admission to the IVF program should be performed. All patients should be counseled before treatment about the rare possibility of thrombosis thus to avoid immobilization. Also, recurrent episode in a next pregnancy, especially for cerebral infarction and intracerebral hemorrhage, is rare, if patient is under preventive antithrombotic treatment [140]. Although low molecular weight heparin anticoagulation could be administered in OHSS, the inclusion of other preventive measures, such as low molecular weight dextran expansion and albumin infusion, might not help avoiding it. In an experimental basis, procoagulable detection has been tested with the use of thrombin generation measurement and overall hemostasis potential. Both they increase during ovarian stimulation in IVF [141]. On the other hand, screening for the Factor V Leiden (FVL) and prothrombin gene G20210A mutation (PGM) genes does not offer any benefit, because they do not add to the thrombosis risk [142]. Also, thrombophilia mutations, in patients, may demand for a natural cycle process than ovarian stimulation IVF [143]. Systemic lupus erythematosus and/or antiphospholipid syndrome, although rare, may have up to 5 % risk for thrombosis and OHSS [144].

In case patients at risk of thrombosis need to take prophylactic antithrombotic therapy with LMWH, before and during ovulation induction, risk of bleeding is not increased [145].

Survival of pregnancy can be achieved, but progressive thrombosis may demand for termination of it [126], so a decision on continuation of early pregnancy upon progressive thrombosis should be made.

The timely cesarean section should be decided according to the patient's clinical picture.

10.8 Ovarian Complication

10.8.1 Adnexal Torsion

Many cases of adnexal torsion have been presented. It occurs at various points, mainly in the first trimester. From the pregnant women who had a torsion, it is evident that this takes place at 11.5 (7.7) weeks of gestation, while 56 % of them developed after IVF treatment [146].

There is a case report of 32-year-old woman who developed left adnexal torsion 2 days after embryo transfer. She also developed a right adnexal torsion, at 7 weeks of gestation. Again, at 10 weeks of pregnancy, right adnexal torsion occurred again. At all times, laparoscopic detorsion of adnexa was performed, and in the third case, shortcoming of the uteroovarian ligament was performed [147].

Another case of a second episode of adnexal torsion after IVF was observed after IVF, at 7 weeks of gestation. At 19 weeks of gestation, a contralateral adnexal torsion was performed. In the first time, laparoscopic adnexal detorsion was performed, and in the second time, this laparotomy with salpingo-oophorectomy was the treatment choice. Pregnancy was successful, even after salpingo-oophorectomy [148].

Adnexal torsion in a twin pregnancy after IVF was presented at 25 weeks. Diagnosis was established after the use of color Doppler that compared the ovarian blood flow between the two ovaries. A three-port laparoscopy was employed to unwind left adnexa [149]. In another case of an IVF twin pregnancy, a left adnexal torsion at 25 weeks of pregnancy was presented and treated with single-port laparoscopy [150].

Bilateral megalocystic ovaries have been observed at 36 weeks of gestation of a twin pregnancy, as the remains of IVF. This woman has developed deep vein thrombosis at 32 weeks of pregnancy. During cesarean section, both adnexa were markedly enlarged with minimal ascites in the abdominal cavity. After an ovarian biopsy, the diagnosis of bilateral follicular cyst was revealed. Although a rare case, pregnant IVF patient's close follow-up will ensure the existence of such pathological events and subsequent ovarian torsion [151].

Another twin pregnancy after IVF presented at 23 weeks with maximal tenderness in the right lower abdominal quadrant and guarding. A right-sided adnexal mass of 5–6 cm with free fluid in the pouch of Douglas was revealed. Laparoscopic detorsion of the right adnexa that was twisted three times was successful. Eventually, she delivered at 35 weeks of pregnancy two healthy children [152].

From a large retrospective study, the incidence of ovarian torsion in 10,583 cycles was 9 ovarian torsion cases and 104 ovarian hyperstimulation syndrome (OHSS) cases, which are susceptible to ovarian torsion. Only three of them had torsion of the adnexa and two of them have been pregnant.

At diagnosis time, five of the patients were clinically pregnant and one was chemically pregnant. Only in one of these patients, laparoscopic detorsion was failed and followed by laparotomy. This was due to the large ovary [153].

After IVF, ovarian torsion is one of the major complications but rare. Pregnancy and ovarian hyperstimulation are the two main factors, coexisting with ovarian torsion. Immediate diagnosis with Doppler ultrasound for absence of flow [154] and emergency laparoscopic intervention are needed, to preserve the ovary(ies). In case of laparoscopic failure, laparotomy is needed. Recurrence of torsion is also rare, but it associated with pregnancy [146].

10.9 Ectopic Pregnancy (EP)

10.9.1 Heterotopic Pregnancy

Heterotopic pregnancy is considered as rare (1/30,000) and could be seen especially after IVF (<0.01) [155, 156]. It has been presented in literature in various forms: (1)

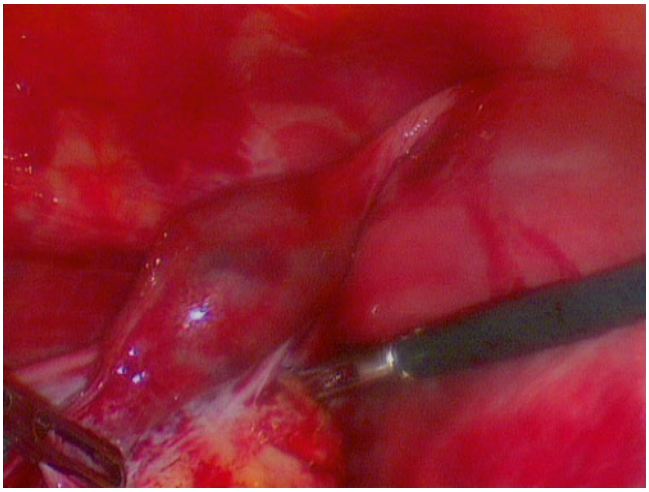

Fig. 10.16 A laparoscopic image of a tubal pregnancy

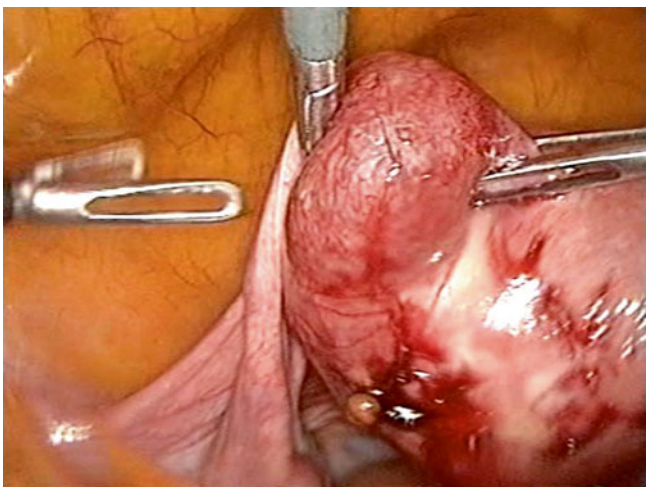

Fig. 10.17 A laparoscopic image of corneal pregnancy

Heterotopic triplet pregnancy: (a) in a cesarean scar with an intrauterine pregnancy, (b) tubal singleton pregnancy (Fig. 10.16) and two intrauterine pregnancies combined with an ovarian abscess, (c) bilateral tubal and intrauterine pregnancy. (2) Cornual pregnancy (Fig. 10.17): (a) recurrent cornual pregnancy, (b) cornual pregnancy combined with twin intrauterine pregnancy, (3) heterotopic pregnancy and intrauterine dizygotic twins after blastocyst transfer. (4) Heterotopic cervical pregnancy (Fig. 10.18): (a) twin cervical and intrauterine pregnancy, (b) cervicoisthmic pregnancy. (5) Heterotopic pregnancy combined with ovarian hyperstimulation syndrome. (6) Heterotopic pregnancy ruptured after spontaneous abortion. The presence of an intrauterine gestation sac in a patient without symptoms should not exclude the diagnosis of a concomitant extrauterine pregnancy until the pelvis is carefully visualized [157].

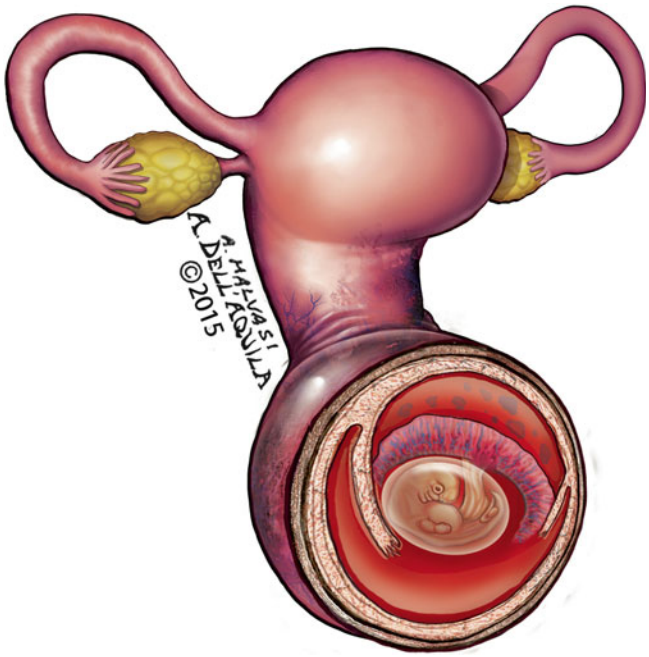

Fig. 10.18 The image shows a cervical pregnancy post-ART

10.9.1.1 Differences in the Prevalence in Different Countries of the World

EP complicates about 2 % of all pregnancies. Although no studies exist that describe the prevalence of the EP, in different countries, especially after IVF treatment, many studies present prevalence of the EP, as a secondary outcome. From specific studies, in Nigeria, prevalence for the EP, after IVF, was 7.8 %, while in the general population, EP rate was 1.74 % [158].

For other countries like Jordan, EP percentage is 0.005 % [159], while in Cameroon, this percentage is 0.72 % [160]. In a large follow-up study in Sweden, ectopic pregnancy rates were compared between women from different countries of birth, but small differences were found [161]. In New York, ectopic pregnancy rates in black women are 4.78 % [162].

10.9.1.2 Contraception as a Risk Factor

It is discussed that LNG contraception leads to ectopic pregnancy. In a case report, Ghosh et al. described a right ampullary ruptured ectopic pregnancy after levonorgestrel failure as emergency contraception [163], while Fabunmi and Perks reported a case of cesarean section scar pregnancy after LNG failure [164]. From retrospective cohort studies, no association of LNG failure with ectopic pregnancy was found.

10.9.1.3 Ectopic Pregnancy Rates in Fresh Versus Frozen Cycles

There is still controversy in this issue. Jun et al. found no difference in ectopic pregnancy rates between fresh and frozen cycles, whereas Yanaihara et al. found a significant

difference in ectopic pregnancies when two frozen blastocysts were transferred, compared to one [165, 166]. From the other side, Ishihara et al., in a retrospective study, found that frozen-thawed single blastocyst transfer significantly reduced EP rates [167]. EP rates varied when data were stratified for age, but remained low.

10.9.1.4 Day 3 Versus Day 5 Embryo Transfer

Milki et al. found no difference in ER rates between blastocyst and day 3 embryo transfers [168]. Important confounding factors have been checked between the two groups (like tubal disease between the two groups, cryopreserved transfers, but not number of embryos transferred) but no significant difference was found.

10.9.1.5 Blastocyst (Single Versus Double Blastocyst Transfer)

A heterotopic abdominal pregnancy was reported, after the transfer of two blastocysts [169]. Intrauterine pregnancy miscarried first while abdominal pregnancy ruptured 2 weeks later and ectopic pregnancy removed by laparoscopy. EP rates are significantly lower with the single frozen-thawed blastocysts transfer as compared with two blastocysts [166].

10.9.1.6 Oocyte Donation and Ectopic Pregnancy Rates

Cohen et al., in an oocyte donation program, found that hydrosalpinx patients present with higher ectopic pregnancy rates than patients without hydrosalpinx [170]. Chronic alteration of endometrium rather than direct embryotoxic effect of hydrosalpinx fluid is a possible cause. If after oocyte donation an ectopic takes place, minimal monitoring may allow rupture of ectopic with significant complications [171]. Mantzavinos et al. reported three cases of ovarian pregnancy after oocyte donation [172]. Patients have been treated laparoscopically, with removal of ovarian pregnancy tissue. Pantos et al. found only one ectopic pregnancy in a large series of donation patients [173]. Rosman et al. found that there is no difference in ectopic pregnancy rates between donor and IVF cycles, in a large retrospective study (4186 non-donor IVF cycles vs. 884 donor ET cycles) [174]. From the other side, donor patients showed significant lower incidence of tubal disease than standard IVF patients.

10.9.1.7 The ICSI Role

From a large retrospective study, that use of ICSI was found not to be associated with EP, while male factor infertility was associated more with EP with all other races than white non-Hispanic [175].

10.9.1.8 Ultrasound-Guided Embryo Transfer

In a meta-analysis of clinical trials (on 5968 ET cycles), comparing ultrasound-guided ET vs. clinical touch ET [176], no difference was found in ectopic pregnancy rates between the two groups. In another meta-analysis of 17 studies [177], same results have been found, even though that EP is relatively rare and study sample sizes limit the ability to detect such differences. When a single clinician performs all guided embryo transfers (Fig. 10.19), [178], no difference in EP rates has been found.

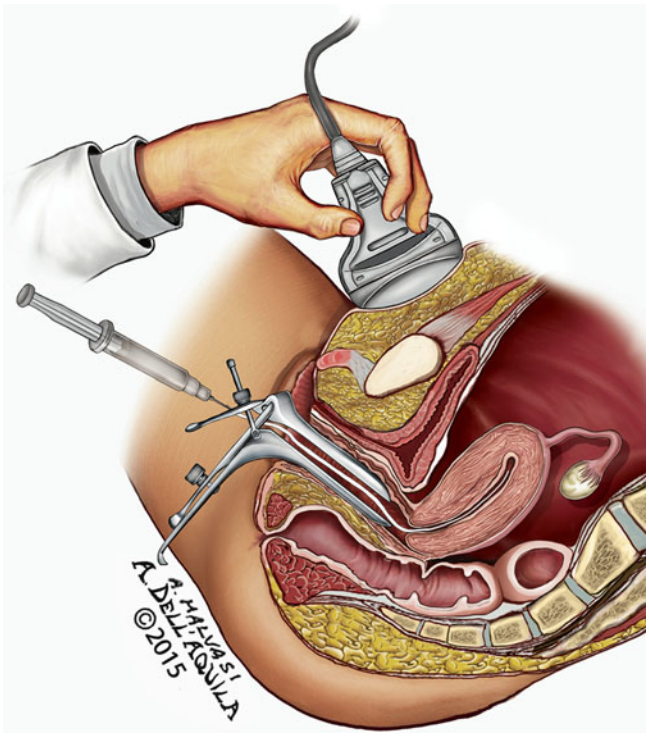

Fig. 10.19 An echo-guided embryo transfer

10.9.1.9 Assisted Hatching

Hagemann et al. found no difference in ectopic pregnancy rates after embryos that had assisted hatching or not [179]. On the other hand, Jun et al., in a large series of retrospectively examined patients, saw that a significant higher ectopic pregnancy rate was found in cases where assisted hatching (AH) was performed when compared with cases where hatching was not preformed [180]. Pathophysiologic explanations include (1) assisted hatching may accelerate embryo implantation; (2) a mechanism exists that prevents embryos that reached the fallopian tube to divert back to the uterus, and (3) the much higher embryo transfer volume used in certain IVF programs.

10.9.1.10 Air Bubble Position After Embryo Transfer

No difference in ectopic pregnancy rates has been observed with different distances of embryo deposition, as measured, from the uterine fundus (10–15 mm or < 10 mm) [181].

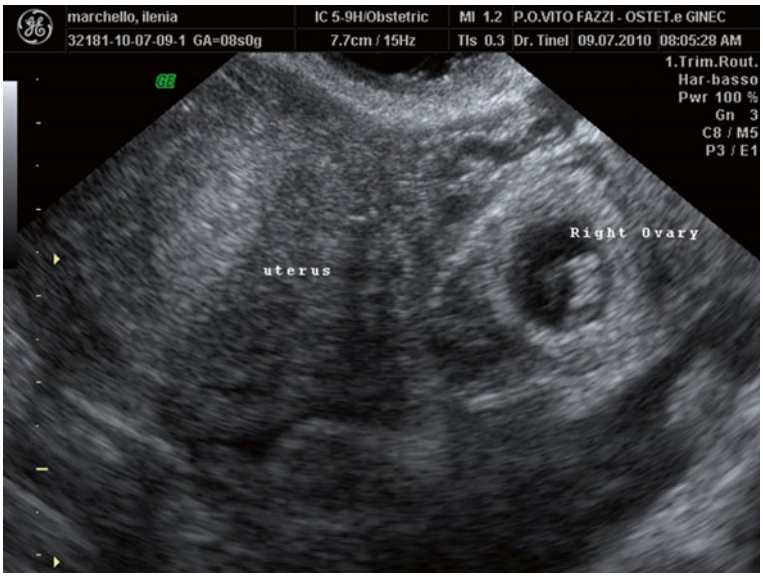

Fig. 10.20 The ultrasonographic image shows a *right* ovarian pregnancy

10.9.1.11 Reanastomosis

Tubal infertility patients, after former sterilization, may undergo microsurgical reconstructive surgery of the fallopian tubes for adhesiolysis, anastomosis, fimbrioplasty, and salpingostomy. These patients, which follow the microsurgical approach, present with higher ectopic pregnancy rates after a single IVF trial [182]. In a small series of patients, higher incidence of ectopic pregnancies has been observed when previous tubal sterilization was reversed by laparoscopy compared with open microsurgical reversal [183]. By using a serosamuscular fixation/biological glue technique, a sutureless laparoscopic tubal reanastomosis can be performed, but ectopic pregnancy rate remains high at 3.9 % [184]. When robotic tubal reanastomosis is performed [185], more ectopic pregnancies have been observed when compared with open reanastomosis.

10.9.1.12 Other Complications of Ectopic Pregnancies

After a ruptured ectopic pregnancy, Rh immunization could be observed.

10.9.2 Rare Cases of Ectopic Pregnancies

Ectopic pregnancies after IVF and subsequent clinical picture will be presented in this section. Case studies will be categorized according to anatomical location.

10.9.2.1 Ovarian Ectopic Pregnancies

In a large series of patients, Raziel et al. found that ovarian ectopic pregnancy (Fig. 10.20) rate comprises 2.7 % of all ectopic pregnancies, is highly associated with the use of intrauterine device, and is treated with laparoscopic wedge resection [186]. Ultrasound use in hemoperitoneum diagnosis makes culdocentesis not essential. Case reports presenting ovarian ectopic pregnancies present (1) ovarian heterotopic pregnancy after IVF [187], (2) bilateral ovarian pregnancy after IVF and previous tubal pregnancy after reanastomosis [188], (3) left ovarian pregnancy after empty follicle syndrome in IVF treatment [189], and (4) ovarian pregnancy from cornual fistulae after bilateral salpingectomy and IVF treatment [190].

Management of a Late Ectopic Pregnancy

A case of a cervical intrauterine pregnancy after IVF has been reported [191]. At the 13th week of gestation, two pregnancies have been diagnosed, a viable intrauterine pregnancy and a nonviable cervical pregnancy. The cervical pregnancy was restricted anteriorly, near a thick cervical blood vessel that presented at Doppler ultrasound with the low resistance flow. There was increased risk of bleeding associated with a cervical pregnancy expulsion, due to the proximity to the cervical venous vessel. After hospitalization and observation, cervical pregnancy was expulsed at 15th week + 6 days of gestation. Hemorrhage was managed through cervical curettage and multiple cervical stitches under general anesthesia. Subsequently, intrauterine pregnancy expulsed also, some hours later, leading to a curettage. Another case of heterotopic pregnancy after IVF and diagnosed at 16 weeks gestation was presented by the late Hassiakos [192]. When it was ruptured, intra-abdominal bleeding and hemorrhagic shock were a consequence.

Maternal-Embryo Complications from Use of Potassium Chloride

A cervical heterotopic pregnancy (one in the intrauterine cavity and the other in the upper portion of the cervix) was

treated with KCl (3 mL) injection and aspiration of the gestational sac [193]. A blood supply was seen at 19 weeks, separate from that of the remaining pregnancy by color Doppler. Remaining trophoblastic tissue did not resolve, leading to obstetric hemorrhage at 31 weeks of gestation. An emergency cesarean hysterectomy took place, with a viable infant, as the patient waited for an elective CS (cesarean section) at 32 weeks. Another possible complication of this technique is that KCL diffuse in the target amniotic sac may lead to diffuse to adjacent sac, thus contributes to harm to the intrauterine embryo.

10.9.2.2 Cervical Pregnancies

A heterotopic cervical pregnancy developed uterine varices at the cervical site and treated with TVS-guided aspiration 34 days after ET. Bilateral hypogastric artery occlusion was used, while a fundal classic cesarean section at 37 weeks was used to give birth to an infant [194]. Uterine varices were diagnosed at 28 weeks gestation, as prominent vessels associated with the empty sac located anteriorly and posteriorly occupying a significant portion of the myometrium at the lower uterine segment and cervical stroma. In Doppler studies, venous waveforms have been observed. To avoid entry into the gestational tissue and vasculature that occupied the lower uterine segment, a fundal cesarean section was planned. After delivery, the patient went for pelvic angiography and possible embolization to diminish the risk of bleeding.

Another heterotopic cervical pregnancy was treated with TVS-guided aspiration and instillation of hypertonic solution of sodium chloride, while, in parallel, ligation of descending cervical branches of the uterine arteries was performed [195]. The latter took place before TVS-guided aspiration. By vagina retraction, two DEXON sutures were placed bilaterally on the cervix, high below the fornix vaginae, thus reducing hemorrhage, significantly. Twin pregnancy in the uterine cavity continued to grow till 12th week of pregnancy, but no data exist thereafter.

A cervical twin ectopic pregnancy has been also described [196]. Treatment consists of TVS-guided aspiration plus systemic methotrexate injection. A 37-year-old woman developed severe ovarian hyperstimulation syndrome, after IVF. Two gestational sacs with one viable fetus located below the internal cervical os at 7 weeks of gestation have been revealed. Doppler imaging demonstrated a cervical mass with numerous tortuous and dilated blood vessels, including vascular communication beds at the implantation site, and established abundant peritrophoblastic arterial flows. Two days later, vaginal bleeding developed and intracervical Foley catheter tamponade was performed. Persistently active gestational tissue and bleeding is followed by hysteroscopic endocervical resection (with a 12° resectoscope with an outer diameter of 8 mm) in combination with temporary balloon occlusion of bilateral common iliac arteries (CIA).

When gestational tissue was removed, electrocoagulation for hemostasis was performed, using the rollerball. As a second measure for hemostasis, a 24-Fr Foley balloon catheter was placed at the cervical canal and methotrexate (50 mg i.m.) was injected on the next day. The 24-Fr Foley balloon catheter was removed 3 days after [197]. Same method of treatment was used by Peleg et al. [198].

A 45-year-old woman was diagnosed by ultrasound with a triplet gestation 7 weeks following IVF. Transvaginal ultrasound showed a triplet heterotopic pregnancy consisting of two gestational sacs in the cervix and one in the uterine cavity. Termination of pregnancy with catheterization and methotrexate treatment was performed, for future fertility preservation. The right femoral artery was catheterized with catheter and uterine arteries have been cannulated; 42 mg of methotrexate was injected into the right and left uterine arteries (at a total dose of 84 mg (50 mg/m^2). After that, both artery embolization was performed with pledgets of Gelfoam. Follow-up by ultrasound scan (after 48 h) revealed an absence of cardiac activity in both embryos. A gradual shrinkage of the cervical and intrauterine sacs was seen later [199]. On a 37-year-old woman that had an ICSI cycle, due to severe oligoasthenoteratospermia, two gestational sacs with embryonic heartbeats have been diagnosed, one in the cervical region and the second intrauterine. To preserve the intrauterine pregnancy, a hysteroscopic removal of the cervical gestational sac was decided. The gestational sac was observed on the left side of the endocervical canal, 2 cm away from the internal cervical ostium. The tip of the resectoscope remained below the internal cervical os at the operation, and the uterine cavity was not touched. Rollerball electrocautery was used to cauterize the conception products. Continuous ultrasound guidance with an abdominal probe was used during the entire procedure [200].

After four IVF attempts, a viable intrauterine and cervical pregnancy was diagnosed in a 34-year-old woman. With transabdominal scanning guidance, the needle was inserted transcervically and maneuvered into the embryo fetal heart that ceased. After that, KCl was injected. With 3 cm^3 of saline injection in the cavity, better visualization of the cervical fetus was achieved, and absence of heart beat was confirmed. The intrauterine pregnancy was delivered at 36, 5 weeks [201].

A heterotopic cervical pregnancy was diagnosed 25 days after ET with the patient complaining of mild vaginal bleeding. Confirmation of the suspected heterotopic cervical pregnancy was achieved by transvaginal ultrasound and for the vascular blood flow with use of Doppler. Cervical pregnancy was treated with transvaginal ultrasound-guided aspiration and KCL injection in the heterotopic pregnancy cavity.

Hemostatic synthetic absorbable sutures were placed high on the cervix at 1, 3, 9, and 10 o'clock, ultimately

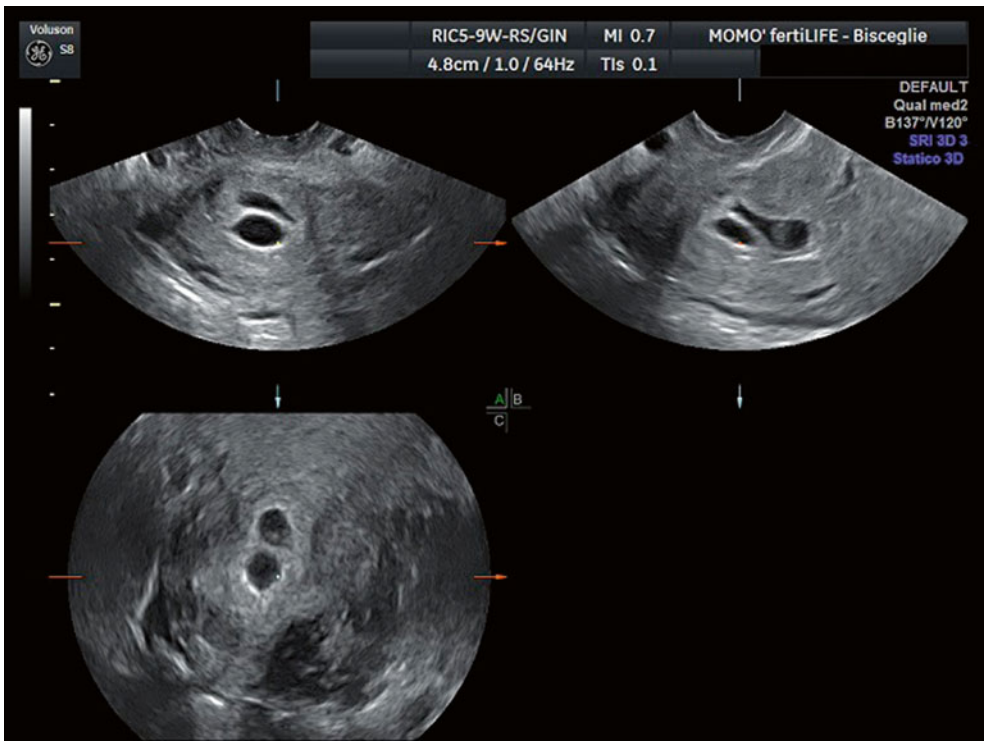

Fig. 10.21 An ultrasonographic image of a twin cesarean pregnancy scar

circumferentially tying the cervix after a period of 16 days after the first procedure and under epidural anesthesia. Cervical-stay sutures were dissolved by the 18th–20th weeks of gestation. No cervical incompetence was observed. At 38 weeks of gestation, an infant was delivered via cesarean section. For safety precautions, during the procedure, interventional radiologists were on standby to perform uterine artery embolization if necessary [202].

10.9.2.3 Ectopic Pregnancies Developed in a Scar

Previous Myomectomy Scar

Although pre-IVF myomectomy is not a necessity to achieve an ongoing pregnancy [203], other authors prefer to perform it, especially when repeated implantation failures take place [204] or uterine cavity involvement exists [205]. In a retrospective study for laparoscopic myomectomy outcomes, Paul et al. mentioned a 5.2 % EP rate [206]. In the same year, Seracchioli et al. reported an EP rate of 2.6 % [207]. From the other side, Campo et al. found no ectopic in their series after laparoscopic [208]. None of the ectopic pregnancies developed in the scar of the previous myomectomy.

Previous Cesarean Scar pregnancy (CSP)

Cesarean scar pregnancy (Fig. 10.21) carries the risk of uncontrollable bleeding requiring hysterectomy, so management has to include this risk in its treatment options. Wang et al. described a heterotopic pregnancy combined with intrauterine pregnancy after IVF [209]. Embryo reduction was performed with transvaginal ultrasound-guided KCL injection (0.2 ml) at 10 weeks of gestation. A mass 3×3 cm remained till 32 weeks of gestation. A male was delivered at 35 weeks by CS. Remaining gestational tissue leads to massive blood loss after CS, blood transfusion, and bilateral internal iliac arteries ligation. Another author [210] found a cesarean scar pregnancy (within the isthmic area of the lower anterior wall of the uterus) and an intrauterine pregnancy after IVF. At this time, management was performed by hysteroscopy evacuation at 7 weeks of gestation and coagulation of the implantation vessel site. Cervix was dilated to 11 mm, not beyond the endocervical canal, and gestational sac was pulled out, under sonographic guidance. Suction curettage was used to clear the residual gestational tissue and a hysteroscopic rolling ball was used to stop the bleeding point. A healthy infant was delivered by CS at 39 weeks of gestation. From the other side, two different cases were presented by Chueh [211]. Both cases were a twin cesarean scar pregnancy. Ectopic pregnancies were treated either by laparotomy excision of the scar twin pregnancy (first case) and hysteroscopic resection (second case) with resectoscopic coagulation of placenta bed vessels. In both cases, no fluid was seen in the cul-de-sac.

More pregnancies could be observed in cesarean scar. Litwicka et al. described a triplet heterotopic cesarean scar pregnancy after IVF, a twin pregnancy in the anterior isthmic wall, close to the CS scar (separated from the bladder wall by a thin myometrial layer) and one intrauterine

gestational sac [212]. Cesarean scar gestation sacs have been diagnosed, 1 week later than the intrauterine sac. Transvaginal ultrasound-guided potassium chloride (2 ml) and methotrexate (15 mg) were injected in the ectopic gestational sacs while the intrauterine pregnancy continues ongoing pregnancy.

In another case, described by Hsieh et al., a heterotopic triplet pregnancy was evident after an IVF treatment; the two have been intrauterine pregnancies and one cesarean scar pregnancy [213]. Color Doppler sonography revealed proliferated peritrophoblastic vessels around the cesarean scar pregnancy and the intrauterine twin pregnancy. CSP was treated with embryo aspiration under vaginal ultrasonography with preservation of intrauterine twin pregnancy. Due to preterm labor, two infants were delivered at 32 weeks of gestation. Rare CSP may exist in different forms after IVF treatments and previous CS. The management of these pregnancies may be performed with laparotomy or hysteroscopic resection of CS ectopic tissue after KCL injection to embryo. Also, MTX may be used for the second case. Complications of the second treatment include spontaneous abortion and congenital abnormality of MTX or diffuse KCL in the target amniotic sac that may lead to diffuse adjacent sac.

10.9.2.4 Live Twin Pregnancy in the Same Fallopian Tube

A left fallopian tube twin pregnancy has been described, an isthmic pregnancy and another ampullary sac in the same tube [214]. Both were treated with a left laparoscopic salpingectomy.

10.9.2.5 Cul-De-Sac Pregnancy

A case of a cul-de-sac ectopic pregnancy after IVF has been described [215]. After 4 weeks from ET, an ectopic gestational sac was found with the fetal heart beat in the left adnexa. By performing a diagnostic laparoscopy, it was revealed that an ectopic mass in the congenital blind pouch was connected to the posterior cul-de-sac. Laparotomy was performed for removal of conceptus and homeostasis.

10.9.2.6 Hepatic Pregnancy

Although a lot of case reports exist for a hepatic pregnancy in the literature [216], none of them is reported after IVF, so they were mentioned as primary hepatic pregnancy. Chlamydia infections may be involved also in this type of ectopic because adhesions between the liver and the diaphragm (Fitz-Hugh-Curtis Syndrome) were demonstrated in 34 % of those with EP [217]. Treatment of this type of pregnancy included direct methotrexate injection [218], laparoscopic suctioning, and hemostasis [216] or laparotomy. In case an advanced week's live pregnancy is diagnosed, then laparotomy with intact placenta may be performed [219].

10.9.2.7 Interstitial Pregnancy

Intrauterine and Twin Bilateral Tubal Pregnancy

Pan et al. report a case of bilateral tubal pregnancy and intrauterine pregnancy [220]. Because of cervical stenosis, a right tubal embryo transfer of four embryos was performed. After 5 weeks of gestation, a laparotomy showed a ruptured right tubal pregnancy, hemoperitoneum, and a dilated left tube. Bilateral salpingectomy was performed, with preservation of intrauterine pregnancy and delivery of a male at term.

Intrauterine and Interstitial Heterotopic Pregnancy After Bilateral Salpingectomy

After two previous unsuccessful IVF cycles and both tubes removal for bilateral hydrosalpinges and a successful third IVF cycle, the patient had an intrauterine pregnancy and an interstitial pregnancy. Interstitial pregnancy ruptured at the left salpingectomy site by its lateral position to the insertion of the ipsilateral round ligament. After laparotomy and left cornual resection, intrauterine pregnancy survived 2 more weeks and eventually miscarried. In aborted fetus, trisomy 21 was revealed [221].

Cornual Pregnancy

Two studies exist that describe cornual pregnancy after IVF. The first case was a heterotopic triplet pregnancy after in utero transfer of three embryos [222]. Cornual pregnancy was treated with resection by laparotomy. A special technique was presented in this patient. A Vicryl string with a tight knot was inserted at the base of the implantation site. The base of the uterine wall above this string was sectioned. Cornual scar was closed with the same stitches in X form while a base knot left in place. The patient delivered two girls with cesarean section at 31 weeks of gestation. The site of the corneal pregnancy was well vascularized and not ruptured.

The second case was a recurrent spontaneous cornual pregnancy 2 years after a heterotopic cornual pregnancy occurred after IVF cycle [223]. Previous corneal heterotopic pregnancy was treated with an injection of 0.5 ml of 15 % potassium chloride into the fetal heart while normal pregnancy was delivered at 39 weeks of gestation by elective cesarean section. Spontaneous cornual pregnancy was treated by injection of 40 mg methotrexate in the gestational sac and systemic methotrexate (1.0 mg/kg orally alternated with 15 mg folinic acid).

Interstitial Pregnancy

A unilateral triplet ectopic pregnancy has been reported on a woman with a history of right salpingectomy [224]. After IVF, in the left fallopian tube, a triplet pregnancy was found (two pregnancies at interstitial and one at ampullary location). Color flow Doppler sonography revealed intensive

peritrophoblastic blood flow around the two gestational sacs with live embryos, while TVS showed three gestational sacs, in the left interstitial area, in the isthmic part of the fallopian tube, and in the ampullary part next to the left ovary. After methotrexate multiple doses, hCG levels have been lowered. Ectopic pregnancies have been ruptured, so a laparotomy was performed with the removal of the left tube and cornual part of the uterus. Another case of previous bilateral salpingectomy and IVF was described [225]. An intrauterine monozygotic twin and an interstitial monozygotic twin pregnancy have been reported. By laparotomy, interstitial pregnancy was removed and intrauterine pregnancy was allowed to deliver at 38 weeks of gestation. Another intrauterine monochorionic diamniotic twin pregnancy and an interstitial pregnancy were reported [226]. Also, after bilateral salpingectomy and IVF, interstitial heterotopic pregnancy was developed that ruptured [221]. A recurrent interstitial pregnancy in uterine horn was seen after IVF [227].

Qin et al. used laparoscopic loop ligature, for heterotopic interstitial pregnancy [228]. Perez et al. reported medical therapy in two cases of interstitial pregnancy, one with transvaginal ultrasound-guided injection of methotrexate and second with potassium chloride into the ectopic sac of the heterotopic twins [229]. As a conclusion, interstitial pregnancies are always possible after tubal occlusion.

10.9.3 Rare Cases of Mild Ovarian Hyperstimulation and Ectopic Pregnancy

The coexistence of ovarian hyperstimulation and ascetic fluid accumulation enlarged ovaries after IVF, and a right tubal ectopic pregnancy has been reported [67]. Right salpingectomy was performed. Same case was presented by Fujii et al., which ended in a bilateral salpingectomy and continuation of intrauterine pregnancy till 32 weeks of gestation [230].

10.9.4 Consecutive Recurrent Ectopic Pregnancies

Three consecutive recurrent pregnancies have been reported in the same patient with pelvic inflammatory disease, two in the right and one on the left fallopian tube. The laparotomy option was chosen in all three cases, to preserve the tubes while removing conceptus [231]. Another case of two consecutive ectopic pregnancies after IVF has been reported [232]. Three consecutive cases of ectopic pregnancy on the same patient were presented [233]. The first involved simultaneous intrauterine and left tubal pregnancy, the second was a right tubal pregnancy, and the third was a right interstitial pregnancy. Another case of two ectopic pregnancies in consecutive menstrual cycles was presented [234]. Left distal ectopic pregnancy was seen and treated with left partial salpingectomy. In the next cycle, a right distal ectopic pregnancy was observed, which treated with right partial salpingectomy. Except the second case, the other two patients were conceived by coitus, so cases are presented in this review because they are rare. Another report of recurrent cornual ectopic pregnancies has been presented [235].

10.10 Chorioamnionitis

10.10.1 *Candida glabrata* and *Candida lusitaniae*

Chorioamnionitis with *Candida glabrata* represents a rare but catastrophic entity after in vitro fertilization. It takes place, usually, during the second trimester. There is increased probability of stillbirth of neonatal death [236]; early recognition and initiation of antifungal treatment may assist us in delivery of a baby once fetal maturity is achieved [237]. By this way, premature rupture of membranes may be avoided [238]. *Candida glabrata* chorioamnionitis can be developed after amniocentesis; thus, the women of increased age should be monitored for this event.

Another case report presented chorioamnionitis in pregnancy after infection with *C. glabrata*. The patient had undergone in vitro fertilization and eventually delivered after systemic antifungal treatment [237].

In another case report, a 41-year-old woman who was treated with combined in vitro fertilization with immunosuppressive therapy had sepsis at 18 weeks of pregnancy. She gets antifungal therapy with amphotericin, but she had premature rupture of membranes and preterm twin delivery at 23 weeks. The dichorionic diamniotic twins did not survive. After that, treatment changed to high dose fluconazole, for weeks. In our case the immunosuppressive therapy is the main factor for infection [239].

In a triplet pregnancy (after IVF) of a 33-year-old woman, premature rupture of membranes at 16 weeks of gestation ended to oligohydramnios in all three fetuses. After pregnancy termination and fetuses' examination, a *Candida lusitaniae* chorioamnionitis was observed. All three fetuses had developed pneumonia and granulomatous intraplacental inflammation [238].

Another 30-year-old patient, with a dichorionic diamniotic pregnancy after IVF, presented with vaginal bleeding at 15 weeks of pregnancy and eventually delivered both twins at 16 weeks. She had developed chorioamnionitis with *Candida glabrata*. She received boric acid. In subsequent IVF cycle, she had a dichorionic diamniotic pregnancy that delivered at 38 weeks of pregnancy. Obviously, complete

eradication of all *Candida glabrata* colonies ensures a successful subsequent IVF cycle.

10.11 Uterine Rupture and Pathophysiology

10.11.1 Uterine Rupture

Uterine rupture after laparoscopic myomectomy and subsequent IVF pregnancy (Fig. 10.22) is a rare complication that takes place in the third trimester of pregnancy. In the first case, the patient had a uterine rupture at 30 weeks of gestation on a twin pregnancy. She had IVF after 14 months after a laparoscopic myomectomy although she had an open myomectomy beforehand. It was presented as a sudden abdominal pain [240]. In another case after laparoscopic removal of a pedunculated fibroid, she had an IVF and conceived in 6 weeks after laparoscopy. She had uterine rupture at 35, 5 weeks of gestation at the uterine wall of the myoma site [241]. Also, a patient that had removal of adenomyosis and got pregnant in 5 months after the operation had a ruptured uterus at 33 weeks of gestation. At emergency CS, rupture was recognized at the posterior wall of the uterus, at the site of the scar. A healthy male was delivered and scar repaired by suture [242].

From a large retrospective study of 635 patients with 1170 fibroid that has been laparoscopically removed, 105 patients achieved pregnancy and no uterine rupture at the site of the scar was observed [243]. In a smaller retrospective study of 202 patients, 65 pregnancies took place with no uterine rupture at all. In 21 pregnancies, IVF was performed. Cesarean section was performed in 80 % of the cases [244].

Uterine rupture may take place at second trimester of gestation. In a Turner patient that received an oocyte donation, she had a uterine rupture at 14 weeks of pregnancy. After laparoscopy, operators have seen uterine rupture, partial pregnancy exteriorization, and placenta percreta. Due to hemodynamic instability, urgent laparotomy and hemostatic hysterectomy was performed [245]. Placenta percreta, which invades myometrium, can be a cause of uterine rupture. A case report of a woman after ten IVF cycles had a uterine rupture at 24 weeks of gestation. After ultrasound pregnancy confirmation, the location of placenta percreta and myometrial thinning was revealed. Confirmation with MRI revealed also that the full thickness of both myometrium and serosa was involved. Due to uterine contractions, a spontaneous vaginal delivery was performed. A decision was made to leave the placenta in situ, and pelvic arterial embolization was performed. Subsequently, hemorrhage occurred, and laparotomy with removal of placenta percreta and the closure of the perforated uterine wall were performed [246].

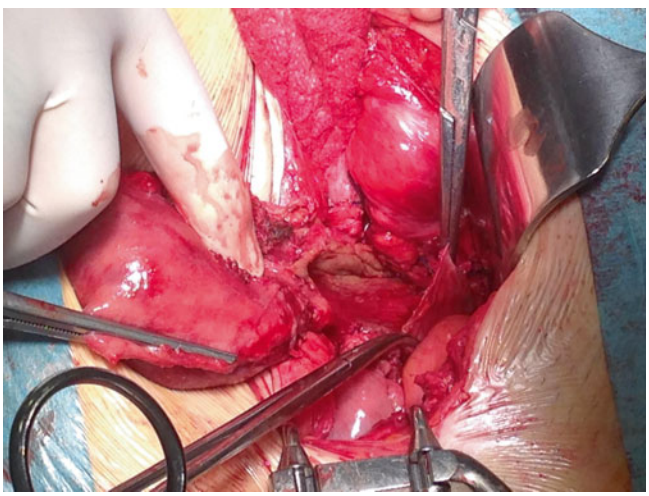

Fig. 10.22 Laparotomic image shows a spontaneous uterine rupture after ART

Intramyometrial pregnancy after IVF can cause uterine rupture at second trimester. A rare case of a twin intramyometrial pregnancy has been discussed, with pelvic pain, hemorrhage, and shock at 14 weeks of gestation. Surgical excision of pregnancy with adjust area of myometrium was performed [247]. In general, due to delayed diagnosis, intramyometrial pregnancy is managed by hysterectomy, but with early diagnosis of pregnancy with vaginal ultrasound, it may lead to early diagnosis and conservative management.

A uterine rupture was reported in a gestational carrier after embryo transfer. Although, a singleton pregnancy uterine rupture took place and the carrier had a hysterectomy [248].

Three rare cases of spontaneous rupture of subserous uterine veins have been reported after IVF achieved pregnancies. Rupture and intra-abdominal bleeding took place between 29 and 35 weeks of gestation. Exploratory laparotomy and appropriate treatment took place [249]. It is not clear whether this rupture of subserous uterine veins was due to in vitro fertilization or focal points of endometriosis that remained despite pregnancy. In pregnant patients that had endometriosis, awareness of such complication may lead to faster diagnosis and treatment, leading to uncomplicated pregnancy.

Spontaneous uterine rupture at 29 weeks has been observed during preterm labor of an IVF-conceived twin pregnancy. No risk factors have been observed and no explanation has been given for this [250].

10.11.2 Pathophysiology of Pregnancy That Leads to Uterine Rupture

Most of our cases involve a previous uterine trauma (from CS or myomectomy) that results in a sinus tract within the endometrium. Other mechanical reason includes false

passage creation through the cervix (difficult ET or dilatation and curettage) that leads to an ectopic embryo deposition in a later embryo transfer, thus leading to intramural pregnancy. Another pathophysiological factor is embryo penetration into the myometrium, because of increased trophoblastic activity and defective decidualization.

10.12 Laboratory Practices

10.12.1 Media Culture Effects

In a large retrospective study, the effect of media culture was analyzed on various newborn parameters, to minimize bias of investigating two different media (a commercially available, single-step culture medium and a commercially available sequential medium) on patients that undergo single embryo transfer. Also, fresh and frozen SET have been analyzed. From the results, it was found that there is no difference in all parameters of neonatal outcome, except the small-for-gestational-age (less than 10th percentile) babies born after frozen-thawed embryo transfer cycles that cultured with the single-step culture medium [251].

It was reported also that the age of the G-1 PLUS medium is inversely associated with birth weight, after controlling for all confounding factors. A difference of 234 g in birth weight is evident as the difference in age from media production to oocyte retrieval is up to 65 days [252].

In another retrospective study [253], the authors focused on the protein source of media for embryo culture. They compared two media, the GI-PLUS v5 media and the GI v5 media. They found differences in gestational age and infant gender-adjusted birth weight. More large-for-gestational-age infants are observed in the GI-PLUS v5 media group. They conclude that protein source affects birth weight in human.

Furthermore, in a prospective cohort study, two sequential culture media have been tested and found that in vitro culture of embryos in media from one company (Cook) resulted in singletons with a lower mean birth weight (adjusted mean difference 112 g) and more singletons with a LBW (2500 g) and LBW for GA ≥37 weeks, when compared with media from another company (Vitrolife AB). The same applied for twins [254].

It is questionable whether those differences exist in embryonic life. By measuring various parameters of fetal growth in the first and second trimester, researchers found that at around 8 weeks of gestation, fetal CRL showed no difference between the two different media compared while at 12 weeks of pregnancy, except nuchal translucency and PAPP-A that show no significance, but fB-hCG was significantly higher in the Vitrolife group.

At 20 weeks of pregnancy, head circumference and transcerebellar diameter were significantly higher in the Vitrolife group also. Increased fetal growth is associated with the Vitrolife group [255].

From animal studies, it is known that the addition of amino acids and protein in culture media leads to heavier offspring, but lack of serum inside these media leads to lighter offspring.

What about obstetric and perinatal outcomes after vitrification of oocytes? In a retrospective cohort study, they found no difference in all neonatal parameters, gestational age of delivery, birth weight and defects, perinatal mortality, and puerperal problems [256].

In another retrospective study, the authors compared the obstetric and neonatal outcomes between vitrified early cleavage embryos, slow freezing, and fresh transfers. They found that the mean birth weight of vitrified oocytes was higher (3455, 3 g) when compared to the other two groups. Perinatal mortality was the same in all transfer groups. No difference was observed in gestational age and preterm birth rate. In addition, fresh embryo transfers show the highest percentage of low birth weight white vitrified oocytes showed the lowest [257].

More studies are needed to better define the effect of culture media on embryo development. Further analysis of randomized controlled trials will lead to a conclusion.

10.13 Complications During Pregnancy

10.13.1 Preeclampsia

10.13.1.1 Preeclampsia: Male Factor

Several studies checked for preeclampsia in women that underwent ICSI. In a single-center, retrospective study, three groups have been compared, women that had ICSI with ejaculated or surgically obtained sperm, with women that underwent ICSI for female factor. There was 1.5 (0.67–3.22) times more risk for preeclampsia predisposition in male factor group, but no significant difference between the ejaculated and surgically obtained sperm. In parallel, there were significant differences between the two male factor subgroups and the female factor group [258].

In another retrospective study, 2392 single pregnancies that conceived either naturally or through IVF (4.5 %), when compared for preeclampsia, IVF pregnancies showed a percentage of 15.7 %. In addition, IVF pregnancies had significantly higher levels of sFlt-1 and lower levels of PIGF at 18 and 35 weeks of gestation. Increased antiangiogenic profile through gestation is associated with IVF pregnancies, and this might lead to abnormal placentation and preeclampsia.

In a large retrospective study of 3084 women that included IVF and not IVF pregnancies, preeclampsia was found in 15 (3.2 %) cases in the IVF group and 31 (1.2 %) cases in the non-IVF group. Patients with early-onset preeclampsia

(<32 weeks of gestation) was developed at two (13.3 %) for the IVF group and three (9.7 %) for the non-IVF group (NS). Preeclampsia severity was not different between the two groups (53.3 % versus 54.8 %, respectively). From this study, birth weight was significantly higher (3042.7 vs. 2988.1 g, $p=0.008$) in the IVF group, while no significant difference was observed between them. This is controversial, according to recent findings. Eventually, propensity score matching revealed no significant difference in preeclampsia in both groups [259].

No significant difference for preeclampsia was found between women that conceived after two or more failed IVFs [124] compared to the women that conceived after the first IVF [260].

10.13.1.2 Preeclampsia: Oocyte Donation

When examining donor oocyte cycles for preeclampsia, there is a significant difference for this pathologic entity in these cycles compared with autologous IVF [261].

In a retrospective, matched cohort study of 158 pregnancies, 77 ovum-donor recipient/81 autologous oocyte pregnancies were compared for preeclampsia or gestational hypertension in the third trimester. A significant difference was observed in ovum-donor recipients compared with women undergoing autologous IVF (24.7 % compared with 7.4 %, $P<0.01$, and 16.9 % compared with 4.9 %, $P=0.02$, for gestational hypertension and preeclampsia, respectively) [262].

10.13.1.3 Preeclampsia: Endometriosis

When it comes to endometriosis, a major factor for infertility, the incidence of preeclampsia was found in these women compared to normal woman (1.2 %) versus control (7.4 %) ($P=0.032$; OR = 6.6, 95 % CI: 1.2–37).

The odds of developing preeclampsia were 5.67 times higher in the normal women than in pregnancies after endometriosis-associated infertility, while on multiple gestation, no significant difference was found between the two groups. In both groups, there was an increased incidence of 1.93 times per additional child [263].

From another population-based study of 208,879 women with a singleton first delivery, 3239 had endometriosis. Of the 205,640 women without endometriosis, 4935 had an IVF cycle, and 841 of endometriosis women had IVF. The significant difference was found between the two groups for preeclampsia (OR 0.67 (0.4–1.1) $P=0.09$). When a regression model was built, there was no association between endometriosis and preeclampsia. The same applied for second or higher pregnancies following diagnosis of endometriosis [264].

10.13.1.4 Preeclampsia: Obesity

In a large hospital-based cohort study of 10,013 singleton pregnancies, which researchers controlled confounding factors for preeclampsia, the pregnancies after IVF, and obesity, higher risk of preeclampsia is observed compared to spontaneous nonobese pregnancies (OR 6.7, 95 % CI 3.3–13.8) [265].

When controlling for twin pregnancies in a population-based cohort study of twin deliveries, IVF treatment, parity, and maternal age are risk factors for preeclampsia. Also for women younger than 35 years that conceived following IVF treatments, an independent risk factor for the development of preeclampsia existed [266].

In another study, only in vitro fertilization was associated with an increased risk for preeclampsia (OR = 1.78, 95 % CI: 1.05–3.06), whereas intrauterine insemination (OR = 2.44, 95 % CI: 0.74–8.06) and ovulation induction (OR = 1.34, 95 % CI: 0.31–5.75) were not associated with the risk for preeclampsia [267].

Most importantly, IVF alone is statistically significantly associated with stillbirth, preterm birth, low birth weight, and low Apgar scores (<7 at 5 min), irrespective of the socioeconomic status of women that undertook it [268].

Another case report of preeclampsia in a 34-year-old woman was developed on a basis of lupus anticoagulant (LAC), anticardiolipin (ACL), and anti-dsDNA (ADD)-positive SLE and APLA syndrome, with multiple small cerebral infarcts. She had this pathological entity from 13. After her pregnancy conceived with IVF, she presented at 26 weeks of gestation with preeclampsia and HELLP syndrome. After CS, severe hypertension with CT confirmed multiorgan infarcts have been developed.

10.14 Twins and IVF

10.14.1 Chorionicity in Twins After IVF

In a large retrospective study, they found that ART twins were mostly dichorionic, and monochorionic twins were conceived either spontaneously or with ICSI [269].

A case of dichorionic triamniotic triplets was presented after blastocyst transfer in an IVF cycle. This pregnancy was complicated with twin anemia polycythemia that was diagnosed at 28 weeks of gestation. A single intraperitoneal transfusion was performed, thus extending pregnancy for 2 more weeks. In a recurrence anemia, cesarean section was performed [270].

In a small retrospective study, 17 cycles that ended to monozygotic pregnancies found that overall incidence is 1.3 %. No difference existed between women aged <35 years and ≥35 years (1.5 % and 0.8 %, respectively ($p=0.319$)). The same applied to ICSI and non-ICSI cycles (1.4 % vs. 1.0 %; $p=0.620$). Also, assisted hatching (AH) group showed no difference when compared to those without AH (0.9 % vs. 2.1 %; $p=0.103$). Blastocyst transfer did not contribute to the monozygotic pregnancies incidence when compared to

cleavage-stage embryo transfer (1.4 % vs. 1.3 %, respectively; $p = 1.000$). The incidence of each type of chorionicity, dichorionic-diamniotic, monochorionic-diamniotic, and monochorionic-monoamniotic was 33.3 %, 46.7 %, and 20.0 %, respectively [271].

The exact opposite picture is presented from a nested case control study of 6223 gestations. Although 131 monozygotic twins (2.1 % incidence; 2.0 % in autologous and 2.7 % in donor IVF cycles) have been diagnosed, 10 were dichorionic, and 121 were monochorionic. Young oocyte age, extended culture (non-cleavage embryos transferred on/after day 4), and year of IVF treatment cycle were significantly associated with monozygotic twins. Day 3-assisted hatching correlated more with dichorionic-monozygotic twins, whereas extended culture and day 5 blastocyst transfers correlated with monochorionic-monozygotic twins. Authors conclude that assisted hatching may play an important role in the type of chorionicity [272].

A slightly different outcome was presented after a large retrospective study of 4975 pregnancies after IVF, which combined autologous and donation cycles. Ninety-eight monozygotic pregnancies (2 %) have been diagnosed. When autologous oocytes have been transferred, MZT pregnancies have been at 1.7 and 3.3 % with donor oocytes. No significant difference was presented for younger women <35 years old either using their own oocytes (3.1 %) or donor oocytes. The majority of MZTs [79] occurred after the fresh blastocyst transfer (2.6 %), only 14 after day-3 transfer (1.2 %). Hatching did not pose any difference (1.3 % when hatching vs. 1.1 % with no hatching). ICSI also did not pose any difference when performed (2.4 % vs. 2.0 %) on monozygosity. Ninety-five percent of all monochorionic pregnancies have been confirmed as monochorionic-diamniotic [273].

From a large retrospective study from Japanese IVF registry, from 30,405 pregnancies conceived with ART technologies, 425 have been monozygotic. When blastocyst transfer was used (59,692 blastocyst transfers), 0.6 % (348) of monozygotic cases have been presented, while when the cleavage embryo transfer was used, 0.2 % [76] of such cases have been evident. Obviously, blastocyst embryo transfer significantly increases the incidence of monozygotic twins. All other parameters, like assisted hatching, maternal age, frozen-thawed embryo transfer, methods of blood stimulation, and whether ICSI was used, do not play a significant role in MZT.

In another large retrospective study of 9969 fresh-transfer cycles that ended in pregnancy, 234 MZT (2.4 %) have been observed. Of all transfers, 5191 were cleavage stage and 4778 were blastocyst stage. When analyzing, it was found that in the cleavage-stage group, 99 MZT (1.9 %) have been observed, while on the blastocyst ET group, there was 135 MZT (2.4 %). There was a significant difference for blastocyst transfer. As a confounding factor, increasing age was associated with a significant reduction in MZT, regardless of the transfer order. When controlling for patient age, other factors like the time period during which the cycle took place, the number and proportion of six- to eight-cell embryos, and the availability of supernumerary embryos did not result in significant difference in MZT rate when comparing blastocyst and day-3 embryo transfer [274].

10.15 Abnormal Placentation and IVF

10.15.1 Placenta Previa and IVF

There are not a lot of studies that directly associate placenta previa and IVF (Fig. 10.23). In most studies, placenta previa after IVF is presented as a parameter of the study. In addition, the numbers are low and either absolute or as a percentage.

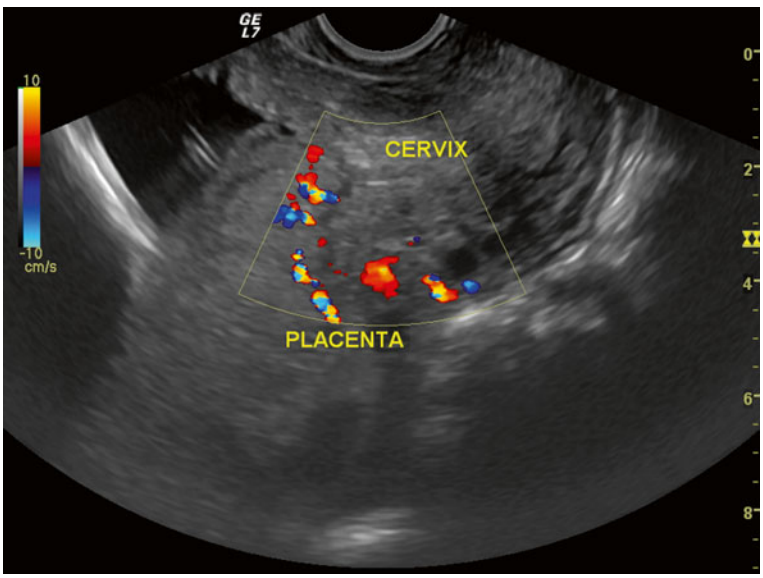

Fig. 10.23 An ultrasonographic image showing a central placenta previa after ART

Placenta previa represents a small % of overall pregnancies, ranging from 0, 22, to 0.54 % in normal conceived pregnancies but it rises to 1.59 % in singleton IVF pregnancies [275].

Vasa previa also is associated with in vitro fertilization [276]. Early associations between vasa previa and IVF exist in literature [277–279].

One of the earlier reports on twin pregnancies, when compared to spontaneous pregnancies with in vitro fertilization, found no difference in placenta previa [280]. Same results have been found from [281], in a case controlled study, that IVF does not appear to increase placenta previa. But in a meta-analysis for perinatal outcomes of singleton pregnancies after IVF, significant difference has been observed for this entity [282].

