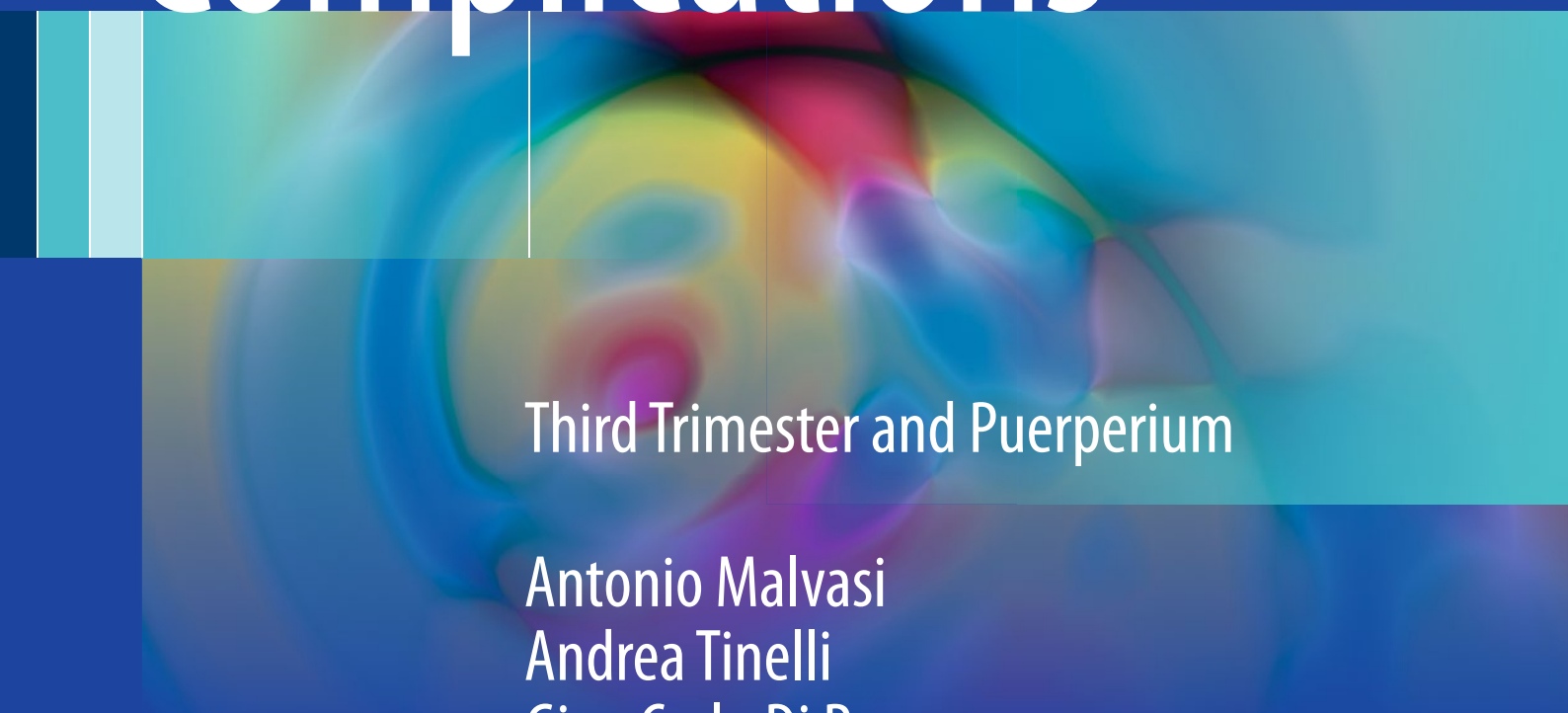
Management and Therapy of Late Pregnancy Complications



Third Trimester and Puerperium

Antonio Malvasi
Andrea Tinelli
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Editors

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This book is dedicated to all those who dedicate their professionalism to care for pregnancies attending the physiological and/or pathological delivery, daily facing the unknown of a successful childbirth, especially without being afraid to face difficulties and always giving the best of themselves.

Andrea Tinelli, Gian Carlo Di Renzo

I dedicate this book to Prof. Vincenzo Traina, prematurely passed, who taught me the basics and beauty of the Ars Ostetrica during his professional life.

Antonio Malvasi

Preface

Pregnancy and birth in humans are events that bring health and happiness independently of the country, the race, and the religious beliefs. Unfortunately, it is not always a happy event; sometimes it gets complicated and ends with fatal or permanent damage either for the mother or for the newborn involved. Currently in the low-income countries, there are more than 90 % of all the complications and mortality due to pregnancy, considering that five countries in the world reach more than 50 % of all the global births. There are still many difficulties to prevent and to bring an appropriate management for all complications, especially those of the second part of the pregnancy and during birth, because it is still missing our capability to understand the etiopathology of many of these complications. In fact, we define the pregnancy complications mostly from their symptoms (hypertension, hyperglycemia) and not from their causes. It is also evident that the enhancement of prevention and prediction will allow to reduce the burden and the consequences of these complications. This book, which is following the previous "twin" book on therapy of early pregnancy complication already published, points to the most common pregnancy and birth complications, but it is opening a window to the prediction and early diagnosis of the major diseases and syndromes. These perspectives can make the difference in outcome of pregnancy both for industrialized countries and for the low-income ones. We are indebted to all the authors for their capacity of synthesis, for the new information, and for their expert contributions to this book. We hope that this book will encourage the reader to aim in the future more to the prediction and prevention than to the management of these complications.

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

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The Placenta as the Mirror of the Foetus

1

Leonardo Resta, Riccardo Rossi, and Ezio Fulcheri

1.1 Introduction

Mammals are called so because of the presence of organs which produce a food (milk) able to satisfy the nutritional needs of their offspring, it being complete in organoleptic components suitable for the immature digestive ability of the whelps. In reality, the new system for generating offspring in mammals includes a prenatal phase when the product of conception is kept inside the mother, where it is protected from adverse conditions such as bad weather, microbes and predators and so can develop, in a relatively brief time, most of the complex functions of an evolved organism. This development does not depend only on the presence of the maternal uterus but even more so on the presence of an organ which is exceptionally good at evolving week by week to adapt itself to the differing needs of the growing embryo-foetus and is able to substitute (even up to birth) various vital activities such as haematopoietic, circulatory, respiratory, endocrine and metabolic functions.

The elimination from the mother of the placenta when its functions are no longer necessary has led the scientific community to almost ignore it, as scientists are naturally more attracted to the investigation of diseases which can harm the life of individuals who are born (and therefore legally existing). Many placental functions and pathologies are still not perfectly known, especially as the human placenta has characteristics strikingly different from those of the animals usually found in the laboratory, so hindering the creation of an animal model upon which to practise. This specificness of the human organ gives us obstetric diseases which are known only in humans, having their origin within the placenta and so still today subject to conjecture. This conjecture means that placental pathology is in continuous evolution, ideas and theories becoming outdated in only a few years yet bringing to light other aspects previously ignored.

The reduction in birth rate, the advancing maternal age and the increase in litigation within medicine have meant that in the last decade much more attention has been given to the physiopathology of the placenta. Many more studies have been carried out with much interesting knowledge acquired which has convinced those who have the right experience and above all the eyes to see that every obstetric incident leaves readable traces within the placenta. Thus today we have many interesting definitions of the placenta as the mirror, or the logbook, or the black box of the pregnancy.

We must remember the placenta is a foetal organ, fabricated by the foetus for itself, with its genetic patrimony for the most part shared by the foetus and with its vascularisation coming from the foetus (the mother supplies the blood, but the blood is returned to the mother). Every day doctors are in error when they register the placenta under the name of the mother. In fact, if the baby is born, the placenta should be registered under the name of the baby, and the report should be given to the neonatologist, with only a copy for the obstetrician. In this way people would be more aware that the placental examination is of more use to the baby in that it can explain or even prevent perinatal disease (infective types) or later conditions inherent to metabolic or psychophysical development.

That said, it is clear that placental development and function are greatly influenced by the conditions of the mother, and many maternal diseases can influence the organ's structure. The study of the placenta can contribute to any investigation of the mother's metabolic or immunitary situations which fall under the responsibility of the obstetrician, especially for future pregnancy.

The role of the father in determining placental functions has until today always been considered marginal, but, on the contrary, as he contributes to the genetic patrimony of the foetus, he can influence the placenta's metabolic

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and immunological functions with repercussions on its physiopathology.

Recently a new idea has been taken further. Knowing that pregnancy can be seen as a stress test for the mother and her metabolic, immunitary, endocrine and cardiovascular systems, also in the case of an apparently completely successful pregnancy, the placenta can show signs of the mother's susceptibility to particular diseases even many years later. Why would it not be the same for the father?

The evolution of knowledge leads us to consider the placenta, other than as a black box, also as a wise indicator of what could happen in the future to the baby, to the mother and perhaps even to the father [1].

With so many pathologies contributing to the placental pattern, you can understand how devilishly complicated it is, and placental pathology cannot be left in the hands of the first pathologist or coroner who shows up.

1.2 Objectives in a Placental Examination

This complex organ, the placenta, has an extremely brief life and is then eliminated, no longer being useful. This discourages the scientist who is not willing to waste time in identifying and understanding mechanisms that cannot be confirmed or corrected, at least at the moment, for the benefit of other organs.

Nonetheless a pathological examination of the placenta has numerous justifications from both a theoretic and a practical point of view:

1. In the case of a major negative event, such as the perinatal death of the product of conception, examination of the cadaver is not enough to fully understand the event's evolution. Today we speak of the "foetal-placental unit" of which, as shown by the name, the placenta is an integral part.
2. When the baby survives, in a good or bad condition, the analyses of any physiopathological anomalies of the placenta are the only ones which allow us to have an idea of the conditions of many of the newborn's functions or to be able to foresee the repercussions that the prenatal environment may have had.
3. Understanding the causes of an unsuccessful outcome can have enormous importance in the management of the inevitable repercussions on the couple's life and on any future plans for pregnancy.
4. In the case of important existing pathologies of the mother, whether metabolic or immunitary or cardiovascular, the study of the placenta can enable us to understand to what extent they have affected the development of the pregnancy, allowing for any specific therapies being followed. To the same extent, previously unknown pathologies can be hypothesised from the results of the analysis of the placenta.

Further to any considerations inherent to the single case under examination, we must not forget that each and every placenta which is subject to analysis can add to the knowledge base of this organ. Owing to the human placenta's specificness and the existence of specific human perinatal pathologies, there are still shortcomings in our awareness of the placenta's mechanisms.

This lack of experience is further complicated by the fact that differing events can combine to determine the same outcome or, vice versa, a single pathology can determine differing results, especially in the case of complications. The analysis of the placenta is different in the case of a pre-existing diabetic state compared to that of diabetes arising during pregnancy, or if it is associated with a vascular disease or hypertension, or if it is complicated by the sudden death of the foetus, or if the disease is recognised and treated or not. Many eventualities and circumstances lead to states which are apparently without explanation so making any reports often confused and contradictory. It is not infrequent, in the literature [2] and in practice, to note how some of the alterations found in the placentas of complicated pregnancies can also be found in the placentas of healthy newborn. Without doubt, in the placenta, as in other organs, adaptive modifications arise, only that we do not know what is the real functional reserve of all the activities that the placenta carries out, and therefore we do not have a clear demarcation between adaptive reactions and pathological reactions which reflect on the metabolism of the foetus. Considering the repercussions that our diagnoses can have, it is the case that the pathologist or scientist keeps within the boundaries of knowledge consolidated from previous observations and uses this to draw any conclusions from the analysis. However, this said, the study of the placenta transcends the single case and allows an increase of knowledge even to overturning long-held beliefs if new observations and experience demonstrate their falseness [3].

1.3 When to Examine the Placenta

The decision to carry out an anatomo-pathological placental examination must today be strictly subject to norms because respecting the guidelines gives protection from any subsequent claims. Some believe that a placental exam should always be required even with no neonatal damage. However, this goes against the policy of the management of cost and also risks overloading the pathological anatomy department as "birth centres" are now organised for high turnover. Others believe that the results from placental analysis are of little use often being inconclusive and therefore should be reserved only for extreme conditions. Another group is happy with a macroscopic assessment in the delivery room to decide which placentas to examine. This decision made by

non-pathologists inevitably limits itself to reporting particulars that have nothing to do with placental physiopathology.

The positive decision for a placental examination is made in the case of:

1. Foetal or neonatal death
2. Malformation
3. Twin births
4. Preterm or post-term birth
5. Intrauterine growth retardation at any moment during pregnancy
6. Any neonatal pathology , including infection
7. Maternal pathology (diabetes, gestosis, hypertension, infection, metrorrhagia in pregnancy, systemic disease of the mother, drug abuse, injury, etc.)
8. Alteration of the adnexa (low or high weight placenta, narrow or macerated umbilical cord, knots and/or constrictions of the funiculus, thickened membranes, premature rupture, oligo-polyhydramnios, etc.)

This basic and schematic table cannot be seen as including all the reasons for placental examination, the prudence of the gynaecologist or obstetrician is paramount. We believe that the placenta should be examined also in cases of previous unsuccessful pregnancy, assisted conception pregnancy, voluntary abortion in the second trimester and any type of emergency in the delivery room.

To avoid an unnecessary increase in workload, the placenta can be kept vacuum sealed and refrigerated for some days until the discharge of the newborn, fixation being carried out if complications appear.

In the case of neonatal emergency, especially infections, it may be useful to carry out a rapid examination of the membranes or the parenchyma. This placental examination is very similar to the procedure usually reserved for organs to be transplanted.

1.4 Development and Structure of the Placenta

Six days after fertilisation, which takes place in the distal part of the salpinx, the fertilised egg reaches the cavity of the body of the uterus, when it has already developed into the blastocystic phase and on its external surface there is a layer of specialised cells (trophoblast) able to link to specific proteins on the external surface of the endometrial cells. The trophoblast allows the penetration of the blastocytes into the thickness of the endometrium and modifies its vascular organisation so creating a suitable habitat for the complete product of conception. Today it is clear that the function of the trophoblast is not limited to the first implantation phase but accompanies the growth of the foetus for all the pregnancy. In particular the trophoblast is able to attack the walls of the spiral arteries (Fig. 1.1) and to progressively destroy the elastic-muscular component of the media so that its replacement with collagen tissue can guarantee a rapid dilation of the vessel according to the functional necessities of rapid growth, without opposing flow. Furthermore, this attack brings the trophoblastic cells inside the lumen leading to the plugging of many vessels around the tenth week (Fig. 1.2).

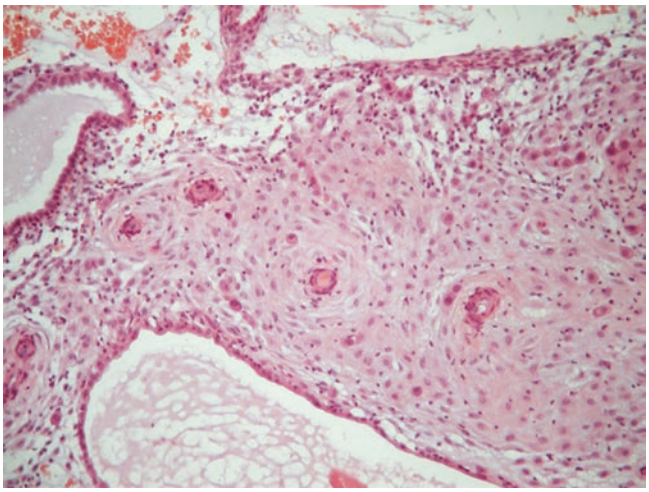

Fig. 1.1 Spiral arteries of the decidua capsularis. The arterial wall, without the action of the trophoblast, preserves the myometrial layer. The lumen is very narrow

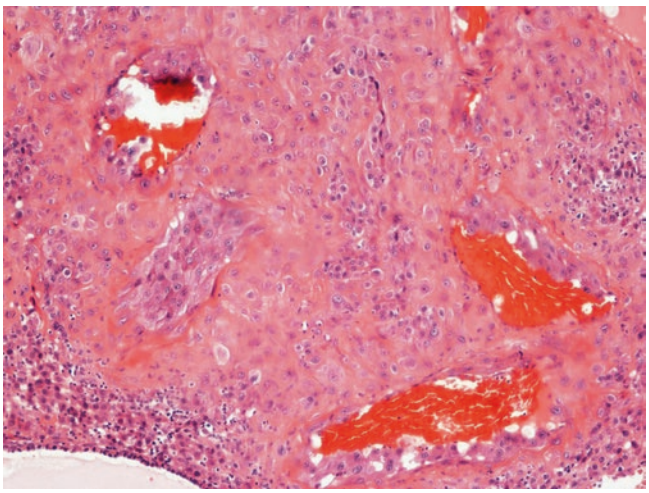

Fig. 1.2 Decidua in an 8-week pregnancy. The interstitium and the arterial wall are invaded by the trophoblast. Trophoblastic cells are present on arterial endothelium and in one artery occlude entirely the lumen

This apparently paradoxical phenomenon has a series of advantages: (i) it reduces the oxidative stress of the foetus in a particular moment of development, (ii) it induces a rapid maturation of the villi in hypoxia, (iii) it expands the peripheral regions of the placenta in the passage to the II trimester,

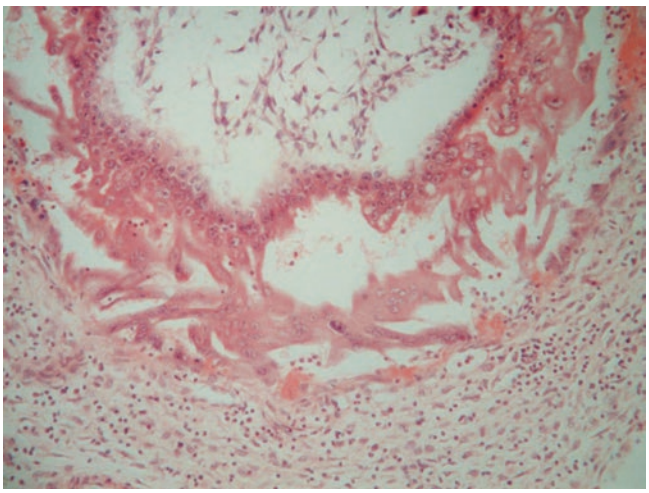

Fig. 1.3 Early stage of a blastocyst in endometrium. The wall of the blastocyst is composed of an internal layer of cytotrophoblast and a thick layer of syncytiotrophoblast in which a complex labyrinth of channel is promptly occupied by maternal blood

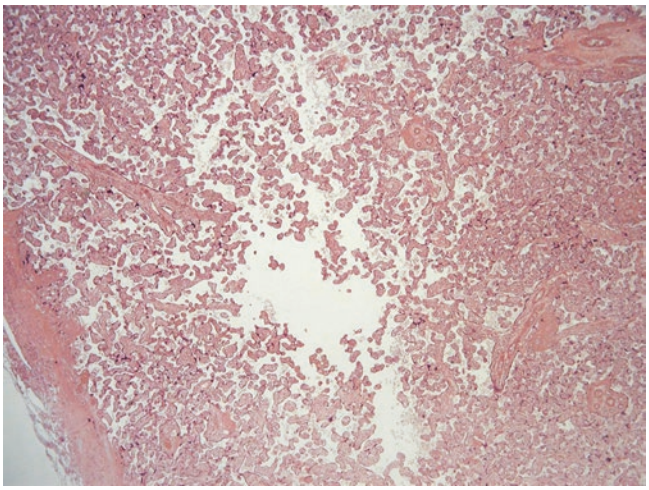

Fig. 1.4 Low magnification of a maternal cotyledon. The haematic lacuna is evident near the centre. Some immature intermediate villi are present around the lacuna

(iv) it allows a more rapid transformation of the arterial wall attacking it both externally and internally, and (v) it allows a progression of the trophoblast against the flow, so progressively extending the transformation of the arterial wall to the vessels of the myometrium.

Intercommunicating clefts appear in the syncytiotrophoblast and these lacunae fill with maternal blood (Fig. 1.3). The columns between the lacunae, originally formed only of the syncytiotrophoblast, now form a central core of cytotrophoblastic cells (primary villus stems), this is followed by a mesenchyme core growth into the stems (secondary villous stems), and finally they are vascularised (tertiary villus). Finally branching occurs and the villi are formed.

The precise description of the placental structure can be found in the specific texts; however, the chorionic plate (on the foetal side) is smooth and shiny due to the presence of amniotic epithelium, and the allantochorionic vessels can be glimpsed which spread from the insertion zone of the funiculus. The maternal side is irregularly separated by deep septa (corresponding to the septa of the decidua) into 16–20 lobules known as maternal cotyledons. The foetal cotyledon is instead the primary stem of a chorionic villus and its branches and sub-branches, that is, the functional unit of the villous tree coming from the chorionic plate. The latter being more numerous than the former, each maternal cotyledon can contain more than one foetal cotyledon.

Near the centre of the maternal cotyledon, the villi are thinned out and form a haematic lacuna (Fig. 1.4) which causes a reduction in the speed of the blood flow and a corresponding reduction in hydrostatic pressure necessary for mother-foetus transfer. It is also the area with the highest levels of oxygen, and therefore the most recent and immature

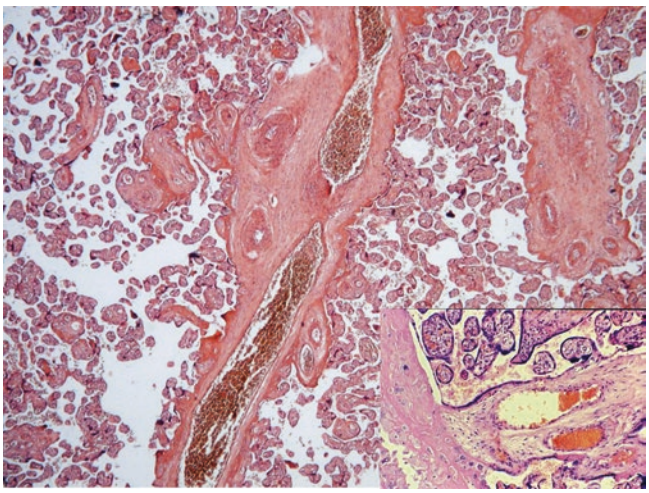

Fig. 1.5 Term placenta. In this picture many principal villi of different sizes are present. All villi are characterised by thick mesenchymal stroma in which two vessels (arteria and vein) are evident. The surface often lacks of the trophoblast, and a layer of fibrin separates the villus by the maternal blood. The size of the villi depends on the degree of ramification of the single villus. In the insertion we observe a principal villus anchoring to the basal fibrinoid layer

villous branching can be found around it. Various villous typologies are found within the placenta:

1. Stem villi (Fig. 1.5): the primary stem with an artery and a vein with a muscular wall, connective tissue and a trophoblast mantle. They can have up to eight orders of branching, reducing in calibre but not in structure. Some are embedded in fibrin and anchored to the basal plate to give stability to the organ.
2. Immature intermediate villi (Fig. 1.6): large villi with a reticulate stroma occupied by active macrophagic Hofbauer cells and capillaries at various distances from

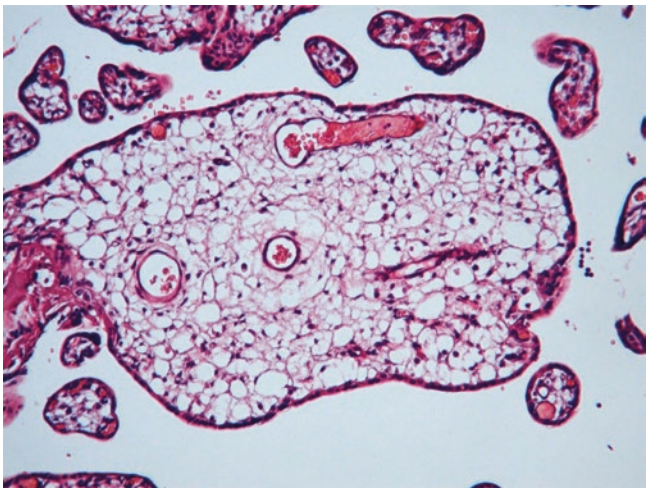

Fig. 1.6 The immature intermediate villus is large, and its stroma shows a reticular shape for the presence of a very complex network of channel. In each lacuna the Hofbauer cells show a dark nucleus anchored by thin cytoplasm projections to the channel wall. The capillary vessels are arranged at different distances from the trophoblast. The maternofoetal changes are possible but in low entity

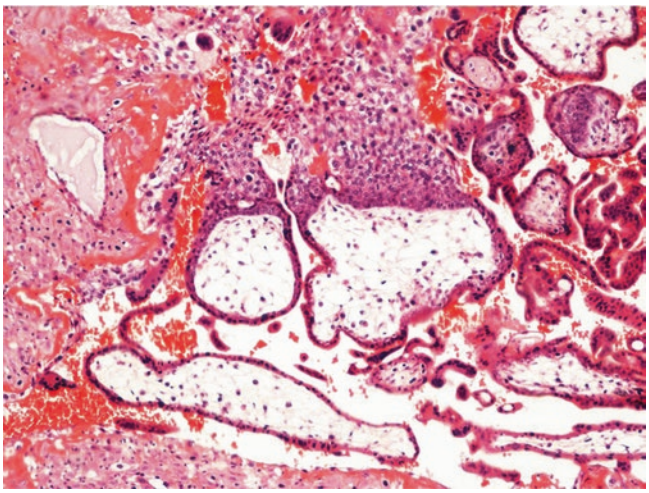

Fig. 1.7 Two mesenchymal villi characterised by a cap of proliferating cytotrophoblast cells, an edematous stroma and absence of vessels

the trophoblast surface. They guarantee transfer in the first phase of pregnancy and continue to branch, maturing into stem villi or mature intermediate villi

3. Mesenchymal villi (Fig. 1.7): they are the first generation of villi becoming immature intermediate villi. Starting as trophoblastic sprouts from the underlying mesenchymal layer they undergo a proliferation of cytotrophoblastic cells within the trophoblast mantle. Capillary formation completes their transformation into new immature intermediate villi.
4. Mature intermediate villi (Fig. 1.8): The reticulate stroma disappears reducing the diameter of the villi, and the capillaries reach the outer mantle of the structure. On the surface and the extremities of the villus, we find the terminal villi.

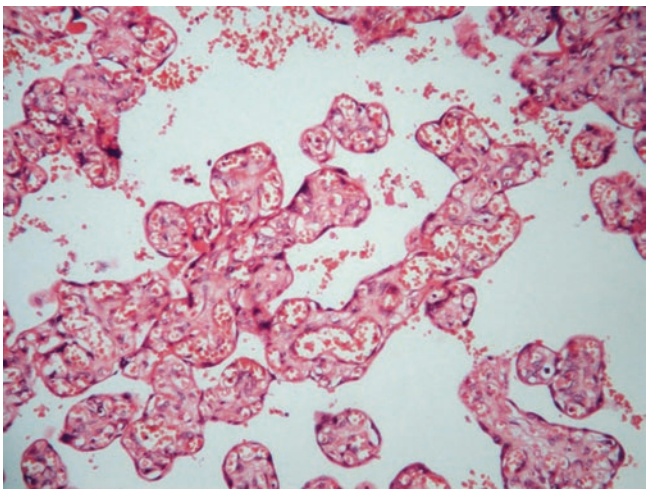

Fig. 1.8 The intermediate mature villi are smaller than the immature ones. Their axes contain expanded capillary vessels. Several term villi are exposed on their surface

5. Term villi (Fig. 1.9): they are formed of looping capillaries (4–6, but in section they seem less) which are very close to the basal membrane of trophoblast so creating the vasculo-syncytial membrane, that is, the optimal structure for maternofoetal transfer.

All types of villi are not always present during the pregnancy. The mature intermediate villi and the terminal villi proliferate in the third trimester to satisfy the increased needs of the foetus, even if around the haematic lacuna we still find immature intermediate and mesenchymal villi to allow for placenta growth. On the maternal side, we find the fibrinoid deposits forming the Rohr and Nitabuch striae which create a physical and immunological barrier and the decidual endometrium infiltrated by extravillous trophoblast.

1.5 Anomalies of Shape, of Structure or of Function?

The understanding of placental pathology has made great strides in recent years both because of demands from clinical research and legal medicine and because of the new genetic and molecular techniques. We now know that many "lesions" over which many words have been spilt are much less important than they seemed. Even modifications of shape, thickness and structure which fascinated traditional pathologists have been found to be of little practical interest.

Modern placental diagnosis, like in all the daily practice of the pathologist, must aim to give a convincing interpretation of the pathological event. For this reason the diagnostic process has to include three phases.

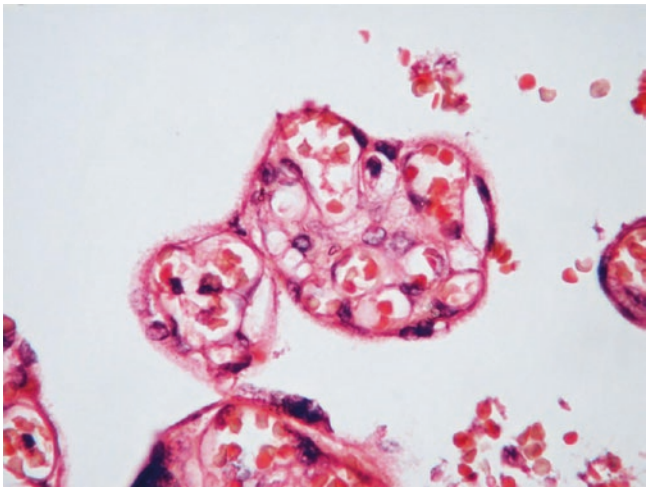

Fig. 1.9 Term villi are composed of some loops of capillary vessels, few interstitium and trophoblast. The dilated vessels are very close to the basal membrane in a region of the trophoblast without nuclei. The distance between foetal and maternal blood is minimal, and the maternofoetal changes reach the maximum of possibility

1. Correct information on the clinical data and perinatal risk: possible maternal causes of foetal damage, age of the pregnancy, foetal weight and evolution of the pregnancy and of the delivery.
2. Correct examination of the placenta: macroscopic assessment, observation of the membrane and the funiculus, evaluation of the lesions for character, age (recent or old), intensity and extension.
3. Correct interpretation for a correct conclusion: assessment of the extent of the damage and its incidence on the evolution of the disease, presence of multiple causal or concausal factors and discriminatory assessment of causal signs from consequent signs. These last observations can account for inappropriate past assessments such as the fact that fibrous obliteration of the stem villi arteries is a consequence of the death of the foetus, not the cause.

From what is written above it becomes clear that a presentation of placental pathology can start only from the solution to specific clinical queries.

1.6 Placental Anomalies Secondary to the Intrauterine Death of the Foetus

The examination of the placenta after a pregnancy complicated by the intrauterine death of the foetus is a classic example when the observer can be misled into confusing "the signs of death", that is, the alterations secondary to foetal death, with the signs actually linked to the cause of death.

An accurate discrimination not only allows us to distinguish between the two phenomena but also can give us information on the time of death which is more accurate than that given by thanatological observations of the foetal autopsy. In fact the thanatological alterations of the foetus are subject to several variables such as the temperature, the quantity of amniotic fluid, the presence of meconium, infections prior or consequent to death and the concurrence of anaemia and/or haemolysis, which drastically interfere in the evolution of the phenomena [4]. Differently, the placenta, which depends on maternal blood for its oxygenation and tropism, at the moment of death of the foetus, begins to show a precise series of events which are correlated to the cessation of foetal circulation [5, 6]. This has enormous value in medical-legal disputes as it allows the objective description of a relatively precise time span for interpretation of time of death of the foetus over and above the subjective opinions of the mother and the obstetrician.

Many of the foetuses suffering an intrauterine death are expelled within the first 24 h, but the exact percentage is not known. Conversely, there have been cases of foetal retention lasting more than a week. The alterations observable in the placenta are for the most part linked to the arrest of foetal circulation and proceed over time from the large vessels of the funiculus to the foetal capillaries. These are joined by lesions caused by the suffering of the vessel walls and of the haematic crasis of the foetus.

In conclusion, based on the literature and on our experience, we can use the following time scale to be able to determine the time passed between the death of the foetus and its expulsion:

(a) After a few hours: "fibromuscular" thickening of the walls of the umbilical arteries (Fig. 1.10) and swelling of the endothelium of the arteries of the stem villi (Fig. 1.11). These aspects, tightly linked to vascular collapse due to cardiac arrest, are non-specific because they are also found in a prolonged afterbirth expulsion.
(b) After 6 h: the start of intracapillary karyorrhexis of the villi (Fig. 1.12). It progresses with time. The start of intimal fibrous sedimentation of the vessels of the stem villi.
(c) After 24–48 h: the start of mineralisation of the villi (a non-specific phenomenon because it can be found in living foetuses with anomalies of the metabolism), the anomalies of the vascular lumina increase (Fig. 1.13), regressive areas of Wharton jelly are observed, and haemoglobinic diffusion begins (Fig. 1.14).
(d) Forty eight hours to 7 days: anomalies of umbilical vessels (loss of nuclei of the muscle wall cells) (Fig. 1.15), endarteritis of principal vessels becomes more and more extensive (Fig. 1.16).

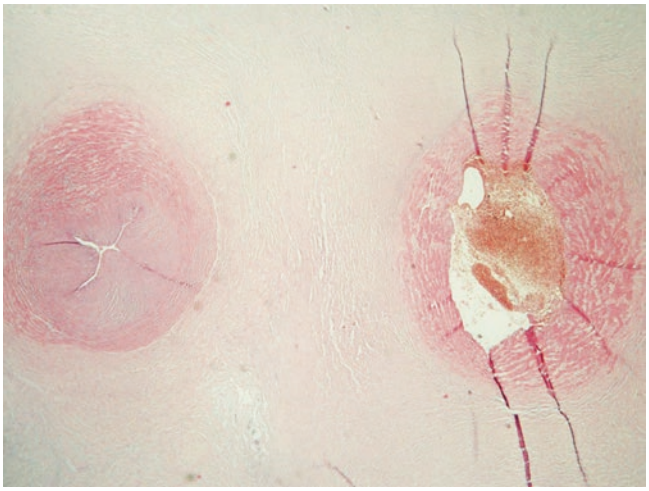

Fig. 1.10 Few hours after the foetal death, the arteries of the umbilical cord are contracted, the lumen is often virtual and the wall is apparently thickened

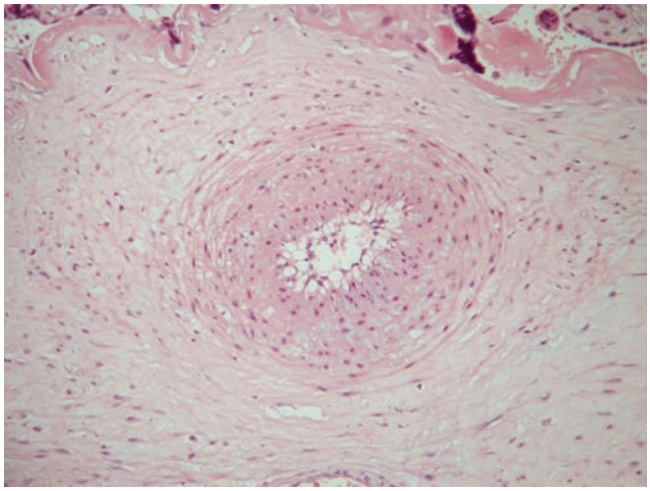

Fig. 1.11 In the stem villi the contracted arteries have an endothelial swelling. This picture was in the past confused with a glycogenic degeneration in diabetic placenta

(e) After 7 days: fibrosis of the villi is more and more compacted (Fig. 1.17).

The above listed alterations, important for the definition of the time of death of the foetus, must not be used to define the cause of death, which must be studied with accuracy and patience to avoid inconclusive diagnostic opinions which suggest that the post-mortem alterations mask the causes of death. The criterion must be that of defining the lesions which are common and synchronous, so leading to retention of the dead foetus, and focal lesions not in line with the time of death, which more probably pertain to its cause.

Defining the cause of death is not considered to be easy. Many observed lesions, especially histologic lesions, can also be present in the healthy placenta, and the level of involvement of the parenchyma must be well analysed. Often a careful macroscopic analysis can be very useful: retroplacental haematoma, velamentous cord insertion with rupture of the membrane, thrombosis of the foetal vessels, extensive infarction, vast haemangioma, constriction of the funiculus, etc.

1.7 Disorders of Maternal or Foetal Circulation

This is discussed in depth in a separate chapter.

1.8 Alterations in Villi Maturation

The maturation of the villi during pregnancy is crucial in that during the third trimester it allows for the enormous increase in maternofoetal transfer, as during this period the weight of the foetus increases dramatically without a corresponding growth of the placenta. As we don't know precisely what factors drive villi maturation, even less is known about any interference in the process. If we add that maturation seems to be disconnected from branching and from the vascularisation of chorionic villi, our lack of understanding of all the factors involved complicates any possible analysis.

We know that the oxygen levels in maternal blood, in the placental bed and in the foetus affect transfer and villi maturation [7]. We also know that particular agonist/antagonist enzymatic balance mechanisms drive maturation. Particular attention has been given to endothelin/NOS, prostaglandins/thromboxane and PDGF-B vs. VEGF. These observations relate to oxygen levels but also to arterial pressure, phlogistic/reactive factors, coagulation state, immunity, etc.

From a practical point of view, the effect to be studied is the comparison of the state of villi in their maturation/branching/vascularisation and the nutritional needs of the foetus based on its age and general conditions. Foetal anaemia is a grave condition in which an unusual level of immaturity can be seen in the villi. This was originally thought to be due only to maternofoetal incompatibility of erythrocyte antigens (foetal erythroblasts), while today it refers to all the conditions of foetal anaemia: viral infections, haemoglobinopathy and idiopathic anaemia. The placenta, very heavy and rosy coloured (Fig. 1.18), under the microscope shows large villi that are not immature intermediate villi as they are much larger, and they do not have a structure which is reticulate but vacuolous with capillaries full of erythroblasts (Fig. 1.19). These are signs of heart failure associated with anaemia and of the effort sustained by the heart, also because of the concurrent foetal anasarca, all leading to cardiac arrest.

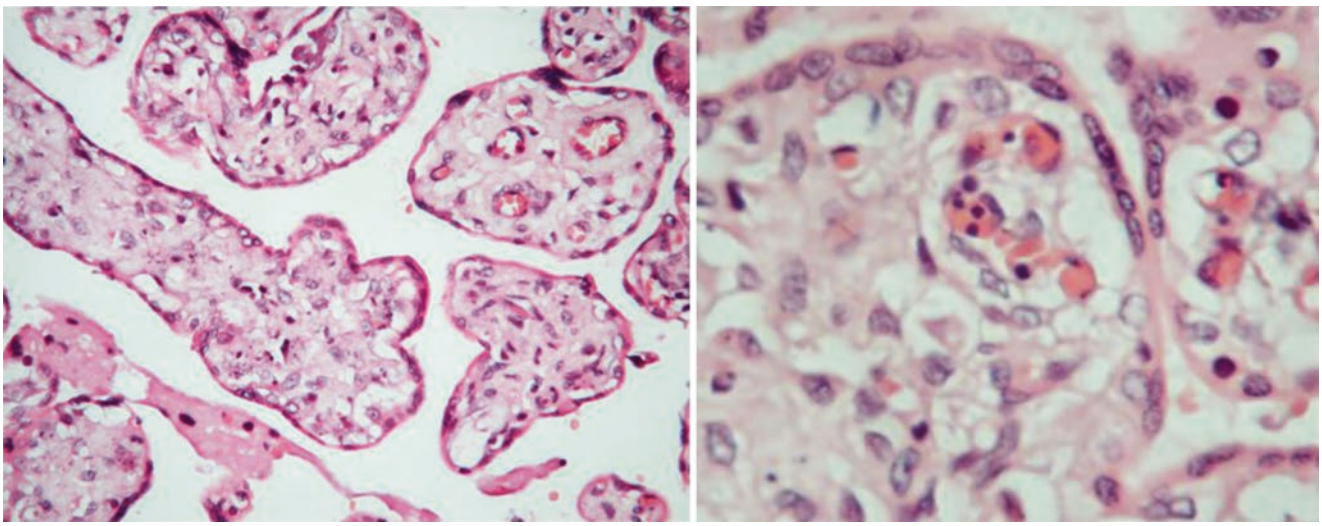

Fig. 1.12 Intravascular karyorrhexis. Nuclear fragments of the leukocytes are present in the lumina of the capillary vessels

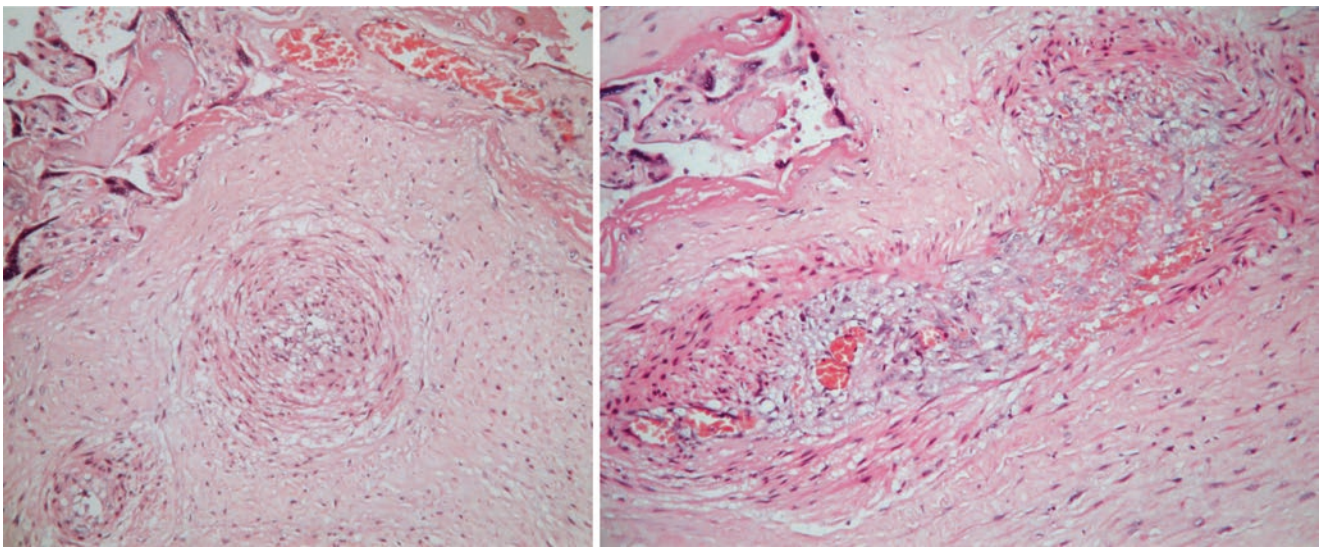

Fig. 1.13 Regressive aspects of the villar arteries, with intimal fibrosis, some days after the foetal death

1.9 Infections

Placental infection does not only mean germs getting to the placenta but also the conditions, many not well known, of an inflammatory infiltrate at different degrees with no identifiable phlogistic agent and so which, in all probability, has a reactive aetiology. In this, the placenta does not much differ from other organs. It is specific of the placenta to put together a histological picture of both the foetal and maternal inflammatory cells (in the sub-chorionic and intervillous spaces).

We can roughly divide infections into two groups, those of the amniochorionic membranes (chorioamnionitis and funisitis), the infective noxa usually arriving ascending from the contiguity of the endometrium and of the endocervix, and those of the villi complex (villitis and perivillitis) which mainly arise from germs arriving in the maternal blood.

Chorioamnionitis (Fig. 1.20), with any funisitis, is a frequent form of placental infection, complicated by both a possible transmission to the foetus in the perinatal period and a risk of cerebral damage due to the action of cytokines activated by phlogosis. The exudate present in the membranes is made up of maternal granulocytes on the chorionic side and of foetal granulocytes on the amniotic side (Fig. 1.21). The seriousness of the infection is classified in three grades [8]: (i) invasion of the fibrin and the contiguous chorionic layers, (ii) invasion of the connective tissue plane of the chorionic plate and (iii) invasion of the connective tissue and

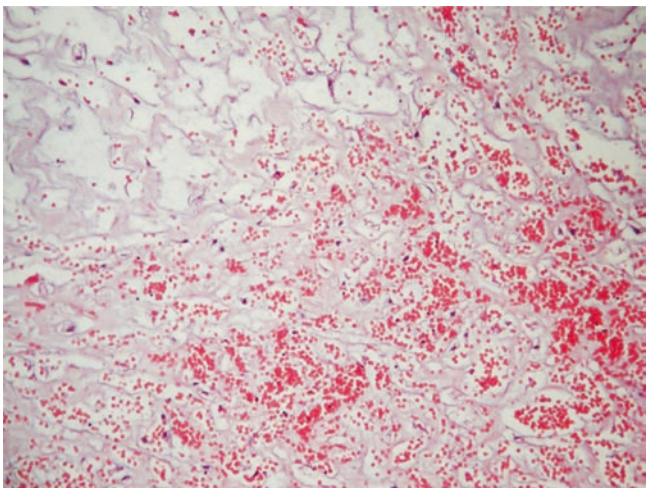

Fig. 1.14 Diffusion of the erythrocytes in the Wharton jelly of the umbilical cord. Macroscopically the cord appears red brown some days after the foetal death

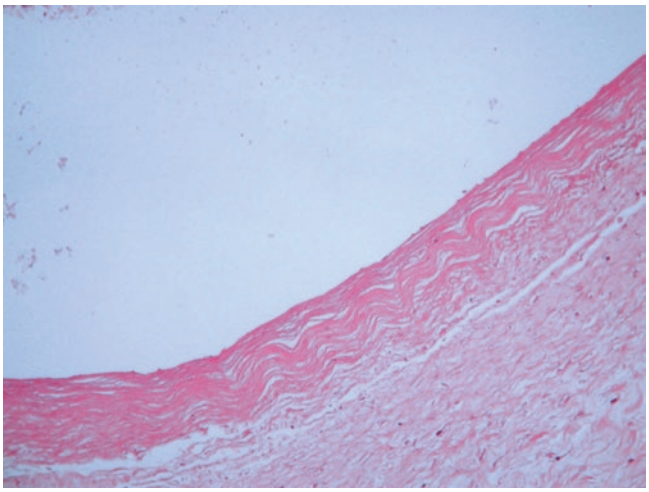

Fig. 1.15 Coagulative necrosis of the muscular cells of the cord vessels, with cytoplasm hypereosinophilia and absence of nuclei. The foetus is dead from 1 week

of the amniotic epithelium (necrotising chorioamnionitis) (Fig. 1.22). The foetal response starts from the amniochorionic vessels and the funiculus with exudate from the endothelium towards the wall and the connective tissue or the surrounding jelly (Fig. 1.23).

An acute villitis is the result of an infection arriving from maternal blood, mainly of a viral nature (Fig. 1.24). The bacterium *Treponema pallidum* induces a widespread villitis. The identification of the bacteria (Fig. 1.25) or of the specific viral cytological lesions (Fig. 1.26) allows the diagnosis. Acute perivillitis (Fig. 1.27) is often associated with a chorioamnionitis and/or a lethal infection of the foetus, commonly caused by *Listeria*, *Escherichia* or streptococci.

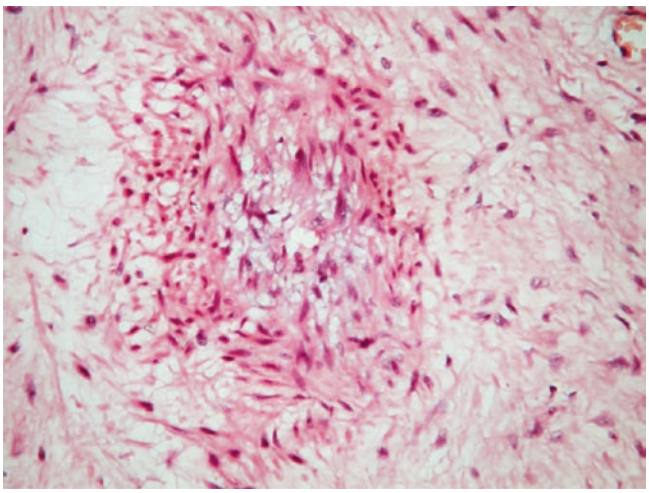

Fig. 1.16 Complete dissociation of the arterial wall after the disappearance of the lumen

Chronic villitis (Fig. 1.28) and perivillitis of unknown aetiology are present in 3–5 % of completed pregnancy and are not linked to any specific germ. Recent study of this process, that is associated with chorioamnionitis, thrombosis of microcirculation, fibrinoid necrosis of the villi, chronic endometritis, etc., has shown a not yet clear link with IUGR, IUD and other less serious pathological conditions of the neonate [9].

1.10 Anomalies from Maternal Diseases

The pathological aspects expressed by the placenta during serious maternal syndromes which are linked to and/or aggravated by pregnancy will be described in this paragraph. Among the most frequent we find hypertension, diabetes mellitus and maternal thrombophilia.

(A) *Hypertension in pregnancy and preeclampsia*. In this group we will consider both the condition of essential hypertension prior to pregnancy (once quite rare while today, with first pregnancy at over 30 years of age, more frequent) and pregnancy-induced hypertension (PIH). These conditions are not the same as more serious conditions such as preeclampsia, HELLP syndrome and actual eclampsia. Preeclampsia is hypertension associated with proteinuria of varying seriousness, at times complicated by haemolysis, elevated liver enzyme levels and low platelet count (HELLP) or by liver and/or brain damage. The causes of preeclampsia (an exclusively human condition) are not yet clear. According to the theory of Robertson [10], it is the result of an inadequate remodelling of the spiral arteries of the endometrium by the extravillous trophoblast, in other words the lack of destruction of the muscolo-elastic tonaca of the

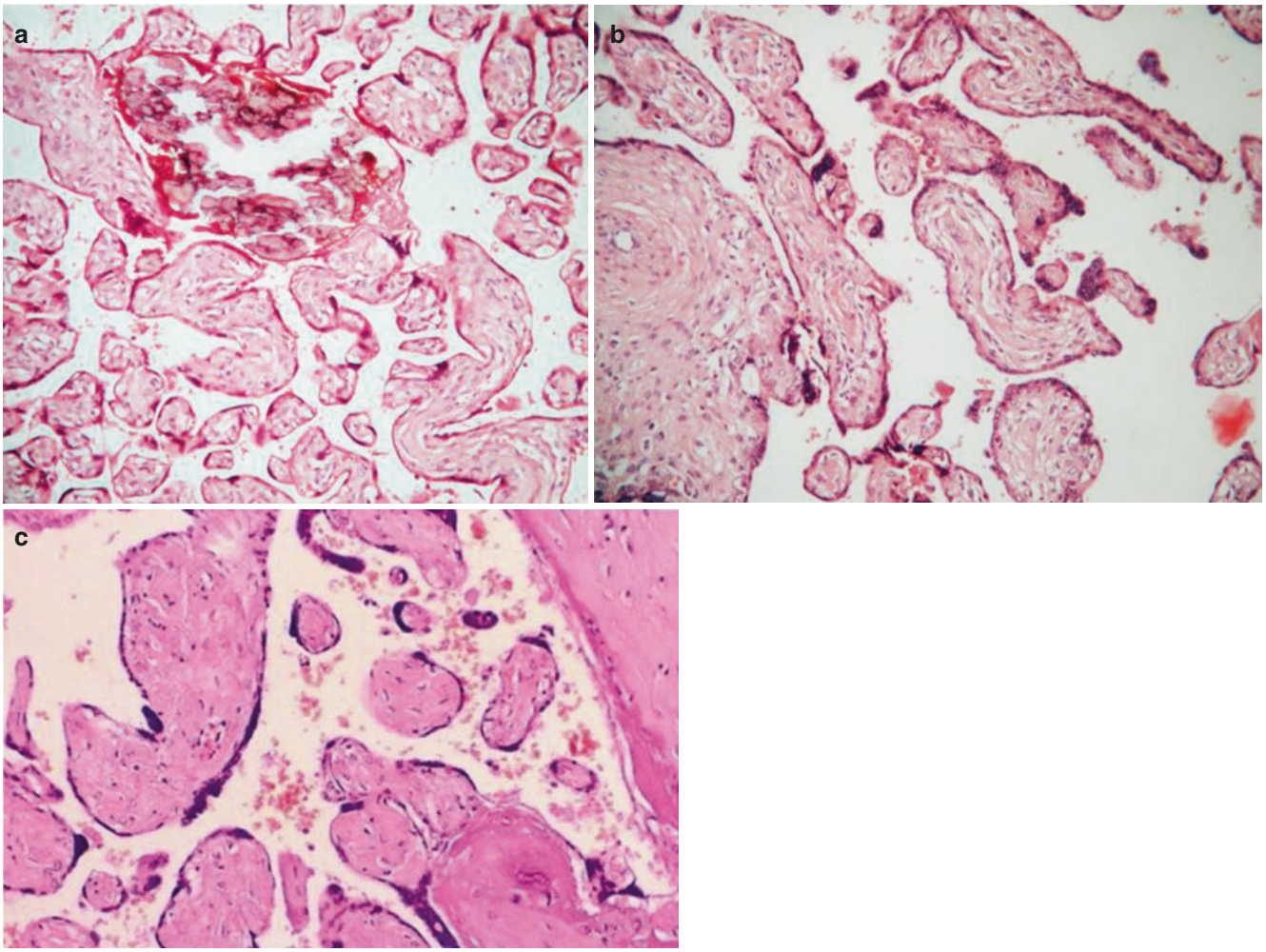

Fig. 1.17 (**a**–**c**) Disappearance of vessels, progressive fibrosis and reduction of cells in villi after a week of foetal death. The trophoblastic nuclei are amassed in large and dark nodules

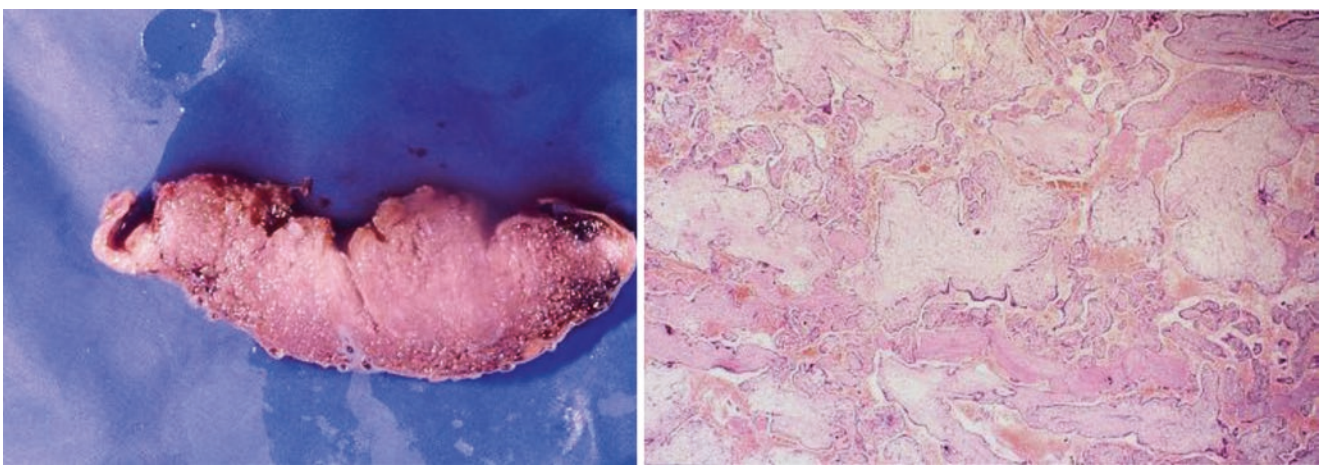

Fig. 1.18 Placenta in a case of foetal anaemia: large and pale aspect in the macroscopical section. At histology we can observe giant edematous villi with scanty vessels

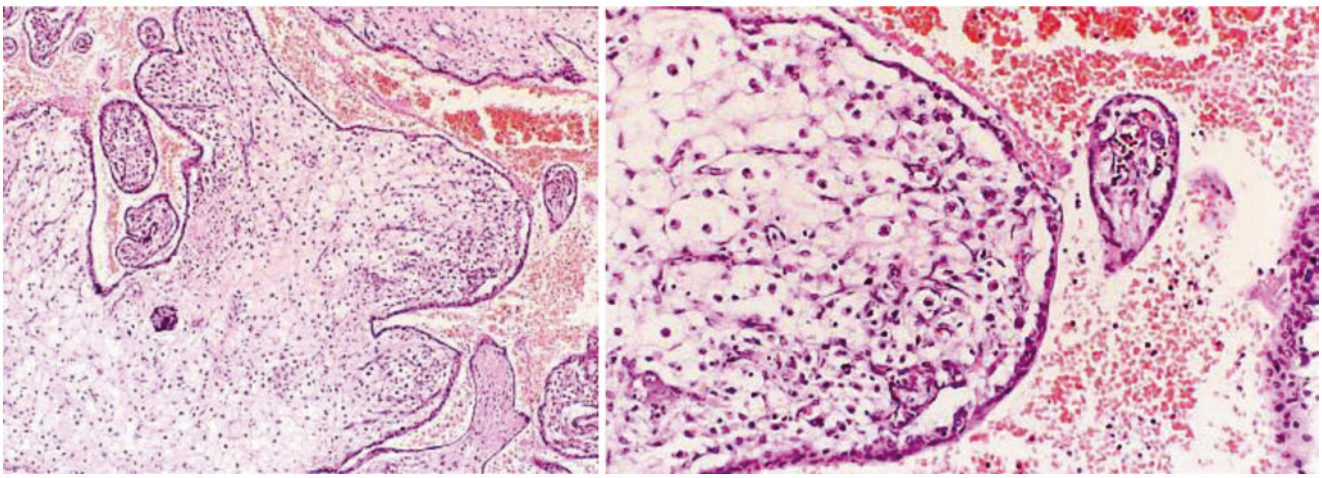

Fig. 1.19 Foetal anaemia. The large villi present a large amount of the Hofbauer cells and numerous erythroblasts in the vessels

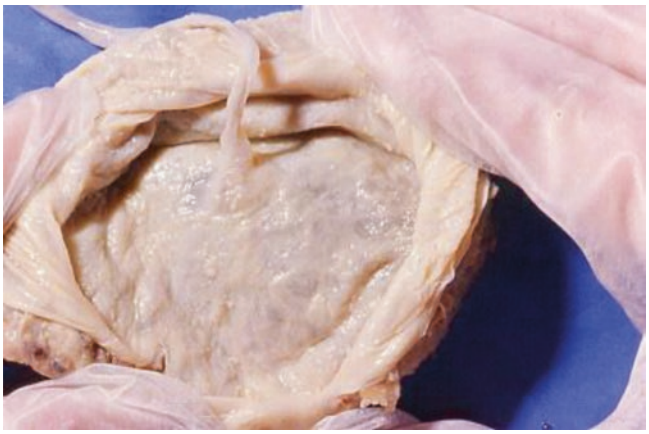

Fig. 1.20 Severe amnionitis. The membranes are opaque and covered by a fibrin exudate

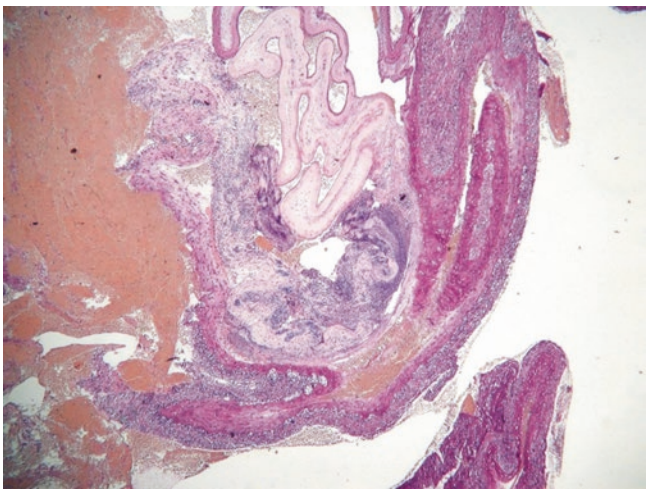

Fig. 1.22 In this case the neutrophil infiltration is more severe in the site of the membrane rupture. We can conclude that the premature rupture of membranes is the consequence of the chorioamnionitis

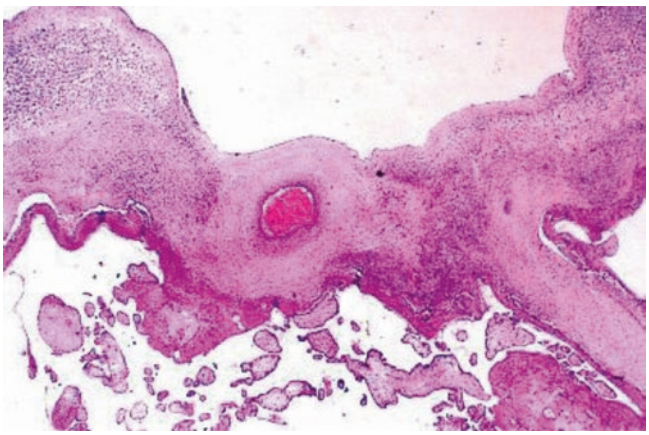

Fig. 1.21 Histologically, the severe chorioamnionitis is characterised by a diffuse and intense infiltration of neutrophils. Also the chorial vessels are included in the phlogosis

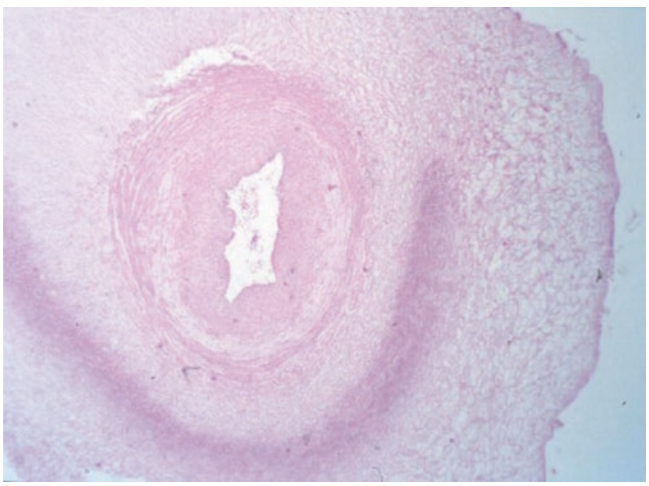

Fig. 1.23 A case of congenital syphilis with a dissecting infiltration of the umbilical cord near an arteria

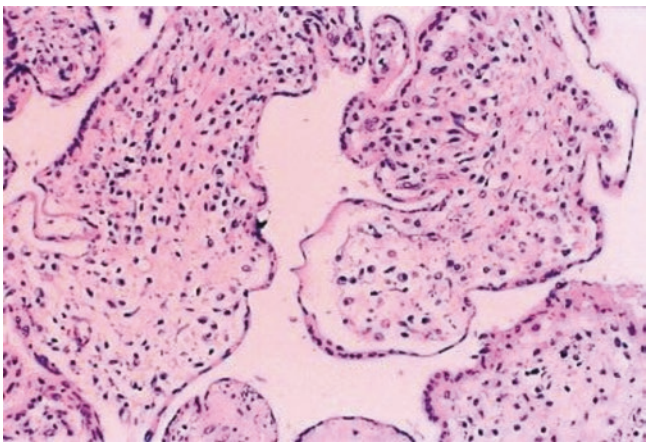

Fig. 1.24 Chronic viral villitis characterised by an infiltration of lymphocytes and plasma cells

media and its replacement with fibrinoid which is less resistant to blood flow needs especially in the second half of the pregnancy (Figs. 1.29 and 1.30). This results in a placental hypoxia with an increase in turnover of villous trophoblast, an increase in freely circulating syncytial knots and renal damage. However, the theory does not explain all the events. The pathogenic mechanism is exceedingly complex and also involves maternal immunitary factors against invasive extravillous trophoblast, the maternal genetic predisposition, oxidative stress and inflammatory factors [11, 12]. The result of the placental hypoxia is a preeclamptic placenta which is small, dry and multi-infarcted (Figs. 1.31 and 1.32). The different times of the onset of the infarctions can be considered pathognomonic. Histologically [13], the characterising lesion, though not always able to be observed, is atherosis of the decidual arteries in the maternal plate (Fig. 1.33). Their thrombosis provokes the infarction, while their rupture generates abruptio placentae or retroplacental haemorrhage. The villi have a characteristic hypoplastic aspect (accelerated maturation), with an increase of cytotrophoblastic cells. The capillaries of the villi show a narrowed lumen, further restricting the maternofoetal flow of metabolites [14]. When the preeclampsia is kept under control by appropriate therapy, serious pathologies are not observed, and the morphological picture is limited to hyper-branching villi and an increase in turnover of the trophoblast [15], as shown by the persistence of cytotrophoblast and an increase in syncytial knots (see alterations of Tenney-Parker) (Fig. 1.34). Such modifications are to be considered as an adaptive phenomenon by the villous tree to the maternal hypoxia, and it is in common with other conditions such as maternal anaemia, smoking, periods at high altitude, etc. It is important to note that though such adaptation can guarantee a normal foetal development, it cannot resist the stress of labour, and the situation can suddenly worsen even to the death of the foetus. A second type of preeclamptic placenta sees an increase in volume with a certain level of immaturity of the villi and of their trophoblast mantle. This occurs more often in combination with diabetes mellitus or in multiple pregnancies. The occurrence of preeclampsia in trophoblastic disease without a foetus shows that it is intimately linked to the presence of trophoblast and recedes only after placenta elimination.

(B) *Diabetes*. It is an important and complex complication which can even be controversial in placental pathology and in perinatal pathology in general. Pregnancy is onerous for the maternal metabolism, and therefore any tendency towards insulin resistance can manifest itself in those women who will later go on to develop diabetes II. Of course there are women who already suffer from diabetes (generally type I), and we must think of possible presence of consequences such as vascular, cardiac or renal complications before the beginning of the pregnancy. Commonly used laboratory tests are not always sensitive enough for pregnant women who will have biochemical constants at variance with the normal levels of non-pregnant women. Furthermore, the impossibility of utilising oral hypoglycaemic agents makes the search for the correct levels of insulin dosage even more difficult. During the first part of the pregnancy, achieving a glycidic balance is difficult for the mother with the mutated demands her body makes, and so episodes of imbalance can occur with a certain frequency. However, in the second half of pregnancy, the intervention of foetal insulin largely improves the condition of the mother but at the same time puts the health of the foetus at risk because of the effects of the insulin: macrosomia, a tendency to thrombosis, cardiac overload and an increased risk of sudden death in the last weeks of pregnancy. Placental alterations are still not well known, but if diabetes is not suitably treated, the macrosomia of the foetus is reflected in the placenta which is large, heavy and plethoric. If there is also a hypertensive condition or a maternal vasculopathy, together with the restriction in foetal growth, the placenta will be small with possible infarcts. A microscopic examination, not taking into account any signs of complications, principally shows a general immaturity of the villi accompanied by a widespread chorangiosis, that is, a randomly distributed proliferation of capillaries without a special connection to the transfer membrane. This has been defined as a "dysmaturity" of the villi (Figs. 1.35 and 1.36). These pictures are confirmed in ultrastructural studies (Fig. 1.37), in which the abnormal aspects of the endothelium are also evident (Fig. 1.38) The traditional belief of a thickening of the basal membrane of the villi has been shown

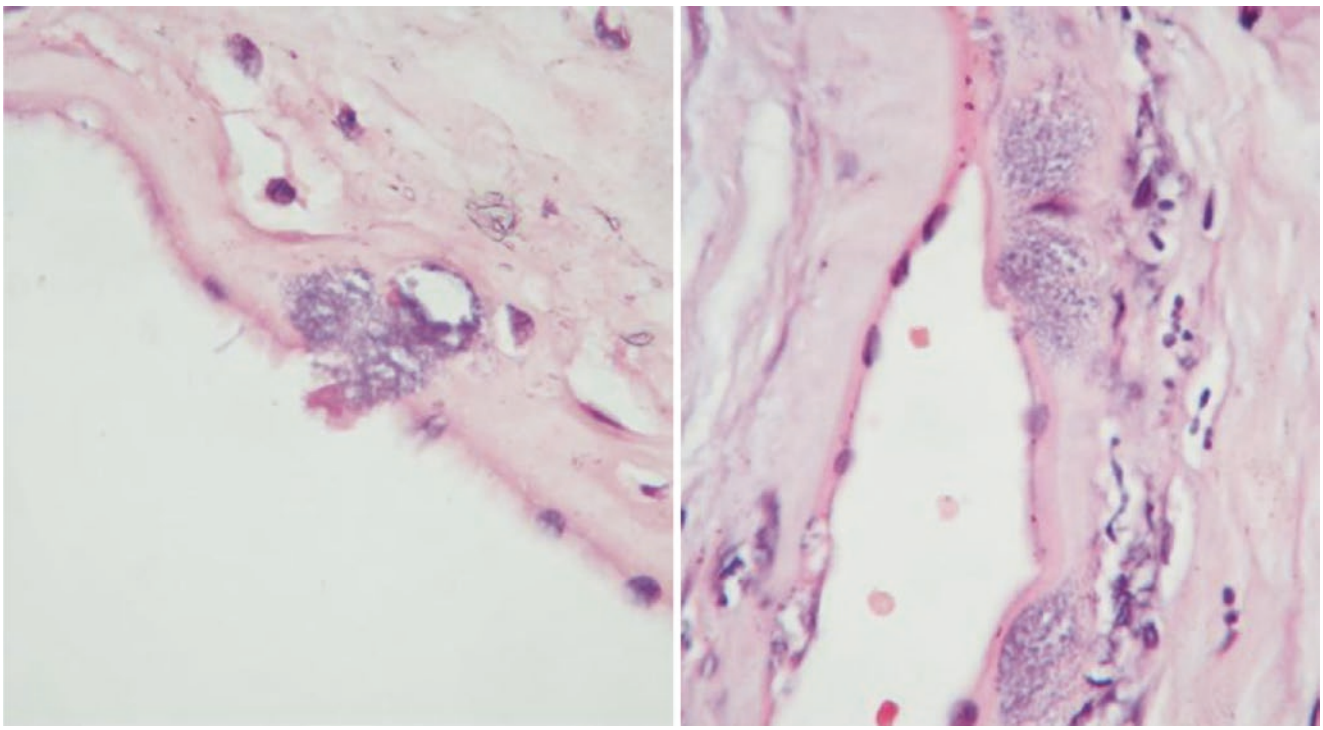

Fig. 1.25 Proliferation of *Listeria* colonies in the amniotic membrane

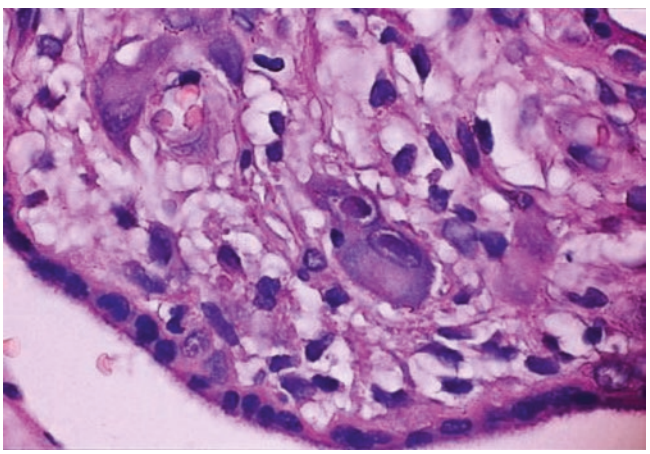

Fig. 1.26 Cytomegalovirus infection. Presence of large cells with eosinophilic cytoplasm, giant nuclei and evident nuclear inclusion. In this condition the viral cytopathy may be present in all kinds of placental cells

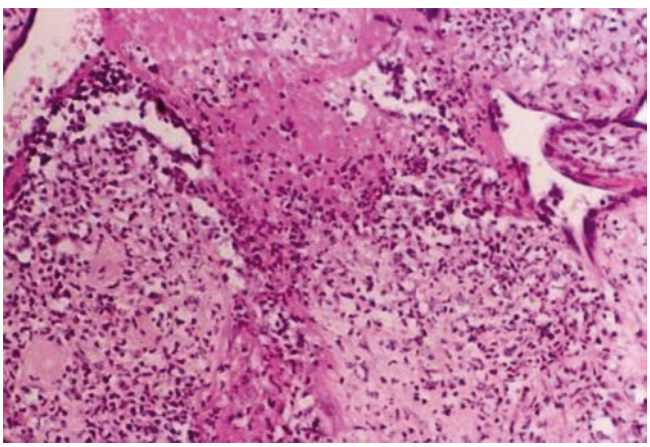

Fig. 1.27 Infection of *Listeria*. Infiltration of granulocytes in the villi and in the perivillar space with abscessual evolution

not to be correct by morphometric studies [16] and can be attributed to immune deposits.

(C) *Maternal thrombophilia*. This condition, either acquired with anti-phospholipidic antibodies present in the blood or congenital with deficiencies in particular coagulation factors, is associated with a higher risk of thromboembolism in the mother. There is also a higher risk of thrombotic episodes in the placenta and in the foetus with even perinatal death. Often there is a history of repeated miscarriage and IUGR. The placental lesions are connected with a higher level of thrombotic events and resemble aspects of those of preeclampsia whose conditions seem to be related [17]: thrombotic microangiopathy, abruptio placentae, haematomata and infarction.

1.11 Twin Pregnancy

Twin pregnancies are actually rather rare in humans, even if their incidence among populations varies with ethnicity and family history. Recently there has been an increase

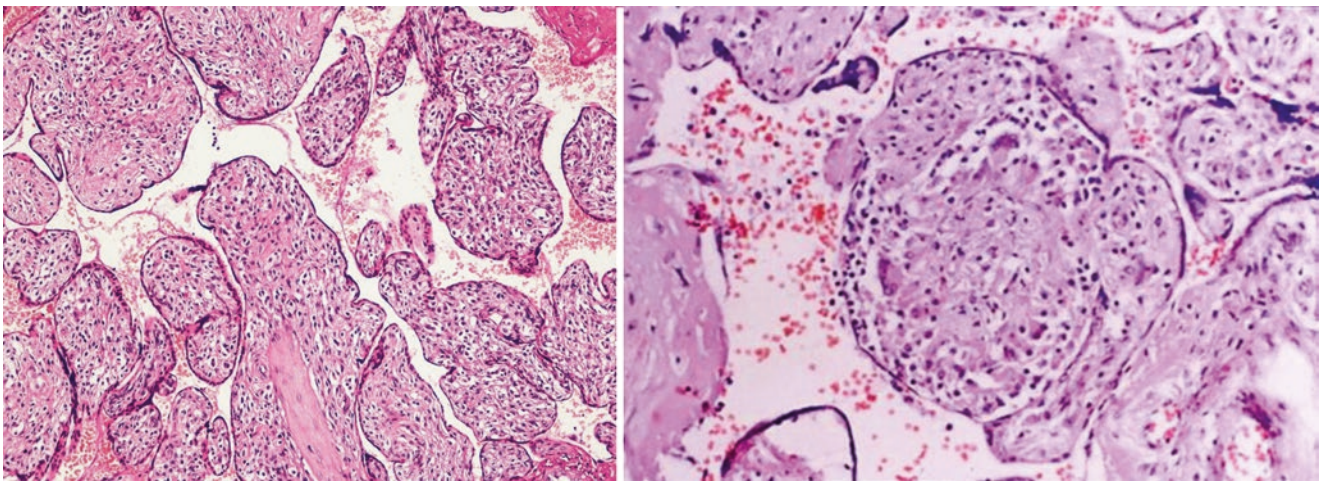

Fig. 1.28 Villitis of unknown etiology (VUE). This condition is not correlated with a known microbial inflammation. The villi are heavily infiltrated by leukocytes, and some giant multinucleated cells may be present. This picture may be associated with different foetal diseases, as a consequence of a maternal-foetal immune response

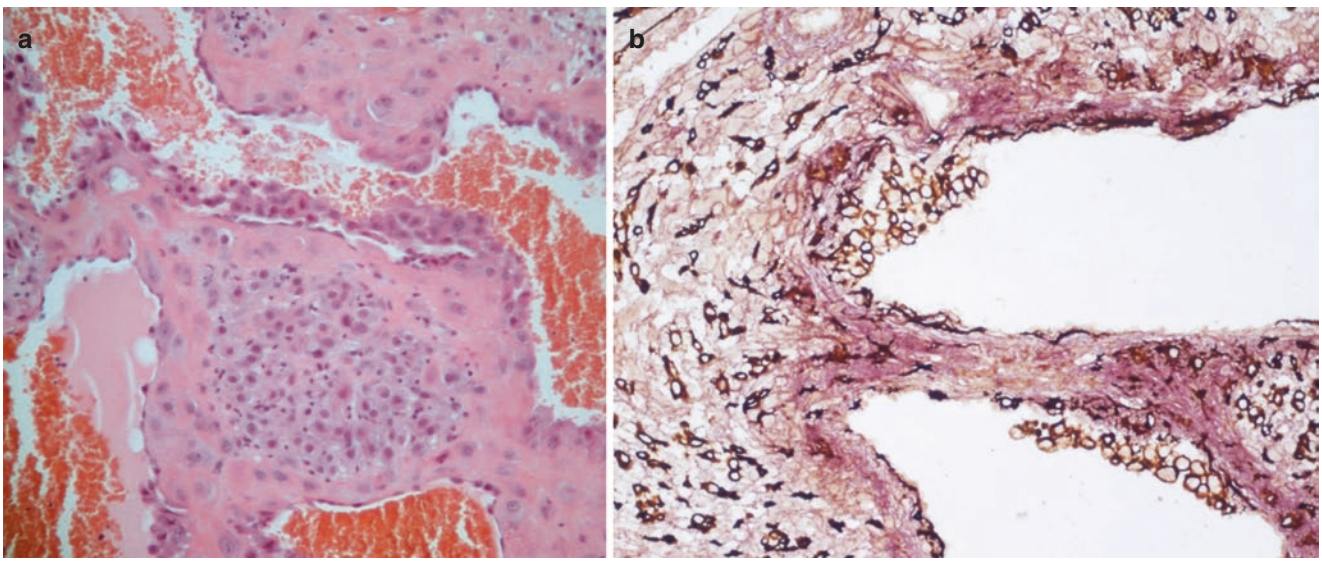

Fig. 1.29 (**a**) A physiological transformation of the utero-placental arteries. In (**b**) an original stain shows in *violet* (orcein) the scanty elastic fibres and in *black* (immunohistochemical reaction with anti-keratin antibodies) the cytoplasm of the trophoblastic cells. The latter are abundant and present in the decidua, in the arterial wall and in the lumen

because of multiple implantations of embryos in medically assisted pregnancies. To establish the level of risk, the nature of the pregnancy must be determined: di-(multi-) zygotic or monozygotic. If the pregnancy is dizygotic, the placental plates can be fused or separate, and distinct amniotic and chorionic structures can be seen (dichorionic and diamniotic placenta). If the pregnancy is monozygotic, produced by the division of a unique zygote, the adnexa will be in common (Fig. 1.39) if they are formed before the cleavage of the zygote. Thus, if the division occurs in the first 3 days (an exceptional event), the placenta is dichorionic and diamniotic. If the division is within 1 week, the placenta is monochorionic and diamniotic (Fig. 1.40). If at the nine to tenth day, it is monochorionic and monoamniotic (Fig. 1.41). If cleavage is at the 11–12th day, there will be two umbilical vesicles. Cleavage after the 13–15th day results in conjoined twins (Figs. 1.42 and 1.43). Most complications arise in a monozygotic pregnancy with a higher risk of malformation (asymmetric cleavage) or vascular problems. In a heterozygotic pregnancy, vascular problems can be present, but other events are more common. For example, an insufficient or superficial insertion of a plate can lead to growth restriction of one of the twins with consequent dysmetria and an erroneous hypothesis of twin-to-twin transfusion. In other cases an ascending phlogosis can generate a chorioamnionitis in the amniotic

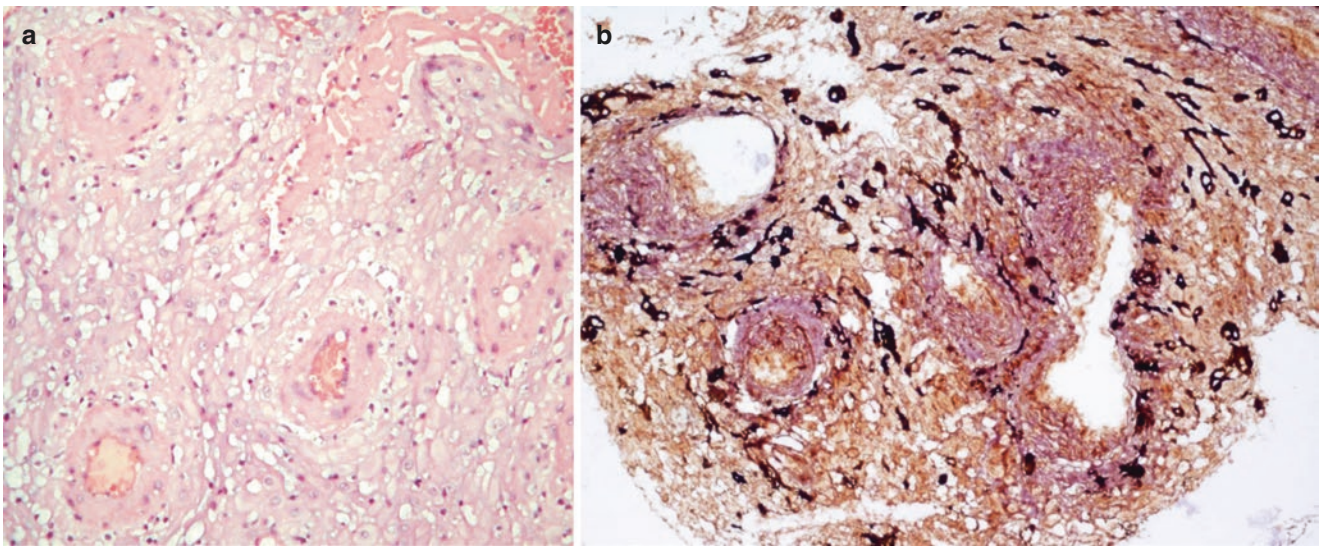

Fig. 1.30 (**a**) In this preeclamptic placenta, the utero-placental arteries lack the physiological transformation, and they show a thick muscular wall and a small lumen. The special stain (**b**) shows a large amount of elastic fibres (*violet*) in the arterial wall and the absence of cytotrophoblastic cells in the wall and the lumen of arteries

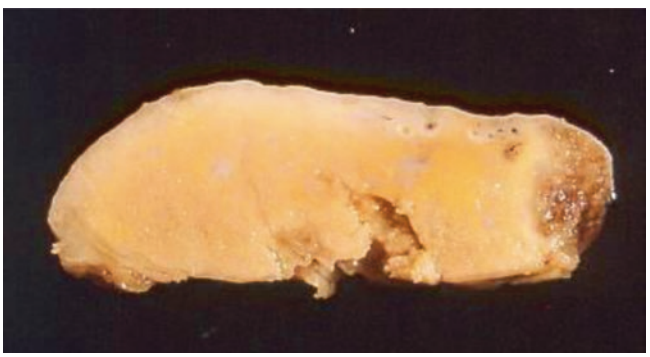

Fig. 1.31 A large infarction in a preeclamptic placenta, involving almost all the frontal section

sac nearer to the isthmus, without affecting that/those farther away. Also, a preterm birth from a stretched uterus is a greater risk of perinatal death compared to a single foetus pregnancy. In the death (spontaneous or not) of one twin foetus, it remains in the uterus until the birth of the other. The dead foetus will be found compressed and dehydrated in its amniotic sac and is known as a papyraceus foetus (Fig. 1.44).