From a retrospective study of 47 patients with succenturiate lobes of placenta, IVF patients showed a significant higher incidence ($P<0.01$) for this placenta shape aberrations than unaffected controls [283].

Also for PCOS patients that undergone in vitro maturation and fresh ET, no difference has been observed in the rate of placenta previa, when compared with conventional IVF [284].

When performing a single embryo transfer, an increased risk for placenta previa has been observed when compared with the spontaneously conceived women ($n=15{,}037$). When comparing SET and DET for placenta previa, no difference was found [285].

In a population-based study in Norway, with 845,384 pregnancies, after IVF, a sixfold increase of the risk of placenta previa in singleton pregnancies was found compared with naturally conceived pregnancies [adjusted OR 5.6, 95 % confidence interval (CI) 4.4–7.0]. In parallel, for women with consecutive pregnancies, both natural and after assisted fertilization, the risk of placenta previa was nearly increased threefold in the pregnancy following assisted fertilization (adjusted OR 2.9, 95 % CI 1.4–6.1), when compared with the risk in the naturally conceived pregnancy [286].

After IVF, placenta previa was associated with first trimester intrauterine hematomas (OR, 8.7 95 %; CI 3.4–22.2) [287]. Also, from a retrospective study of 318 IVF pregnancies, it was found that endometriosis (odds ratio = 15.1; 95 % CI = 7.6–500.0) and tubal disease (odds ratio = 4.4; 95 % CI = 1.1–26.3) are significantly associated with placenta previa [288]. In general population, increased maternal age (≥30 year) is an independent risk factor for placenta previa [289].

When comparing pregnancies after fresh and frozen ET, significant differences for placenta previa and third trimester bleeding were observed ($p=0.002$). Placenta previa was more common after fresh ET [290]. In addition, birth weight was significantly lower after fresh ET.

10.15.2 Placenta Accreta and IVF

From another case control study, a strong association has been observed between cryopreserved embryo transfer and placenta accreta (Fig. 10.24) (adjusted OR 3.20, 95 % CI 1.14–9.02). Also, these patients with placenta accreta had the lowest endometrial thickness and estradiol levels [291]. Also, from a British case control study, IVF pregnancy is a risk factor for placenta accreta/increta/percreta (adjusted OR 32.13, 95 % CI 2.03–509.23) [292]. In a retrospective study of women with placenta accreta but without previous cesarean section, the rate of pregnancies obtained by IVF was higher (5/35 [15 %] vs. 2/63 [3 %], [$P=0.05$]) when compared to normal conceived pregnancies [293].

Furthermore, in a rare case report from a twin pregnancy of a 33-year-old patient, a sack was a complete mole; the other sack contained a fetus and placenta accreta. Embryo survived and was delivered at 37 weeks of gestation after CS, and subsequently with a hysterectomy for the placenta anomalies, the molar pregnancy, and the placenta accreta was performed [294].

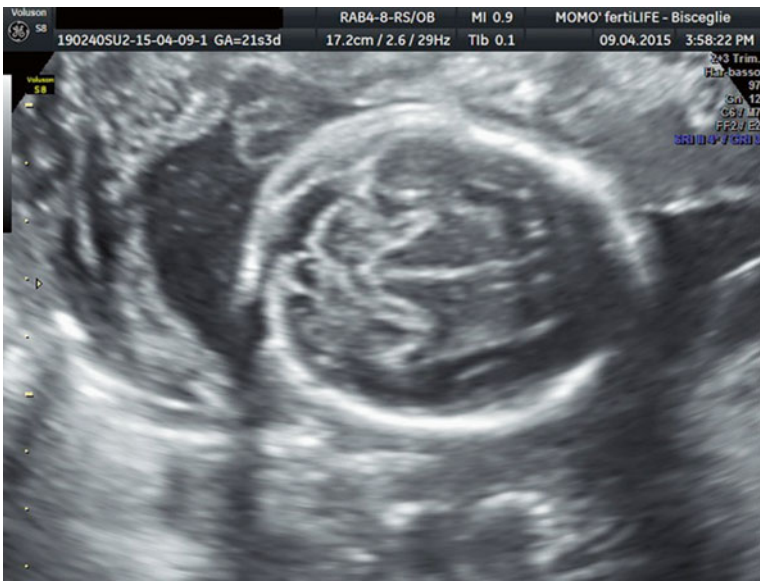

Fig. 10.24 A placenta accreta in a pregnant at 21 weeks; at 29 weeks, patient was urgently operated for cesarean section for massive bleeding, with a successive cesarean hysterectomy

10.16 Embryo, Child, and Delivery Effect After IVF

10.16.1 Sex Ratio

Children born after testicular sperm aspiration and ICSI when evaluated for singleton and twins outcomes together show a significantly lower sex ratio (♂/♀) against males (0.47 %) compared with conventional IVF (1.11; $P=0.017$) [295]. On the other hand, when this analysis transferred to singletons and twins only, no significant difference was observed.

10.16.2 Birth Defects

There is a great deal of controversy whether ART and especially ICSI are associated with birth defects. Studies include limited data and limited long-term follow-ups of infants born after IVF. Studies of special defects do not exist. Factors that may predispose to birth defects include the underlying infertility of couples, the ART procedures themselves, paternal subfertility with a genetic background, and female infertility itself, comparing ICSI with standard in vitro fertilization (IVF).

In a small retrospective study of 74 ART children born after the transfer of very poor-quality embryos compared with 1507 children born after the transfer of very good-quality embryos, no significant difference was found in the prevalence of birth defects, the rate of chromosomal abnormalities, and the perinatal mortality rate [296]. Congenital malformations are associated with the reason for infertility and not the ART technique [297].

From a large retrospective study of 978 births, 56 (5, 7 %) infants have been found with major malformations. An increase in the risk for these malformations has been observed (OR = 2.04), and the IVF group showed a 2.73 times higher prevalence than ICSI group, from major malformations. In this study, no other causes have been taken into account [298]. In a meta-analysis of Lie et al. [299], overall risk of a major birth defect after ICSI after comparing after standard IVF is estimated at 1.12, 95 % CI: 0.97–1.28, $P=0.12$, while no significant difference for cardiovascular defects, musculoskeletal defects, hypospadias, neural tube defects, or oral clefts was observed [299].

A very interesting study compared pregnancy outcomes from children conceived after ICSI both with ejaculated or aspirated sperm with normal IVF and naturally conceived pregnancies [295].

For singleton boys conceived with epididymal/testicular sperm, an increased rate of cardiac malformations (3.6 %) (such as Fallot's tetralogy and ventricular septal defects) was observed when compared with singleton boys after conventional IVF [295]. Also, twins that undergone ICSI with epididymal/testicular sperm showed an increase rate of neoplasms in bones and joints, thus indicating the role of imprinting related disorder [295].

However, in a large meta-analysis [300] involving 124,468 infants, the authors found no significant difference in birth defects between IVF and ICSI, but a significant risk difference has been found when compared with normal conceived children. It was evident for genitourinary, digestive, circulatory, myoskeletal, eye, ear, face, neck, and especially for the nervous system (RR ¼ 2.01, 95 % CI 1.27–3.20). They conclude the difference of the results from previous studies in the way data are collected. They do think that hospital-/clinical-based studies underestimate the rate of birth defects.

A retrospective study of 7120 IVF patients compared with 11,890 patients who received other fertility treatments and patients in the control group found that the relative risk for birth defects (RR 1.43 (95 % CI 1.19–1.72)) is increased for singleton infants. Specific defects associated with IVF/ICSI have been reported also in this study, like patent ductus arteriosus, hypospadias, and obstructive defect in the renal pelvis and ureter [301]. From the EVIAN decision group [302], no increased risk of birth defects and no difference in cognitive function were found in ART children. On the other hand, lower birth weight and higher fasting glucose concentrations have been observed in these children. No direct link could be established between IVF treatment and congenital anomalies, but rather an association of parents' age with these anomalies.

10.16.3 Perinatal Mortality

No difference was found at perinatal mortality rates [295, 303]. A recent study [304] focused in birth asphyxia. Singletons after IVF had an increased risk for low Apgar score (<4) (it can be more readable [OR] 1.29; 95 % CI, 1.14–1.46) and intrauterine fetal death (adjusted OR 1.61; 95 % CI, 1.35–1.91).

10.16.4 Neonatal Complications

Increased incidences of twin pregnancy and low birth weight ($P<0.01$) have been observed in IVF group, but decreased average birth weight ($P<0.05$) when compared with the control group [305].

10.16.5 Mother

In the IVF group, mother's age was increased [305] with higher incidence of cesarean section. This is also true for women over 35 years old [303]. When comparing for

testicular sperm aspiration, significantly, more cesarean sections have been performed after IVF (27.3 % for singletons) and ICSI (25.1 % for singletons) with ejaculated sperm compared with the aspirated sperm group (16.4 % for singletons) [295].

10.16.6 Pregnancy Complications

In pregnancy, complications considered are lower birth weight, very low birth weight, small for gestational age, and perinatal mortality.

When controlling factors contributing to adverse perinatal outcomes in singleton IVF, one is premature rupture of membranes [305], with spontaneous onset [303] and lower average birth weight. Preterm birth at different stages and intrauterine growth restriction are increased [306]. These singletons show a significant tendency for late preterm birth at 32–36 weeks (RR 1.52, 95 % CI 1.01, 2.30) [306], moderate preterm birth <32–33 weeks (RR 2.27, 95 % CI 1.73, 2.97), very LBW (<1500 g, RR 2.65, 95 % CI 1.83, 3.84), and a mean birth weight (−97 g, 95 % CI −161 g, −33 g).

Same findings are reported elsewhere. In a large Danish cohort study [307], mean birth weight was 65 g ([CI], 41–89] lower in all assisted reproductive technology children. Also, higher risk of low birth weight ([OR], 1.4; 95 % CI, 1.1–1.7]) and preterm birth (OR, 1.3; 95 % CI, 1.1–1.6]) was observed in IVF/ICSI children compared with spontaneous conception children.

In a meta-analysis [308], the factors for preterm birth in singleton pregnancies were examined. Might be eradicated that time to pregnancy (TTP) is one factor (spontaneous conception with (TTP) >1 year, IVF/ICSI singletons from subfertile couples with TTP > 1 year, IVF/ICSI singletons, singletons with a "vanishing co-twin," conception after ovulation induction, and/or intrauterine insemination). More specifically, when IVF/ICSI singletons have been examined, compared with spontaneous conception singletons from subfertile couples (for more than 1 year); preterm birth was significantly increased in the IVF group (OR 1.55, 95 % CI 1.30, 1.85). When it comes to conception after ovulation induction and/or intrauterine insemination compared with SC singletons (where time to pregnancy is ≤1 year), preterm birth is higher in the ART group (AOR 1.45, 95 % CI 1.21, 1.74).

In between ART technique comparison, ICSI versus IVF, lower risk of preterm birth was observed (AOR 0.80, 95 % CI 0.69–0.93) for ICSI. The same was applied for frozen embryo transfer when compared with fresh embryo transfer (AOR 0.85, 95 % CI 0.76, 0.94).

In the Chinese population, also increased incidence of low birth weight and decreased average birth weight was observed [305].

10.16.6.1 Vanished Twins and Pregnancy Complications

Vanished pregnancy (twins and triplets) is a different entity, but contributes to pregnancy complications. The risk of preterm birth in singletons with a "vanishing co-twin" versus a single gestation is against IVF siblings (AOR of 1.73 (95 % CI 1.54, 1.94) [308, 309].

In a retrospective study by Barton et al. [309], significantly lower mean birth weight (2192 g ($P=0.01$)) was observed in the vanished triplet group with a 64 % with at least one infant with LBW.

Preterm birth <37 weeks of gestation is affected at 83 % of the vanished triplets and 73 % of the non-varnished twins. However, vanished triplets had an increased risk of early preterm birth (<32 weeks) (OR 3.09, 95 % CI 1.63–5.87), and the length of gestation of these pregnancies was on average 1.5 weeks shorter [309].

In another study [310], preterm birth before 28 weeks was significantly increased by 7 % compared with 1, 2 % of normal singletons. In a study of vanishing twins in the Chinese population, lower mean birth weight and increased preterm delivery rate were observed [311].

10.16.6.2 Effect on Gestational Age

The mean gestational age (GA) for singletons delivered after testicular sperm extraction is (279 ± 12 days). This is significantly higher compared with the gestational age of IVF children (276 ± 18 days; $P=0.02$) [295]. In twin pregnancies, the duration of gestation (−0.5 weeks, 95 % CI −1.2 weeks, 0.2 weeks) was not significantly different compared to spontaneously conceived twins/IVF twins [312].

10.16.6.3 Low Birth Weight

IVF, prematurity, twin pregnancy, and pregnancy complications were risk factors for low birth weight [305] with IVF infants presenting the higher incidence of LBW. From two meta-analysis [306, 312], it is clear that IVF singletons present with LBW <2500 g (RR 1.60, 95 % CI 1.29, 1.98) and very LBW <1500 g (RR 2.65, 95 % CI 1.83, 3.84) when compared with spontaneously conceived singletons. The same is applied to twins. They present with LBW <2500 g (RR 1.14, 95 % CI 1.06, 1.22), very LBW <1500 g (RR 1.28, 95 % CI 0.73, 2.24), and extremely LBW <1000 g (RR 0.88, 0.04, 19.40) when compared with spontaneously conceived twins. When elective single embryo transfer is performed, the LBW is decreased (RR 0.25, 95 % CI 0.15–0.45) compared with double embryo transfers, but not when compared with spontaneously conceived singletons (RR 2.13, 95 % CI 1.26–3.61) [313]. When the sperm was extracted from the testes (TPT), the adjusted risk of LBW was significantly higher for offsprings that came from TPT versus NC singletons [adjusted odds ratio (AOR) = 0.67 (0.48–0.93)]; [295]. Vanishing twins may play an important role in low birth

weight. When vanishing twin pregnancy was diagnosed, the proportion of low birth weight (<2500 g) in remaining embryo was 33.3 % versus 11.7 % ($P=0.0001$) and very low birth weight (<1500 g) 3.5 versus 0.6 %, when compared with singleton IVF pregnancies, respectively [310].

Although children conceived with IVF showed significantly lower birth weight that may act as an important predictor of mental development, these children present with no differences on long-term growth and neurodevelopment of children compared with spontaneously conceived children [314].

Low birth weight is associated with a high number of oocytes (>20) retrieved (OR 1.17, 95 % CI 1.05–1.30), while no increased risk for LBW is found for normal response (10–15 oocytes) and poor response (≤3 oocytes) patients OR 0.92, 95 % CI 0.79–1.06 [315]. An association of media culture and the newborn birth weight is already indicated, but it will be further developed in the appropriate chapter.

10.16.7 Paternal Factor

Several factors have been implicated in male infertility. In infertile men with reciprocal translocation of autosomal chromosomes usually on their efforts to conceive, partners undergo abortions due to unbalanced translocations of the embryos. In a case report a male underwent testicular sperm extraction and IVF with preimplantation genetic screening [316] in a well-designed case control study, men with azoospermia and oligozoospermia (but without obstructive azoospermia, varicocele, cryptorchidism, hypogonadotropic hypogonadism, karyotype abnormalities, or complete deletion of AZF a, b, or c). SNPs rs7867029 and rs7174015 are associated with oligozoospermia; SNP rs12870438 is associated with azoospermia and oligozoospermia but no associations between rs724078 and azoospermia or oligozoospermia have been found [317]. A deletion mutation of adenine in location 11,337 of the Nsun7 gene in asthenospermic men has been found [318].

Advanced paternal age (PA) is associated with reduced semen volume; reduced sperm count, motility, and morphology; and a significant increase in the prevalence of both genomic and epigenomic sperm defects [319].

10.16.8 Explanations Given from Basic Sciences

10.16.8.1 DNA Methylation

DNA methylation differences observed between ART and in vivo conceptions are associated with some aspect of ART protocols [320]. Placental DNA methylation levels have been checked at 37 CpG sites in 16 candidate genes. Twenty of the 37 CpGs analyzed had been identified as differentially methylated between ART and fertile control groups. Also, differences in placental DNA methylation have been observed in 12 CpG sites, between oocyte donor offspring and fertile control groups.

Although children conceived through IVF have a higher incidence of preterm birth and lower birth weight, clinical follow-up for 7 months to 3 years showed that none of the children had clinical symptoms of any imprinting diseases. Also, all children had normal DNA methylation patterns at six DMRs (KvDMR1, SNRPN, MEST, MEG3, TNDM, and XIST) [321].

When it comes to ICSI evaluation, malformation rates in these offspring ranged from 3.5 to 6.2 %. At 3 years of age ($n=811$), the proportion of children at risk for developmental delays was 10.4 % in ICSI and 10.7 % in *IVF* singletons. For singleton pregnancies, obstetric and neonatal outcomes are dependent upon maternal age, while epigenetic analysis of these fetuses found minor imprinted gene expression imbalances [321, 322].

10.16.8.2 Maternal Factors

Placental Animal Studies Associated with Lower Birth Weight

Although placenta weight shows no difference between IVF (ICSI or IVF) and normal conceived mice, the levels of placental estriol were significantly lower in the ART group, thus showing the efficiency of total steroid production. Levels of steroid metabolites androstane-3alpha-17beta-diol glucuronide and dehydroepiandrosterone sulfate were higher in fetal compared to maternal blood in ART-conceived animals. The authors conclude that the ART placenta has greater capacity to metabolize and remove steroids through glucuronidation and that this phenomenon is associated with lower steroid hormone levels transiting the placenta to the fetal unit [323].

Based on the fact that since steroid hormones, especially progesterone, prevent oxidative stress and inflammation in pregnancy, the same authors proved that placental inflammation and oxidative stress exist in ART placenta and may mediate low birth weight.

Placentas from ART contained significantly less lipids, with greater levels of apoptosis and degraded nucleotides. No significant difference was observed in placenta reactive oxygen species between ART placenta and normal conceived embryos. In parallel, maternal livers from normal fertilization had less ROS than maternal livers from ART. Placentas from ICSI pregnancies had lower activities of superoxide dismutase (SOD), thioredoxin reductase (TrxR), xanthine oxidase (XO), catalase, glutathione-S-transferase (GST) glutathione peroxidase, and glutathione reductase (GR). Furthermore, GR, GST, and SOD were also lower in fetal livers from ICSI pregnancies. Placentas from IVF pregnancies had decreased levels of SOD, TrxR, and XO; only both ICSI and IVF pregnancy IL-6 levels were significantly increased. The authors conclude that IVF/ICSI is associated with placental inflammation (IL-6), oxidative stress, and apoptosis [324].

In another study [325], researchers examined the placental growth and function and its association with fetal weight. Although placental weights did not differ also, between IVF and natural mating embryos, proliferation was increased in IVF placentae. Both fetal weights and fetal-to-placental ratios were lower in the IVF group. Also in these placentas, the mRNA for selected glucose, system amino acid transporters, and imprinted genes was downregulated. Also, GLUT3 protein level was decreased in the IVF group. Fetal accumulation of glucose was not different, but the amino acid accumulation was significantly (36 %) lower in IVF fetuses.

The same working group tried to define whether changes in placental structure take place and assess the net flow of hormones between the maternal, placental, and fetal circulations. ART increased 3β-HSD activity in maternal livers, but there were no other changes in 3β-HSD- or CYP17-mediated steroidogenesis. Cholesterol levels were significantly lower in maternal livers of ICSI pregnancies and in placentas from both IVF and ICSI pregnancies. Progesterone levels were higher in maternal and fetal livers after IVF and ICSI, respectively, but were significantly lowered in ICSI placentas, compared to normal fertilization. No differences in E1 or E2 levels were observed in maternal livers but ICSI significantly increased both E1 and E2 levels in placentas, while both IVF and ICSI significantly lowered E1 but raised E2 levels in fetal livers. In summary, while steroid production was normal, steroid diffusion/flow from mother to fetus was altered in murine pregnancies conceived by ART [326].

Embryo biopsy (single blastomere removal from cleavage-stage mouse embryos) affected the levels of steroids (estradiol, estrone, and progesterone) in fetal and placental compartments, but in maternal tissues, decreased activities of steroid clearance enzymes (uridine diphosphate-glucuronosyltransferase and sulfotransferase) were observed in IVF placentas; the weights of fetuses derived from biopsied embryos were lower than those of their non-biopsied counterparts [327].

From placentas from biopsied cleavage embryos, the same authors found an activation of MMP9, activation of STAT1, and lower levels of SOCS2 and SOCS3, thus indicating that Janus kinase/signal pathway may be associated with premature rupture of membranes and preterm birth [328].

Abnormal placentation may be another cause for low birth weight in ART offspring. Also in a mouse model, fetuses from IVF blastocysts showed a modest but significant delay in development compared with normal blastocysts. In addition, IVF conceptuses were consistently smaller than normal blastocyst fetuses.

IVF mice have a higher abortion rate, smaller fetuses, and relative larger placentas. The fetal placentation area is smaller but morphologically normal in IVF mouse, so the placental-to-fetal ratio was larger in the IVF group [329].

Conclusion

One of the minor complications that literature neglects is the accidental puncture of the bowel (Fig. 10.25). Often the bowel is adherent to the internal genitalia, for diseases

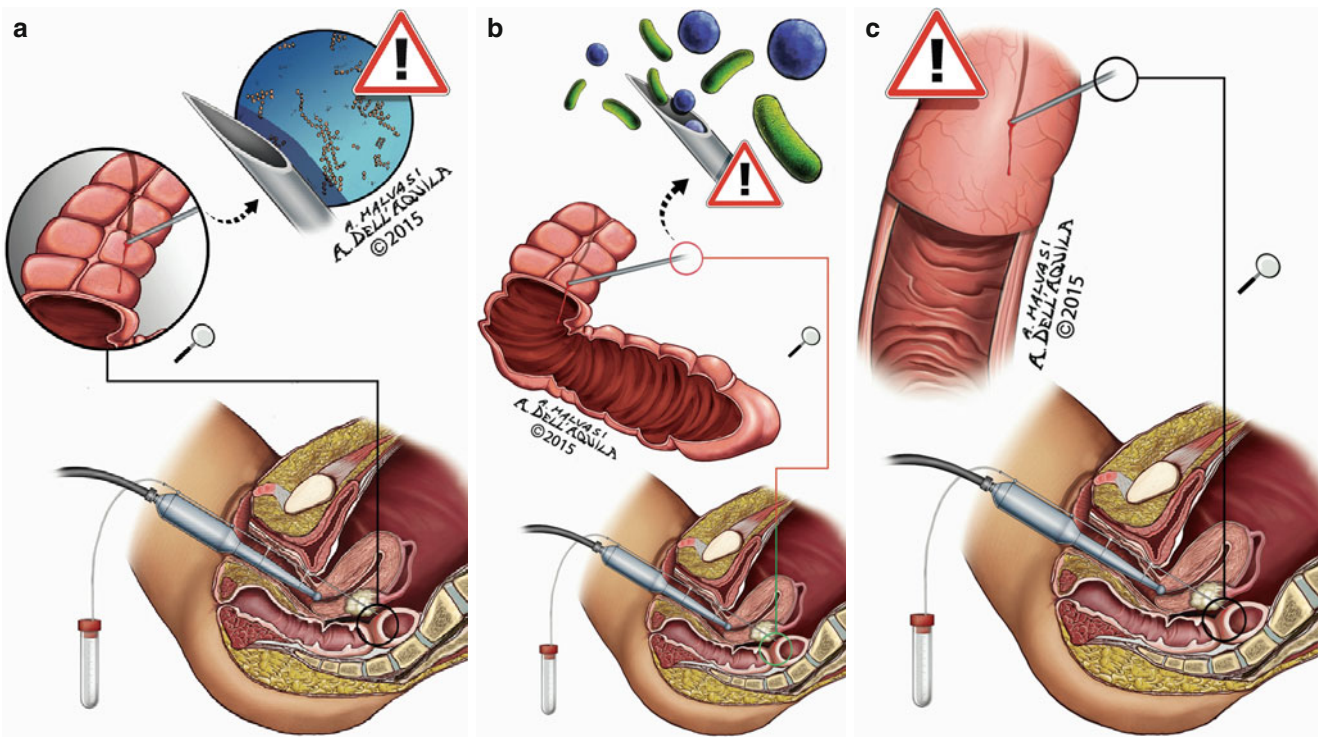

Fig. 10.25 (**a**–**c**) An accidental puncture of bowel with bacteria spreading: on the *left* is represented *streptococci*; on the *right*, *enterococci*

such as endometriosis, pelvic inflammatory disease outcomes, previous interventions, etc. Normally, after the accidental puncture of the intestine, nothing serious happens, since the drilling is minimal and closes again immediately. Sometimes, however, it may be that intraintestinal bacteria can spread in the abdominal and pelvic cavity and can cause abdominal infections.

Current notion is that complications of pregnancy depend rather on the pathophysiology and the genetic basis of infertility than on the technique of ART.

IVF complications may serve as a base to study pathophysiologic mechanisms of common gynecologic and obstetrics diseases.

This chapter might help viewers understand the complexity of in vitro fertilization and all possible complications that may arise even when the operator is very experienced.

Techniques may have a high accuracy and safety record, but underlying pathophysiology from infertility or from the pharmacological intervention may lead to more unstable condition.

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Spontaneous Uterine Rupture Prior to Twenty Weeks of Gestation

11

Stephanie H. Guseh, Daniela A. Carusi, Andrea Tinelli, and Antonio R. Gargiulo

11.1 Introduction

Rupture of the gravid uterus is a rare obstetrical emergency that is immediately and simultaneously life threatening to both mother and fetus. An infrequent occurrence during labor and at the end of a pregnancy, this complication is even more infrequent during the first 20 weeks of gestation (Fig. 11.1). Although the overall rate of uterine rupture has increased significantly over the last few decades – likely paralleling the rising rate of cesarean deliveries [52], uterine rupture early in gestation is still extremely uncommon (Fig. 11.2). Here, we review in detail the risk factors for early uterine rupture in addition to the common interventions for this rare catastrophic event.

11.2 Definition

Uterine rupture refers to complete separation of the uterine wall in the absence of direct penetration (Fig. 11.3) and is described almost exclusively in pregnancy. The gravid uterus is highly vascular, leading to significant hemorrhage when arterial branches and vascular sinuses become exposed. Rupture may occur in three contexts: labored, in which one area of the uterus separates under the contractile myometrial forces; spontaneous, referring to a tear in the uterus in the absence of regular contractions and traumatic, in which blunt force pressure disrupts the myometrium. In contrast, uterine perforation refers to an iatrogenic tear in the myometrium, caused by surgical instruments or trauma from a penetrating object (Fig. 11.4). Unlike later pregnancy, during which labor accounts for the majority of uterine ruptures, rupture in the first half of pregnancy is generally spontaneous.

11.3 Risk Factors

Certain risk factors place women at risk of suffering an early rupture, most notably uterine anomalies (Fig. 11.5), abnormal placentation, prior uterine surgery (Fig. 11.6), ectopic pregnancies (Fig. 11.7), and uterine tissue abnormalities – such as those following radiation exposure. Particularly when combined, the above features in a patient's history should alert the clinician to the possibility of an early, spontaneous rupture.

11.4 Uterine Anomalies

Uterine rupture during a woman's first pregnancy is an extremely rare occurrence. A rupture in the unscarred uterus, during either the first or early second trimesters, is nearly always the result of a congenital uterine anomaly [28]. Uterine anomalies occur in up to 9.8 % of the general population, many of which are undiagnosed prior to a woman's first

S.H. Guseh, MD • D.A. Carusi, MD
Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: dcarusi@partners.org; sguseh@partners.org

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

A.R. Gargiulo, MD, PhD (✉)
Center for Infertility and Reproductive Surgery and Center for Robotic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: agargiulo@partners.org

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_11

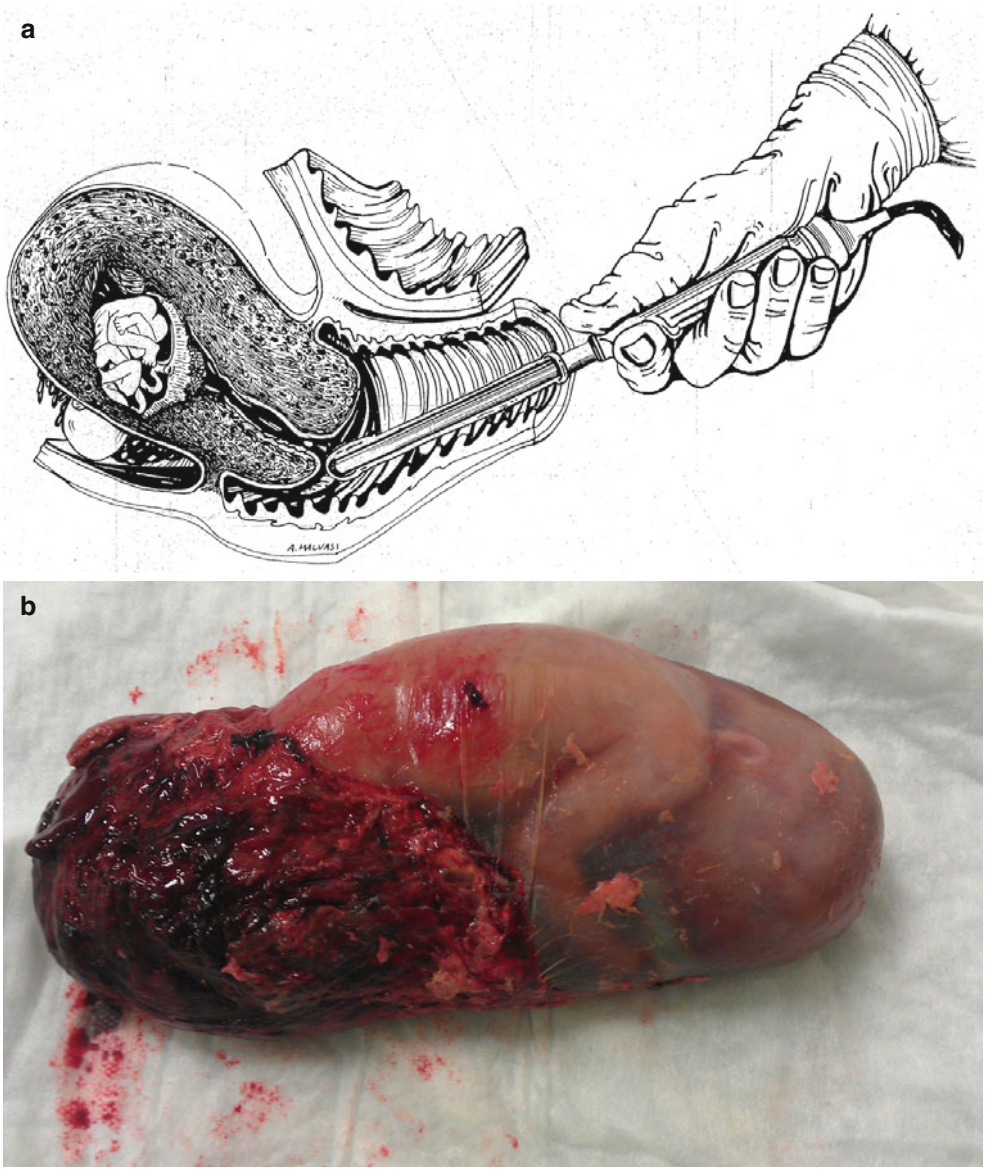


Fig. 11.1 A spontaneous posterior uterine rupture, detected by transvaginal ultrasonography in a patient at 11 weeks of pregnancy (**a**); the fetus inside the gestational sac, expelled with placenta in abdominal cavity (**b**)

attempt at conception [11]. Such anomalies include arcuate, septate, bicornuate, didelphys, and unicornuate uteri. There have been no studies defining the impact of uterine anomalies on uterine rupture exclusively prior to 20 weeks of gestation. Even studies investigating pregnancies later in gestation have shown discrepant findings. One group found an 8% rate of uterine rupture during labor in women with uterine anomalies, which was statistically different than the control group [51]. A more recent cohort, however, found no difference and recorded no incidences of rupture in their study population [14].

There is likely a greater rate of early uterine rupture among anomalies that confine a growing pregnancy to a restricted space or have poorly developed musculature, such as bicornuate, didelphys, or unicornuate uteri [28]. Rupture typically occurs in the late first or early second trimester in pregnancies within a communicating rudimentary horn, as the malformed organ fails to adequately expand [28]. The incidence of such pregnancies has been reported to be approximately as common as 1/40,000 to 1/150,000 pregnancies [42, 58]. Although such pregnancies are prone to rupture and life-threatening hemorrhage, early identification and intervention has led to a marked reduction in mortality – from 23% around 1900 to less than 0.5% in the year 2000 [42].

Case reports of spontaneous uterine rupture secondary to implantation in a bicornuate or unicornuate uterus have ranged in timing from 9 to 20 weeks. All of these ruptures were treated with emergent laparotomy secondary to acute abdominal pain and evidence of active hemorrhage [10, 23, 28]. Of note, one additional report of rupture of a pregnancy within a noncommunicating uterine horn was described in the setting of an 18-week induction-termination with misoprostol [54].

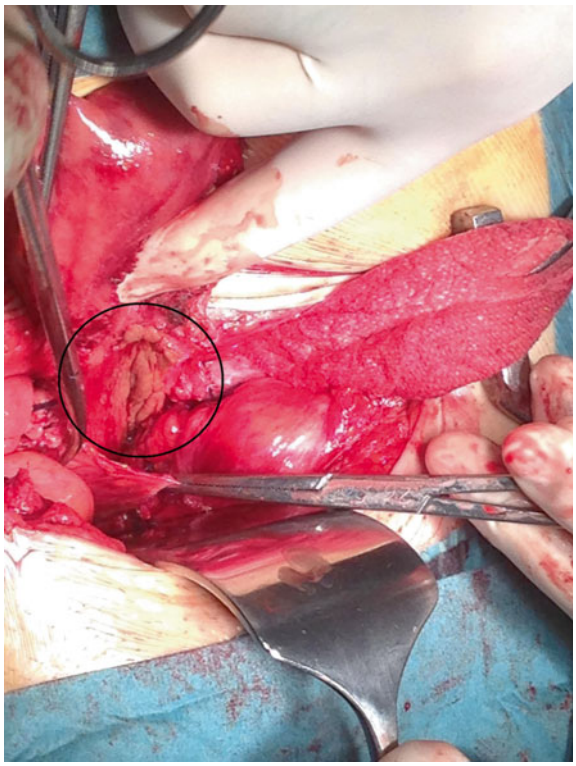


Fig. 11.2 An urgent laparotomy for anterior uterine rupture at 14 weeks of pregnancy; uterine rupture is highlighted under the index finger of the surgeon, in the black ring

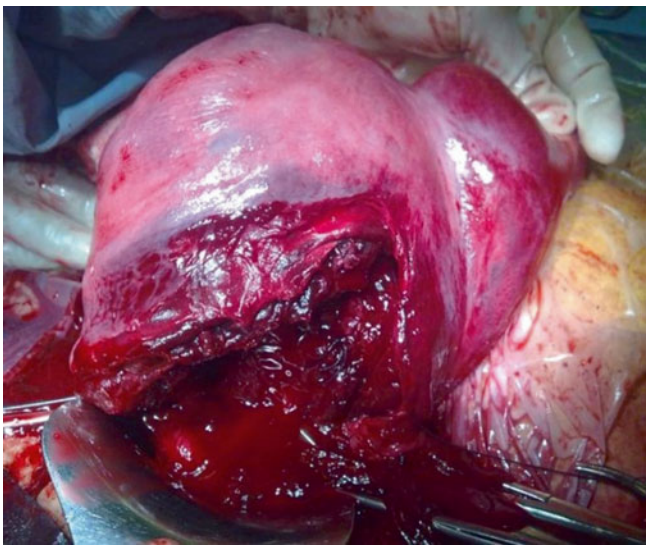
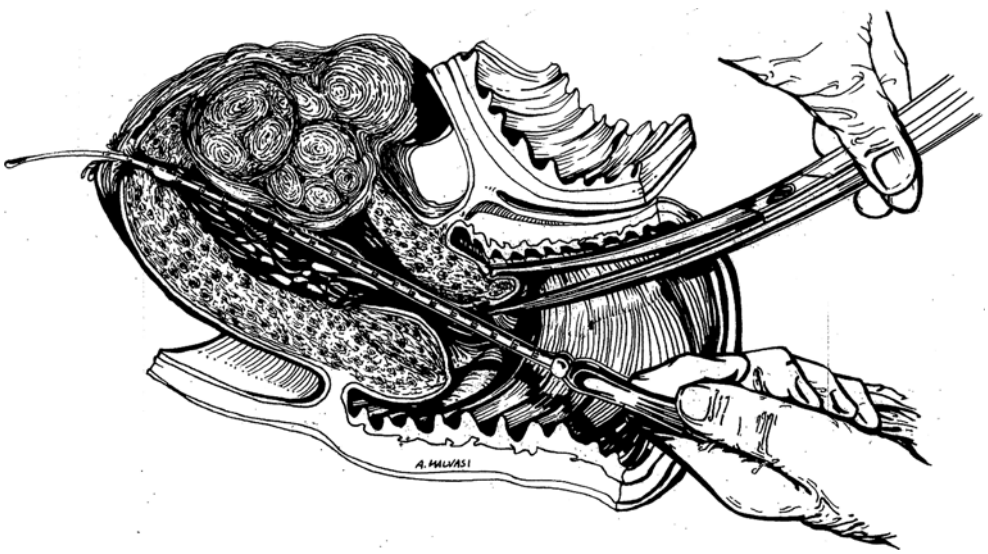


Fig. 11.3 A spontaneous uterine rupture, detected during a laparotomy in a patient at 19 weeks; uterine rupture refers to complete separation of the uterine wall in the absence of direct penetration

Fig. 11.4 The figure shows a uterine perforation by hysterometer, in a uterus with anterior multiple fibroids; this condition can facilitate a subsequent uterine perforation (by creating an iatrogenic tear in the myometrium)



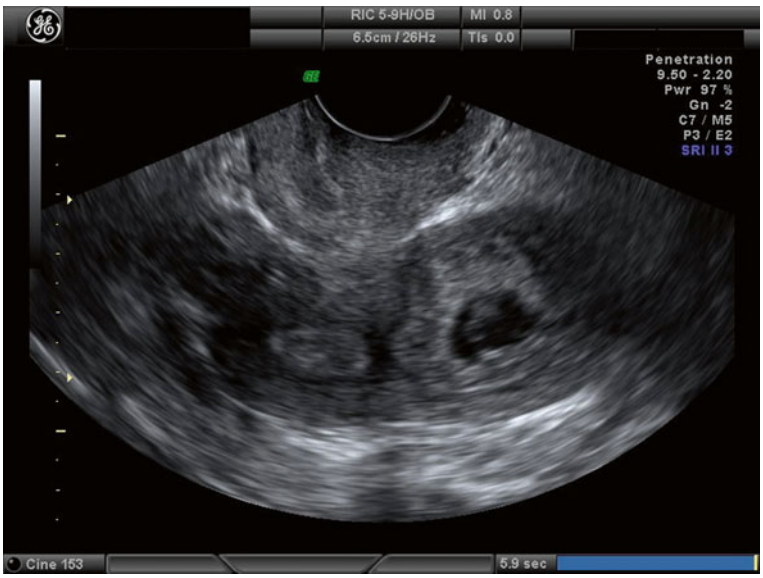


Fig. 11.5 The ultrasonographic transvaginal image shows a bicornuate uterus at 7 weeks of pregnancy, a risk factor for uterine rupture, especially in case of previous uterine surgery

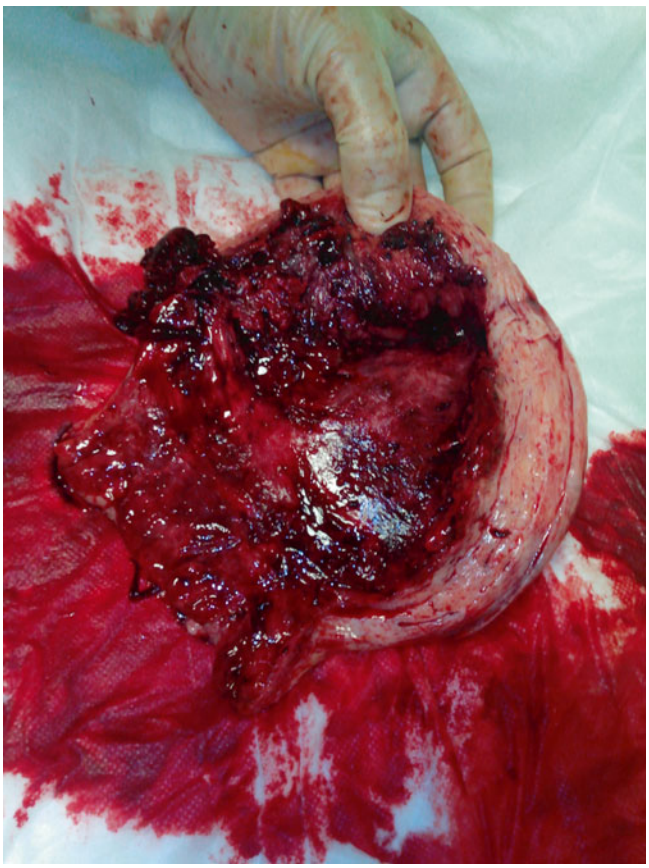


Fig. 11.6 A surgically scared uterus removed laparotomically during second trimester of pregnancy for a spontaneous rupture and massive hemoperitoneum; the photo shows the placental fragments attached to uterine walls

11.5 Abnormal Placentation

In addition to uterine anomalies that restrict a growing pregnancy, the presence of abnormal placentation in normal and abnormal uteri represents another large group of women who are at risk of early uterine rupture [3, 15, 30, 38, 47, 50, 62].

Abnormally adherent and invasive placentas are believed to result from a defect in the uterine decidua basalis and can only formally be diagnosed on pathologic review [41].

Morbidly adherent placentation may be classified as one of three subtypes: placenta accreta, in which chorionic villi attach directly to the myometrium; placenta increta, in which there is partial invasion of the myometrium; or placenta percreta, in which there is complete penetration of chorionic villi through the uterine wall [34].

Although major risk factors for placenta accreta include the presence of a placenta previa or history of prior uterine surgery (including manual extractions of the placenta), accretas have been described without these risk factors. The incidence of placenta accreta is approximately 1 in 500, and this number has been steadily rising, likely secondary to the increasing rate of cesarean deliveries [40, 65].

Although increasing efforts are being directed at early recognition of placenta accreta through advances in sonography, several reports in the literature describe the event of uterine rupture as the index sign of abnormal placentation as early as 14 weeks [15].

Ruptures have been most often described in the setting of placenta percreta, with complete placental invasion through the uterine wall or a prior scar. Because progres-

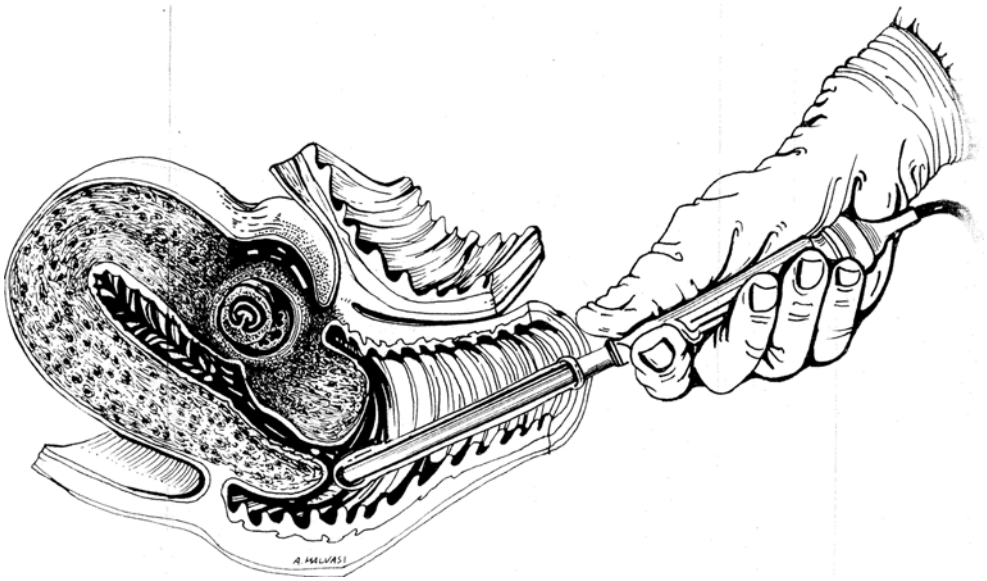


Fig. 11.7 An ectopic pregnancy leading to a successive uterine rupture

sive placental invasion into and through the myometrium is a painless process, patients may not present until the time of a uterine rupture, when intraperitoneal bleeding results in abdominal pain or signs of shock [3, 47]. Such early uterine ruptures, especially in patients without known risk factors for placenta accreta, can result in sudden morbidity and mortality [38].

11.6 Uterine Anomalies and Abnormal Placentation

Although there are selected cases of uterine rupture in the setting of a uterine anomaly and an otherwise normally developing pregnancy, there are many more reported instances of uterine rupture secondary to abnormal placentation within a malformed uterus [4, 44, 58]. These cases of rupture similarly presented between 14 and 16 weeks of gestational age with severe abdominal pain and evolving shock and were found to have a ruptured rudimentary horn at the time of laparotomy [4, 44, 58].

The first case of placenta accreta described in a rudimentary horn pregnancy was in 1983 [24]. Since that time, other case series have been published highlighting the increased incidence of placenta accreta within rudimentary horns and their ensuing tendency to cause preterm, often previable, deliveries. One review identified 8 cases of placenta accreta among a total of 97 rudimentary horn pregnancies, all of which were delivered preterm and 7 of which suffered spontaneous rupture [44]. One proposed theory behind the higher incidence of abnormally adherent placentation among pregnancies within uterine anomalies is the scant decidualization within underdeveloped horns [44].

11.7 Prior Uterine Surgery

Perhaps the most widely known risk factor for uterine rupture is a history of prior uterine surgeries, including cesarean section, myomectomy, cornual resection, and metroplasty [21, 37]. However, these are most often reported as labored ruptures in the second half of pregnancy.

Spontaneous rupture of a prior uterine scar has also been reported, particularly when a transmural incision was used outside of the lower uterine segment [19, 46]. Again, these more often occur in the second half of pregnancy, when the uterus is more distended. While labor technically does not occur until the second half of pregnancy, early uterine ruptures have been described during medical terminations of pregnancy (Fig. 11.8), during which contractions are induced with uterotonic agents, such as oxytocin or prostaglandins [5, 7].

Prior uterine surgery appears to be a significant risk factor for uterine rupture in this clinical situation, though is it not considered an absolute contraindication [5, 20].

11.8 Prior Uterine Surgery and Abnormal Placentation

One additional group of patients at risk of early uterine rupture includes women with a combination of prior uterine surgery and abnormal placentation. This cohort of women comprises a majority of case reports that exist in the literature regarding rupture during the first and early second trimesters. Case reports of such events include ruptures ranging from 9 to 20 weeks of gestation, most of which present with acute abdominal pain and progressive signs of hypovolemic shock [9, 16, 22, 25, 49, 61].

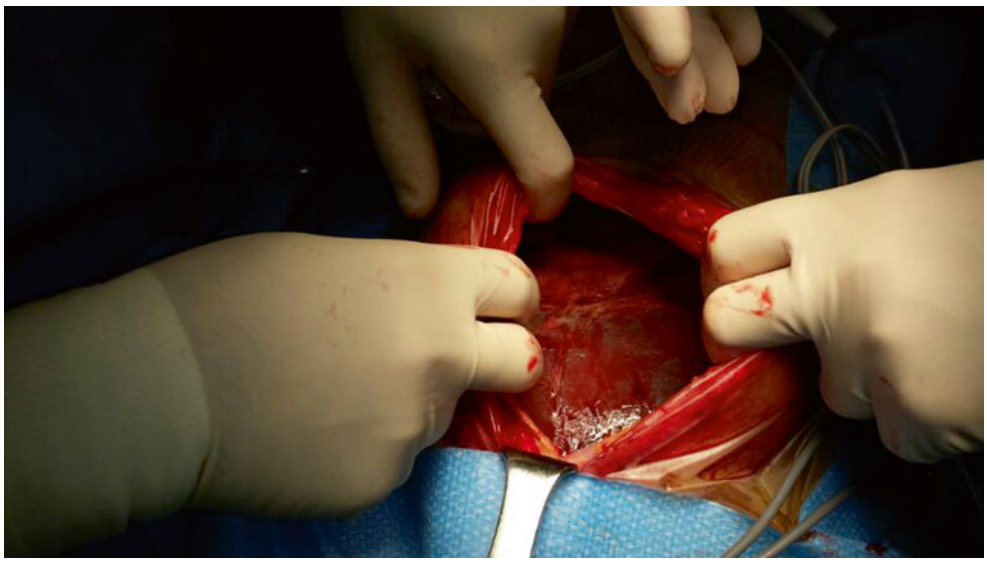


Fig. 11.8 The image shows an early uterine ruptures during medical terminations of pregnancy by oxytocin stimulation: surgeons performed an urgent laparotomy for complete placental-fetal expulsion in abdomen for uterine rupture at 18 weeks

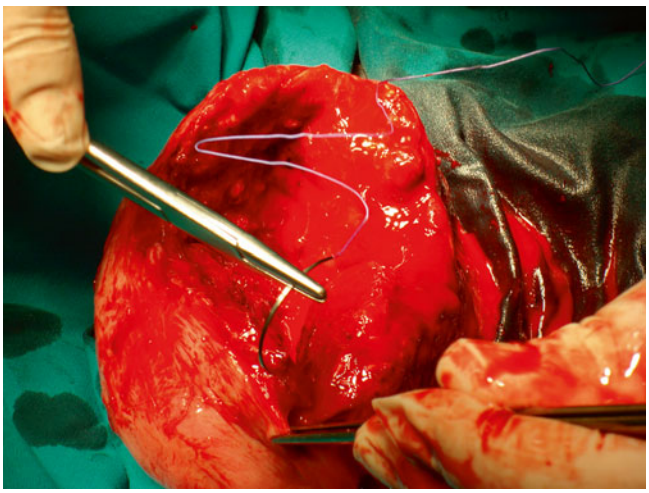


Fig. 11.9 A case of spontaneous rupture in early pregnancy at the site of a prior hysterotomy for myomectomy

Early uterine ruptures have been described both in women with abnormal placentation at the site of a prior low transverse hysterotomy, prior classical incision, or prior hysterotomy for a myomectomy (Fig. 11.9) [13, 56]. Such cases include cesarean scar implantations, in which embryos implant directly into the uterine wall in a small dehiscence at the site of a previous cesarean delivery [33]. Speculation remains as to whether some cases of spontaneous rupture in early pregnancy at the site of a prior hysterotomy might, in fact, represent undiagnosed cesarean scar implantations [64]. Although most case reports describe placenta accreta at the site of prior cesarean sections (Fig. 11.10), there are also

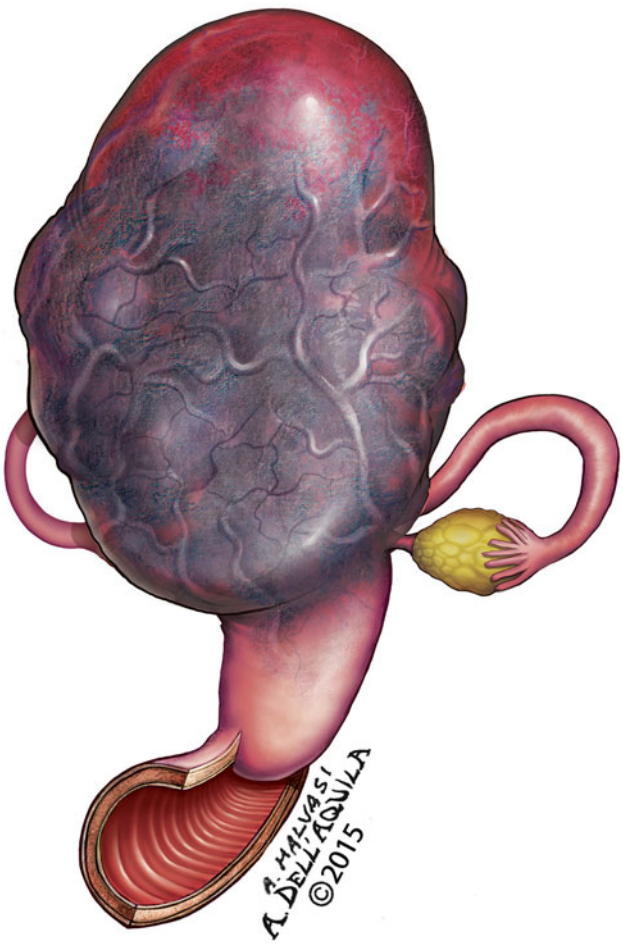


Fig. 11.10 A placenta accreta at the site of prior cesarean sections could be a possible risk factor for uterine rupture

case reports of rupture in the setting of abnormal placentation following uterine curettage alone [26].

Unfortunately, given the small number of patients with uterine rupture at early gestational ages, no quantitative studies exist to define the absolute risk of early uterine rupture when accreta is observed within a uterine scar. Similarly, the relative risks of early rupture based on hysterotomy location and early accreta diagnosis have not been determined. The concern for rupture is highest when the pregnancy is located eccentrically in the uterine scar as opposed to low, but centrally located in the uterine cavity. The close proximity to the uterine serosa raises the potential for extension outside of the uterus and rupture of the scar.

11.9 Ectopic Pregnancies

Similar to the pathology behind pregnancies implanted in uterine anomalies or those with abnormally adherent placentas, some ectopic pregnancies are also at risk of early uterine rupture given their atypical implantation. Ectopic pregnancies overall are increasing recently due to the rising rates of pelvic inflammatory disease, cesarean sections, and assisted reproductive technologies [32, 67].

Locations of ectopic pregnancies that might lead to a uterine rupture prior to 20 weeks include implantations within the cervix (Fig. 11.11), the cornua (Fig. 11.12), the interstitial portion of the fallopian tube (Fig. 11.13), and within a defective scar from a previous cesarean section (11.14, 11.15, and 11.16) [35, 55, 63, 67].

Diagnosis of these pregnancies often requires a high index of suspicion in addition to expert imaging, ideally including transvaginal sonography (Fig. 11.17). It is also important to remember the possibility of heterotopic pregnancies, in which one pregnancy is implanted within the uterine cavity and another is implanted ectopically [6].

Early uterine ruptures have been described both in known and in previously undiagnosed ectopic pregnancies [55, 63]. Known ectopic pregnancies are occasionally managed conservatively, either because they are thought to be resolving or because the diagnosis is yet uncertain and there is hope for an ongoing, viable pregnancy [2, 57].

Even with close monitoring, these pregnancies are at significant risk of unexpected rupture [63]. Cesarean scar

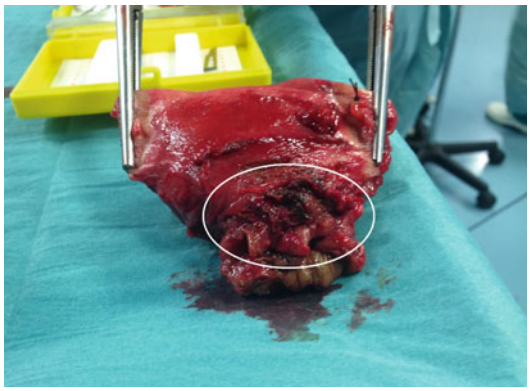


Fig. 11.11 A cervical pregnancy with the uterus removed by hysterectomy (**b**), with the ruptured cervix in the white ring

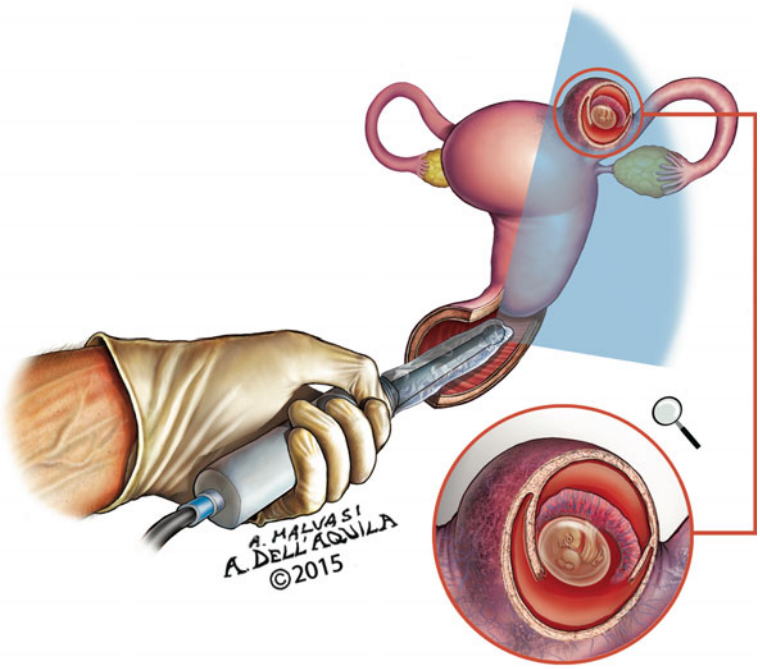


Fig. 11.12 The transvaginal ultrasonographic image of a cornual pregnancy

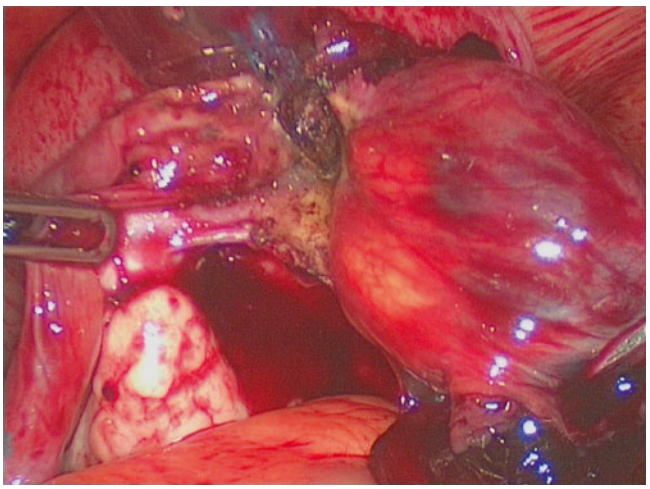


Fig. 11.13 Laparoscopic image of ectopic pregnancy located in the interstitial portion of the fallopian tube, with initial hemoperitoneum

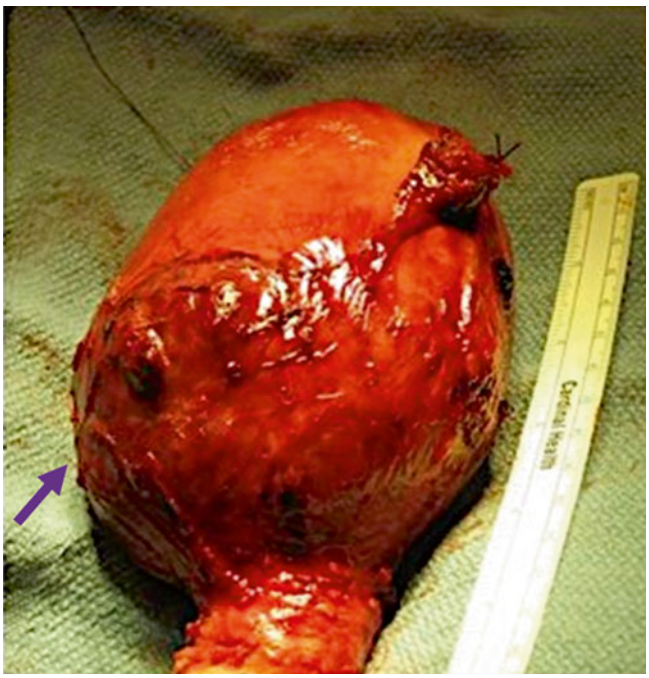


Fig. 11.14 A cesarean implantation growing into the uterine cavity, in a first trimester gestation within a cesarean scar

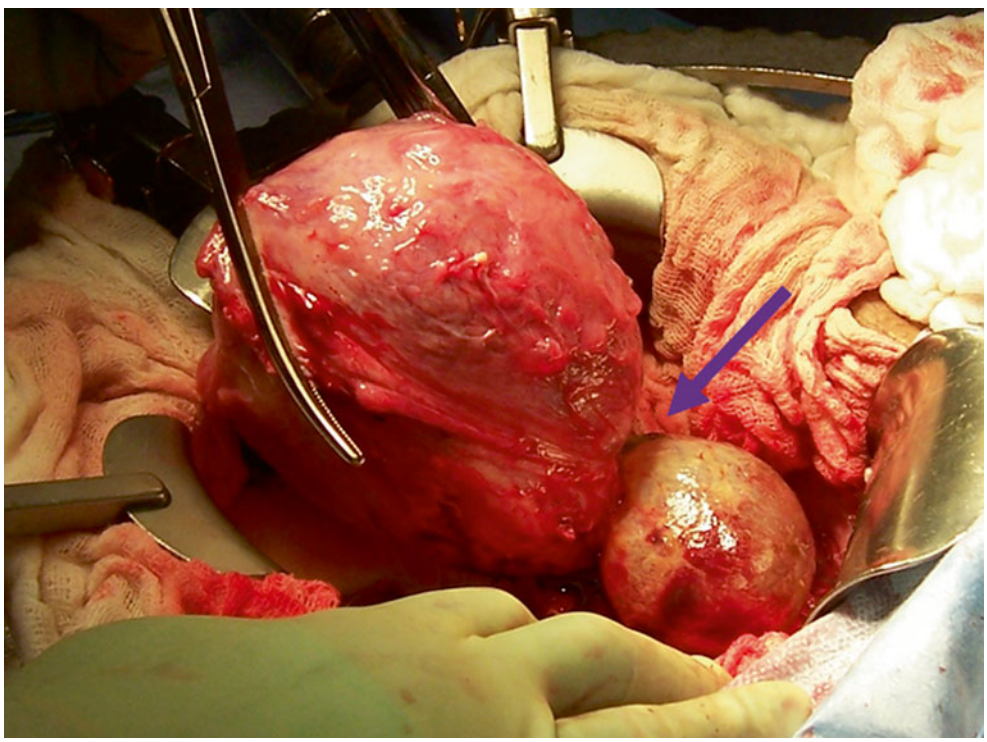


Fig. 11.15 A pregnancy growth into the cervix, in a first trimester gestation within a cesarean scar

implantations have been managed expectantly with the hope that the pregnancy will grow within the uterine cavity; however, ruptures have been reported also in this scenario [53].