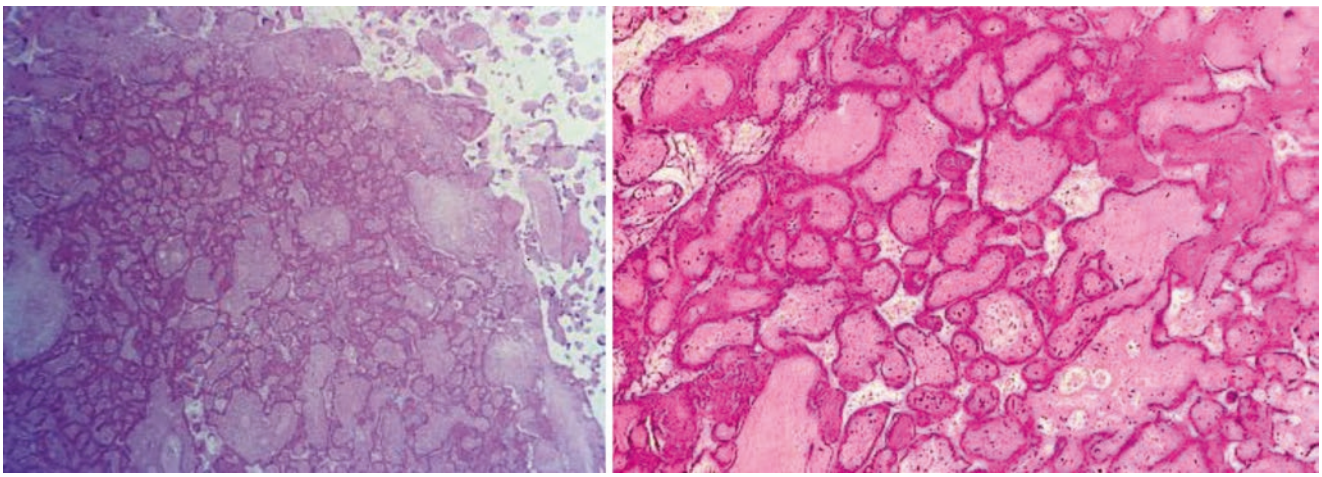

Fig. 1.32 Histological aspect of an infarct dated from several days. The intervillar space is collapsed. A diffuse coagulative necrosis makes the villi hyper-eosinophilic and acellular (ghost villi)

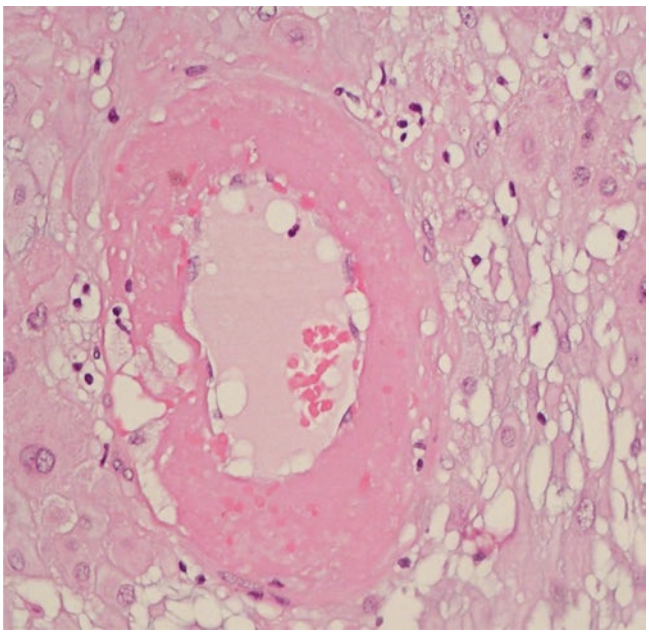

Fig. 1.33 Atherosis of a decidual utero-placental arteria. The arterial wall presents fibrinoid necrosis and infiltration of macrophagic foam cells. The lumen is narrow. This lesion predisposes to vascular thrombosis and rupture

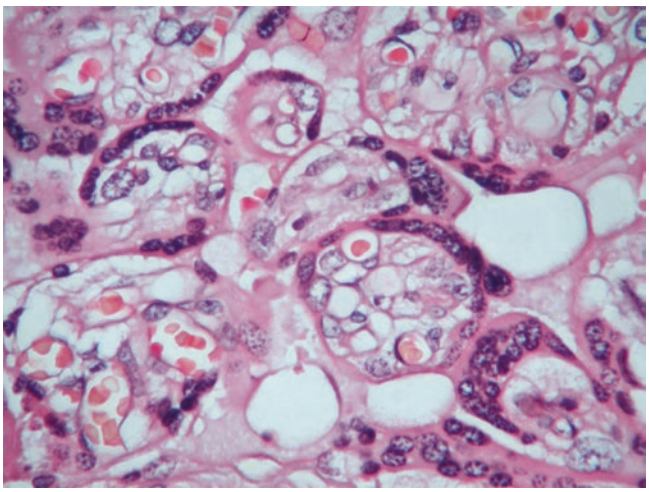

Fig. 1.34 Tenney-Parker changes: term villi present several hypertrophic cytotrophoblast cells, a sign of an anoxic damage of the trophoblast and an accelerated turnover of the trophoblast. Apoptotic nuclei are recovered in a region of the trophoblast (syncytial knots) and then expelled in the maternal blood. The vasculo-syncytial membranes have small surface and higher thickness

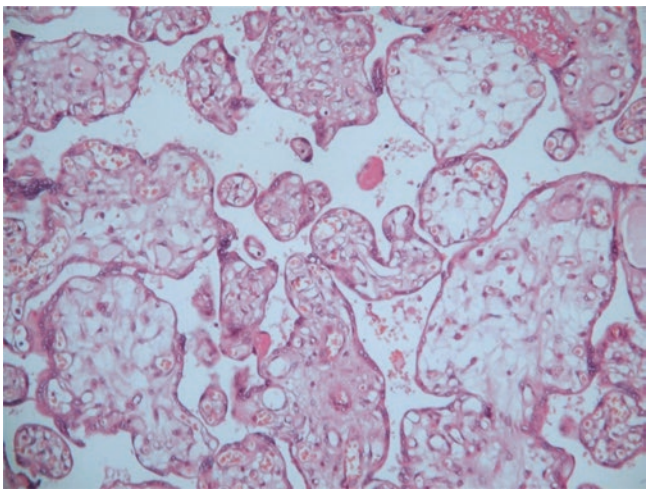

Fig. 1.35 Diabetic placenta with "dysmature" villi: large ("monster villi"), with pale stroma and several capillaries disposed at different distances from the basal membrane

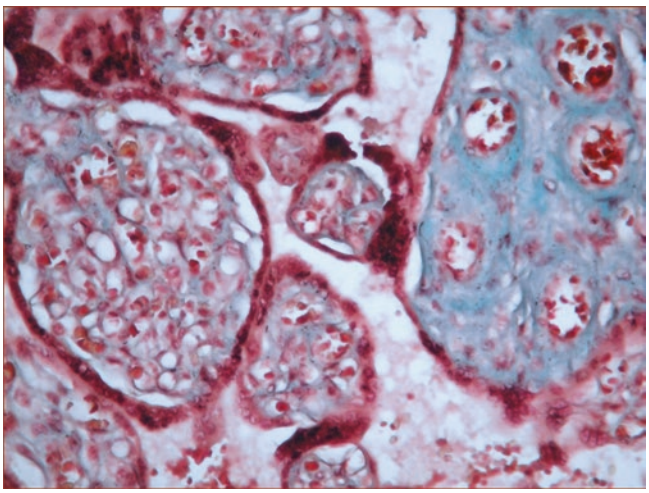

Fig. 1.36 The trichromic stain shows the very numerous capillaries present in a large intermediate villus in diabetic placenta

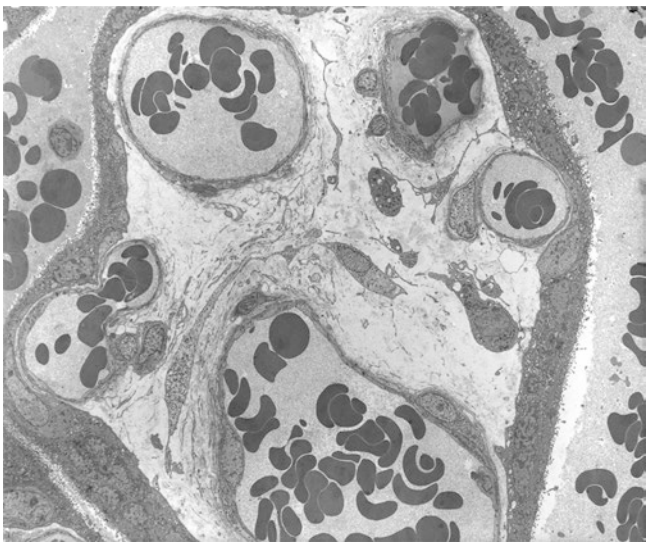

Fig. 1.37 Ultrathin section of a diabetic villus. The numerous vessels are arranged in different sizes. Note the unusual form of the fibroblasts which have very long and ramified cytoplasm connecting the different cells of the villus

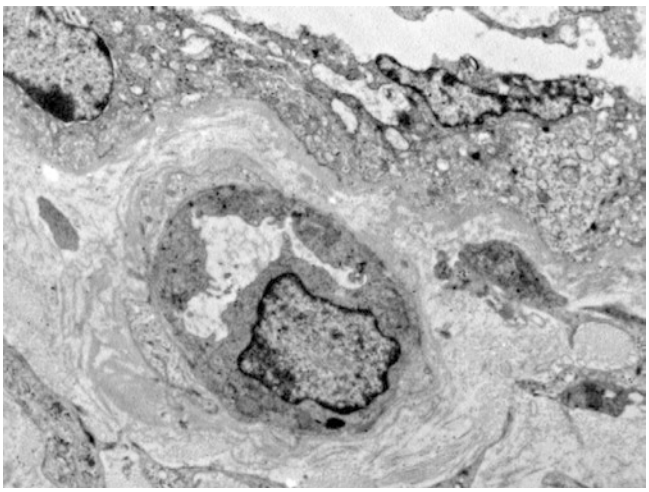

Fig. 1.38 Villus of a diabetic placenta. This vessel is distant from the membrane and shows a swollen nucleus and a consequent restricted lumen

Fig. 1.39 Twin pregnancy. The membranes of the interamniotic septum are thick and opaque and present a multistratification

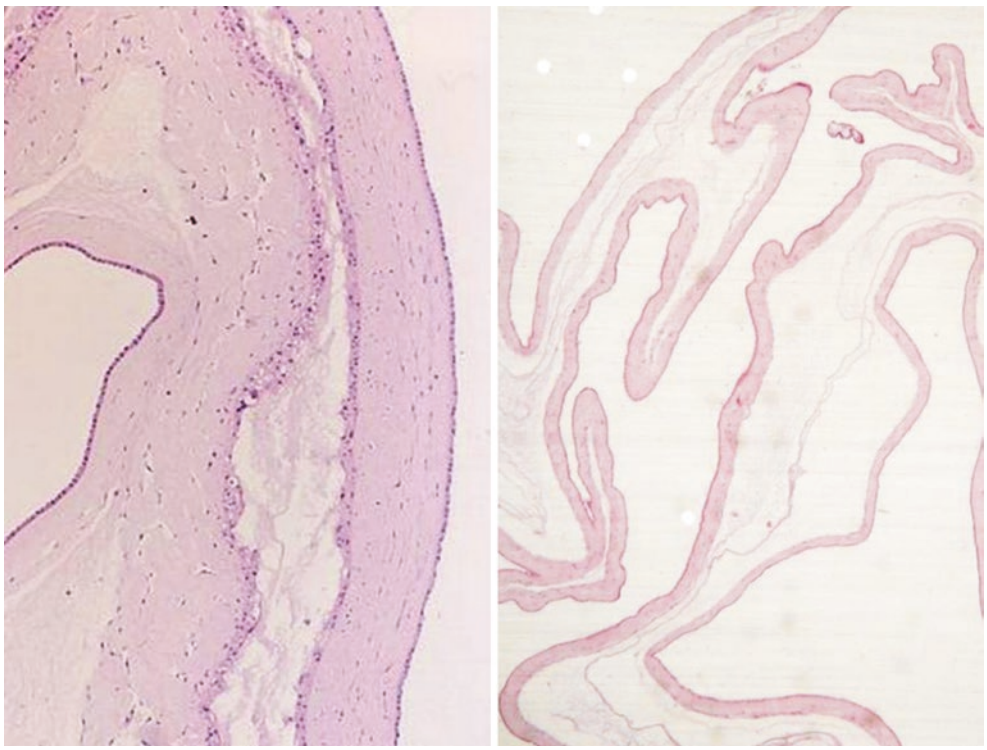

Fig. 1.40 On the *left*, the interamniotic septum in a dichorionic diamniotic placenta is composed of two distinct layers of amnions/chorion. On the *right* the septum of a monochorionic diamniotic placenta shows only two amniotic membranes without interposed chorion layers

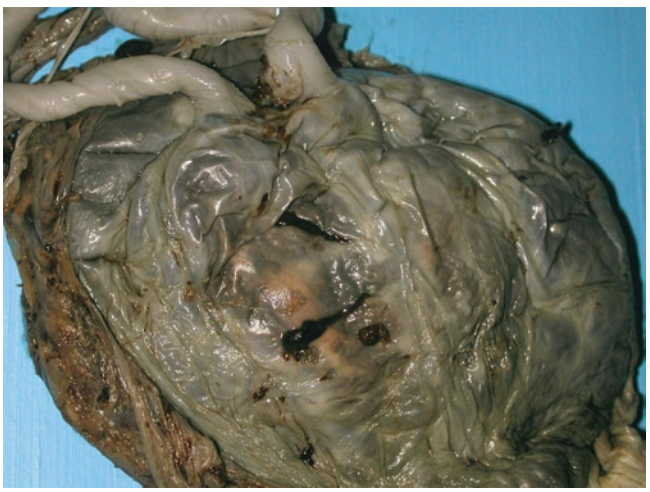

Fig. 1.41 A monochorionic monoamniotic placenta: a single amnion cavity presents two umbilical cords

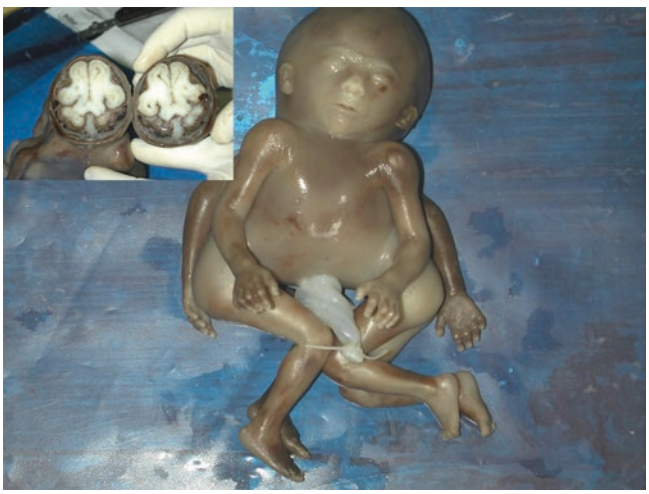

Fig. 1.42 An example of conjoined twins (cranio-thoracopages), with a single umbilical cord. In the insert, the encephalon shows one cerebrum and two distinct posterior fossa and cerebellum

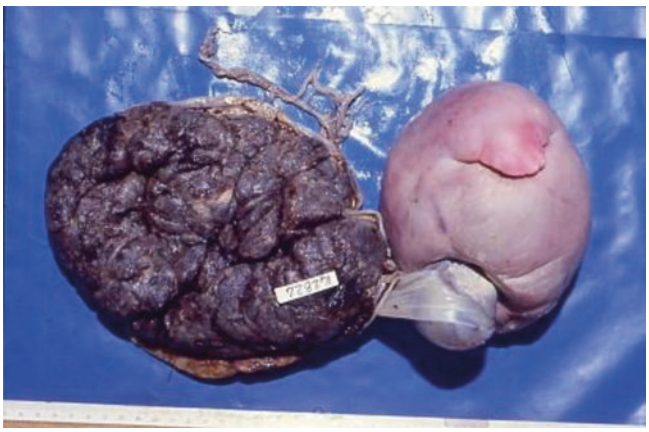

Fig. 1.43 An acardiac twin. The placenta permits the full development of the foetus which was circulatory connected with an amorphous embryo without a heart

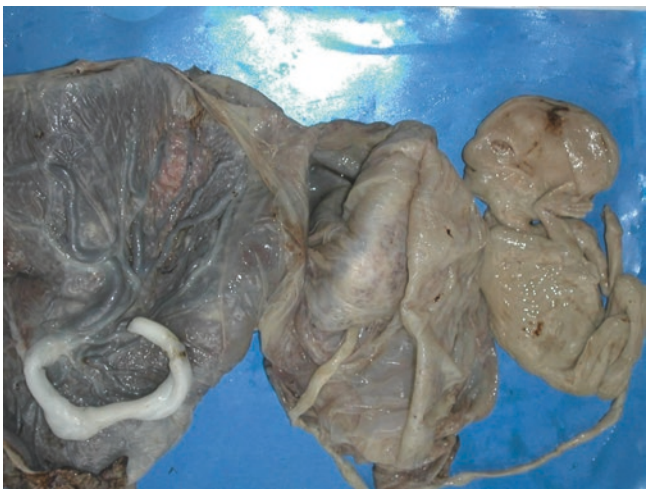

Fig. 1.44 In this tween pregnancy, an embryo dead precociously and remained in his amniotic sac till the birth of the healthy foetus. Dehydration and mummification produced a particular aspect defined as papyraceus foetus.

Conclusions

The aim of this chapter is not a list of placental lesions but how they can be used to open a window onto maternal and foetal conditions during pregnancy with an accurate description of the pathologies or occasional events which can arise. Many of these events leave signs on the chorionic plate or on the amniochorionic membranes or on the funiculus. The ability to understand them, document them and above all explain them, not only to fellow doctors, obstetricians and paediatricians but also to the parents, especially those who have suffered an adverse event, with reasoning and knowledge, is a challenge for the pathologist working in perinatal pathology. Following this route not only holds back any idea of contention but can create an atmosphere of collaboration between professionals who, together with the real heroes of the story, the parents, can rectify a very difficult situation.

Special treatment must be reserved for the mother who, if well advised, can utilise the placental examination to evaluate her performance in such a demanding test as pregnancy and turn the issue to her advantage for the future, adopting the necessary countermeasures against previously unknown health problems.

Often unjustly overlooked in these situations is the father. Although the foetus is within the maternal habitat and must participate in and cooperate with the mother's metabolism, around half of the foetus's genetic make-up is from the father, which can bring problems that are the expression of being a child of such father. Only recently have we realised that we must start studying the stamp of the father on foetal life and, with extreme difficulty, we have taken the first steps.

Certainly a lot of water has passed under the bridge since it was believed that the mother was only the incubator of the seed of the man as the man is the source of life, as the divine Apollo and the wise Athena sustained before the Areopagus in the Eumenides of Aeschylus. Though this was a long-held belief, opinion changed only in the last few hundred years.

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Placental Vascular Pathology

2

Ezio Fulcheri, Maria Pia Brisigtti, and Leonardo Resta

2.1 Framing the Problem

Placental vascular pathology can be divided into two main areas:

(A) Pathology of the vessels that link the chorionic plate with the foetus
(B) Vascular and circulatory pathology of the chorionic plate

The first case essentially deals with the lesions of the funicular vessels and the chorioamniotic vessels, while the second case deals with lesions of the vessels of stem villi whether of first, second or third order and of the chorionic vessels of intermediate mature or immature villi and also of the capillaries in the transfer terminal villi.

This seemingly rough and ready distinction has significant consequences in the interpretation not only of so-called vascular accidents [1] that assume a very important role in the understanding of the causes of late foetal death or foetal neurological damage [2] but also of signal importance in the understanding of physiopathology and pathology, the growth and maturation of villi, the maternofoetal transfer and the pathology of placental implantation [3–6].

2.1.1 Pathology of the Vessels That Link the Chorionic Plate with the Foetus

This is a complex topic which has been oversimplified in recent years. Here, we will consider the funicular vessels, from where they emerge at the umbilical level until their insertion in the chorionic plate, and the chorionic vessels that are those that come from the umbilical cord spreading onto the chorionic plate under the amnion and penetrating into the cotyledons becoming stem villi. Lesions can be mechanical or caused by vascular placental pathologies.

2.1.1.1 Lesions Consequent to an Extrinsic Mechanical Force Applied to the Vessels

Umbilical Cord

These lesions presuppose a normal vascularisation with properly developed and normally formed vessels which are then mechanically affected such that blood flow is completely or partially interrupted between the foetus and the chorionic plate. There is a perfect functioning of the cord when it is of the correct length and of a uniform calibre, the coiling is regular and its vascular structure is well protected by the Wharton jelly.

At the end of pregnancy, the cord length is about 50 cm, with a normal variation of ±5 cm, being proportional to a series of anthropological measurements of the foetus and so allowing its movement in utero including turning over and, above all, insertion into the birth canal.

A cord shorter than 30 cm or longer than 70 cm is dangerous and can cause acute and dramatic events. A short cord can be responsible for growth retardation and the blocking of the head in a fixed position. Its shortness can be responsible for pulling movements on the chorioamniotic vessels and their rupture with subamniotic haemorrhage (pseudo-Breus mole) (Fig. 2.1). In some cases the umbilical vessels can rupture with haemorrhage into the Wharton jelly, or even with simultaneous rupture of the cord itself (if there is particularly reduced coiling of the cord and/or a facilitating degeneration of the jelly) leading to a fatal haemorrhage.

A short cord is a risk in that it can provoke unexpected foetal death or sudden intrapartum death, but just as dangerous is an excessively long cord (Fig. 2.2) which can form true knots (Fig. 2.3) and make it easy for the foetus to get entangled in it, wrapping it around its chest (even more than once), or to tie up its limbs or to get it around its neck. Much

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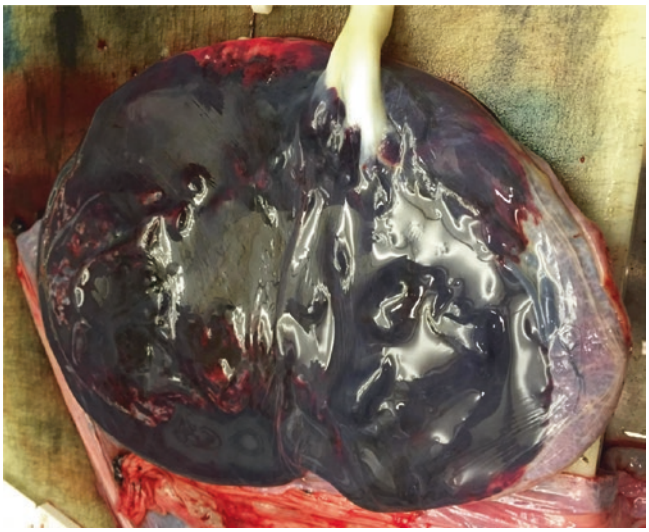

Fig. 2.1 Recent extensive subamniotic haemorrhage due to a fracture of the amniochorial vessels (pseudo-Breus mole)

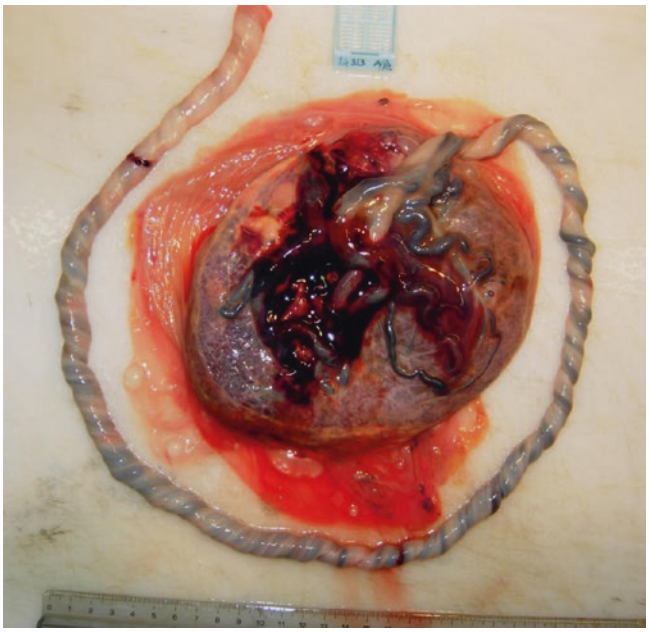

Fig. 2.2 Abnormal length of the umbilical cord with hypercoiling of the vessels. An angiodystopia of the amniochorial vessels with phlebectasias is present

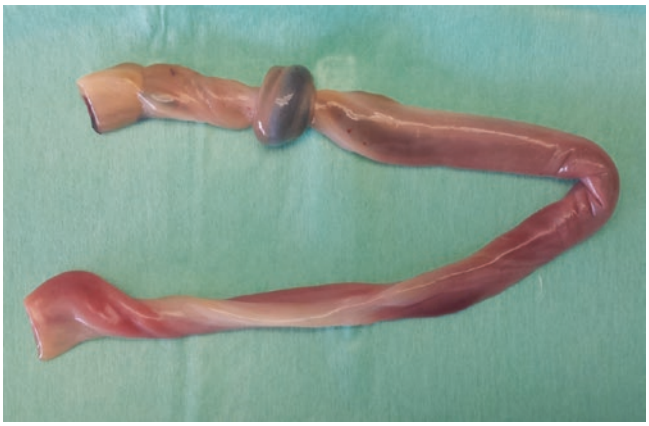

Fig. 2.3 A true closed knot of the cord caused an intrauterine foetal death. Note the post-mortal haemoglobin suffusion of the Wharton jelly

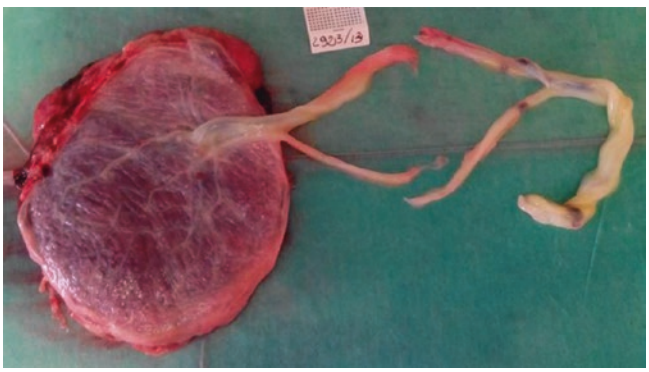

Fig. 2.4 In this cord the abnormal composition of the Wharton jelly caused the separation of one umbilical artery which for a tract uses a kind of accessory parallel cord

has been written on stillbirth simply explained by choking due to nuchal cord syndrome. However, for a real understanding of the situation, we must be aware that the excessive and exaggerated movements of the foetus which lead to entanglement are always consequent to a state of hypoxia. The foetus responds to acute hypoxia with bulbar reflexes giving accentuated activity and movement. The reasons for this acute hypoxia are the real diagnostic objectives to explain the pathogenesis of the sudden death of the foetus for mechanical causes. There are two mechanisms in operation when the cord is wound around the neck, the first being the compression of the carotid vessels leading to an acute ischaemia causing irreversible damage to the brain and the second being a similar compression but to the cord, especially when on the nuchal region where there is the rigid spinal column, so leading to an occlusion or substenosis of the vessels within the cord, particularly the vein.

There is also the case where the cord vessels are compressed from outside forces, and so blood flow is partially or completed interrupted by the presence of a tight constriction. There can also be a reduction in the amount of Wharton jelly in the cord, which, though rare, gives rise to a non-uniform distribution of Wharton jelly around the funicular vessels which can even be found running separately along parts of the cord before continuing in the normal fashion nearer the placenta (Fig. 2.4). These features are extremely susceptible to compression and/or rupture.

Similarly, segments of the cord can have a reduced diameter. These coarctations are seen to be the results of previous infections or the focus of degenerative lesions, but whichever the cause of this narrowing of the cord, these points are a

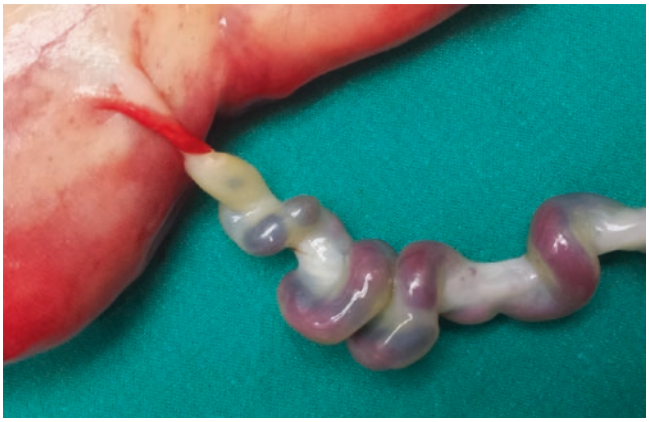

Fig. 2.5 Umbilical hypercoiled cord with closed torsion near the foetal umbilicus and vascular coarctation

serious risk within the placental vascular system, not particularly because of knotting or entanglement with the foetus but because of it winding around itself and so creating acute constriction of the vessels.

Umbilical cord coiling and its anomalies have recently been given more attention. As its component blood vessels follow a helical course, with the two arteries spiralling together around the vein, unusual differences in the length of either the arteries or the vein can cause hypocoiling or its opposite, hypercoiling. The cord can also on occasion curl up on itself with epidermisation of the amniotic mantle and degeneration of the Wharton jelly. Neither anomaly is normally linked to sudden death, but hypercoiling can cause stricture (Fig. 2.5), especially of the vein along the length of the cord, so causing severe foetal distress and its associated problems. The part of the cord most at risk is where it inserts into the foetus as here there is very little play and any excessive torsion can cause a real coarctation of the cord and its vessels even leading to a blockage in circulation and foetal death.

Chorioamniotic Vessels

On reaching the placenta, the vessels from the umbilical cord run on the chorial surface branching in either a dispersal pattern or a magisterial pattern, though there are no substantial differences in terms of functionality, haemodynamic variability or associations with foetal problems. Mechanically caused lesions are extremely rare with little information in the literature, principally because the chorionic plate cushions any compressive force which could impact the vessels. The critical point is where the umbilical cord enters the placenta as this point can act as a pivot for the twisting of the vessels (Fig. 2.6).

There may also be a lack of Wharton's jelly at the insertion point into the placental disk, and this "furcate insertion" leaves the vessels at risk of damage from creasing or twisting. These rare abnormalities can cause sudden death especially if the foetus is macrosomic or the cord is very short.

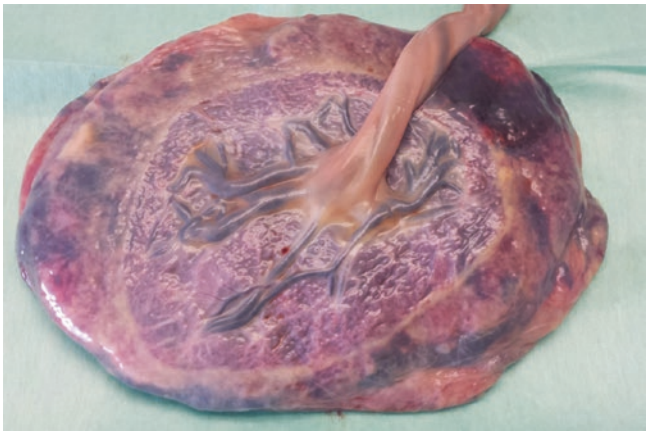

Fig. 2.6 Placenta with extra-chorionic membrane insertion. The amnio-chorionic vessels are distributed only to the central portion of the chorionic disc; the extra-chorionic portion of the disc is devoid of large vessels. The vessels have an irregular form and size and different "crossings"

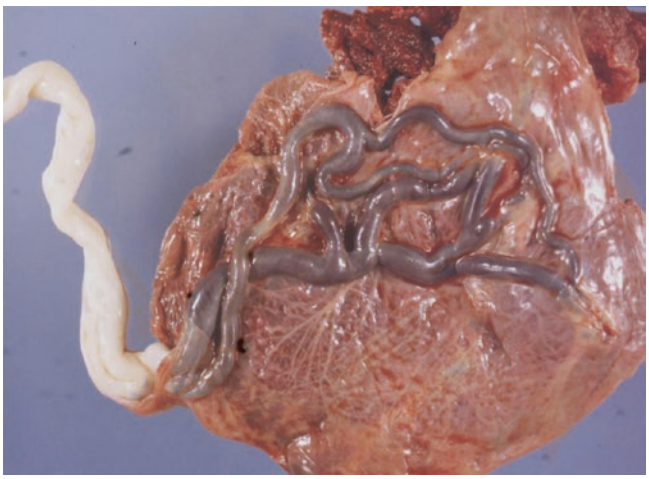

Fig. 2.7 Marginal insertion of an umbilical cord in a "racket-like" placenta: the amniochorial vessels are ectasic and irregularly distributed. A large amount of the chorionic disc do not receive any arterial or venous branch. An abnormal deep intracotyledon network supplies the blood distribution

Similarly, creasing or compression can occur when there is a marginal insertion (Fig. 2.7) of the cord in a twin pregnancy (monochorionic/diamniotic or dichorionic fused diamniotic). The compressive force exerted by one twin, especially by the feet, can determine a blockage of circulation in the cord of the other, just at the insertion point.

2.1.1.2 Actual Vessel Lesions

Umbilical Cord [7, 8]

Vessel Angiodysplasia

Angiodysplasias of the umbilical cord vessels have been little studied though they are an interesting and important

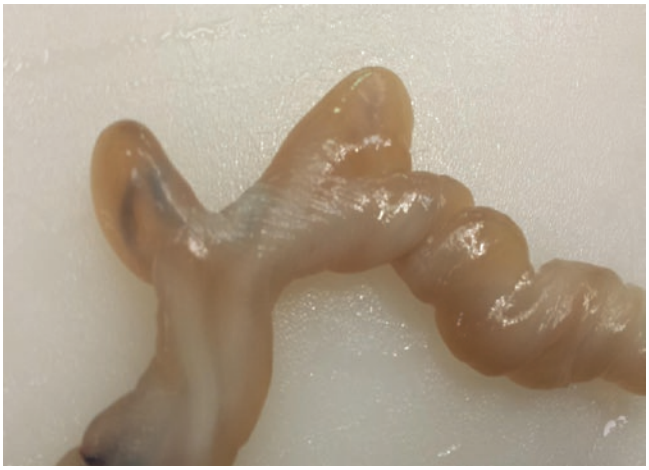

Fig. 2.8 False knots of the umbilical cord. The oedema of the Wharton jelly allows to note in translucency the tortuous vessels

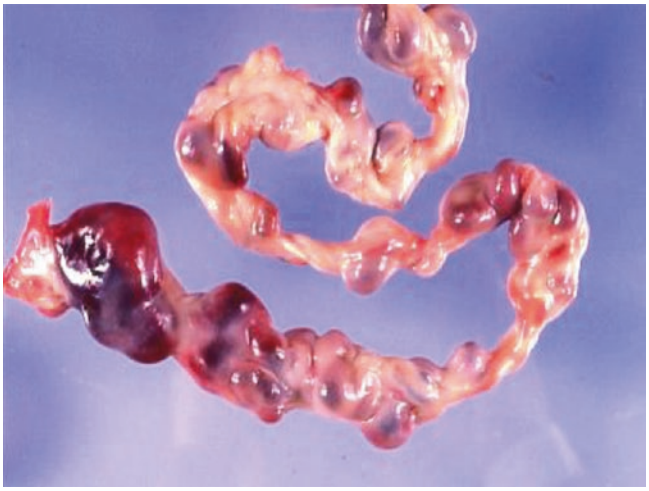

Fig. 2.9 Umbilical cord with numerous arterial and venous ecstasies

aspect of foetal development. For example, when the vein and arteries are not of regular length, loops and kinks can form within them, usually in the vein, and these appear as knots in the cord within the Wharton jelly. They are known as false knots (Fig. 2.8) and are thought to have no clinical significance though, in fact, if the phlebectasia is significant and microthrombi form within the vein, these may arrive at the foetal heart [9].

Vasculopathies

Similar to the false knots which are circumscribed venous ectasias, there can also be a widespread phlebectasia in a varicose condition of the umbilical vein (Fig. 2.9) where repetitive significantly important phlebectasias can increase the probability of endovascular thrombosis. The vascular damage is limited to the part of the wall where the muscle layer is too thin without compensating elastic fibre or fibrous material. Unlike in the lower limbs, there is no inflammatory aspect so rendering the situation much less dangerous. Analogous aneurysmatic dilations of the arteries are much rarer.

A careful programme of coloration of the various parts of the funicular artery walls must be utilised to be able to identify the lesions (Fig. 2.10). The correct histochemical staining will identify the elastic components of the walls and the elastic layers and also the components of hyaluronic acid, collagen and acid or neutral polysaccharide mucins. Immunohistochemical staining with smooth muscle actin antibodies and desmin antibodies is indispensable to see the myofibroblasts and smooth muscle cells of the intima and the tunica media. In this way a series of elementary lesions can be identified which can be ascribed to four conditions.

The first of these is a hypertrophy of the intima which is not usually circumferential but involves only a segment of the internal circumference and is a proliferation of smooth muscle cells and myofibroblasts. The second condition is a concentric hypertrophy of the tunica media due to hyperplasia of the smooth muscle cells. The third is a non-muscular thickening of the wall from the tunica media due to reactive fibrosis and an increase of the collagen and elastic components. The fourth and last condition is a degeneration of the tunica media with a reduction in elastic fibres, delamination of the smooth muscle bundles and an accumulation of mucopolysaccharide acids and particularly hyaluronic acid. The lack of information in the literature, other than some case studies, does not allow any analysis or correlation with genetic diseases; however, it is clear that vascular lesions of this type cannot but reflect a pathology in placental circulation and, at the same time, indicate possible actual or latent similar alterations in the foetal circulatory system.

Vasculitides

Unlike the vasculopathies of the previous paragraph, inflammations of the umbilical cord have been widely studied by clinicians and researchers. They can be associated or not with inflammation of the Wharton jelly including various types of funisitis. Inflammations of the umbilical cord are as a rule associated with a pervasive and serious chorioamnionitis. More frequently the problem is with the vein than with the arteries, probably due to two factors, the first being in the different histological characteristics of the two typologies of vessel with the arterial walls having an intrinsic resistance while the vein walls are much more vulnerable and the second being that the blood flows from the placental chorioamniotic structures to the foetus, indicating a progression gradient of diffusion and extension of inflammation and therefore indirectly of infection. Arterial inflammation may indicate an advanced infection of the cord vessels, but more likely it is a sign of a massive colonisation of the foetus itself, with the infection now being brought from the foetus in the blood flow towards

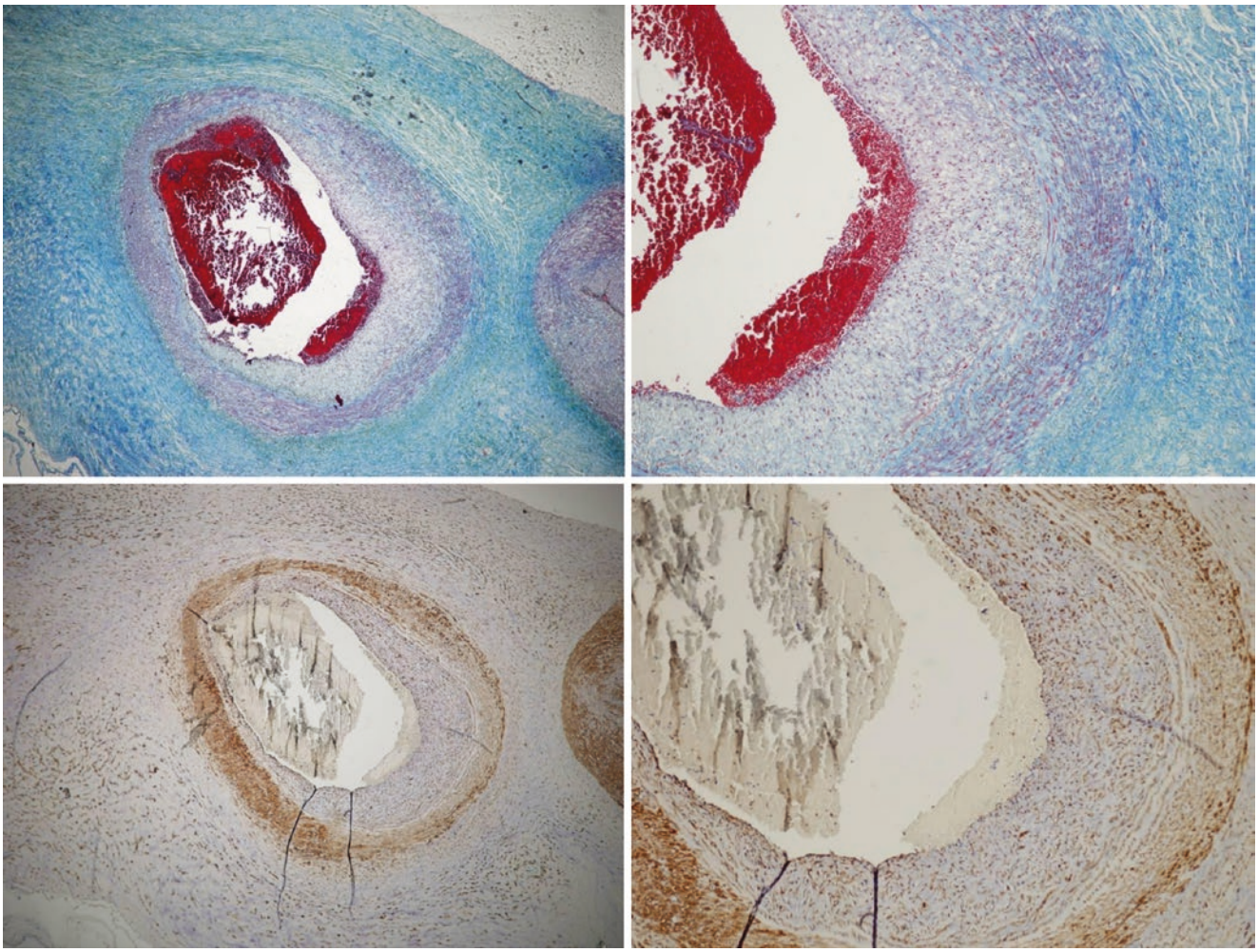

Fig. 2.10 Non-concentric thickness of the intimal layer with a thinness of the tonaca media in amnio-chorionic arteries. The lesion, documented by the trichromic stain, is more evident with the immunohistochemical reaction with against actin antigen. About one half of the vessel circumference shows a deficit of contractile function and that phenomenon favours an abnormal haemodynamic and thrombosis

the placenta. Bacterial agents are essentially responsible for cord vasculitides, most of which are common germs such as staphylococchi, streptococchi, *Ureaplasma urealyticum*, *Escherichia* and *Enterobacteriaceae*, while in the case of many chorioamnionitic and vascular infections, the causal agent cannot be identified, as is also the case in inflammatory states of the membranes. Except in extremely serious infections, the neonatal outcome does not depend on the seriousness of the lesion nor on its extent in any way. Many chorioamnionitic infections are reported in neonates without any clinical problems. However, there are times when the inflammation is correlated to an unfavourable or critical clinical progression and the guidelines for the prevention of perinatal streptococcal disease must be scrupulously followed. Additionally, it can happen that an inflammatory state of the vein is established in a condition of angiodysplasia or vasculopathy, in which case there is a significant increase in risk of thrombosis inside the phlebectasia and/or dysplasia.