11.10 Tissue Abnormalities

There are a few case reports detailing spontaneous rupture of abnormal myometrium prior to 20 weeks. For example, a patient with Turner syndrome is reported to have experienced a spontaneous rupture at 14 weeks in the setting of an IVF pregnancy, with a history notable only for a hysteroscopic polyp resection [36]. Interestingly, patients with Turner syndrome are known to be at risk of having hypoplastic uteri, and thus, it has been suggested that they be treated with higher doses of estrogen for endometrial preparation during IVF cycles [27]. Even still, these pregnancies should be followed very closely and with a high index of suspicion for uterine pathology and ensuing sequelae.

There is also one case report of a posterior-fundal rupture secondary to placenta percreta in a patient with a remote history of childhood chronic myeloid leukemia, who had received whole body irradiation as part of her cancer treatment [43]. The etiology of this rupture was thought to be caused by classic radiation-induced injury including delayed scarring and fibrosis as well as endometrial atrophy of the uterus and its blood supply [29].

11.11 Management

Given that early spontaneous uterine rupture prior to 20 weeks is an acute process, most patients described in the literature present in a dramatic fashion – with severe abdominal pain, intra-abdominal bleeding, and often impending signs of hypovolemic shock. In these settings, the most common management strategy is an urgent laparotomy and often hysterectomy (Fig. 11.18). As techniques in minimally invasive surgery become more advanced, however, an increasing number of case reports describe the use of laparoscopy (Fig. 11.19) for diagnosis and treatment at the time of an early uterine rupture [26, 36, 45, 59].

Depending on the findings at the time of exploratory surgery, a decision can be made regarding definitive surgery with hysterectomy versus an attempt at conservative management, even in laparoscopy. Hemodynamic stability and, if known, patients' desire for future fertility might influence

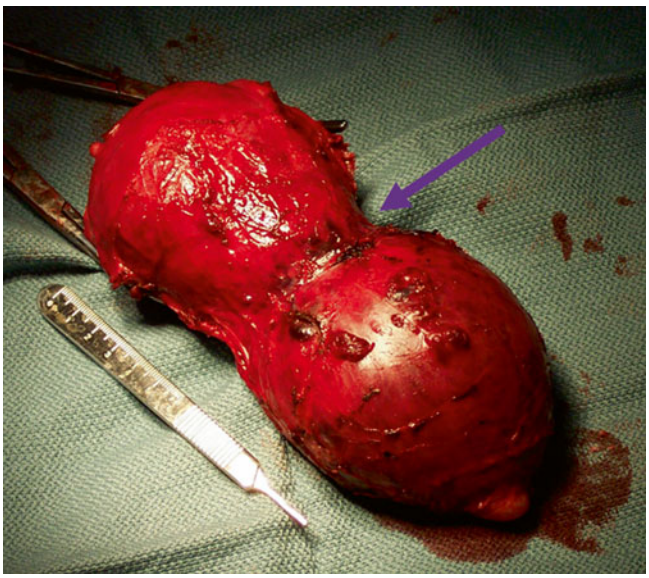


Fig. 11.16 A dehiscence encountered at the time of hysterectomy, in a first trimester gestation within a cesarean scar

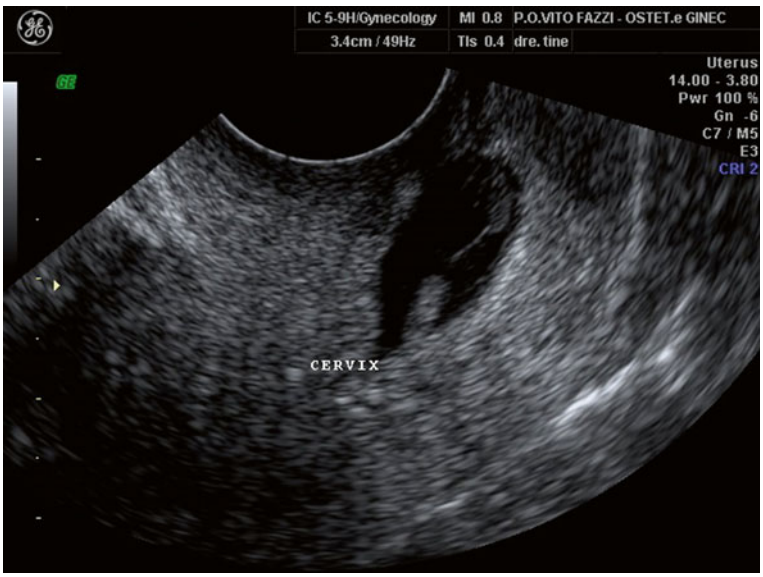


Fig. 11.17 A transvaginal ultrasonographic scan showing a cervical pregnancy at 7 weeks

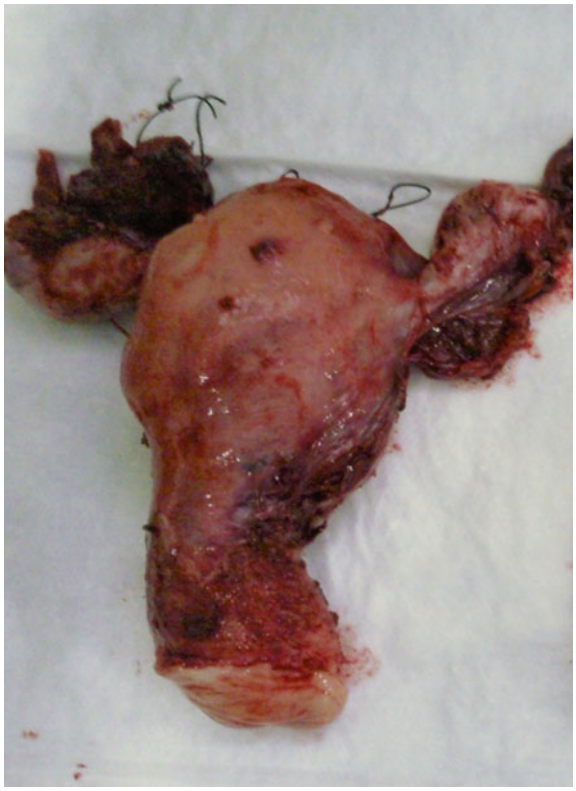


Fig. 11.18 An hysterectomy for a uterine rupture at 15 weeks with patient hypovolemic shocked for massive hemorrhage

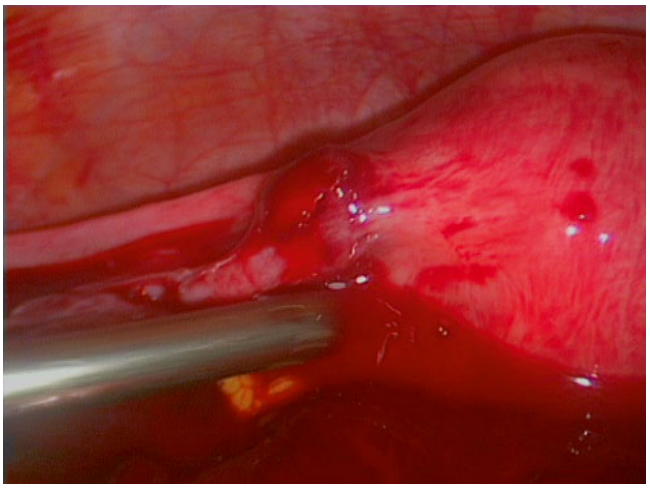


Fig. 11.19 Laparoscopic treatment of an ectopic pregnancy into the *left* interstitial portion of the fallopian tube

the decision at the time of surgery. Intraoperative strategies range from oversewing the uterine defect [1, 8], to removing the pregnancy alone [60, 68], to resecting a noncommunicating uterine horn [10, 59], to subtotal or total hysterectomy (Fig. 11.20) [62]. Interestingly, there have been reports of heterotopic pregnancies in which an ectopic pregnancy leading to uterine rupture is successfully removed followed by

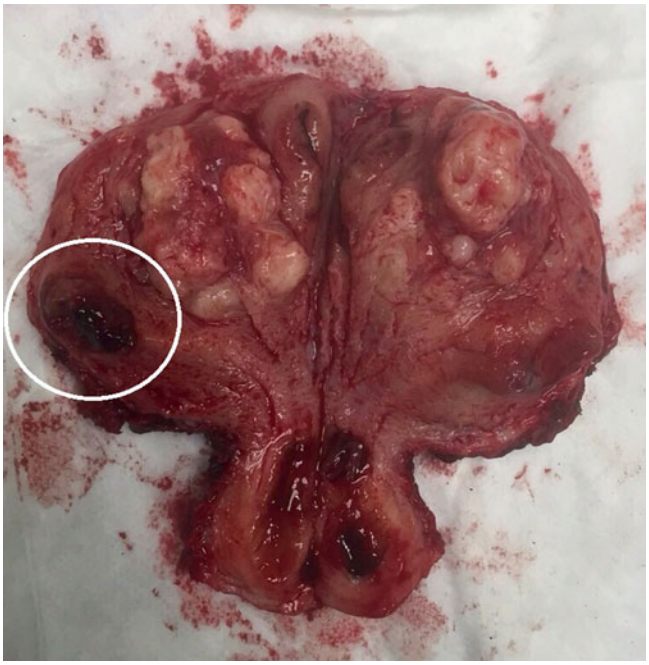


Fig. 11.20 Hysterectomy in 45-year-old women with interstitial pregnancy and fibrotic uterus

successful conservation of a viable, intrauterine pregnancy [45]. Guidelines and outcome statistics exist for operative management of late uterine rupture and in cases of abnormal placentation [17, 61], however, early uterine rupture remains too rare for an expert opinion, and its management relies on the clinical judgment of individual care providers. It is not known whether a patient who experiences early uterine rupture can safely carry a future pregnancy – a factor that should be taken into account when considering conservative management.

11.12 Prevention

Given the acuity and morbidity of a uterine rupture, any opportunity to intervene prior to the rupture should be considered and discussed with the patient. Unfortunately, intervention usually requires pregnancy termination at these early gestational ages, which may be a difficult decision for patients and their families.

In general, women diagnosed with a cesarean scar or rudimentary horn implantation in the first trimester are offered termination of pregnancy. This avoids the risks of extrauterine pregnancy extension and uterine rupture and may allow for successful medical management or treatment with minimally invasive surgery [12, 31, 48]. Expectant management of cesarean scar implantations has been linked to both uterine rupture and live births, albeit with a high risk of hysterectomy for placenta accreta (Rotas 2006; [39]). Criteria have yet to be

established that will distinguish which of these patients may carry their pregnancies to viability and which are high risk for early rupture. Patients opting for expectant management should be monitored with ultrasound, and termination should be reconsidered if the pregnancy begins to extrude outside of the normal uterine cavity (Fig. 11.21).

Because implantations within rudimentary uterine horns increase the risk of rupture, some advocate for routine. Removal of such pregnancies has recently been reported using a minimally-invasive approach [66]. However, it is not clear that any other management of uterine anomalies, such as metroplasty for a septate uterus, will improve patient outcomes.

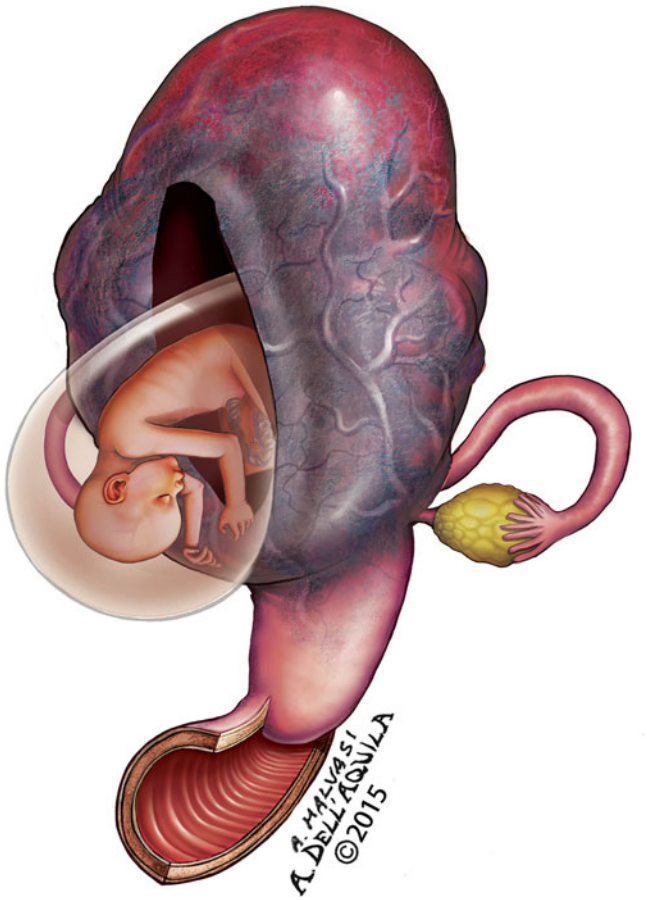


Fig. 11.21 The image shows the pregnancy extruding outside of the normal uterine cavity

11.13 Summary

Uterine rupture during the first half of pregnancy is one of the most morbid complications that the gravid woman may face. Although a number of individual reports have been published in the literature, there remains a paucity of data and experience from which to define and quantify risks or predict outcomes. The sudden morbidity and mortality associated with early uterine ruptures demands that this diagnosis remain high in the differential when a woman presents with acute onset abdominal pain, a positive pregnancy test, and signs or symptoms of intra-abdominal bleeding, as prompt recognition and surgical treatment of early uterine ruptures is critical (Fig. 11.22). Early pregnancy termination should be considered when an early pregnancy is identified within a rudimentary uterine horn or is eccentrically located within a prior cesarean section scar or uterine cornua.

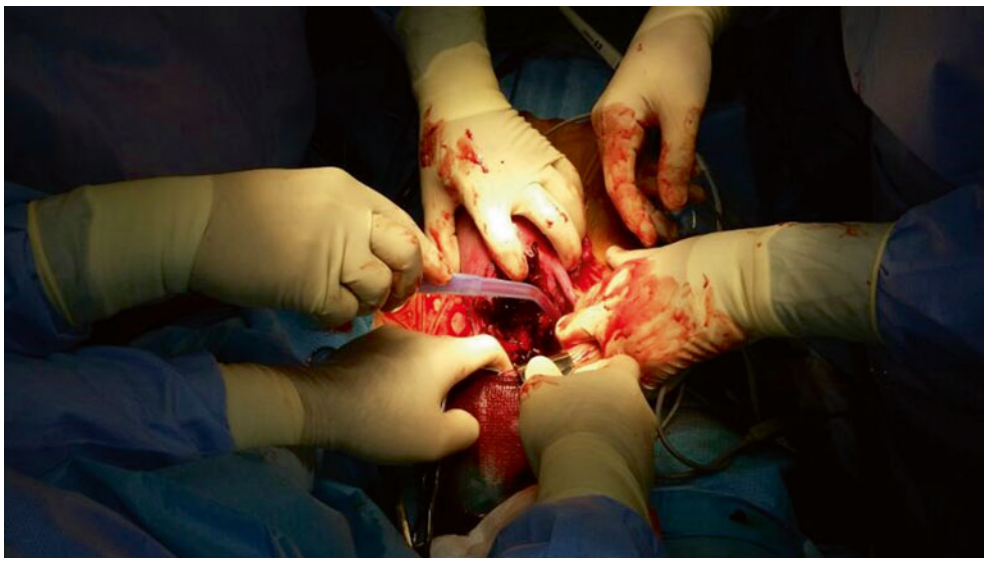


Fig. 11.22 A urgent laparotomy for second trimester uterine rupture and hemoperitoneum: the rupture is on the uterine anterior body

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Cervicoisthmic Incompetence

12

Keun-Young Lee, Ji-Eun Song, Ga-Hyun Son,
and Gian Carlo Di Renzo

12.1 Introduction

There are 15 million babies delivered prematurely every year, and the incidence of preterm birth is rising. Each year, 1.1 million babies die of complications from preterm birth, making preterm birth one of the important issues in the obstetrics field worldwide [1]. Preterm birth complicates between 5 and 12 % of all pregnancies and is associated with high perinatal morbidity and mortality. The inability of the uterine cervix to retain a pregnancy in the second trimester is referred to as cervical incompetence (Fig. 12.1). At less than 23 weeks of gestation, the fetus is not able to survive, and even if it does, there is very high morbidity. Among the topics related to preterm birth, cervical incompetence is a very important keyword. However, controversy in the medical literature exists pertaining to issues of pathophysiology, screening, diagnosis, and management (especially with cerclage) of cervical incompetence. Many reviews concerning cervical cerclage have been published, most of them based on randomized controlled studies and the Society for Maternal-Fetal Medicine and American College of Obstetricians and Gynecologists guidelines. Most of the guidelines suggest that the decision to perform cerclage should not be based solely on a poor obstetric history, because of the availability of TVU surveillance [2, 3] of cervical length (CL) and progesterone prophylaxis. However some clinicians have been performing cerclage based on the history of classic cervical insufficiency only, not following this suggestion [4]. We would like here to review the literature on cervical insufficiency and other clinical points of view and then discuss in detail the major surgical techniques for cerclage. Although the term "cervical incompetence" has been used for many years, this condition is now referred to as "cervical insufficiency" to avoid the negative connotations that the term "incompetence" may have for patients [5].

12.2 Definition

Cervical insufficiency has no consistent definition, but some authorities have suggested it to be characterized usually by dilatation and shortening of the cervix before 37 weeks of gestation in the absence of preterm labor and to be most classically associated with painless, progressive dilatation of the uterine cervix in the second or early third trimester, resulting in membrane prolapse (Fig. 12.2), premature rupture of membranes, midtrimester loss, or preterm birth [6, 7]. Others have suggested that the definition should include a functional component of repeat pregnancy loss [8]. To complicate matters further, the advent of ultrasonic cervical length measurement has reframed the concept of the definition of cervical insufficiency.

12.3 Cervical Remodeling

It is essential to understand the physiology of the normal cervix (Fig. 12.3), because any untimely disarray in cervical remodeling could end in cervical insufficiency and preterm delivery. Although complex biochemical and hormonal changes are involved with the cervical ripening, these effects on cervical change are still not fully understood.

The cervix is a dynamic organ responsible for the physiology of gestation and parturition (Fig. 12.4); it has to be firm

K.-Y. Lee, MD, PhD (✉)
Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, South Korea
e-mail: mfmlee@hallym.ac.kr; mfmlee@empas.com

J.-E. Song, MD • G.-H. Son, MD
Department of Obstetrics and Gynecology, Hallym University, Seoul, South Korea

G.C. Di Renzo, MD, PhD
Department of Obstetrics and Gynecology, Centre for Perinatal and Reproductive Medicine, Santa Maria della Misericordia University Hospiatal, Perugia, Italy

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_12

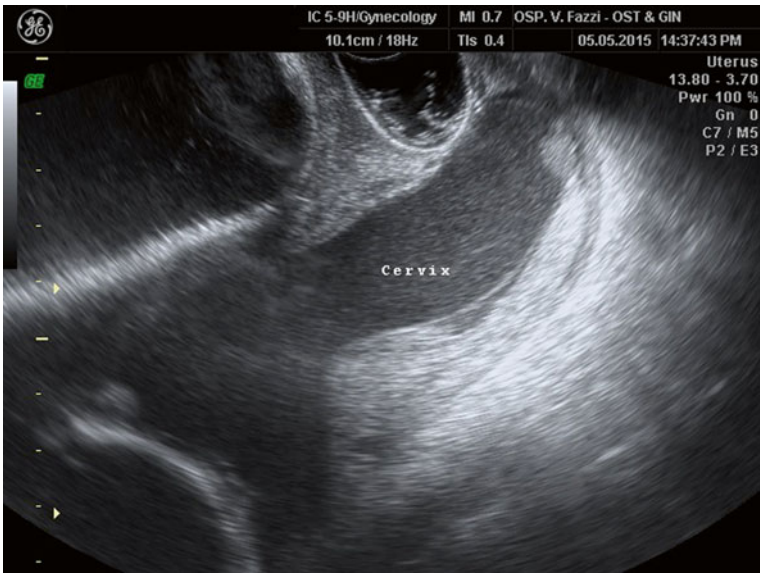

Fig. 12.1 Ultrasonographic transvaginal scan of an incompetent cervix at 21 weeks, with an amniotic sac protrusion into the cervical canal

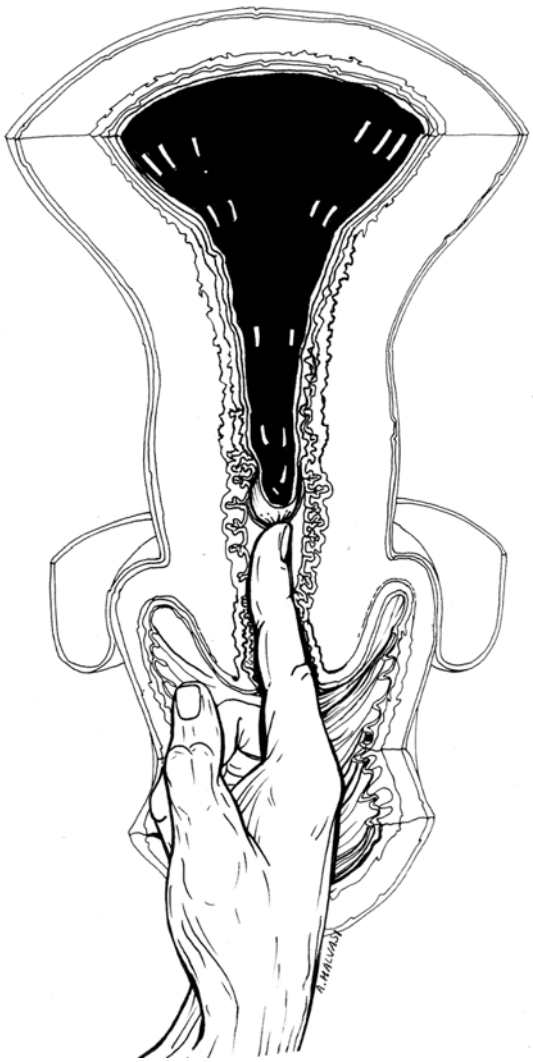

Fig. 12.2 The image shows a membrane prolapse; the finger of the clinician covers the entire cervical canal till to touch the amniotic membrane

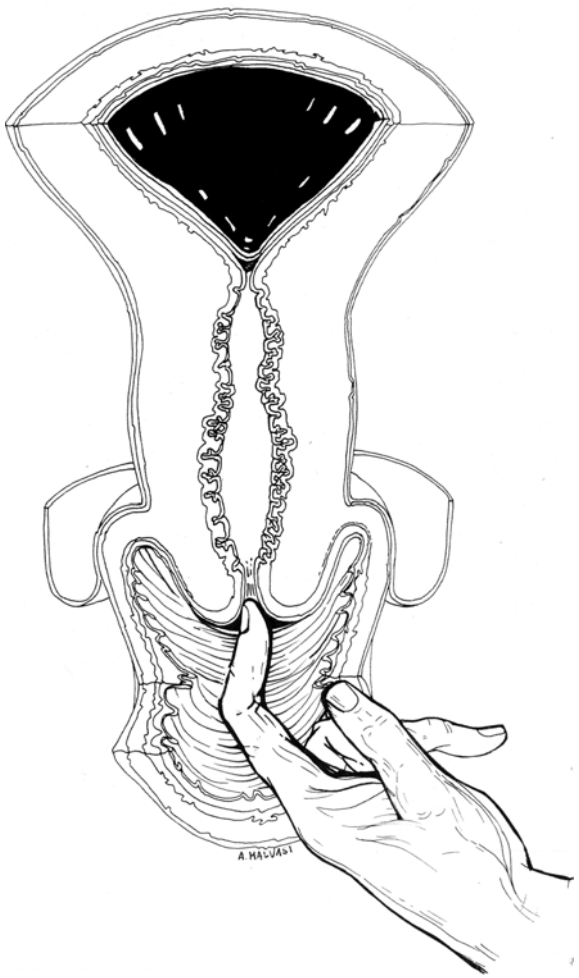

Fig. 12.3 Normally, the normal uterine cervix is closed during the vaginal examination

enough to retain the fetus from the beginning (Fig. 12.5) until the term and to soften during the labor for the delivery of the infant. The cervix consists of fibrous connective tissue and an extracellular matrix (70 % type I and 30 % type III), along with elastin, proteoglycans, and cellular compartments [9]. The cervical remodeling can be subclassified into four sequential phases: softening, ripening, dilation, and postpartum repair [10]. Cervical remodeling was once considered to be a passive process, which was induced by uterine contraction. But by now many investigators have confirmed that it is a complex process that can occur independent of uterine contractions [11, 12]. The uterine body and the cervix undergo separate functional changes in preparation for the labor (Fig. 12.6). Cervical remodeling might begin due to hormonal changes (e.g., a loss of progesterone), genetic predisposition, or infection and inflammation. During the cervical softening phase, poorly cross-linked collagen and extensive changes in the extracellular matrix lead progressively to a weakening of the tensile strength of the cervix and result in a cascade of cervical ripening and dilation [11, 12]. Other cellular compartments of the cervix also seem to be involved with cervical remodeling, but their roles are generally unknown.

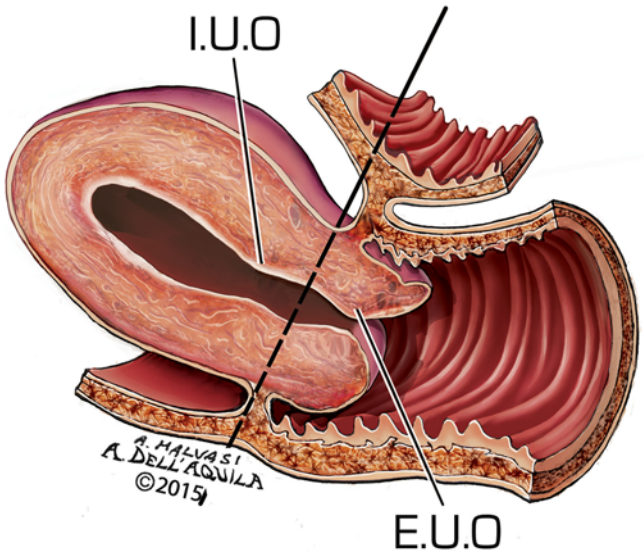

Fig. 12.4 A schematic representation of the normal uterine cervix included between internal uterine orifice (IUO) and external uterine orifice (EUO)

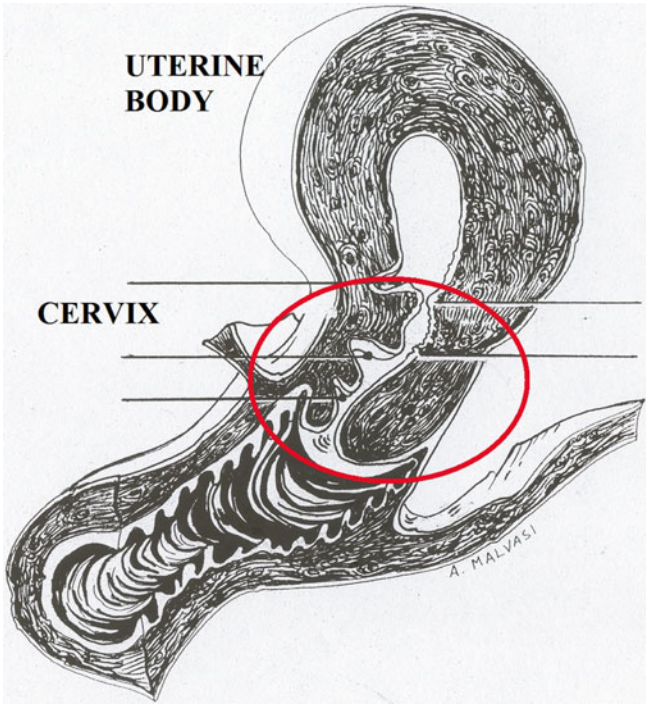

Fig. 12.6 The image shows the uterine body and the cervix (in the *red ring*); they undergo separate functional changes in preparation for the labor

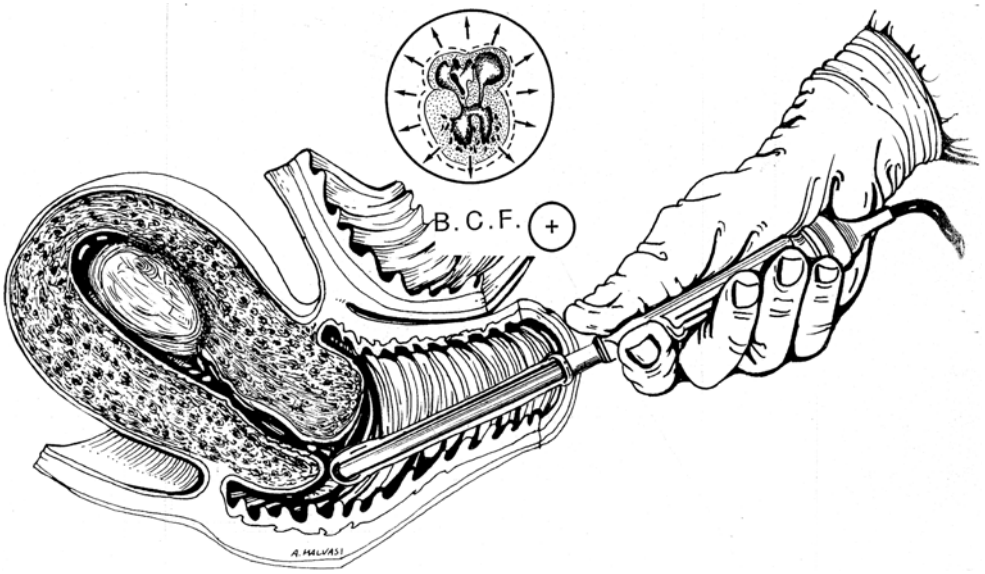

Fig. 12.5 A transvaginal scan at early pregnancy, showing a normal cervix

12.4 Risk Factors for Cervical Insufficiency

Risk factors for cervical insufficiency include uterine anomaly, previous cervical surgery (conization or trachelectomy), prior induced (Fig. 12.7) or spontaneous abortions (Fig. 12.8), genetic defects in collagen and in elastin synthesis (e.g., Ehlers-Danlos and Marfan syndromes), a history of cervical insufficiency or midtrimester short cervix, and in utero diethylstilbestrol (DES) exposure [13–15]. Cervical competence is also influenced by infection (Fig. 12.9) and inflammation (Fig. 12.10) [16]. It however also occurs in a substantial number of patients without there being any identifiable risk factors.

12.5 Diagnosis

Although numerous investigators have tried to find accurate means of cervical insufficiency diagnosis, there is no reliable and objective standard as of yet. Because cervical insufficiency is usually diagnosed retrospectively, it is difficult to lay out any well-defined diagnostic criteria. Furthermore, there is difficulty in the diagnosis or prediction of cervical insufficiency in the nonpregnant state. Patients often have vaginal pressures without vaginal bleeding or labor pains. Obstetricians coincidentally find a short cervix or membrane protruding into the vagina in such patients. In the past, digital palpation of the cervix or pull-through techniques using a Hegar dilator were performed as tools for CI diagnosis [17], and some investigators sought to develop a cervical compliance score [18]. Currently, however, these techniques are not recommended for use in the diagnosis of cervical insufficiency, as they are subjective and not well reproducible [19].

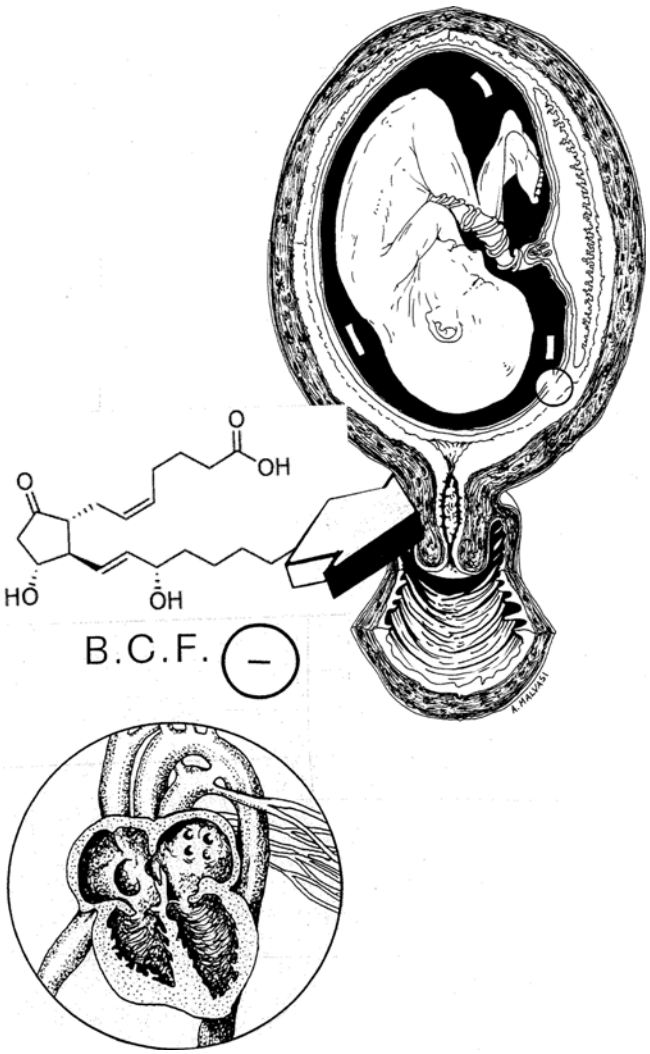

Fig. 12.7 An abortion induced by prostaglandins at 18 weeks

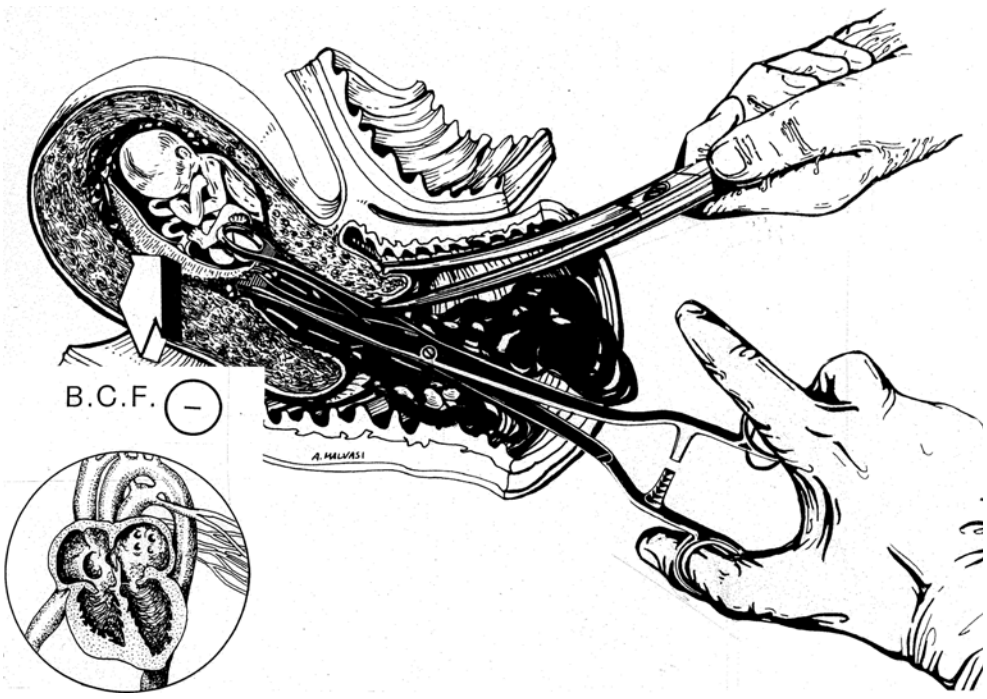

Fig. 12.8 A spontaneous abortion at 11 weeks; the clinician remove, by ring clamps, the gestational sac with the fetus inside

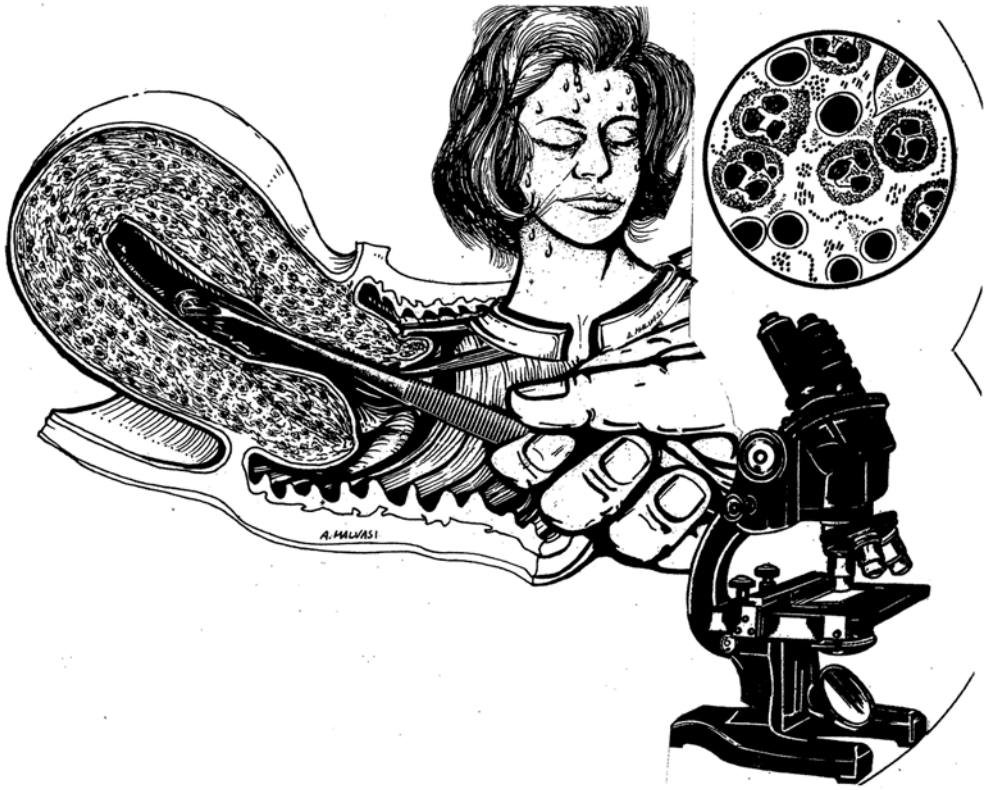

Fig. 12.9 An instrumental revision by curette for initial septic abortion

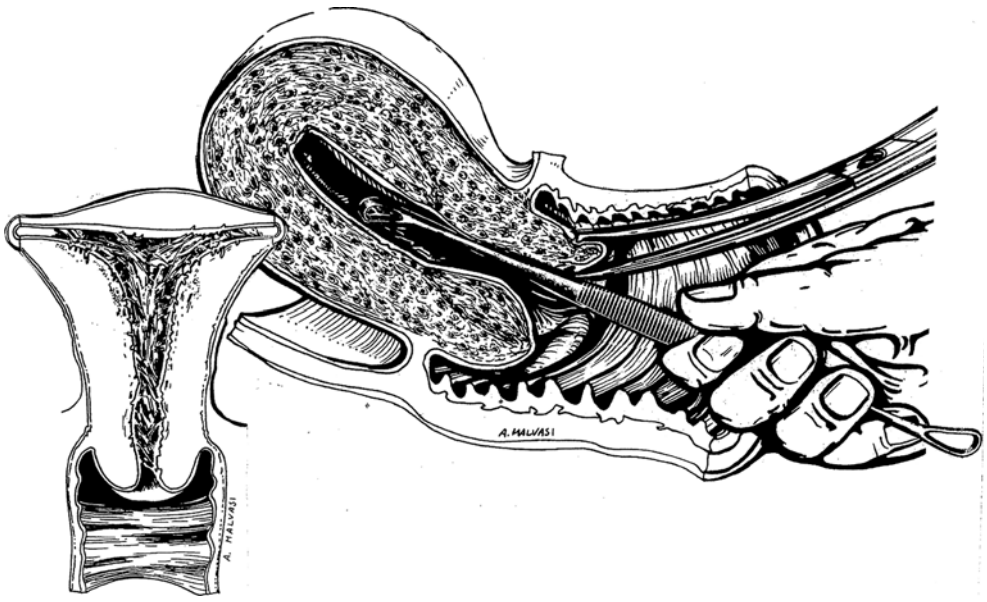

Fig. 12.10 A uterine cavity inflammation; the surgeon revises by curette the uterine cavity to spot bleeding

Transvaginal ultrasonography (TVU) is the most powerful diagnostic tool for the assessment of cervical competence [20]. TVU is superior to transabdominal or translabial ultrasound for the assessment of the cervix. It is an accurate, reliable, and reproducible method for the measurement of cervical length (CL) and funneling. It has been well documented that a short CL (<25 mm) preferentially increases the risk of midtrimester birth [21–24]. The risk of preterm birth is inversely associated with CL, from <1 % at 30 mm to 80 % at 5 mm [25]. Serial measurements of CL can help identify high-risk patients for whom cerclage placement is beneficial, given that 12–40 % of "at-risk" patients will not present CI in subsequent pregnancies [19]. In 2012, the Society for Maternal-Fetal Medicine stated that universal CL screening in singleton pregnancies without prior PTB is controversial, while CL screening in singleton pregnancies with prior preterm birth is beneficial for the prevention of preterm birth [26].

However, they also emphasized that CL screening in singleton pregnancies without prior preterm birth should be

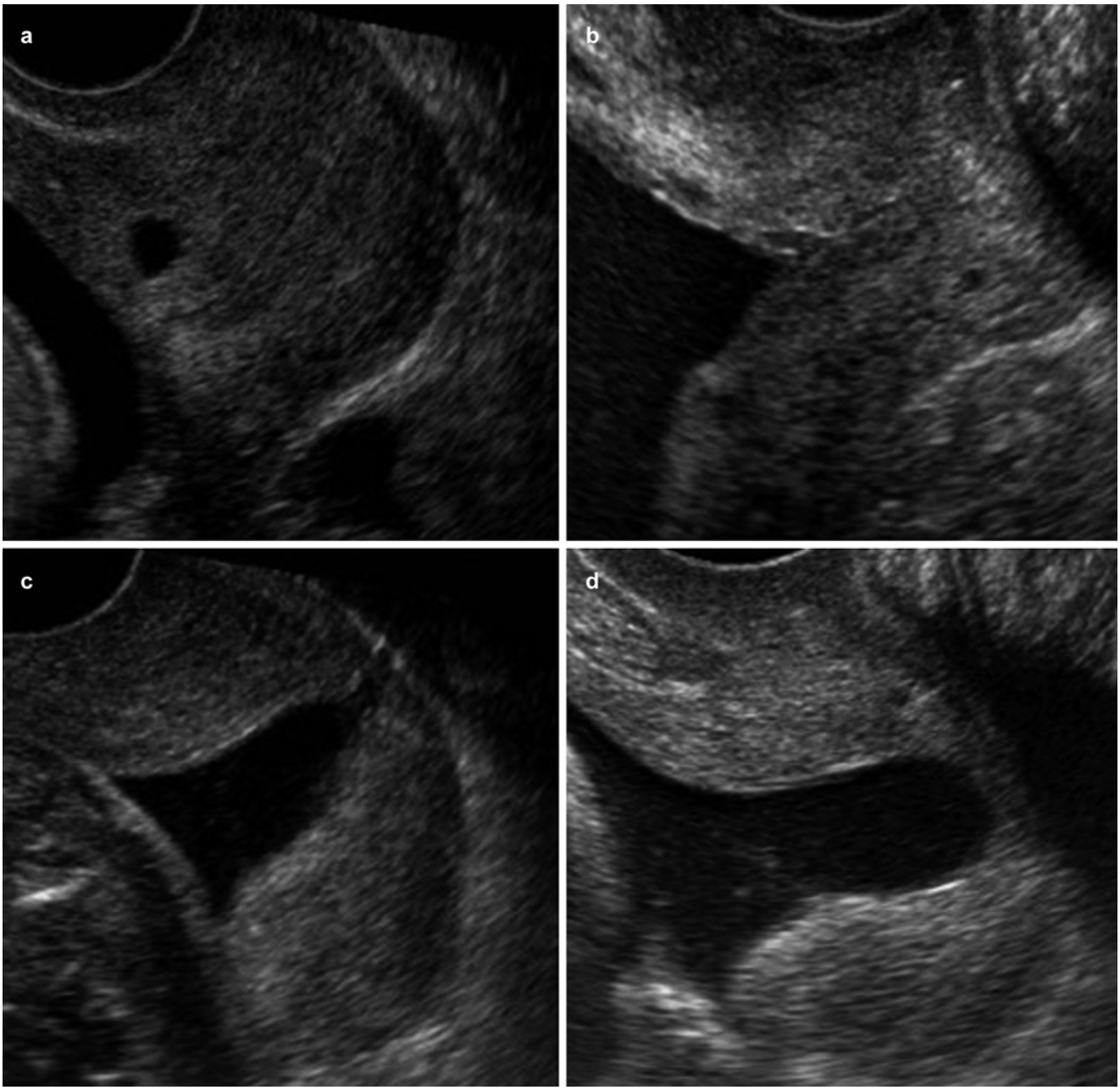

Fig. 12.11 Transvaginal sonography of the cervix shows the respective shapes of the cervical funnels (TYVU shapes)

considered when necessary [26]. CL measurement usually begins at 15 weeks, as CL screening prior to 15 weeks does not predict the risk of PTB [27].

It is recommended that TVU CL in singleton pregnancies with prior preterm birth can be started at 16 weeks and be repeated every 2 weeks until 23 weeks; TVU CL <25 mm is detected; the placement of cerclage should be considered, as cerclage significantly reduces the risk of PTB at less than 35 weeks [28]. Unfortunately, TVU CL screening in twin pregnancies cannot be recommended due to a lack of evidence [23]. For as a CL screening, the proper TVU technique is pivotal. The bladder should be emptied before TVU, as a full bladder compresses and elongates the cervix. After obtaining a sagittal long-axis view of the cervix, excessive pressure against the cervix should be avoided as it exaggerates CL [29].

Funneling, which is defined as the opening of the internal cervix, is characterized by funnel length and funnel width. Funneling occurs along with cervical effacement, which is easily remembered by the use of the mnemonic "trust your vaginal ultrasound" [30] (Fig. 12.11).

The T shape represents a normal closed cervix. The Y shape represents a small breaking funnel, and further funneling is shown by the V shape. A more advanced funnel takes the shape

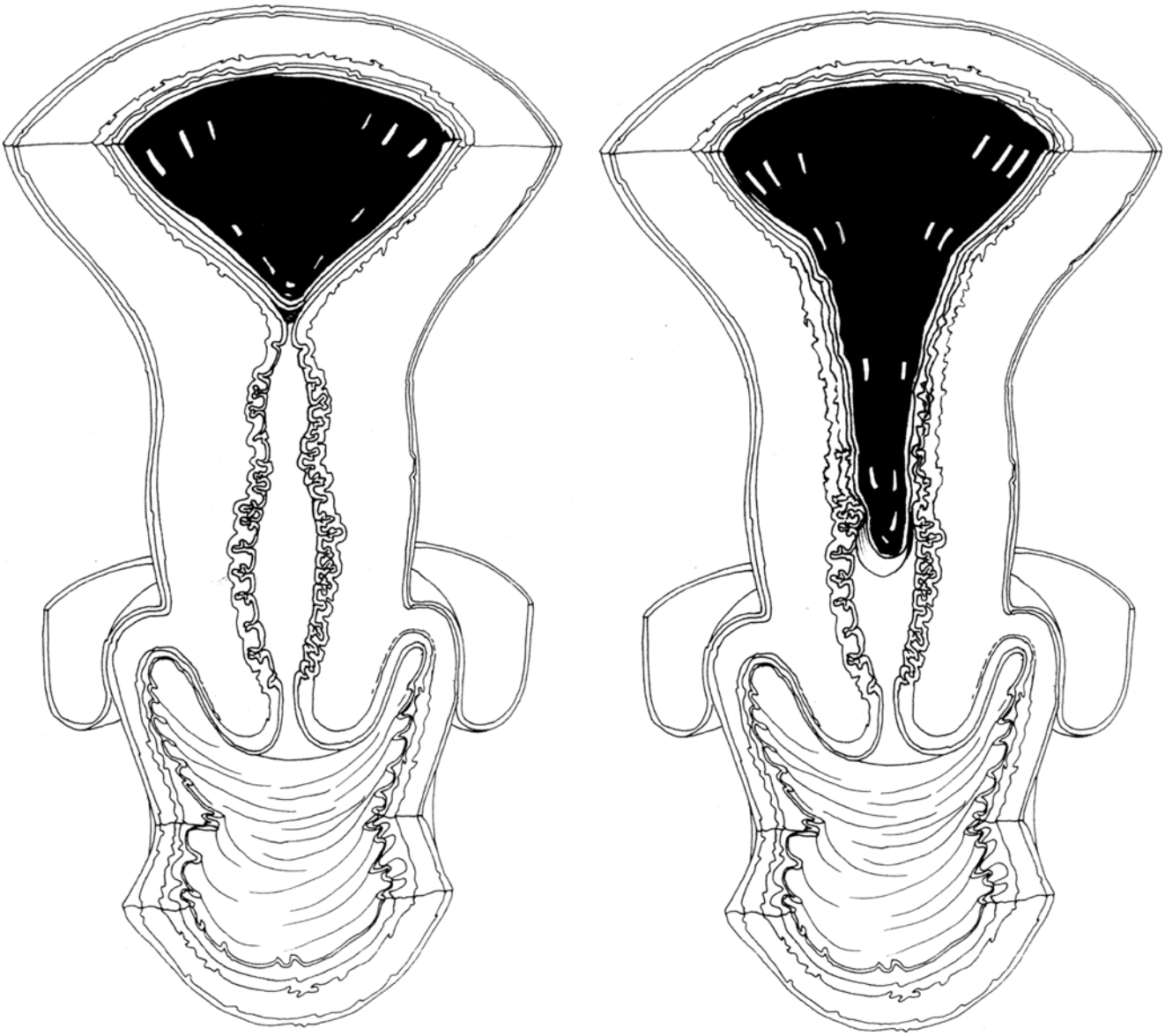

Fig. 12.12 The image shows the difference between a normal cervix and a cervix with a membrane prolapsed in the cervical canal

of a U, which is the worrisome finding of PTB [30, 31]. Unlike CL, there is high interobserver variability in measuring funneling [22]. Despite the high interobserver variability, funneling is useful for predicting preterm birth when combined with CL. The combination of a short CL (<25 mm) and the presence of funneling increases the sensitivity of predicting preterm birth compared to when there is a short CL alone [32].

In some cases, microbial invasion of the amniotic cavity (MIAC) is found in women with painless cervical dilation in the midtrimester [33]. It may be beneficial to have an amniotic fluid culture in the case of CI. However, there is the limitation that amniotic fluid bedside testing is not available for prompt decisions on management. Cervicovaginal fetal fibronectin (fFN) may be positive in some women with cervical insufficiency [34]. Positive fFN could predict an increased risk of preterm birth in women with prior preterm birth history [34].

Genetic predisposition is also helpful for the diagnosis of cervical insufficiency (Fig. 12.12). Polymorphisms in the promoter region of the interleukin-10 (IL-10) gene are found to be more common in women with cervical insufficiency compared to the controls [35]. Collagen 1alpha1 and transforming growth factor-beta polymorphisms are also related to cervical insufficiency [36]. These results suggest that cervical insufficiency is partly mediated by alterations in inflammatory processes or familial genetic factors [35, 36]. Women with Ehlers-Danlos syndrome and Marfan syndrome have genetic predispositions for cervical insufficiency [37, 38].

12.6 Treatment of Cervical Insufficiency

Several nonsurgical and surgical modalities have been proposed for treating cervical insufficiency. Certain nonsurgical approaches, including activity restriction, bed rest, and pelvic rest, have not been proven effective for the treatment of cervical insufficiency, and their uses are discouraged. Another nonsurgical treatment to be considered in patients at risk of cervical insufficiency is a vaginal pessary [39]. Vaginal pessaries are intended to alter the axis of the cervical canal and displace the weight of the uterine contents away from the cervix. Evidence is limited as to the potential benefits of pessary placement in select high-risk patients.

12.7 Cerclage

Cervical cerclage has become the mainstay for management of cervical insufficiency, but it remains one of the more controversial surgical interventions. Cervical cerclage is a surgical procedure that is carried out during pregnancy to position a suture around the neck of the cervix (Fig. 12.13). The purpose of this procedure is to provide a mechanical support to the cervix and so reduce the risk of preterm birth. During a normal pregnancy, the neck of the cervix stays tightly closed (Fig. 12.14), allowing the pregnancy to reach full term. Toward the end of pregnancy, the cervix then starts to shorten and becomes progressively softer in preparation for normal labor and delivery. Sometimes, the cervix begins to shorten and dilates too early, causing either late miscarriage or preterm birth. Cervical cerclage has been the treatment of choice for patients in this situation, although the effectiveness and safety of this procedure remain controversial.

Cerclage placement may be indicated based on a history of cervical insufficiency (history-indicated cerclage), on a history of preterm birth and certain ultrasonographic findings (ultrasound-indicated cerclage), and on a physical

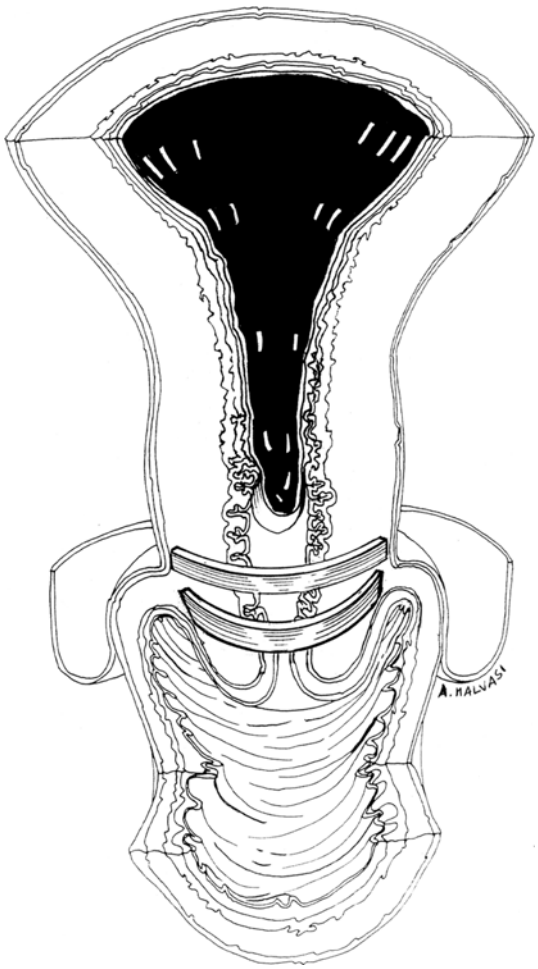

Fig. 12.13 The cervical cerclage is carried out during pregnancy to position a suture around the neck of the cervix

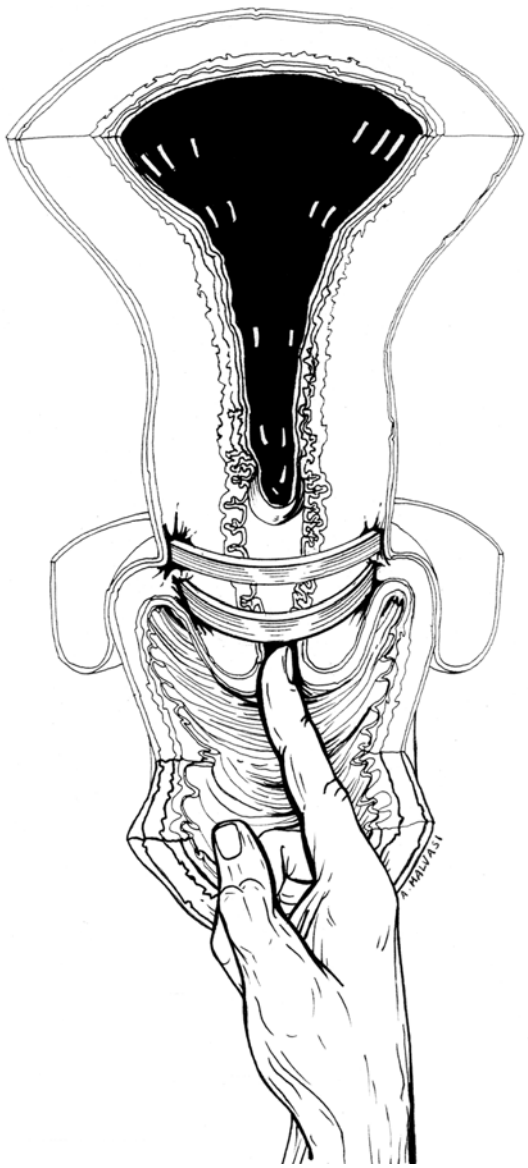

Fig. 12.14 The cervical cerclage provides a mechanical support to the cervix, allowing to the cervical neck to stay tightly closed, and reduces the risk of preterm birth

examination findings (physical examination-indicated cerclage). Transabdominal cerclage may be indicated in women having had prior transvaginal cerclage resulting in preterm birth at less than 33 weeks. Cerclage should be limited to pregnancies in the second trimester, before fetal viability has been achieved.

12.8 History-Indicated Cerclage

Patient selection for history-indicated cerclage (also known as prophylactic cerclage) is based on classic historical features of cervical insufficiency, and history-indicated cerclages are typically placed at approximately 13–14 weeks of gestation. Cerclage indicated based solely on poor obstetric history is less commonly performed, however, given the availability of transvaginal ultrasonographic surveillance of cervical length and progesterone prophylaxis [2, 3]. Based on trials of the efficacy of cerclage indicated by obstetric history, history-indicated cerclage can be considered in a patient with either of the following [40]: history of one or more second-trimester pregnancy losses, when risk factors for cervical insufficiency are present and other differential diagnoses have been ruled out, and prior cerclage due to painless cervical dilation in the second trimester.

Lotgering's review of the clinical aspects of cervical insufficiency claimed that cerclage is regarded as ineffective because the data of randomized controlled trials is pooled and as a result shows no reduction in fetal loss [41]. This raises the question of whether the absence of proof from randomized controlled trials should be taken as proof of an absence of reduction in fetal loss, thanks to cervical cerclage in cases at high risk for cervical insufficiency. One may wonder why no large-scale randomized controlled trials have been performed to definitively prove the effectiveness of cervical cerclage, while there is such an obvious need for these studies. One reason could be that patients at high risk of yet another fetal loss are unwilling to give their consents to randomization after being informed that observational studies have shown approximately 90 % infant viability after cerclage and a low rate of procedure-related complications. This may explain why studies of the effectiveness of cerclage have been relatively small scale and/or have not been performed on truly high-risk patients. Lotgering also points out that small-scale studies of relatively low-risk patients are minimally informative of the true value of cerclage, as their power is low and both groups in the studies will have relatively good outcomes. He also notes the obvious reluctance of women and their doctors "to wait till the diagnosis of classic cervical insufficiency has been established by recurrence of fetal loss." He points out the finding of uncontrolled studies that infant viability is around 25 % if cerclage is not used, but 75–90 % when it is. He stresses the critical fact that "without prophylactic cerclage, one accepts the risk that the cervix may open quite suddenly within days after the documented absence of funneling and normal cervical length." He notes in conclusion that fetal loss is a painful experience. In cases of classic cervical insufficiency, recurrence is high, and a policy of prophylactic cerclage may be safer than one of serial cervical length measurement followed by cerclage, tocolysis, and bed rest in cases of cervical shortening or dilation. In low-risk cases, however, he states that prophylactic cerclage is not useful.

Fox et al. did a study entitled "History-Indicated Cerclage: Practice Patterns of Maternal-Fetal Medicine Specialists in the USA" [4]. They performed a mail-based survey of 827 specialists in the USA, asking them whether they would recommend history-indicated cerclage at 12–14 weeks, in a patient whose prior pregnancy was her first and had ended in spontaneous, painless loss at 19 weeks with no identifiable causes. Of the specialists surveyed, 75 % said that they would recommend a history-indicated cerclage for this patient. Twenty-one percent meanwhile indicated that they would not recommend it, but would place one if desired by the patient. Only 4 % said they would not place a history-indicated cerclage in this scenario. In reality, then, many clinicians seem to perform cerclage, not following the ACOG or textbook guidelines.

A large-scale randomized controlled trial is needed of high-risk classic cervical insufficiency that responded to history-indicated cerclage, to obtain exact data on the side effects of cerclage and on the progesterone effect.

Transvaginal methods currently use either the McDonald (Fig. 12.15) or the Shirodkar techniques. In the McDonald procedure, a simple purse-string suture of non-resorbable material is placed in four to six bites circumferentially at the cervicovaginal junction (Fig. 12.16). The Shirodkar procedure involves the dissection of the vaginal mucosa off the bladder and the rectum cephalad, so as to place the suture as close to the cervical internal os as is safely possible. The superiority of either technique over the other has not been established [42, 43]. The McDonald technique is preferred over the Shirodkar because of its ease of placement and removal. Mersilene 5-mm tape is most commonly used for cerclage, as it provides better tensile strength and is less likely to pull through the cervix in later gestation. The suture is placed below the level of the internal os and must be placed deep into the substance of the cervix to prevent lacerations. Suture removal is recommended at 36–37 weeks of gestation.

Although no trials have evaluated the efficacy of 17-alpha-hydroxyprogesterone caproate weekly supplementation after the cerclage procedure, progesterone can be administered after history-indicated cerclage [44].

12.9 Ultrasound-Indicated Cerclage

Ultrasound-indicated cerclage is often recommended for women with short cervical length on second-trimester transvaginal ultrasonography. Meta-analyses of multiple random-

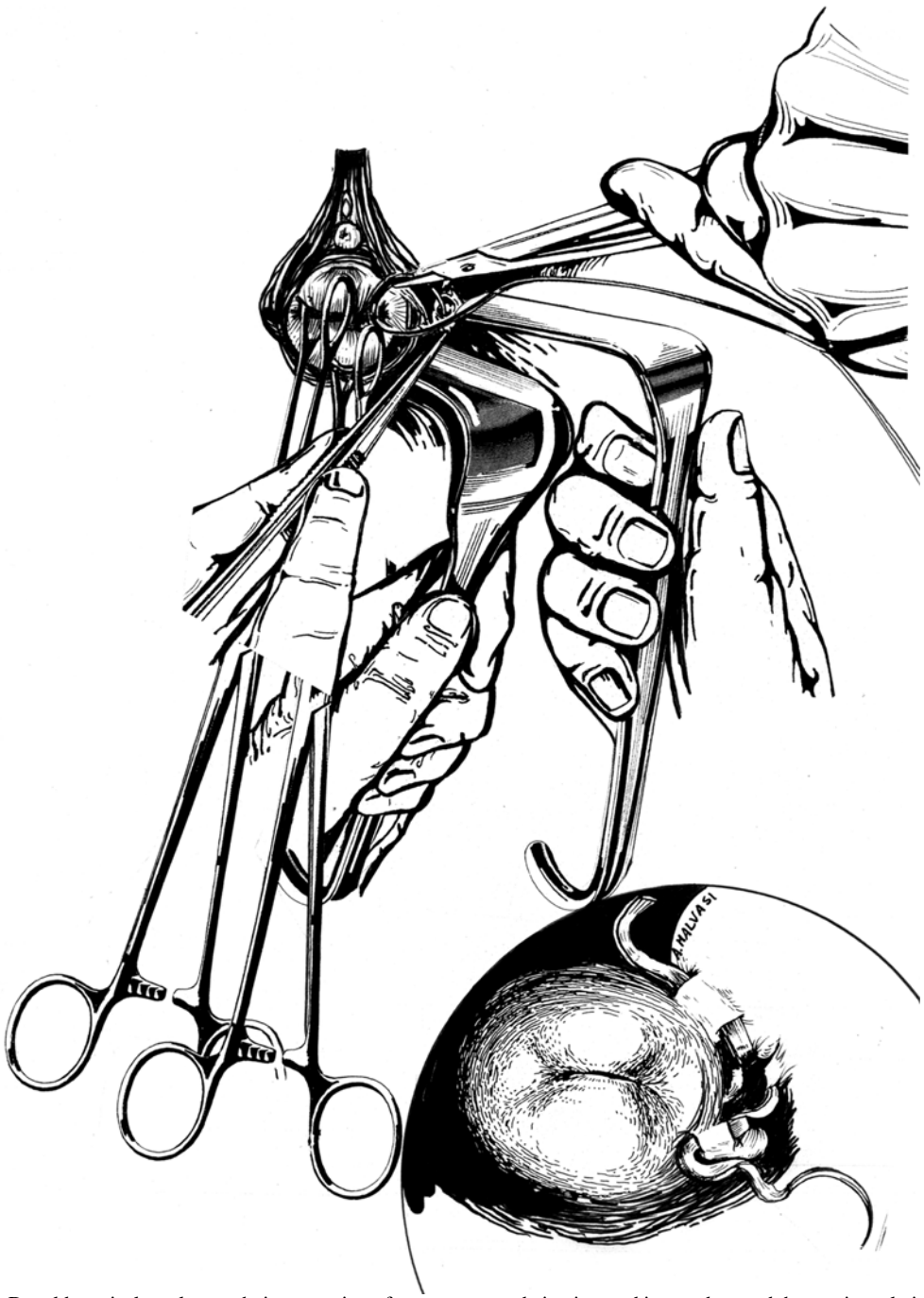

Fig. 12.15 The McDonald cervical cerclage technique consists of a strong suture being inserted into and around the cervix early in the pregnancy

ized trials comparing cerclage versus no cerclage in patients with short cervical length during the second trimester have reached the following conclusions [2, 45, 46]: Ultrasound-indicated cerclage may be effective in women with current singleton pregnancies, prior spontaneous preterm birth at less than 34 weeks of gestation, and short cervical length (less than 25 mm) before 24 weeks of gestation. Between 30 and 40 % of women with singleton gestations who have had prior spontaneous preterm birth will develop a short cervix (<25 mm) before 24 weeks. In these cases ultrasound-indicated cerclage is associated with significant decreases in preterm birth outcomes, as well as improvements in composite neonatal morbidity and mortality. On the other hand, ultrasound-indicated cerclage in women without history of prior spontaneous preterm birth and with cervical length less than 25 mm detected between 16 and 24 weeks of gestation has not been associated with any significant reduction in preterm birth [46]. Therefore, incidentally detected short cervical length in the second trimester in the absence of a prior singleton preterm birth is not diagnostic of cervical insufficiency, and cerclage is not indicated. Vaginal progesterone is recommended as a management option for reducing the risk of preterm birth in this setting [47].

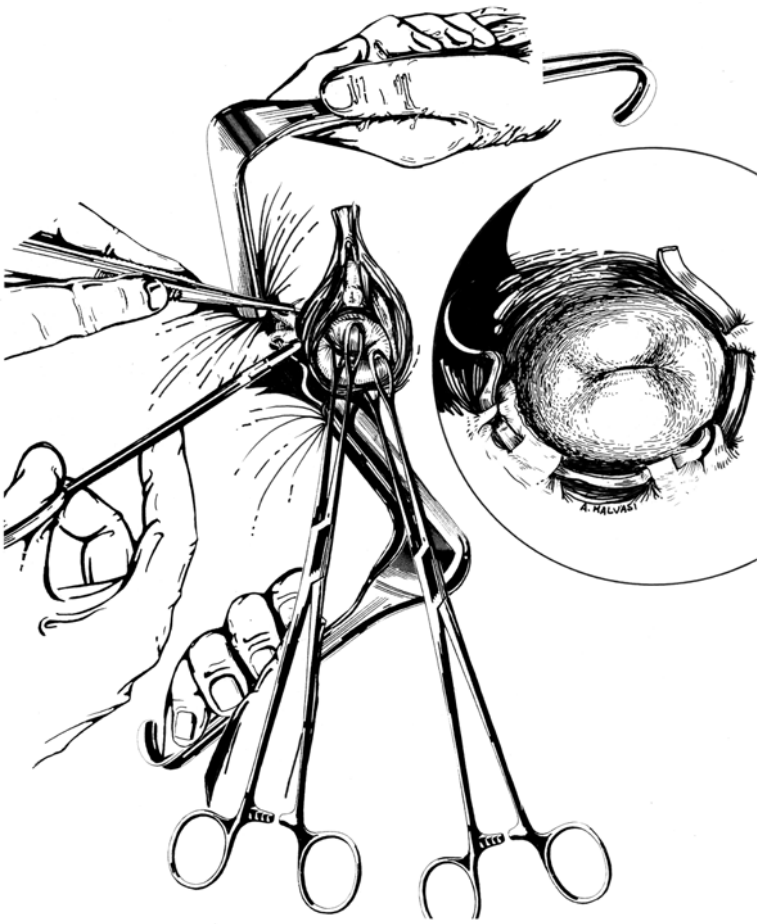

Fig. 12.16 The McDonald cervical cerclage is by a simple purse-string suture of non-resorbable material that is placed in four to six bites circumferentially at the cervicovaginal junction

There has until now been no mention in the literature of how to perform ultrasound-indicated cerclage. When we do perform it, the cervix can have various different shapes—such as a short cervix (e.g., 2.1 cm) with funneling or a very short cervix (0.5 cm) with funneling. Iatrogenic membrane can sometimes occur during this procedure, when the membrane is located very near the cervix. We have used four different small-size uniconcave balloons in ultrasound-indicated cerclage, for protection of the amniotic membrane.

Prior to or concurrent with any cerclage, the mother should be screened and as necessary treated for genitourinary tract infection, bacteriuria, vaginitis, bacterial vaginosis, cervicitis, and sexually transmitted infections. After receiving the results, we have used perioperative antibiotics, tocolytics, and progesterone.

12.10 Physical Examination-Indicated Cerclage

Occasionally, women presenting with advanced cervical dilation on speculum or digital examination with minimal or no symptoms before 24 weeks have been candidates for physical examination-indicated cerclage (known as emergency or rescue cerclage). Limited data from one small randomized trial and retrospective cohort studies have suggested that placement of cerclage in women with dilated cervix and visible membranes appears to prolong pregnancy by about 1 month and improve pregnancy outcomes compared with the use of expectant management [48]. Emergency cerclage is recognized as an essential procedure for prolonging gestation in women with advanced cervical changes and/or prolapsed membranes in the second trimester. After intra-amniotic infection, ruptured membranes, advanced labor, and significant hemorrhage are ruled out, physical examination-indicated cerclage placement may be beneficial. The rate of emergency cerclage success is relatively low, however, certainly compared with elective cerclage. Membranes are easily ruptured intraoperatively, especially when the cervix is widely dilated and the fetal membranes are prolapsed beyond the cervix [49, 50]. Pushing bulging fetal membranes back into the uterine cavity during cerclage with a sponge swab or Foley catheter is difficult. Overfilling the urinary bladder to reduce prolapsed fetal membranes without direct mechanical contact is often insufficient as a single method [51]. Other less utilized techniques include inflatable devices such as a metreuryter or a rubber balloon, although few studies of their use have as yet appeared [50, 52, 53]. Recently Son et al. have developed a new uniconcave balloon device for repositioning fetal mem-

branes into the uterus during emergency cerclage and reported its use in 103 patients who underwent emergency cerclage [54]. This device has a shape similar to that of a red blood cell or a donut, providing maximum surface area to allow the force exerted on the membranes to push them back into the uterus safely and effectively (Fig. 12.17).

Cerclage was technically successful in all cases, and there were no ruptures of membranes in any patients and no operative or anesthetic complications. Son et al. concluded that obstetricians could perform emergency cerclage with this uniconcave balloon easily and safely with few complications (Fig. 12.18).

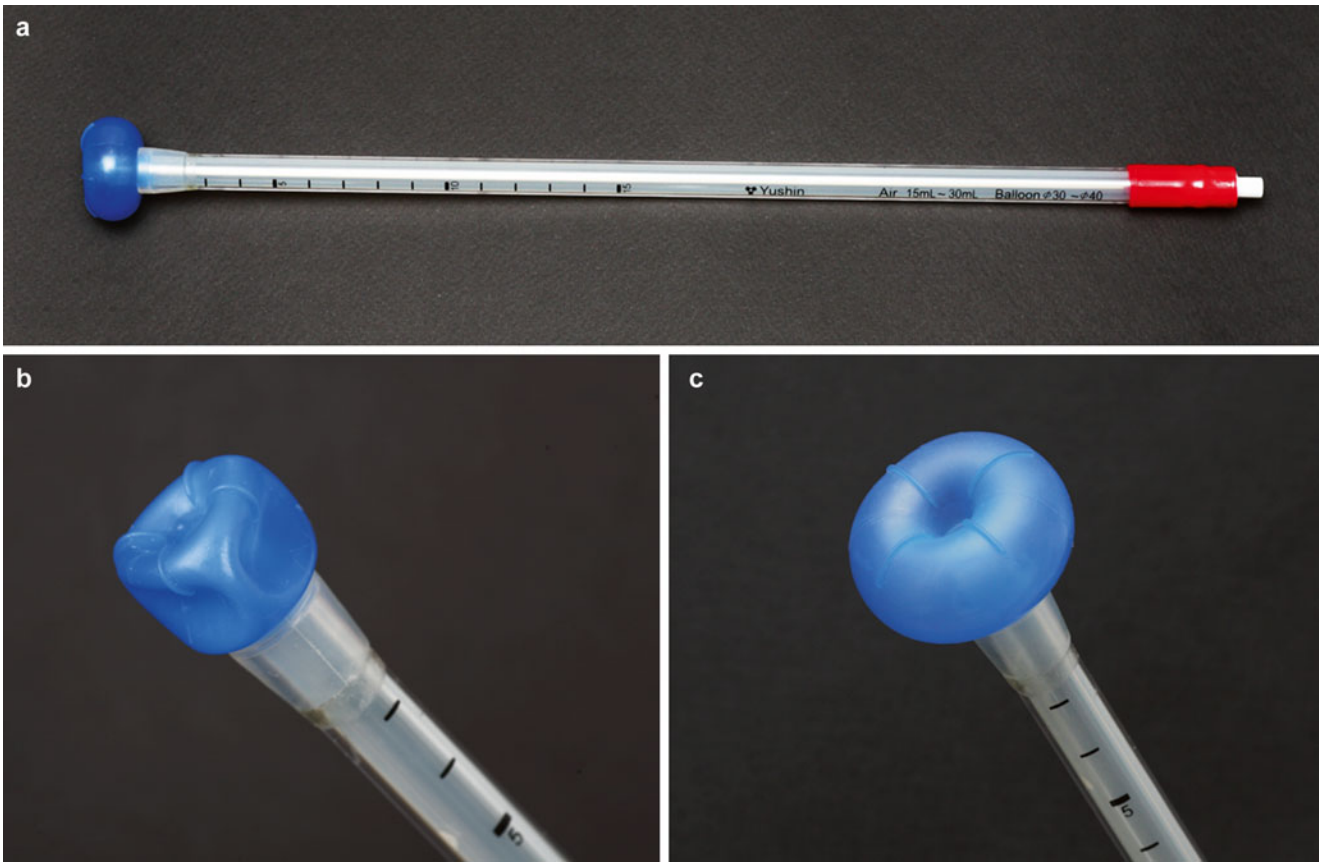

Fig. 12.17 A uniconcave balloon. (**a**) This device is composed of a balloon, a shaft, and a valve for air injection. The inflated balloon is not deformed or moved backward when pushing the bulging fetal membranes because of the supportive part on the rear side of the balloon. This device has centimeter gradations on the shaft, so that the depth of insertion can be noted. (**b**) Deflated balloon. (**c**) Inflated balloon, shaped like a red blood cell or a donut (Copyright permission obtained from: Am J Obstet Gynecol 212:114, 2015)

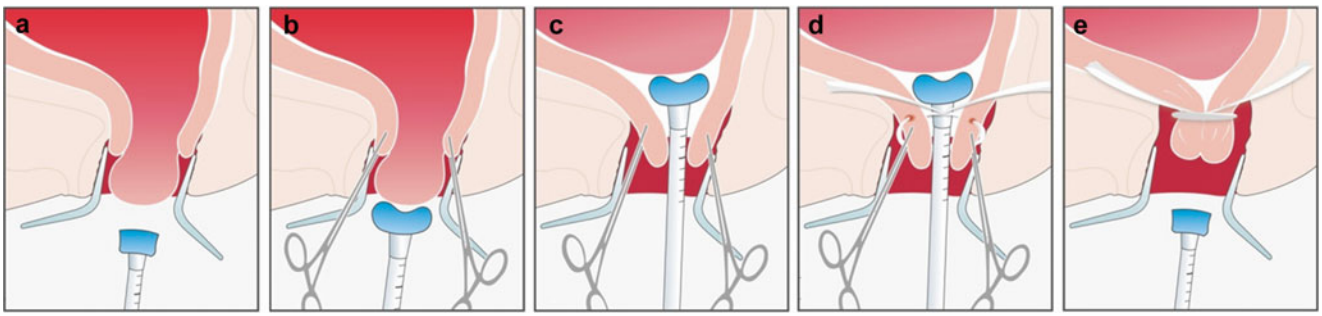

Fig. 12.18 McDonald operation using uniconcave balloon. Illustration of a uniconcave balloon used in cerclage procedure. (**a**) Bulging fetal membranes are visualized. (**b**) The cervix is grasped and retracted with two atraumatic forceps, and adequately inflated balloon then gently pushes fetal membranes back into the uterus. (**c**, **d**) After fetal membranes are replaced in the uterus, sutures are placed as high as possible in accordance with McDonald technique. (**e**) Balloon is deflated. Purse-string suture is tied as instrument is withdrawn from the cervix (Copyright permission obtained from: Am J Obstet Gynecol 212:114, 2015)

Amniocentesis before emergency cerclage is not obligatory, but has two important benefits. One is the decompression of amniotic fluid to place a satisfactory cerclage, especially for hourglassing bulging membranes, and the other is the detection of intra-amniotic infection. Data from uncontrolled retrospective studies has suggested the perioperative use of tocolytics and broad spectrum antibiotics [55–58]. There are no studies of emergency cerclage comparing general with regional anesthesia, but in the writers' experience, general anesthesia is better for performing cerclage with marked membrane bulging [59]. The recommended gestational age for emergency cerclage is less than 24 weeks, the threshold of fetal viability (i.e., >24 weeks of gestation), because the potential for harm likely outweighs the potential benefit [60, 61]. All contraindications to emergency cervical cerclage should be excluded—preterm labor, evidence of intra-amniotic infection, unexplained vaginal bleeding (abruption), preterm premature rupture of the membrane, fetal demise, and major fetal anomalies [59, 62].

Emergency cerclage in twin pregnancies with membrane bulging had not appeared useful and has not been studied in a dictated trials. Recently, however, Rebarber et al. [63] performed emergency cerclage on 12 women with twin gestation and cervical dilation and showed that emergency cerclage can be associated with favorable outcomes including a high likelihood of delivery at >32 weeks and high likelihood of survival. Levin et al. [64] and Zanardini et al. [65] also found favorable outcomes.

Kuon et al. [66] studied neonatal outcomes after emergency cerclage with a special focus on adverse effects in very low birth weight infants. Neonates of less than 1500 g after rescue cerclage showed significantly impaired outcomes, i.e., need for respiratory support and higher rates of chorioamnionitis after rescue cerclage. They concluded that the higher incidence of chorioamnionitis indicates a potential inflammatory factor in the pathogenesis. Several predictors for emergency cerclage success have been reported, such as intra-amniotic markers of infection and systematic markers of infection. Lee et al. [67] reported that elevated amniotic IL-6 predicts a cerclage short-interval latency. Linear regression analysis with latency as the independent variable revealed a significant relationship ($r = -6.62$, $p < 0.001$). Study of intra-amniotic markers of infection and their correlations with perinatal outcomes appears important.

Cases with bulging membranes following prior cerclage are also surgically challenging, as there are no relevant guidelines. Song et al. [68] evaluated 22 women with bulging membranes after primary cerclage, comparing 11 women with repeat cerclage and 11 with bed rest [28]. After repeat cerclage the median gestational age at delivery ($p = .004$), average birth weight ($p < .01$), and median prolongation of pregnancy (<.01) were higher, and the neonatal survival rate was also significantly higher ($p < .009$).

12.11 Transabdominal Cervicoisthmic Cerclage

Transabdominal cervicoisthmic cerclage is indicated for patients in whom cerclage is required but cannot be placed because of anatomical limitations of the cervix or in cases of prior failed transvaginal cervical cerclage procedures that resulted in the delivery before 33 weeks [69]. In patients having had prior failed transvaginal cerclage, transabdominal cerclage was associated with fewer recurrent preterm births compared to undergoing another history-indicated transvaginal cerclage [69]. Transabdominal cerclage can be performed through open laparotomy or operative laparoscopy. It is usually performed between 10 and 14 weeks of gestation or in the nonpregnant state. The suture may be removed by posterior colpotomy or laparoscopy to allow vaginal delivery, but is more often left in place, with cesarean section planned before the labor. There are different techniques for cerclage. The classic approach is transabdominal cerclage during pregnancy, while some authors support the procedure prior to pregnancy [70]. More recently, laparoscopic transabdominal cervicoisthmic cerclage (Figs. 12.19, 12.20, 12.21, 12.22, 12.23, 12.24, 12.25, and 12.26) and even robotic techniques have been described. In addition, one may consider performing transabdominal cerclage in the same session with trachelectomy performed for malignancy.

Although successful outcomes of transabdominal cervical cerclage have been reported, predictors of the success of transabdominal cerclage have not been thoroughly evaluated. Lee et al. [71] investigated pregnancy outcomes follow-

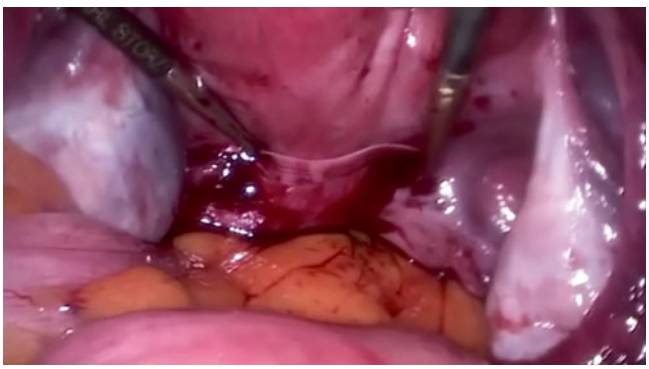

Fig. 12.19 Laparoscopic cervical cerclage. A 5-mm nonabsorbable Mersilene polyester suture, with adjacent straightened blunt needles to allow passage through the trocar, is introduced into the abdominal cavity. The stitch is placed from posterior to anterior, at the level of the internal cervical os bilaterally (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

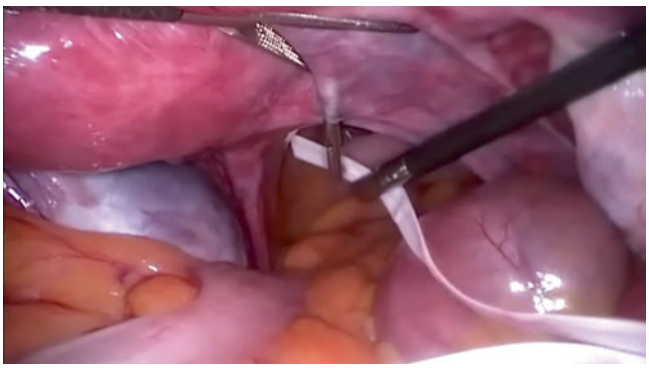

Fig. 12.20 Laparoscopic cervical cerclage. A distance of 1.5 cm superior and 1 cm lateral to the insertion of the uterosacral ligament on the posterior uterus is a good initial guide for needle placement (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

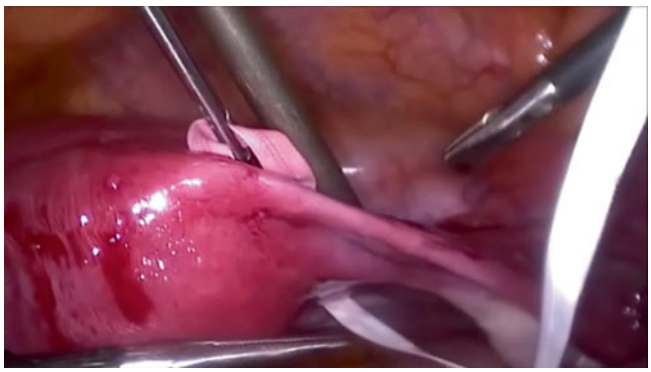

Fig. 12.21 Laparoscopic cervical cerclage. The stitch is placed by passing each needle medial to the uterine vessels, from posterior to anterior (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

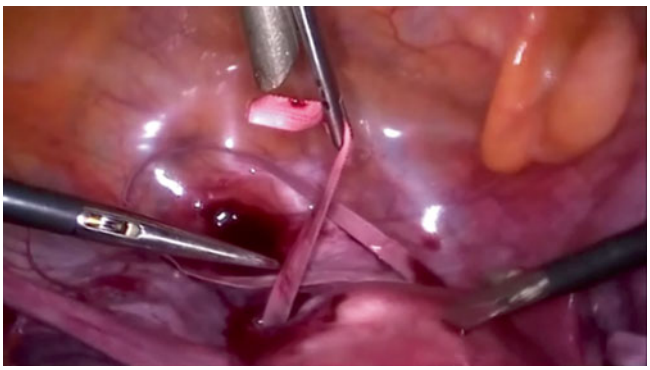

Fig. 12.22 Laparoscopic cervical cerclage. The vesicouterine peritoneum is opened and dissected off the lower uterine segment, exposing the uterine vessels anteriorly on both sides, before holding the thread ends of Mersilene (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

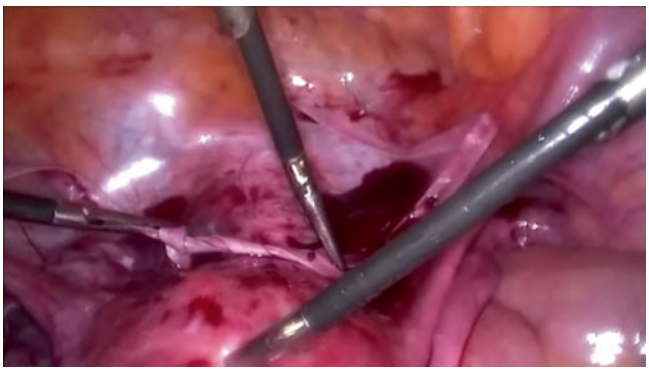

Fig. 12.23 Laparoscopic cervical cerclage. The leaders of the suture are knotted on the isthmus (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

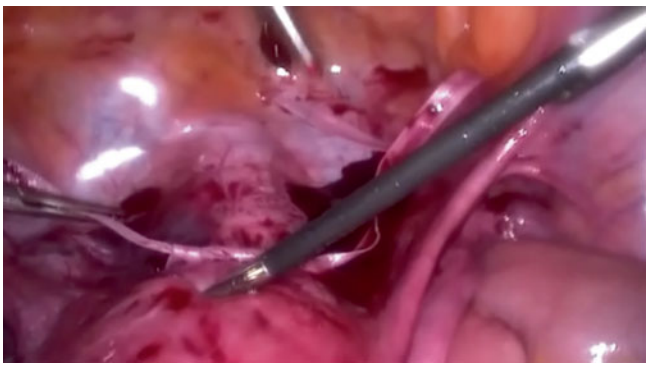

Fig. 12.24 Laparoscopic cervical cerclage. The vesicouterine peritoneum is left out of the cervical cerclage suturing (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

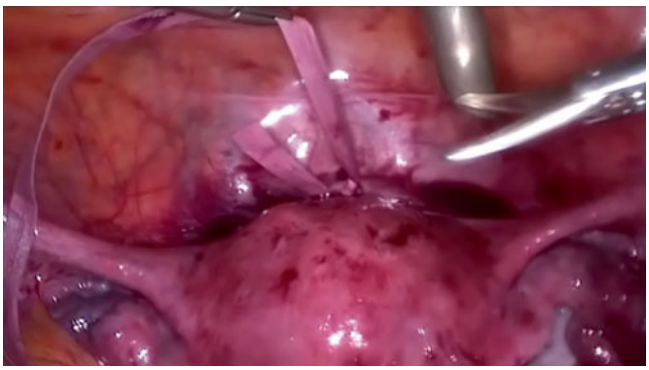

Fig. 12.25 Laparoscopic cervical cerclage. Removing of a needle of the Mersilene thread after laparoscopic cerclage knotting (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

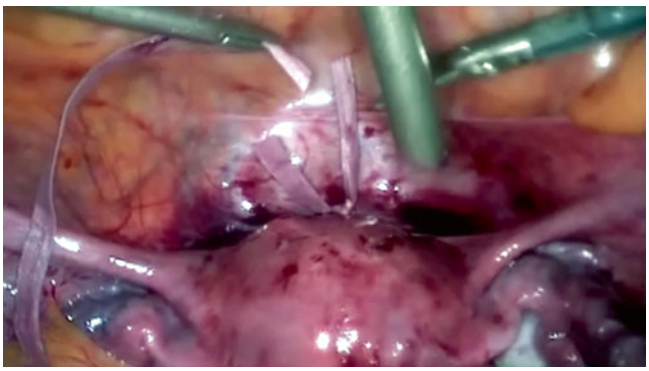

Fig. 12.26 Laparoscopic cervical cerclage. Removing of the second needle of the Mersilene thread (Courtesy of Dr. Helena Ban Frangež, Department of Reproduction, University Medical Center Ljubljana, Slovenia)

ing transabdominal cerclage in 161 women with cervical insufficiency and explored parameters for predicting pregnancy outcomes following TAC. The mean gestational age at delivery after transabdominal cerclage was 36.3 weeks, with a neonatal survival rate of 96 %. Univariate analysis demonstrated that a short CL (<25 mm) at 20–24 weeks and adenomyosis were associated with delivery at <34 weeks of gestation following transabdominal cerclage ($p=0.015$ and $p=0.005$, respectively). They found that maternal adenomyosis was a good predictor of TAC. However, multivariate analysis demonstrated that only a short CL (<25 mm) at 20–24 weeks was a significant predictor ($p=0.005$). In their study there were only 15 cases of adenomyosis, and they postulated that the small number of patients with adenomyosis might not have been sufficient for evaluating its effects as a predictor of transabdominal cerclage outcome.

12.12 Cervical Cerclage in Multiple Gestations

The use of cervical cerclage to prevent preterm delivery is still controversial, particularly in multiple pregnancies. According to the available systematic reviews, cervical cerclage in twin pregnancies seems to be associated with a significant increased risk of preterm birth [72]. Cerclage based solely on the presence of a twin gestation has not been shown to be beneficial [72], and in women with twins and a short cervix, it is potentially harmful. There have however been some published studies showing different results. Zanardini et al. [65] reported on 28 cases of ultrasound-indicated cerclage and 14 of physical examination-indicated cerclage, finding 96 % perinatal survival in the former group and 86 % in the latter. Cervicovaginal and rectal swabs were gotten preoperatively, and perioperative antibiotics and tocolysis were administered. They noted Berghella's conclusion that ultrasound-indicated cerclage in twin pregnancies is associated with a higher risk of preterm delivery (75 % before 35 weeks). However, this data is related to a relatively small population of 49 pregnancies from two randomized controlled trials, all of which had different inclusion criteria and management protocols and neither of which was intended to specifically evaluate the role of cervical cerclage in twin pregnancies [73]. Zanardini et al. [65] concluded that their data stressed the importance of reevaluating the efficacy of cerclage in twin pregnancies through properly designed clinical trials, particularly if cerclage is physical examination indicated.

Data on transabdominal cerclage in twin gestation is scarce. We reported one case of "successful twin pregnancy after vaginal radical trachelectomy using transabdominal cervico isthmic cerclage" [74]. Kyvernitakis also reported a similar case [75]. From now on transabdominal cervicoisthmic cerclage should be considered in twin pregnancies in cases of extreme short cervix after radical trachelectomy and previous transvaginal cerclage failure, as it would also be considered in single pregnancy. We have had some experience of transabdominal cervicoisthmic cerclage in twin pregnancy, although it is as yet not published.

12.13 Clinical Considerations for Cervical Insufficiency

Cervical insufficiency is a very important keyword related to preterm birth and is not uncommonly encountered. Despite this, however, there have been many controversies about diagnosis and treatment. A thorough obstetric history and risk factors for cervical insufficiency should be reviewed and all possible options for treatment discussed. Treatment should be decided based mainly upon the obstetric history and risk factors for cervical insufficiency and monitoring of cervical length and shape (TVU) by ultrasound. After careful review of all obstetric historic risk factors, a therapy plan should be agreed on with the patient involving cerclage and/or other methods. All women having high-risk factors should have CL checked by ultrasound especially during the period from 16 to 24 weeks of gestation. When finding a short cervix of less than 25 mm, we should discuss cerclage and progesterone therapy with uterine monitoring and vaginal examination. A Cochrane review regarding "cervical cerclage for preventing preterm birth" suggests that "The decision on how best to minimize the risk of recurrent preterm birth in women at risk, either because of poor history or a short or dilated cervix, should be 'personalized', based on the clinical circumstances, the skill and expertise of the clinical team, and, most importantly, the woman's informed choice" [76].

Emergency cerclage may be the best hope for rescuing pregnancy in women with advanced cervical changes and prolapsed membranes in the midtrimester. The operative risk

is surgically challenging, but recent new devices may be of great help to the patient.

Transabdominal cervicoisthmic cerclage is beneficial to a patient with extremely short cervix or in cases of prior failed transvaginal cervical cerclage procedures.

In the future, intensive study is needed to determine the true pathogenesis of cervical insufficiency. Some new standard treatment protocol is needed as well. The discovery of new biomarkers for cervical insufficiency will of course also be essential for reducing cervical insufficiency.

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Thrombophilia and Pregnancy

13

Paul W. Hendrix, Andrea Tinelli, Antonio Malvasi, and Michael J. Paidas

13.1 Introduction

Thrombophilias, both hereditary and acquired, are frequently encountered by today's obstetricians. The complexity of the disorders makes both patient counseling and management challenging. Our knowledge of thrombophilias is expansive and evolving, causing both debate and frequent clinical practice changes over the past few decades. As new genetic risk factors for thrombosis have been discovered, the clinical implications are slowly being determined. The goal of this chapter is to discuss both hereditary and acquired thrombophilias, emphasizing the first and second trimesters of pregnancy. We will examine the evolving literature of each disorder and discuss current recommendations regarding screening and therapy.

P.W. Hendrix, DO
Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520-8063, USA
e-mail: paul.hendrix@yale.edu

A. Tinelli, MD, PhD
Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Laboratory of Human Physiology, The International Translational Medicine and Biomodelling Research Group, Department of Informatics and Applied Mathematics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Institute of Physics and Technology (State University), Moscow, Russia

Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Department of Obstetrics & Gynecology, Vito Fazzi Hospital, Lecce, Italy
e-mail: andreatinelli@gmail.com

A. Malvasi, MD
Department of Obstetrics and Gynecology, Santa Maria Hospital, G.V.M. Care and Research, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

M.J. Paidas (✉)
Division of Maternal Fetal Medicine, Yale Women and Children's Center for Blood Disorders and Preeclampsia Advancement, New Haven, CT, 06520-8063, USA

Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA
e-mail: michael.paidas@yale.edu

13.2 Pregnancy and Hemostasis

Pregnancy is a true test of the human coagulation system. From implantation through the puerperium, the maternal system must carefully balance between hypercoagulability and hemorrhage. Among the earliest challenges is the establishment of the maternal-fetal interface. The invading embryo's cytotrophoblasts access the maternal decidual vessels to establish early placental circulation. The endovascular trophoblasts invade the maternal spiral arteries, which after morphological conversion, provide the high-flow, low resistance blood supply necessary to support the rapidly growing gestation. Implantation provides a multitude of opportunities for both hemorrhage and thrombosis, either of which could initiate miscarriage or pathological placentation. Many of the poor obstetrical outcomes discussed later in this chapter are theorized products of a compromised maternal-fetal placental interface, including preeclampsia, intrauterine growth restriction, pregnancy loss, and abruption.

Delivery and the puerperium make up another serious challenge to the maternal coagulation system. The rapid transition from the 600 to 700 ml/min blood flow to a term placenta (approximately 80 % of uterine blood flow) to appropriate postpartum bleeding is critical [1].

Though much of the hemostatic burden is carried by myometrial contractions and vasospasm, a substantial amount is left to the maternal coagulation cascade to prevent life-threatening postpartum hemorrhaging. This

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_13

responsibility leads to an increased risk for thrombotic complications, particularly in the setting of a concurrent clotting disorder. Venous thromboembolism (VTE) complications remain a leading cause of maternal death (Fig. 13.1), accounting for an estimated 9.3 % of maternal deaths in the United States from 2006 to 2010 [2]. Risk factors for maternal venous thromboembolism are presented in Table 13.1 [3–7].

Pregnancy has multiple physiological changes that make women susceptible to VTE. All three elements of Virchow's triad (Fig. 13.2) are present, including venous stasis, endothelial injury, and a hypercoagulable state. Hormone changes of pregnancy lead to lower extremity pooling and venous stasis secondary to vasodilation (Fig. 13.3). The uterine compression of the pelvic venous return further augments maternal lower extremity venous stasis (Fig. 13.4). Whether provider recommended or self-prescribed, decreased maternal activity can be an additional contributor to decreased lower extremity venous flow. Endothelial injury and thrombus formation (Figs. 13.5, 13.6, 13.7, 13.8, and 13.9) are present especially at time of delivery. The primary endothelial injury occurs at the uterine placental site, and the risk of VTE is enhanced by cesarean section and operative delivery [8].

There is also increased risk of VTE with infection, postpartum hemorrhage, and preeclampsia, all of which are associated with endothelial injury [9].

The physiology accounting for the hypercoagulability of pregnancy is complex and generated by a factor combination (Fig. 13.10). Many of the procoagulant factors of the clotting cascade are progressively increased throughout pregnancy including factors II, VII, VIII, and X (Fig. 13.11). Decreases

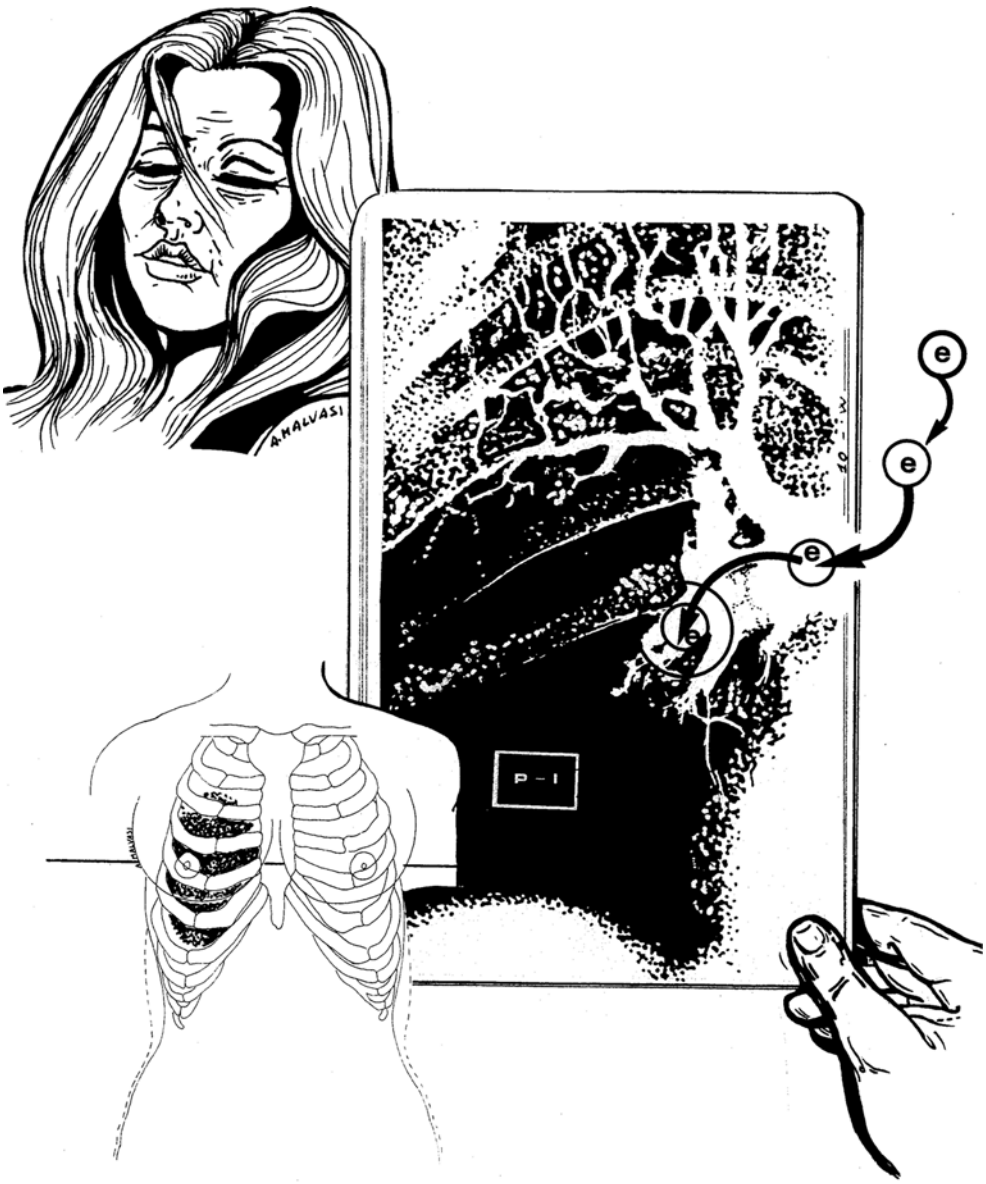

Fig. 13.1 A maternal death for venous thromboembolism (VTE) in pregnancy

Table 13.1 Antepartum and postpartum risk factors for VTE in pregnancy

Antepartum and Postpartum VTE	Odds ratio (95 % CI)
Thrombophilia [3]	51.8 (38.7–69.2)[a]
Previous VTE [3]	24.8 (17.1–36.0)
Family history of VTE [4]	3.9[b]
Superficial venous thrombosis [5]	10.0 (1.3–78.1)
BMI >25 kg/m^2[c] [6]	1.8 (1.3–2.4)
Antepartum immobilization [6]	7.7 (3.2–19.0)
BMI >25 kg/m^2[c] and antepartum immobilization [6]	62.3 (11.5–337.6)
Antepartum VTE [6]	
Assisted reproduction	4.3 (2.0–9.4)
Smoking	2.1 (1.3–3.4)
Postpartum VTE [6]	
Hemorrhage (without surgery)	4.1 (2.3–7.3)
Hemorrhage (with surgery)	12.1 (3.9–36.9)
Infection (vaginal)	20.2 (6.4–63.5)
Infection (cesarean)	6.2 (2.4–26.3)
IUGR	3.8 (1.4–10.2)
Preeclampsia	3.1 (1.8–5.3)
Preeclampsia and IUGR	5.8 (2.1–16.0)
Emergency cesarean delivery	2.7 (1.8–4.1)
Other possible risk factors	
Cesarean delivery [3]	2.1 (1.8–2.4)
Cesarean delivery [6]	1.3 (0.7–2.2)
Age [3]	2.1 (2.0–2.3)
Age [6]	0.8 (0.6–1.1)
Parity [5]	1.1 (0.9–1.4)
Parity [6]	1.7 (1.2–2.4)

Adapted from Bourjeily et al. [7]
VTE venous thromboembolism, *BMI* body mass index. *IUGR* intrauterine growth restriction, [ ] = reference
[a]Risk varies by type of thrombophilia
[b]95 % CI not reported; $p<0.05$
[c]BMI at the time of the first prenatal visit

in protein S and resistance to activated protein C also suppress fibrinolysis, further tilting the system toward coagulation [8].

The addition of a thrombophilia, to a varying extent depending on the specific dysfunction, makes the possibility of VTE substantially higher. The incidence of VTE in pregnancy is approximately 1 per 1500 pregnancies, a prevalence four to six times higher than the rate of women of childbearing ages outside of pregnancy [8, 11–13].

Though venous thromboembolism events can happen at anytime throughout pregnancy, it is generally thought 50 % occur before delivery and 50 % occur in the postpartum period. Data regarding specific trimester-related frequency of VTE is contradictory, but it is clear that the increased risk starts with conception, and the most recent data suggest that the thromboembolic risk is exponential as pregnancy proceeds, with the greatest risk in the peri-delivery period [8, 13–16].

Seventy to ninety percent of DVTs in pregnancy occur in the left leg (Fig. 13.12). This is explained anatomically due to the right iliac artery crossing the proximal left iliac vein, compressing the vessel. The prompt identification and treatment of thrombosis are important in decreasing mortality or complications of thrombotic disease in pregnancy.

13.3 Hereditary Thrombophilias

The inherited thrombophilias addressed in this chapter are all mutations affecting the coagulation cascade (Fig. 13.13). The multiple enzymes and cofactors required for effective hemostasis make opportunities for genetic variation (Fig. 13.11) [10].

The most common genetic prothrombotic mutations include heterozygous carriers of factor V Leiden (FVL) and prothrombin gene mutation (PGM) G20210A. Others we will address in this chapter are far less common including deficiencies in protein C, protein S, and antithrombin (Table 13.2) [18].

We will describe the available data regarding both VTE and adverse pregnancy outcomes (Table 13.3).

Treatment and management of these disorders will be reserved for the end of the chapter.

13.3.1 Factor V Leiden

The inherited thrombophilia most commonly encountered by obstetricians is factor V Leiden (FVL). It is a gene mutation named for the city in which it was first identified in 1994: Leiden, Netherlands [24]. On the procoagulant side of the clotting cascade, factor V is activated by prothrombin to factor Va, which is then a cofactor for the conversion of prothrombin to thrombin. On the anticoagulant side of the equation, factor Va is cleaved by activated protein C and acts as a cofactor for the negative feedback on factor VIII [25]. FVL results from a point mutation in the factor V gene on chromosome 1q23, which codes for an arginine to glutamine substitution at position 506 of the protein. This single amino acid change distorts activated protein C's cleavage site, impairing its ability cleave factor Va.

FVL is most prevalent in Caucasians of European descent with carrier frequencies estimated at 5–9 % of the population. It is less prevalent in those of Asian and African descent [26]. The rate of homozygosity is approximately of 1 % of those with the gene mutation, and they tend have to have a higher incidence of VTE [20, 27].

Screening for FVL can be performed by a second-generation APC resistance assay with confirmatory genetic testing for the FVL mutation. However, most providers go directly to genetic testing which is not affected by anticoagulation.

Retrospective data suggests heterozygous carriers of FVL have a five- to tenfold relative risk for VTE during pregnancy, and it is present in 43 % of pregnant women with their

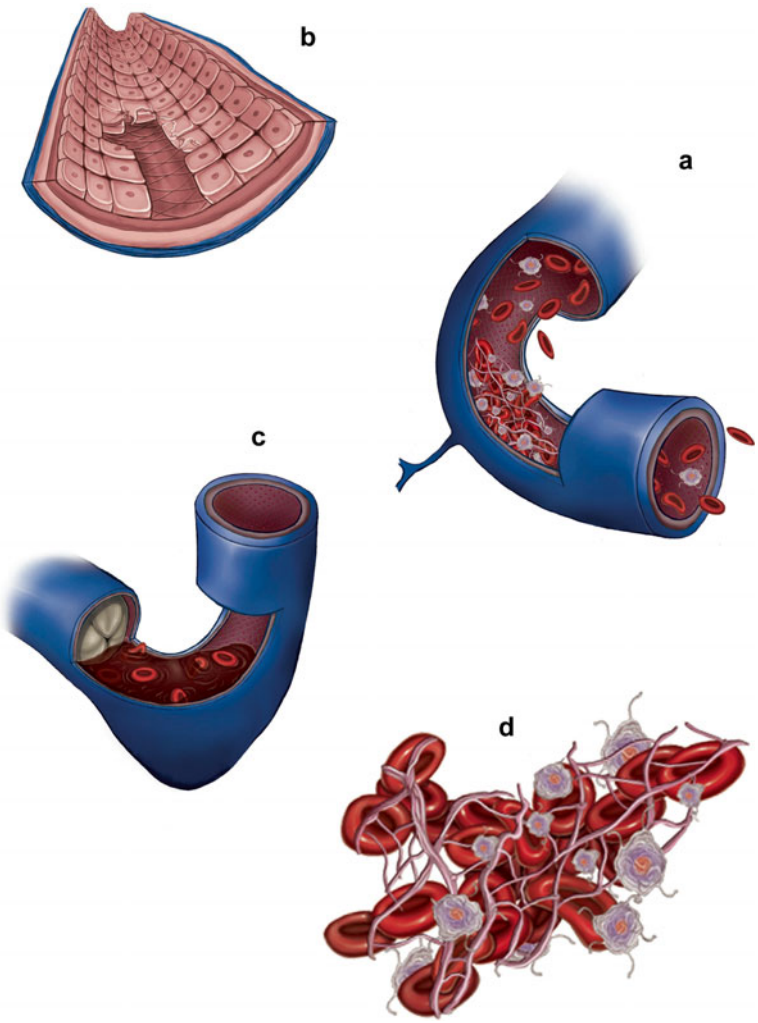

Fig. 13.2 The elements of Virchow's triad, (**a**) venous stasis, (**b**) endothelial damage, and (**c**) venous thrombus formation; (**d**) magnification of the thrombus

first thrombotic event [28–31]. It should be pointed out that the overall carrier rate is high and the overall thrombotic incidence is low. The risk of VTE is only 0.25 % in heterozygotes without a family or personal history of thrombosis. For patients with a family or personal history of VTE, the risk could be as high as 10 % [29]. One large multicenter prospective NICHD study looked at 4885 gravid patients without a personal history of thrombotic event. In the 134 FVL carriers found, there was no increase risk of VTE (0 %; 95 % CI, 0–2.7 %) [32].

Contradictory findings confound the association of FVL and spontaneous abortions. A 2003 meta-analysis looking at seven retrospective studies evaluating FVL and recurrent fetal loss before 13 weeks of gestation suggested an association (OR 2.01; 95 % CI, 1.13–3.58) [23]. Similar findings were found in a later systemic review (OR 1.91; 95 % CI 1.01–3.61) [20]. Contrary to this, Roque et al. found FVL to be protective from recurrent fetal losses prior to 10 weeks of gestation in a cohort of women with poor obstetrical outcomes (OR .229; 95 % CI, 0.07–.77) [33]. Another large case-controlled study of 3496 matched women found an association with fetal loss starting after the 10th week of gestation (OR 3.46; 95 % CI, 2.53–4.72) but not from the 3 to 9th week of gestation (OR 1; 95 % CI, 0.4–2.52) [34]. Overall, it appears FVL might be a small risk factor for first trimester loss, and this increased risk is likely limited to after 10 weeks of gestation.

Many studies have found FVL associated with second trimester fetal losses and stillbirth [23, 35–37]. One meta-analysis associates FVL with second and third trimester loss with a pooled OR 3.6 (95 % CI, 2.2–5.8). This risk increased with each prior fetal loss and with prior losses at later gestations [38]. Kocher et al. used a prospective case-controlled study of 5000 pregnancies and found a stillbirth association (OR 10.9; 95 % CI, 2.07–56.94) [39].

The protective association of FVL in the first trimester of pregnancy and the association with fetal loss later in pregnancy could be explained by the contrasting environments necessary at the placental interface during different stages of development. The partial pressures of oxygen are low in the

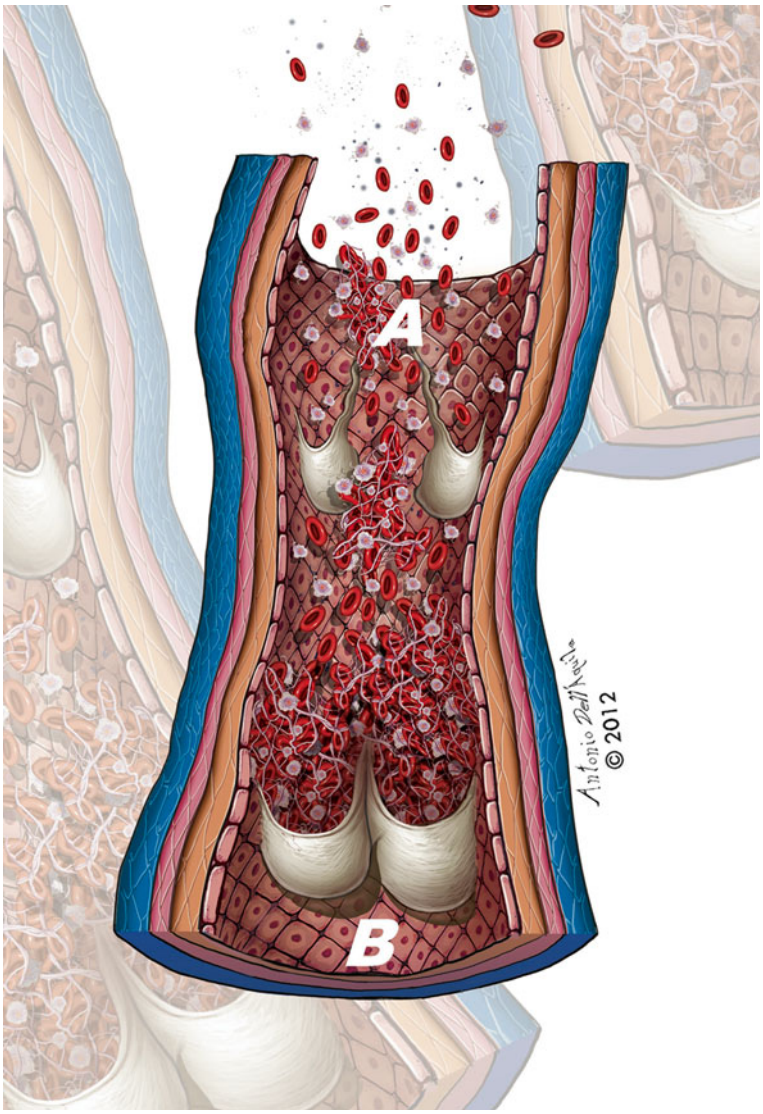

Fig. 13.3 Front section of saphenous vein: (**a**) incontinence of the venous valves and (**b**) thrombus formation

mid first trimester: 17 ± 6.9 mmHg at 8–10 weeks when compared to 60.7 ± 8.5 mmHg at 13 weeks [40]. This hypoxia prior to 10 weeks occurs when trophoblasts are invading and plugging the spiral arteries as evidenced by low Doppler blood flow found on ultrasound [41]. If the hypoxic environment persisted or occurred at later gestations, pregnancy loss would be more likely. This provides a plausible mechanism of how an increased clotting tendency would not affect pregnancy viability prior to 10 weeks but be associated with pregnancy loss when a more oxygen-rich milieu is necessary after the first trimester.