Single Umbilical Artery

This condition is present in an imprecise number of pregnancies, thought to be about 0.5–1.0 %; however, in a series of foetal malformation, the condition has been reported at 8.7–46 %, leading many authors to consider a missing artery as a marker for other congenital abnormalities. The artery could be missing because it was never originally formed or because it was absorbed after formation owing to a preponderance of flow in the other artery. This second hypothesis can be confirmed by findings of remains of smooth muscle fibres along the cord. Malformations which can induce the reabsorption of an artery are those connected to the abdominal wall such as hernia, persistent urachus, bladder exstrophy, etc. or those of the urinary apparatus with a consequent destruction of the part of the abdominal wall where the artery passes through. In the case of sirenomelia, where there is hypoplasia of the lower half of the body with fused legs and anogenital defects, we find the lack of formation of the umbilical arteries from the allantoid vessels with a single cord artery coming directly

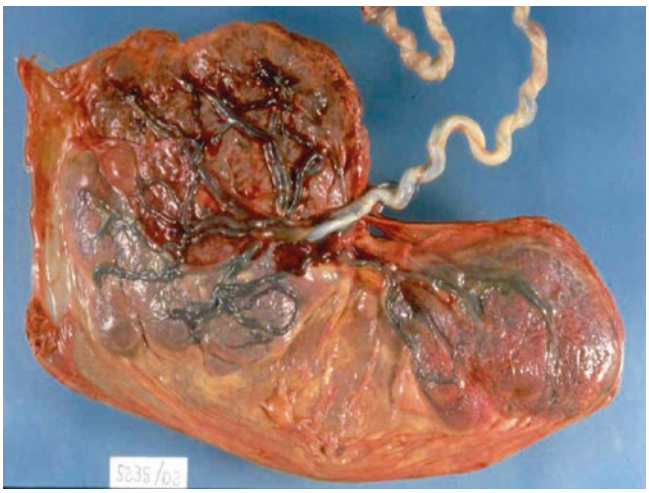

Fig. 2.11 Single placenta with an accessory lobe regularly perfused by branching vessels from allanto-chorial circulation without vascular lesions

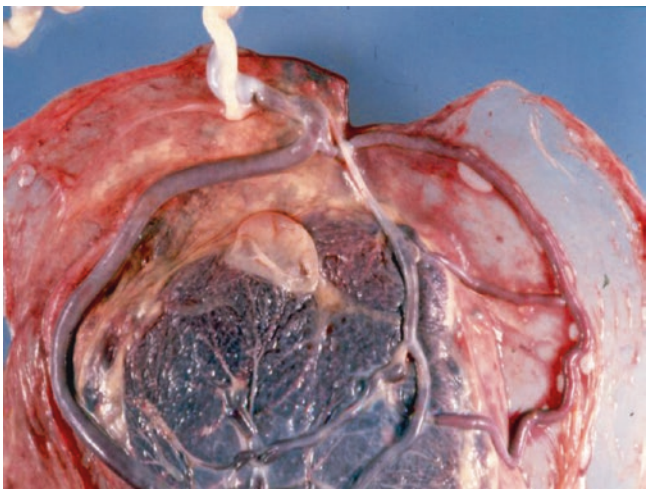

Fig. 2.13 Angiodystopia of the allanto-chorial vessels in a case of velamentous insertion of the cord. Note the large vascular arcades delimiting areas of thin and lucent membranes free of the chorionic disc

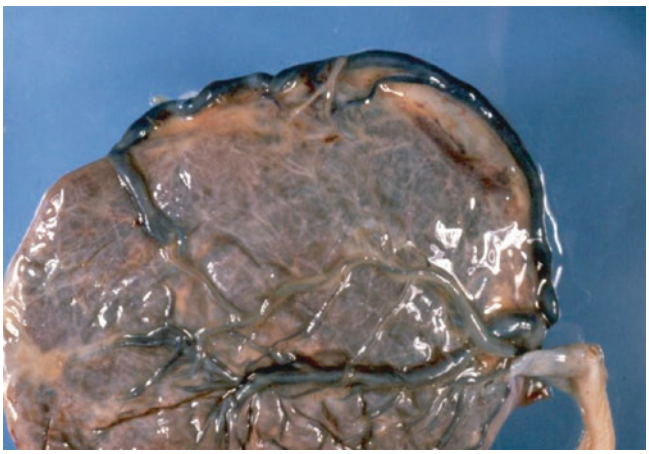

Fig. 2.12 Angiodystopia of an allanto-chorionic vessel disposed on the edge of the chorionic disc

from the abdominal aorta below the superior mesenteric artery as an evolution of the primitive omphalomesenteric artery.

Chorionic Vessels

Lesions of the chorionic blood vessels can be separated into two main categories: angiodystopia and angiodysplasia.

Angiodystopia

When the umbilical cord is abnormally positioned relative to the chorionic plate (Fig. 2.11) either marginally (Fig. 2.12) or even on the membranes (velamentous insertion) (Fig. 2.13), the blood vessels must run abnormally to reach their cotyledons. Such abnormalities can create critical conditions for placental circulation and thus for the foetus. In a velamentous cord insertion, the vessels run not in straight lines but freely over the membranes reaching lengths of 20–30 cm, even arriving at the opposite margin of the placenta. On some occasions they form minor branches that can have larger diameters than the original. Clearly, during foetal engagement or labour, a vessel can rupture and cause sudden and massive foetal exsanguination and death [10, 11]. Less dramatically, compression of these vessels can create stop and go alterations in blood flow with repercussions on the flow rates of the cord vessels and thus foetal perfusion, especially serious for the intracranial and cerebral regions. The incidence of velamentous insertion is higher in twin pregnancies, and therefore the risk is higher for anomalous conditions of the chorionic vessels. These conditions are more serious in twin pregnancies with fused placentas, whether monochorionic diamniotic or dichorionic diamniotic, as, at the dividing membrane, the vessels, unprotected by Wharton's jelly, are more susceptible to pressure or squeezing by one or both of the twins.

Abnormal or unusual routes of the blood vessels on the chorionic surface (Fig. 2.14) are not limited to markedly eccentric or marginal cord insertion. Even when the cord is centrally inserted in a single placenta, routes can be complex and tangled. Vessels, both arteries and veins, can be found touching, crossing, overlapping or even plaited together, and at times dystrophic alterations of the walls can be observed. Clearly, in these conditions, narrowing takes place and bottlenecks are formed so altering blood flow.

Angiodysplasia

Dysplasia of the walls of both veins and arteries can occur. In the veins we may observe ectasia either limited to small tract or extended to varicosity with a sudden increase of vessel calibre. As in the case of the funicular vessels, such lesions can give rise to wall thrombi just as can all phlebectasias or varicose states of the adult. These lesions may create a critical situation especially if associated with an inflammatory

Fig. 2.14 On the amniotic surface of the disc, the angiodystopic vessels form some crossing of the veins and subsequent ectasias

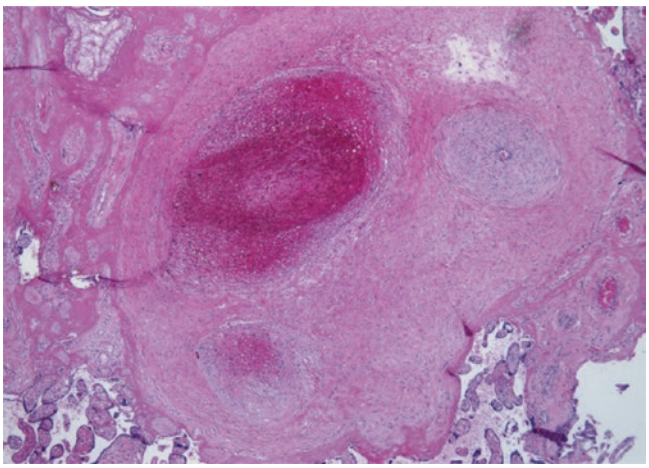

Fig. 2.15 Vessels of a primary stem villous with severe sclero-obliterative disease and recent thrombosis of a large vein

state of subamniotic or perivascular connective tissue (on the foetal side of the chorionic plate).

Vasculopathy

One of the most serious conceptual errors in placental vascular pathology is not taking into consideration degenerative lesions of the chorioamniotic and cord vessels even though these types of lesion are widely described and codified in vascular pathology of the child and of the adult. Sclero-obliterative vasculopathy (Fig. 2.15) due to smooth muscle hyperplasia or overlapping and repetitive degenerative fibrosing alterations of the tunica media are known, and these lesions are correlated with cigarette smoking or pathologies of foetal hypertension. However, even if the correlation between the lesions of the chorioamnionitic vessels and smoking and the mother's age is known, a numerically or statistically significant number of case studies are difficult to find in the literature to able to define a proven risk situation.

Instead, the topic of foetal hypertension is as widely debated as it is not studied. Previously seen as impossible, except in certain pathologies determined by genetic anomalies, today this concept of increased heart activity against increased resistance in foetal circulation has been accepted by serious researchers. In these cases we can observe myocardial hypertrophy and an endocardial fibroelastosis in both ventricles together with a thickening of the tunica media of the chorioamniotic and the cord vessels. This muscular hypertrophy is associated with fibro-sclerotic or fibrous degenerative phenomena with activation of myofibroblasts in the tunica media (Fig. 2.16).

Recently much attention has been given to foetal thrombotic vasculopathy that is the thrombotic occlusion of the lumen involving mainly the chorioamniotic veins. There is primitive damage to the walls which can be seen as a substrate for an anomalous aggregation of platelets in foetal coagulative diseases. The simple description of the elementary lesion gives rise to a series of terms and situations that immediately evoke the idea of serious damage. However, paradoxically, while thrombotic vasculopathy creates alarm in an adult, the illogical but ingrained idea that the foetus does not have its own pathologies leads this disease to be minimised if not completely ignored in placental pathology. Microthrombi can pass directly by umbilical cord vein, ductus venosus (Arantius' duct) and inferior vena cava to the right atrium of the heart and to the arterial network of the carotids and the circle of Willis. The chorioamniotic vessels can contain old thrombi complicated by recent thrombotic coagulates, and this alternation of old lesions, limited phlebectasias and recent thrombotic coagulates can create a dynamic situation which can modify the course of the third trimester but also suddenly and dramatically influence the birth itself in that the pulling on the cord by the foetal engagement can determine massaging and squeezing of the vessels so provoking a quick release of the thrombi.

Foetal thrombotic vasculopathy must not be confused with thrombotic vasculopathy of the arteries because, though it is difficult to physically distinguish the chorial veins from the arteries because of their intrinsic similarities, pathogenetically they have very dissimilar outcomes. Thrombi from an artery will cause the occlusion of a vessel of a branch of a villous tree, and as a consequence a villous ischaemia perhaps leading to infarct through this event is rarer than the damage caused by the vasculopathy itself to the chorioamniotic vessels that are involved both synchronously and metachronously. These lesions will be discussed later in the chapter as lesions of the chorionic plate.

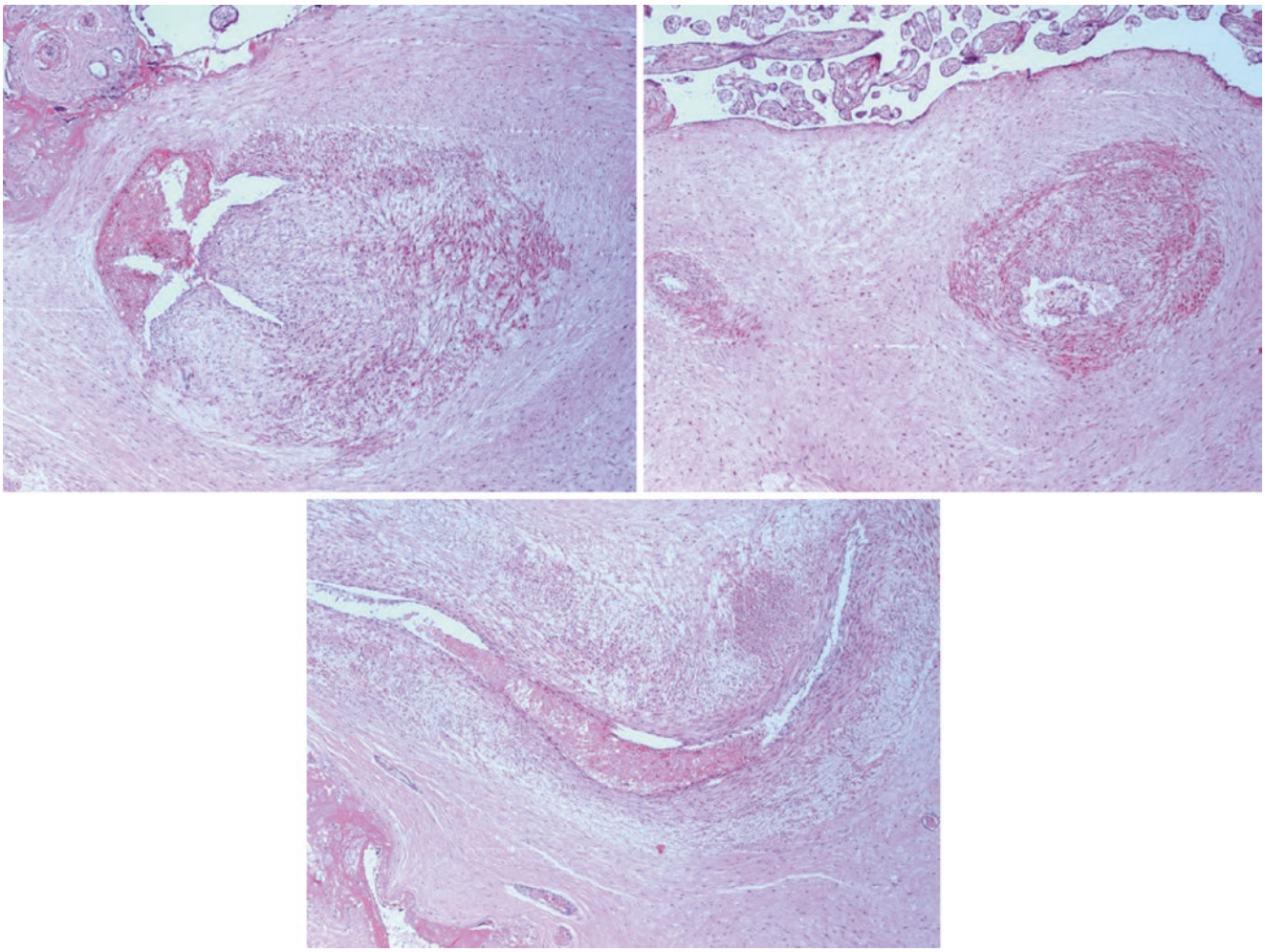

Fig. 2.16 Histological pattern of stem arteries with irregular arrangement of the muscular fibres of the tunica media. Note the eccentric hypertrophy of the vascular wall

Vasculitis

From a strictly morphological point of view, a vasculitis (Fig. 2.17) of the chorioamniotic vessels is completely conformed to that of the umbilical cord. These vessels run under the amnion on the foetal side of the chorionic plate, so, clearly, any chorioamnionitis of the plate can easily extend to the vessels and to their venous branching, thus for most cases making the vessels the means of transferring the chorioamnionitis of the membranes to the vasculitides of the umbilical cord.

2.1.2 Vascular and Circulatory Pathologies of the Chorionic Plate

The pathologies of the chorionic plate can be classified into three distinct categories, the first being of the stem and intermediate villi, the second of the maternofoetal transfer at the terminal villi and the third of the circulation dependent on alterations of maternal blood flow both intracotyledon and in

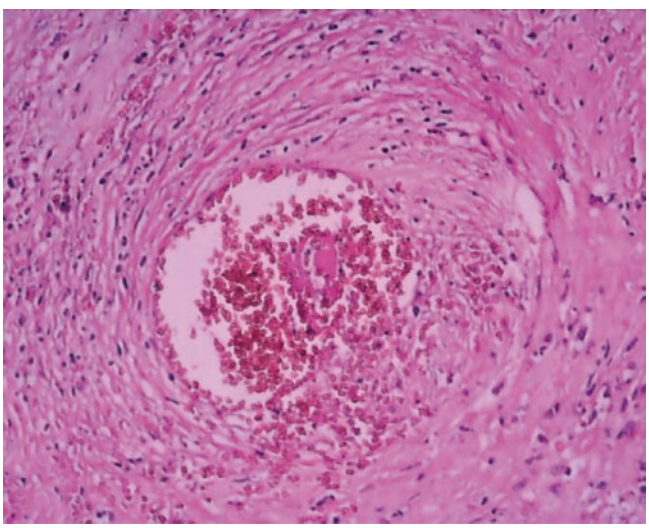

Fig. 2.17 Vasculitis of an amnio-chorionic vein in a case of severe chorioamnionitis. The endothelial damage is associated with an early thrombosis

Fig. 2.18 Recent intervillar haemorrhage. The blood clot compresses the placental parenchyma producing a pseudocapsule

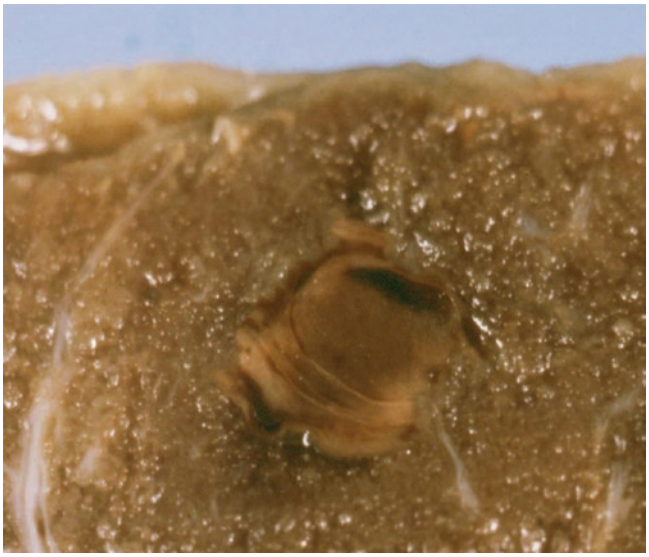

Fig. 2.19 Kline's intervillar haemorrhage. The "onion bulb" stratification of the fibrin witnesses the advanced process of organisation

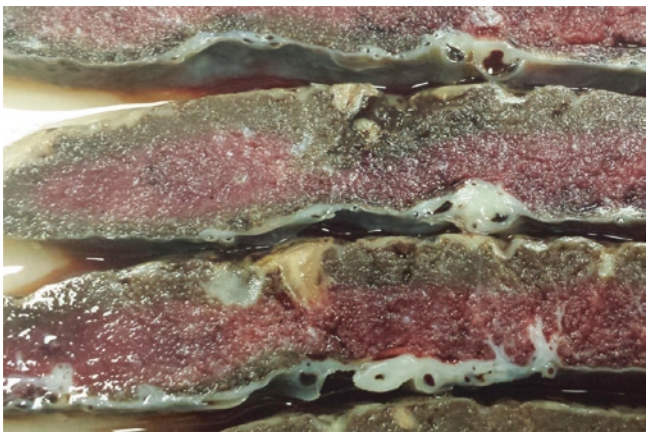

Fig. 2.20 With macroscopic subserial sections of the chorionic disc, we can observe several minimal intervillar haemorrhages. These foci are superficial (corresponding to the apex of maternal cotyledons), but may be responsible of the progressive foetal anaemia

the decidua basalis. Vascular lesions must be divided into those of maternal circulation and those of foetal circulation, this distinction constituting the pathological base to clearly understand them. The maternal side of the chorionic plate is irregularly separated by deep septa (corresponding to the septa of the decidua) into 16–20 lobules known as maternal cotyledons containing various branches of one or more villous stems. In the direction of the decidua basalis, it is covered by the fibrinoid deposits forming the Rohr and Nitabuch striae which create a physical and immunological barrier and the decidua infiltrated by extravillous trophoblast. There are also the Langhans striae which are fibrinous deposits which accumulate between the stem villi bases.

Inside the maternal cotyledon the maternal blood arrives from modified spiral arteries at a reduced speed, and, after circulating inside the cotyledon and carrying out a complex series of transfers with the foetal blood, it flows out of it in the reverse direction through breaks in the fibrinous striae to further drain into the venous system of the decidua structured with lacunae and sinuses and decidual veins to be returned to the mother.

2.1.2.1 Actual Vascular Pathologies

Intervillous haemorrhages (Fig. 2.18), once called "intervillous haematomas" or Kline's haemorrhage, whether single or multiple, are usually of small dimensions, 0.5–1.5 cm, so that they can easily escape notice in a fast or superficial macroscopic examination of the chorionic plate. Macroscopically they present as a clot or a collection of haematic fluids, delimited by a wall of villi compressed against it (Fig. 2.19). Recent and acute lesions can present with various levels of organisation and stratification so documenting the chronology of the lesion. From a pathogenetic viewpoint, it is interesting that the haemorrhage is due to the rupture of a second- or third-order stem vessel from a structural alteration of the wall or from acute foetal hypertensive events.

Our experience has shown us that the seriousness of the situation depends not only on the number of lesions but, more importantly, on where they were. If there are multiple haemorrhages localised at the top of the cotyledons, they can bring about a progressive anaemisation of the foetus (Fig. 2.20); the bleeding is serious but not massive and immediately drained by the decidual venous vessels such that neither observable haematomata nor bruising is formed.

Widespread haemorrhaging from the rupture of capillaries or capillaries inside of terminal or intermediate villi will

Fig. 2.21 An old intervillar haemorrhage with a complete fibrous organisation near an ischaemic lesion

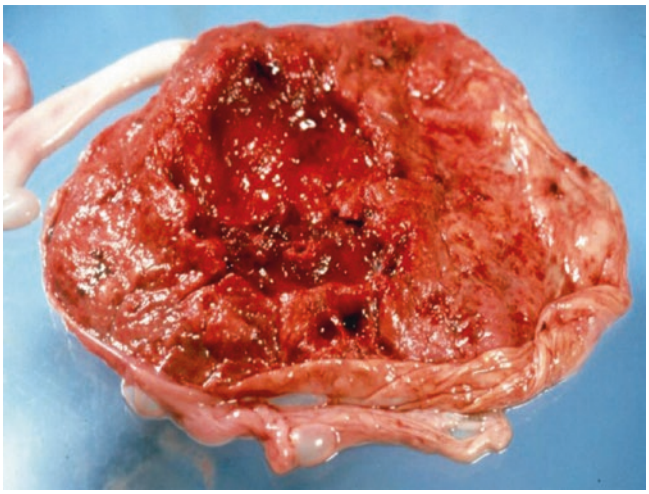

Fig. 2.22 Recent intervillar haematoma: the chorionic villi are distanced by the blood clot, and an initial stratification of the fibrin is present upon the broken stem vessels, origin of the haemorrhage

also not determine cavitation or circumscribed haematomata (Fig. 2.21).

Often due to a diabetic placentopathy with a dysmaturity of the villi, there is intense congestion of the vessel network and a hypercapillarisation, or a real chorangiosis (Fig. 2.22).

The bleeding first involves the stroma of the villi (intravillous haemorrhage) (Fig. 2.23) and, successive to laceration of the trophoblast mantle, spreads to the intervillous spaces (Figs. 2.24 and 2.25). These events are haemodynamically relevant only if they are many and a significant part of the cotyledon is involved, though even a small lesion increases the contact and commingling of maternal and foetal blood, so increasing risk of transmission of infective agents especially viruses (e.g. HIV is vertically transmitted from mother to child) or of a histo-incompatible reaction.

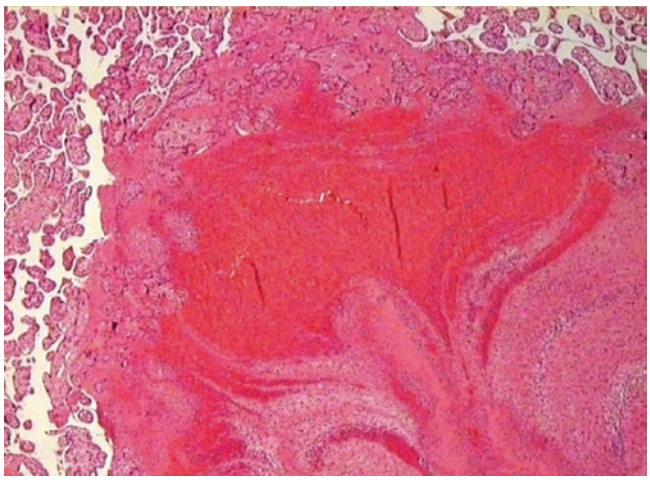

Fig. 2.23 Intracotyledon haemorrhage with haematic spread among the compressed villi. The clot is partially organised in fibrinoid substance

While ischaemic infarction in the cotyledon is well known and most extensively studied in placental pathology, villous ischaemic infarction [12], much less visible and so less known (Fig. 2.26), deserves more attention. It is caused by the occlusion of a stem vessel within the villous tree (Fig. 2.27), and though the trophoblast mantle remains vital as it is bathed in the mother's oxygenated blood, the stromal supports suffer an ischaemic necrosis with sclero-fibrosing degeneration (Fig. 2.28).

This strange effect of a florid exterior on a dead interior is not very important in itself as the lesions are usually of modest extent and the number of villi which are non-functional is limited; however, what originally caused the occlusion is very important. It can be from the inflammation of the root, or from an obliterative vasculitis with proliferation of the intimal cushion and microthrombi. We can follow the chronology of these lesions because we find recent occlusions, both partial and complete, of dense fibrin thrombi; occlusions stabilised by intimal elements such as myofibroblasts or fibroblasts; and recanalised occlusions with the formation of small endoluminal vessels. These lesions in the placenta are autoimmune vasculopathies, as can be seen in adults in cutaneous and splanchnic vasculitis, indicating an abnormal foetal reactive state or a latent or self-limiting autoimmune disease. Important as these pathologies are in themselves, they are more important in that they open a window to the foetal thrombotic vasculopathy which involves the chorioamniotic vessels.

2.1.2.2 Vascular Pathologies of the Maternal Foetal Transfer Structure

The terminal villi in the chorionic plate are where there is the transfer of oxygen, nutriment, water, hormones, minerals, vitamins, etc. between the mother's circulatory system and

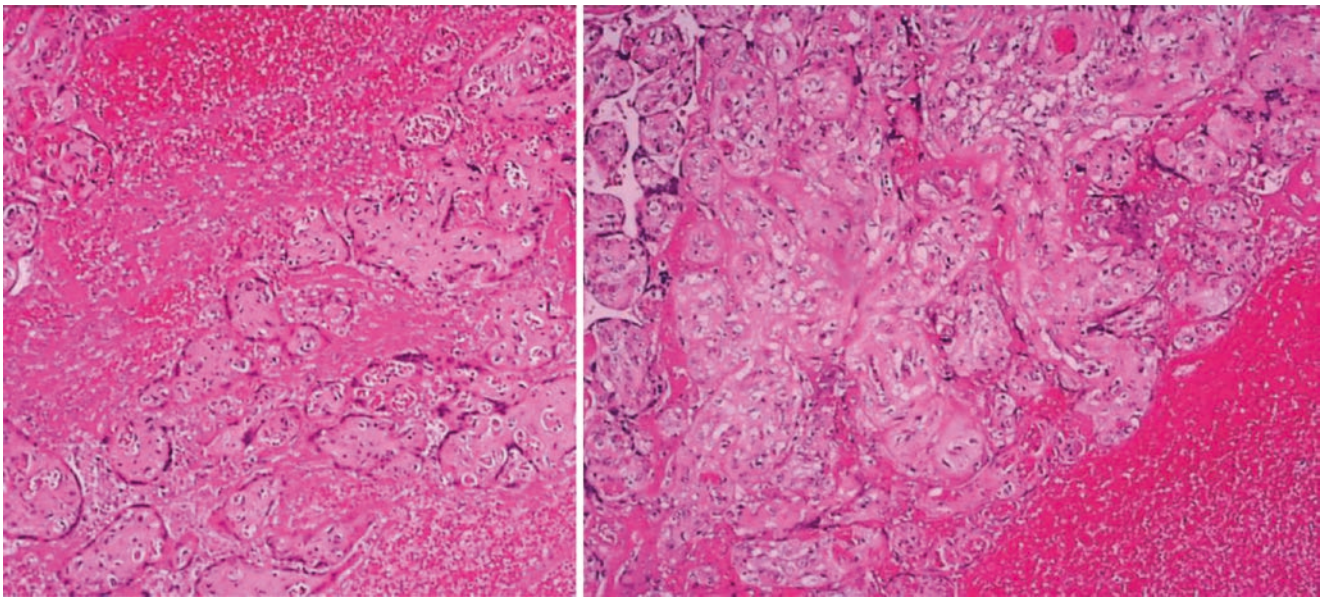

Fig. 2.24 Old intervillar haematoma organised in multiple fibrin stratifications

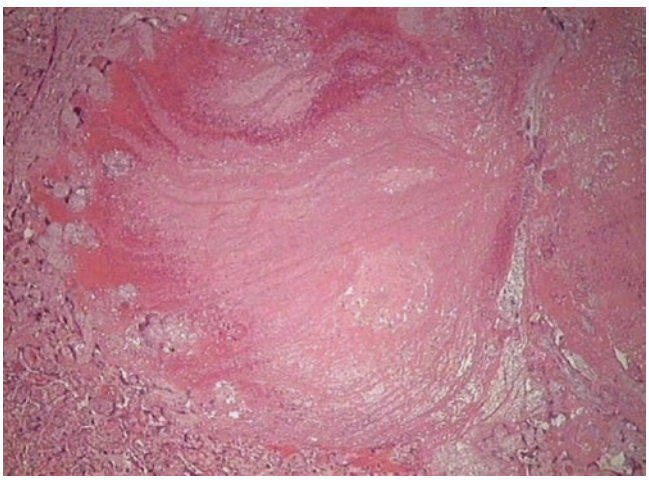

Fig. 2.25 Macroscopic view of an ischaemic villar infarction. At difference with a cotyledon infarction, the lesion is more extensive in the maternal floor. The thrombosis of the stem vessel is evident in the figure

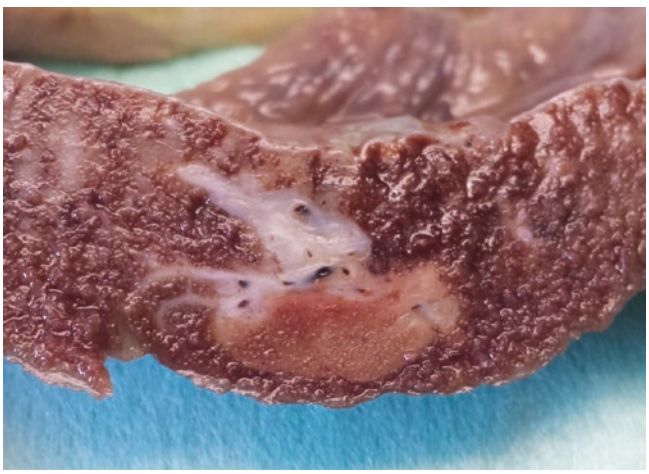

Fig. 2.26 Evidence of a complete thrombosis of an artery of a third-level stem villous before the branching of the intermediate villi

that of the foetus. The transfer is not carried out in the interface between the two anatomical structures of the maternal and foetal capillaries but between the maternal blood which circulates inside the cotyledon of the chorionic plate and the foetal blood in the capillary network of the terminal villi. In the human body a similar system is found only in the lungs between the air, which is external to the organism, in the alveoli and the blood in the alveolar capillary network.

It was previously believed that the placenta and, in particular, the chorionic plate were in two sections, the maternal part and the foetal part, and that the villi buried themselves into the decidua with branching to find the mother's vascular system. Though today clearly known to be untrue, these old conceptions conditioned the thinking, not so much of pathologists but, of clinicians so as to lose sight of the essential point of the pathology of the maternofoetal transfer.

It is not possible to discuss pulmonary pathology using only the macroscopic characteristics of the lesions or the conventional histology of the lung. Only by defining the ultrastructures and the alveolar structures designated for exchange, whether epithelial or stromal or vascular, has allowed a clear and correct classification of pneumopathies with real correlations and known repercussions on the interpretations of various symptomologies and thus on treatment regimes. A similar analysis of the placental exchange shows that five structures are involved in the terminal villi. They are the endothelium of the capillaries of the chorionic plate,

the basal membrane of the endothelium, the villous stroma, the basal membrane of the trophoblast, and the trophoblast which, in a full-term placenta, is in fact, for large stretches, a cytoplasmic extension of the syncytiotrophoblast. The villous stroma becomes thinner and thinner, and in many terminal villi, the basal membrane of the capillary fuses with the basal membrane of the trophoblast forming a single structure.

Each of elementary histological structures can be subject to paraphysiological modifications or clearly pathological alterations. However, substantially, the main lesion is the thickening of the two basal membranes so creating a real barrier to exchange. Electron or optical microscopic observation of specimens embedded in resin and of semi-thin sections has clearly shown that such alterations are not correlated to or dependent on anomalies of villous branching or maturation, as these latter are seen in substantially normal histological situations. The thickening is responsible for a reduced functioning of the chorionic plate even when there are no lesions which are important or macroscopically identifiable. These problems come to the fore when there is an unexplainable growth restriction with nearly normal blood flows or in silent situations due to pathologies or structural anomalies of the placenta.

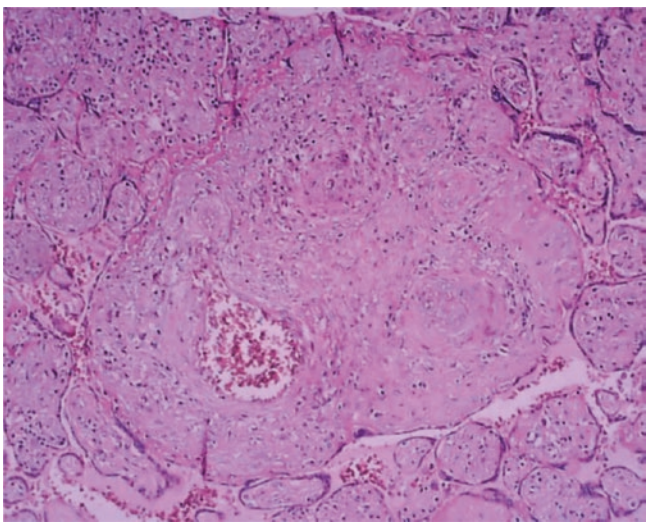

Fig. 2.27 Same case of the previous figure. Recent ischaemic infarctions of the villi associated to the arterial thrombosis of stem villus. The damaged villi are fibrotic with several syncytial knots. The noninvolved villi are normally present around the lesions

Other than basal membrane thickening, there may be a measurable increase in the stroma interposed between the capillaries and the villous surface. The surface layout of the capillary vascular network is what characterises the transfer villi, and it fully develops only in the third trimester, and thus a placement of the network at distance from the villous surface shows a dysmaturity of the villi (not an immaturity in which intermediate villi would predominate and therefore without surface capillaries).

Chorangiosis is another problem, but not only because of the increased entanglement and risk of bleeding as mentioned above. In fact, when the network is unevenly distributed, there can be much capillary crowding with increased blood flow, but the areas of transfer are found between the capillaries, and so no exchange is possible, leading to a situation where the chorangiosis may take over much of the foetal haematic mass normally involved in maternofoetal transfer.

Chorangiosis is typical of a diabetic placentopathy and of a placentomegaly which are often found together. However, it is clear that an increase in volume of the cotyledon mass does not correspond to an increase in maternofoetal exchange but can on the contrary undermine the physiological transfer

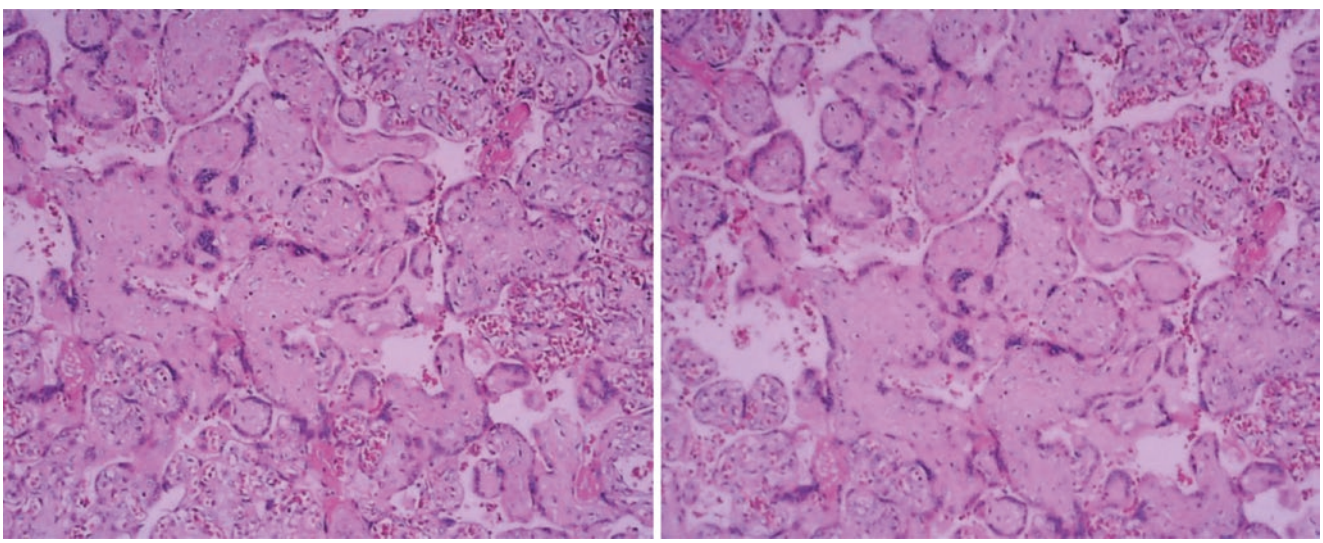

Fig. 2.28 Coagulative necrosis of the villi in an ischaemic cotyledon infarction due to a sudden interruption of the maternal circulation in the utero-placental arteries

functions. Such an event brings about increased placental resistance (peripheral circulation in the foetal haemodynamics) and so leads to myocardial hypertrophy of the left ventricle, often with endocardial lesions of hypertension such as endocardial fibroelastosis, or to platelet sequestration.

Additionally, we find that with a reduction in transfer ability, there is also a corresponding immaturity of both the placenta and the foetal organs.

2.1.2.3 Circulatory Pathologies of the Chorionic Plate

All of the ischaemic infarction lesions of the cotyledon depend on an alteration of the maternal blood flow. They can be acute or progressive so that the complete evolutionary range of placental hypoxic ischaemic lesions may be found. It is well known that some ischaemic infarctions have no effect on the overall state of foetal health, meaning not only its general well-being and its normal growth but also the state of maturation of its organs. If the infarctions are numerous, involving more than 10 % of the volume of the chorionic plate, and have established themselves in differing time periods, then ischaemic infarction of the cotyledon can cause damage, even serious damage including late foetal death.

In a macroscopic examination of the chorionic plate, ischaemic infarction can be recognised only in its evolutive phases, and recent areas of ischaemic infarction cannot be recognised with any certainty but only hypothesised, and this is only because of an increase in the consistency and compactness of the cotyledon structure.

Microscopically they are characterised by a crowding and overlapping of villi without an intervillous space and without blood. The caving in of the villous structures, due to the lack of blood circulating within the cotyledon, causes ischaemic necrosis of the trophoblast mantle of all orders of villi (Fig. 2.29), while the stroma and internal vascular structures of the villi remain as they continue to be irrorated by foetal blood. Only with the continuing evolution of the lesion will the damage extend to vascular and stromal components of the villi, starting with the less robust terminal villi to arrive at the stem villi. Intra-lesion fibrous reactions are a minimum as it is not necessary to fill empty spaces, while, in contrast, the degenerative stromal phenomena are a progressive fibrosing and hyaline sclerosis of the more resistant structures. The reactive-type inflammatory infiltrate is mainly perilesional, or intralesional in the more peripheral parts. This evolving microscopic clinical picture can be identified macroscopically in compact areas, of white/grey areas surrounded by a dark red band, and by white/mother-of-pearl areas which are clearly sclerotic (Figs. 2.30 and 2.31).

In the intermediate evolutionary phases, some ischaemic infarctions can be complicated by haemorrhage, not due to rupture of the villous vessels but rather to a spreading of intracotyledon blood inside the breaches or fissures in the ischaemic villous mass. In the differential diagnosis, it is easy to confuse this analysis with that of widespread intervillous haemorrhaging (described above) that has resulted in a peripheral ischaemic reaction of the villous tissue which is thus compressed.

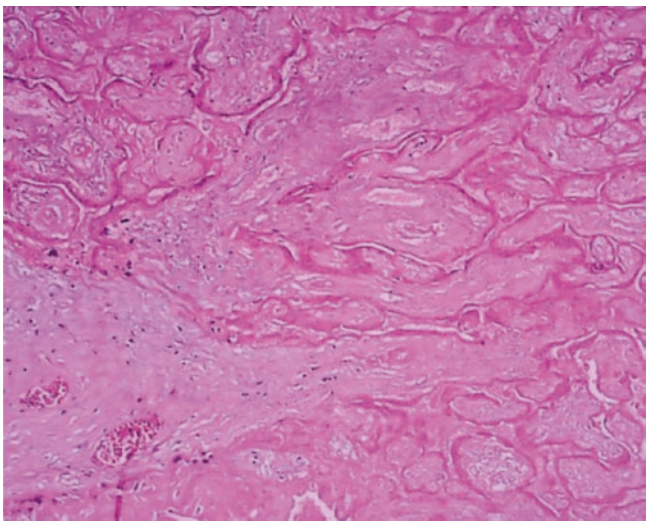

Fig. 2.29 A term placenta with multiple infarctions: the cotyledons have different sizes and shapes, and the chorionic disc presents an irregular profile. The large ischaemic lesions fully organised appear through the amniotic layer

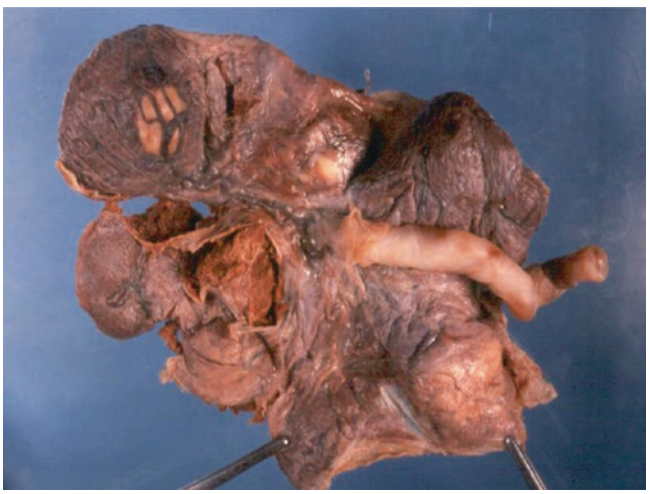

Fig. 2.30 Several cotyledon infarctions risen in different times and with different stages of organisation

From the mother's circulation there can be a retroplacental haemorrhage, either centrally or at the margins (Fig. 2.32), that can provoke various grades of separation of the placenta or simple disconnections from the decidual site, so in turn causing situations of hypoxia or ischaemia in the cotyledons. Macroscopically they are difficult to identify as they can easily be confused with clots attached to the maternal side of the chorionic plate. Two main diagnostic criteria must be applied to arrive at a correct identification of

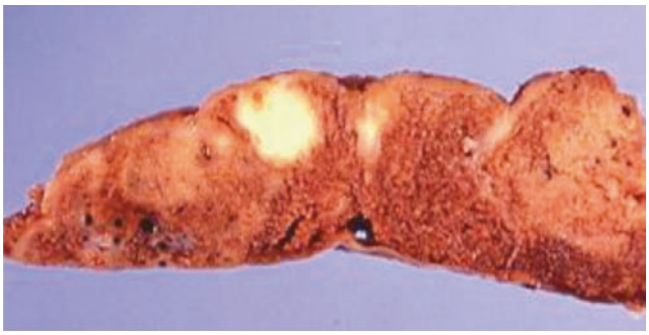

Fig. 2.31 Old infarction

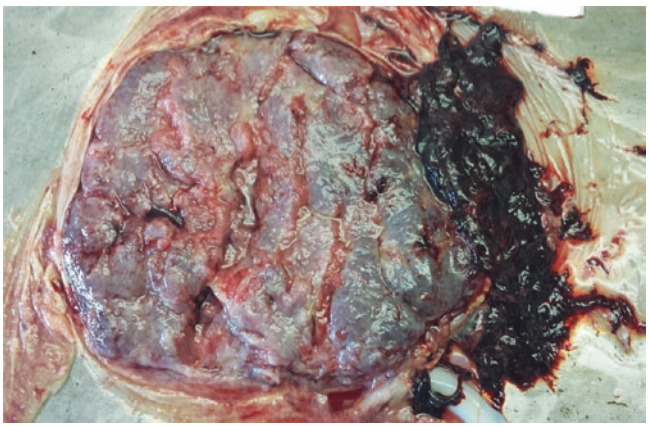

Fig. 2.32 Recent large blood clot adherent to the edge of the chorionic disc and part to the free membranes

retroplacental bleeding, the first being the observation, especially in a fresh placenta, of a depression or a squashing of the cotyledons in correspondence with the blood clot and, secondly, how strongly they adhere to the top of the cotyledon. These findings are valid and unequivocable only if supported by clinical data or magnetic resonance imaging diagnostics.