While early studies indicated FVL might be a risk factor for intrauterine growth restriction, most studies indicate that an association is not present. Facco et al. evaluated 12 retrospective case-control studies and four retrospective cohort studies in a systemic review [42]. When all studies are included, an association is suggested (OR 1.23; 95 % CI, 1.04–1.44). When the cohort studies were isolated, the pooled OR for the association did not reach statistical significance (OR 1.16; 95 % CI, 0.98–1.38) [42]. Others have found similar findings [19, 43, 44].

Some available evidence shows an association between the FVL gene mutation and preeclampsia. Lin et al. published a meta-analysis of 12 case-control studies showing an association with both preeclampsia (OR 1.81; 95 % CI, 1.14–2.87) and severe preeclampsia (OR 2.24; 95 % CI, 1.28–3.94) [45]. More recently, a nested case-controlled cohort study of the Danish National Birth Cohort took 519 cases of severe preeclampsia out of 91,661 women and found a positive association (OR 1.94; 95 % CI, 1.27–2.96) [46]. An interesting Italian prospective cohort study showed a higher risk of recurrent preeclampsia in women with FVL (59 %) compared to those without a thrombophilia (25.9 %) [47]. Other studies have failed to find an increased risk of preeclampsia

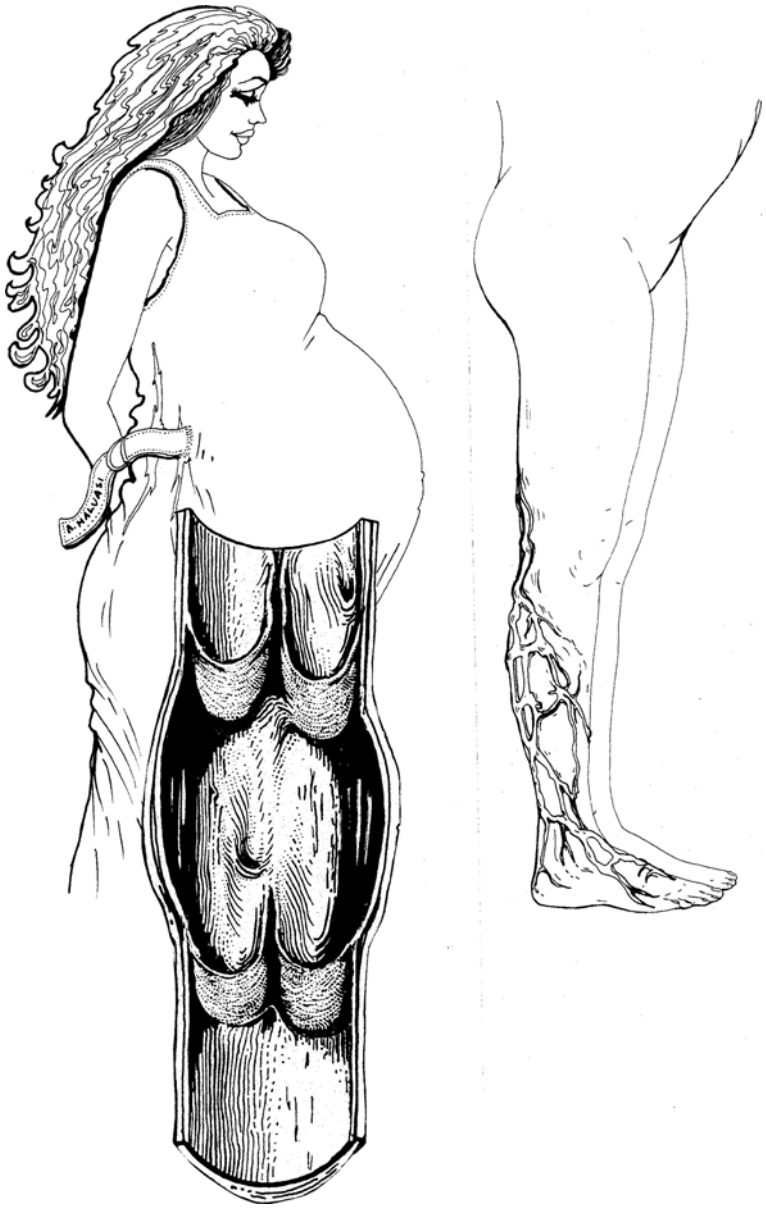

Fig. 13.4 The venous stasis secondary to vasodilation in pregnancy in combination with incontinence valve causes the formation of varicose veins in the legs

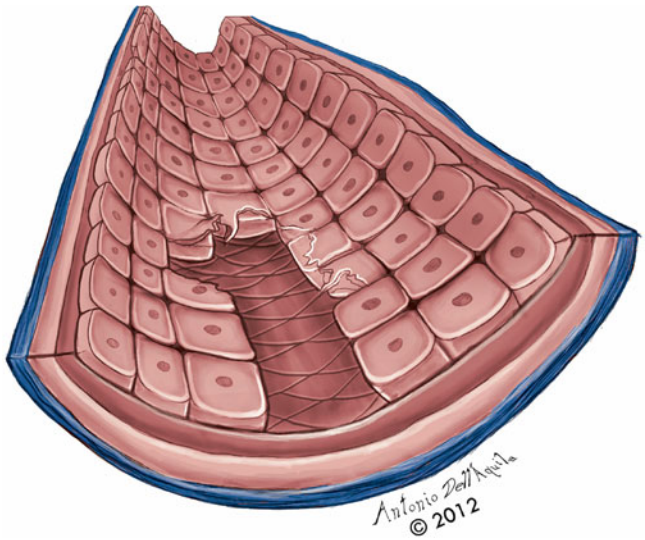

Fig. 13.5 Endothelial injury

with FVL carriers [32, 36, 48], including a meta-analysis of nine prospective cohort studies (OR 1.23; 95% CI 0.89–1.7) [19]. If an association with preeclampsia is present, it is likely not sufficiently significant to alter clinical practice.

Due to the relative infrequency of placental abruption, there are few and conflicting studies evaluating its relationship to FVL. Zdoukopoulos et al. found a positive association in five out of ten retrospective case-control studies. A meta-analysis of those ten studies showed an associative risk (OR 3.42; 95% CI, 1.42–8.25) [49]. The case–cohort study using the Danish Cohort showed a lower but present association (OR 1.87; 95% CI 1.25–2.81) among its 378 cases of placental abruption [46]. No association was found in a NICHD multicenter prospective cohort study in which 134 FVL mutation carriers were identified in a cohort of 4885 women. Nested carrier-control analysis found no association with placental abruption [32].

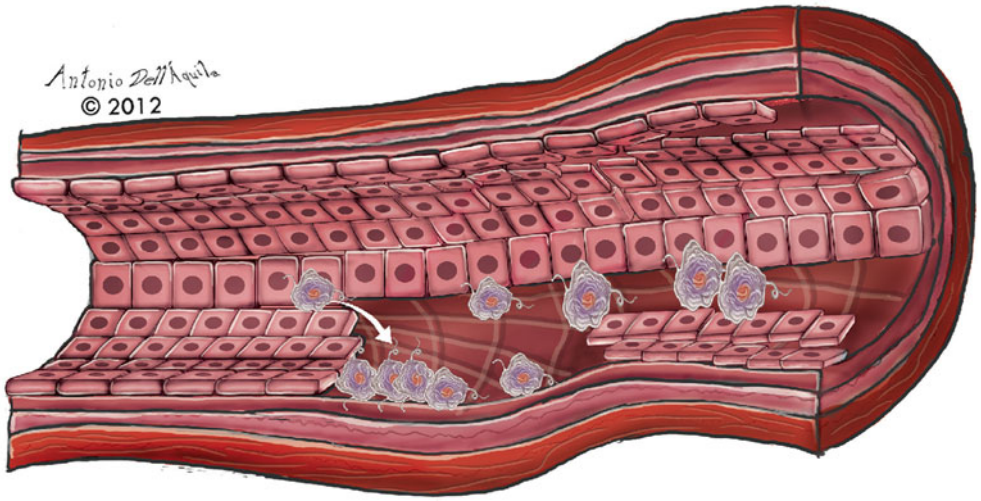

Fig. 13.6 Platelet adhesion to damaged endothelium

Currently, a consistent association between FVL and abruption has not been shown.

Overall, FVL carriers are at increased risk of VTE in pregnancy. FVL is also associated with fetal losses after 10 weeks and stillbirths. There is not enough evidence to strongly support FVL as a risk factor for preeclampsia, fetal growth restriction, or abruption.

13.3.2 Prothrombin Gene Mutation (PGM)

The second-most prevalent inherited thrombophilia results from a polymorphism in the untranslated 3′ region of the gene coding for prothrombin (factor II). A single guanine (G) to adenine (A) nucleotide point mutation, G20210A, leads to enhanced translation and gene expression. The result is elevated circulating prothrombin plasma levels. The carrier prevalence of PGM is 2–4 % in European Caucasians. Similar to FVL, PGM is much less common in those of Asian and African descent [26, 27]. Testing is performed by PCR for the specific G20210A mutation.

PGM is a risk factor for VTE, especially during pregnancy. Gerhardt et al. found that 17 % of 119 patients diagnosed with VTE in pregnancy were carriers of the mutation compared to 1.3 % of matched unaffected controls [28]. Other studies have shown a large variation in carrier percentages among patients with their first VTE related to pregnancy, from 31 % out of 42–3.8 % out of 313 [31, 50]. Like FVL, the overall probability of a thrombosis during pregnancy among PGM carriers without a personal or family history of VTE is as low as 0.37 %. The risk increases to over 10 % for those who have had a prior VTE. The probability appears to be higher for those who are homozygous for PGM mutation, but the available data is sparse [31]. The risk appears much higher for compound heterozygotes for both FVL and PGM, with a 4.6 % probability of a VTE during pregnancy and puerperium even without a prior history [28].

There is conflicting data regarding an association between early fetal loss and PGM carriers (Fig. 13.14). In a meta-analysis of four pooled retrospective studies, PGM carriers had increased risk of recurrent losses before 13 weeks (OR 2.32; 95 % CI, 1.12–4.79) [23]. A similar systemic review of six studies also showed an association with recurrent first trimester loss (OR 2.70; CI 1.37–5.34) [20].

Both of these pooled studies included multiple small retrospective case-control studies that are prone to bias. Subsequent prospective studies have failed to show an association. In one prospective cohort of 4872 pregnancies tested, 2.8 % were carriers for the PGM G20210A gene, and no association with early fetal loss was found (OR 0.74; 95 % CI 0.30–1.84) [39].

Most available data suggest G20210A gene mutation is not a strong risk factor for stillbirth. Korteweg et al. found in a pooled cohort of 1025 fetal deaths that the rate of PGM was no different than the normal population (2.4 % of mothers) [51]. Kocher's prospective cohort study of over 4872 women also found no evidence of PGM as risk factor for stillbirth [39]. In secondary analysis of a large prospective multicenter NICHD cohort study of 4167 women enrolled, no association was noted with pregnancy losses across all gestational ages (OR 0.98; 95 % CI 0.49–1.95) [52]. A 2003 systemic review including five case-controlled studies addressing nonrecurrent losses after 20 weeks suggests an association (OR 2.66; 95 % CI 1.28–5.53) [20]. A more recent meta-analysis of four prospective studies failed to show an association with pregnancy loss (OR 1.13; 95 % CI, 0.64–2.01) [19]. Overall, the association between both early pregnancy loss and stillborn is likely modest if present at all.

Studies regarding PGM and fetal growth restriction generally do not support an association. Lykke's nested case–cohort study of the Danish National Birth Cohort did not show an increased risk of growth restriction in PGM carriers (OR 0.82; 95 % CI 0.46–1.43) [46]. This was similar to prospective data from Silver et al. regarding PGM and for small

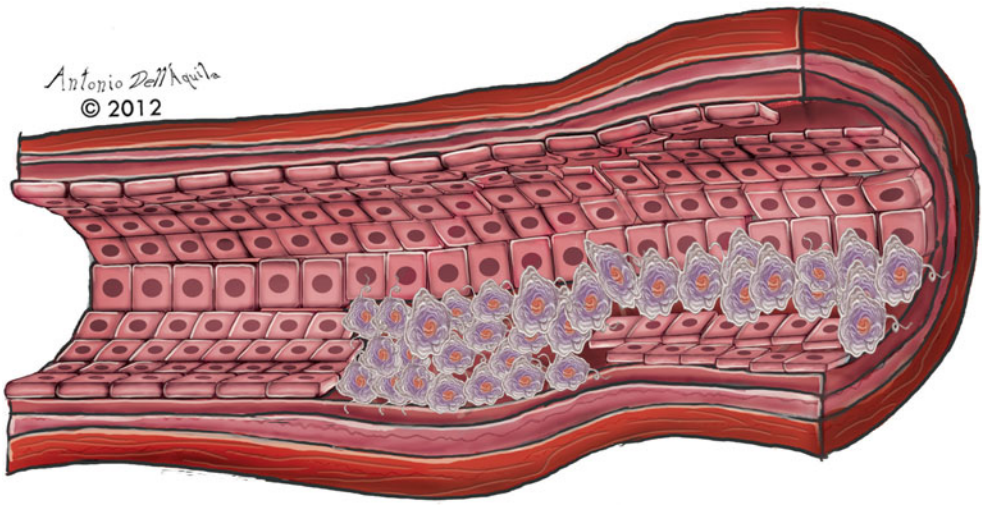

Fig. 13.7 Platelet aggregation on the damaged endothelium

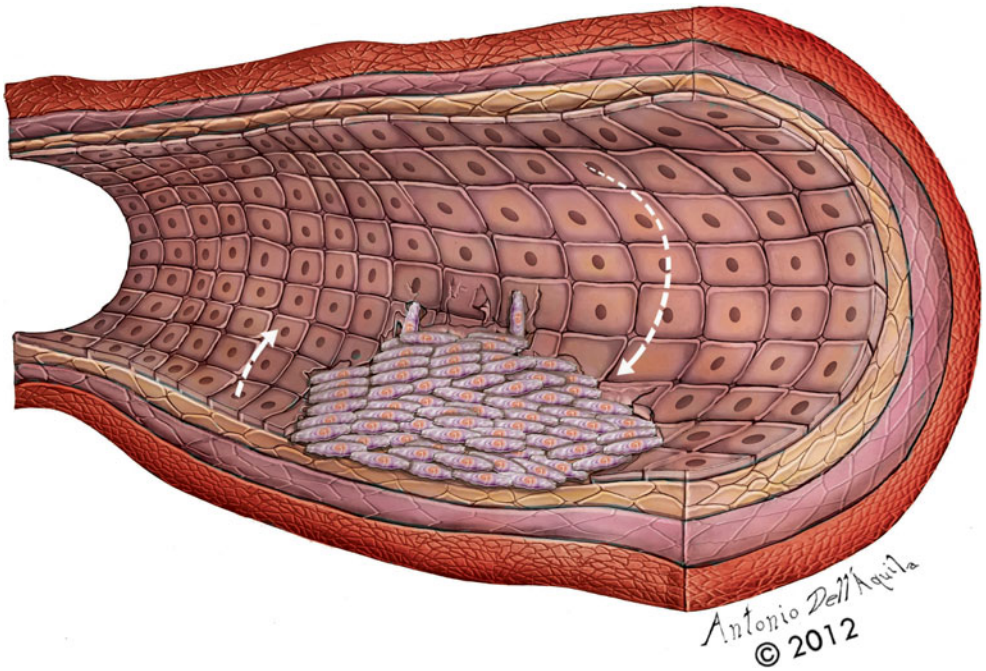

Fig. 13.8 Formation of the platelet plug

for gestational age less than 10 % (OR 1.34; 95 % CI; 0.8–2.25) and less than 5 % (OR 1.39; 95 % CI, 0.67–2.89) using sex- and race-specific growth curves [52]. Similar findings were made by others [19, 36, 39, 53, 54].

Studies showing an association between PGM and IUGR have been limited to case-control studies [37, 55].

Prothrombin gene mutation has not been linked to preeclampsia. In the nested case–cohort evaluation of Danish National Birth Cohort, no association between PGM and severe preeclampsia was found (OR 0.81; 95 % CI, 0.29–2.30) [46].

Rodger et al.'s meta-analysis of prospective studies, including 549 women with PGM, also failed to show an association with preeclampsia (OR 1.25; 95 % CI, 0.79–1.99) [19]. Multiple other studies have shown that PGM is not a risk factor for preeclampsia [36, 48, 52, 56, 57].

The association between PGM and placental abruption is difficult to assess due to the infrequency of abruption. A systemic review including three retrospective case-control studies found a positive association (OR 7.71; 95 % CI 3.01–19.76), but even when pooled, the number of PGM carriers was low ($n = 20$) [20].

In a prospective cohort of 2034 women, Said et al. found that PGM was an isolated risk factor for abruption (OR 12.15; 95 % CI, 2.45–60.39) [36]. The strongest study available comes from pooled prospective data in a 2010 meta-analysis, which failed to find a significant association (OR 2.02; 95 % CI, 0.81–5.02) [19].

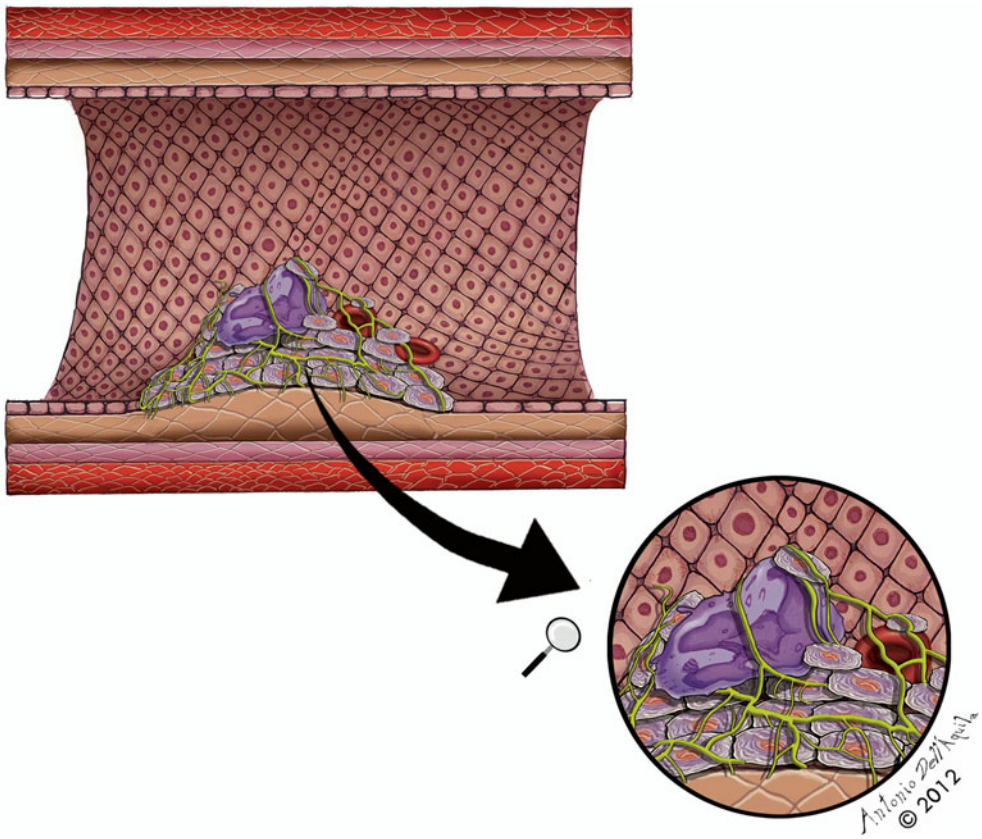

Fig. 13.9 Thrombus formation

In summary, the prothrombin gene mutation G20210A is a relatively common heritable risk factor for thrombosis especially in pregnancy. VTE risk appears higher in homozygotes and those with compound heterozygotes. There has been contradictory data regarding PGM's effect on first trimester losses, stillbirth, and abruption. If associations are present, they are likely weak. There is little evidence that preeclampsia and IUGR are associated with PGM.

13.3.3 Protein C Deficiency

Protein C is an anticoagulant responsible for the deactivation of factor Va and factor VIIIa. It is activated by thrombin to activated protein C (APC) which then degrades factors Va and VIIIa, inhibiting clot formation [27].

Protein S, a nonenzymatic cofactor for this action, will be discussed later in this chapter. Protein C's synthesis (Fig. 13.15a) or functional deficiency is found in 0.2–0.3 % of individuals of European descent. It appears more frequently in those of Asian and African descent [26]. The gene coding for protein C is located on chromosome 2. It is vitamin K dependent and is synthesized by the liver. Two major subtypes of APC deficiencies have been delineated. The more common phenotype, type I, has both reduced protein C levels and activity. Type II phenotypes have quantitatively normal levels of protein C but have compromised functional activity. Laboratory evaluation includes both protein C antigen levels and activity levels. Laboratories typically use activity levels of <50–60 % as abnormal. Testing is unreliable during an acute thrombosis or during anticoagulation therapy.

In regard to a thrombotic event risk in pregnancy, protein C deficiency is moderately pro-thrombogenic (Fig. 13.15b). The risk is likely proportional to the deficiency of substrate and/or function. Zotz et al. found the relative risk of a first VTE in pregnancy to be RR 3.0 (95 % CI: 1.4–6.5) if using a <73 % of normal protein C activity cutoff and RR 13.0 (95 % CI, 1.4–123) if using a <50 % cutoff in his case-control study of 173 women with VTE compared to 325 normal controls [29]. A 2006 systemic review of available retrospective case-controlled studies showed a modest risk of VTE (OR 4.76; 95 % CI, 2.15–10.57) in patients with hereditary protein C deficiency [20]. Because both DVT and protein C deficiency are rare, prospective studies regarding their association are unlikely.

Data regarding the association of protein C deficiency and poor obstetrical outcomes is sparse, and the studies available are underpowered. The diverse genetic variants and phenotypes make it difficult to make any conclusion regarding management strategies. Many studies that do include protein C deficiency pool data with protein S and antithrombin deficiency. Preston et al. found the risk of loss in the first or

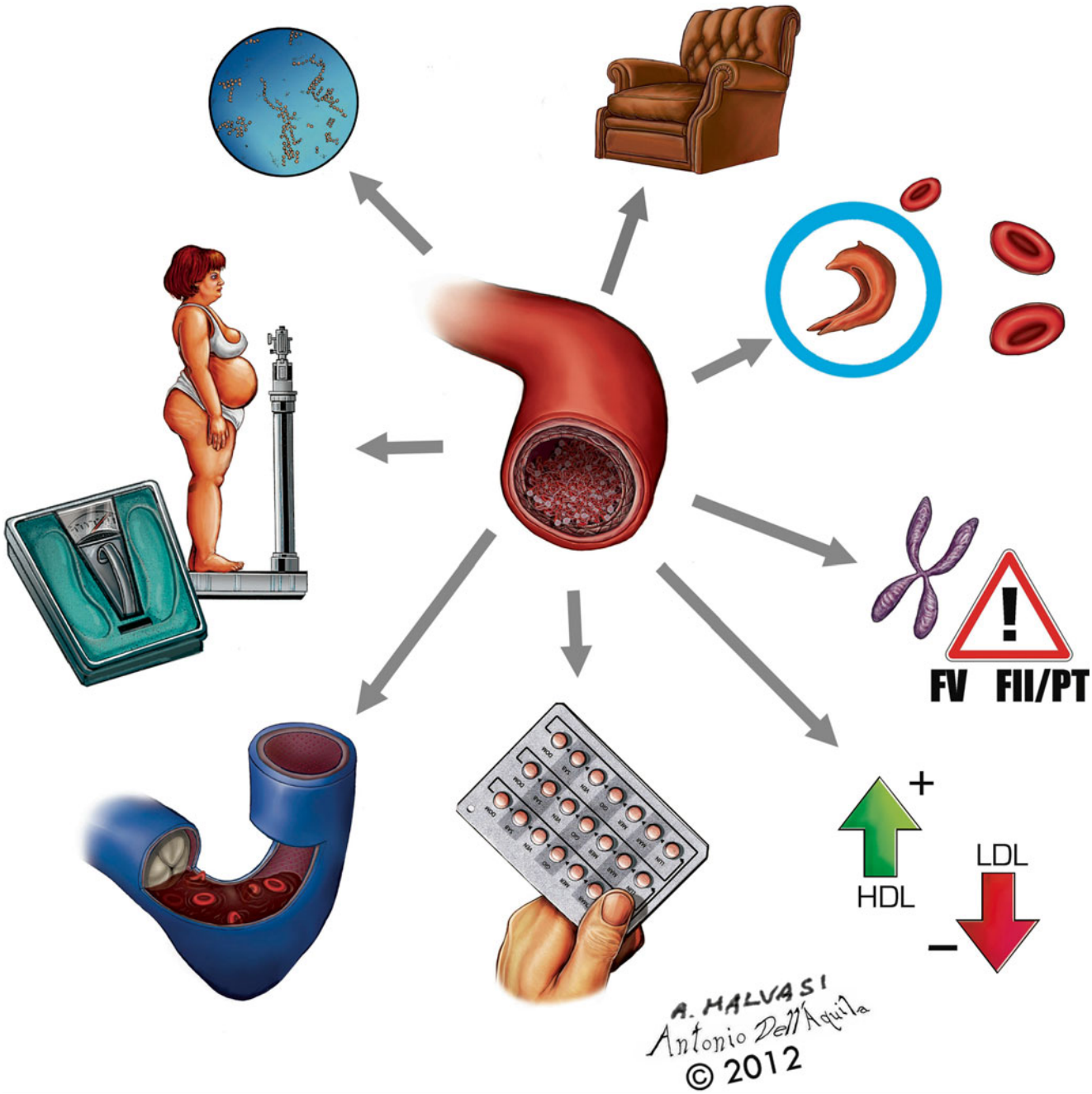

Fig. 13.10 A factor combination accounting for the hypercoagulability of pregnancy

second trimester to be OR 1.4 (95 % CI, 0.9–2.2) compared to a third trimester loss OR 2.3 (95 % CI, 0.6–8.3) [22]. Others have not been able to find associations between recurrent early pregnancy loss and protein C deficiency [58]. In systemic review of retrospective case-controlled studies, Alfirevic et al. found that protein C deficiency was not associated with stillbirth (OR 1; 95 % CI, 0.1–11.1) but was associated with preeclampsia (OR 21.5; 95 % CI, 1.1–414.4). All of the included studies were limited by small study size and large confidence intervals [21]. Our retrospective cohort found an association with preeclampsia (OR 6.85; 95 % CI, 1.09–43.21) and abruption (OR 13.86; 95 % CI, 2.21–86.94) but failed to show associations with the other poor pregnancy outcomes studied [33].

13.3.4 Protein S Deficiency

Protein S is a vitamin K-dependent anticoagulant cofactor in the clotting cascade. It accelerates activated protein C's dis-

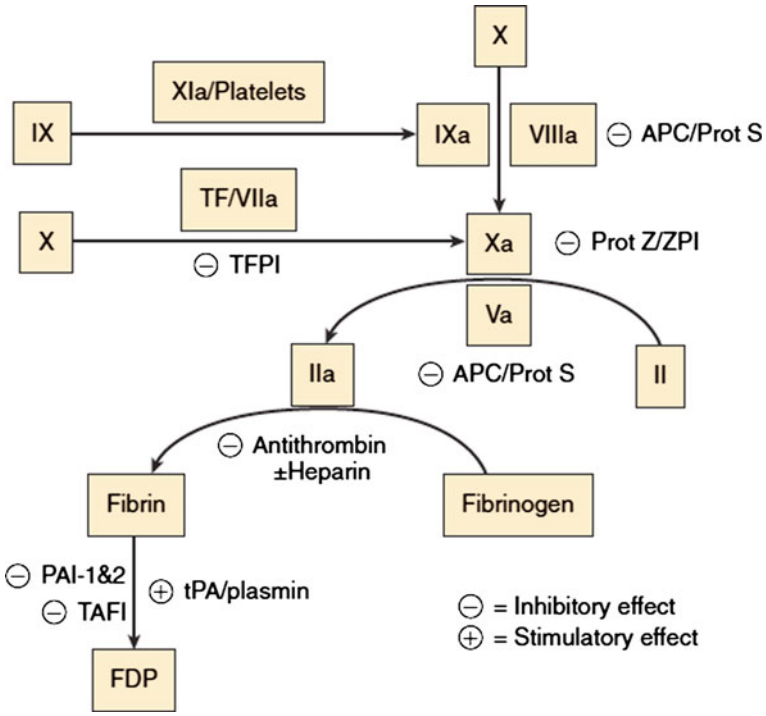

Fig. 13.11 Hemostatic, thrombotic, and fibrinolytic pathways. *FDP* fibrin degradation product. *TPA* tissue-type plasminogen activator (From Pettker and Lockwood [10])

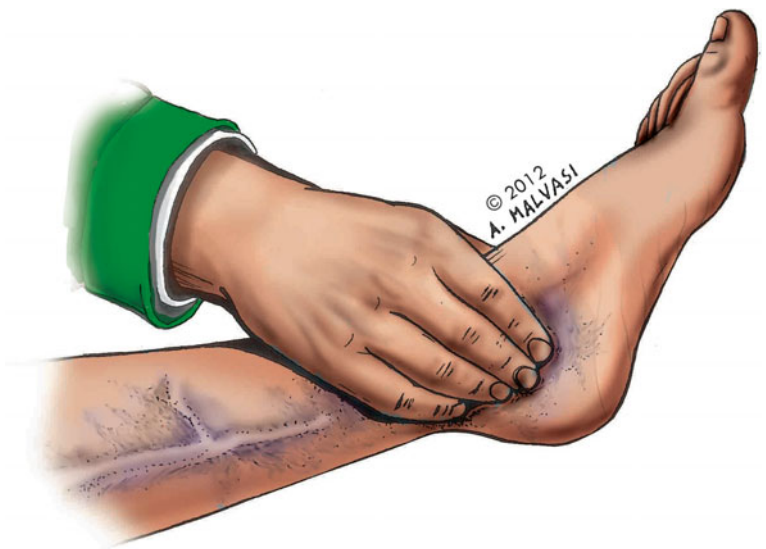

Fig. 13.12 Seventy to ninety percent of DVTs in pregnancy occur in the left leg

ruption of factor Va and factor VIIIa, ultimately suppressing thrombin formation. It is a less common thrombophilia with prevalence of 0.03–0.13 % in the Caucasian European population. The coding gene, PROS1, is located on chromosome 3. There have been over 130 mutations found to cause protein S deficiency with variable expression.

Deficiency of protein S has been divided into three major phenotypes. Type I disease has quantitatively low levels of protein S antigen, both free and total, and decreased function. Type II is characterized by normal free and total protein S levels but compromised functional activity. Type III disease has normal total antigen levels but low of free protein S antigen and activity levels. Protein S activity is variable secondary to fluctuating levels of complement 4B-binding protein, a regulator in the compliment system. Free levels fall throughout pregnancy due to increasing C4b-binding protein. We found in pregnancy free protein S levels substantially lower than nonpregnant values, with free levels of 38.9 ± 10.3 % in the second trimester and 31.2 ± 7.4 % in the third trimester [59]. When indicated, testing for the dysfunction is generally differed until 6-week postpartum to avoid confounding information. Laboratory evaluation is by free protein S antigen levels, which are not reliable in pregnancy, on anticoagulants, or with an active

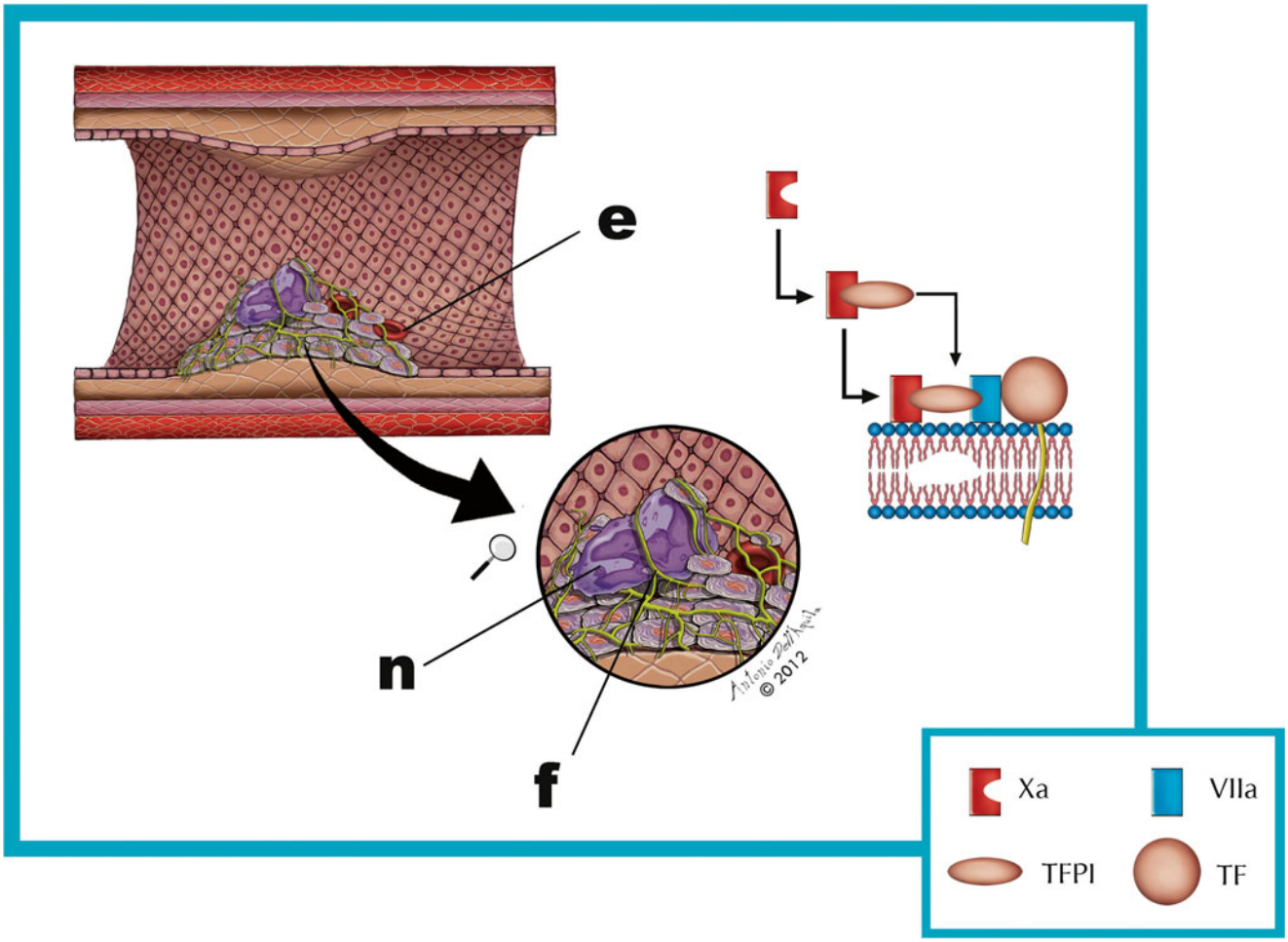

Fig. 13.13 Schematic description of how it is formed a vascular thrombus; at the bottom right, the factors of the coagulation cascade: (*e*) erythrocytes, (*n*) leukocytes, and (*f*) network of adhesion to endothelium

Table 13.2 The risk of venous thromboembolism in pregnant patient with selected thrombophilias

Condition	Prevalence in European populations	Prevalence in patients with VTE in pregnancy	Risk of VTE without prior history	Risk of VTE with prior history
Factor V Leiden (FVL)				
Heterozygous	5.3 %	44	0.26 %	>10 %
Homozygous	0.07 %	<1	1.50 %	>10 %
Prothrombin mutation (PGM)				
Heterozygous	2.90 %	17	0.37–0.5 %	>10 %
Homozygous	0.02 %	<1	2.8	>10 %
Compound FVL/PGM	0.17 %	<1		4.70 %
Protein C deficiency	0.2–0.3 %	<14	0.8–1.7 %	
Protein S deficiency	0.03–0.13 %	12	<1–6.6 %	
Antithrombin deficiency	0.02–1.1 %	1	11.6 % [17]	11–40 %

Adapted from Han et al. [18]

VTE. Free antigen levels below 60 % are considered abnormal, but a diagnosis of hereditary protein S deficiency cannot be made on the basis of protein S activity or free antigen levels when these levels are only determined in pregnancy. Protein S levels must be determined outside of pregnancy and the postpartum period, as well as in the absence of hormonal contraception to confirm the presence of a hereditary protein S deficiency.

Because of the relative infrequency of protein S deficiency, the number of studies regarding its risks

Table 13.3 Association between hereditary thrombophilias and selected pregnancy complications

	Preeclampsia	Pregnancy loss	IUGR	Abruption	Recurrent pregnancy loss	Late pregnancy loss[b]
FVL	1.23 (0.89–1.7) [19]	1.52 (1.06–2.19) [19]	1.0 (0.8–1.25) [19]	1.85 (0.92–3.7) [19]	1.91 (1.01–3.61) [20][a]	2.06 (1.1–3.86) [20]
PGM	1.25 (0.79–1.99) [19]	1.13 (0.64–2.01) [19]	1.25 (0.92–1.7) [19]	2.02 (0.81–5.02) [19]	2.70 (1.37–5.34) [20][a]	2.66 (1.2–5.53) [20]
Protein C deficiency	21.5 (1.1–414.4) [21]	1.4 (0.9–2.2) [22]	NA	5.93 (0.23–151.58) [20]	1.57 (0.23–10.54) [23]	2.3 (0.6–8.3) [22]
Protein S deficiency	2.83 (0.76–10.57) [20]	1.3 (0.8–2.1) [22]	10.2 (1.1–91) [21]	0.3 (0–70.1) [21]	14.72 (0.99–218.01) [23]	7.39 (1.28–42.83) [23]
Antithrombin deficiency	7.1 (0.4–117.4) [21]	2.1 (1.2–3.6) [22]	NA	4.1 (0.3–49.9) [21]	NA	5.2 (1.5–18.1) [22]

Resources: [19–23]
Data are odds ratio (confidence interval 95 %)
IUGR fetal growth restriction, [] = resource
[a]Only first trimester losses included
[b]Definition of late varied from >20 to >28 weeks of gestation depending on study

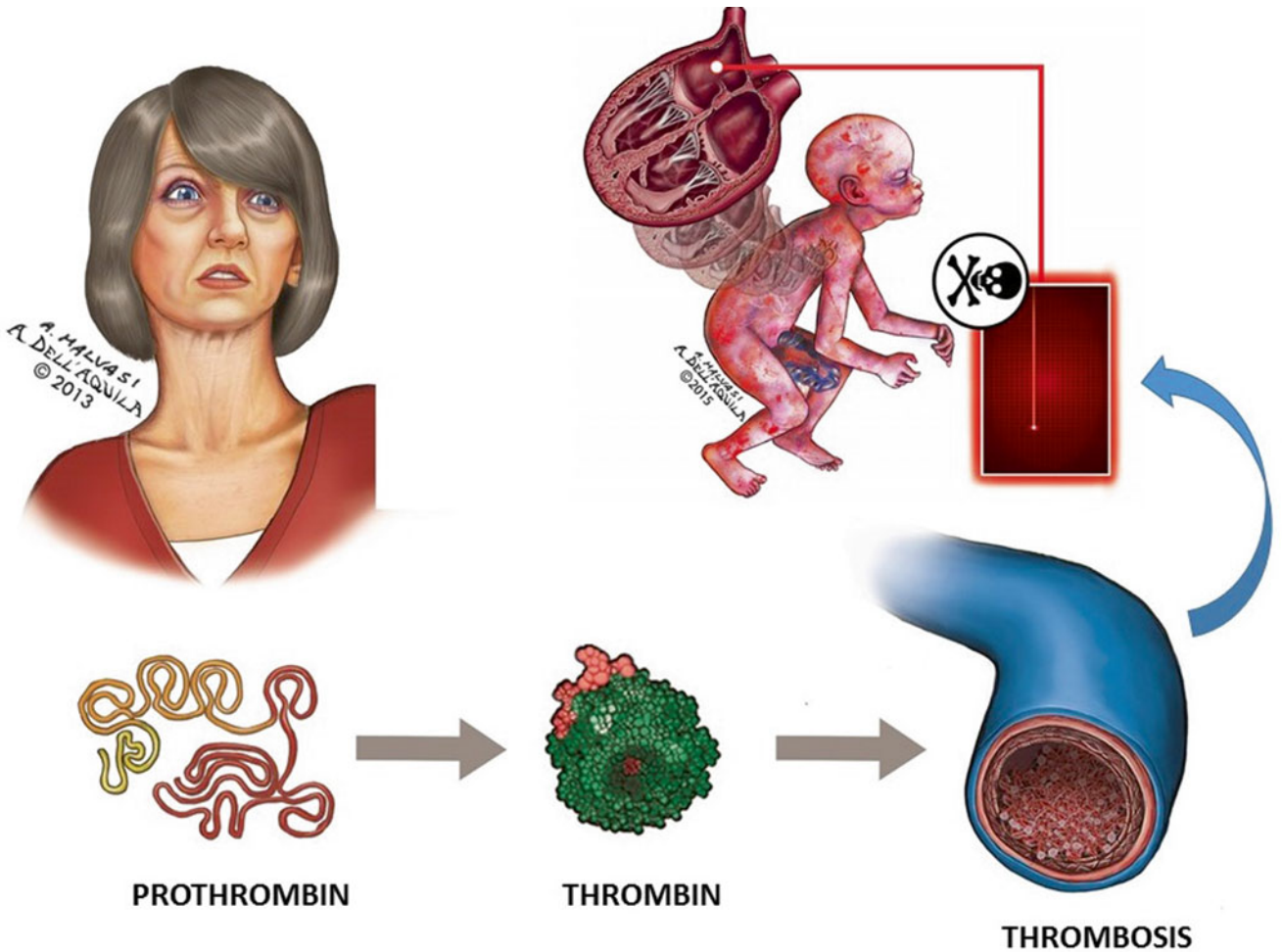

Fig. 13.14 The second-most prevalent inherited thrombophilia of the gene coding for prothrombin (factor II) is associated with early fetal loss

during pregnancy is limited. Robertson's systemic review of available case-controlled studies in 2006 showed an OR 3.19 (95 % CI 1.48–6.88) of VTE and pregnancy [20].

Conard et al.'s evaluation of 44 pregnancies in 17 patients with congenital protein S deficiency showed no thrombosis during pregnancies without anticoagulation but had 5 thrombotic events in the postpartum 17 % (95 % CI 3–31) [60].

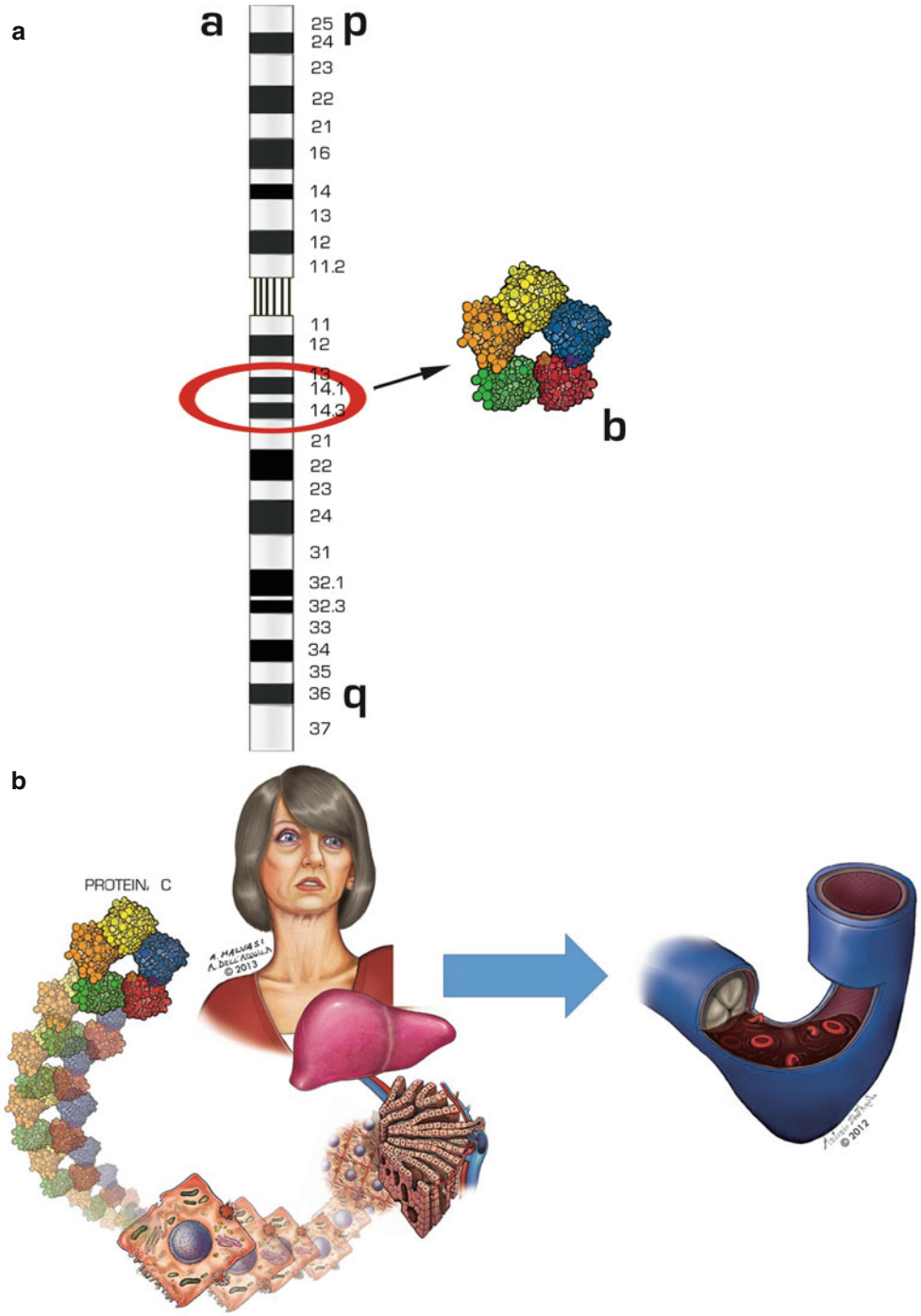

Fig. 13.15 Protein C's synthesis (**a**); protein C is an anticoagulant and its deficiency is moderately pro-thrombogenic factor (**b**)

The most compelling findings regarding protein S deficiency and pregnancy outcomes have been in regard to late fetal loss, although study sizes are small. A systemic review found a relatively strong association with stillbirth defined as unexplained fetal loss after 20 weeks with no fetal abnormalities (OR 16.2; 95 % CI, 5–52.3) [21]. Similar findings were published by Saade and McLintock, who found an association when looking at fetal losses after 28 weeks (OR 41; 95 % CI, 4.8–359) [61]. Although Alfirevic's group found associations with both preeclampsia (OR 12.7; 95 % CI, 4–39.7) and IUGR (OR 10.2; 95 % CI, 1.1–91.0) [21], others have failed to find associations with other poor obstetrical outcomes [20].

13.3.5 Antithrombin Deficiency

A less common but more thrombogenic hereditary dysfunction is caused by mutation in the serine protease inhibitor antithrombin (AT) gene. Sometimes referred to as antithrom-

bin III, AT inhibits active thrombin's conversion of fibrinogen to fibrin. It is also a known inhibitor of factors Xa and IXa, XIa, XIIa, trypsin, plasmin, and kallikrein. Besides its role as anticoagulant, AT has also been found to have anti-inflammatory characteristics [62].

Over 250 mutations have been identified at the AT gene loci which provide a wide spectrum of phenotypes. Type I disease infers a quantitative dysfunction. Type II is the qualitative class of dysfunction, which is further divided into subtypes. Type IIa is characterized by a defect in the reactive site of the protein and is generally more thrombogenic. Type IIb dysfunctions have a defect in the heparin-binding site and are less prone to thrombosis. Type IIc has defects in both binding sites. Type I makes up only 12 % of the total of cases of ATD, but it is much more thrombogenic, accounting for 80 % of symptomatic cases. The prevalence of ATD in Caucasian Europeans is estimated at 0.02–1.15 %. It has been found to be even more common in some Asian populations, with a prevalence of up to 2–5 % [26, 63].

The laboratory assay of choice is plasma AT activity, which, using heparin, measures how well AT inhibits thrombin or factor Xa. Activity <80 % is considered abnormal, but most patients with hereditary ATD have levels <60 %. Testing can be abnormal secondary to anticoagulation and acute thrombosis and should be delayed until after completing treatment.

The risk of VTE in pregnancy can be high with antithrombin deficiency, though as discussed previously there is large variability among phenotypes. A systemic review reported an OR 4.69 (95 % CI 1.30–16.96) regarding VTE and pregnancy [20]. A more recent systemic review which included 112 pregnancies with AT deficiency without a personal history of VTE, found the incidence risk of VTE to be 11.6 % in each pregnancy (OR 6.09; 95 % CI 1.58–24.43) [17].

Retrospective studies have however estimated the risk for the more thrombogenic type I disease (OR 282; 95 % CI, 31–2532) compared to a much smaller risk with type II disease (OR 28; 95 % CI, 5.5–142) [9, 64]. It is estimated that the lifetime risk of VTE in those with type I disease is 50 % [65]. One case series of 63 untreated women with type I ATD who went through pregnancy without anticoagulation found that 18 % had a thrombotic complication during pregnancy and another 33 % had a thrombotic complication postpartum [60].

Though it is the first inherited thrombophilia identified, the data regarding its association to poor obstetrical outcomes is less robust due to its rarity. Regarding early fetal loss, a retrospective cohort found a modest risk of a fetal loss <28 weeks in patients with ATD (OR 1.7; 95 % CI, 1–2.8) [22]. A meta-analysis did not find a significant increased risk of recurrent loss before 17 weeks OR 0.88 (95 % CI 0.17–4.48) or nonrecurrent loss at any gestational age 1.54 (95 % CI 0.97–2.45) [23].

Other studies have failed in demonstrating an association with ATD and early pregnancy loss [20, 33, 58, 66, 67].

Studies investigating the relationship between stillbirth and ATD are even more limited due the infrequency of both diagnoses. Prestin's retrospective cohort study found a significant association (OR 5.2; 95 % CI, 1.5–18.1) [22]. Other attempts to evaluate the risk have been limited by small numbers, but they have not identified a significant association [21, 23, 68].

We found an increased risk of IUGR (OR 12.93; 95 % CI, 2.72–61.45) and abruption (OR 60.01; 95 % CI, 12.02–300.46) in our retrospective cohort of 491 patients with poor pregnancy outcomes [33]. To the contrary, other small studies have failed to show a significant association [20, 21, 68].

The relationship between hereditary antithrombin deficiency and preeclampsia requires further refinement. Lariciprete et al. reported an association between hereditary antithrombin deficiency and preeclampsia in a case-controlled study including 12 patients with ATD (RR 0.88 95 %; CI 0.83–0.94) [68]. A systemic review, however, which included only one study by D'Ellia et al., was not able to identify a significant increased risk (OR 3.89; 95 % CI, 0.16–97.19) [20].

The relationship between ATD and preeclampsia is an intriguing subject. A gradual decline in AT activity during the late stage of pregnancy, namely, pregnancy-induced AT deficiency, has been reported in literature, in healthy parturients at term [62, 69]. Antithrombin activity levels appear to be decreased in pregnancies complicated by preeclampsia. Weiner et al. found mean antithrombin activity to be 60 % ± 15 % in women with preeclampsia compared to 85 % ± 15 % in normal pregnant controls. Using a cutoff ≥ 70 % of AT activity levels provides a negative predictive value of 89 % for preeclampsia. The positive predictive value using a < 70 % AT activity level is 80 % [70, 71]. Others have found falling AT activity levels in preeclampsia patients that was associated with worsening disease [72].

Antithrombin has a few properties that make it a potential pharmacologic therapy for preeclampsia. AT is a potent anticoagulant and anti-inflammatory agent [73]. Both plasma-derived and recombinant forms of AT are currently available for other indications in pregnancy [74]. Some promising studies have used plasma-derived AT to successfully prolong pregnancy in early onset preeclampsia [75–79]. Currently, a large prospective multicenter double-blinded trial is evaluating recombinant AT therapeutic benefits in patients with preterm preeclampsia between 23 and 30 weeks [74].

13.3.6 Methylenetetrahydrofolate Reductase Mutations

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in the folate metabolism pathway. It reduces 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is active in reducing homocysteine to methionine. Defects in the MTHFR gene can lead to elevated levels of

homocysteine, which is known to be prothrombotic. The well-studied MTHFR gene is located on chromosome 1p36.4, and two major mutations are common: C677T and A1298C [80].

The C677T allele (cysteine to thymine at nucleotide 677) is relatively common worldwide, with a carrier frequency ranging from 44 % in Italians to 7 % in sub-Saharan Africans. The activity of the enzyme for which it codes is thermolabile, making it less active at temperatures >37 °C. Homozygotes for the C677T allele can have elevated plasma homocysteine levels if they are folate deficient, but normal homocysteine levels are found in those with normal folate levels.

The second commonly discussed mutation is A1298C, which has a less drastic decrease in enzyme function. However, when present compounded with a C677T mutation, it can produce an elevated homocysteine similar to C677T homozygotes when folate deficient [80].

So while MTHFR gene mutations are relatively common, diet and food fortification with folic acid (Fig. 13.16) make hyperhomocysteinemia rare. Hyperhomocysteinemia has been associated with VTE OR 2.5 (95 % CI 1.8–3.5) [81]. MTHFR mutations in the absence of elevated homocysteine levels do not increase VTE risk in isolation regardless of pregnancy status [64, 82].

A recent large meta-analysis including 11,000 cases and 21,000 controls found those homozygous for MTHFR C677T were not at increased risked for VTE [83].

Though attempts have been made to link MTHFR and hyperhomocysteinemia to adverse pregnancy outcomes, evidence has been contradictory. One meta-analysis found a small association between fetal loss <16 weeks and hyperhomocysteinemia (OR 2.7; 95 % CI, 1.4–5.2) and even smaller with isolated MTHFR (OR 1.4; 95 % CI, 1.0–2.0) [84]. Another group studying homocysteine levels in 5883 woman and their 14,492 pregnancy outcomes found a tendency between elevated levels and stillbirth which did not reach statistical significance (OR 2.03; 95 % CI, 0.98–4.21) [85, 86]. Other more recent publications have failed to show a relationship between MTHFR and first trimester loss, early fetal loss, or stillbirth [20, 36].

Though some report the contrary, hyperhomocysteinemia or MTHFR do not appear to be associated with preeclampsia [87], abruption [88], or fetal growth restriction [42, 89]. If associations do exist, they are likely mild and overcome with folic acid fortification and standard supplementation. Because of the lack of strong evidence between MTFHR and the outcomes discussed above, screening is not recommended. In the often encountered scenario of a patient with a known MTHFR mutation presenting for pregnancy recommendations, folic acid supplementations should be encouraged. No other special care is necessary regarding MTHFR management during pregnancy.

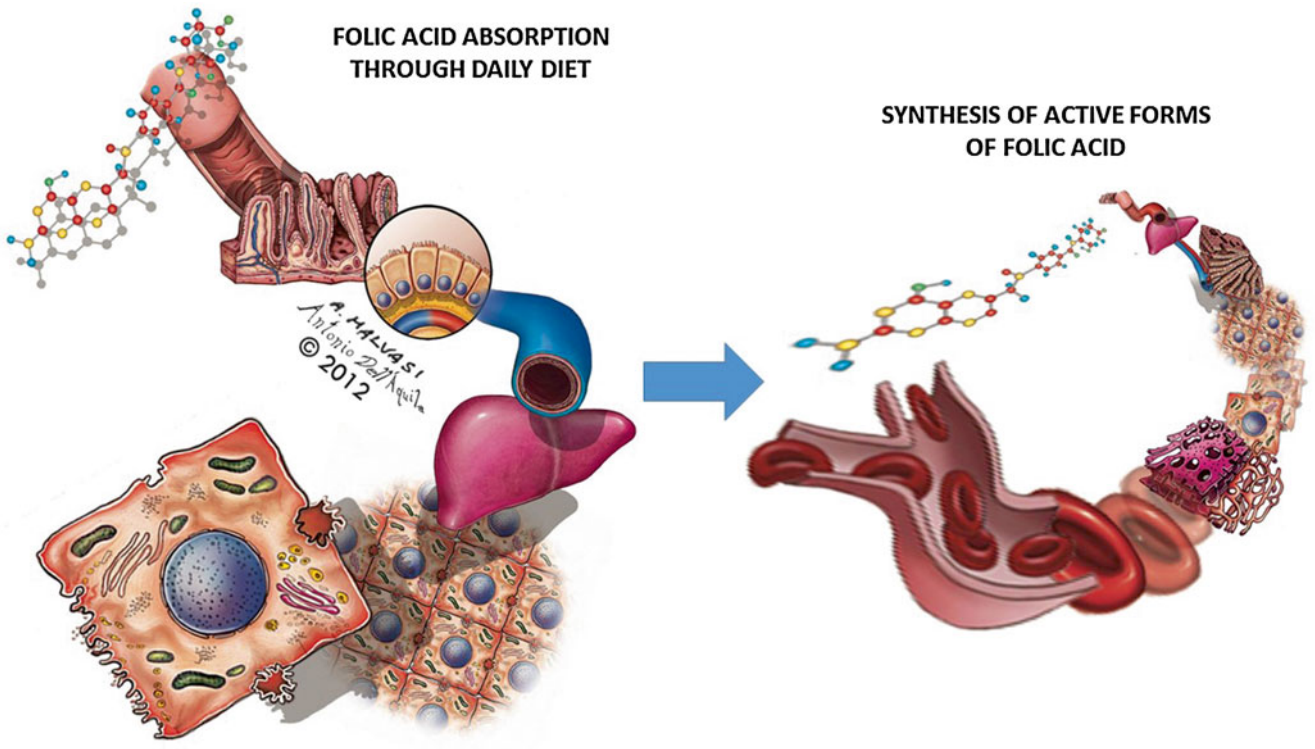

Fig. 13.16 On the *left*, folic acid adsorption by diet and food fortification; on the *right*, synthesis of active forms of folic acid, reducing homocysteinemia and risk of venous thromboembolism (VTE)

13.4 Acquired Thrombophilia

13.4.1 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia faced by obstetricians. It has been well associated with both VTE and poor obstetrical outcomes, and it is an important disease for obstetrical providers to understand. APS is an autoimmune disorder in which antibodies are produced targeting endothelial cell membrane phospholipids including cardiolipin, β2-glycoprotein 1, and phosphatidylserine. The subsequent clinical consequences of these antibodies are thrombosis, both venous and arterial, and adverse pregnancy outcomes. These clinical outcomes make up a large part of the diagnosis criteria.

Fifty percent of patients affected by APS have an underlying disease making them at risk for developing the autoantibodies, most commonly systemic lupus erythematosus (SLE). APS was first identified in SLE patients with anticardiolipin antibodies that developed a clotting disorder. Lupus and related rheumatic diseases injure an intact endothelial membrane, exposing anionic phospholipids that bind specialized proteins. This process presents new antigens to an often already compromised immune system. Once the autoantibodies to the endothelial proteins are established, they inhibit endogenous anticoagulants (protein C, annexin V, antithrombin) and promote procoagulants (platelets, tissue factor, and compliment activation). The determination of the mechanism of these modulations is still ongoing [90–92].

Diagnosis of APS requires both specific clinical pathology and laboratory criteria as determined by an international consensus group in 2006 (see Table 13.4) [93, 94]. The first requirement is at least one of the listed clinical outcomes including a thrombotic event or poor obstetrical outcome. The second criterion is the presence of at least one of the listed laboratory abnormalities above the normal threshold, measured twice at least 12 weeks apart.

Antiphospholipid antibodies without the present clinical findings are found in 1–5 % of healthy individuals, many of which are transient [93]. This supports the diagnosis requirement of laboratory abnormality persistence for at least 12 weeks. Many of the studies regarding antiphospholipid antibodies and obstetrical outcomes do not use the strict criteria for APS, often lacking confirmatory lab work at least 12 weeks apart. Other studies were done prior to the establishment of the current diagnosis requirements. It is important to take these limitations into considerations when evaluating the available APS evidence.

APS accounts for 14 % of VTE events during pregnancy. The risk of thrombotic event is varied by the specific laboratory abnormalities. Lupus anticoagulant (LAC) reactivity is a sign of downstream alteration of prothrombin activation and evidence of active disease. Antibody presence alone without LAC abnormality is less likely to cause a thrombotic event. This is well demonstrated in a systemic review of 25 studies (non-obstetric) including 4184 patients and 3151 controls. They found that with lupus anticoagulant (LAC), the venous thrombotic OR was 4.1–16.2 and the arterial thrombosis OR

Table 13.4 Classification criteria for the antiphospholipid syndrome

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria below are met
Clinical criteria
Vascular thrombosis
One or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated (unequivocal findings on appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without evidence of inflammation in the vessel wall
Morbidity pregnancy
One or more unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognized features of placental insufficiency
Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomical or hormonal abnormalities excluded and paternal and maternal chromosomal caused excluded
Laboratory criteria
Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
Medium or high titer (>40 lgG or lgM phospholipid unit (1 units is 1 μg of antibody), or >99th centile) of l gG or lgM anticardiolipin antibody in serum or plasma on two or more occasions, at least 12 weeks apart, measured by standardized enzyme-linked immunosorbent assay (ELISA).
Medium or high titer (>40 lgG or lgG or lgM phospholipid units, or >99th centile) of lgG or lgM anti-β_2 glycoprotein I antibody serum or plasma on two or more occasions, at least 12 weeks apart, measured by standardized ELISA, according to recommended procedures

Chart from Cohen et al. [93]
Original source: Miyakis et al. [94]

was 8.6–10.8. In the same study, anticardiolipin antibodies (ACA) were more associated with arterial events (OR 1–18) than venous events (OR 1–2.5). The data regarding anti-β2-glycoprotein 1 antibodies was less clear [95, 96]. Similar findings from a meta-analysis of nonpregnant APS patients with coexisting SLE showed an increased risk of primary VTE OR 6.32 (95 % CI, 3.7–10.8) and recurrent VTE OR 11.6 (95 % CI, 3.7–36.9) in LAC patients compared to ACA carriers primary VTE OR 2.5 (95 % CI, 1.5–4.1) and recurrent VTE OR 3.91 (95 % CI, 1.1–13.4) [97].

The association with APS and first trimester loss is controversial; nonetheless, three unexplained consecutive spontaneous abortions at ≤10-week gestation are part of the diagnostic criteria for APS [98]. Most available studies regarding APS and early pregnancy loss use 13 weeks as a cutoff and do not discriminate before and after 10 weeks. As discussed previously, the pathology of losses before 10 weeks and the rest of the third trimester weeks are different. Fifty percent of losses in patients confirmed to have APS are after 10 weeks of gestation [99].

In a study looking at recurrent miscarriage patients with APS, fetal cardiac activity was identified in 86 % of eventual pregnancy losses compared to 43 % in patients without APS ($P < 0.01$) [100].

An association between fetal loss after the first trimester and APS has been better described [58, 101, 102]. In a systemic review of 25 case-control studies, LAC was associated with recurrent pregnancy loss after 24 weeks (OR 7.79; 95 % CI, 2.30–26.45). Similar finding was found with moderate to high ACL IgG (OR 4.68; 95 % CI, 2.96–7.40) [103]. In a recent case-controlled study from the Stillbirth Collaborative Research Network (SCRN), 582 stillbirths diagnosed after 20 weeks were controlled with 1547 live births. They found associations with elevated ACL IgG (OR 3.43; 95 % CI 1.79–6.60) and anti-β2-glycoprotein 1 IgG (OR 3.17; 95 % CI 1.30–7.72). This study was limited by a lack of confirmatory laboratory evaluation 12 weeks apart and inconsistent assessment for lupus anticoagulant [104].

Though more often affecting pregnancies in third trimester, APS has been associated with second trimester placental-mediated obstetrical complications including IUGR and preeclampsia. When APS complicates second trimester pregnancies, the outcomes are often poor [98]. A meta-analysis of 28 studies by Abou-Nassar found LA associated with preeclampsia (OR 2.34; 95 % CI, 1.18–4.64) and IUGR 4.65 (95 % CI 1.29–16.71) in case-controlled studies but not significant with cohort studies [105]. A more recent prospective observational cohort study followed 280 women after a single <10-week embryonic demise with and without positive aPL antibodies and evaluated for their subsequent pregnancy. They found an association between LAC and IUGR (OR 10.27; 95 % CI, 2.37–44.52), ACL IgG and preeclampsia (OR 3.09; 95 % CI 1.13–8.48), and anti-β2-glycoprotein 1 IgG and preeclampsia (OR 4.61 95 % CI 1.53–13.88) [106].

A rare variant form of APS named catastrophic antiphospholipid syndrome (CAPS), also known as Asherson's syndrome, is an important consideration. It presents as multiple thrombosis (Fig. 13.17a, b) and multi-organ failure secondary to multiple small-vessel occlusions. Though most often associated with infection and trauma, it can be initiated with pregnancy. Of the 255 cases

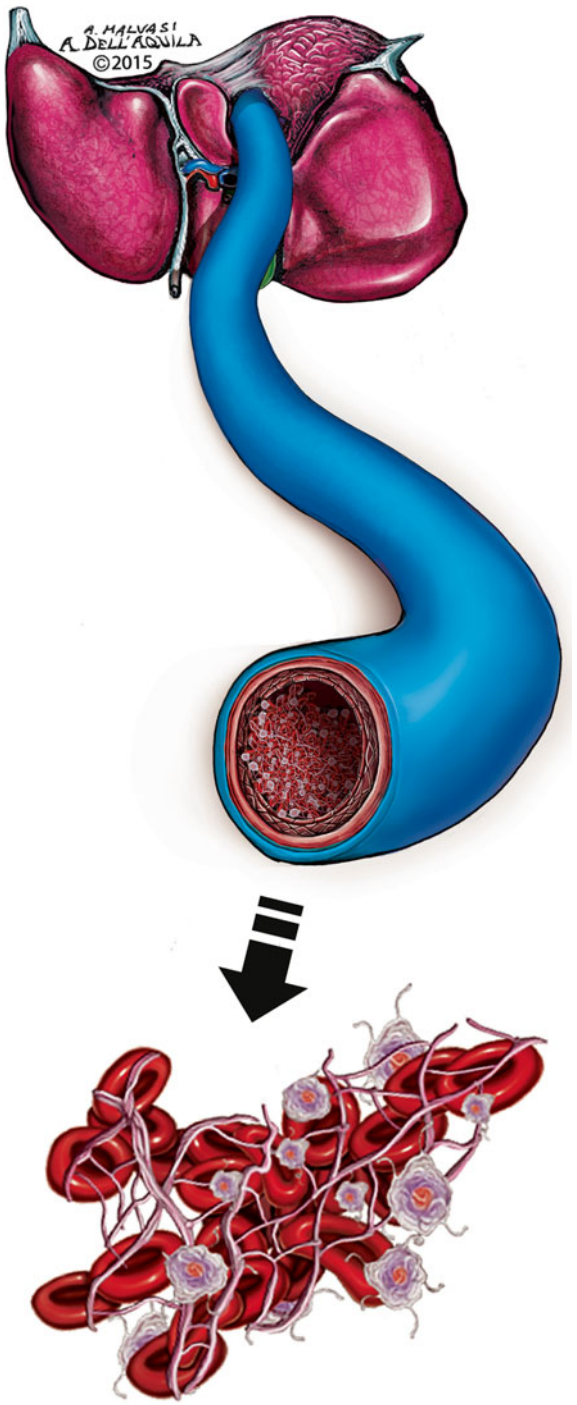

Fig. 13.17 (**a**) Hepatic vein thrombosis; (**b**) retinal thrombosis detected by retinal angiography

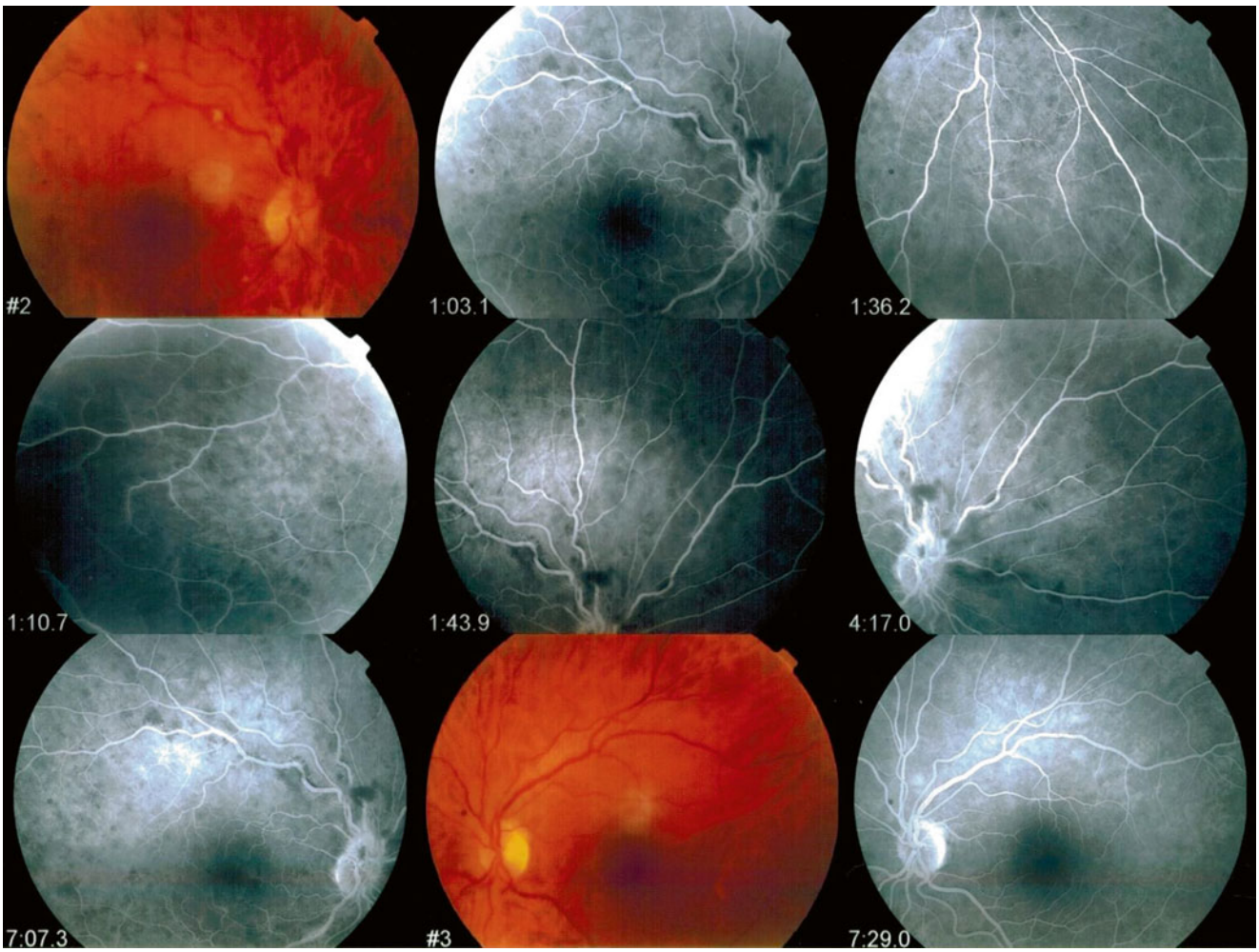

Fig.13.17 (continued)

in one international registry, 15 cases were associated with pregnancy. Of those pregnancy related, 50 % occurred during the antepartum, 43 % occurred during the puerperium, and one occurred 2 days after a D and E for an 18-week fetal demise. The mortality among the cases was 46 % [107]. A more recent study reviewed 13 patients with pregnancy-related CAPS in a French APS referral center. Twelve out of 13 patients held the diagnosis of HELLP syndrome prior to CAPS diagnosis at a mean gestational age of 26.6 weeks. Twelve out of 13 of their patients had postpartum CAPS. No maternal deaths were reported. Treatment combinations varied between patients but included heparin, aspirin, steroids, IVIG, cyclophosphamide, plasma exchange, and dialysis [108].

Another APS consequence to consider is neonatal antiphospholipid syndrome, a product of transplacental transmission of maternal aPL antibodies affecting the newborn. It is a rare entity which can lead to neonatal thrombosis, thrombocytopenia, livedo reticularis, and pericardial effusions [109].

While neonatal APS is rare, the transplacental transfer of maternal aPL antibodies is found in 5–16 % of APS pregnancies, the clinical significance of which is still being investigated [110, 111].

In summary, APS is associated with VTE and poor outcomes in pregnancy. Providers should use the current APS criteria when diagnosing patients. Management and treatment of APS will be described in the next section.

13.5 Thrombophilia Evaluation and Management

Obstetrical providers are often faced with prenatal management decisions in women with known or suspected thrombophilias. The management recommendations have been moving targets over the last three decades as more evidence has been published. In this section, we will discuss which patients should be tested for thrombophilias. We will finish the chapter discussing treatment options.

13.5.1 Thrombophilia Evaluation

Recommendations regarding testing for hereditary thrombophilias have been modified multiple times since their discoveries. Stillbirth, abruption, and recurrent pregnancy loss are among the most difficult conditions obstetrical providers must manage. Optimism for new treatments to potentially prevent such tragic outcomes led to the premature adoption of testing and treatment of hereditary thrombophilias with sparse evidence.

As larger prospective studies and meta-analysis have been published, the hereditary thrombophilias have been an overall disappointing therapy target for adverse outcomes. They may assist providers in the evaluation, management, and prevention of VTE associated with pregnancy.

The correct setting for testing for hereditary thrombophilia is a controversial subject. Most agree testing is appropriate for women with a personal history of VTE not associated with a nonrecurrent risk factor (e.g., surgery, immobilization, bone fracture). Testing is also recommended for patients with first-degree relatives diagnosed with high-risk thrombophilia regardless of the patients' personal VTE history including homozygous FVL and PGM, compound heterozygous FVL and PGM, and antithrombin deficiency. Testing for hereditary thrombophilias is not recommended as part of the evaluation for recurrent pregnancy loss, IUGR, abruption, or preeclampsia.

Thrombophilia evaluation in women experiencing a stillbirth should be limited to those cases where thrombophilia is plausible as an etiology of the stillbirth.

On the other hand, testing for antiphospholipid syndrome is a valuable part of the evaluation in a few obstetrical conditions. The outcomes which make up part of the APS diagnosis criteria are also indications for testing (vascular thrombosis, morphologically normal fetal loss after 10 weeks, three unexplained consecutive pregnancy losses prior to 10 weeks, or a prior delivery prior to 34 weeks for severe preeclampsia or placental insufficiency). See Table 13.4. It is critical that positive testing be repeated after 12 weeks have lapsed to avoid an incorrect diagnoses and unwarranted therapy.

Our screening protocol for inherited and acquired thrombophilia is provided in Table 13.5. The laboratory reliability varies under different clinical scenarios, and some testing should be performed after the anticoagulant course or 6-week postpartum, when using functional assays, not genetic screening tests.

Table 13.5 Screening for thrombophilia

Lupus anticoagulant[a]
Anticardiolipin IgG, IgM
Anti-β2-glycoprotein I IgG, IgM
Factor V Leiden (PCR)
Prothrombin gene mutation 20210A (PCR)
Protein C activity[a, b]
Protein S activity[c,a,b,d]
Antithrombin III activity[a,b]

[a]Not reliable on anticoagulation
[b]Not reliable with active thrombus
[c]Not reliable in pregnancy
[d]Use protein S free antigen in pregnancy

13.5.2 Pregnancy Management

Antenatal care for mothers with hereditary and acquired thrombophilia depends on the specific dysfunction and required therapy. Patients should be screened routinely for preeclampsia including BP, urine protein screening, and symptoms. Fetal growth should be routinely monitored by ultrasound in any patient receiving anticoagulation. In APS patients, we start weekly antenatal testing on patients at 36 weeks and deliver at 39 weeks if no complications warrant delivery earlier.

13.6 Anticoagulants in Pregnancy

Common dosing regimens for anticoagulation in pregnancy are reviewed in Table 13.6 [9, 15, 112, 113].

Unfractionated heparin (UFH) is an injectable or intravenous anticoagulant commonly used in the obstetrical population. UFH binds to antithrombin, inducing a conformational change that enhances antithrombin's ability to deactivate coagulation factors IIa and Xa. It is an attractive anticoagulant because it is not teratogenic, it does not cross the placenta, and it is reversible with protamine sulfate. Its side effects include hemorrhage, bone loss, and heparin-induced thrombocytopenia, all of which are rarely seen with prophylactic dosing. If UFH therapy is started, calcium supplementation and periodic platelet monitored should be started.

Low-molecular-weight heparins (LMWH) are a similar group of injectable anticoagulants also commonly used during pregnancy. They are often the preferred therapy over heparin due to ease of use and improved safety profile (Fig. 13.18). LMWH has a longer half-life, requiring less injections, and rarely causes heparin-induced thrombocytopenia. Because of the longer half-life, patients are typically transitioned to UFH at 36 weeks of gestation or earlier if preterm delivery is expected. This therapy conversion is typically performed to decrease the risk of neuraxial anesthesia and bleeding complications around the time of delivery (Fig. 13.19). However, a recent recommendation suggests continuation of LWMH until delivery [114].

LWMH is not teratogenic and it also does not cross the placenta. Protamine is less effective in reversing LMWH.

Table 13.6 Suggested anticoagulation doses

Prophylactic regimens	**First trimester**	**Second trimester**	**Third trimester**		
Unfractionated heparin (UFH)	5000 units twice daily	7500 units–10,000 units twice daily	10,000 units twice daily		
Low-molecular-weight heparin (LMWH)	**Weight based (initial prenatal weight)**				
	<50 kg	**50–90 kg**	**91–130 kg**	**131–170 kg**	**>170 kg**
Enoxaparin	20 mg daily	40 mg daily	60 mg daily[a]	80 mg daily[a]	0.6 mg/kg daily[a]
Dalteparin	2500 units daily	5000 units daily	7500 units daily[a]	10,000 units daily[a]	75 units/kg daily[a]
Tinzaparin	3500 units daily	4500 units daily	7000 units daily	9000 units daily	75 units/kg daily
Therapeutic regimens	**Initial dose**	**Adjusted target**			
Unfractionated heparin (UFH)	10,000 units twice daily	aPTT 1.5–2.5 6 h after injection			
Low-molecular-weight heparin (LMWH)		Twice daily dosing: antifactor Xa level 0.6–1 units/mL 4–6 h after dose[b] Once daily dosing: antifactor Xa level >1 units/mL 4–6 h after dose[b]			
Enoxaparin	1 mg/kg twice daily				
Dalteparin	200 units/kg daily[a]				
Tinzaparin	175 units/kg daily				
Warfarin (postpartum only)		Target INR 2.0–3.0			

Resources: [9, 15, 112, 113]
[a]May be given in two divided doses
[b]If anti-Xa level monitoring is indicated

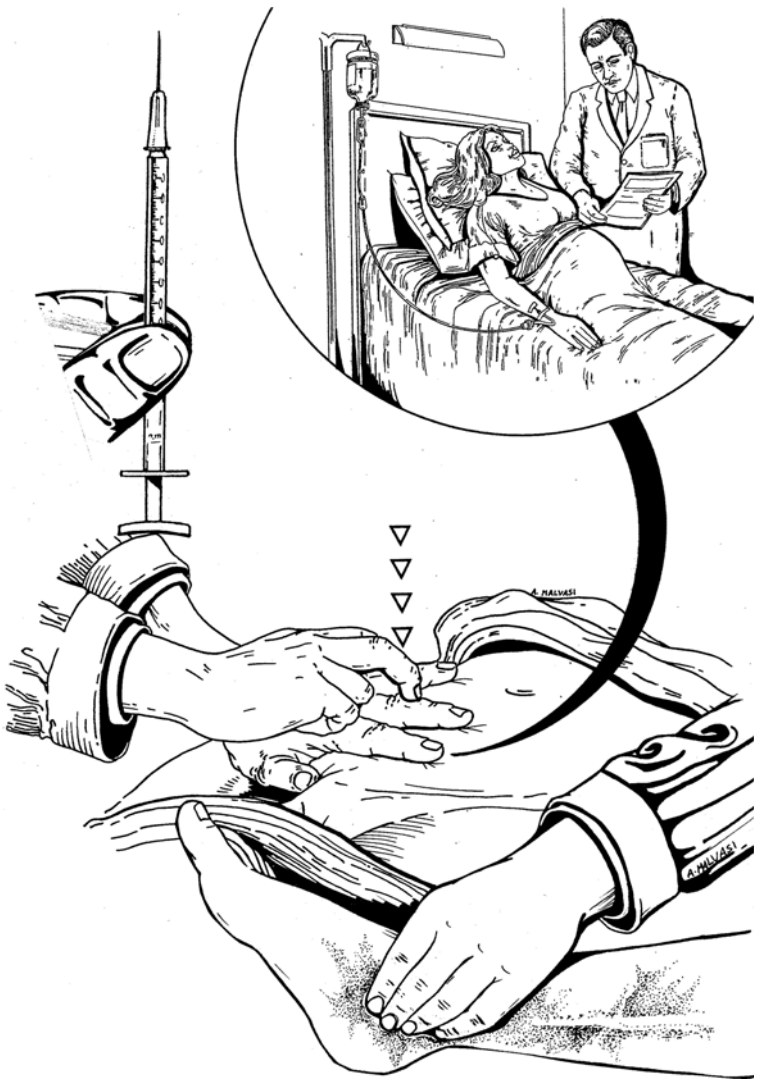

Fig. 13.18 On the *top*, pregnant patient, pregnant woman, pregnant to submit to scheduled cesarean section at risk for thrombophilia; on the *bottom*, patient under antithrombotic prophylaxis by low-molecular-weight heparins (LMWH) in puerperium

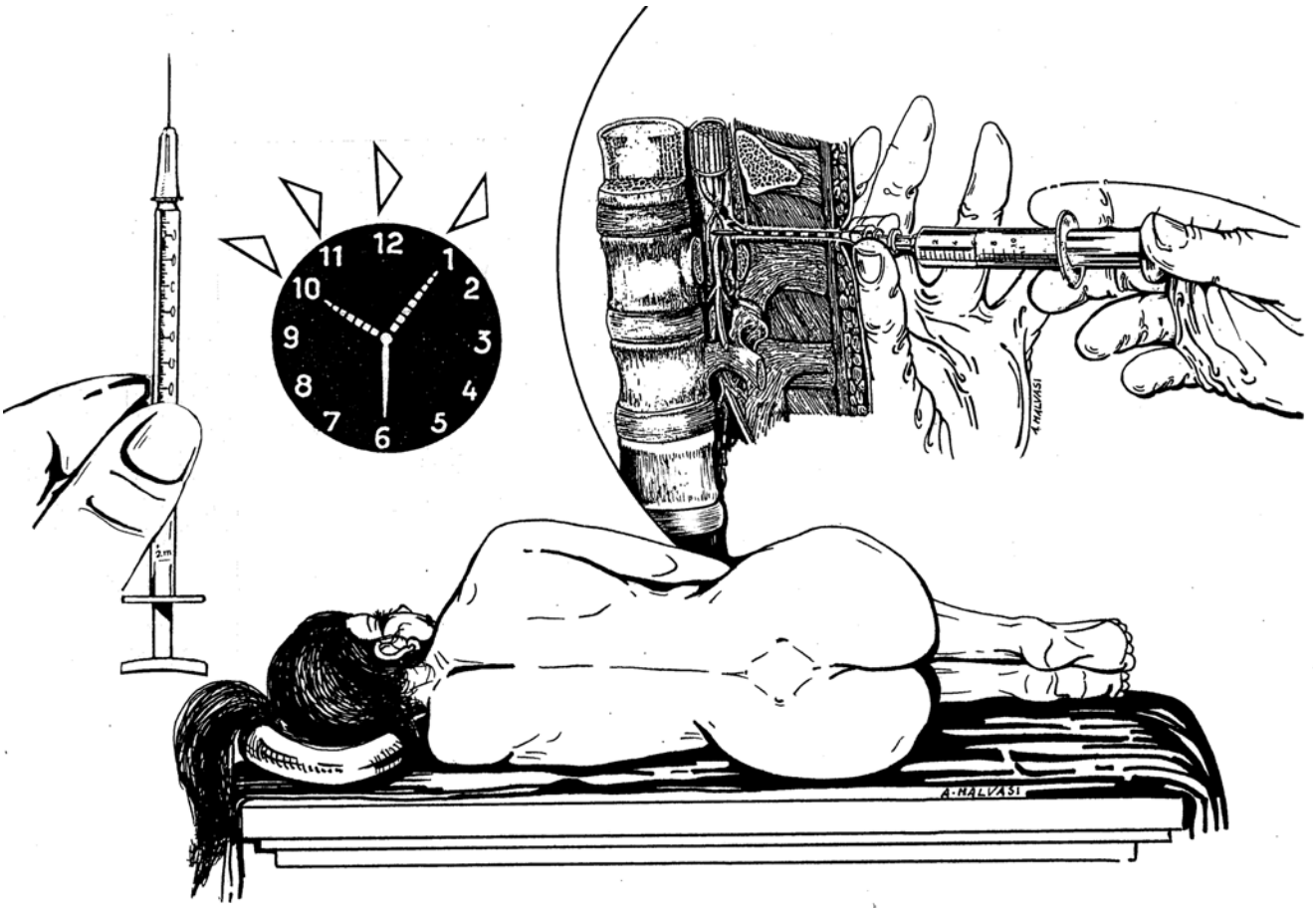

Fig. 13.19 A woman receiving regional anesthesia. See text for details

Fondaparinux is a synthetic pentasaccharide that binds antithrombin, effectively inhibiting factor Xa. Though its use in pregnancy is limited, there are some small patient series published showing its use in safely pregnancy [115]. It is a promising anticoagulant alternative for patients with heparin hypersensitivity or a history of HIT. Fondaparinux can cross the placenta causing a small but measurable amount antifactor Xa activity in umbilical cord blood samples. More studies are needed to thoroughly evaluate its safety in pregnancy, but its use might be appropriate in carefully selected patients [9, 116].

Warfarin in pregnancy is a more complicated matter. Warfarin is an oral vitamin K antagonist commonly used for anticoagulation in the nonpregnant population. For patients who conceive on warfarin, conversion to another anticoagulant (typically LMWH) should occur as early as possible once pregnancy is documented, around 5 weeks of gestation, due to its known teratogenic effects. One option is to convert patients from warfarin anticoagulation to LMWH anticoagulation prior to achieving pregnancy. The warfarin-associated embryopathy occurs with early fetal exposure and includes nasal and midface hypoplasia, CNS abnormalities, and skeletal malformations. Warfarin is also usually avoided later in pregnancy because it crosses the placenta, placing the fetus at risk for bleeding complications. The exceptions are in pregnancies complicated by mechanical heart valves, where it is suggested that warfarin is superior in preventing thrombotic complications.

13.7 Hereditary Thrombophilia Treatment

Recommendations regarding anticoagulation in women with hereditary thrombophilias are provided in Table 13.7 [9, 15, 112, 113].

In patients with risk factors requiring prophylactic antepartum anticoagulation, patients are started on subcutaneous LMWH dosing after a positive pregnancy test is confirmed. The patient is converted to subcutaneous UFH if any complications arise suggesting an early delivery or at 36 weeks of gestation. Because the risk of VTE continues into the postpartum period, we restart LMWH after delivery for 6 more weeks of prophylaxis. Patients and providers must have a high suspicion for any sign of DVT or PE, and

Table 13.7 VTE prophylaxis in pregnancy

Thrombophilia classification	History	Antepartum	Postpartum
High-risk thrombophilia	No VTE	P	P
Factor V Leiden (FVL) homozygous	Family VTE or risk factors	P	P
Prothrombin G20210A mutation (PGM) homozygous	One prior VTE	T	T or K
Antithrombin deficiency	Long-term anticoagulation	T	T or K
Compound heterozygote (FVL/PGM)			
Low-risk thrombophilia	No VTE	Vigilance	Vigilance
FVL heterozygous	Family VTE or risk factors	Vigilance	P
PGM heterozygous	Personal VTE	P	P
Protein C deficiency	Long-term anticoagulation	T	T or K
Protein S deficiency			
Acquired thrombophilia	No VTE	Vigilance	P
Antiphospholipid antibody syndrome	One prior VTE	T	T or K
	On long-term anticoagulation	T	T or K
No thrombophilia	One prior VTE associated with nonrecurrent condition	Vigilance	P
	One prior VTE in the absence of nonrecurring condition, or on OCPs, or in pregnancy	P	P
	Two prior VTE	T	T or K

Resources: [9, 15, 112, 113]

P prophylactic dose LMWH or UFH, *T* therapeutic dose LMWH or UFH, *K* vit K antagonist

patients should be evaluated promptly if any concerns arise. In patients on long-term anticoagulation planning for pregnancy, two options are available and management can be individualized. One option is to transition to therapeutic LMWH dosing prior to attempting conception. This approach eliminates the risk of warfarin-related embryopathy but is associated with longer treatment with LMWH. The second option is to maintain the patient on warfarin and transition to LMWH very early in pregnancy, once pregnancy is documented, ideally around 5-week gestation. This must be done understanding the risk of teratogenicity from 6 to 12 weeks of gestation and the implications of missing the conversion window. LMWH can be transitioned to UFH if early delivery becomes likely or at 36 weeks of gestation. Anticoagulation postpartum can be with LMWH or warfarin depending on patient preference. LMWH, UFH, and Coumadin are all compatible with breast-feeding [9]. Due to the highly thrombogenic nature of hereditary antithrombin deficiency, antithrombin replacement therapy is recommended to prevent thromboembolism in high-risk settings of delivery and surgery during pregnancy [117–119].

13.8 Antiphospholipid Antibody Syndrome Treatment

In patients with APS, treatment during pregnancy depends on which clinical criteria determined their diagnosis. For those with a history of VTE on lifelong anticoagulation, transitioning to therapeutic LMWH dosing prior to conception is appropriate. They can be transitioned back to warfarin postpartum. If the patient has a personal history of a VTE but is not on long-term anticoagulation, therapeutic dosing of LMWH should be started when pregnancy is diagnosed. If they also have APS-defining pregnancy morbidity, low-dose aspirin should be added in the antepartum.

The optimal treatment of APS patients diagnosed by obstetrical clinical criteria and no VTE history has not yet been determined. Most agree that prophylaxis with LMWH during the pregnancy and 6-week postpartum and clinical surveillance are both appropriate options. For those with a history of a fetal loss, low-dose aspirin in addition to prophylactic dosing LMWH has been found to decrease the risk of reoccurrence [99]. Low-dose aspirin alone or with LMWH can be used for patients that meet APS criteria with a history of a preterm delivery before 34 weeks due to preeclampsia, eclampsia, or placental insufficiency without a VTE history. There is no current evidence regarding isolated positive APS laboratory values in the absence of clinical criteria, though experts suggest low-dose aspirin would be a reasonable prophylaxis in the setting of SLE [93].

The management of pregnancy in rare cases of refractory adverse pregnancy outcomes secondary to APS can be particularly challenging. There are reports of successful use of hydroxychloroquine and corticosteroids in addition to the standard therapies for these rare scenarios, but more studies are needed to prove their efficacy [120].

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Diabetes in Pregnancy

14

Reshama Navathe, Sandro Gerli, Elena Pacella, and Vincenzo Berghella

14.1 Pregestational Diabetes Mellitus

14.1.1 Diagnosis/Definition

Diabetes mellitus (DM) is defined as a metabolic abnormality characterized by elevated circulating glucose. The diagnoses of diabetes and impaired glucose tolerance outside of pregnancy are established on the basis of formal laboratory criteria (Table 14.1) [3, 4].

14.1.2 Basic Pathophysiology

The etiology of DM varies. Type I diabetics are insulin deficient, secondary to the autoimmune destruction of the pancreatic islet beta-cells [3]. These individuals develop disease early in life. They often present with significant weight loss, polydipsia, and polyuria. They are at risk of becoming acutely ill and developing ketoacidosis if no therapy is initiated. In contrast, type II diabetics produce insulin, but at diminished levels. Insulin resistance is the cardinal feature of type II diabetics and many exhibit insulin resistance at the level of the end-organ receptor. As a result, they are often hyperinsulinemic, at least in the early stages; relative hypoinsulinemia may develop later [3]. The onset of disease is usually later in life, the course is gradual but progressive, and the disease is linked to obesity [3]. As the obesity epidemic rises, type II diabetes is now being seen at earlier ages, including childhood and adolescence.

Both groups can be further subclassified on the basis of the presence of vascular complications, such as hypertension, renal disease, and retinopathy. The same physiologic changes of pregnancy that cause gestational diabetes also complicate the achievement of optimal glucose control in the pregestational diabetic. In a meta-analysis, women with type II diabetes had a 1.5× increased risk of perinatal mortality, decreased risk of diabetic ketoacidosis, and decreased cesarean delivery rate as compared to those with type I diabetes; however, there were no significant differences between the two groups in the frequency of major congenital malformation, stillbirth, or neonatal mortality [5].

14.1.3 Classification

The White classification has been used to categorize the severity of pregestational diabetes [6]. This system attempts to provide a standardized definition for describing pregnant women with diabetes and has some correlation with pregnancy outcome [7, 8]. However, the White classes are not mutually exclusive, and therefore, some have argued that the classification of diabetes should be reassessed.

The classification criteria for diabetes are issued and updated by the American Diabetes Association (ADA) [3]. This provides a general classification system for diabetes (ADA). Including the presence/absence of vascular complications is a better predictor of adverse outcome than the specific White classification [9].

Vascular complications include nephropathy, retinopathy, hypertension, and arteriosclerotic disease.

R. Navathe, MD, FACOG (✉) • V. Berghella, MD, FACOG
Department of Obstetrics and Gynecology, Sidney Kimmel Medical College at Thomas Jefferson University,
833 Chestnut Street, Mezzanine, Philadelphia, PA 19146, USA
e-mail: Reshama.navathe@jefferson.edu; Vincenzo.berghella@jefferson.edu

S. Gerli, MD, PhD
Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy
e-mail: sandro.gerli@unipg.it

E. Pacella, MD
Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy
e-mail: elena.pacella@uniroma1.it

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_14

Table 14.1 Criteria for the diagnosis of diabetes mellitus in the nonpregnant state

Normal values	Impaired fasting glucose or impaired glucose tolerance	Diabetes mellitus
FPG: <100 mg/dL 75-g, 2-h OGTT: 2-h PG <140 mg/dL	FPG: 100–125 mg/dL 75-g, 2-h OGTT: 2-h PG 140–199 mg/dL Hemoglobin A_{1C} 5.7–6.4 %	FPG:≥126 mg/dL (7.0 mmol/L)[a] 75-g, 2-h OGTT: 2-h PG ≥200 mg/dL (11.1 mmol/L)[a] Hemoglobin A_{1C} ≥6.5%[a] Symptoms of hyperglycemia and PG (without regard to time since last meal) ≥200 mg/dL (11.1 mmol/L)

Source: ADA diabetes diagnosis guidelines [2]
The diagnosis of diabetes mellitus should be confirmed on a separate day by any of these three tests
Abbreviations: *FPG* fasting plasma glucose, *OGTT* oral glucose tolerance test, *PG* plasma glucose
[a]Repeat testing to confirm result unless unequivocal hyperglycemia is present

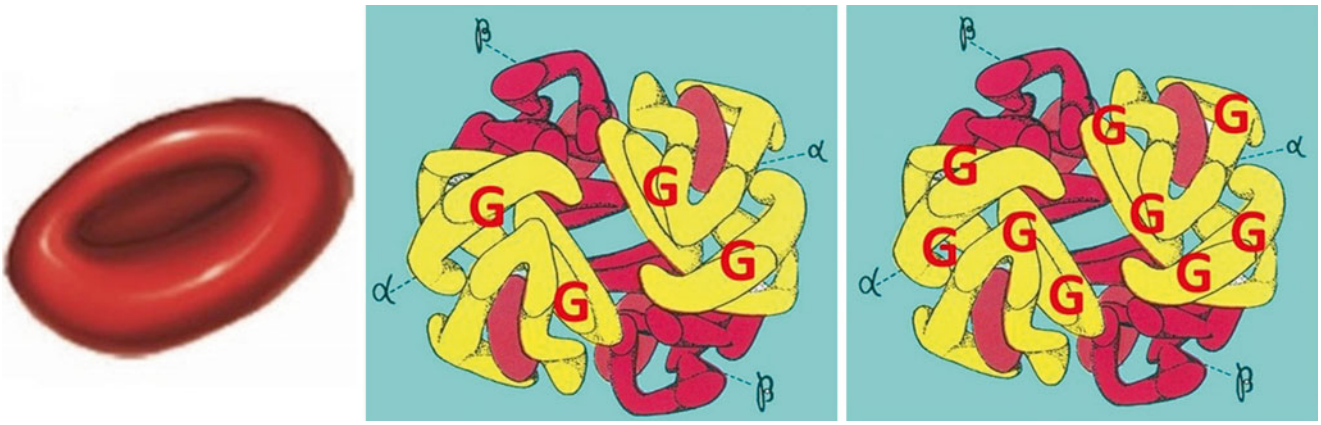

Fig. 14.1 The image shows the red cell, on the *left*; the normal hemoglobin with adherent glucose (*G*), in the *middle*; and, on the *right*, the glycosylated hemoglobin, rich of glucose (*G*). *α* alpha globin chains, *β* beta globin chains

As a result, the following system has been proposed [10]:

- Type 1 diabetes, with or without vascular complications
- Type 2 diabetes, with or without vascular complications
- Gestational diabetes (diabetes diagnosed during pregnancy)
- Other diabetes (e.g., genetic origin, drug or chemical induced)

14.2 Preconception Counseling

The care of the pregestational diabetic is best instituted in the preconception period. The frequency of maternal hospitalizations, length of NICU admission, congenital malformations, and perinatal mortality are reduced in women with DM who seek consultation in preparation for pregnancy; unfortunately, only about one third of these women receive such consultation [11].

The evaluation should emphasize the *importance of tight glycemic control*, *with normalization of the hemoglobin* A_{1C} (*aim for <6 %*) (Fig. 14.1) [12–14]. Multiple studies, including RCTs, show that there is a decrease in spontaneous miscarriage, congenital anomalies, and other complications when optimal glucose control is attained via multiple daily insulin doses adjusted to glucose monitoring ≥4 times per day [15, 16].

This consultation affords the opportunity to screen for end-organ damage and other comorbidities. Ophthalmologic evaluation, EKG, and renal evaluation via a 24-h urine collection for total protein and creatinine clearance will ascertain end-organ damage and determine ancillary pregnancy risks. As 40 % of young women with type 1 diabetes have hypothyroidism, thyroid-stimulating hormone (TSH) should be checked [17].

14.2.1 First Trimester

Ideally, women with pregestational diabetes have received preconceptional counseling and are optimized in their health status. Unfortunately, this is often not the case. Therefore, the first prenatal visit becomes the first opportunity to assess the patient's baseline medical status and educate her about the management and potential complications of diabetes in pregnancy, as well as routine aspects of pregnancy care.

In the first trimester, emphasis should be placed on adherence to diet, exercise, and medication. Women who are not on insulin pumps should be counseled on frequent self-monitoring of blood glucose. Even in early pregnancy, women with pregestational diabetes are often seen more frequently than women with uncomplicated pregnancies. These extra visits can be used to review monitored blood glucose values, to discuss baseline testing results, and to manage comorbidities. A team-based approach, including the obstetrician, endocrinologist, nutrition, and primary care provider is often employed with these patients to provide the necessary expertise.

In addition to routine prenatal laboratory tests performed in the first trimester, there are several additional tests aimed at assessing diabetic disease control. Glycosylated hemoglobin reflects recent average glycemic control and can be used preconceptually or prenatally to aid in counseling regarding the risks of miscarriage, congenital malformations, and preeclampsia. If not performed preconceptually, testing should include the ophthalmologic evaluation, EKG, and renal evaluation via a 24-h urine collection for total protein and creatinine clearance to assess for comorbidities. TSH should be checked, especially in type 1 diabetics [17].

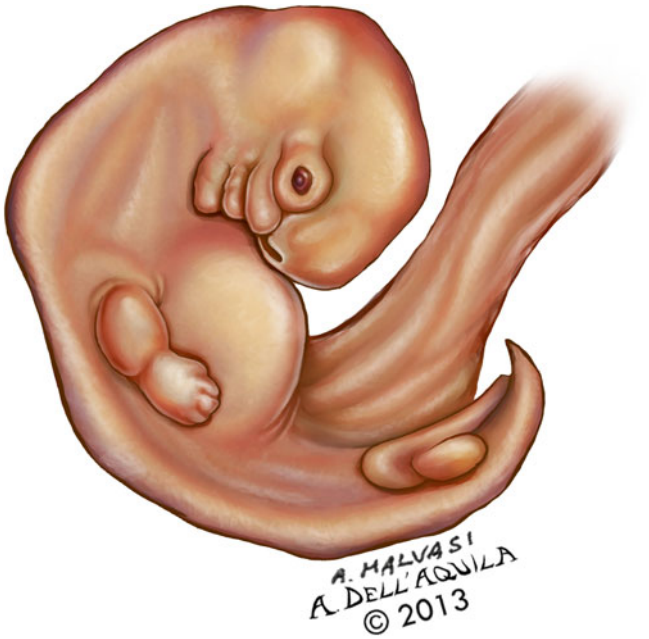

Fig. 14.2 Image shows a spontaneous miscarriage in the first trimester in diabetic pregnant

14.2.2 Miscarriage

First trimester ultrasound examination is often obtained to document viability, as the rate of miscarriage is higher in women with diabetes. This is especially true of those with poor glycemic control in the periconception period. In a 1984 study done looking at progressively severe White classification of diabetes, the rates of miscarriage for White classes C, D, and F were 25 %, 44 %, and 22 % respectively. This is compared to an approximate rate of 15 % in the nondiabetic population. Other studies on populations with better glycemic control reported miscarriage (Fig. 14.2) rates similar to those in the nondiabetic population.

First trimester ultrasound is also helpful in estimation of gestational age. Accurate estimation of gestational age is critical since many of these pregnancies undergo scheduled delivery.

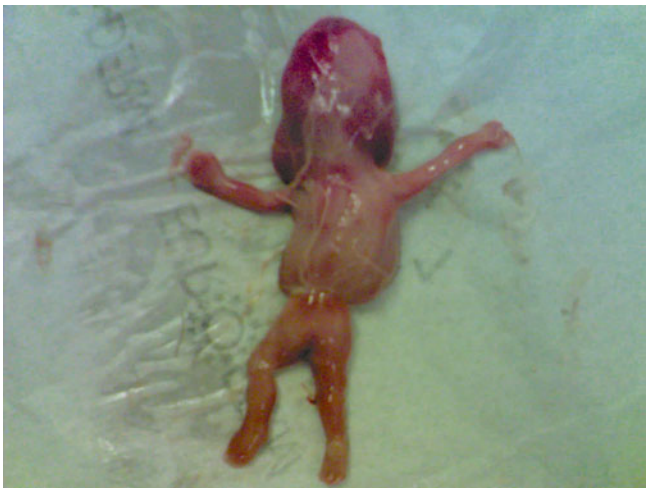

Fig. 14.3 A major congenital malformation in diabetic pregnant, at 15 weeks of pregnancy

14.2.3 Congenital Anomalies

There are many studies that have shown a higher risk of major congenital malformations (Fig. 14.3) and miscarriage associated with increasing first trimester glycosylated hemoglobin values (Table 14.2) [18–20]. The risk of a structural anomaly in the fetus is increased three to eight times when compared to the 2 % risk for the general population. It is important to inform patients that elevated levels of

Table 14.2 Risk of congenital malformations based on hemoglobin A_{1c}

HbA_{1c} (%)	Risk
<7	No increased risk
7–10	3–7 %
10–11	8–10 %
≥11	10–20 % or more

Source: Guerin, *Diabetes Care* 2007 [14]

glycosylated hemoglobin increase the risk of congenital anomalies, particularly neural tube and cardiac defects [21]. Miller and associates showed that women with a glycosylated hemoglobin level > 8.5 % was 22.4 % [19]. Another study comparing 1600 diabetic gravidas with 400,000 controls showed a threefold to sixfold increased risk of anomalies in the diabetic cohort.

The critical time for teratogenesis is during the period of 3–6 weeks after conception. As such, intervention should be planned for in the preconception period. This includes preconception optimization of glycemic control. Several trials of preconceptional metabolic care have demonstrated that malformation rates can be decreased to that of the general population with strict glycemic control. Additionally, in a 10-year case–control study, folic acid supplementation decreased the incidence of congenital heart defects by 20–25 % when compared with the general population [22]. The American College of Obstetricians and Gynecologists (ACOG) recommends preconception and first trimester pregnancy supplementation with 4 mg of folic acid (Fig. 14.4) for "women at high risk for neural tube defects" [23].

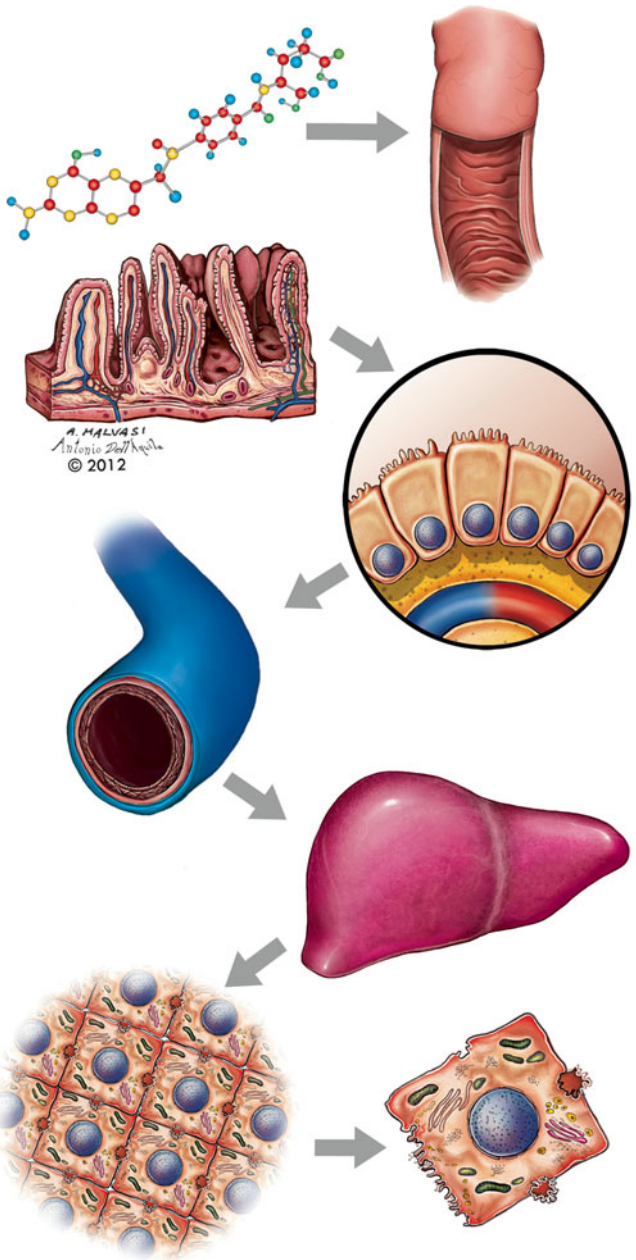

Fig. 14.4 Absorption of folic acid in the daily diet

14.2.4 Second Trimester

The most important aspect of diabetic care in the second trimester is management of blood glucose. As the placenta begins to secrete human placental lactogen, glucose control can become more and more difficult. It is in this trimester, once eating patterns have normalized after first trimester nausea has ended, that women tend to require increases in the medication to achieve optimal glucose control. Women should be seen by the obstetrical provider every two to four weeks to help them achieve glucose control. More frequent visits should be planed based upon the severity of the diabetes, the degree of glycemic control, and the presence of other pregnancy complications. Emphasis should be placed on reviewing the blood sugar log and modifying the treatment regimen as needed. This can also be done remotely via phone or email.

14.2.5 Aneuploidy

As diabetes does not increase the risk of fetal aneuploidy, patients should be offered standard genetic screening and testing options. However, several serum analytes are reduced in women with diabetes, and this can mimic Down syndrome. Second trimester maternal serum levels of AFP are significantly decreased in women with pregestational diabetes [24]. Levels of uE3 are modestly reduced (5–10 % lower), while beta-hCG and inhibin A levels are not significantly altered in this population [25, 26]. Therefore, reference values should be adjusted in women with diabetes.

14.2.6 Open Neural Tube Defects

The prevalence of neural tube defects (NTDs) (Fig. 14.5) is higher in women with pregestational diabetes mellitus. In a study from 2004, NTDs occurred in 0.19 % of pregnancies complicated by diabetes versus 0.07 % of pregnancies in women without diabetes [27].

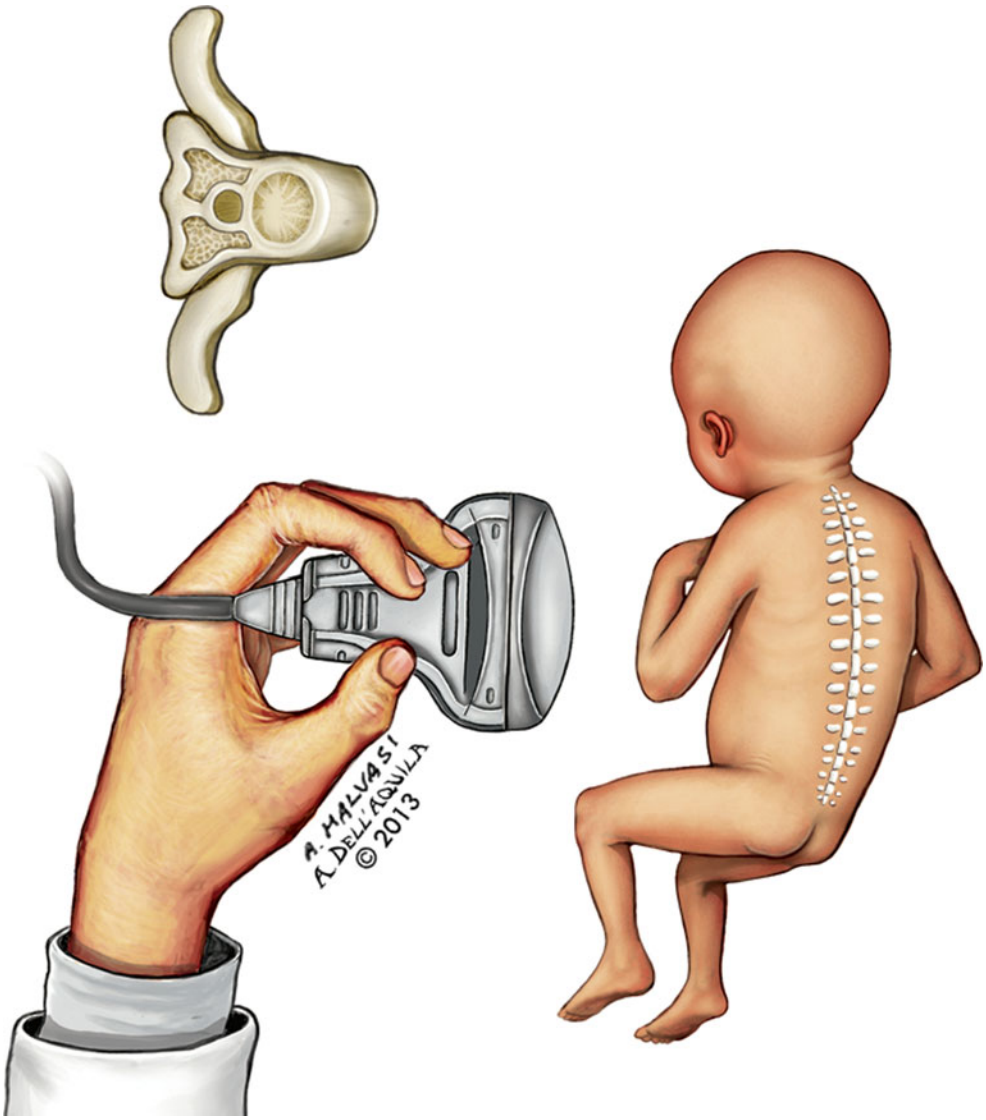

Fig. 14.5 Ultrasonographic control of fetal neural tube defects

14.2.7 Cardiac Anomalies

Congenital heart disease occurs more frequently in the offspring of women with diabetes than in the general population and accounts for about one-half of diabetes-related major congenital anomalies [21, 28]. As an example, in a series of 535 pregnant women with preexisting diabetes, 30 (5.6 %) delivered an infant with confirmed congenital heart disease (Fig. 14.6); the risk was 8.3 % in women with $A_{1C} \geq 8.5\,\%$ versus 3.9 % of those with an A_{1C} below this level [29].

Conotruncal and ventricular septal defects are the most common cardiac defects found in these fetuses.

Interventricular septal thickening may be noted in midtrimester fetuses of diabetic women with very poor control. Although this condition is usually mild and asymptomatic, congestive cardiomyopathy, which is a more diffuse process of hypertrophy and hyperplasia of the myocardial cells, can also occur. Both disorders are transient and managed with supportive care.

Fetal surveillance for the above is recommended in the second trimester of pregnancy. The nature of this surveillance is by convention and expert consensus rather than supported by well-performed trials (Table 14.3). Diabetic gravida should be offered alpha-fetoprotein screening at 16–18 weeks of gestation and targeted ultrasonography at 18–20 weeks. Because of the high risk of cardiac anomalies, some experts suggest fetal echocardiogram as well.

14.2.8 Third Trimester

In the diabetic patient, the major concerns of the third trimester include monitoring of complications necessitating premature delivery. Obstetrical management consists

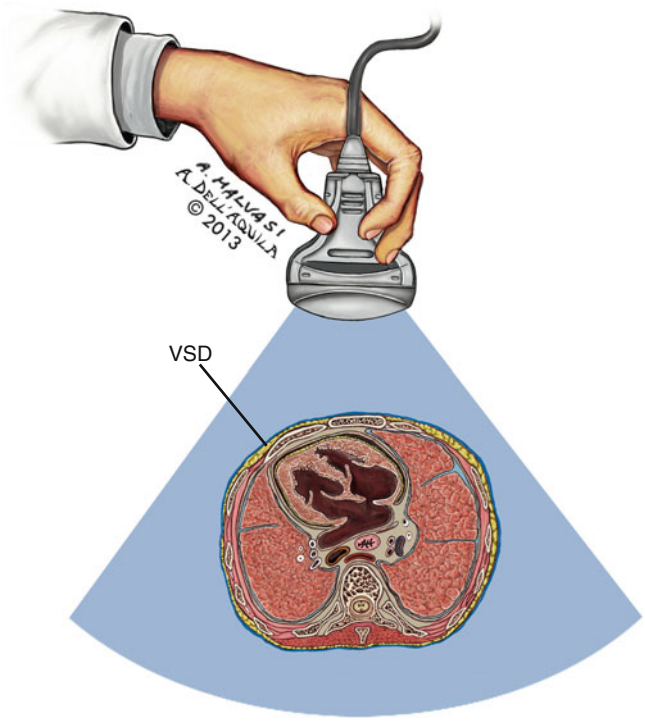

Fig. 14.6 Ultrasonographic detection of intrauterine congenital heart disease

Table 14.3 Antepartum testing

A. Assessment of viability and exact GA: first trimester ultrasound
B. Detection of congenital malformations
(a) If hemoglobin A_{1C} is elevated, consider transvaginal ultrasound at about 14 weeks to rule out structural defects, including cardiac
(b) Maternal serum alpha-fetoprotein level at 16 weeks
(c) Level II ultrasound at 18–20 weeks
(d) Fetal echocardiogram at 20–22 weeks
C. Assessment of fetal growth
(a) Serial growth ultrasounds in third trimester every 3–4 weeks
D. Assessment of fetal well-being
(a) Maternal assessment of fetal activity ("fetal kick counts")
(b) Weekly nonstress tests (NSTs) starting at 32 weeks; twice weekly NSTs at 36 weeks until delivery. Begin at 32 weeks if maternal glycemic control is satisfactory, fetal growth is appropriate, and there are no coexisting maternal medical or obstetric complications. Begin earlier (~28 weeks) and increase frequency if the above conditions are not met

Source: Mackeen, *Evidence Based Medicine* 2011 [75]

of reinforcement of good glycemic control, initiation of antenatal surveillance, estimation of fetal size, and monitoring for pregnancy complications such as preeclampsia (Table 14.3).

During the second trimester, generally only small changes in insulin doses are needed in women whose glucose control was stable by the end of the first trimester. In contrast, during the third trimester, insulin resistance due to the hormones produced by the placenta increases rapidly, and changes in insulin dose are commonly required to maintain euglycemia.

14.2.9 Fetal Death

Intrauterine fetal demise is now a rare complication of diabetic pregnancy (Fig. 14.7), primarily due to achievement of good glycemic control. The fetus of the diabetic mother is at risk for hypoxia primarily from fetal hyperglycemia and hyperinsulinemia leading to increased fetal oxygen consumption, which may induce fetal hypoxemia and acidosis [30–33].