At a microscopic level there are no sure diagnostic criteria except for non-recent marginal or retroplacental bleeding of modest dimensions, where we can find organised parts of the clot with fibrin layers adhering to the layer of connective tissue cells and to extravillous intermediate trophoblast external to the fibrinoid layer.

An examination of the chorion plate carried out on parallel-cut specimens of fixed material can show a reduction in the thickness of the plate, surrounded and characterised by flattened cotyledons such as to allow the supposition (but without direct proof) of a previous limited separation which cannot be reported because the clot has been reabsorbed.

In an overall view of the pathology of blood vessels and perfusion in the chorionic plate, each and every separation or disconnection from the decidua basalis will necessarily determine ischaemic lesions in the corresponding part of the cotyledon, and therefore any separation of the placenta due to retroplacental haemorrhage will have corresponding ischaemic infarctions and will also have underperfusion lesions resulting from a compensation for the redistribution of the flow within the cotyledon.

2.2 Pathology of the Chorioamniotic Vessels in Twin Placentas

In the previous paragraphs we have spoken of certain particular conditions of twin placentas when vessels run dystopically on the membranes at the juxtaposition of the two amniotic sacs, or when the cord insertion in one or both cases is near the region where the dividing septal membranes are attached to the chorionic plate, known as the t-zone.

These situations occur when there is, macroscopically speaking, only a single chorionic plate, though it may be derived from the fusion of two separate plates (dichorionic diamniotic), or it is originally a single plate (monochorionic diamniotic).

In a monochorionic placenta, whether monochorionic diamniotic, other peculiar pathological vessel conditions can arise. Vascular communication between the placenta networks of each twin is extremely common. These anastomoses can have no discernible effect or can lead to the serious twin-to-twin transfusion syndrome (TTTS). Other anomalies in the vessel network are not part of this category, but extrachorionic direct anastomoses would be better classified as "vascular steal", as in the well-known conditions of "coronary steal" or "subclavian steal syndrome".

For humans, a monochorionic placenta is a real malformation as two foetuses must share the one organ of the chorionic plate, and this can lead to serious complications in pregnancy which may compromise its outcome. Some such serious outcomes are Twin Reversed Arterial Perfusion (TRAP) with a pump twin and an acardiac twin, or symmetric or asymmetric conjoined twins.

The increased use of assisted reproductive technology has seen a net increase in twin and multiple pregnancies, and not only of the dichorionic type but also with a monochorionic placenta, perhaps for embryo splitting or the manipulation that may foster blastocyst division.

That anastomoses are present in the monochorionic placenta is perfectly normal so allowing vascular communication between the twins' circulatory systems (Figs. 2.33, 2.34, 2.35, and 2.36).

This communication of the chorioamniotic vessel can be direct arterio-arterial (AA), veno-venous (VV) and arteriovenous (AV), and the repercussions of a combination of these anastomoses can vary from a positive/null effect to serious problems including death (Fig. 2.37).

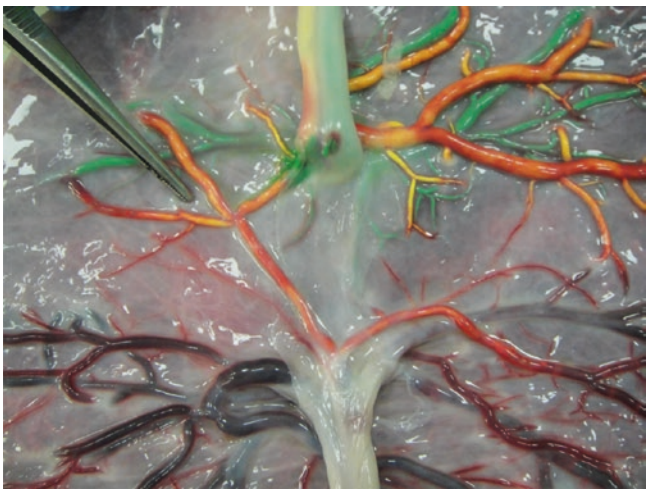

Fig. 2.33 Arterio-arterial anastomosis between two umbilical cords with near insertion in a biamniotic monochorionic placenta (after removal of the amniotic sacs). In the cord A the arterial vessels are stained in *yellow* and the veins in *green* by oil-coloured substances

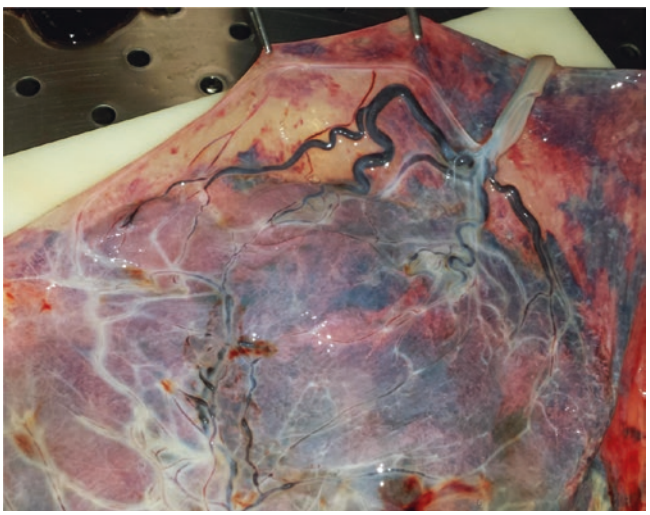

Fig. 2.34 Twin monochorionic biamniotic placenta: in the central portion of the chorionic disc, the signs of intrauterine laser coagulations are evident. On the free membrane we can observe dystopic vessels due to a velamentous insertion of a cord

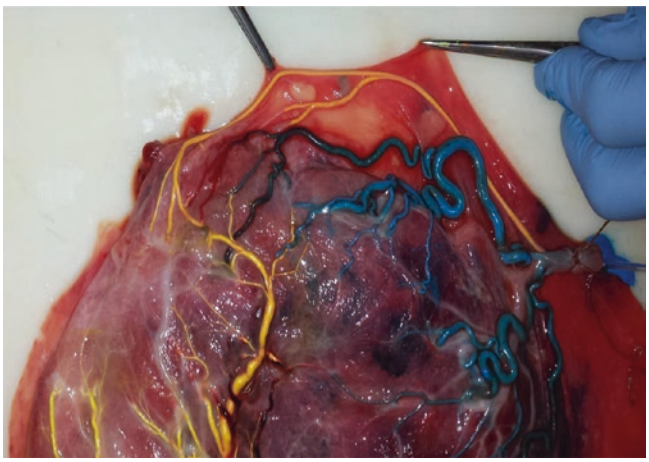

Fig. 2.35 Angiodystopia of an artery disposed along the free membranes anastomosing in a large vein at the root of the contralateral cord

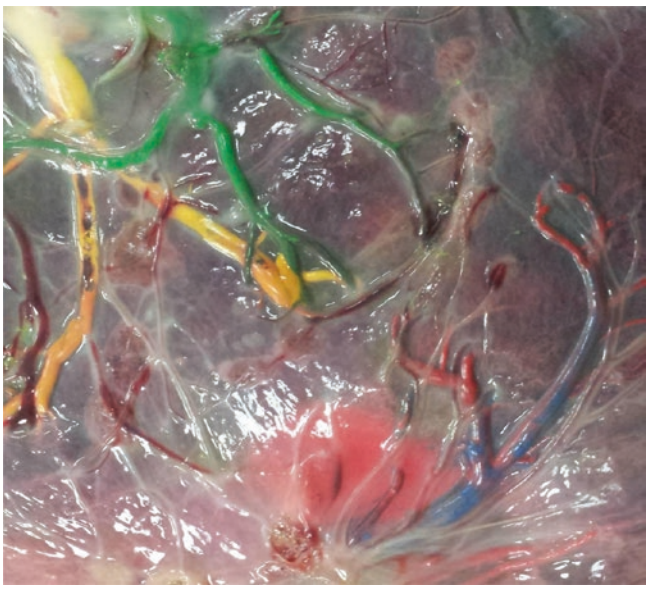

Fig. 2.36 Results of an intrauterine intervention of laser coagulation in a TTTS with deeper arteriovenous anastomoses

A precise analysis of the networks and their combinations is necessary, and this can be done by injecting into the arteries and veins different colour dyes which can slowly diffuse without overflowing.

The superficial anastomoses on the foetal surface of the plate are AA and VV, with the flow being bidirectional from either twin to the other depending on the relative flow forces in each system. Differently and more importantly, the AV communications are found deep within the substance of the placenta with blood being supplied from an artery of one twin and flowing into a vein of the other, while, at the same time in other locations, there can be AV anastomoses with blood from the second twin flowing into the vein of the first. To see what is the clinical importance of the anastomoses, beyond their precise morphology and identification, it is necessary to evaluate the volume of each portion of the chorionic plate for each umbilical cord by following the tributaries.

Knowing that serious selective IUGR (SIUGR) can occur solely because of discrepancies within the cotyledon mass, it is evident that in a dichorionic twin pregnancy, SIUGR can occur because of discrepancies of volume of the two chorionic plates. These cases are always serious and often lead to inauspicious outcomes for one of the twins in that there are no protective anastomoses as there are in the monochorionic placenta.

When the two portions of the plate are substantially the same and the cords are well inserted (central to each portion, or at the most at the margins), that anastomosis organisation

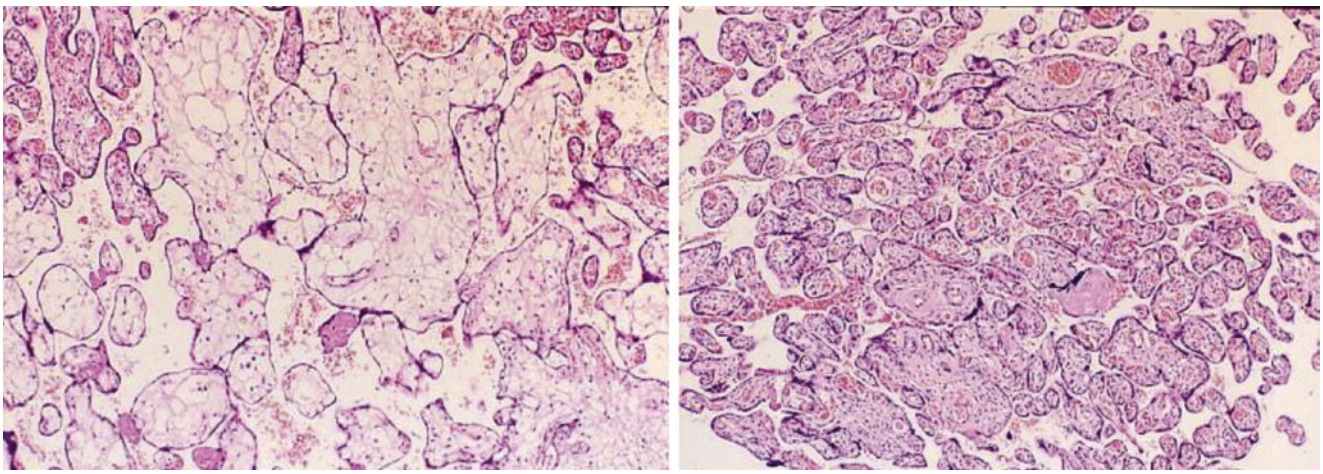

Fig. 2.37 Histological findings of a monochorionic biamniotic placenta: the disc portion of the donor foetus has hydropic and anaemic villi (on the *left*), while the portion of the receiver presents a haematic plethora (on the *right*)

which does not complicate the pregnancy, but on the contrary carries out a protective role in regularising the circulations, is the AV type, deep and uniformly distributed; rare AA type, only one or maximum two with small calibre vessels and a para-marginal route over the chorionic plate; and absent VV type, or very rare.

Different organisations of the anastomoses give rise to TTTS, often with SIUGR, so much so that some authors believe that both conditions are found necessarily together, though with variously different predominant aspects.

In TTTS the anastomoses are large and frequent AV type, evidently unidirectional and deep; rare AA type of small calibre, superficial and bidirectional; and more frequent VV type, superficial and bidirectional.

In SIUGR the anastomoses are frequent AA type with large calibre that, with the discrepancy in the chorionic plate volumes, allows the twin with the larger portion to haemodynamically balance the twin with the smaller volume (that would otherwise suffer a haematic overload). This condition is frequently associated with velamentous insertion of the cord of one of the twins and with a discrepancy in the vascular distribution between the two sectors.

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Abruptio Placenta

3

Miroslaw Wielgos, Patrycja Jarmuzek,
and Bronislawa Pietrzak

3.1 Definition

In normal pregnancies, placental separation occurs immediately after birth, in the third stage of labor. Preterm detachment of the placenta, known as placental abruption (Lat. *ablatio placentae praecox)*, is defined as a complete or partial separation of a normally implanted placenta before the delivery of the fetus and remains one of the most important causes of maternal morbidity and neonatal mortality (Fig. 3.1).

3.2 Epidemiology

The prevalence of placental abruption (PA) ranges from 0.4 to 1 % of all pregnancies and depends on the population. In Nordic countries, approximately 0.38–0.51 % of all pregnancies are complicated by placental abruption. This rate tends to be higher in the USA (0.6–1 %). In the developing areas, e.g., in some African countries, PA incidence can reach up to 2 %. According to epidemiological reports, the incidence of PA has been steadily increasing. The recurrence rate of placental abruption is 8.8 and 25 % after one and two events, respectively [1–8, 11].

Preterm detachment of the placenta is potentially disastrous, especially for the fetus, with perinatal mortality of 25 %. The incidence of PA is the highest at 24–26 weeks of gestation and decreases with advancing gestation. Over 50 % of the cases occur before 37 completed weeks of gestation. In the developed countries, almost 10 % of preterm deliveries are caused by placental abruption [9, 10]. High neonatal mortality is mainly related to prematurity, low birth weight, IUGR, and asphyxia. A 25-fold higher mortality is present even in term pregnancies complicated by PA. Although the stillbirth rate due to abruption has declined, it remains an important cause of neurological deficits in the first year of life. Approximately 20 % of the survivors delivered between 26 and 36 weeks present cerebral palsy [12].

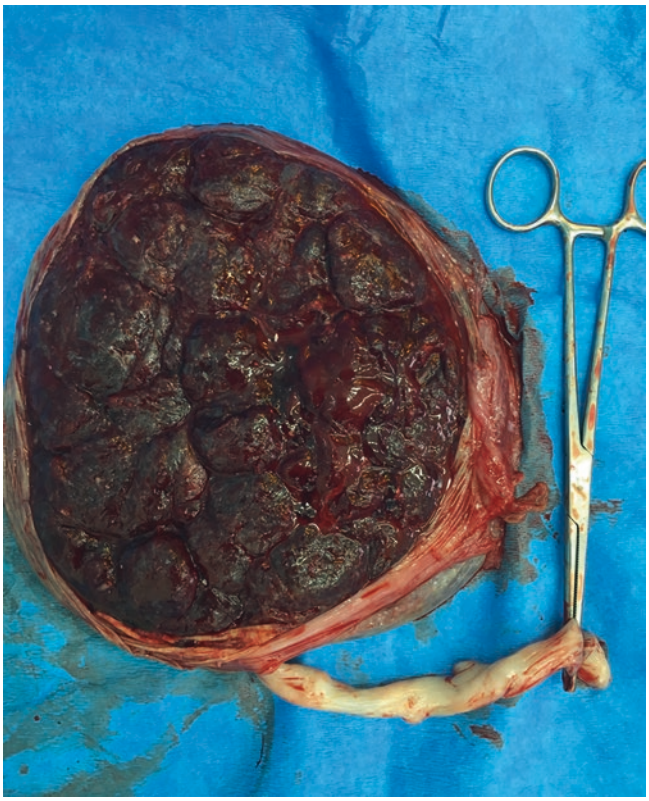

Fig. 3.1 Partial placental abruption

Maternal morbidity and mortality associated with PA include massive blood loss, disseminated intravascular coagulation, emergency hysterectomy, the need for blood transfusion, renal failure, and maternal death. In Western Europe and the USA, PA-related maternal mortality is 0.4 per 1,000 births. The rate of maternal deaths depends on the level of medical care, ranging from 1 to 4.7 in the developing countries [10, 13, 14].

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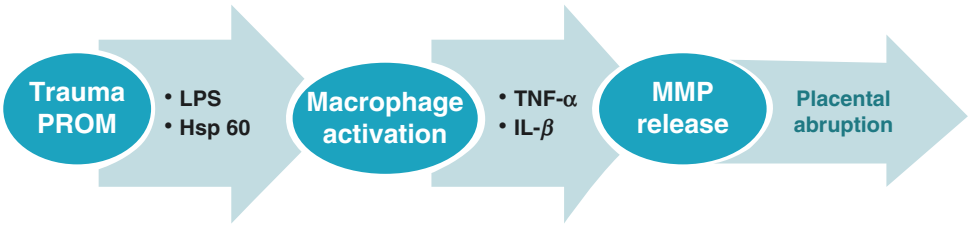

Fig. 3.2 Pathway of acute inflammation. *Definition*: *PROM* premature rapture of membranes, *LPS* lipopolysaccride, *Hsp* heat shock protein, *IL* interleukin, *TNF* tumor necrosis factor, *MMP* matrix metalloproteinase

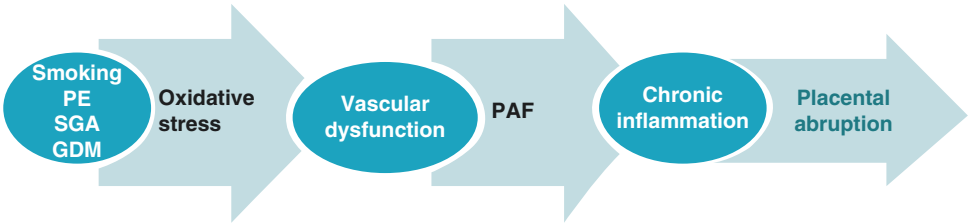

Fig. 3.3 Pathway of chronic process. *Definitions*: *PE* preeclampsia, *SGA* small for gestational age, *GDM* gestational diabetes mellitus, *PAF* platelet activation factor

3.3 Pathology

The underlying pathomechanism of placental abruption remains unclear. PA seems to be a multifactorial disease, with different causative patterns in preterm and term gestations. Several risk factors, i.e., abdominal trauma, hypertension, or coagulopathy, have been defined as strongly related to placental abruption. However, there are still many cases which occur without any perceptible causes [15].

The placenta is fixed to the uterine wall by the anchoring villi. When spiral arteries lack the physiologic trophoblast invasion, abruption might occur. Infusion of thromboplastic material induces disseminated intravascular coagulation. Hypertonicity of the uterus occurs probably to prevent the entrance of further thromboplastic material into the maternal circulation. The conditions which contribute to the avulsion of the anchoring placental villi from the expanding lower uterine segment, which in turn leads to bleeding into the decidua basalis, can be explained by a number of hypotheses [16–20].

3.3.1 Pathway of Acute Inflammation

Infection (chorioamnionitis) and tissue injury (trauma, PROM) cause a rapid release of macrophage activators (lipopolysaccharide, heat shock protein 60) at the maternal-fetal interface. Increased production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-β leads to an elevated release of matrix metalloproteinases by trophoblast cells. In consequence, increased level of necrosis and apoptosis processes leads to preterm placental detachment (Fig. 3.2).

3.3.2 Pathway of Chronic Processes

A strong coincidence between PA and other pregnancy complications, e.g., preeclampsia, preterm labor, SGA, or diabetes, can indicate an impaired placentation process in early pregnancy as the main pathological mechanism. Long-standing vascular lesions lead to elevated oxidative stress and platelet activation, resulting in chronic inflammatory processes. Chronic inflammation pathway is more common for premature PA (Fig. 3.3).

3.3.2.1 Fetal-to-Maternal Hemorrhage

In cases of nontraumatic placental abruption, the detachment occurs in the layer of maternal decidua. The origin of the bleeding is almost always maternal. The evidence for fetal-to-maternal bleeding has been reported in only 20 % of the cases, but with the volume of ≤10 mL [22]. The occurrence of fetal bleeding is much more likely in case of preceding trauma, when placental abruption follows a tear or fracture of the placental tissue, resulting in fetal bleeding [21].

3.4 Risk Factors

Lack of one hypothesis about the mechanism which leads to placental abruption is the reason why identification of the most frequent risk factors for this severe pregnancy complication is a subject of much heated debate. The literature offers reports on numerous multicenter analyses which have been conducted to identify the most common risk factors (Table 3.1) [38].

Advanced maternal age (>35 years) and parity have the strongest correlation with placental abruption out of the sociodemographic and behavioral risk factors. Some authors also mention maternal age of <20. In general analyses, black ethnic origin, marital status (unmarried), and lower socioeconomic status are related to higher prevalence of placental abruption [24, 25].

Several studies have demonstrated that maternal smoking during pregnancy increases the risk for abruption even by 2.5-fold. Interestingly, paternal smoking doubles the risk. Probably, quitting smoking before pregnancy reduces the risk to the level of nonsmokers. Among drug-using women, cocaine use is the strongest risk factor for abruption, increasing the risk even by 8.6-fold [5, 23, 25, 26].

Among pregnancy-related risk factors, pregnancy-induced hypertension and preeclampsia have been demonstrated to have the strongest correlation with PA (2.5 and 4.4, respectively). Many studies have shown that the more severe

Table 3.1 Risk factors for placental abruption

Risk factor	Odds ratio
Maternal risk factors	
Chronic hypertension	1.8–2.4
Hyperhomocysteinemia	1.8–5.3
Thrombophilia	1.4–7.7
Uterine anomaly	8.1
Historical risk factors	
Cesarean section	1.3–2.4
Miscarriages	1.4–3.4
Placental abruption	3.2–25.8
Preeclampsia	1.9
Stillbirth	1.6–13.1
Behavioral risk factors	
Cigarette smoking	1.5–2.5
Alcohol use	1.6–2.8
Cocaine use	3.9–8.6
Pregnancy-associated risk factors	
Pregnancy-induced hypertension	1.5–2.5
Preeclampsia	1.9–4.4
PROM	1.8–5.9
Chorioamnionitis	2.5–3.3
Placenta previa	3.2–5.7
Multiple pregnancy	2.0–2.9

the hypertension, the higher the risk for abruption [2, 6, 28, 29]. Other pregnancy complications which can increase the incidence of placental abruption include placenta previa, vaginal bleeding in the early pregnancy, and multiple gestations. The risk for PA in case of premature rupture of membranes is 5.9 % and is related to sudden changes of intrauterine pressure and increased risk for chorioamnionitis [1, 2, 6, 29].

Chronic hypertension is one of the most frequent maternal risk factors for PA. Chronic hypertension complicates 0.3–0.8 % of all pregnancies and often corresponds with other risk factors, including advanced maternal age, black race, smoking, and parity. According to the literature, chronic hypertension increases the risk for abruption by 2.4-fold [2, 27, 28]. Also, thrombophilia and hyperhomocysteinemia are strongly related with the risk for PA. Hyperhomocysteinemia is associated with folate and vitamin B12 deficiency, which can be the direct cause of the abruption. In most studies, homozygous methylenetetrahydrofolate reductase point mutation 677 is related to an even sevenfold increase of PA. Literature data about the wide range of thrombophilia are insufficient, but a Swedish study of Prochazka failed to show a correlation between factor V Leiden carrier rate and placental abruption [30–33].

In the group of history-related risk factors, special attention should be paid to patients after previous cesarean section. According to the literature, the first cesarean delivery increases the risk for abruption by 30–40 % in the next pregnancy, as compared to the first vaginal delivery. The risk increases to 52 % if the inter-pregnancy interval is <1 year [4, 34, 35].

Approximately 6 % of all trauma cases in pregnancy and 20–25 % of major traumas are associated with PA. The first manifestation of placental abruption after abdominal trauma occurs mainly within 6–48 h. In rare cases, placental abruption can manifest even up to 5 days after the initial trauma [21, 36, 37].

3.5 Clinical Findings

3.5.1 Vaginal Bleeding

Placental abruption is the leading cause of vaginal bleeding in the second part of pregnancy. Vaginal blood loss is presented in approximately 80 % of all cases. Hemorrhage into the decidua basalis occurs as the placenta separates from the uterus, resulting in external bleeding or formation of a hematoma behind the placenta. Further bleeding accelerates the detachment of the placenta from the uterine wall, causing vessel compression and compromising blood supply to the fetus. This alarming sequence of events may lead at the end stage to myometrial rupture. The amount of vaginal bleeding can vary greatly, and it does not necessarily correspond to how much of the placenta has separated from the inner wall of the uterus (Fig. 3.4b) [39].

In some cases of central placental abruption, blood does not escape externally but remains within the retroplacental area. Concealed hemorrhage soon leads to a complete detachment of the placenta. It is related to higher rate of fetal death and maternal consumptive coagulopathy. No visible vaginal bleeding in case of severe placental abruption is a rather poor prognostic sign, and, in most cases, the diagnosis is typically delayed (Fig. 3.4a).

3.5.2 Abdominal Pain

Abdominal pain often occurs suddenly and is mostly defined as strong and sharp. Pain may be limited to the area where placental detachment begins or may give a general tenderness in the abdomen. It may radiate to the back in cases when the placenta is localized on the posterior wall of the uterus. Pain is often followed by nausea and vomiting.

3.5.3 Contractions

During the examination, the uterus may be disproportionately enlarged and an increased tonicity is often present. Moreover, rapid, painful contractions which follow one another can occur. In case of massive placental abruption, the uterus becomes hard and very painful.

3.5.4 Fetal Distress

Placental abruption results in fetal distress in almost 60 % of the cases [39]. Altered fetal activity is one of the most alarming signs. The patient may present with decreased or absent fetal movements. Cardiotocography (CTG) reveals symptoms of

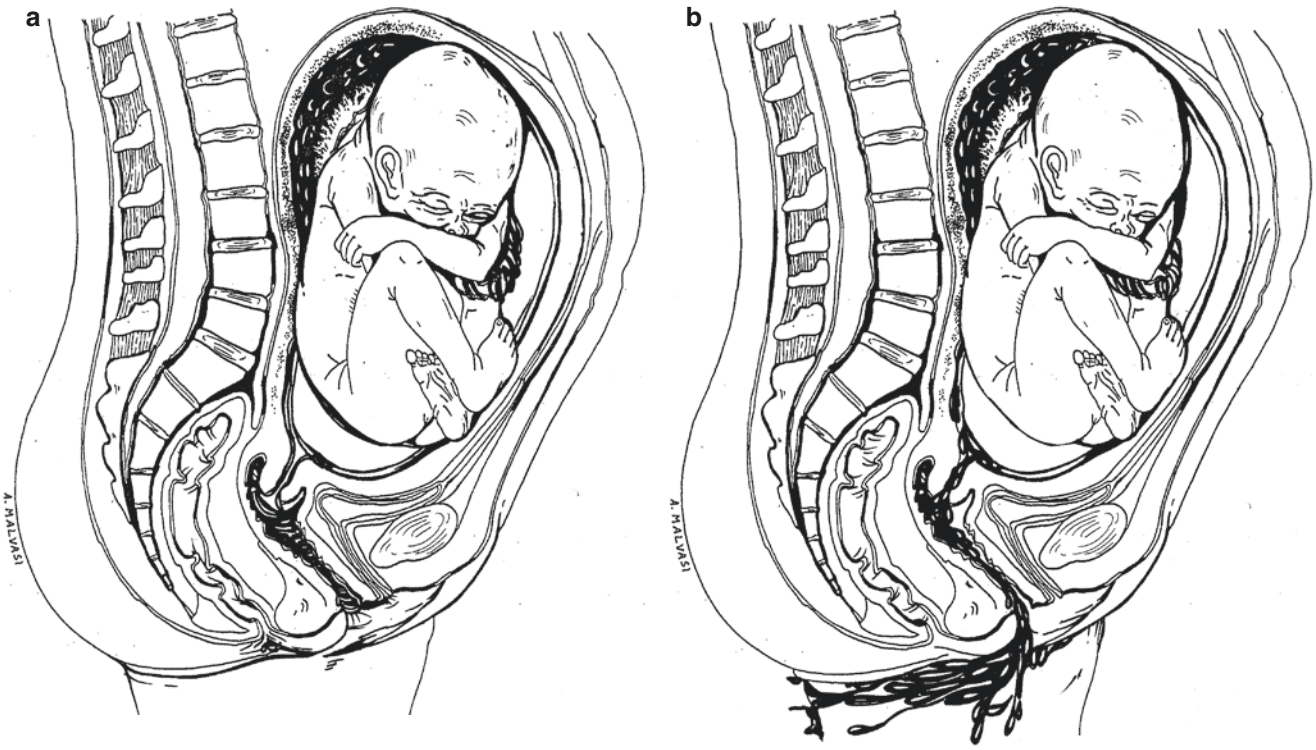

Fig. 3.4 Placental abruption with concealed hemorrhage (**a**) and vaginal bleeding (**b**)

fetal distress, which occurs mainly due to placental separation, maternal hemorrhage, fetal hemorrhage, or uterus hypertonus. In case of severe placental abruption, no fetal heart tone may be demonstrated (Fig. 3.5a, b). Rarely, intrauterine fetal death is the only sign of PA, and the diagnosis is made postpartum, after visualization of the blood clot on the placental surface.

3.6 Classification

Depending on the extent of the separation, placental abruption can be partial or complete. Due to localization of the detachment, abruption can be classified as marginal or central.

Clinical classification contains 0–3 classes and is based on the severity of the clinical symptoms.

Class 0 – asymptomatic:

The diagnosis is made retrospectively by finding an organized blood clot or a depressed area on a delivered placenta.

Class 1 – mild (48 % of the cases); the characteristics include the following:

- No vaginal bleeding to mild vaginal bleeding
- Slightly tender uterus
- Normal maternal BP and heart rate
- No coagulopathy
- No fetal distress

Class 2 – moderate (27 % of all cases); the characteristics include the following:

- No vaginal bleeding to moderate vaginal bleeding
- Moderate to severe uterine tenderness with possible tetanic contractions
- Maternal tachycardia with orthostatic changes in BP and heart rate
- Fetal distress

Class 3 – severe (28 % of all cases); the characteristics include the following:

- No vaginal bleeding to heavy vaginal bleeding
- Very painful tetanic uterus
- Maternal shock
- Hypofibrinogenemia (i.e., <150 mg/dL)
- Coagulopathy
- Fetal death

3.7 Diagnosis

Placental abruption should be taken into consideration in each case of vaginal bleeding in the second and third trimester of pregnancy. The presence of a large retroplacental hematoma in most cases results in typical signs such as abdominal pain, contractions, and uterine tenderness. In case of strong suspicion of PA and signs of fetal distress, immediate management should be initiated, without any delay caused by an additional examination. Regardless, numerous hematomas do not reach significant size and remain asymptomatic. If the course of the events is not rapid, an ultrasound examination could be performed. According to the literature, sensi-

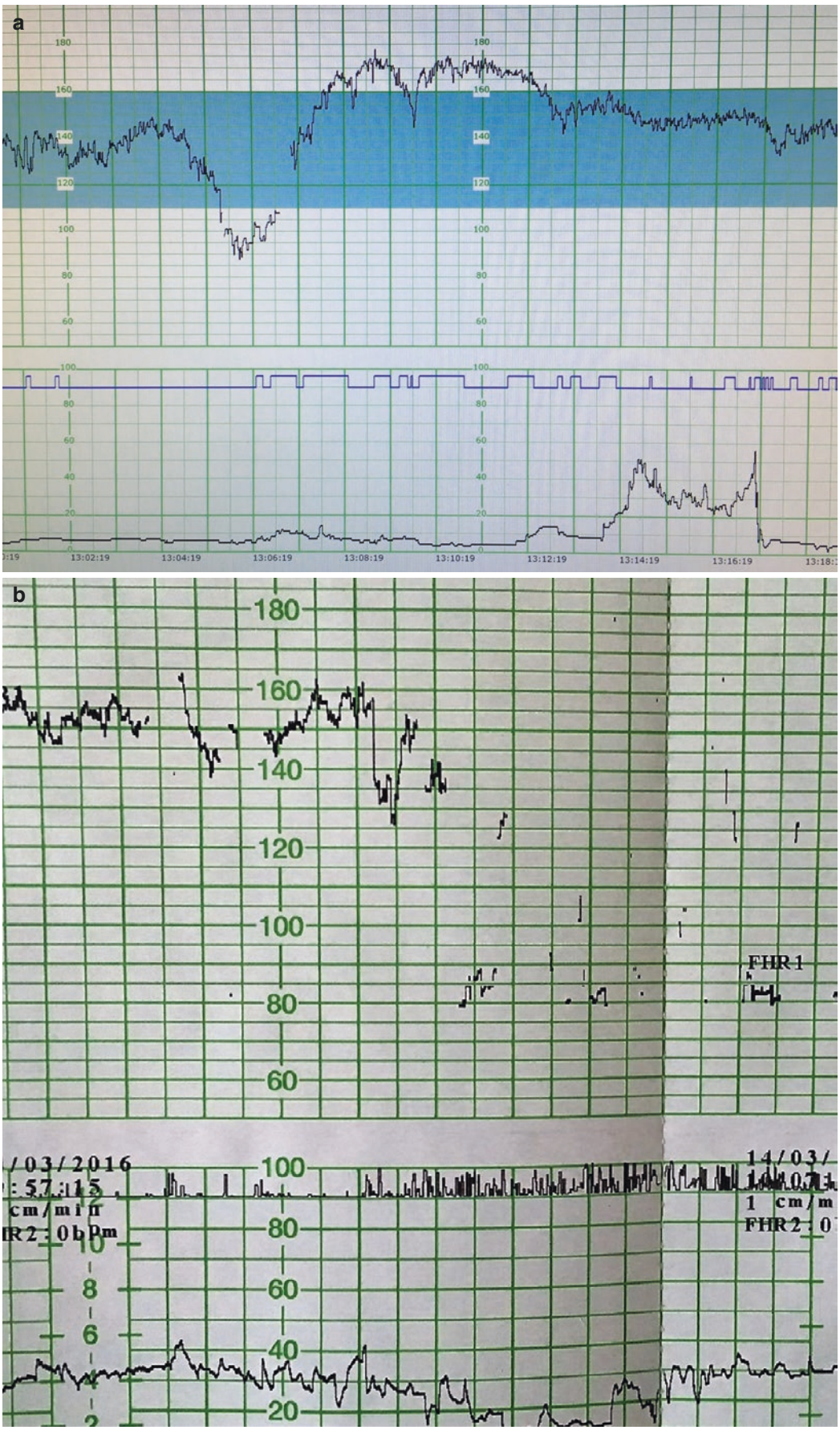

Fig. 3.5 Signs of fetal distress due to placental abruption in the third trimester of pregnancy in cardiotocography. *Upper panel*: the fetal hart rate demonstrates late decelerations (**a**) and baseline bradycardia (**b**)

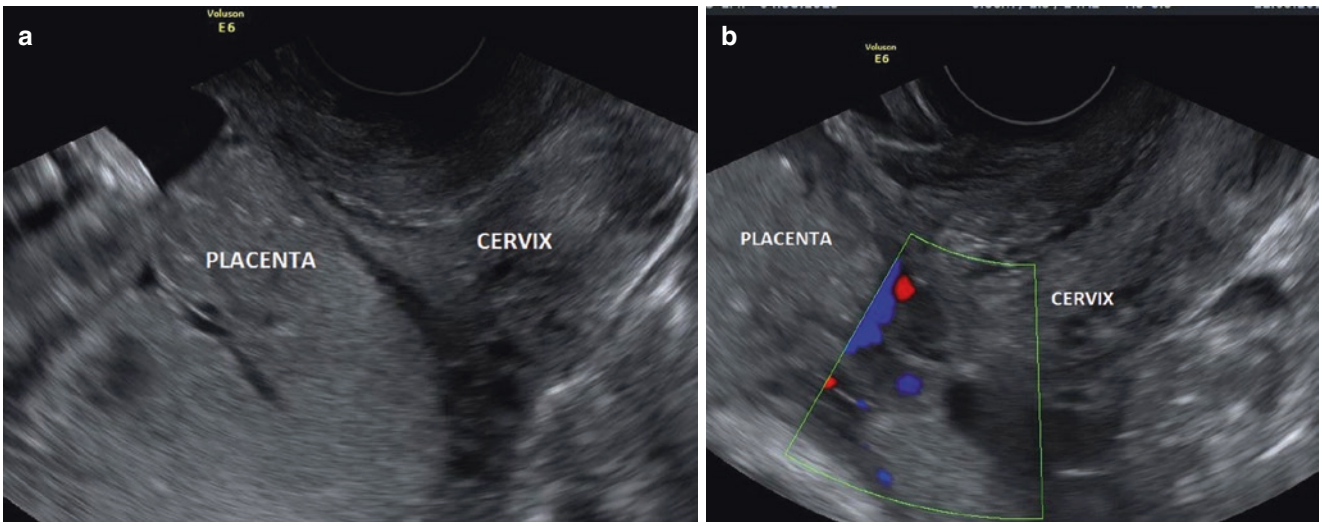

Fig. 3.6 Transvaginal sonogram of total placenta previa (**a**) and marginal placenta previa (**b**)

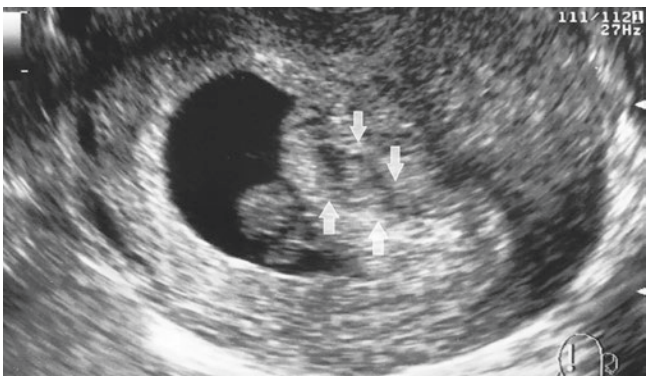

Fig. 3.7 Transvaginal presentation of acute subchorionic hematoma (*white arrows*) in early pregnancy

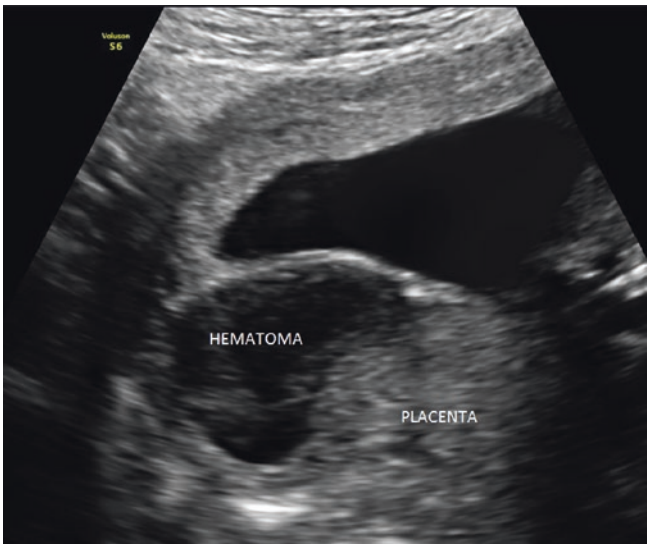

Fig. 3.8 Transabdominal scan. Presence of marginal hematoma in patient with the history of slight vaginal bleeding

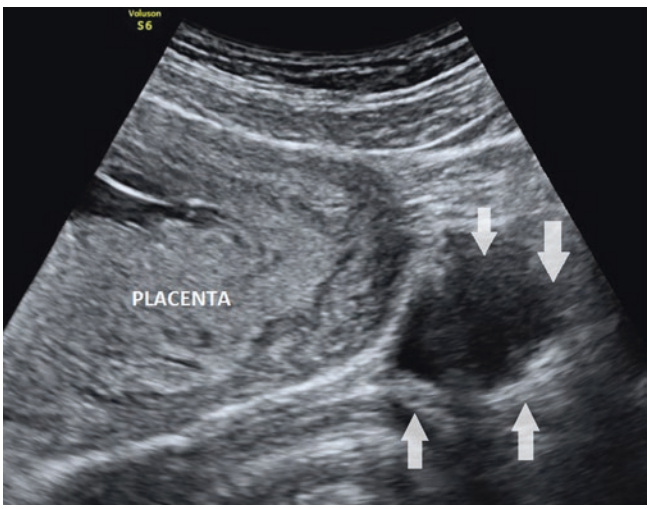

Fig. 3.9 Transabdominal sonogram of subchorionic hematoma (*white arrows*)

tivity of ultrasound diagnosis of a hematoma is not higher than 50 %. Nevertheless, due to its availability and short time required for the exam, ultrasound examination of the placenta is considered very helpful and can be useful in the differential diagnosis between PA and placenta previa (Fig. 3.6a, b).

Placental abruption results in a wide variety of sonographic findings, e.g., preplacental fluid collection (between the placenta and the amniotic fluid); jellylike movements of the chorionic plate induced by fetal activity; presence of marginal, subchorionic, or intra-amniotic hematoma; and increased heterogeneous placental thickness (>5 cm in the perpendicular plane) (Figs. 3.7, 3.8, 3.9, and 3.10). Most of them depend on the location of the bleeding and its duration. The locations of the hemorrhage can be categorized as follows: most frequent, *subchorionic* (between the myometrium and the placental membranes), *retroplacental* (between the placenta and the myometrium), and *preplacental* (between the myometrium and the amniotic fluid). Most subchorionic hematomas are contiguous with the placental margin. However, in some cases the majority of the blood separates from the placenta and forms a hematoma on the myometrial surface, opposite the placenta.

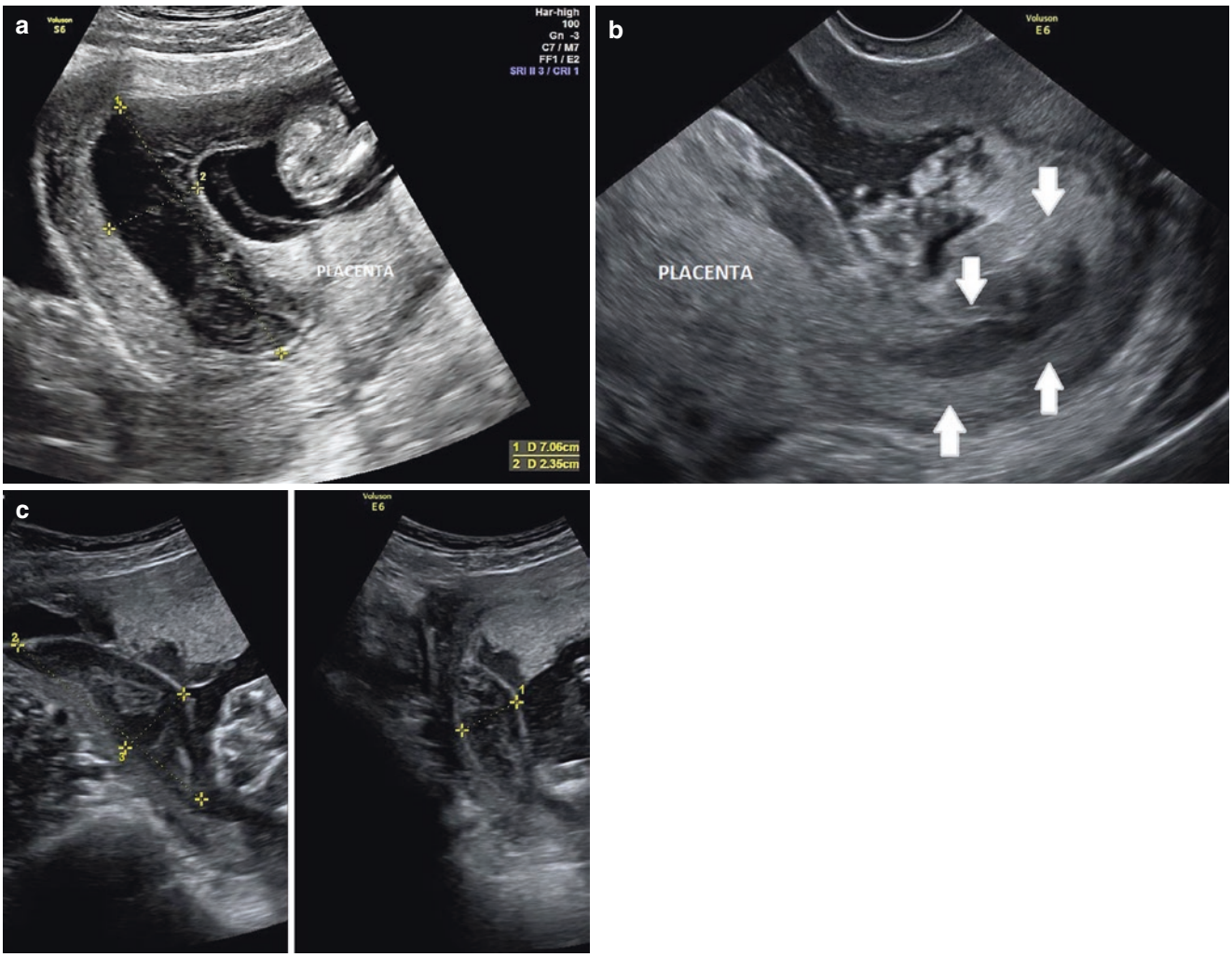

Fig. 3.10 Transabdominal sonogram of marginal sonolucent hematoma (**a**–**c**)

Echogenicity of a hematoma strictly correlates to the time of the bleeding. Acute bleeding (<48 h) can be presented as a hyperechoic area, defined as equal to or greater than the adjacent placenta. Acute hematoma often imitates placental tissue, making the correct diagnosis challenging even for experienced sonographers (Fig. 3.11a, b). In order to avoid misdiagnosis, the examination may need to be repeated in the next 24 h. In the next 3–7 days, the hematoma is presented as a hypoechogenic area similar to the myometrium. After 2 weeks, the major part of the hematoma becomes sonolucent (anechoic) and can be compared to the amniotic fluid.

The volume of the hematoma and the size of the detached area of the placenta are the most appropriate prognostic factors in a sonographic examination. Three perpendicular diameters (D) need to be measured and put into the following formula:$0.52 \times (D1 \times D2 \times D)3$, to estimate the volume of the hemorrhage (Figs. 3.12 and 3.13). In cases when the detachment exceeds 50 % of the placenta or the hematoma volume is over 50 ml, the prognosis is very poor [40, 42–44].

Color Doppler flow images add a considerable value to sonographic examination by excluding, i.e., placental vascular abnormalities, adhesive disorder, or vasa previa (Fig. 3.14).

Importantly, ***lack of sonographic confirmation does not exclude placental abruption and should never delay management.***

In the last decade, the role of magnetic resonance imaging (MRI) in the diagnosis of PA has been steadily increasing. Recent literature reports have demonstrated that MRI can accurately depict placental abruption with high sensitivity, even in cases with no US findings. Moreover, MRI might indicate, on the basis of the appearance of the clot, whether intrauterine hemorrhage has stopped or is persistently active. The possibility of identifying patients who are at risk for deteriorated maternal and fetal condition may be of great value for the clinical treatment (Fig. 3.15a, b) [41].

Due to the special reference to the paramagnetic effects of methemoglobin, it is possible to determine the exact age of the bleeding. Intrauterine hematomas can be accurately classified as follows: hyperacute (first few hours, intra-

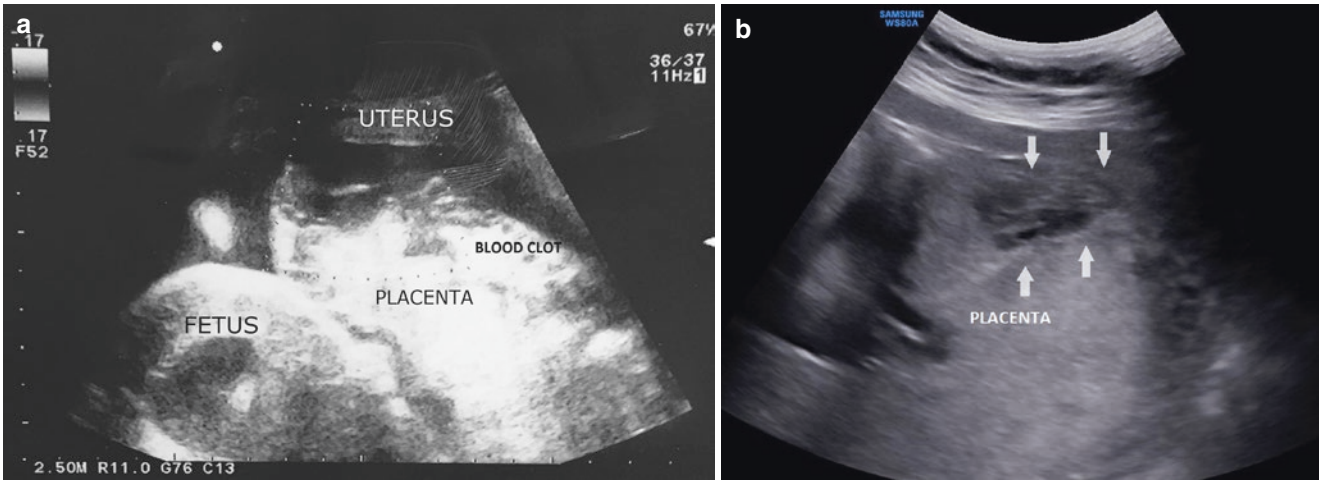

Fig. 3.11 Acute placental abruption. Transabdominal sonogram of a patient at 34 weeks' gestation with sudden abdominal pain, signs of fetal distress, and no vaginal bleeding (**a**). Transabdominal sonogram of a patient at 32 weeks' gestation with chronic hypertension (**b**). Emergency cesarean delivery confirmed acute placental detachment in both patients

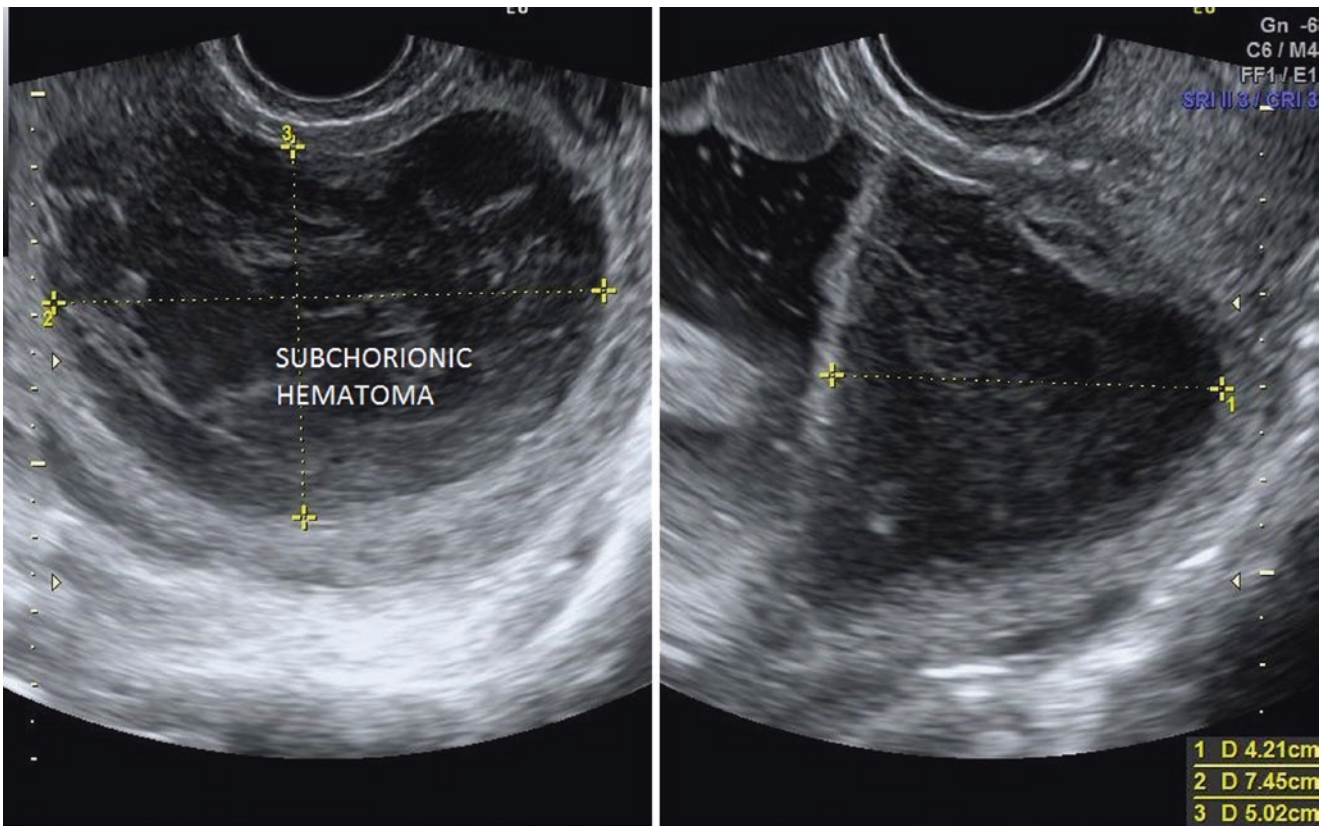

Fig. 3.12 Chronic placental abruption. Transabdominal scan. Presence of subchorionic hypoechogenic hematoma

cellular oxyhemoglobin), acute (1–3 days, intracellular deoxyhemoglobin), early subacute (3–7 days, intracellular methemoglobin), late subacute (>14 days, extracellular methemoglobin), and chronic (>4 weeks, intracellular hemosiderin and ferritin). Hematomas with hyperacute or acute MRI signal intensity characteristics might correlate with progression of the abruption to higher grades (Figs. 3.15 and 3.16a–e) [63, 64].

Despite its great diagnostic value for the diagnosis of PA, the use of MRI remains limited due to the need of advanced training for proper image interpretation.

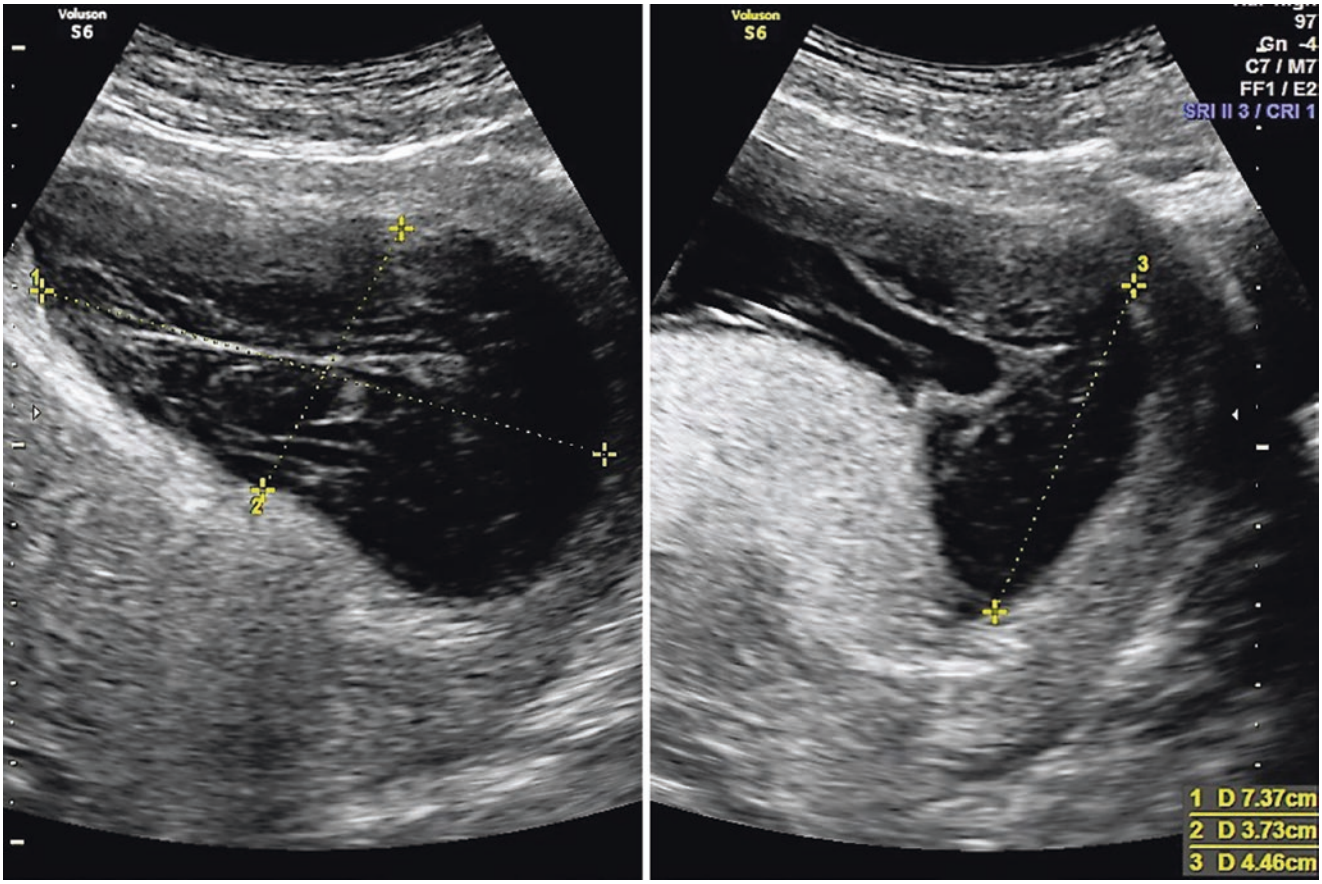

Fig. 3.13 Transabdominal sonogram. Measurement of the volume of hematoma and the size of the detachment in the third trimester of pregnancy

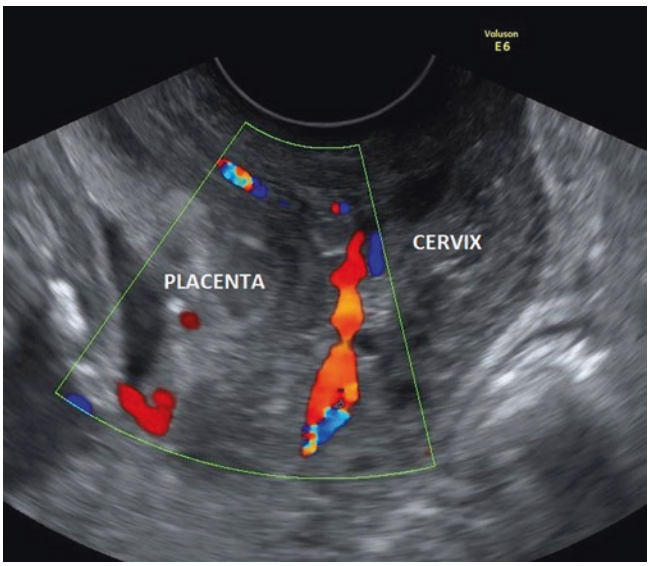

Fig. 3.14 Transvaginal presentation with color Doppler of placenta previa. Sonogram of a 35-year-old patient in 26 weeks of gestation presenting moderate vaginal bleeding

Each suspicion of placental abruption based on the clinical signs, US or MRI findings, needs confirmation after the delivery, either by the presence of a blood clot on the placental surface or by histopathologic examination.

3.8 Differential Diagnosis

In case of severe placental abruption, the diagnosis is obvious. Most often, in case of partial detachment and no signs of fetal distress, the diagnosis might be confirmed only after the delivery. In differential diagnosis, all potential causes of vaginal bleeding in the third trimester of pregnancy should be excluded. The priority is to distinguish between placenta previa and placental abruption (Table 3.2).

More sudden but potentially life-threatening reasons of vaginal bleeding, i.e., vasa previa, uterine rupture, vaginal trauma, vaginal or cervical malignancy, should not be dismissed. Clinically, any event of sudden abdominal pain with no vaginal bleeding needs an exclusion of preterm labor or the most

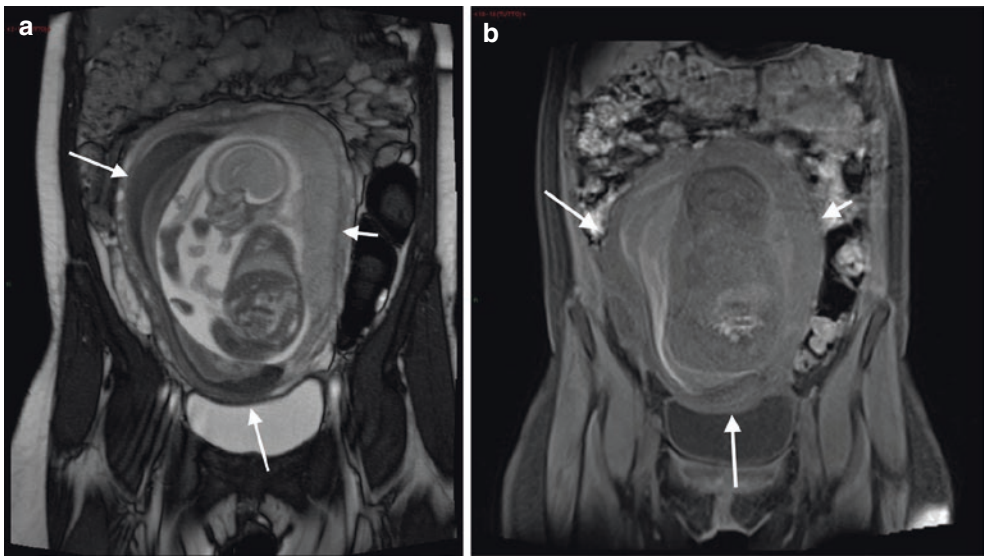

Fig. 3.15 A 25-year-old woman at 28 weeks' gestation with acute pelvic pain and vaginal bleeding. Coronal T2-weighted image shows the intrauterine clot with hypointense areas placed along the right side of the uterine cavity and extended inferiorly (**a**). Coronal T1-weighted fat-saturated gradient-echo image shows the hyperintense subchorionic hematoma (**b**). Placenta located on the left side (*short arrows*) [63]

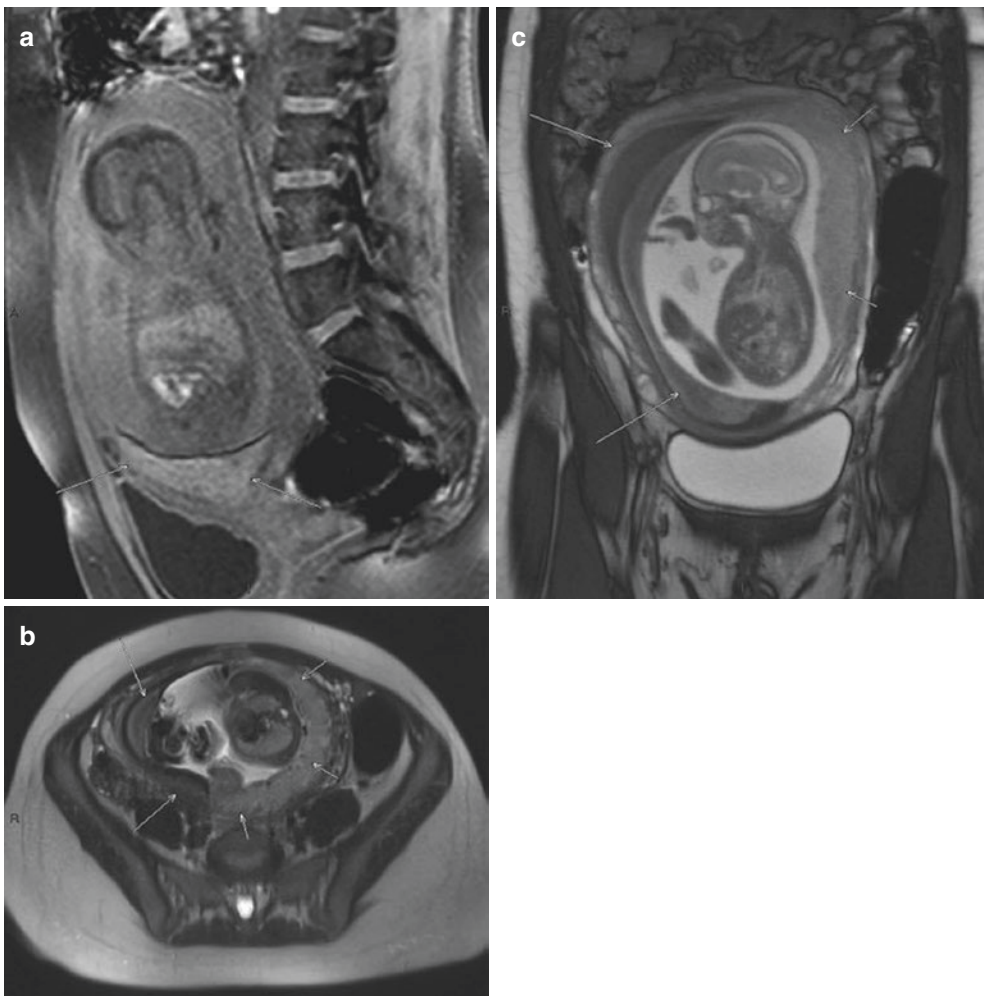

Fig. 3.16 Subacute subchorionic hemorrhage in 25-year-old women at 27 weeks' gestation. Sagittal T1-weighted gradient-echo image shows the hyperintense subchorionic hematoma (*arrows*) located above the internal os (**a**). The intrauterine clot is mildly hyperintense to the placenta on the axial T2-weighted half-Fourier RARE (**b**) and coronal True Fisp images (**c**). Sagittal diffusion-weighted MR image (**d**) and ADC map (**e**) show the hematoma (*long arrows*) has hypo- and hyperintense areas. The signal intensity characteristics are suggestive of hyperacute hematoma [64]

Fig. 3.16 (continued)

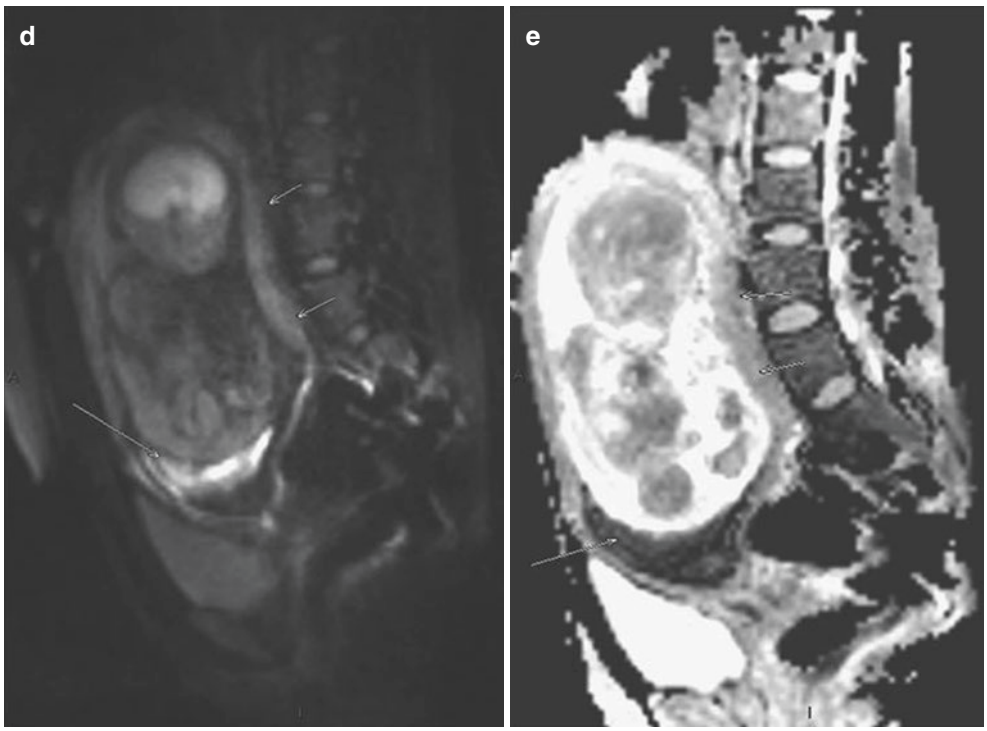

Table 3.2 Differential diagnosis of placental abruption from placenta previa

Symptoms	Placental abruption	Placenta previa
Bleeding	Internal (retroplacental) or external (vaginal) with dark blood hemorrhage decreases during contractions	Always external with bright red blood hemorrhage increases during contractions
Beginning	Sudden hemorrhage	Event of light red spotting often precedes hemorrhage
Risk factors	Hypertension, abdominal trauma	Uneventful prenatal course
Pain	Sudden and sharp, uterine tenderness	Painless hemorrhage with normal uterine tonus
Contractions	Rapid, painful	Often non-present
Fetal distress	Often present	Rare
Sonographic evaluation	Nonspecific	Important

common causes of acute abdomen: acute appendicitis, i.e., acute peritonitis, acute pancreatitis, or acute pyelonephritis.

3.9 Complications

3.9.1 Hypovolemic Shock

In severe placental abruption, it is difficult to evaluate the actual volume of maternal blood loss. Lack of vaginal bleeding can be misleading but should not be underestimated. An extreme concealed hemorrhage and rare intramuscular uterus bleeding can lead to massive blood loss and hypovolemic shock, with hypoperfusion and ischemia of other internal organs, especially the kidneys, as the most grave consequences. Vigorous intravenous blood and fluid infusion, as a response to hypotension, causes additional oliguria. Blood transfusion is necessary in over 16 % of PA patients.

3.9.2 Consumptive Coagulopathy

Clinically, significant consumptive coagulopathy occurs relatively often (7.7 %) in the course of placental abruption. Statistically, every third patient with severe abruption which caused fetal death had changes in coagulation factors presented in the laboratory tests. Defibrination is the major mechanism activating intravascular coagulation. Pro-coagulation factors are mostly actively consumed by the formation of retroplacental clots. The most common measurable disorder is hypofibrinogenemia, known as plasma level of fibrinogen of <150 mg/dL. Hypofibrinogenemia is accompanied by elevated levels of fibrinogen degradation products (>10 μg/ml), which is considered to be the most specific parameter in placental abruption. Moreover, the degradation products of fibrin D-dimers are also significantly elevated. Thrombocytopenia occurs at a later stage of coagulopathy. One of the most important consequences of intravascular coagulation is the

activation of plasminogen. The active form, plasmin, is responsible for the lysis of the microemboli which commonly occur in the peripheral circulation. This is one of the protective mechanisms which ensure organ microperfusion.

Clinical symptoms of consumptive coagulopathy are more common for the concealed hemorrhage. In these circumstances, increased intrauterine pressure causes more thromboplastin to penetrate into the maternal circulation [45, 46].

3.9.3 Renal Failure

Acute renal failure is one of the most serious maternal consequences of placental abruption. Renal disorders occur as the effect of hypovolemia in the course of massive hemorrhage and/or microemboli formed in the intravascular coagulation. Ischemic necrosis can be related to acute damage of the renal tubes or the renal cortex. Most cases of acute renal failure are reversible by treatment with blood and crystalloid solution. Sometimes, although rarely, renal damage is prolonged and the patient may require dialysis in cases of acute cortical necrosis. In each case of renal failure, intensive monitoring of the diuresis should be performed.

Additionally, preeclampsia coexists with PA 4.4-fold more often than in normal pregnancy. Typical changes of the renal function which occur in hypertension overlap hypoperfusion caused by hemorrhage and escalate renal failure [47].

A direct correlation between renal failure and placental abruption remains unclear, but retrospective clinical studies have concluded that a third of pregnant women with renal disorders had suffered an abruption. Moreover, proteinuria occurs in more severe forms of placental abruption, even without preeclampsia [48].

3.9.4 Couvelaire Uterus

Couvelaire uterus, also known as uteroplacental apoplexy, is a rare and life-threating complication of severe PA, in which retroplacental blood penetrates through the thickness of the myometrium and reaches the peritoneal cavity. The patients present with uterine contractions, uterine tetany, or tenderness. Signs of hypovolemic shock are observed in case of massive blood loss. The uterus may adopt a bluish/purplish, mottled appearance due to extravasation of blood into the uterine muscle. This syndrome can only be diagnosed by direct visualization or biopsy [49, 50].

3.9.5 Amniotic Fluid Embolism Syndrome

Placental abruption, especially due to abdominal trauma, increases the risk of an extremely rare obstetric emergency, i.e., the embolism of the amniotic fluid. Fetal cells and amniotic fluid enter the maternal circulation via the placental bed and trigger the immune response. Cardiopulmonary failure rapidly progresses as the consequence of an allergic reaction. The subsequent phase is characterized by massive hemorrhage and is seldom reversible. Although the prevalence of amniotic fluid embolism is low, high mortality makes it the fifth most common cause of maternal mortality [51, 52].

3.9.6 Sheehan Syndrome

One of the consequences of excessive blood loss or consumptive coagulopathy is intrapartum or early postpartum pituitary failure. Hypopituitarism occurs due to ischemic necrosis of the gland and is clinically known as Sheehan syndrome. An impaired secretion of the trophic hormones causes lactation failure, breast atrophy, amenorrhea, hypothyroidism, and adrenal cortical insufficiency [53, 54].

3.10 Management

Each case of PA requires an analysis of specific factors and an individualized approach. The evaluation of the maternal hemodynamic status is vital. The condition of the fetus should be considered almost simultaneously. Management hinges on the knowledge of gestational age and evaluation of the relative risks of delivery versus the risks of expectant management.

3.10.1 Maternal and Fetal Monitoring

Clinical care of patients with suspicion of PA always includes careful maternal hemodynamic and fetal monitoring (Table 3.3):

Table 3.3 Maternal monitoring

Maternal and fetal monitoring
Measurement of maternal blood pressure and heart rate
Monitoring urine output
Indicate blood type and Rh status (if Rh negative, a Kleihauer-Betke test should be sent)
Serial evaluation of hemoglobin, hematocrit, platelet count, and coagulation profile with special account of the level of fibrinogen
Secure of large-bore (16- to 18-gauge) intravenous line
Start crystalloid infusion
Ensure the blood products for replacement (packed of blood cells and fresh frozen plasma)
Continuous monitoring of the fetal heart rate
Delivery plan

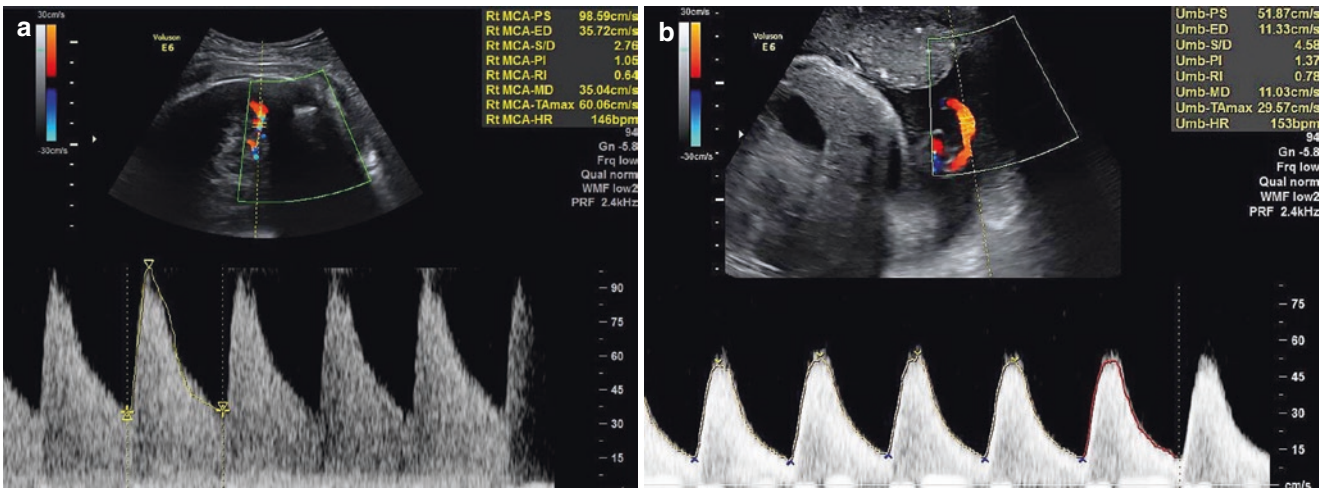

Fig. 3.17 Transabdominal scans with color Doppler of middle cerebral artery (**a**) and umbilical artery (**b**) flow of the fetus showing brain-sparing signs in 27-year-old women at 36 weeks' gestation. Patient presented normal CTG and no vaginal bleeding. During cesarean section the detachment of the one fourth of the placenta was revealed

3.10.2 Cesarean Delivery

Usually, patients who present to the emergency room with typical symptoms such as vaginal bleeding, abdominal pain, and fetal distress need urgent treatment (Fig. 3.17). Most clinicians choose an emergency cesarean delivery. At the same time, the massive hemorrhage should be treated with fluid and blood replacement. Moreover, cesarean delivery provides a possibility of surgical management of hemorrhage, if needed. In severe placental abruption, rapid diagnosis and immediate treatment are lifesaving procedures both for the mother and the child.

Kayani et al. studied a correlation between time from the decision to the delivery and neonatal outcome in patients with severe placental abruption and fetal bradycardia. Cerebral palsy and fetal death were significantly more frequent if the interval was longer than 20 min. In the majority of the cases, good neonatal outcome was related with cesarean delivery performed within 20 min [55].

Boisrame et al. analyzed retrospectively 247 cases of PA in three maternity units of French University Hospitals. The typical clinical triad including metrorrhagia, abdominal pain, and uterine hypertonus occurred in only 9.7 % of the cases. An emergency cesarean delivery was performed in the vast majority of the patients (90.3 %), and general anesthesia was used in over half of all cases [56].

3.10.3 Vaginal Delivery

Vaginal delivery is recommended if the fetus is reasonably mature and PA grade is no greater than I. The major method of stopping the bleeding from the implantation site is myometrial contraction. Pharmacological stimulation and uterine massage may efficiently compress placental site vessels, thus avoiding massive hemorrhage, even in case of coexisting coagulopathy. Amniotomy is believed to have a positive impact on the course of labor. Rupture of membranes usually hastens the delivery. Moreover, lower pressure in the amniotic sac reduces the entry of thromboplastin to the maternal circulation and meliorates spiral artery compression. Intensive monitoring of both the mother and the fetus is required during the entire course of labor in case of rapid deterioration of maternal or fetal condition. An emergency cesarean delivery may be necessary at any point during labor. In case of severe PA in the second stage of labor and symptoms of fetal distress, an operative vaginal delivery should be considered. If special conditions are fulfilled, the use of forceps or vacuum extraction is the fastest way to deliver the infant and avoid fetal hypoxia.

3.10.4 Delivery After Severe Placental Abruption

Treatment of patients after severe PA complicated by fetal death requires a particular approach from the clinicians. In such cases, maternal outcome remains absolutely imperative. According to Prichard et al., over 40 % of women after severe PA progress to disseminated intravascular coagulation, with the first laboratory changes presenting no sooner than 8 h from the detachment [57]. On the one hand, urgent cesarean section may appear most appropriate. However, surgical treatment may lead to increased blood loss and escalation of the consumptive coagulation, with possible emergency hysterectomy. Although vaginal delivery is preferred, maternal hemodynamic status is often a major contraindication.

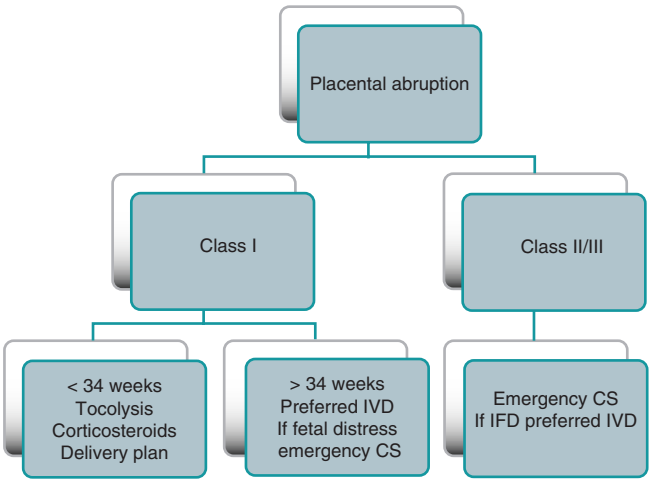

Fig. 3.18 Algorithm for the management in different grades of placental abruption. *Definitions*: *CS* cesarean section, *IVD* induced vaginal delivery, *IFD* intrauterine fetal death

Both kinds of management should always be preceded by appropriate crystalloid infusion and/or blood product replacement to achieve satisfactory coagulative balance. Despite delaying the delivery, adequate patient preparation improves the final outcome.

3.10.5 Expectant Management

Over 50 % of PA cases are women at 37 weeks of gestation. In special circumstances, an expectant management to avoid the consequences of prematurity is acceptable. A group of patients with mild abruption (class I), in stable maternal hemodynamic status and no signs of fetal compromise, may benefit from delayed labor [58, 59].

3.10.6 Tocolysis

The use of tocolytic drugs in case of PA is considered controversial by many authors. Undoubtedly, one of the major advantages of tocolysis is decreasing the tonus of the uterus, followed by limited hematoma formation and lower penetration of thrombotic factors. The opponents often recall the study of Hurd et al., who reported worse recognition of detachment progression if tocolysis was initiated. On the other hand, more current studies have confirmed the safety of expectant management in selected cases. In the study by Combs et al., a third of the patients delivered after >1 week from placental detachment. Interestingly, data showed neither increased maternal morbidity nor perinatal mortality [60–62].

Taking into account the unstable character of this obstetric complication, the use of tocolytic therapy is reasonable in selected cases of mild placental abruption and in patients at <34 weeks of gestation, if only for the time to administer a course of corticosteroids to promote fetal lung maturity (Fig. 3.18).

3.11 Prognosis

Both maternal and neonatal outcomes depend on PA severity. Unfortunately, premature detachment of the placenta places the fetus at a significant risk for hypoxia and death. Neonatal outcome is further hampered by coexisting complications such as fetal growth restriction, cesarean delivery, and prematurity. Almost 15 % of third trimester stillbirths occur due to placental abruption. As many as 15 % of the survivors have significant neurological impairment.

The most common maternal complication is consumptive coagulopathy. DIC occurs in 20 % of all severe abruptions. Moreover, massive bleeding, if left uncorrected, leads to hypovolemic shock and renal failure. In single rare cases, severe complications may lead to maternal death.

High level of medical care, immediate diagnosis, and prompt time from the decision to delivery (<20 min) may significantly improve maternal and fetal outcome.

3.12 Prevention

Although great efforts have been made to improve medical care in perinatal units, placental abruption remains a life-threatening complication of late pregnancy for both the mother and the fetus. So far, no intervention has been shown to prevent these circumstances. The only management which may reduce the incidence of placental abruption is modification of the risk factors, i.e., counseling patients against smoking and cocaine use or improving blood pressure control in women with hypertension.

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Twin Pregnancies

4

Miha Lučovnik, Antonio Malvasi, Andrea Tinelli, and Nataša Tul

4.1 Introduction

Incidence of twin pregnancies has risen over the last decades in developed countries from the natural occurrence rate, which is just below 1 %, to between 2 and 4 % of all gestations (Fig. 4.1) [1–4]. This increase has been associated with expanded use of fertility therapies (in vitro fertilization and ovulation induction techniques) and older maternal age [5, 6].

Despite this increase in incidence, twin pregnancies still represent a relatively small proportion of all deliveries. However, they make a disproportionate contribution to overall perinatal mortality and morbidity. Ten to 15 % of perinatal deaths and around 15 % of cerebral palsy cases are associated with twin gestations [7–9]. This association is mostly due to an overrepresentation of twin births among very preterm births (<32 weeks of gestation). In fact, the proportion of twins among all very preterm deliveries has risen in the last decades and now approaches 35 % (Fig. 4.2) [4]. In addition, an increased risk for cerebral palsy has also been reported in twins at >37 weeks' gestation [9].

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Twin pregnancies are, therefore, a very important clinical entity in perinatal medicine, which requires vigilant follow-up, and timely recognition plus management of several possible complications. This chapter reviews most common late pregnancy complications associated with twins, as well as current recommendations on their prevention and treatment.