Additionally, maternal vasculopathy and hyperglycemia can lead to reduced uteroplacental perfusion, which may be associated with reduced fetal growth [34].

ACOG recommends antepartum fetal testing for pregnancies complicated by pregestational diabetes [12]. There are no data from large or randomized trials on which to make an evidenced-based recommendation as to which pregnancies complicated by diabetes should undergo fetal surveillance, when to start, what test to order, or how often to perform it [35].

As a result, management is largely based upon clinical experience and expert opinion. ACOG has suggested antepartum monitoring using fetal movement counting, biophysical profile, nonstress test (NST), and/or contraction stress test at "*appropriate intervals*" with initiation of testing generally at 32–34 weeks of gestation (Table 14.3) [12].

For women with good glycemic control, antepartum testing can start at 32 weeks with weekly NSTs and continue until delivery [12]. For women with poor glycemic control, antepartum testing may need to begin earlier. Any significant deterioration in maternal status necessitates reevaluation of the fetus. The frequency of intrauterine fetal death (excluding congenital malformations) with such protocols is approximately 3 per 1000 pregnancies in women with type 1 diabetes [36].

If non-reassuring fetal testing is related to a potentially reversible problem such as hyperglycemia or ketoacidosis, it is advisable to resuscitate the fetus in utero by treating the medical disorder. Pathologic fetal heart rate patterns will often revert to normal when the mother's metabolic status is corrected.

14.2.10 Fetal Growth

Pregnancies complicated by maternal diabetes are commonly associated with accelerated growth but are also at increased risk of impaired fetal growth [37]. Serial ultrasounds in the third trimester to evaluate fetal growth and frequent prenatal visits to review glucose control are also advocated. These can begin at 28–32 weeks of gestation and then every 3–4 weeks thereafter until delivery.

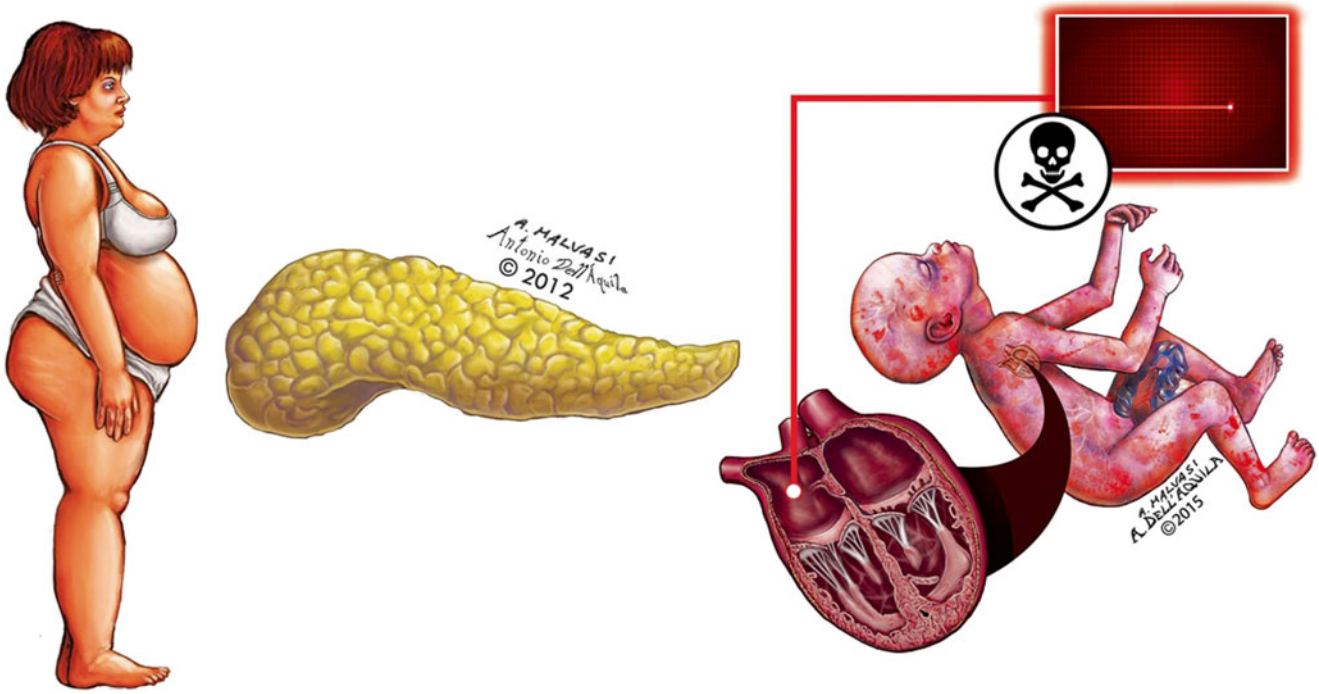

Fig. 14.7 Intrauterine fetal death is a complication of diabetic pregnancy

Accelerated growth is most common among women whose diabetes is marked by insulin resistance; high insulin requirements are associated with accelerated fetal growth even in euglycemic pregnancies [38].

The term "*large for gestational age*" (LGA) usually refers to a fetus or newborn that is greater than the 90th centile for fetuses or infants of that gestational age (possibly including adjustments for fetal gender and ethnicity). At 40 weeks of gestation, the 90th percentile for birth weight in the United States is about 4060 g [39]. The term "macrosomia" refers to a fetus or infant that is greater than some defined weight regardless of gestational age, gender, or ethnicity. The American College of Obstetricians suggests a threshold of 4500 g because maternal and infant morbidity increases sharply above this level [40].

Maternal diabetes mellitus may double the incidence of LGA infants; it also changes the measurements of infants of diabetic mothers (IDMs) compared with offspring of women without diabetes [41]. Specifically, the chest-to-head and shoulder-to-head ratios are increased in IDMs. [42] LGA fetuses are at increased risk for a prolonged second stage of labor, shoulder dystocia, operative delivery, maternal and infant birth trauma, and perinatal death [43].

Maternal diabetes mellitus increases the likelihood of shoulder dystocia two- to sixfold compared to the population without diabetes and increases the likelihood of dystocia-associated fetal morbidity, such as brachial plexus injury (Fig. 14.8) [44, 45].

Although ultrasound is used to determine estimated fetal weight, it is evident that there is no highly reliable method for identifying LGA fetuses before delivery [46,

Fig. 14.8 Rubin maneuver in shoulder dystocia in diabetic patient. Shoulder dystocia, especially in patients with diabetes, is due to internal forces (*IF*) and external forces (*EF*). The IF comes from uterine contractions, whereas the EF, fetal macrosomia and inadequacy of the diameters of the pelvis and maneuvers

47]. This was illustrated in a review of studies of ultrasound for predicting EFW >4000 g in women with diabetes [28]. Sensitivity ranged from 33 to 83 % and specificity ranged from 77 to 98 %. Given the limitations of fetal weight estimates, some investigators have used other measurements for predicting LGA and shoulder dystocia, such as enlarged abdominal circumference [46, 47]. Although this assessment can be somewhat predictive of LGA and shoulder dystocia, many of the measurements are difficult to obtain and reproduce accurately, and these formulas have not been validated in large studies or at a variety of sites.

Impaired growth is more common among women with diabetic vasculopathy and/or superimposed preeclampsia. It is associated with increased fetal and neonatal morbidity and mortality and has long-term health implications. If there is evidence of intrauterine growth restriction, tests of fetal well-being are initiated.

14.2.11 Polyhydramnios

Maternal diabetes is one of the most common etiologies of polyhydramnios, although the mechanism for the increased amniotic fluid volume has not been clearly defined. Possibilities include fetal polyuria secondary to maternal and fetal hyperglycemia, decreased fetal swallowing, or an imbalance in water movement between the maternal and fetal compartments [48]. Polyhydramnios is frequently associated with accelerated fetal growth. Fetal outcomes in pregnancies with diabetes-associated polyhydramnios may not be as poor as outcomes in pregnancies in which polyhydramnios is associated with fetal neurologic disease, twin to twin transfusion, or other syndromes. The antenatal surveillance that has been initiated for the diabetic gravida is sufficient in the setting of polyhydramnios.

14.2.12 Preterm Labor

Compared with controls without diabetes or hypertension, women with pregestational diabetes have significantly higher rates of both indicated preterm delivery and spontaneous preterm delivery [49]. Preterm delivery is primarily initiated because of preeclampsia, but both gestational and pregestational diabetes have been associated with indicated preterm delivery independent of preeclampsia [49, 50]. The reasons for an increased risk of spontaneous preterm delivery are not clear [51, 52].

The indications for inhibition of preterm labor are similar to those in the general obstetrical population. The preferred tocolytic therapy is nifedipine or indomethacin. These are preferred over beta-adrenergic receptor agonist therapy, as these drugs can cause severe hyperglycemia in women with diabetes. If preterm birth is anticipated or planned, administration of betamethasone improves neonatal outcome. It is important to manage the transient hyperglycemia induced by glucocorticoids [53, 54]. The hyperglycemic effect begins approximately 12 h after the first steroid dose and lasts for about five days [55, 56].

14.2.13 Maternal Complications

Women with pregestational diabetes are at risk for a number of obstetric and medical complications when compared to nondiabetic gravida, including worsening diabetic diseases, hypertension (Fig. 14.9), preeclampsia, cesarean delivery, and preterm delivery [57].

14.2.14 Retinopathy

In the White classification system, class R diabetes designates patients with proliferative diabetic retinopathy (Table 14.2). Diabetic retinopathy (Fig. 14.10) is the leading cause of blindness between the ages of 24 and 64 years [2]. Some form of retinopathy is present in 100 % of women who have had long-standing T1DM for 25 years or more, and approximately 20 % of these women are legally blind. Diabetic retinopathy progresses from mild nonproliferative abnormalities to proliferative diabetic retinopathy, which is characterized by growth of new blood vessels on the retina.

Some studies have shown that progression of retinopathy in pregnancy occurs at an accelerated rate; this is usually in the setting of long-standing diabetes [58]. Other trials have failed to show accelerated progression when pregnant diabetes were compared to nonpregnant diabetics. Baseline retinopathy status was the only independent risk factor that predicted progression of retinopathy [59]. As stated earlier, screening for retinopathy is recommended, ideally in the preconception period. Patients with minimal disease should be examined yearly; those with significant pathology may need monthly exams during pregnancy [60]. Proliferative retinopathy is best treated with laser therapy, ideally before conception [61].

14.2.15 Nephropathy

Diabetes is the most common cause of end-stage renal disease (ESRD) and kidney failure in the United States [2]. The pathophysiology of diabetic renal disease is poorly understood. Duration and severity of hyperglycemia and the presence of other comorbidities such as hypertensive disease are thought to contribute to the deterioration of renal function.

Diabetic nephropathy is categorized by the presence and amount of urine protein excretion and can be detected

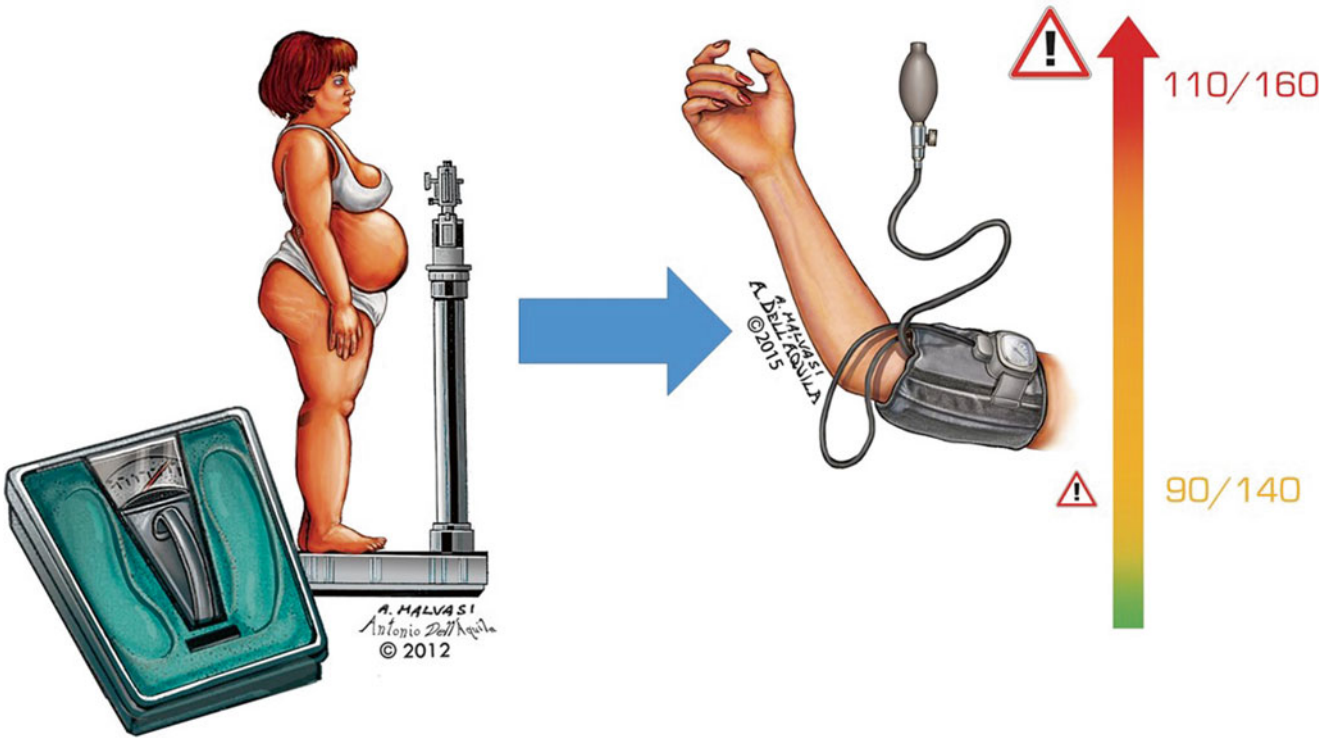

Fig. 14.9 An obese diabetic pregnant with hypertension

by protein to creatinine ratio or 24-h urine collection. Progression of diabetic nephropathy is closely related to glycemic control; several studies have shown that pregnancy itself does not contribute to progressive of nephropathy. In fact, positing that pregnancy is a window of time for closer monitoring, and therefore potentially better glycemic control, well-controlled individuals may see a slowing of disease progression. In one prospective study that compared nonpregnant and pregnant diabetics with similar degrees of renal function, the pregnant diabetics were less likely to progress in their renal disease or their transition to ESRD.

14.2.16 Hypertensive Disorders

The diabetic gravida is at high risk of developing a hypertension spectrum disorder. In several studies of all types of diabetics, the incidence of hypertensive disorders during pregnancy varied from 15 to 30 %, more than four times the rate in the nondiabetic population. This appears to be related to pregestational hypertension and vascular and renal disease. Poor glycemic control also appears to play a role [62].

Chronic hypertension complicates 10–20 % of pregnancies in diabetic women and almost half of pregnancies with diabetes with vascular complications. The perinatal problems encountered with chronic hypertension including maternal stroke, preeclampsia, fetal growth restriction, and placental abruption. Women being treated for hypertension should be switched to beta blockers or calcium channel blockers to. Reasonable target blood pressure goals during pregnancy are systolic blood pressure of less than 140/90 mmHg, as pressures in this range may benefit long-term maternal health, and are unlikely to impair fetal growth [10].

In one review, the incidence of preeclampsia in diabetic women with and without vascular disease was 17 and 8 %, respectively, compared to a rate of 5–8 % in women without diabetes [42]. In another study, the risk of preeclampsia increased significantly with increasing A_{1C} values above optimal levels [62]. Diagnosis and management of preeclampsia are similar to that in women without diabetes, except among those who enter pregnancy with preexisting nephropathy. In these women, diagnosing preeclampsia can be difficult and requires relying on deterioration of other markers.

14.2.17 Obesity

Whether obesity adds to the risks associated with diabetes in pregnancy is an area of ongoing investigation. Obesity itself is a risk factor for developing many of the later complications of pregnancy that are also associated

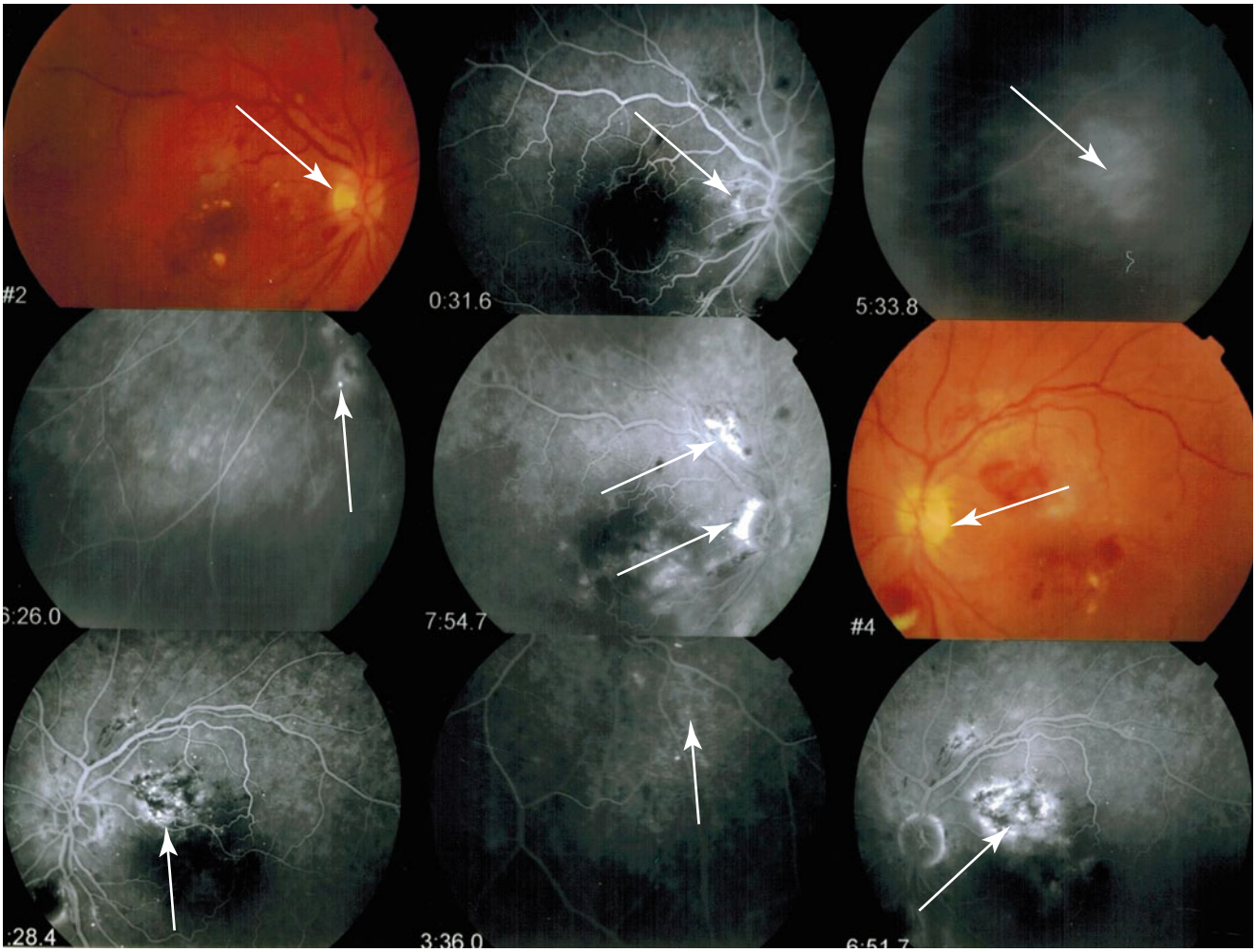

Fig. 14.10 Fluorescein angiography of eye suffering from type II diabetes retinopathy at the posterior pole shows numerous fluorescent-type aneurysmal and lock points for microhemorrhage areas of ischemia

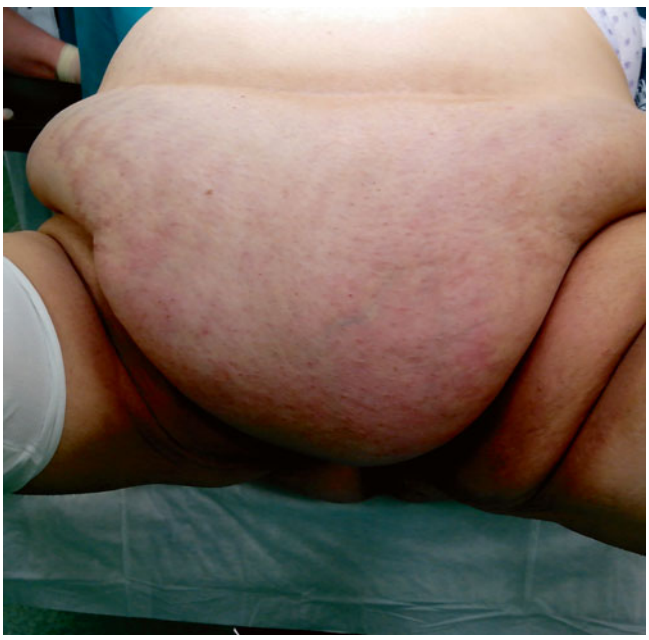

Fig. 14.11 A severe obese pregnant in the delivery room

with diabetes (Fig. 14.11). Obese women are at significantly increased risk of labor dysfunction, operative VD, shoulder dystocia, need for c-section, and subsequent increased risk of DVT and poor wound healing. Clinicians should be mindful of the patient's weight gain and set goals for limited weight gain or even modest weight loss, and this should be brought up at every prenatal visit. The problem of obesity reflects also in epidural analgesia, for the difficulty to insert the needle in the right space of the column (Fig. 14.12).

14.2.18 Heart Disease

Atherosclerotic heart disease may affect the diabetic gravida, especially those with long-term poorly controlled disease. Emphasis should be placed on preconception cardiac evaluation (history and electrocardiogram, consider echocardiogram). The prognosis is poor for these women with cardiac involvement, with a maternal mortality rate of 50 % or higher [63].

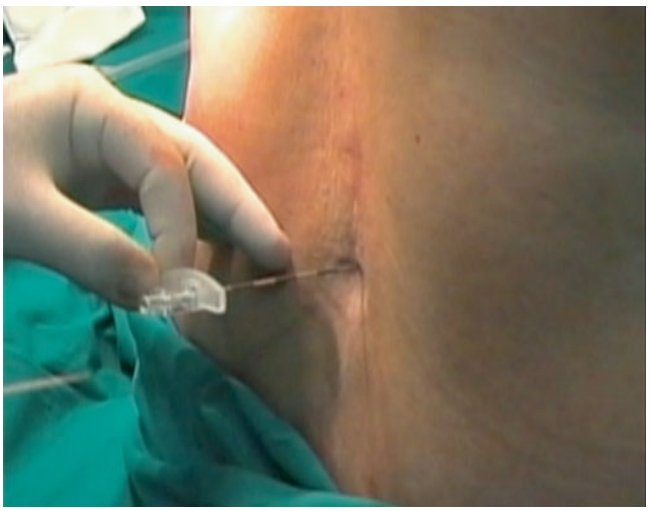

Fig. 14.12 The insertion of the needle in the correct column space is not always easy for the anesthetist, due to the abundant subcutaneous fat that restricts proper digital recognition of the correct spaces where to insert the needle

14.3 Special Considerations: Diabetic Ketoacidosis (DKA)

DKA is an uncommon but life-threatening disease that occurs as a result of absolute or relative insulin deficiency. It occurs in 0.5–3 % of diabetic pregnant women [64]. In gravidas with T1DM, DKA can occur in 5–10 %. Risk factors include type I diabetes, new onset diabetes, infections (e.g., urinary or respiratory tract infections), poor compliance, insulin pump failure, and treatment with betamimetics or steroids [12].

The presentation of DKA is similar in pregnant women to that in nonpregnant persons, with symptoms of nausea, vomiting, thirst, polyuria, polydipsia, abdominal pain, and, when severe, a change in mental status. Laboratory findings include hyperglycemia (usually >250 mg/dL [13.9 mmol/L]), acidemia (arterial pH < 7.30), an elevated anion gap (> 12 mEq/L), ketonemia, low serum bicarbonate (<15 mEq/L), elevated base deficit (> 4 mEq/L), and renal dysfunction [65]. Severe hyperglycemia can cause an osmotic diuresis resulting in maternal volume depletion. This, in turn, can result in reduced uterine perfusion and, in association with the metabolic abnormalities of DKA, produce life-threatening fetal hypoxemia and acidosis. Maternal mortality is less than 1 %, but fetal mortality rates of 9–36 % have been reported, as well as increased risks of preterm birth [64]. Thus, DKA is a true obstetrical emergency. During acute DKA, the fetal heart rate often has minimal or absent variability and absent accelerations, as well as repetitive decelerations [64]. These abnormalities usually resolve with resolution of DKA, but it may take several hours before the tracing is normal [66].

Table 14.4 Management of diabetic ketoacidosis in pregnancy

IV hydration: use isotonic saline (0.9 % NS)
First hour: give 1 L NS
Hours 2–4: 0.5–1 L NS/h
Thereafter (24 h): give 250 mL/h 0.45 % NS until 80 % deficit corrected
Body water deficit = {[0.6 body weight (kg)] + [1–(140/serum sodium)]} ≈ 100 mL deficit/kg body weight
Insulin: mix 50 units of regular insulin in 500 mL of NS and flush IV tubing prior to infusion
Loading: 0.2–0.4 units/kg
Maintenance: 2–10 units/h
Continue insulin therapy until bicarbonate and anion gap normalize
Potassium replacement: maintain serum K^+ at 4–5 mEq/L
If K^+ is initially normal or reduced, consider an infusion of up to 15–20 mEq/h
If K^+ is elevated, do not add supplemental potassium until levels are within normal range and then add 20–30 mEq/L
Phosphate: consider replacement if serum phosphate < 1.0 mg/dL or if cardiac dysfunction present or patient obtunded
Bicarbonate: if pH is < 7.1, add one ampule (44 mEq) of bicarbonate to 1 L of 0.45 % NS
Laboratory tests: check arterial blood gas on admission; check serum glucose, ketones, and electrolytes every 1–2 h until normal
Consider doubling insulin infusion rate if serum glucose does not decrease by 20 % within the first 2 h
When blood glucose reaches 250 mg/dL, change IVF to D5NS
Continue insulin drip until ketosis resolves and the first subcutaneous dose of insulin is administered

Source: Adapted from ACOG practice bulletin. *Pregestational diabetes* [12]
Abbreviation: *NS* normal saline, *IVF* intravenous fluids, *K^+* potassium, *kg* kilograms

DKA is similarly managed in pregnant and nonpregnant patients. Aggressive hydration, intravenous insulin, and correction of the underlying etiology are the most important interventions, with close electrolyte (especially glucose and potassium) monitoring (Table 14.4) [12, 65]. It is important to determine the etiology of DKA, such as infection or insulin noncompliance. Glucocorticoids and betamimetics should be avoided during DKA, as they will worsen hyperglycemia.

DKA alone is generally not an indication for delivery. Emergent delivery before maternal stabilization should be avoided because it increases the risk of maternal morbidity and mortality and may result in delivery of a hypoxic, acidotic preterm infant for whom in utero resuscitation may have resulted in a better outcome. The timing of delivery needs to be individualized based on multiple factors including gestational age, maternal condition (whether the mother is responding to aggressive therapy or deteriorating), and fetal condition (whether the fetal heart rate pattern is improving or deteriorating). Fetal heart rate abnormalities resulting from maternal acidosis will often improve as DKA is treated and maternal condition improves [64].

14.4 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a diagnosis of diabetes first recognized or diagnosed during pregnancy [67]. It has been estimated that there is an overall 7% incidence of GDM, representing one of the most common medical complications facing obstetricians [3]. Of cases of DM in pregnancy, 88% are GDM [67]. The importance of screening for GDM, and treatment to optimize glycemic control to reduce hyperglycemia-associated complications, has been established [68, 69]. If GDM is diagnose in early pregnancy, then it is most likely preexisting diabetes and should be treated accordingly to minimize the complications of pregestational diabetes (above).

14.4.1 Pathophysiology

The pathophysiology of GDM is insulin resistance caused by circulating hormonal factors: increased maternal and placental production of human placental lactogen, progesterone, growth hormone, cortisol, and prolactin. As the placental mass increases, the circulating hormones increase; correspondingly, the incidence of GDM increases with increasing gestational age. Increased body weight and caloric intake also contribute to the insulin resistance associated with pregnancy and may offset the normally increased insulin production in the pregnant woman [70]. Women with GDM have been found to have lower basal islet cell function, in addition to insulin resistance, when compared to a nondiabetic cohort. The combination of the two factors contributes to the development of GDM. This insulin resistance and decreased insulin production persists in the postpartum state and can lead to the development of type II diabetes in this population.

14.4.2 Screening

Who, when, and how to screen and the diagnostic glucose cutoffs to establish the diagnosis of GDM are controversial.

The population who should be offered screening has not been uniformly identified [67]. Low-risk women in whom screening may not be necessary (selective screening) must meet all of the following criteria: age <25 years, ethnic origin of low risk (not Hispanic, African, native American, south or east Asian, or Pacific Islander), BMI <25, no previous personal or family history of impaired glucose tolerance, and no previous history of adverse obstetric outcomes associated with GDM [71]. However, universal screening is most commonly adopted. The risk of developing GDM is directly associated with prepregnancy BMI [72].

Screening is typically recommended at 24–28 weeks gestation [67]. Women with risk factors (Table 14.5) should be screened preconception or at first prenatal visit [71]. About 5–10% of women with these risk factors will have early GDM, and these represent 40% of all GDM diagnosed later at 24–28 weeks [73]. If the early screen is negative, a repeat screen should be performed at 24–28 weeks gestation. Typically, if a patient fails the early 1 h glucose screen and passes the early 3 h glucose tolerance test, the 3 h test should be repeated at 24–28 weeks. GDM is diagnosed with 2 abnormal values on the 3 h glucose test. Table 14.6 provides normal values.

Screening for GDM is somewhat controversial and can be performed in general either with a one-step or two-step process. One large trial has shown that two-step screening is more cost-effective than the one-step screening [74].

14.4.3 Complications

The incidence of complications is inversely proportional to glucose control. In poorly controlled DM, increased glucose in the mother causes abnormal metabolism, while in the fetus, it causes hyperinsulinemia and its consequences. However, treatment of even mild GDM reduced birth-weight percentiles and neonatal fat mass [75]. Other complications are hypertensive disorders and preeclampsia, macrosomia, operative delivery, and birth injury (see above, pregestational diabetes) [71]. Apart from transient neonatal hypoglycemia, no other metabolic derangement has been reported in the infant of the GDM mother. Long-term adult disorders, such as glucose intolerance and obesity, have been postulated to occur as frequently in these neonates as in neonates of women with

Table 14.5 Risk factors for GDM

Prior unexplained stillbirth
Prior infant with congenital anomaly (if not screened in that pregnancy)
Prior macrosomic infant
History of gestational diabetes
Family history of diabetes
Obesity
Chronic use of steroids
Age >35 years
Glycosuria

Source: ACOG practice bulletin. *Gestational diabetes mellitus* [67]

Table 14.6 Criteria for standard 100-g glucose load to diagnose gestational diabetes

	National Diabetes Data Group		Carpenter–Coustan criteria	
	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	105	5.8	95	5.3
1 h	190	10.6	180	10.0
2 h	165	9.2	155	8.6
3 h	145	8.0	140	7.8

pregestational diabetes, but this has not been verified by observational studies [76]. Approximately 50 % of women identified as having GDM will develop frank diabetes within 10 years, if followed longitudinally [77].

14.5 Treatment

Optimizing health outcomes and decreasing risk of the complications in both pregestational and gestational diabetes can be achieved by a combination of diet, exercise, glucose monitoring, and pharmacotherapy.

14.5.1 Diet

Nutritional requirements are adjusted on the basis of maternal body mass index (BMI); women with normal BMI require 30–35 kcal/kg/day. Individuals <90 % of their ideal body weight (IBW) may increase this by an additional 5 kcal/kg/day, while those >120 % of their IBW should decrease this value to 24 kcal/kg/day [12].

14.5.2 Exercise

Moderate exercise decreases the need for insulin therapy in type II diabetics by increasing the glucose uptake in skeletal muscle, and therefore, should be strongly encouraged for diabetic patient.

14.5.3 Glucose Monitoring

Preprandial and postprandial home glucose monitoring, have been associated with enhanced glucose control and shorter interval to achieve target blood sugars. Capillary blood glucose ("fingerstick") measurements using a glucometer should be obtained at least four times a day—fasting and 2 h postprandial. Target levels are in Table 14.7 [78]. Though not in widespread use, continuous glucose monitoring is associated with decreased birth weight and incidence of macrosomia compared to routine monitoring [79, 80]. More recent studies showed no improvement in glycemic control or in maternal/fetal outcomes in women using continuous glucose monitoring versus four times per day glucometer use [81, 82].

Table 14.7 Target venous plasma glucose levels

Fasting	60–90 mg/dL
Preprandial	60–100 mg/dL
One-hour postprandial	≤140 mg/dL
Two-hour postprandial	≤120 mg/dL
3 AM	60–90 mg/dL

Glycosylated hemoglobin A_{1c} <6 % is normal [83]. Hemoglobin A_{1c} of 6 % reflects a mean glucose level of 120 mg/dL; each 1 % increment in hemoglobin A_{1c} is equal to a change in mean glucose level of 30 mg/dL. There is evidence that blood sugars (and hemoglobin A_{1c} measurements) should be maintained within normal limits throughout gestation and not just in a particular trimester to decrease the risk of poor pregnancy outcomes [84].

14.5.4 Oral Hypoglycemic Agents

There is insufficient evidence to assess the effectiveness of these agents on glucose control in the pregestational diabetic gravida. Therefore, even in women on oral hypoglycemic control before pregnancy, insulin therapy is suggested for glucose control. Occasionally, a woman well controlled on either glyburide or metformin prepregnancy, and a normal hemoglobin A_{1c}, can be managed by continuing these medications (Fig. 14.13) [16, 85]. Newer evidence suggests that metformin is preferred over glyburide when oral hypoglycemic agents are employed (at least for GDM management) [86]. Improved maternal glycemic control and reduced neonatal hypoglycemia, respiratory distress syndrome, and NICU admission were noted when metformin was added to an insulin regimen in women with poor control despite high-dose insulin therapy [87].

14.5.5 Insulin

Multiple-dose insulin (MDI) injection therapy is the mainstay in the management of pregestational diabetes. All subcutaneous insulin types have been approved during pregnancy.

A review of the types of insulin, their onset, and duration of action are listed in Table 14.8. Human insulin is preferred to animal insulin. Women, particularly those new to insulin therapy, need to be counseled about the differences in the various insulins in order to use them to their greatest efficacy. Close monitoring with at least weekly contact with a provider is suggested to maximize insulin adjustment. Hypoglycemia is a side effect of insulin treatment. *Glucagon* should be available for home use in emergency situations.

Satisfactory glucose control may be obtained solely with an intermediate-acting insulin rather than a short-acting insulin [88]. However, *more optimal metabolic control is more likely achieved with one evening injection of long-acting insulin* (*e.g., insulin glargine*), *and meal-time injections of short-acting insulin* (*e.g., lispro or aspart*). Glargine cannot be mixed in the same syringe with other insulins. Intermediate-acting insulin (e.g., Neutral Protamine

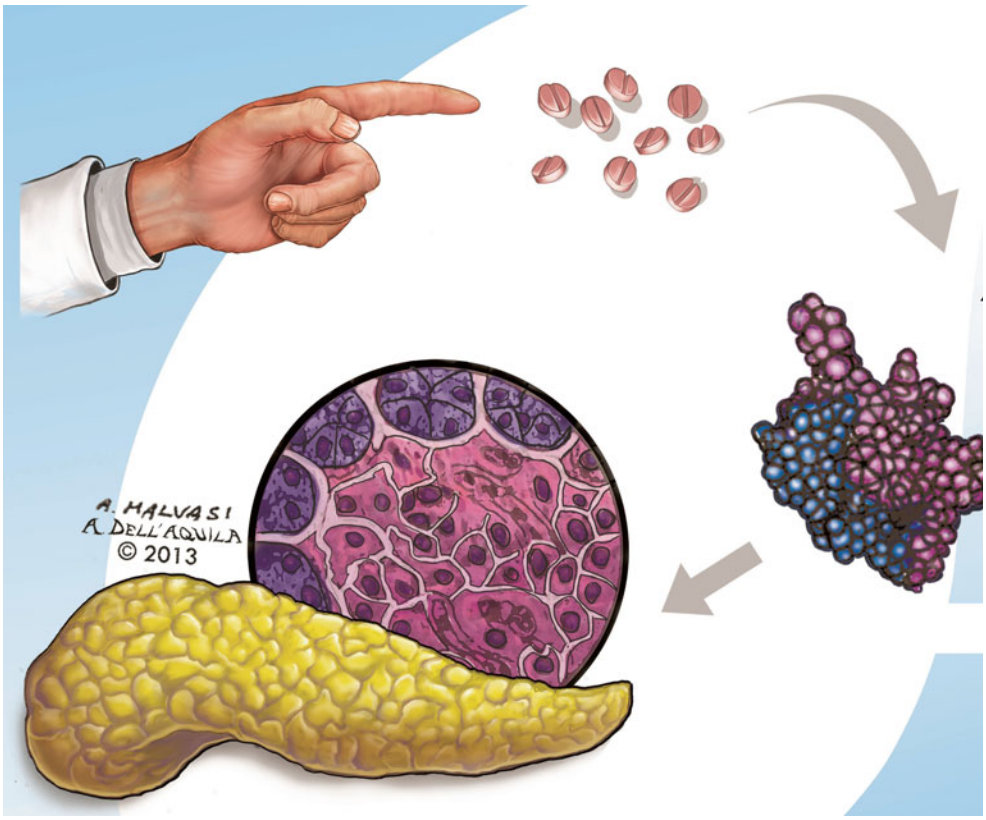

Fig. 14.13 The administration of metformin reduces glycemia in diabetic pregnants

Table 14.8 Types of insulin and their pharmacokinetics

Type	Onset	Peak	Duration
Lispro/aspart	15–30 min	0.5–3 h	≤5 h
Regular	30 min	2.5–5 h	4–12 h
NPH	1–2 h	4–12 h	14–24 h
Detemir	3–4 h	3–9 h	6–23 h (dose dependent)
Glargine	3–4 h	None	24 h

Source: ACOG practice bulletin. *Pregestational diabetes* [12]

Hagedorn [NPH]) twice daily can also be used, instead of insulin glargine. Studies have shown that short-acting insulin is as effective as regular insulin and may result in improved postprandial glucose control and less preterm deliveries [89, 90]. Insulin lispro should be given immediately before eating. As compared to two daily insulin injections, additional doses are associated with improved glycemic control [91]. A meta-analysis of cohort studies comparing insulin glargine to NPH did not reveal any significant differences in outcomes including infant birth weight, congenital anomalies, and respiratory distress [92]. A randomized trial including 310 pregnancies compared insulin detemir with NPH and found no differences between maternal hemoglobin A_{1c}, the frequency of major hypoglycemic episodes, early fetal loss, congenital anomalies, and adverse events [89, 93].

Subcutaneous insulin pump therapy (continuous subcutaneous insulin infusion therapy (CSII)) may be continued in women already compliant with this mode of therapy. In nonpregnant adults, women compliant with insulin pumps have increased satisfaction, decreased episodes of severe hypoglycemia, and better control of hyperglycemia [12]. Basal infusion rates tend to increase and carbohydrate-to-insulin ratios decrease during the course of pregnancy [94]. There is currently insufficient evidence to recommend CSII versus MDI in pregnancy in women not already on pumps [95, 96]. Inhaled insulin has been tested in nonpregnant adults, but there are yet insufficient data for pregnancy management [97].

Carbohydrate counting and the use of an insulin-to-carbohydrate ratio of 1 unit of insulin for every 15 g of carbohydrate in early gestation can allow for greater flexibility in eating but have not been studied in a trial. As pregnancy advances with its concomitant increased insulin resistance, an increased ratio is required with 1 unit covering a lower amount of carbohydrates, for example, 1 unit/3 g of carbohydrate [94].

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Hypertensive Disorders of Pregnancy

15

Jamil ElFarra, Richard Viscarello, Cynthia Bean, and James N. Martin Jr.

15.1 Introduction

Hypertensive disorders of pregnancy complicate approximately 10 % of pregnancies and are considered one of the leading causes of maternal and fetal morbidity and mortality. There are an estimated 50,000–60,000 preeclampsia-related deaths per year worldwide. Hypertensive disorders can either predate pregnancy (i.e., chronic hypertension) or be specific to pregnancy (i.e., gestational hypertension and preeclampsia) [1–4].

Chronic hypertension is more common in patients over the age of thirty. The prevalence of chronic hypertension ranges from 4.6 to 22.3 % among those between the ages of 30 and 39 as opposed to 0.6–2 % in those between the ages of 18 and 29. As more women delay childbearing and with the increased use of egg donation (Fig. 15.1) and assisted reproduction infertility treatment (Fig. 15.2), the average age of pregnancy is increasing. As a result, chronic hypertension and its complications will certainly be encountered more often in pregnancy. This will inevitably increase the incidence of preeclampsia. Approximately 25 % of chronic hypertensive patients will develop preeclampsia during pregnancy compared to 4 % without underlying hypertension. Preeclampsia is associated with even greater maternal and fetal risks, rendering the pregnancies of patients with both chronic underlying hypertension and preeclampsia to be at very high risk [1, 2, 5].

Elevated blood pressures (BP) initially encountered in the first and early second trimester, especially those occurring prior to 20 weeks of gestation, are usually a result of chronic hypertension (Fig. 15.3). When hypertension is encountered early in pregnancy, this is usually due either to a known hypertensive disorder or previously undiagnosed chronic hypertension rather than a pregnancy-induced pathology. Hypertension predating pregnancy can be either primary hypertension or secondary hypertension. In primary/essential hypertension, an underlying cause is not found. However, in secondary hypertension, an underlying etiology is identified. If secondary hypertension is suspected, further investigation is warranted, as the majority of secondary causes are potentially treatable [1, 2, 5].

Understanding the classification and management of hypertensive disorders is essential. It is critical to identify those patients with underlying hypertensive disorders in pregnancy as they are at greater risk for complications. Some women with underlying hypertensive disorders may require outpatient treatment with medications, urgent treatment in the hospital setting, transfer to a higher level of care, or in some cases termination of pregnancy. Identifying those pregnant patients with hypertensive disorders early and treating them accordingly allow for an overall reduction in maternal and perinatal morbidity and mortality [1].

15.2 Establishing the Diagnosis of Hypertension in Pregnancy

Hypertension can easily be missed, as blood pressure elevation is usually silent and asymptomatic. A diagnosis can occur only when hypertension is elicited on physical exam. There is a physiologic decrease in blood pressure in early pregnancy, which may normalize previously elevated blood pressure. This

J. ElFarra, MD • C. Bean, MD
J.N. Martin Jr., MD, FACOG, FRCOG (✉)
Department of Obstetrics and Gynecology,
Winfred L. Wiser Hospital for Women and Infants,
The University of Mississippi Medical Center, Jackson, MS, USA
e-mail: jelfarra@umc.edu; cmbean@umc.edu;
jmartin6@comcast.net

R. Viscarello, MD
Department of Obstetrics and Gynecology,
Maternal Fetal Care P.C.,The Stamford Hospital,
Stamford, CT, USA
e-mail: perinatal@aol.com

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_15

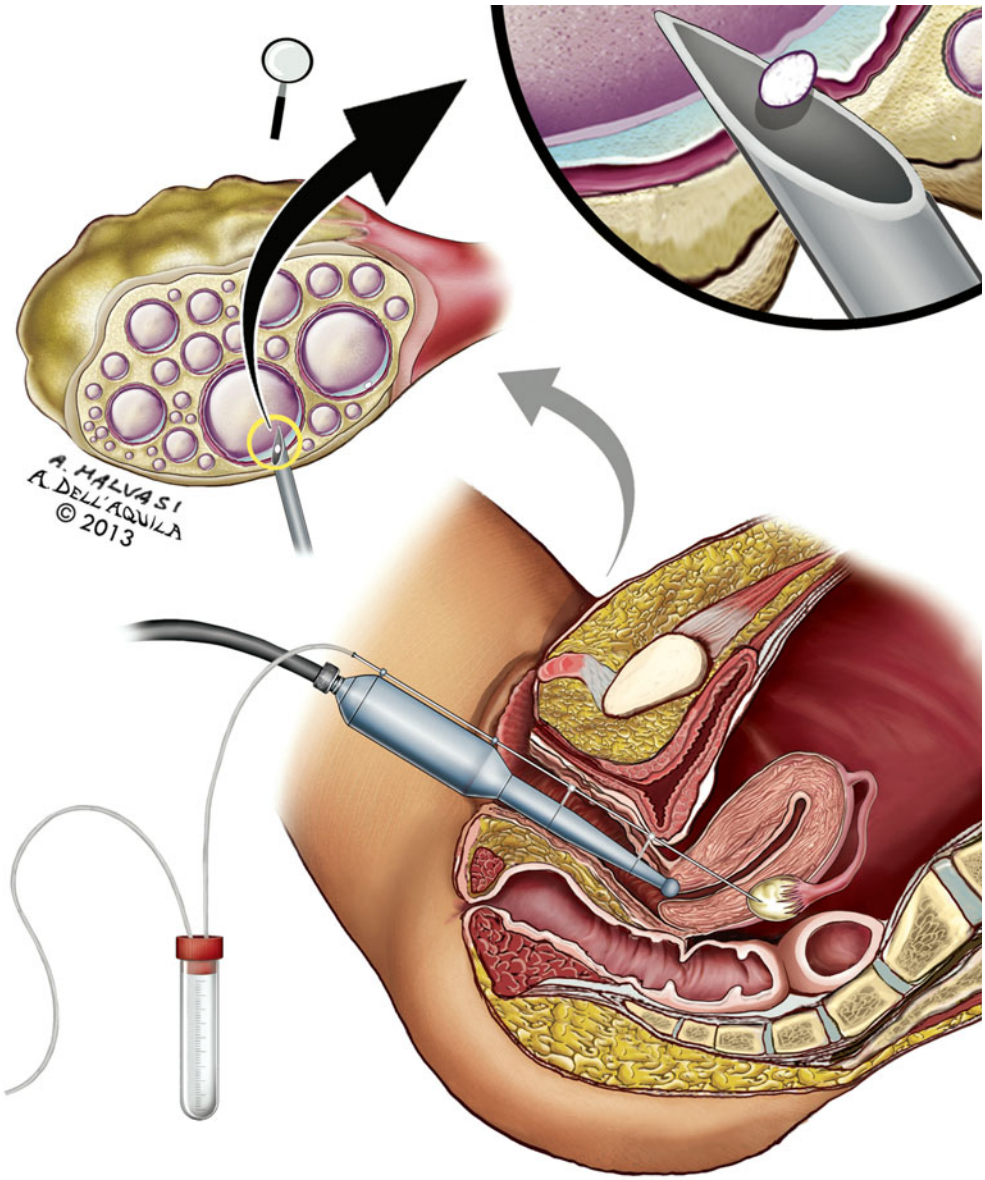

Fig. 15.1 The figure represents an ovarian pickup

physiologic decrease in blood pressure may mask preexisting hypertension, particularly before 16 weeks of gestation [1, 5].

15.2.1 Definition

Hypertension in pregnancy is defined as either a systolic blood pressure of greater than or equal to 140 mmHg *OR* a diastolic BP of greater than or equal to 90 mmHg (Fig. 15.4). In order to establish the diagnosis of hypertension, one must have at least two elevated blood pressure measurements taken correctly at least 4 h apart [1, 2, 5].

Blood pressure elevation is further classified into mild versus severe. Hypertension is considered mild until systolic and/or diastolic levels reach or exceed 160 mmHg and 110 mmHg, respectively. In the setting of persistent severe-range blood pressures, a diagnosis of severe hypertension can be made without waiting 4 h. More importantly, therapy can be initiated promptly when severe-range blood pressure elevations are persistent [1].

White coat hypertension, defined as elevated BPs in the presence of a healthcare provider, is found in up to 15 % of individuals outside of pregnancy. White coat hypertension may lead to a false diagnosis of hypertension. It is suspected when the reported BP measurement at home is less than the BP measurements in the hospital or office. In the setting of suspected white coat hypertension, ambulatory blood pressure monitoring is recommended [1].

15.2.2 Optimal Measurement of Blood Pressure

Measuring blood pressure correctly is crucial in establishing the diagnosis of hypertension. Inaccurate BP measurements can lead to an inappropriate diagnosis. Inaccurate high BP readings could lead to the false diagnosis of a hypertensive

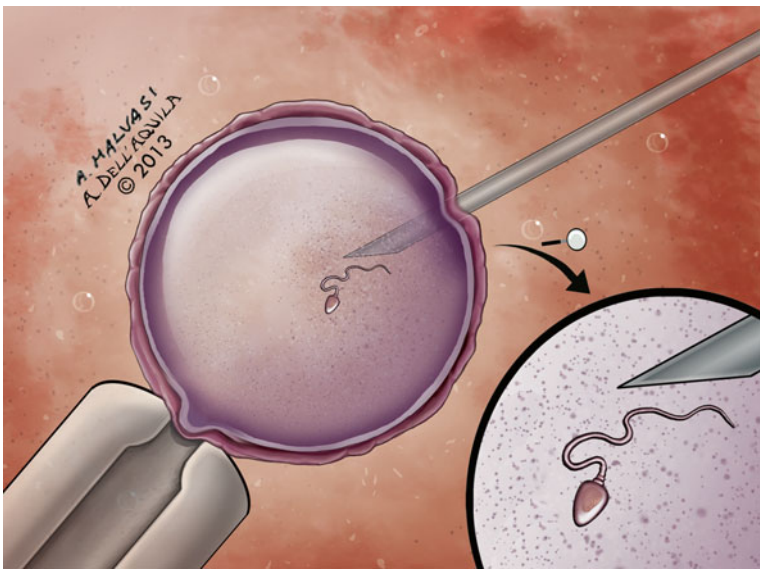

Fig. 15.2 The figure shows the intracytoplasmic sperm injection (ICSI) technique

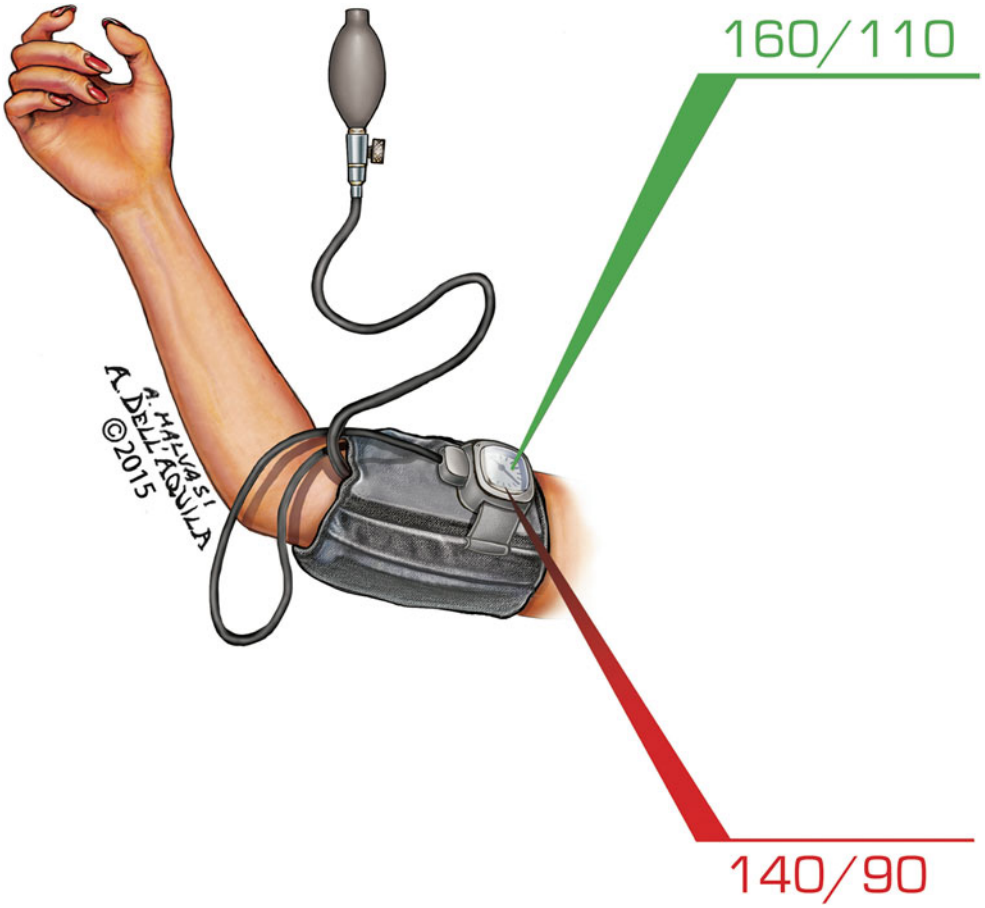

Fig. 15.3 A patient underwent blood pressure measurement, referring a chronic hypertension

pregnancy. Inaccurately low BP measurements can label a patient as normotensive when he/she is actually hypertensive. Below are some of the important requirements needed for obtaining accurate blood pressure measurements [6–10]:

- Proper cuff size
- Patient comfortably seated
- Back supported
- Legs uncrossed

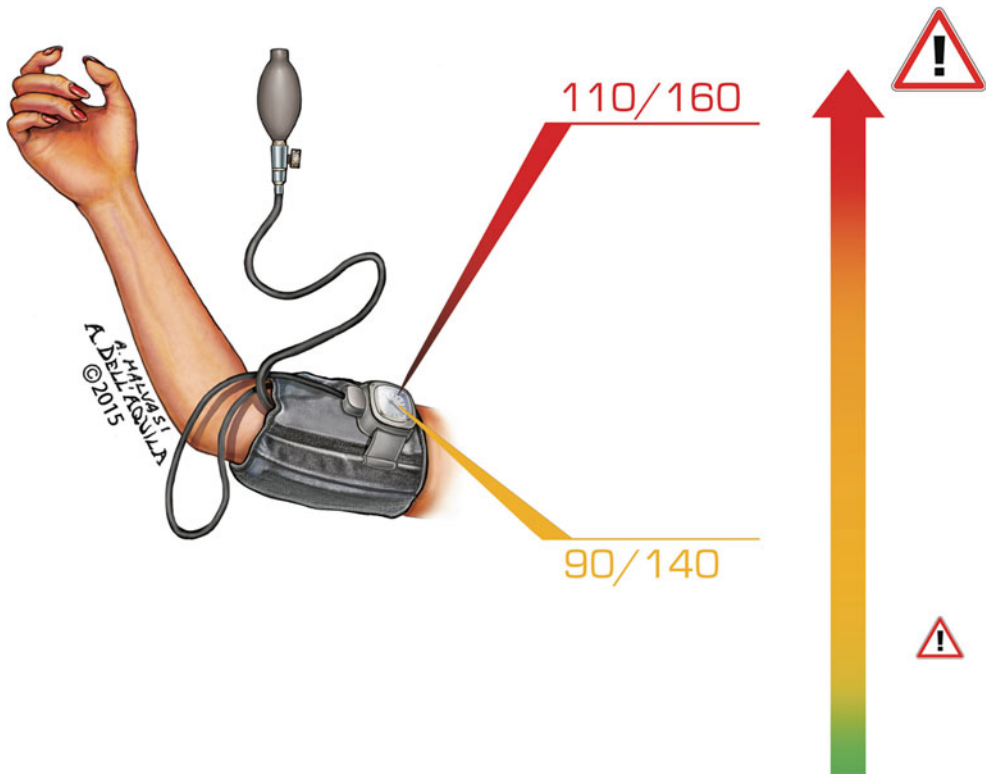

Fig. 15.4 Hypertension in pregnancy is defined as either a systolic blood pressure of greater than or equal to 140 mmHg or a diastolic BP of greater than or equal to 90 mmHg. The systolic and diastolic numbers reversed

The arm should be supported so that the middle of the cuff on the upper arm is at the level of the right atrium.

The patient should be instructed to relax and not talk.

If the BP is elevated, at least 5 min should lapse before a repeat blood pressure is retaken.

The BP cuff should be placed with the bladder midline over the brachial artery pulsation, and the arm should be without restrictive clothing.

15.3 Evaluation of Hypertension in Early Pregnancy

Early recognition of hypertension in pregnancy, establishing the extent of organ damage, and identifying comorbidities are of paramount importance. These can only be achieved by conducting a thorough history and physical exam, ordering the appropriate laboratory tests and imaging studies, and making appropriate referrals. This ensures proper management of the patient, which will help decrease maternal and fetal risks.

Paying attention to the patient's history (medical, surgical, obstetrical, family, and social) as well as abnormal physical exam findings may yield valuable information in establishing the correct diagnosis and management options. Spending enough time with patients and giving them the opportunity to express their concerns and ask questions help establish a strong and healthy patient-physician relationship. This relationship allows further building of trust and confidence, which may allow patients to share vital information that may have otherwise remained uncovered. Reviewing the patient's medication list is of equal importance, as this helps minimize the potential for teratogen exposure.

Laboratory evaluation is another important step when taking care of patients with hypertensive disorders. Obtaining lab tests on patients with chronic hypertension as well as those in whom blood pressure elevation is initially encountered in the first half of pregnancy serves two main purposes. First, it helps to assess the extent of end-organ damage and severity of disease and to investigate coexisting comorbidities. Second, it enables us to establish a baseline for comparison purposes later in pregnancy. The baseline labs are especially helpful in distinguishing a chronic hypertension exacerbation from superimposed preeclampsia. As mentioned earlier, the distinction between the two is very important as the complication rates and management differ dramatically.

The appropriate labs and studies should be obtained at the first prenatal visit or prior to pregnancy if possible.

The recommended labs and studies include the following [1, 2]:

- Urinalysis, urine culture, and a quantitative assessment of urine protein (i.e., 24-h urine collection or a protein/creatinine ratio)

- Renal function tests
- CBC with platelet count
- Glucose
- Electrolytes
- Uric acid and liver enzymes
- Thyroid-stimulating hormone (TSH) level
- EKG and possible echocardiogram

Establishing an accurate gestational age and due date in a hypertensive patient is imperative given the high likelihood that fetal growth restriction may occur and/or early delivery may be required. Performing a dating ultrasound as early as possible is highly recommended [1, 2].

Ideally, patients with chronic hypertension planning to become pregnant should be seen for preconception counseling. The extent of end-organ damage should be evaluated at this time, as pregnancy risks and recommendations may change depending on severity of disease.

Patients should be counseled about the risks pregnancy poses and the expectations during the pregnancy. Patients should also be changed to pregnancy safe medications when possible and folic acid supplementation should be started. Appropriate vaccines should also be recommended at this time [1, 2].