4.2 Types of Twin Gestations

Twin pregnancies occur when two oocytes are fertilized to form dizygotic (nonidentical or fraternal) twins or when a single fertilized ovum divides to form monozygotic twins (often referred to as identical, although genetic as well as phenotypic differences always exist) (Fig. 4.3) [10]. In dizygotic twin pregnancies, each fetus has its own amnion and chorion. There are, on the other hand, several variations of monozygotic twins. According to the most popular (but unproven) theory, these depend on the timing of the division of monozygotic conceptus (Fig. 4.4):

- Diamniotic/dichorionic: If the division of the conceptus occurs within 3 days from fertilization, each fetus will be surrounded by his own chorion and amnion (Fig. 4.5).
- Diamniotic/monochorionic: If division occurs between fourth and eighth day following fertilization, the chorion has already began to develop, whereas the amnion has not. Consequently, each fetus will be surrounded by its own amnion, but a single chorion will surround both twins (Fig. 4.5).
- Monoamniotic/monochorionic: In less than 1 % of all monozygotic gestations, division occurs between days 9 and 12, after development of both amnion and chorion. Fetuses will, therefore, share a common sac. Division after 12 days is incomplete and results in conjoined twins. The fetuses may be fused in a number of ways, with the most common involving the chest and/or abdomen (Fig. 4.6). This is a rare condition with an incidence of 1 in 70,000.

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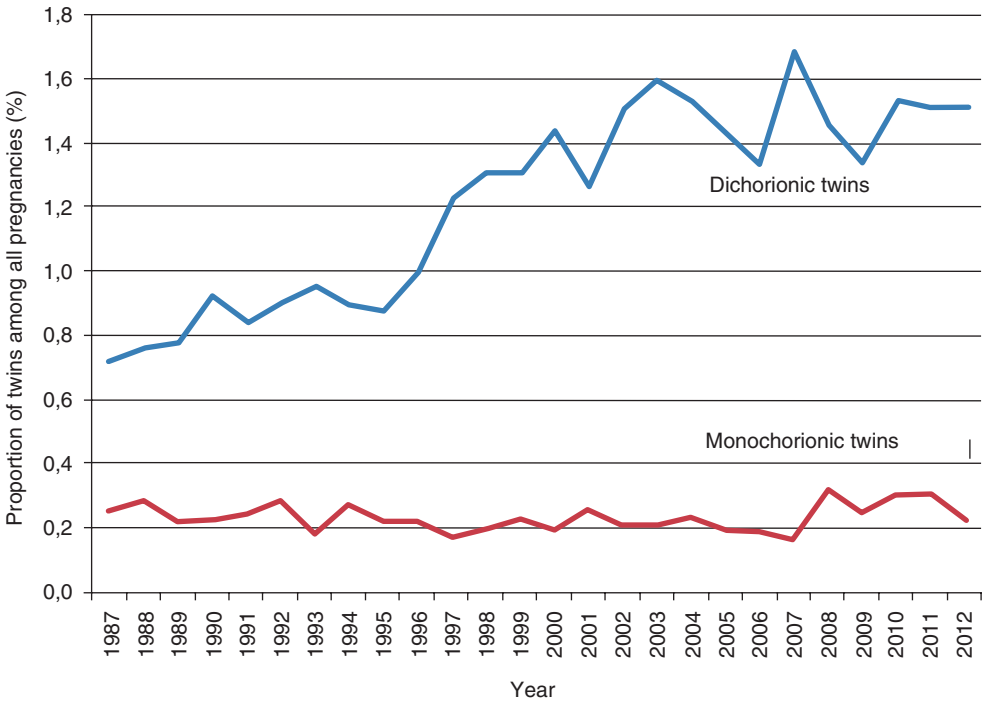

Fig. 4.1 Proportion of dichorionic twins (*upper curve*) and monochorionic twins (*lower curve*) among all pregnancies in Slovenia between 1987 and 2012 (Adapted with permission from Tul [134])

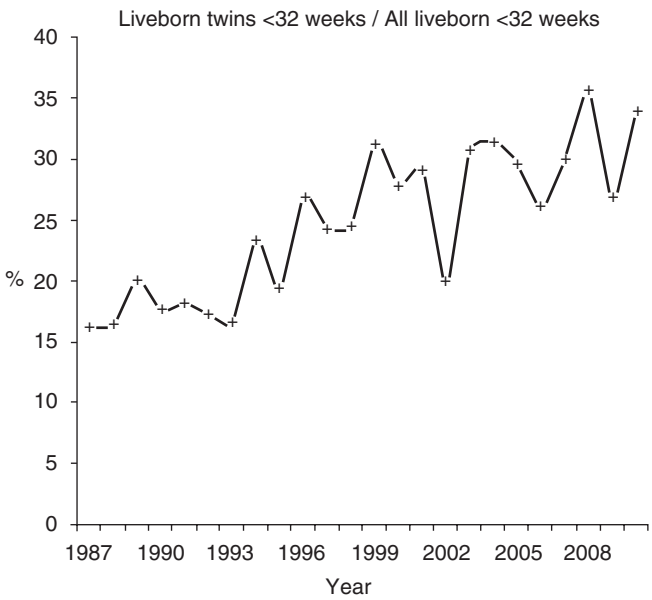

Fig. 4.2 Proportion of twins among all infants born at <32 weeks of gestation in Slovenia between 1987 and 2010 (From Tul et al. [4])

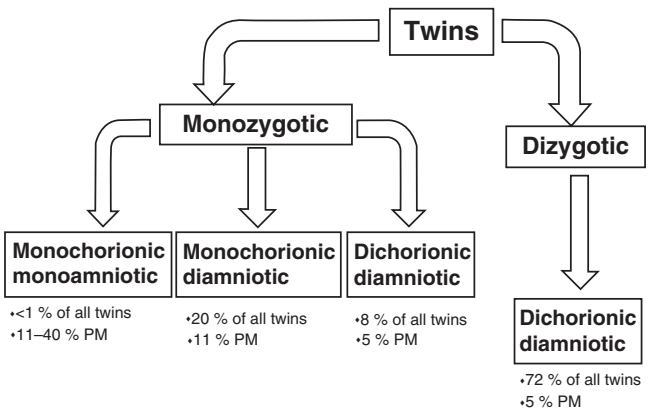

Fig. 4.3 Incidences of various types of twins. The more twins share (genome, chorion, amnion), the greater the risk of perinatal mortality (PM)

Monochorionic twins are associated with significantly higher perinatal risk compared with dichorionic ones, irrespective of zygosity [11]. In one large twin cohort study, the perinatal mortality rate was found to be more than twofold increased in monochorionic compared with dichorionic twins [12]. As a result, establishing chorionicity has become a keystone in the management of twins.

Chorionicity is most reliably ascertained sonographically early in gestation. Before 10 weeks' gestation, evidence of two distinct gestational sacs on transvaginal ultrasound suggests dichorionicity. Determination of amnionicity is less accurate at such early gestation due to the thin amniotic membrane and should be established later to exclude the possibility of monoamniotic twins. At 10–14 weeks, visualization of the so-called lambda sign (also known as the twin peak sign), which is the triangular projection of placental tissue into the base of the intertwin membrane, is an important marker of dichorionic placentation (Fig. 4.7) [13]. The presence of either a lambda sign or two separate placentas at less than 14 weeks' gestation indicates dichorionic placentation with a sensitivity of 97 % and a specificity of 100 % [13]. Conversely, a T sign has been used to describe the ultrasonographic visualization of the attachment of the intertwin membrane to the placenta in cases of monochorionic gestation (Figs. 4.8 and 4.9). The presence of either a single placental mass or a T sign at less than 14 weeks' gestation has a

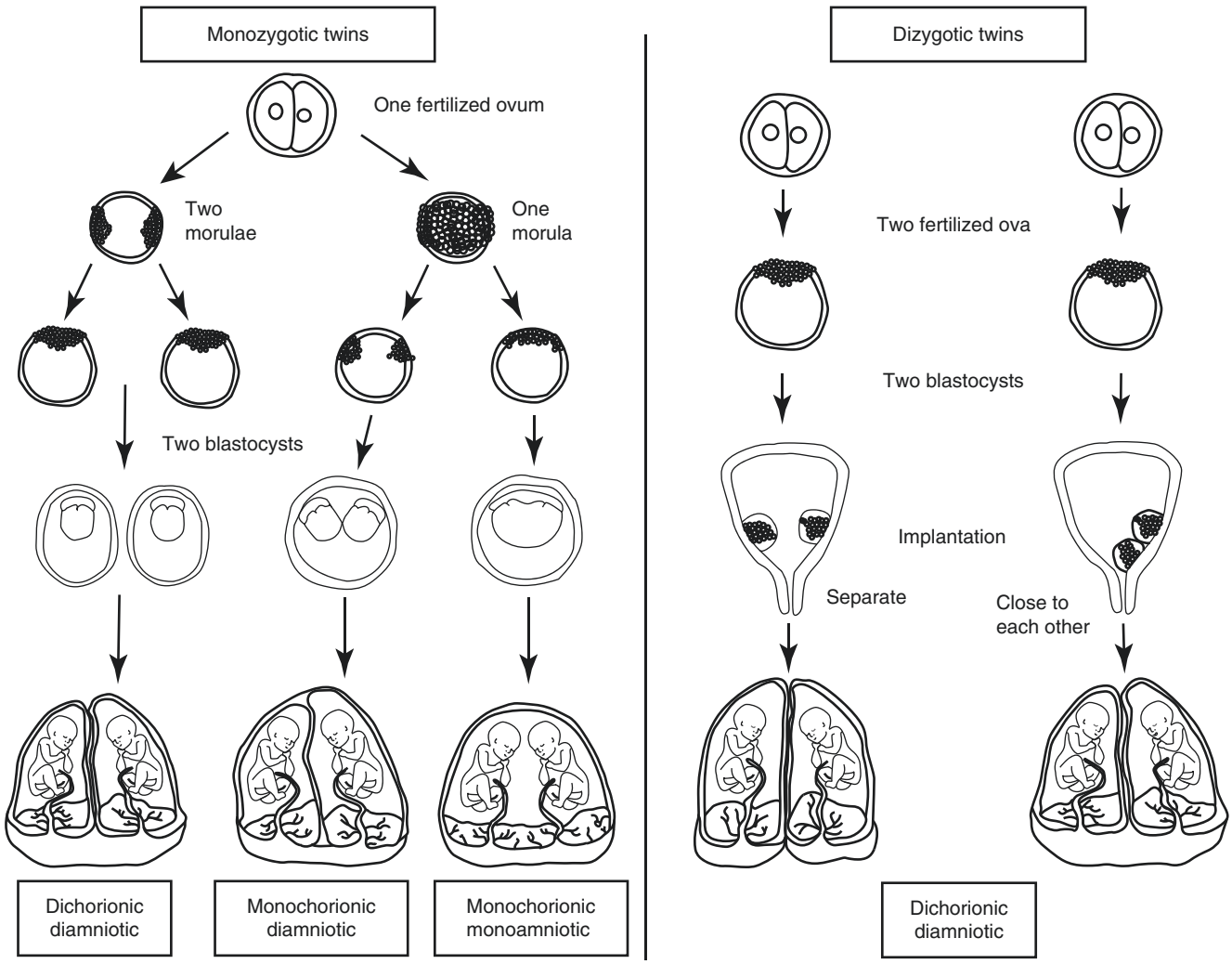

Fig. 4.4 Development of various types of twin pregnancies (Adapted with permission from Tul [134])

sensitivity of 100 % and a specificity of 98 % for monochorionic placentation [13].

Determination of chorionicity in later gestation is much more difficult and less reliable. The lambda sign tends to disappear with advancing gestational age due to regression of the chorion frondosum to form the chorion laeve [13]. Discordance of fetal gender indicates dizygocity and, therefore, dichorionicity. However, only 55 % of all twins have been reported to be of different sex making gender discordance an unreliable sign of dichorionicity [14]. Thickness of the intertwin membrane may be another helpful indicator in determining chorionicity (Fig. 4.5). Membrane thickness of less than 2 mm has been reported to have 90 % sensitivity and 76 % specificity for diagnosing monochorionic/diamniotic twins using standard 2D sonography, and sensitivity can be further improved using 3D sonography [15]. Visualization of two separate placental masses can also be used to confirm dichorionicity. However, this finding is usually present in only about one-third of twin gestations. Moreover, both the presence of a thin bridge of placental tissue between two dominant placental masses and the presence of a succenturiate placental lobe can be seen in a monochorionic gestation, thereby limiting this parameter as a useful diagnostic tool.

As establishing chorionicity becomes increasingly difficult and less reliable as gestation progresses, all women with a twin pregnancy should be offered ultrasound examination in the first trimester to assess chorionicity in addition to viability, crown-rump length, and nuchal translucency [16]. Early establishment of chorionicity allows risk assessment which greatly determines further surveillance strategies in twin pregnancies.

4.3 Preterm Birth

Preterm birth is one of the main complications associated with twin pregnancies and the most important risk factor for perinatal morbidity and mortality in these gestations [17]. Approximately 50–60 % of twins are born preterm (before completed 37 weeks' gestation), and 10 % are born very

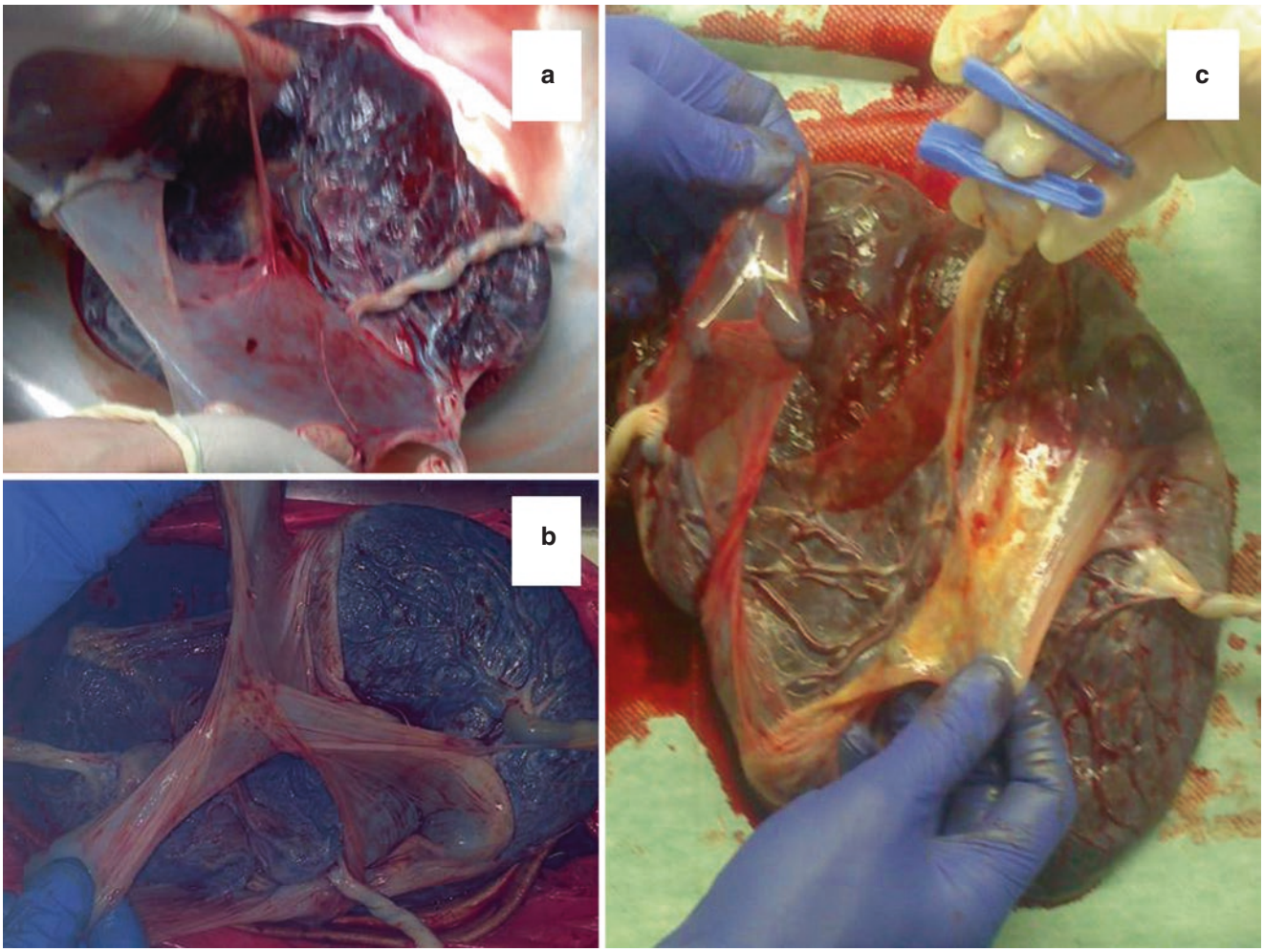

Fig. 4.5 (**a**) Monochorionic triamniotic placenta. Each fetus was surrounded by its own amnion, but a single chorion surrounded all three fetuses. Notice the thin amniotic membranes. (**b**) Trichorionic triamniotic placenta. Each fetus was surrounded by its own amnion and chorion. Notice the *thicker* membranes. (**c**) Dichorionic triamniotic placenta. Difference in thickness of membranes can be seen *thin* monochorionic membrane on the *left* and *thick* dichorionic on the *right*

preterm (before completed 32 weeks' gestation) [4, 18] (Fig. 4.10). Major complications associated with prematurity include respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and sepsis. These complications drive perinatal mortality rate of twins to seven times that of singletons and cerebral palsy rate to between four and seven times that of singletons [9, 17].

Prevention of preterm delivery is one of the most important goals in management of twin pregnancies. There is now substantial evidence that measuring cervical length by transvaginal ultrasound in singleton pregnancies helps to detect patients at increased risk of spontaneous preterm birth [19, 20]. This has been demonstrated to be true in twin pregnancies as well [21, 22]. Souka et al. examined the accuracy of cervical length at 23 weeks to predict spontaneous preterm delivery at less than 32 weeks in twins. Cervical length of less than 25 mm was associated with increased risk for very preterm birth. In addition, 70–80 % of women with cervical length of less than 10 mm delivered at less than 32 weeks [22] (Fig. 4.11).

Progesterone has been known to be important in maintaining pregnancy for more than 80 years, since the classic work of Corner, Allen, and Csapo [23, 24]. A large body of experimental data demonstrates that progesterone exerts overall control on both cervical ripening and myometrial contractility [25]. In addition to basic science support for the use of progestins in pregnancy, there is also substantial empirical evidence of their potential benefit from large clinical trials. Use of progestin supplementation (either as natural (bioidentical, micronized) progesterone administered vaginally or as 17 alpha-hydroxyprogesterone acetate (17-OH P) administered intramuscularly) has been shown to reduce the risk of preterm delivery in two subgroups of pregnant women: women with history of previous spontaneous preterm birth (trials shown benefit from 17-OH P, but not progesterone) and women with a short cervix measured by transvaginal ultrasound at 19–24 weeks' gestation (trials shown benefit from vaginal progesterone, but not 17-OH P) [26–30]. Rouse et al. showed that treatment with 17-OH P

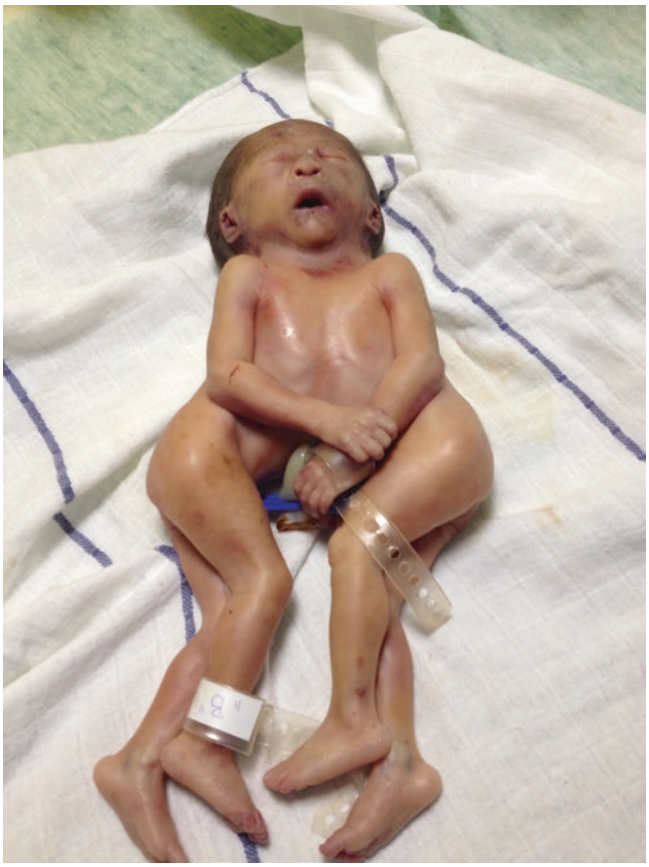

Fig. 4.6 Conjoined twins – case of cranio-thoracopagus. Fetuses may be fused in a number of ways, with the most common involving the chest and/or abdomen

did not reduce the rate of preterm births when administered to all women pregnant with twins, which is in agreement with the results of an earlier study published in 1980 [31, 32]. Two large studies in twin gestation, randomized to receive either vaginal progesterone or placebo, also showed no benefit of vaginal progesterone treatment in twin pregnancies [33, 34]. Increased doses of vaginal progesterone also did not reduce preterm birth rate in twin gestations [35]. There is no single randomized controlled trial looking specifically at effectiveness of vaginal progesterone in women pregnant with twins who are found to have a shortened cervix. However, Romero et al. published an individual patient data meta-analysis of five randomized controlled trials comparing vaginal progesterone treatment to placebo in patients with a sonographic short cervix (≤25 mm), which also included twin gestations [36]. They found no statistical sign of different responses to progesterone among twins compared to singleton pregnancies. One could, therefore, assume that if progesterone reduces the risk of preterm birth in singletons, it should do the same in twins. In fact, there was a 30 % reduction associated with vaginal progesterone treatment in preterm birth rates at less than 33 weeks in twin gestations included in this meta-analysis, but this reduction was not statistically significant. Importantly, however, they also found an almost 50 % statistically significant reduction in composite morbidity in twins whose mothers were treated with progesterone. Based on these data, we recommend treatment of patients pregnant with twins with a cervical length of ≤25 mm with vaginal progesterone.

Similarly to progesterone, cerclage placement in all twin pregnancies does not reduce the risk of spontaneous preterm birth [37]. However, data on efficacy and even safety of ultrasound-indicated cerclage, i.e., asymptomatic twin pregnancies with a cervical length of less than 25 mm, are conflicting. A Cochrane meta-analysis of randomized controlled trials of cervical cerclage in multiple pregnancies showed that cerclage placement in twin pregnancies with a cervical length of less than 25 mm could increase the risk of preterm delivery [36]. On the other hand, a recent multicenter retrospective cohort study showed that ultrasound indicated cerclage was not associated with significant effects on perinatal outcomes compared to controls when the 25 mm cervical length was used. In addition, in women with a cervical length of ≤15 mm before 24 weeks, cerclage was associated with a significant prolongation of pregnancy by almost 4 more weeks [38]. There are even less data on efficacy of emergency or physical exam-indicated cerclage in twins, i.e., cerclage placed in a patient with a dilated cervix on examination or membranes visible at the external cervical os on speculum examination. In the absence of better therapeutic options and in view of extremely increased risk of unfavorable outcomes, many centers will offer a cerclage to such patients prior to viability (24 weeks). A small, single institution retrospective study showed that emergency/physical exam-indicated cerclage in twin pregnancies could be associated with favorable outcomes, including a higher likelihood of delivery at >32 weeks [39]. There is currently an ongoing registered randomized trial of physical exam-indicated cerclage in twin gestations (NCT02490384, https://clinicaltrials.gov/).

Transvaginal placement of a silicon (Arabin) pessary around the cervix has been proposed as an alternative to progesterone and cerclage for preterm birth prevention (Fig. 4.12). It is thought to support the cervix and change its direction toward the sacrum, thereby reducing the direct pressure from the uterine contents on the cervical canal. Studies in singleton pregnancies with short cervix yielded conflicting results regarding its efficacy [40, 41]. Three randomized controlled trials examined the effects of cervical pessary on preterm birth rates in twins. A Dutch trial published in 2013 found no reduction in preterm birth at < 32 weeks in multiple pregnancies overall, but less very preterm births in women with cervical length <38 mm who had the pessary placed [42]. A recently published international randomized multicenter trial did not confirm these findings. Use of Arabin pessary in 1,180 women with twins at 20–24 weeks did not reduce preterm delivery before 34 weeks if inserted to randomly selected women (irrespectively of cervical length), neither did in subgroup of women with cervical length of

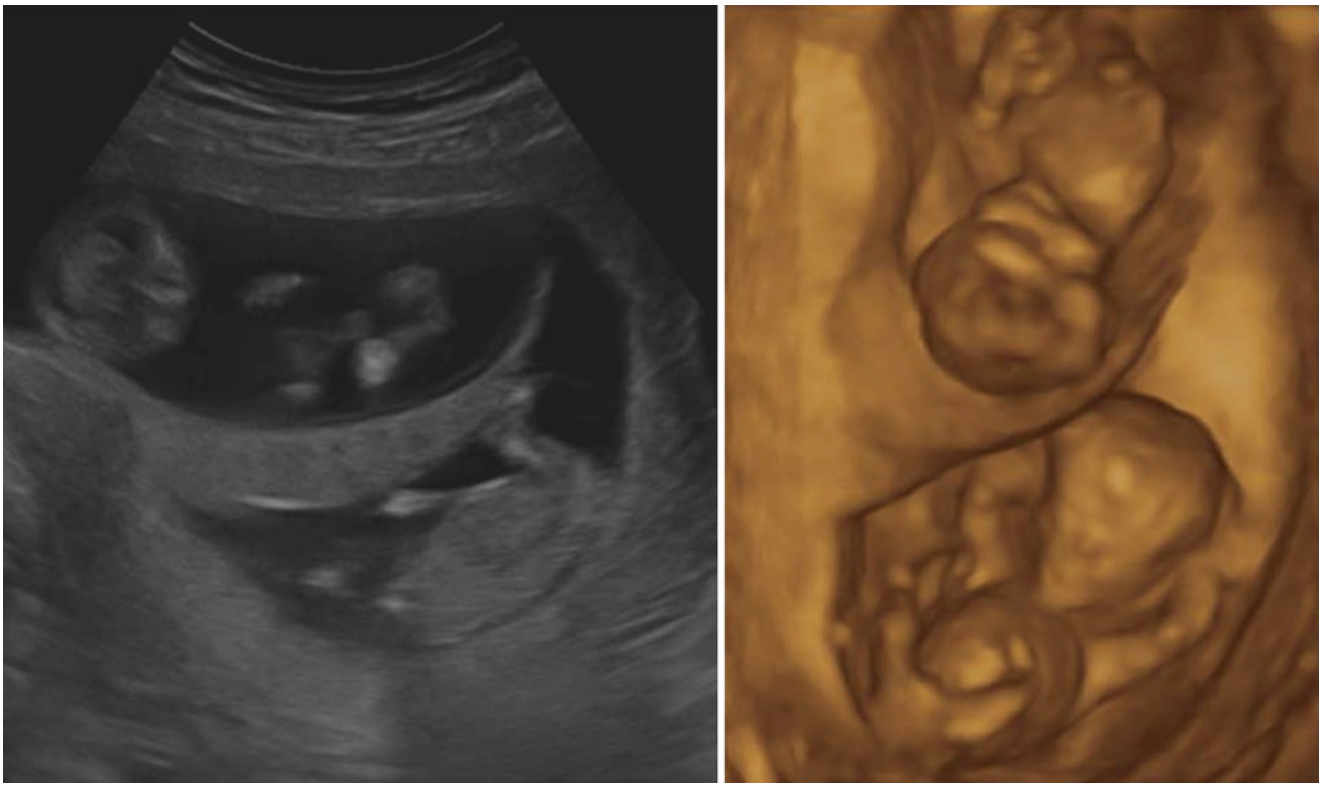

Fig. 4.7 Ultrasonographic picture of dichorionic twins at 12 weeks. On the *left*, 2D picture with visible thick intertwin membrane with *triangular* projection of placental tissue into the base of the intertwin membrane (lambda sign or twin peak sign). On the *right* same dichorionic twins in 3D

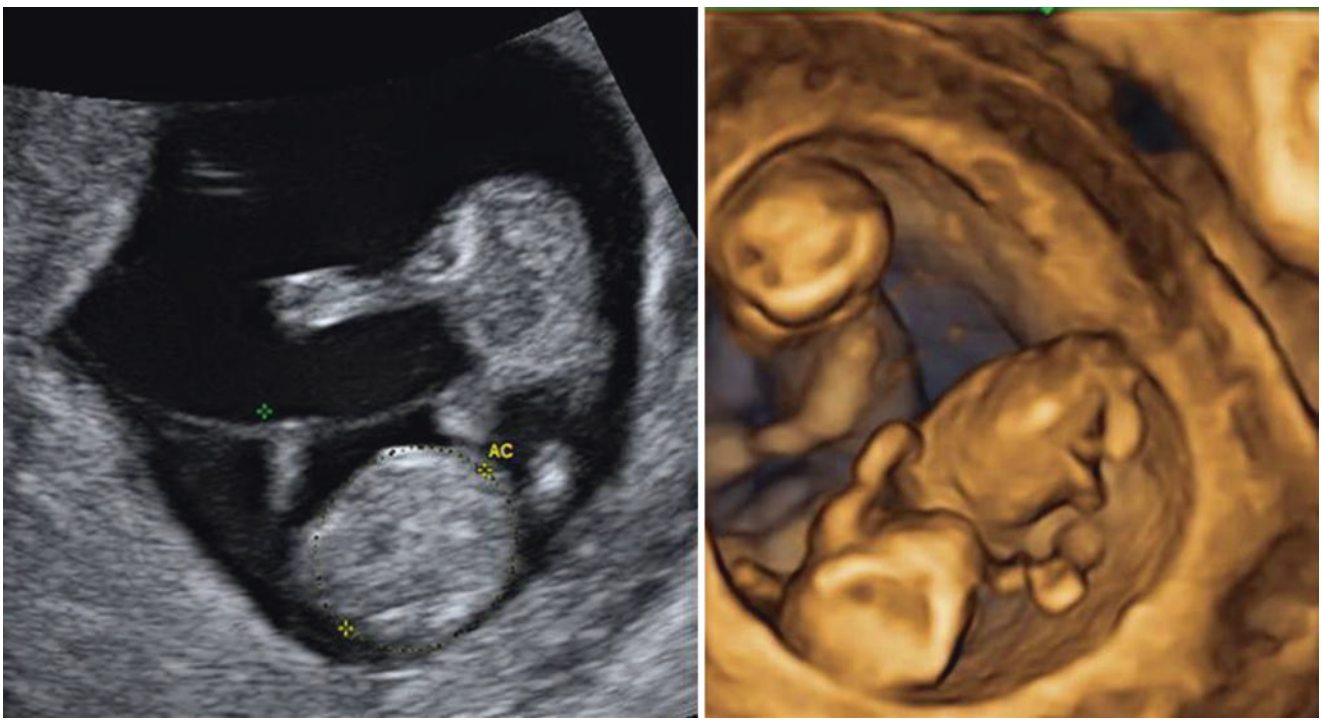

Fig. 4.8 Ultrasonographic picture of monochorionic twins at 12 weeks. On the *left*, 2D picture with visible thin intertwin membrane and no bulging of placental tissue into the base of the membrane (T sign). On the *right*, same monochorionic twins in 3D

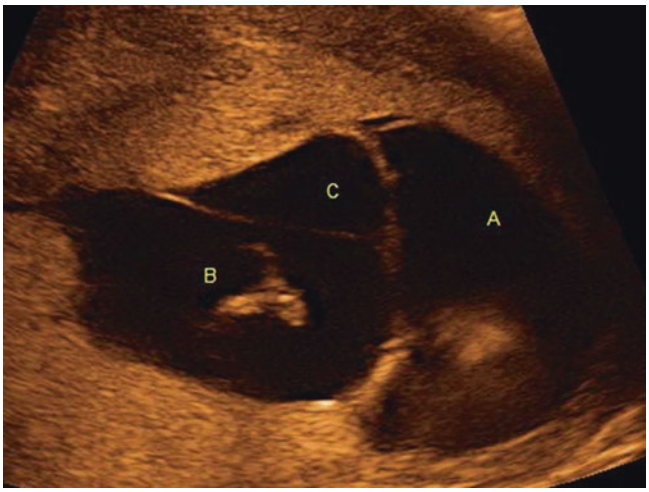

Fig. 4.9 Dichorionic triamniotic pregnancy at 11 weeks. Between fetuses *B* and *C*, the membrane is *thin* and T sign can be seen (monochorionic pair); between the fetus *A* and the other two, the membrane is *thicker* and lambda sign can be seen

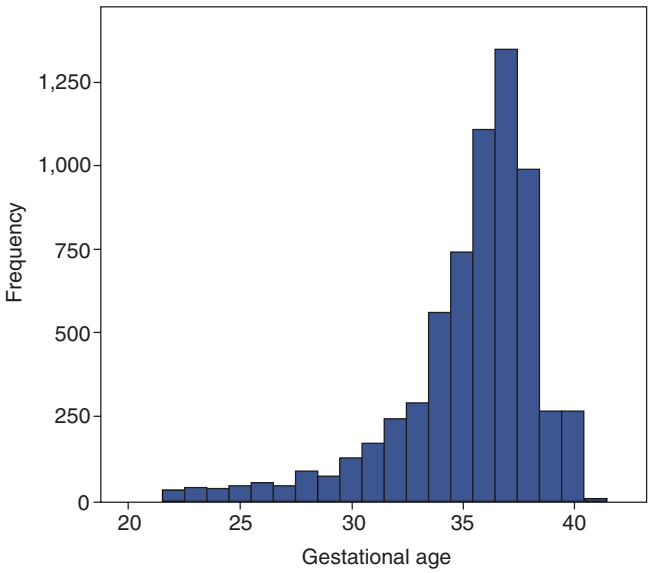

Fig. 4.10 Number of twin births in regard to gestational age in Slovenia between 2002 and 2010. Most births occurred between 34 and 39 weeks (From Bricelj et al. [18])

<25 mm [43]. This is in contrast with the results of a Spanish trial also published in 2016, which found a significant reduction in preterm births at <34 weeks associated with pessary insertion in twin pregnancies with a cervical length of ≤25 mm [44].

4.4 Fetal Anomalies

Congenital anomalies are two to four times more common in twins compared with singletons [44–55]. Most frequent fetal anomalies in twins are cardiovascular defects [41]. These are also the most common congenital anomalies in singletons, but the relative risk is higher for twin gestations [46, 48–54]. Anomalies of the central nervous system, such as hydrocephaly and neural tube defects; of the gastrointestinal system, in particular intestinal atresia; of the genitourinary system; and of the musculoskeletal system were also reported to occur more frequently in twins compared with singletons [46, 47, 49, 50, 54]. In contrast, similar rates of chromosomal abnormalities have been reported in twins and singletons [46, 47, 49–51]. These studies have, however, failed to appreciate the different maternal age distribution between twin and singleton pregnancies [5]. Moreover, although in monozygotic twins the risk of chromosomal abnormalities is the same as maternal age-related risk, in dizygotic pregnancies, each fetus carries an independent risk, and the risk per pregnancy is doubled.

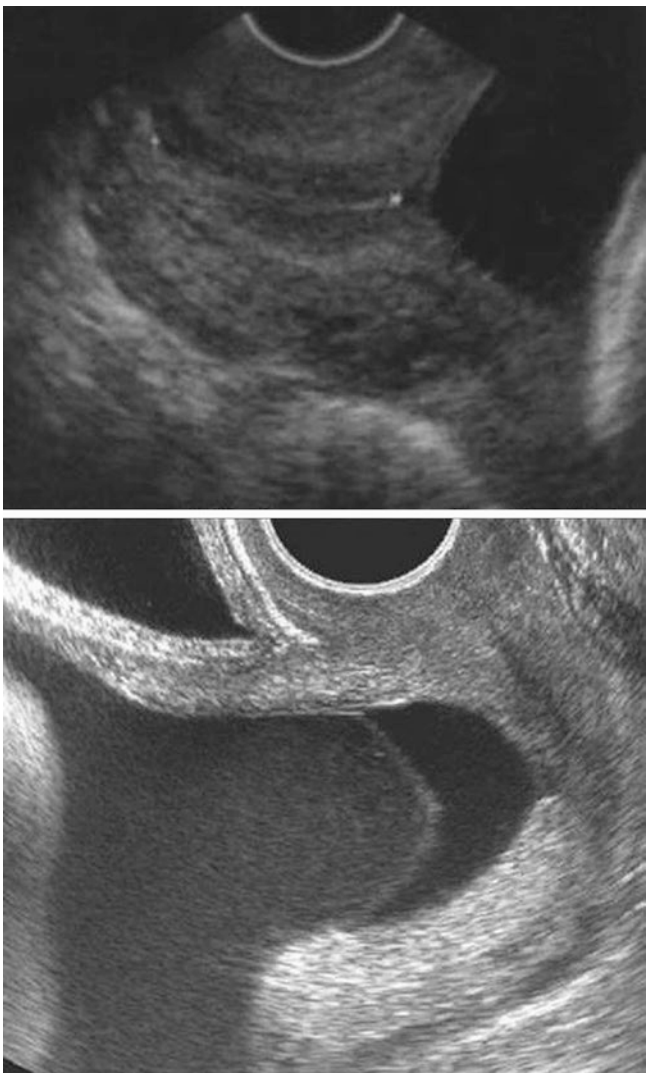

Fig. 4.11 Transvaginal ultrasound image of uterine cervix. The *upper picture* shows a long and closed cervix associated with low risk of preterm birth, while the *lower picture* shows a shortened cervix with "funneling" associated with increased risk of preterm delivery

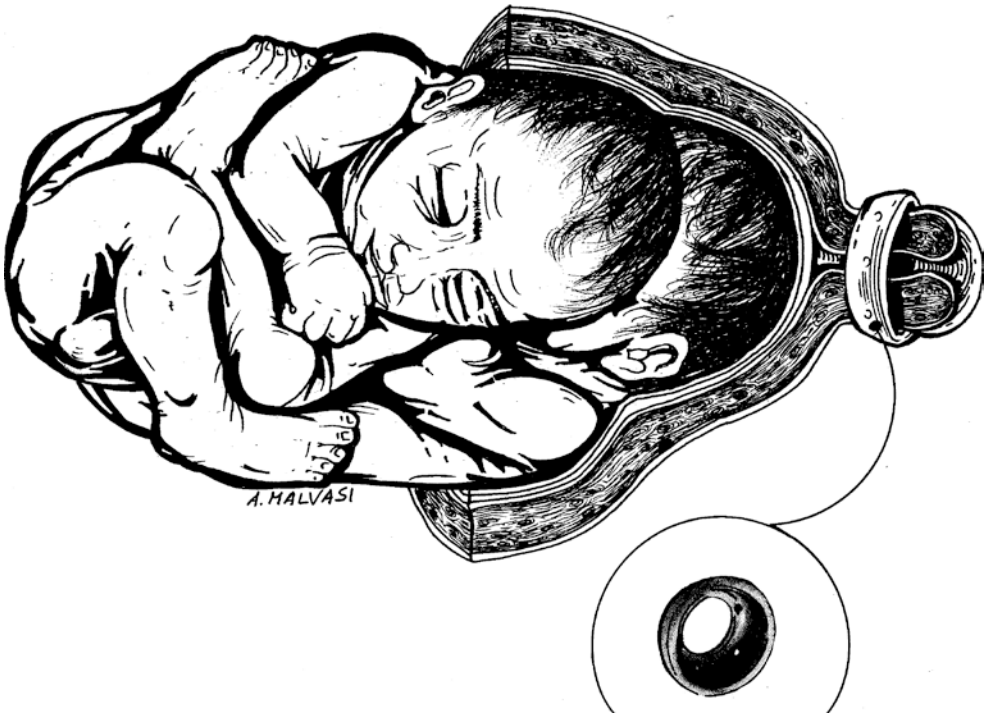

Fig. 4.12 Arabin cervical pessary (in the circumference), placed around the uterine cervix in order to prevent preterm birth

Studies that were able to examine congenital anomalies in twins by chorionicity or zygosity found that most of increased risk for anomalies is attributable to excess risk in monozygotic pregnancies [46, 47, 55, 56]. In dizygotic twins, the prevalence of structural anomalies in each twin is the same as in singleton pregnancies. Consequently, chances of at least one of dizygotic twins to have a structural anomaly are approximately twice as high as in singletons, with the addition of higher rates of compression or crowding anomalies, such as club feet [46, 47]. In monozygotic twins, the risk of congenital anomalies, such as brain, cardiac, renal, intestinal, and other abnormalities, is up to four times higher for each twin than in singletons [45–49, 55, 56]. A number of mechanisms have been proposed for the higher rate of anomalies observed in monochorionic and monozygotic twins. Monozygotic twinning itself can be regarded as an abnormality of morphogenesis since it involves zygotic splitting. This process has been associated with some specific malformations that have a predilection for midline structures, e.g., sirenomelia, cloacal anomalies, and holoprosencephaly, that are much more common in monozygotic twins [57, 58].

Higher rates of fetal congenital anomalies warrant a first trimester ultrasound examination with nuchal translucency thickness measurement and early anatomy scan in all twin pregnancies. At this time, chorionicity must be clearly diagnosed in all cases. In doubts, the patient must be sent to a referring center. We recommend a follow-up for all monochorionic twins in referring centers. Regardless of chorionicity, a detailed anatomical assessment should then be performed at 18–24 weeks' gestation. In a single-center series of 245 consecutive twin gestations, 21 of 24 anomalous fetuses were detected by detailed ultrasound examination at 18–20 weeks (88 % sensitivity, 100 % specificity, 100 % positive predictive value, negative predictive value 99 %) [59].

In addition to structural fetal anomalies, there are also other anomalies specifically related to monochorionicity that result from vascular anastomoses between the circulations supplying monochorionic twins; two most common are twin-to-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS).