15.4 Classification of Hypertensive Disorders in Pregnancy

Four major hypertensive disorders occur in pregnancy [1] (Table 15.1):

A. Chronic (preexisting) hypertension
B. Gestational hypertension
C. Preeclampsia-eclampsia/hemolysis, elevatedliver enzymes and low platelet count (HELLP) syndrome
D. Preeclampsia-eclampsia superimposed upon chronic hypertension

Table 15.1 Etiologies of hypertensive disorders in pregnancy

Pregnancy specific	Nonspecific
Gestational hypertension	Essential hypertension
Preeclampsia	Renal disease
Preeclampsia superimposed on chronic hypertension	Obstructive sleep apnea
	Cushing syndrome
HELLP syndrome	Renal artery stenosis
Gestational trophoblastic disease	Pheochromocytoma
Mirror syndrome	Coarctation of the aorta
	Primary aldosteronism
	Thyroid dysfunction
	Lupus flare
	Drugs and medications

15.5 Chronic Hypertension

Chronic hypertension is defined as blood pressure elevation that predates pregnancy. If blood pressure is unknown prior to pregnancy and elevation is discovered prior to 20 weeks of gestation, the presumed diagnosis is chronic hypertension. However, to make an absolute diagnosis of chronic hypertension in this instance, elevated blood pressures must be demonstrated beyond 12-week postpartum [1].

15.6 Gestational Hypertension

Gestational hypertension is a pregnancy-specific diagnosis. Gestational hypertension is defined as new-onset blood pressure elevations that occur after 20 weeks of gestation in the absence of proteinuria and preeclampsia diagnostic criteria (see below).

Gestational hypertension is a pregnancy-specific transient hypertensive disorder that begins during pregnancy and resolves within 6–12 weeks postpartum. Persistence of BP elevation beyond 6–12 weeks postpartum is indicative of chronic hypertension. Even though gestational hypertension is transient in nature, it can be an indicator of future hypertensive disease [1, 2, 5].

15.7 Preeclampsia/Eclampsia/HELLP Syndrome

Similar to gestational hypertension, the spectrum of preeclampsia-eclampsia and HELLP syndrome is also a pregnancy-specific condition and usually occurs in the latter part of pregnancy (after 20 weeks of gestation). However, unlike gestational hypertension, the hypertension associated with preeclampsia is accompanied by new-onset proteinuria. Proteinuria is defined as the excretion of greater than or equal to 300 mg of protein in a 24-h urine collection or a protein/creatinine ratio in a single void of greater than or equal to 0.3 (each measured as mg/dL). A urine dipstick of 1+ or greater may be used if the other quantitative methods are not available; however, this method has high false-positive and false-negative rates [1].

Recent changes to the diagnostic criteria have made it possible to diagnose preeclampsia in the absence of proteinuria. In addition to acute hypertension, when there is evidence of thrombocytopenia, renal insufficiency, abnormal liver function tests, pulmonary edema, and/or cerebral/visual symptoms, the diagnosis of preeclampsia can be made even in the absence of proteinuria (Table 15.2) [11].

As preeclampsia is a progressive disorder, it is no longer classified as mild or severe. Preeclampsia is now classified as either preeclampsia with severe features or preeclampsia

Table 15.2 The diagnostic criteria for preeclampsia

Blood pressure	Greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 h apart after 20 weeks of gestation in a woman with previously normal blood pressure
	Greater than or equal to 160 mmHg systolic or greater than or equal to 110 mmHg diastolic; hypertension can be confirmed with a short interval (15 min) to facilitate timely antihypertensive therapy
And	
Proteinuria	Greater than or equal to 300 mg per 24-h urine collection
	Protein/creatinine ratio greater than or equal to 0.3
	Dipstick reading of 1+ (use only if other quantitative methods are unavailable)
Or in the absence of proteinuria, new-onset hypertension with new onset of any of the following:	
Thrombocytopenia	Platelet count less than 100,000/uL
Renal insufficiency	Serum creatinine concentrations greater than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal diseases
Impaired liver function	Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual changes	

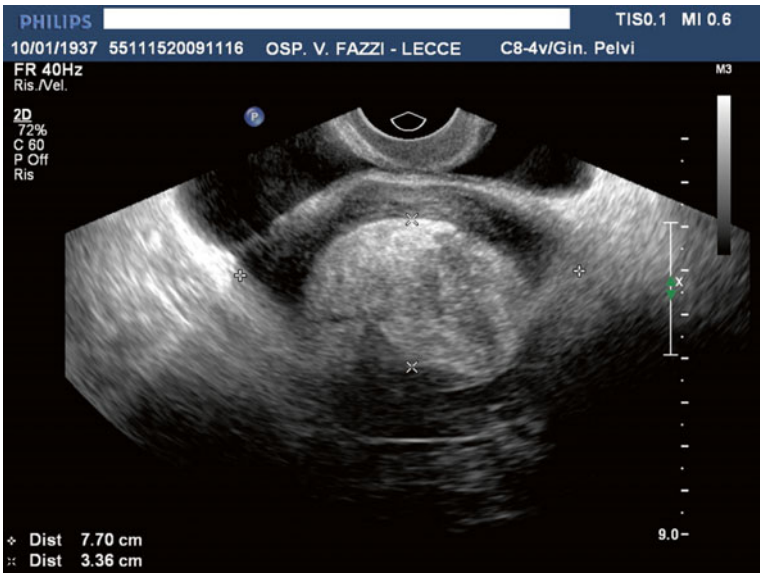

Fig. 15.5 Ultrasonographic transversal image of uterus with gestational trophoblastic disease (GTD) or hydatidiform mole (hyperechogenic part of uterus)

without severe features. Fetal growth restriction and massive proteinuria (>5 g/24 h) are no longer considered diagnostic criteria for severe disease [1].

After the diagnosis of preeclampsia is made, disease severity is assessed. Management options will depend on both the severity of the disease and the gestational age at diagnosis. As preeclampsia is seldom encountered in the first half of pregnancy, detailed management options will not be discussed in this chapter [1]. The development of preeclampsia prior to 20 weeks is extremely rare. If preeclampsia occurs in the first half of pregnancy, the diagnosis of either gestational trophoblastic disease (GTD) or mirror syndrome should be considered. A beta-human chorionic gonadotropin (hCG) and ultrasound should be performed promptly.

GTD or hydatidiform mole (Fig. 15.5) can present with all the typical hallmarks of preeclampsia including hypertension, end-organ damage, and proteinuria. Rare cases of eclampsia have also been reported. Preeclampsia as a sequelae of GTD is more often a result of complete molar pregnancies (46XX or XY); however, preeclampsia can occur with partial moles (69XXX or XXY) and choriocarcinoma (Fig. 15.6) as well. Preeclampsia associated with GTD has declined over the past 40 years secondary to earlier diagnosis and treatment. The mainstay of diagnoses of GTD is via beta-HCG levels and ultrasound. The treatment of GTD is either by uterine evacuation (Fig. 15.7) or hysterectomy, depending on the patient's desire for future fertility. Some patients will also require chemotherapy depending on disease persistence and extent. Similar to preeclampsia that occurs in the latter part of pregnancy, evacuation of uterine contents results in resolution of the preeclampsia disease process [12–23].

Mirror syndrome, also known as Ballantyne syndrome, is a rare condition defined as the development of preeclampsia-

like symptoms in association with fetal hydrops. This syndrome can manifest early in pregnancy and be associated with severe signs and symptoms (features) of preeclampsia. Cases of eclampsia have also been reported. The gestational age at diagnosis usually ranges from 22.5 to 27.8 weeks of gestation. Maternal edema, which occurs commonly and is often impressive, is said to mirror the hydropic fetus. According to a systemic review conducted by Braun et al. that included 56 reported cases, edema was encountered most commonly and seen in 80–100% of patients. Blood pressure elevation and proteinuria were found in 78 % and 20–56 % of patients, respectively. The majority of cases were attributed to fetal malformations (Fig. 15.8) and fetal or placental tumors (Fig. 15.9) (37.5 %) followed by Rh isoimmunization (29 %). Twin-to-twin transfusion syndrome accounted for 18 % of cases and viral infections accounted for 16 % of the cases [2, 24–30].

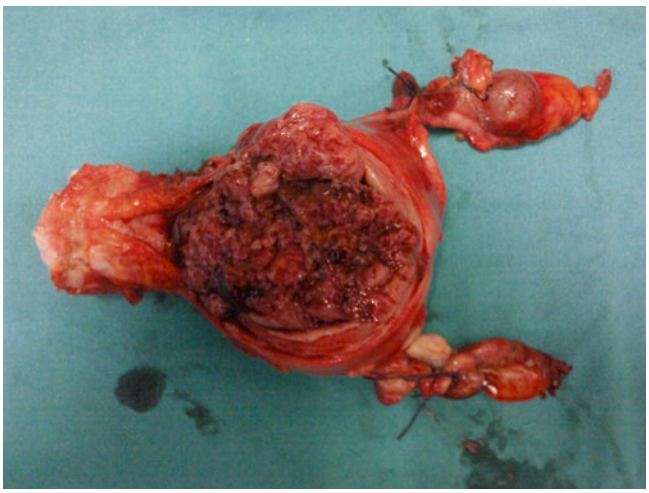

Fig. 15.6 Uterine hysterectomy for a choriocarcinoma (showed by opening of anterior uterine wall)

Patients with mirror syndrome experience some of the signs and symptoms of preeclampsia as described above. However, some of the lab abnormalities and ultrasound findings found in patients with mirror syndrome differ from those with preeclampsia. Hemodilution and polyhydramnios are found in patients with mirror syndrome as opposed to the findings of hemoconcentration and oligohydramnios seen in patients with preeclampsia. Consultation with a maternal-fetal medicine subspecialist is recommended as treatment options may vary depending on the cause of the fetal hydrops and the severity of the disease. Delivery may be the recommended treatment for some patients with mirror syndrome. Resolution of maternal symptoms usually occurs within 4.8–13.5 days after delivery [25, 27–30].

Eclampsia, the occurrence of new-onset grand mal seizures in a pregnant woman that cannot be attributed to another cause, is a severe manifestation of preeclampsia. Unfortunately, occurrence of seizures cannot be predicted by the level of blood pressure elevation, proteinuria, or degree of derangement of laboratory values [1, 2].

The only known curative treatment for eclampsia is delivery after stabilization. In the absence of contraindication such as severe renal compromise, intravenous magnesium sulfate is recommended to stop ongoing seizure activity and prevent further seizures.

Diazepam (Valium) or phenytoin (Dilantin) can be used with caution if magnesium sulfate is unavailable or contraindicated or if seizures recur; however, these medications are less effective than magnesium sulfate [1, 2].

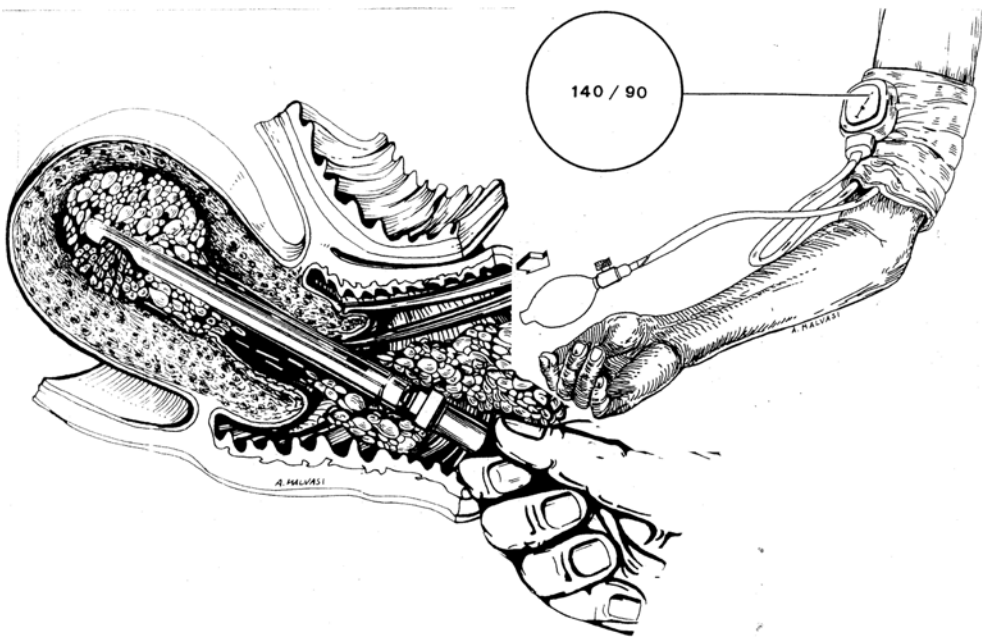

Fig. 15.7 The image shows a uterine evacuation, by Karman cannula, for gestational trophoblastic disease (GTD) or hydatidiform mole

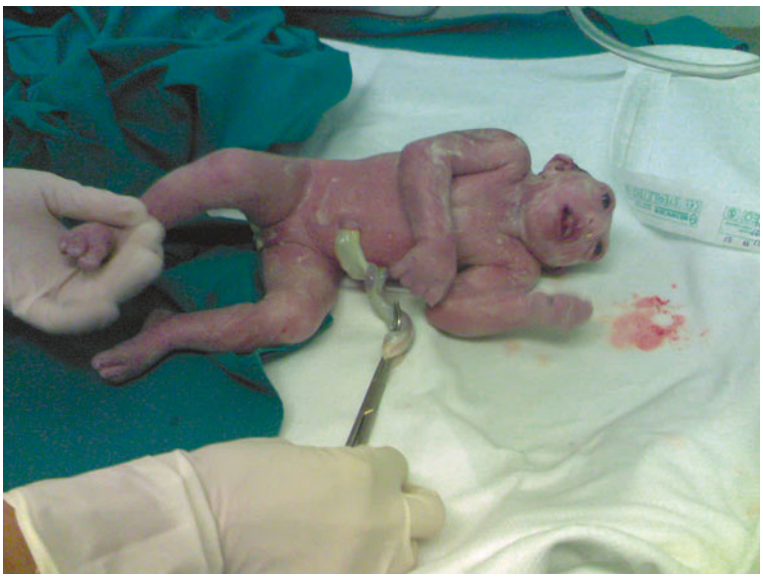

Fig. 15.8 Photos of anencephalic fetuses born to the 34th week in a patient with severe hypertension, polyhydramnios, and abruptio placenta

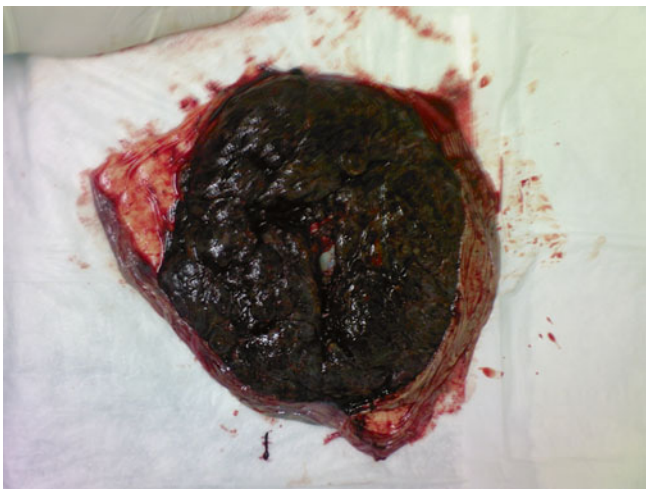

Fig. 15.9 Placenta with placental tumor (with atypical vascular invasion and atypical hyperplasia)

HELLP syndrome is a specific form of preeclampsia/eclampsia that is characterized by the presence of (Fig. 15.10):

- Hemolysis
- Elevated liver enzymes
- Low platelet count

Like preeclampsia, HELLP syndrome is usually a disease of the third trimester.

When HELLP syndrome occurs in the first half of pregnancy, it is most commonly associated with other etiologies such as antiphospholipid syndrome or molar pregnancy. Infrequently, HELLP syndrome can occur prior to 25 weeks of gestation without any secondary contributing factors [31–35].

Delivery is the only definitive cure for HELLP syndrome. Delivery should be undertaken soon after initial maternal stabilization for women with HELLP syndrome regardless of gestational age or likelihood of fetal viability [1].

Maternal stabilization involves treatment of severe-range blood pressures and magnesium sulfate for seizure prophylaxis. Consideration should be given to administration of dexamethasone per the Mississippi protocol [35, 36].

Like previously mentioned, when preeclampsia, eclampsia, or HELLP syndrome is encountered prior to the gestational age of fetal viability, delivery is recommended shortly after initial maternal stabilization.

Delivery is recommended for the safety and well-being of the mother. This can be accomplished either medically or surgically. The mode of delivery is dependent on the gestational age of the fetal-maternal condition, patient preference, and availability of resources.

Regardless of choice, the goal is to achieve a safe and efficient delivery [1, 37, 38].

Distinguishing preeclampsia apart from a lupus flare can pose a diagnostic dilemma, since a lot of overlap exists between the two (i.e., hypertension, proteinuria, and edema). Usually, lupus flares are associated with a low serum complement, rising levels of anti-DsDNA antibody, and erythrocyte casts. Normal complement swings the pendulum in favor of preeclampsia as does rapid worsening of symptoms. When symptoms occur prior to 20 weeks, a lupus flare is more likely to be the correct diagnosis [2, 39, 40].

15.8 Chronic Hypertension with Superimposed Preeclampsia

Patients with chronic hypertension are at increased risk of developing preeclampsia during the course of pregnancy. It is reported that up to one in four pregnant patients with

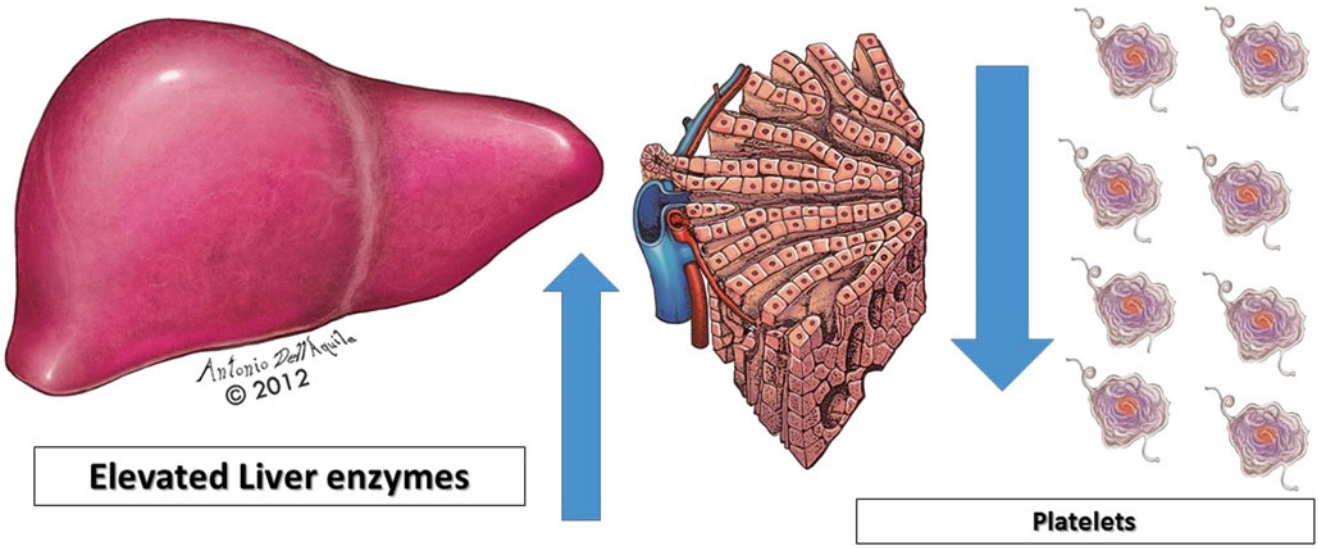

Fig. 15.10 HELLP syndrome is a specific form of preeclampsia/eclampsia that is characterized by hemolysis, elevated liver enzymes, and low platelet count

chronic hypertension will develop superimposed preeclampsia at some point during pregnancy [1, 5].

Establishing the diagnosis of superimposed preeclampsia is challenging, as it is often difficult to distinguish worsening chronic hypertension from developing preeclampsia. Differentiating the two is essential as management options and maternal and fetal complications differ. The diagnosis of superimposed preeclampsia is likely in the following scenarios [1]:

A sudden increase in BP that was previously well controlled or increases in antihypertensive medication(s) required to control blood pressure

New-onset proteinuria or sudden increase in proteinuria in a woman with known proteinuria before or in early pregnancy

The above distinguishing features only highlight the importance of obtaining baseline labs and blood pressure measurements as early as possible in pregnancy. The baseline labs, BP measurements, and 24-h urine protein collection are essential to serve as a baseline for comparison later during gestation.

15.9 Screening for Secondary Causes

Secondary hypertension accounts for approximately 5–10% of hypertensive disorders outside of pregnancy. It is important for the clinician to consider the possibility of secondary causes of hypertension in early pregnancy hypertension as the underlying etiology is often treatable. Secondary causes of hypertension need to be considered in certain pregnant women, and if the etiology is found and corrected, pregnancy outcomes will often improve [1, 2, 10].

Healthcare providers need to pay close attention to patients' symptoms, physical exam findings, imaging studies, and/or lab evaluations that may indicate a secondary cause of hypertension. One must remember that the symptoms may be vague or subtle. It is also important to review the patient's medications and diet, as certain medications and dietary supplements may be responsible for the elevated blood pressures.

Some of the findings on history and physical exam that should prompt further workup include [1, 2, 10]:

- Age less than 35 in non-obese, non-African-American women without a family history of hypertension
- Difficult to control blood pressures despite multiple medications and patient compliance
- Strong family history of renal disease
- Flushing and sweating
- Elevated serum creatinine (>1.1 mg/dl)
- Non-medication-induced hypokalemia (potassium <3.0 mEq/l)
- Renal bruit on abdominal auscultation
- Arm-to-leg systolic blood pressure measurement discrepancy or absent femoral pulses

Once secondary hypertension is suspected, referral to a hypertension specialist is recommended as the diagnostic tests and criteria are not well agreed upon and can vary. It is also worthy to note that apart from suspected renovascular hypertension and pheochromocytoma, which are associated with adverse pregnancy outcomes, there is a tendency to delay thorough evaluation and definitive treatment until postpartum.

This minimizes the diagnostic risk and eliminates the diagnostic confusion that can occur from the overlap between these conditions and the physiologic changes of pregnancy [1, 2].

Listed below are some commonly encountered secondary causes of hypertension (Table 15.1).

15.9.1 Kidney Disease

Renal disease (Fig. 15.11) is the most common identifiable cause of secondary hypertension. It significantly affects pregnancy. Renal disease is associated with adverse maternal and fetal outcomes, which is proportional to the degree of kidney damage. Renal disease is often associated with either a strong family history or comorbidities known to cause kidney damage (e.g., diabetes mellitus and systemic lupus erythematosus). Evidence of chronic kidney disease is elicited via abnormal kidney function tests (elevated serum creatinine) or proteinuria. Once proteinuria is identified, it needs to be quantified. A renal ultrasound should be also performed. Referral to a specialist is advised [1, 2].

15.9.2 Thyroid Dysfunction

Thyroid dysfunction should be suspected in the presence of any suggestive symptoms of either hypothyroidism (e.g., bradycardia, cold intolerance, constipation, weight gain) or hyperthyroidism (e.g., tachycardia, heat intolerance, weight loss) (Fig. 15.12). A TSH level should be checked if thyroid dysfunction is suspected. TSH is considered sensitive for both hypo- and hyperthyroidism, and management should then be directed accordingly. Interestingly, hypothyroidism mainly affects the diastolic blood pressure, while hyperthyroidism exerts an effect on the systolic blood pressure [10, 41].

15.9.3 Primary Aldosteronism

Suspicion for this condition should be raised in the presence of both hypertension and non-medication-induced hypokalemia. The initial recommended test is the measurement of both aldosterone and renin. The aldosterone/renin ratio is then calculated. If this condition is suspected, referral to an endocrinologist is strongly recommended [10, 42, 43].

15.9.4 Obstructive Sleep Apnea

Secondary hypertension can be attributed to obstructive sleep apnea (OSA) (Fig. 15.13). This should be suspected in obese patients or in those that have apneic episodes during sleep or constantly complain of daytime sleepiness. Sometimes, the only complaint is the partner reporting loud snoring. Diagnosis is made through a sleep study [10, 44].

15.9.5 Cushing Syndrome

Suspicion for this condition should be raised in the presence of any of the following physical findings: buffalo hump, central obesity, moon facies, and striae. It is important to ask

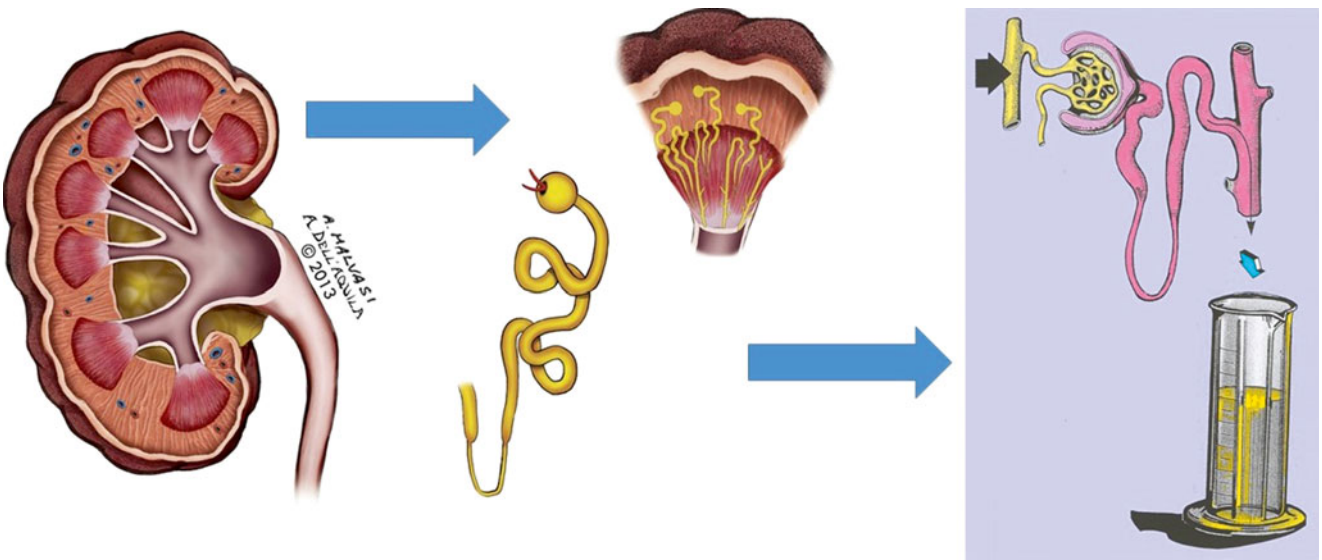

Fig. 15.11 Renovascular hypertension: kidney on the *left*, pathological nephron in the *center*, proteinuria and abnormal kidney function on the *right*

about medication history to rule out iatrogenic causes of hypercortisolism. Initial tests include 24-h urine cortisol, low-dose dexamethasone or late-night salivary cortisol tests. Evaluation is best left to endocrinologists when this condition is suspected [10].

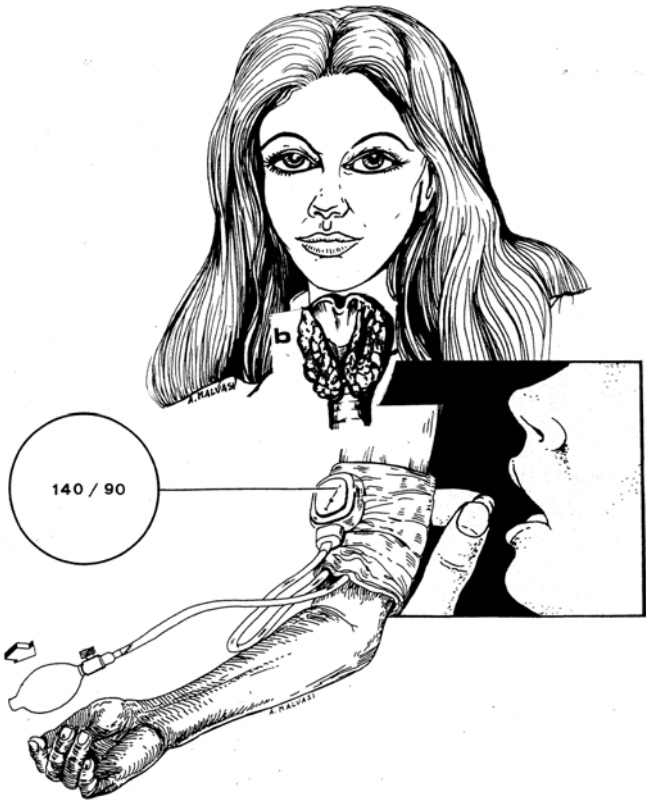

Fig. 15.12 Pregnant with hyperthyroidism and hypertension

15.9.6 Renal Artery Stenosis

This condition should be suspected when a renal artery bruit is auscultated on physical exam. The bruit is an audible high-pitched holosystolic renal artery bruit (Fig. 15.14). Detection of such a bruit has a relative risk of five for renal artery stenosis and should be followed by imaging studies. Commonly used imaging modalities include a CT scan, MRI, and Doppler studies. The risks and benefits of contrast use should be taken into consideration when choosing the modality [1, 2, 10].

15.9.7 Pheochromocytoma

This condition (Fig. 15.15) is associated with flushing, sweating, palpitations, headache, syncope, and labile blood pressures. Testing is done either via measuring metanephrines in a 24-h urine sample or measurement of free metanephrines in the plasma. The treatment is surgical excision of the tumor. If suspected in pregnancy, evaluation and treatment should be undertaken during pregnancy to help minimize the risks associated with an untreated pheochromocytoma [1, 2, 10].

15.9.8 Coarctation of the Aorta

The clue to this diagnosis (Fig. 15.16) lies in the discrepancy between blood pressures at certain anatomic sites (Fig. 15.17). The classic finding includes hypertension in the upper extremities along with low or unobtainable blood pressure in the lower extremities. Delayed femoral pulses may also be found. Imaging is the diagnostic modality of choice and usually is in the form of an MRI. Treatment in pregnancy is recommended after consultation with a specialist [1, 2, 10].

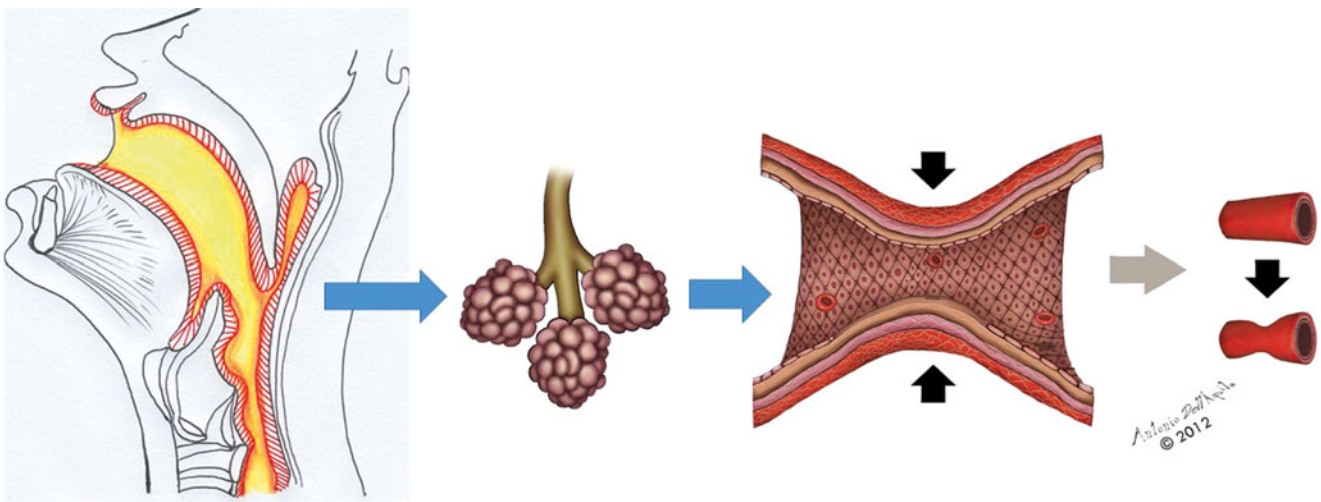

Fig. 15.13 Pregnant with obstructive sleep apnea: on the *left,* apneic episodes during sleep or constantly complain of daytime sleepiness; in the middle, an obstructed pulmonary alveolus; on the *right,* a vasospasm

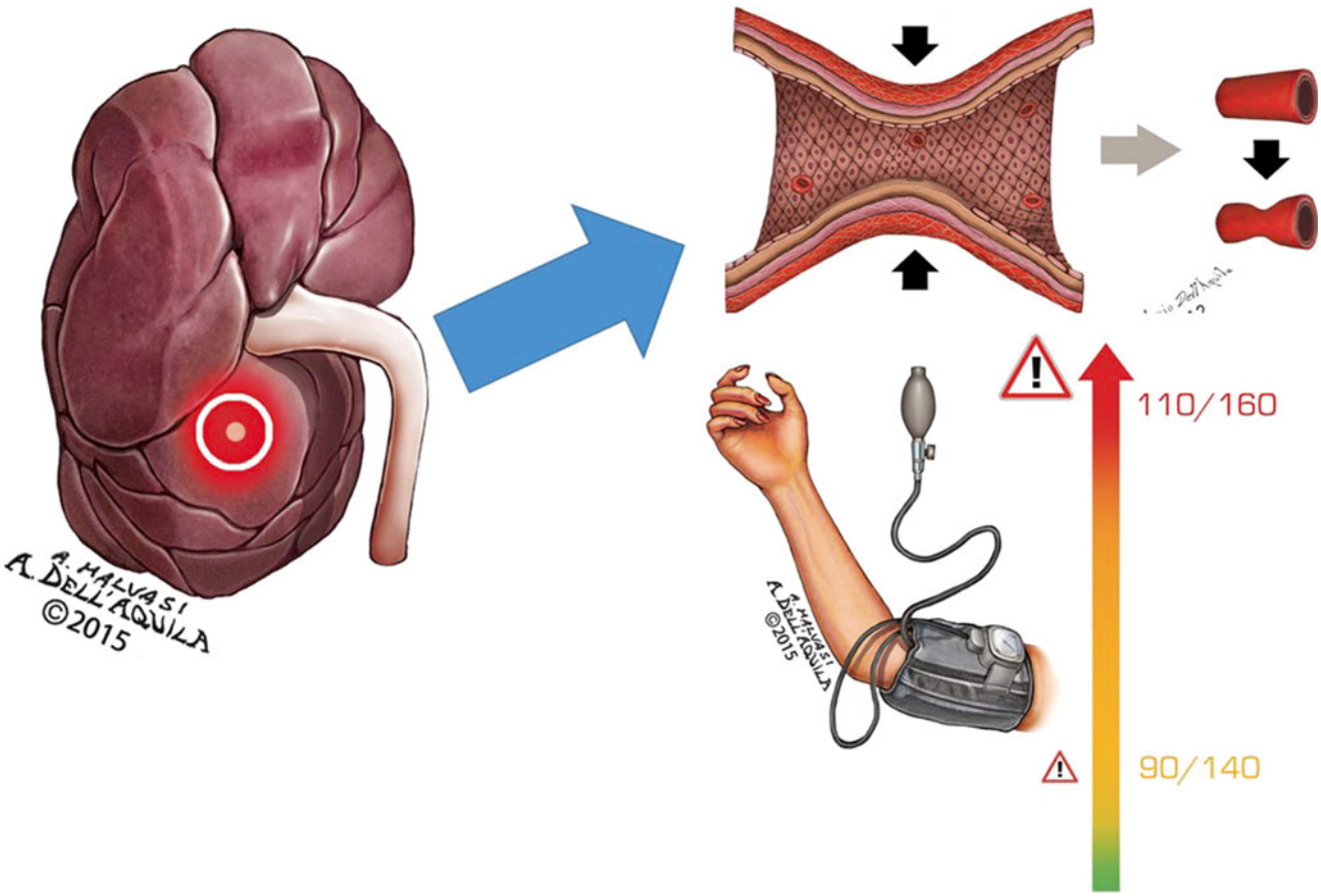

Fig. 15.14 The renal stenosis with hypertension

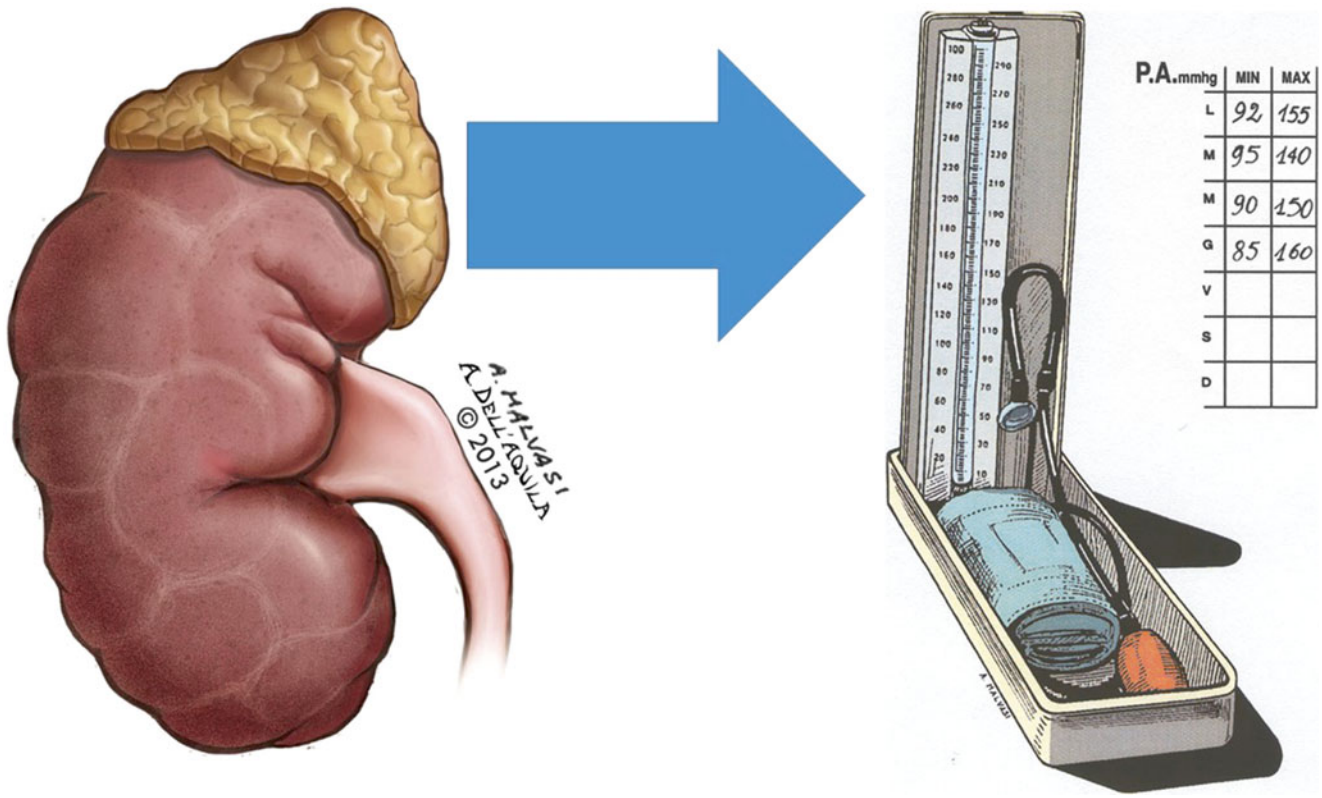

Fig. 15.15 A pheochromocytoma causing hypertension

15.9.9 Drugs and Medications

It is important to ask about medications, supplements, and illicit drug history (Fig. 15.18). Prescription, over-the-counter, and herbal medications may contribute to blood pressure changes. Illicit drugs may also cause acute hypertension.

Some drugs known to affect blood pressure include decongestants (pseudoephedrine), psychiatric medications (TCAs and SSRIs), nonsteroidal anti-inflammatory medications, and steroids. Illicit drugs such as amphetamines and cocaine may cause elevated blood pressures. Herbal medications like ginseng also affect blood pressure. Licorice is also known to cause hypertension as well as hypokalemia [2, 10, 45].

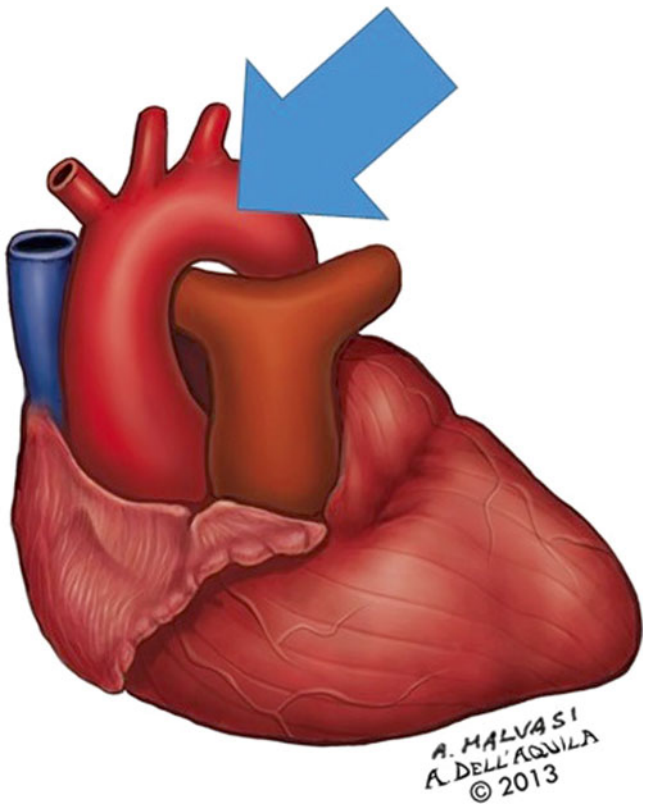

Fig. 15.16 A coarctation of the aorta

15.10 Management of Hypertensive Disorders in Pregnancy

Management strategies are multifaceted and are aimed at preventing complications. However, hypertensive disorders of pregnancy are high risk and complications often occur albeit appropriate treatment. It is critical to know and recognize the various complications that may occur in hypertensive disorders of pregnancy so timely treatment can be initiated. The management of hypertension in pregnancy depends on the type of hypertensive disorder, severity of hypertension, gestational age, maternal comorbidities, and maternal and fetal status.

Outside of pregnancy, weight loss, exercise, and dietary modifications have been shown to improve blood pressure, decrease complication rates and disease progression. The outcomes of these regimens have not been clearly demonstrated in pregnancy in part due to the lack of quality studies. At the present time, the American College of Obstetricians and Gynecologists (ACOG) task force does not recommend weight loss or extremely low sodium diets (<100 mEq/d) in the management of chronic hypertension in pregnancy. The ACOG task force also does not recommend sodium restriction, bed rest, or the restriction of physical activity for the primary prevention of preeclampsia [1].

Pregnant women with persistent severe-range blood pressures defined as a systolic blood pressure of 160 mmHg or higher and/or a diastolic of 105 mmHg or higher require immediate treatment utilizing intravenous labetalol, hydrala-

Fig. 15.17 The coarctation of the aorta clinical diagnosis: discrepancy between blood pressures at certain anatomic sites

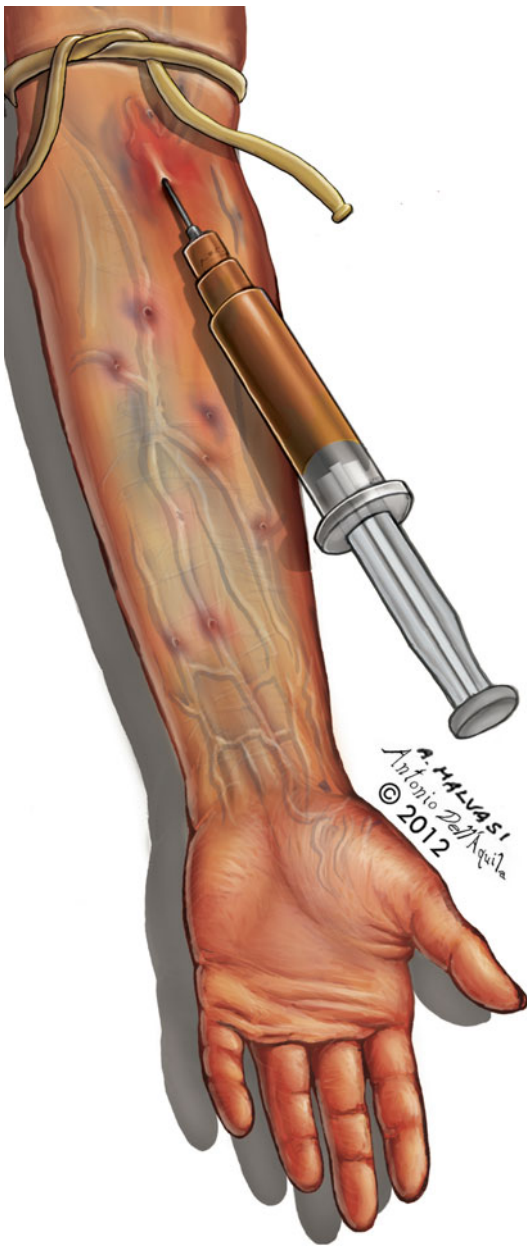

Fig. 15.18 Arm of addict patient injecting illicit drugs during pregnancy

zine, or oral nifedipine as described in ACOG Committee Opinion 623 [46]. However, controversy exists surrounding the management of mild blood pressure elevation in pregnancy. The optimal blood pressure needed to treat in order to decrease adverse maternal and fetal outcomes in pregnancy remains elusive.

Evidence is conflicting and non-conclusive regarding the management of mild blood pressure elevations. Anukumah et al. reported an improvement in adverse maternal and fetal outcomes when blood pressure was lowered below 140/90 mmHg [1, 2, 47]. There was an overall reduction in preterm birth, preeclampsia, and small for gestational age infants. However, a 2007 Cochrane review (46 trials, 4282 pregnant women) did not show improvement in the aforementioned outcomes. This meta-analysis did see improvement in the rate of progression to severe disease [1, 2, 48].

The decision to initiate therapy ultimately depends upon the benefit-to-risk ratio. Does the maternal benefit of treatment outweigh the potential fetal risk of the medication? Secondary to the lack of conclusive evidence showing clear benefit of treatment of mild range blood pressures and the concerns about the safety and possible teratogenic effect of treatment, the majority opinion recommends against initiating antihypertensive therapy with mild blood pressure elevations (140–159 mmHg/90–104 mmHg) unless other comorbidities exist. This recommendation mainly stems from the lack of strong evidence showing benefit of treatment, rather than the teratogenic potential of treatment. This recommendation may change as new studies emerge [1, 2, 5].

Patients already on antihypertensive medications should continue them as long as the medication is considered safe to use in pregnancy (Fig. 15.19); otherwise, a safer alternative should be chosen. Ideally, this should be done during preconception counseling or as early as possible in pregnancy to minimize teratogenic potential [1, 2].

For the nonurgent treatment of hypertension (long-term control) in pregnancy, the following medications are considered first line [1, 2]:

- Methyldopa (oral)
- Labetalol (oral)
- Nifedipine (oral)

Diuretics should be used as second-line medications due to their potential effect on plasma volume. If diuretics are part of a prepregnancy program of blood pressure control, their use can be continued during pregnancy. The initiation of diuretics as adjunctive therapy with antihypertensives poses a hazard to the fetus when there is evidence of placental insufficiency. Angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB) should be avoided in pregnancy secondary to the association with fetal renal agenesis and dysfunction [1, 2, 49–54].

In the instance where urgent blood pressure control is needed (immediate control), the choice of medications depends upon the clinical setting, medication availability, and the comfort level of the provider. In the rare occurrence that blood pressure is not controlled using the recommended medications (see below), consultation with a specialist is advised. The recommended medications include [1, 46, 55]:

- Labetalol (IV)
- Hydralazine (IV)
- Nifedipine (oral)

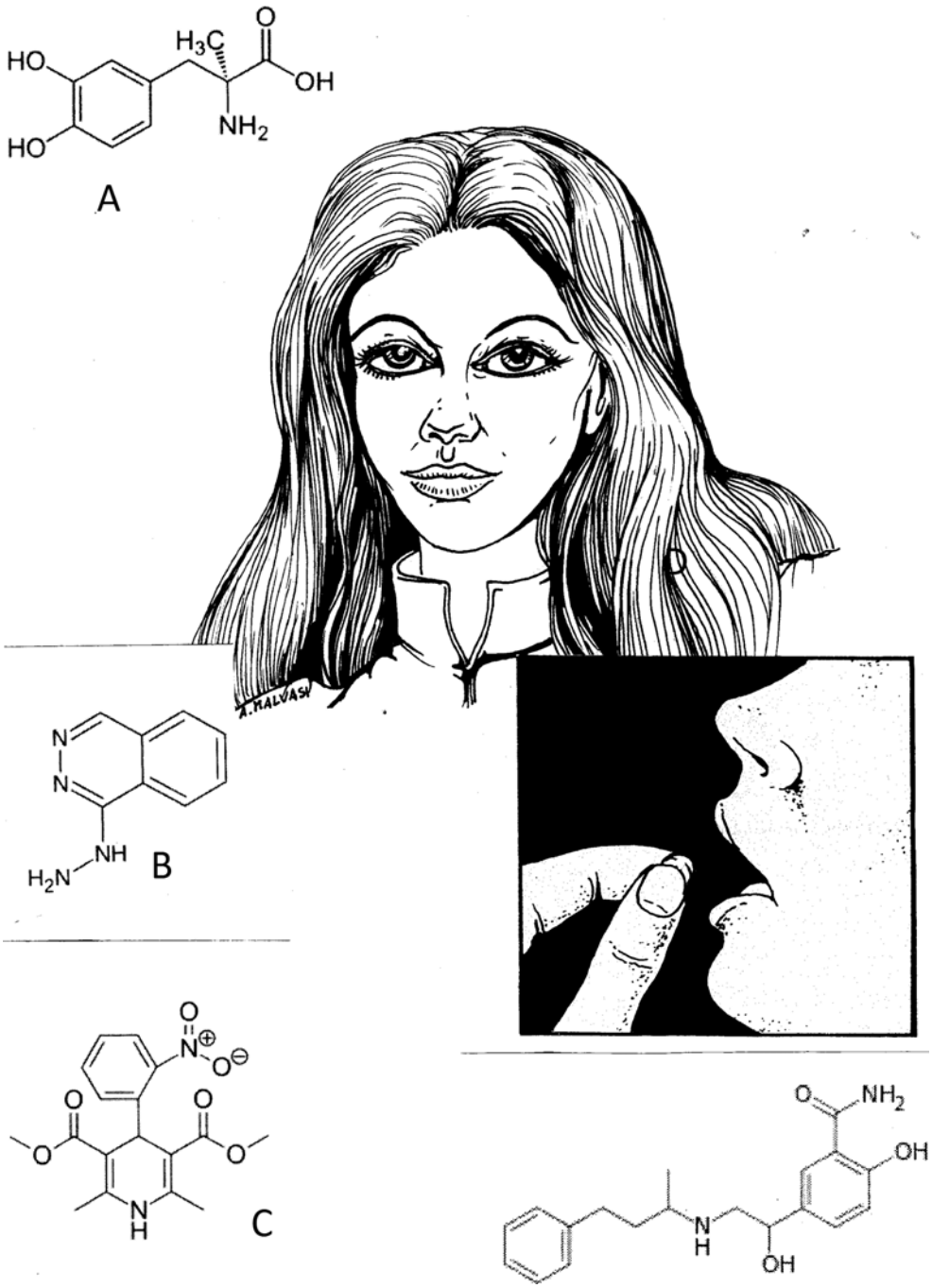

Fig. 15.19 The common gestational drugs in hypertension: (**a**) methyldopa; (**b**) hydralazine; (**c**) nifedipine; (**d**) labetalol

15.10.1 Methyldopa

Methyldopa is a central-acting alpha agonist. It has a long track record of safety and is the only drug that demonstrates safety with long-term follow-up of children. Methyldopa may be less effective in controlling severe-range blood pressures than the other recommended antihypertensive medications. It is not recommended for urgent control of blood pressures [56, 57].

15.10.2 Labetalol

Labetalol is a combined alpha- and beta-blocker. It can be safely used in pregnancy for the treatment of both acute and chronic blood pressure elevation. Concern for fetal growth restriction does exist; however, studies are inconclusive and contradictory with the majority of evidence not showing an association [2, 58–62].

15.10.3 Nifedipine

Nifedipine is a calcium channel blocker that is commonly used as first-line treatment of hypertension in pregnancy. Nifedipine should be used with caution in patients receiving magnesium sulfate as there is a theoretical risk of hypotension and neuromuscular blockade when combined [1, 63].

15.10.4 Hydralazine

Hydralazine is a peripheral vasodilator that is very effective in the urgent treatment of blood pressure elevation. Hydralazine can cause reflex tachycardia as a result of peripheral vasodilation [1, 2].

15.11 Adverse Maternal and Fetal Outcomes

Pregnant woman with elevated blood pressure is at an increased risk of many adverse pregnancy outcomes, both maternal and fetal. The development of such complications varies depending on many factors such as the duration of chronic hypertension, extent of end-organ damage, compliance with prenatal care, and disease severity [1, 2, 5].

With that in mind, the rate of development of superimposed preeclampsia and abruptio placenta can range anywhere from 10 to 50 % and 0.7–10 %, respectively. Some maternal complications are potentially life threatening and include hemorrhagic stroke (Fig. 15.20), heart failure (Fig. 15.21), pulmonary edema (Fig. 15.22), hypertensive encephalopathy, retinopathy and acute renal failure, or acceleration of end-organ damage. The risk of cesarean delivery (odds ratio [OR] 2.7 with a 95 % confidence interval [2.4–3.0]) and postpartum hemorrhage increases (OR 2.2; 95 % CI, 1.4–3.7), as does that of gestational diabetes (OR 1.8; 95 % CI) when compared to their non-hypertensive counterparts [1, 2, 5, 64–70].

In the presence of maternal hypertension, preterm delivery rates also rise and are reported to be as high as 70 % with severe hypertension and between 12 and 34 % in less severe disease. Small for gestational age (SGA) is also more frequently encountered and varies with disease severity (8–15.5 % for mild and 31–40 % for severe). An overall fourfold increase in perinatal mortality is also noted [1, 2, 5, 67–71].

Another contributor to morbidity is the potential for teratogen exposure for those on antihypertensive medications. When preeclampsia results in preterm delivery or if preeclampsia has occurred in more than one pregnancy, low-dose aspirin administration initiated by the end of the first trimester is recommended in subsequent pregnancies [1].

Fig. 15.20 A pregnant patient with cerebral hemorrhagic stroke

15.12 Summary and Conclusions

Hypertension in pregnancy is a commonly encountered major contributor to maternal and fetal morbidity and mortality. Etiologies, prognoses, outcomes, and management are varied. Establishing the correct diagnosis in a timely fashion allows for appropriate management of the patient and pregnancy, which is instrumental in achieving the best outcome for both mother and fetus. Knowing when to look for secondary causes of hypertension is of equal importance as these can be life threatening and potentially curable. Further studies are needed to establish the blood pressure that is associated with adverse outcome in pregnancy, and until studies emerge, it is only recommended to treat severe-range blood pressures.

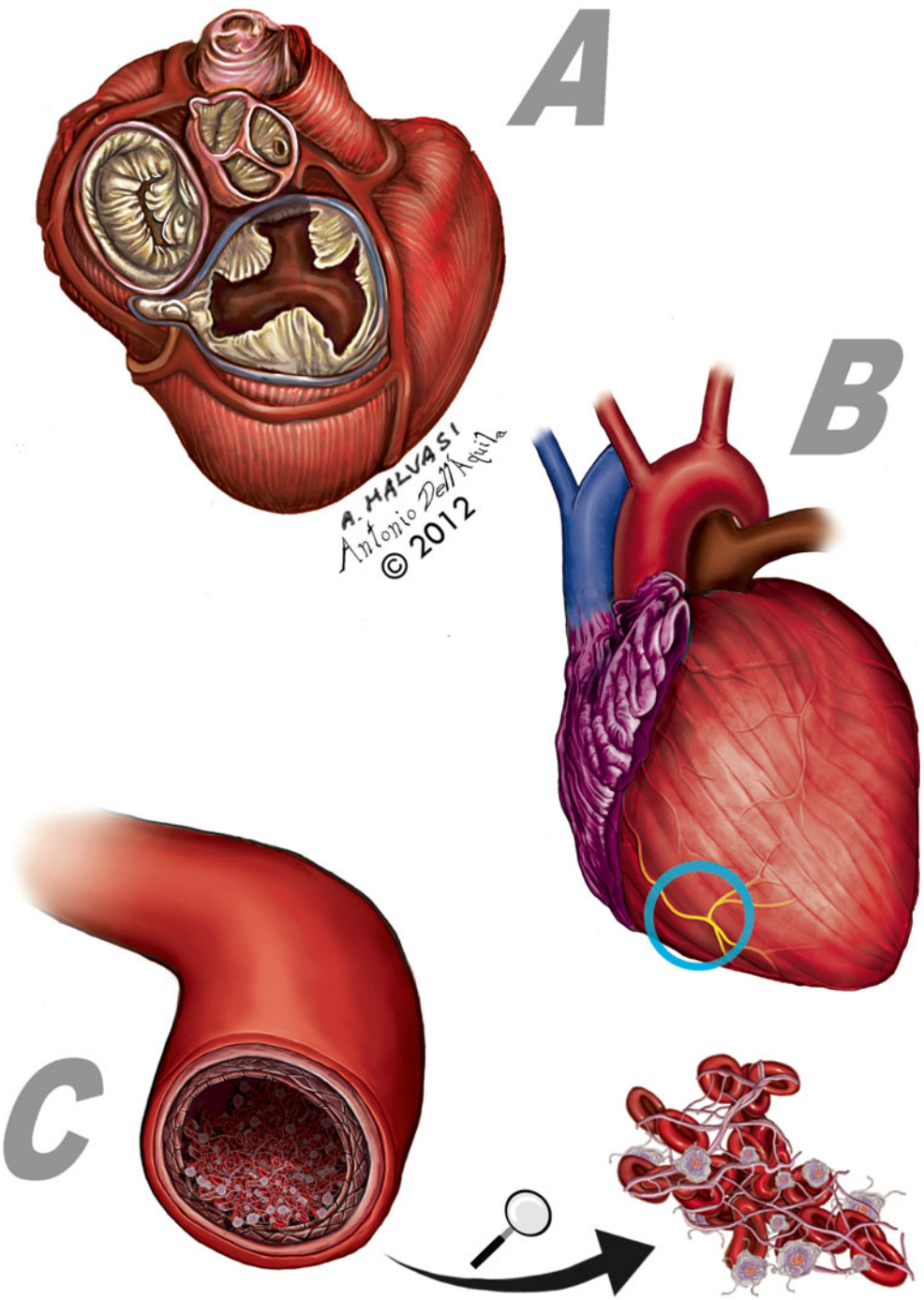

Fig. 15.21 Illustration of heart failure with sequencing phenomena (from the *top* to *bottom*)

Fig. 15.22 Pregnant patient with pulmonary edema

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A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1