4.4.1 Twin-to-Twin Transfusion Syndrome (TTTS)

Monochorionic embryos/fetuses are connected by transplacental vascular anastomoses that lead inevitably to sharing of the circulation. There are three main types of anastomoses in such placentas: venovenous (VV), arterioarterial (AA), and arteriovenous (AV). Both AA and VV anastomoses are direct superficial connections on the surface of the placenta with the potential for bidirectional flow (Fig. 4.13). In most cases, the shared circulation between monochorionic twins is relatively balanced, but in as many as 8–10 % of cases, an unbalanced intertwin shunt may be created through AV anastomoses, leading to so-called TTTS [16]. TTTS can theoretically occur at any time during pregnancy, but usually presents in the second trimester (Fig. 4.14). It is diagnosed by polyuric polyhydramnios in the recipient twin, with a maximal vertical pocket of amniotic fluid measur-

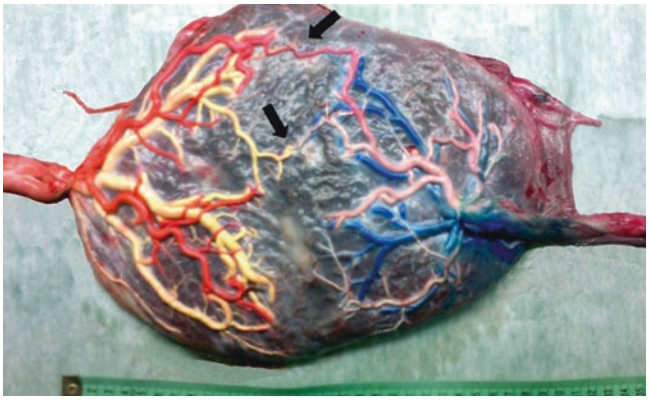

Fig. 4.13 Placenta of monochorionic twins after injection of umbilical blood vessels with dye. Venovenous anastomoses are visible (*arrows*)

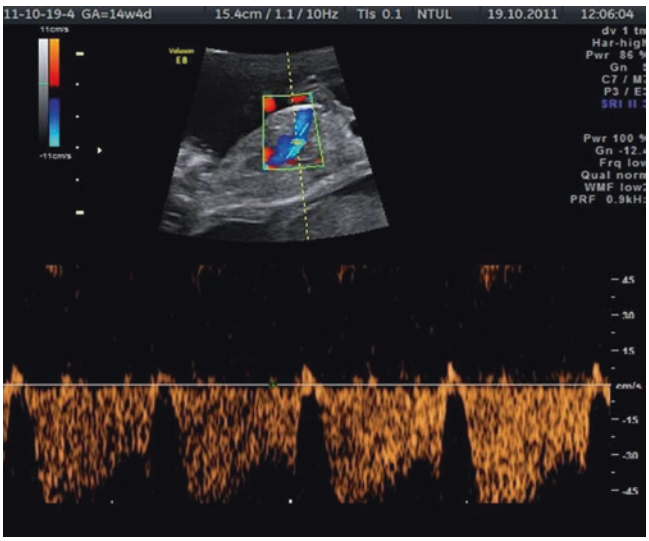

Fig. 4.14 Reversed a wave in the ductus venosus. An early sign of twin-to-twin transfusion syndrome (TTTS) at 14 weeks of gestation

ing at least 8 cm, and oliguric oligohydramnios in the donor twin with a maximum vertical pocket of 2 cm or less (Fig. 4.15) [16]. The most commonly used TTTS staging system was developed by Quintero et al. in 1999 [60]. The TTTS Quintero staging system includes five stages, ranging from mild disease with isolated discordant amniotic fluid volume to severe disease with demise of one or both twins. The criteria for stage I are polyhydramnios in the recipient twin and oligohydramnios in the donor twin with a visible bladder in the donor twin. In stage II the bladder of the donor twin is not visible at any point during the evaluation, but Doppler studies are not abnormal. In stage III Doppler studies are abnormal in either twins and are characterized by absent or reversed diastolic flow in the umbilical artery, reversed flow in the ductus venosus or pulsatile umbilical venous flow. In stage IV ascites, pericardial or pleural effusion, scalp edema or overt hydrops, are present (Fig. 4.16). Stage V is characterized by the demise of one or both twins (Fig. 4.17).

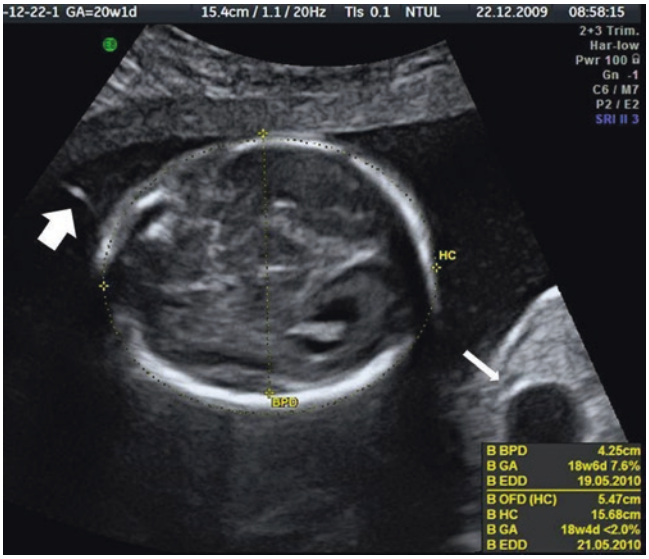

Fig. 4.15 Twin-to-twin transfusion syndrome (TTTS) at 20 weeks of gestation. Polyhydramnios in the recipient twin and oligohydramnios in the donor twin can be diagnosed looking at the position of the amniotic membrane (*thick arrow*). Notice also the dilated bladder of the recipient twin (*thin arrow*). In addition, there is intrauterine growth restriction in the donor twin (not part of the Quintero classification system)

This system has some prognostic significance and provides a method to compare outcome data using different therapeutic interventions. Although the stages do not correlate perfectly with perinatal survival, it is relatively straightforward to apply, may improve communication between patients and providers, and identifies the subset of cases most likely to benefit from treatment. In severe cases of TTTS, perinatal mortality without treatment ranges between 70 and 100 % (Fig. 4.17). Most experts currently consider fetoscopic laser photocoagulation of placental anastomoses to be the best available approach to treat severe TTTS at less than 26 weeks (Fig. 4.18). This procedure has been associated with an overall perinatal survival of 50–70 % in those with severe disease. Other therapeutic options may be considered in selected cases and include expectant management, amnioreduction, intentional septostomy of the intervening membrane, and selective termination [16].

4.4.2 Twin Anemia-Polycythemia Sequence

Another unique anomaly found exclusively in monochorionic gestations is TAPS. It is a form of chronic fetofetal transfusion and complicates up to 6 % of monochorionic diamniotic twin pregnancies, typically in the late second or third trimester [61]. TAPS is defined as the presence of anemia in the donor and polycythemia in the recipient twin, diagnosed antenatally by middle cerebral artery (MCA) peak systolic velocity (PSV) of 1.5 multiples of median in the

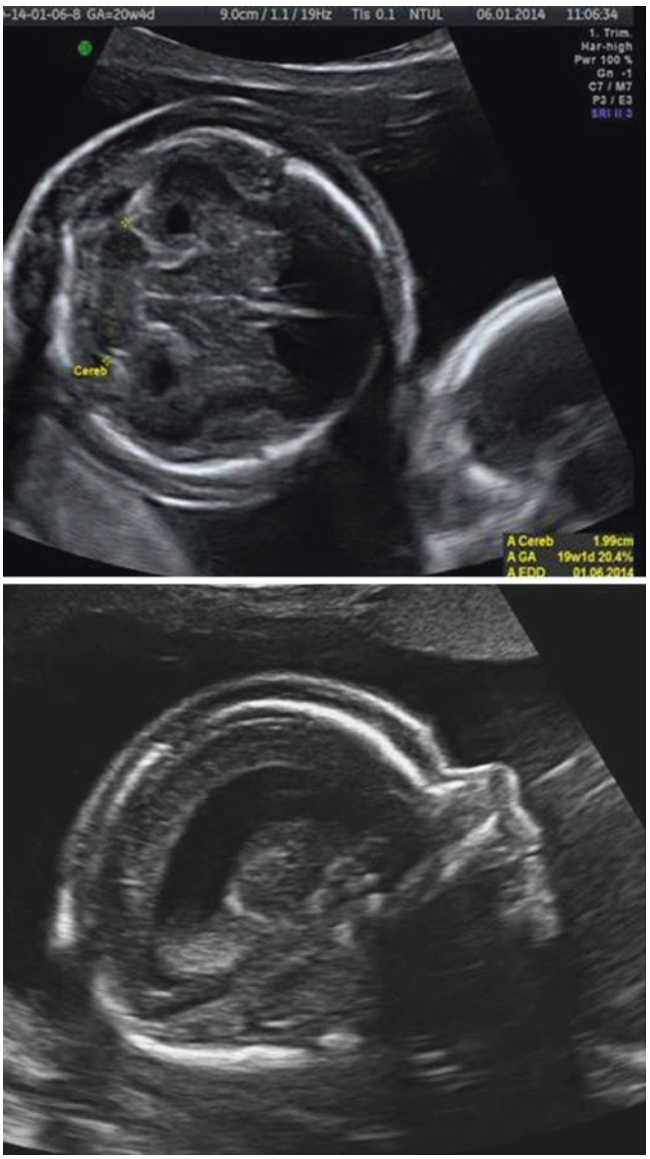

Fig. 4.16 Twin-to-twin transfusion syndrome (TTTS) stage IV according to the Quintero classification system. Notice the scalp edema in one of the fetuses

donor and MCA PSV <1.0 multiples of median in the recipient, in the absence of oligohydramnios-polyhydramnios [61, 62]. Extreme cases of TAPS can progress to fetal death. Suggested treatment options include laser photocoagulation, intrauterine blood transfusion, selective termination, and early delivery, but further studies are required to determine the natural history and optimal management of TAPS.

4.5 Stillbirth

Overall, twins are at an approximately fivefold increased risk of fetal death compared to singletons (Fig. 4.19) [8]. This risk is predominately influenced by the marked increase in rates of fetal demise in monochorionic twins (7.6 % monochorionic versus 1.6 % in dichorionic twins) [12]. Even in apparently uncomplicated monochorionic twins, single fetal deaths may still occur in as many as 2.6 % of pregnancies [63]. Of note, population-based studies yielded much higher incidences of stillbirth in monochorionic-diamniotic twins as compared to hospital-based surveys coming from tertiary centers with special interest in monochorionic twinning [63–68]. This supports the idea that a strict protocol of close surveillance should be implemented for all monochorionic gestations and that elective preterm delivery might be a reasonable policy to avoid unexpected intrauterine fetal deaths in these pregnancies (see Sect. 4.8) [69]. This is the main reason why we recommend follow-up of monochorionic twins in refereeing centers.

Intrauterine death of a fetus in a twin pregnancy may be associated with poor outcome for the co-twin, but the degree of risk is again dependent on chorionicity. Vascular intraplacental connections between twins may place the surviving co-twin in a monochorionic pregnancy at a significantly higher risk. In a recent meta-analysis, death of one twin was associated with co-twin demise in 15 % of monochorionic gestations and 3 % of dichorionic gestations [70]. Similarly, the incidence of neurologic morbidity following death of a co-twin was 26 % in monochorionic gestations, compared with 2 % in dichorionic gestations [70]. Previously thought to be related to the passage of thromboplastin-like substances after the death of the twin, the more widely accepted theory today is that acute hypotension in the dying fetus results in a "sink" phenomenon [71]. Acute exsanguination of the normal co-twin results in its death or survival with neurologic sequelae. Thus, immediate or emergent delivery confers no advantage to the surviving fetus after the death of its co-twin. There is a theoretical concern of maternal complications, such as disseminated intravascular coagulation, due to retention of the death fetus when continuing pregnancy after intrauterine demise of one twin. [71–73]. The incidence of this complication, however, seems to be exceedingly low [72–74].

4.6 Intrauterine Growth Restriction

Data from numerous studies, as well as our own from the Slovenia's National Perinatal Information System, indicate a trend of fetal growth deceleration after the 28th week in twin gestations in comparison with singletons (Fig. 4.20) [18, 75–80]. This may be the result of placental insufficiency when twins approach term [81]. Intrauterine growth restriction (IUGR) of one or both fetuses can be determined by ultrasound, which estimates fetal weight with reasonable accuracy [82]. Numerous sequential measurements must be made as IUGR is defined as inappropriate growth during a certain time period [83]. The appropriateness of fetal growth is assessed by using birth weight by gestational age – growth

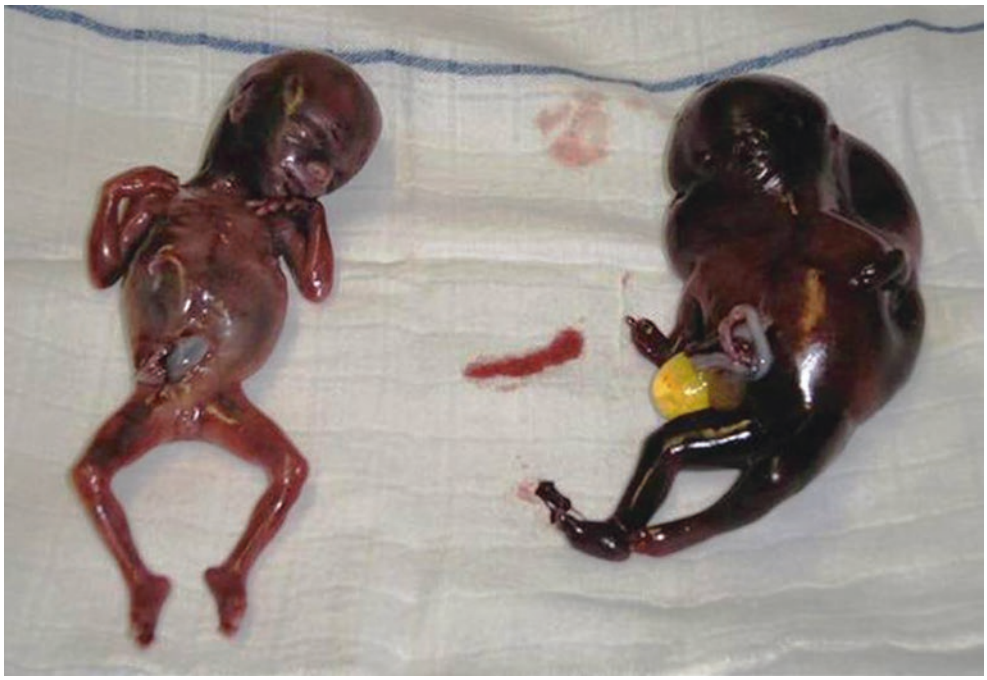

Fig. 4.17 Twin-to-twin transfusion syndrome (TTTS) resulting in demise of both fetuses at 17 weeks. This could be potentially prevented with early recognition and laser therapy

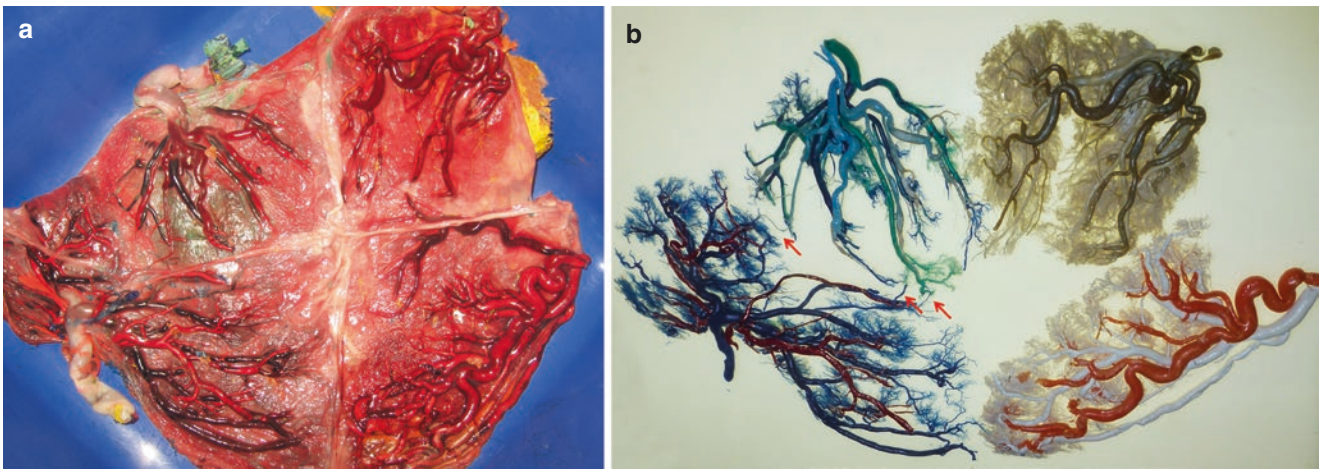

Fig. 4.18 (**a**, **b**) Placenta (*left image*) and placental blood vessels (*right image*) of monochorionic quadramniotic quadruplets after laser therapy for fetofetal transfusion syndrome and injection of umbilical blood vessels with acrylate monomers. Tiny anastomoses are visible even after laser therapy (*arrows*) (With permission from Tul et al. [135])

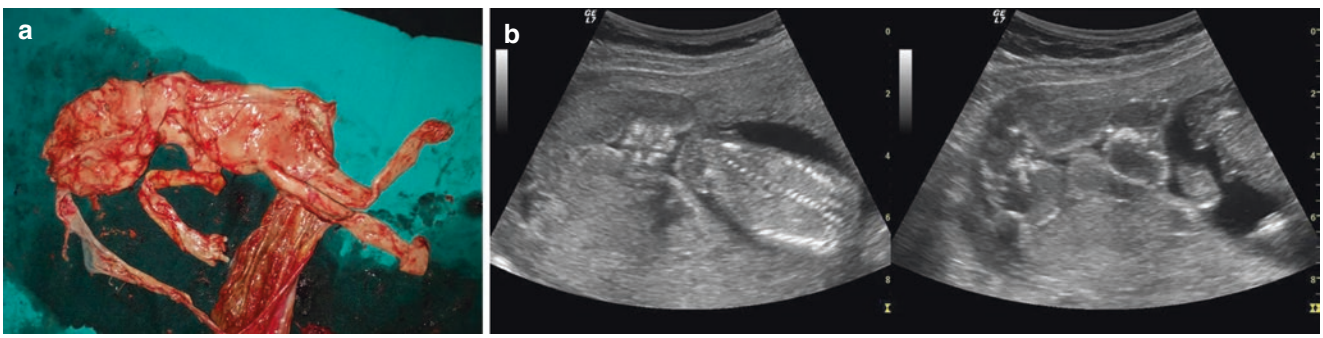

Fig. 4.19 (**a**, **b**) Following an intrauterine death of one of the twins, there may be complete reabsorption of the death fetus (when intrauterine death occurs very early in gestation) or formation of a fetus papyraceus (i.e., a "mummified" or compressed fetus) (*left*). Ultrasound images of fetus papyraceus are shown below (Courtesy of Andrea Tinelli)

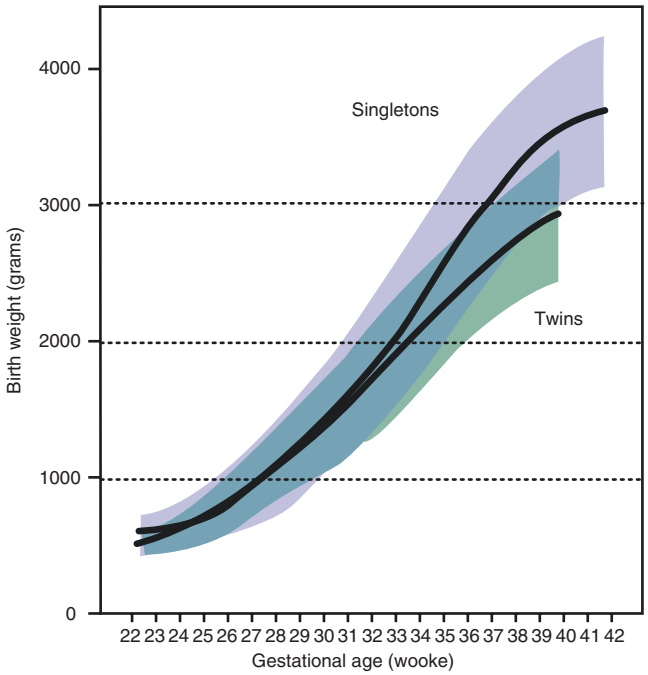

Fig. 4.20 Comparison between growth curves for twins and singletons. Fiftieth centile and areas between 10th and 90th centile are plotted (Notice the slower growth of twins in the third trimester (From Bricelj et al. [18]))

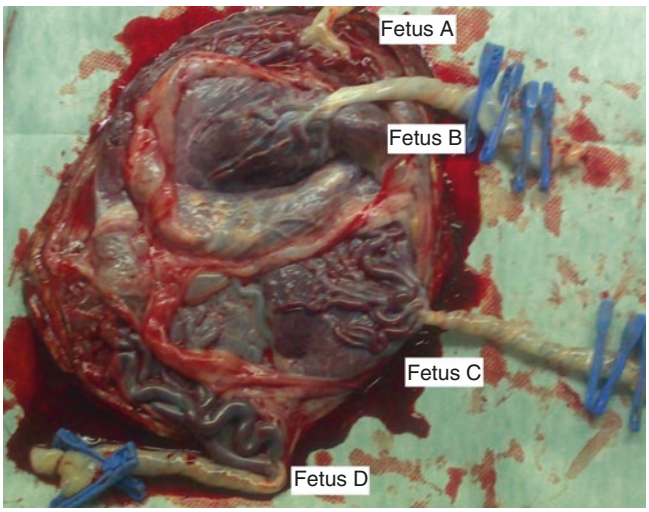

Fig. 4.21 Marginal cord insertions are more common in multifetal gestations compared to singletons (see marginal insertions of cords of fetuses *C* and *D* and central insertion in *A* and *B*). This leads to unequal sharing of the placenta (Image shows a monochorionic quadruplet placenta)

Fig. 4.22 Selective intrauterine growth restriction in monochorionic twins

curves, preferably twin-specific growth curves. Alternatively, IUGR in twins is often defined as estimated fetal weight below the tenth percentile using singleton growth curves or presence of ≥15–25 % discordance in estimated fetal weight between the lighter and heavier twin [75–80].

The prevalence of IUGR has been reported to be 26 % in dichorionic twins and as high as 46 % in monochorionic twins [84]. Monochorionicity increases the overall risk of IUGR in twin pregnancies due to disproportionate placental sharing (Fig. 4.21). In one prospective series, selective IUGR, defined as a birth weight discordance of at least 25 % in the absence of TTTS, was reported to complicate about 15 % of monochorionic pregnancies and was associated with perinatal mortality of 5–10 % (Fig. 4.22) [66].

The question remains whether birth weight discordance alone, i.e., without IUGR of one or both fetuses, is still associated with increased perinatal morbidity and mortality. Earlier studies showed worst outcomes in twin pregnancies with birth weight discordance of more than 15–25 % [85–90]. More recent studies, looking at growth discordance and IUGR separately, however, found a much smaller impact of discordance in the absence of IUGR of either twins [91, 92].

Growth abnormalities should, therefore, be actively sought in the third trimester of every twin pregnancy. Fundal height is not expected to reliably detect growth aberrations in twins, and for this reason, serial sonographic assessment is recommended. In the case of IUGR of one or both twins, strict antepartum surveillance and consideration of early delivery are indicated.

4.7 Hypertensive Disorders, Gestational Diabetes, and Role of Nutrition

Twin pregnancies are at a two- to threefold increased risk of gestational diabetes and hypertensive disorders compared to singletons [93, 94]. These complications also occur at an earlier gestational age and with higher severity in twins [95, 96]. Higher incidence of gestational diabetes in twin gestations is generally thought to be the result of increased placental mass and higher levels of human placental lactogen as well as other hormones with antagonistic actions on insulin [97]. The explanation why twin gestations are at increased risk of developing hypertensive disorders is,

however, lacking. Some of the known association of hypertensive disorders during pregnancy suggests a greater immunological mismatch between fetus and mother. In twins, this immunological mismatch would be expected to increase the incidence of hypertensive disorders in dizygotic compared to monozygotic sets. The latter theory was proposed some 40 years ago, when Stevenson and co-workers suggested that though preeclampsia is more common in all types of twin pregnancies than in single births, it is even more common where the twins are dizygotic than where they are monozygotic [93]. However, data from several studies, including some recent reports, were inconclusive and somewhat conflicting on this issue [98–103]. We have compared twins in our national database using the best clinical estimate of zygocity, namely, all monochorionic twins are monozygotic and all unlike-sex pairs are dizygotic, and found no significant effect of zygocity on the rate of hypertensive disorders in twins.

Studies from our group and others found a profound effect of higher pre-gravid body mass index (BMI) on the incidence of hypertensive disorders and gestational diabetes in twin pregnancies [104–107]. In addition, excessive weight gain during pregnancy was also associated with a trend toward an increased incidence of these disorders [107]. Excessive weight gain during twin gestations has also been shown to correlate with higher risks of preterm birth and small for gestational age neonates [108, 109]. Women pregnant with twins should, therefore, receive appropriate advice about recommended weight gain during pregnancy. There is evidence that receiving such advice correlates with actual weight gain within the guidelines [110, 111]. Unfortunately, according to the literature, up to one third of women receive no counsel at all from their prenatal care providers on how much weight to gain [110]. Most recent recommendations on weight gain in pregnancy were issued in 2009 by the Institute of Medicine (IOM) [112]. Table 4.1 presents these recommendations for twin pregnancies. IOM currently makes no recommendation on weight gain in twin pregnancies for underweight and severely/morbidly obese women (class II and/or III obesity) due to insufficient data. More studies are, therefore, urgently needed in this field, since these subpopulations of women would probably benefit the most from appropriate dietary counseling early in pregnancy.

Table 4.1 Recommendation for total weight gain during twin pregnancy according to prepregnancy body mass index (BMI) (From Institute of Medicine [112])

Prepregnancy BMI	Recommended total weight gain
Underweight (<18.5 kg/m^2)	Insufficient information
Normal weight (18.5–24.9 kg/m^2)	17–25 kg
Overweight (25–29.9 kg/m^2)	14–23 kg
Obese (≥30 kg/m^2)	11–19 kg

4.8 Timing of Delivery

Timing of delivery of twin pregnancies complicated by IUGR, hypertensive disorders, oligohydramnios, etc. must be determined individually based on fetal and/or maternal risks. For uncomplicated twin pregnancies, most of recommendations on optimal timing of delivery come from population-based databases. These data are limited by frequently inadequate information on chorionicity, neonatal morbidity, comorbidities, etc. [63, 64, 66, 113, 114]. Only two randomized trials to date compared delivery of uncomplicated twins at completed 37 weeks vs. expectant management beyond 37 weeks [115–117]. Delivery at 37 weeks' gestation was not associated with an increased risk of harms. Consecutively, the United Kingdom's National Institute for Health and Care Excellence (NICE) recommends birth for women with a dichorionic twin pregnancy at 37 + 0 weeks' gestation. Due to increased risk of unexplained stillbirth in uncomplicated monochorionic diamniotic gestations, NICE recommends elective birth from 36 weeks 0 days, after a course of antenatal corticosteroids [118]. In the USA, the National Institute of Child Health and Human Development and the Society for Maternal Fetal Medicine recommend delivery of uncomplicated dichorionic twins at 38 weeks [119]. Because of higher risk of stillbirth, they also suggest delivery of uncomplicated monochorionic diamniotic earlier, at 34–37 weeks [119].

Although monoamniotic twins comprise <1 % of twin pregnancies, they are at particularly high risk. Historically, monoamniotic twins have been associated with perinatal mortality in up to 80 % of cases, primarily related to umbilical cord entanglement (Fig. 4.23) [120]. Even in recent series, the perinatal mortality rate was approximately 15 %. In an effort to avoid intrauterine fetal death, a number of authors have discussed the role of inpatient management as early as 24–28 weeks, with steroid administration, daily fetal surveillance, serial assessment of fetal growth, and delivery between 32 and 34 weeks [120–122].

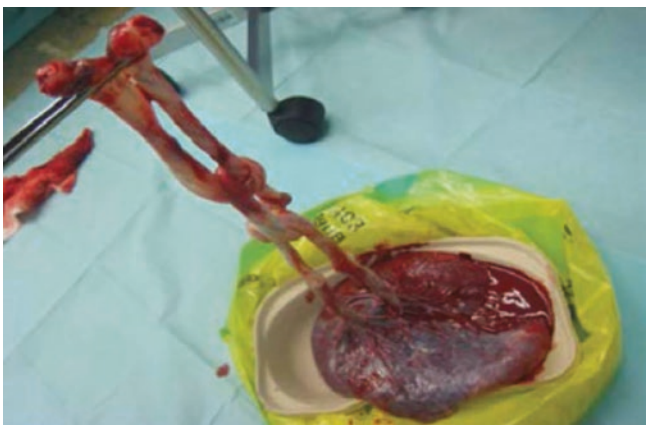

Fig. 4.23 Entanglement of umbilical cords in monoamniotic twins (Adapted with permission from Tul [134])

4.9 Route of Delivery

At the time of delivery, approximately 40 % of twins will be in a cephalic/cephalic presentation and 35 % in a cephalic/non-cephalic presentation, and in the remaining 25 %, twin A will be in a non-cephalic presentation (Fig. 4.24). Several cohort studies have shown a reduced risk of adverse perinatal outcomes for both twins, or for the second twin, when twins at or near term were delivered by planned cesarean section [123–127]. This was especially evident when the first twin was in a breech presentation [123] (Fig. 4.25). In 1987, a small randomized trial compared policy of planned cesarean delivery vs. planned vaginal delivery for twins at >35 weeks with a cephalic/non-cephalic presentation [128]. They found

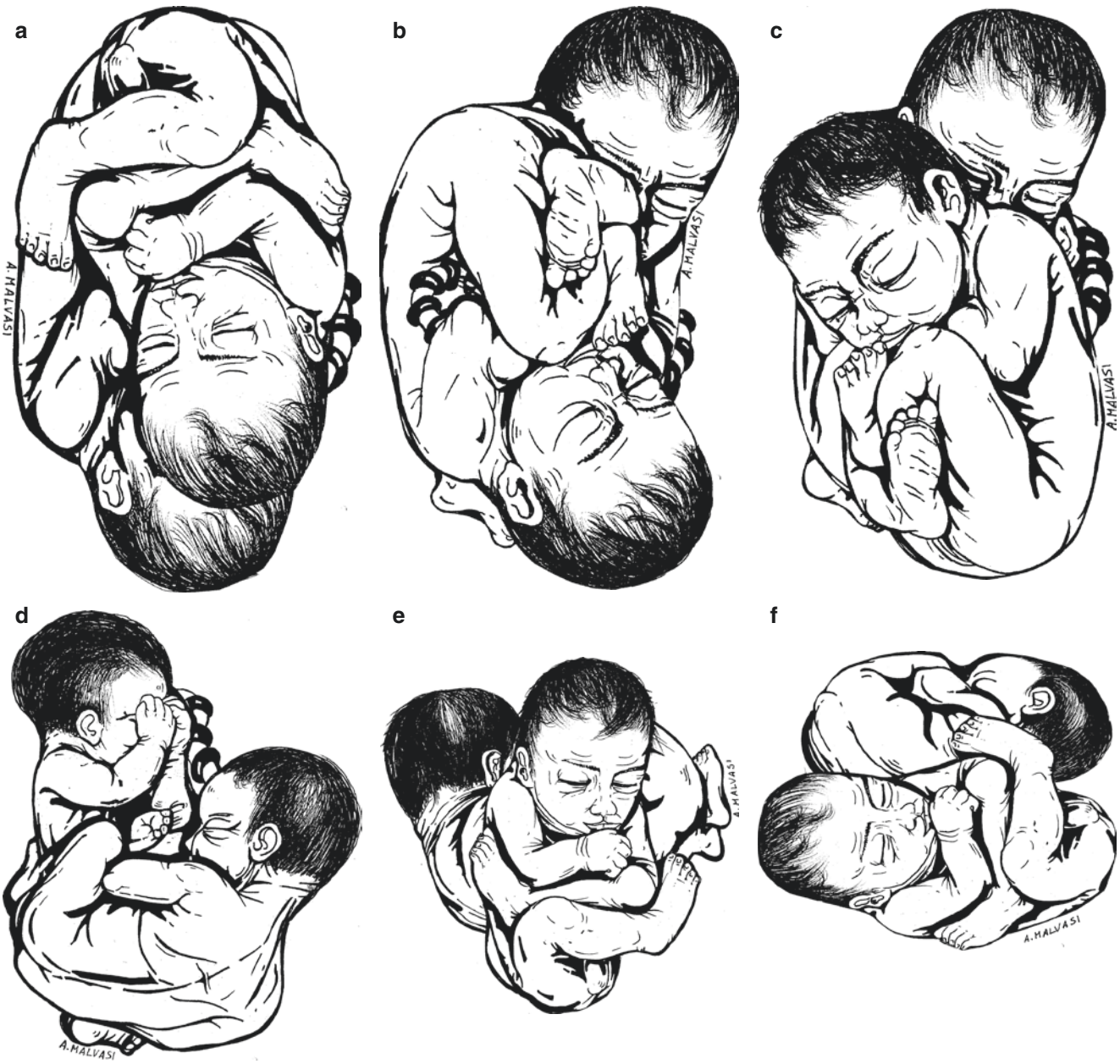

Fig. 4.24 Various presentations of twins at the time of delivery. Approximately 40 % of twins will be in a cephalic/cephalic presentation (**a**) and 35 % in a cephalic/non-cephalic presentation (**b**), and in the remaining 25 %, twin A will be in a non-cephalic presentation (**c–f**)

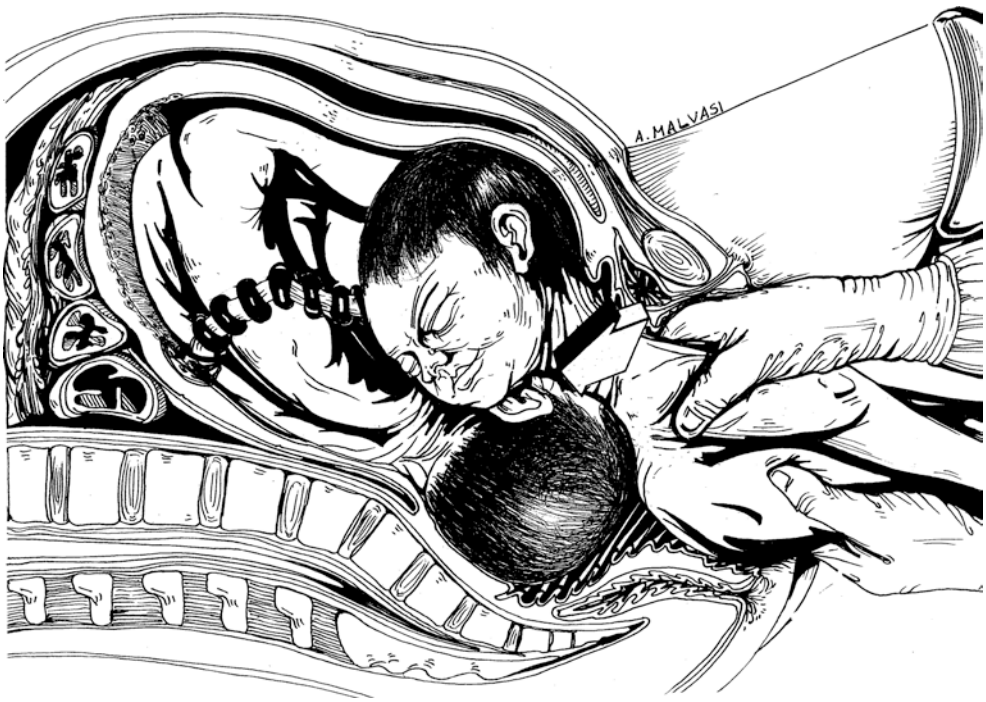

Fig. 4.25 "Twin collision" (arrow), as a complication of non-cephalic (cephalic and breech presentation), twin presentation during labor and delivery

no difference in neonatal outcomes and an increase in maternal febrile morbidity in the planned cesarean delivery group (40 % vs. 11 %), but the trial was underpowered to detect a potential small increase in fetal/neonatal risk associated with vaginal birth [128]. A large, multicenter randomized trial of trial of planned vaginal delivery vs. planned cesarean delivery was then conducted for twins between 32 weeks 0 days and 38 weeks 6 days of gestation, with the first twin in cephalic presentation [129]. Planned cesarean section did not reduce the risk of fetal or neonatal death or serious neonatal morbidity. There was a higher risk of an adverse perinatal outcome for the second twin than for the first twin, as reported in other studies, but planned cesarean section did not reduce this risk [124–127, 129].

The current consensus is, therefore, that trial of vaginal delivery is appropriate for twins with cephalic presentation of the first twin, birth weight discordance <25 %, and estimated birth weights >1,500 g. The question then is how to maximize the chances of a successful vaginal delivery. Discordant routes of delivery, i.e., vaginal delivery of twin A and emergency cesarean delivery of twin B, have been associated with worst neonatal outcomes [130]. Strategies to decrease such combined deliveries should, therefore, lead to improvement in neonatal morbidity and mortality. Data from retrospective cohort studies suggest that protocol-based second-stage management is associated with lower difference in differential outcome between twins A and B and fewer combined vaginal-cesarean deliveries [131–133]. At our institution, presentation of twin B is ascertained by ultrasonography after delivery of twin A. If twin B is vertex or breech, the patient is instructed to push and amniotomy is performed when the presenting part is engaged. Oxytocin is used as appropriate. If twin B is footling or transverse, complete breech extraction is performed using standard obstetric maneuvers. Following this protocol, we found similarly low rates of maternal and neonatal complications in the group of twins delivered by planned cesarean section compared to those who underwent a trial of vaginal delivery. Protocols for management of twin vaginal deliveries should, in our opinion, also include appropriate antenatal counseling and provider training.

4.10 Summary of Recommendations for Management of Twin Pregnancies

- Chorionicity should be routinely assessed in twin gestations, as early as possible in pregnancy and ideally by 14 weeks. Assessment of chorionicity becomes increasingly less reliable as pregnancy progresses and surveillance strategies depend mostly on determination of chorionicity. Screening for chromosomal and structural abnormalities should be offered to all patients at 11–14 weeks.

- All women pregnant with twins should be given advice on optimal gestational weight gain according to their pre-pregnancy BMI. The Institute of Medicine recommends 11–25 kg total weight gain during twin gestations. The lower end of this range is appropriate for obese women, the middle of the range is appropriate for overweight women, and the upper end of the range is appropriate for women of normal weight. Appropriate weight gain has been associated with lower rates of preterm birth, small for gestational age infants, hypertensive disorders, and gestational diabetes.
- All twin pregnancies are at increased risk of preterm delivery. Serial measurements of cervical length using transvaginal ultrasound beginning at 16–18 weeks may identify women at particularly increased risk. Women with a cervical length of ≤25 mm in midtrimester should be offered treatment with vaginal progesterone in standard doses (200 mg capsule or 90 mg gel Crinone® daily). There is no high-quality evidence that this intervention significantly reduces preterm birth rates in twins, but it has been shown to reduce neonatal morbidity in this subset of twin pregnancies.
- A detailed anatomical assessment should be performed at 18–24 weeks' gestation in all twin pregnancies because of increased risk of congenital anomalies (especially high in monozygotic twins).
- In dichorionic twins, ultrasound examinations should be performed every 4 weeks to assess fetal growth because of the increased risk of growth restriction.
- In addition to fetal growth restriction, monochorionic twins are at increased risk of specific complications, including TTTS and TAPS. As a result, in monochorionic twins, ultrasound examinations should be performed approximately every 2 weeks, beginning at 16 weeks.
- Because of placental vascular anastomoses between monochorionic twins, the intrauterine death of one twin in a monochorionic twin pregnancy can cause acute hypotension, anemia, and ischemia in its co-twin, resulting in morbidity or death of the co-twin. However, delivery is unlikely to benefit the survivor after death of one twin of a dichorionic or monochorionic gestation.
- Given the increased risk of stillbirth, women with uncomplicated monochorionic twin pregnancies should be offered elective birth from 36 weeks 0 days. Some authorities suggest prior course of antenatal corticosteroids.
- Women with uncomplicated dichorionic twin pregnancies should be offered elective birth from 37 weeks 0 days and no later than 38 weeks and 0 days.
- Women with monoamniotic twins should be offered elective birth from 32 to 34 weeks due to the risk of cord entanglement.
- Trial of vaginal birth is indicated when the first twin is in cephalic presentation, birth weight discordance is estimated to be <25 %, and birth weights are estimated to be >1,500 g.
- A protocol-based active management of delivery of the second twin reduces the risks of neonatal complications in the second twin.

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Fetal Distress and Labor Management: The Role of Intrapartum Monitoring

5

Gerard H.A. Visser

5.1 Introduction

Electronic fetal heart rate monitoring or cardiotocography (CTG) has been introduced in the 1970s. It has resulted in a 1.6-fold increase in cesarean deliveries (CD; [1]) for fetal distress but has hardly resulted in improvements in neonatal outcome. As stated in an editorial in the *American Journal of Obstetrics and Gynecology*, " The hope that this technology would lower the rate of cerebral palsy from intrapartum asphyxia has not materialized. There is, however, reasonable good evidence that CTG does decrease the rate of perinatal mortality, particularly early infant death because of hypoxia" [2]. At term approximately 11,000 labors should be monitored to prevent one early neonatal death and 4,000 to prevent one infant death [3]. In other words, the contribution of CTG to improve perinatal outcome seems rather restricted. And for the prevention of one neonatal death, an extra 700 CDs will have to be performed. In this chapter, the backgrounds of the disappointing effects of CTG monitoring on perinatal outcome are discussed, and suggestions for improvements are given.

5.2 Why Is the Effect of Intrapartum CTG on Perinatal Outcome So Small?

Absence of improved outcome may be due to changes in patient population, with nowadays more older and obese women. It may also be due to the fact that intrapartum asphyxia contributes less to longer time outcome than thought before. Finally, current CTG monitoring might be inadequate.

Factors influencing the effectivity/reliability of CTG:

- Correct classification and large interobserver variation
- Poor specificity
- Correct action in case of abnormalities
- Low uptake of adjunct technologies

Intrapartum CTG tracings have to be assessed visually, since no reliable computer programs are available yet. Visual assessment is associated with large inter- and intra-observer variation [4], which hampers adequate interpretation and management.

Furthermore, CTG has a poor specificity. This implies that a normal pattern is generally associated with a good fetal condition as far as the oxygenation status is concerned. Poor fetal outcome occurs in cases with an abnormal CTG, but the incidence of poor outcome in this group is rather low, i.e., there are many false-positive cases. So-called experts are likely to identify the majority of abnormal CTG traces that are related to poor outcome [5], but also for them it sometimes remains difficult (Fig. 5.1). The high incidence of false-positive cases results in over-interventions without improving outcome.

The most important issue is most likely the human factor. Studies have shown that not only recognition of abnormal CTG patterns seems difficult but also of taken the correct action or taken actions at all [6, 7]. These include, among others, the lack of correction of a poor-quality CTG tracing, no follow-up after a first fetal scalp blood sample (FBS), increase in oxytocin dose instead of stopping it, and time delay in delivering the baby [7]. Also in some cases monitored with the relatively new STAN technology, it appeared that so-called false-negative STAN cases were not false-negative at all but were due to obstetricians who did not know the STAN guidelines and/or did not take the proper action [8]. So, the human factor may well be the most important limiting factor regarding CTG monitoring.

This should also be taken into account when discussing the use of so-called adjunct technologies. Many colleagues seem to interpret CTG patterns with only two options in mind: everything is fine with the baby (normal CTG), or immediate action should be taken (abnormal CTG), ignoring the fact that the majority of patterns are in between, i.e.,

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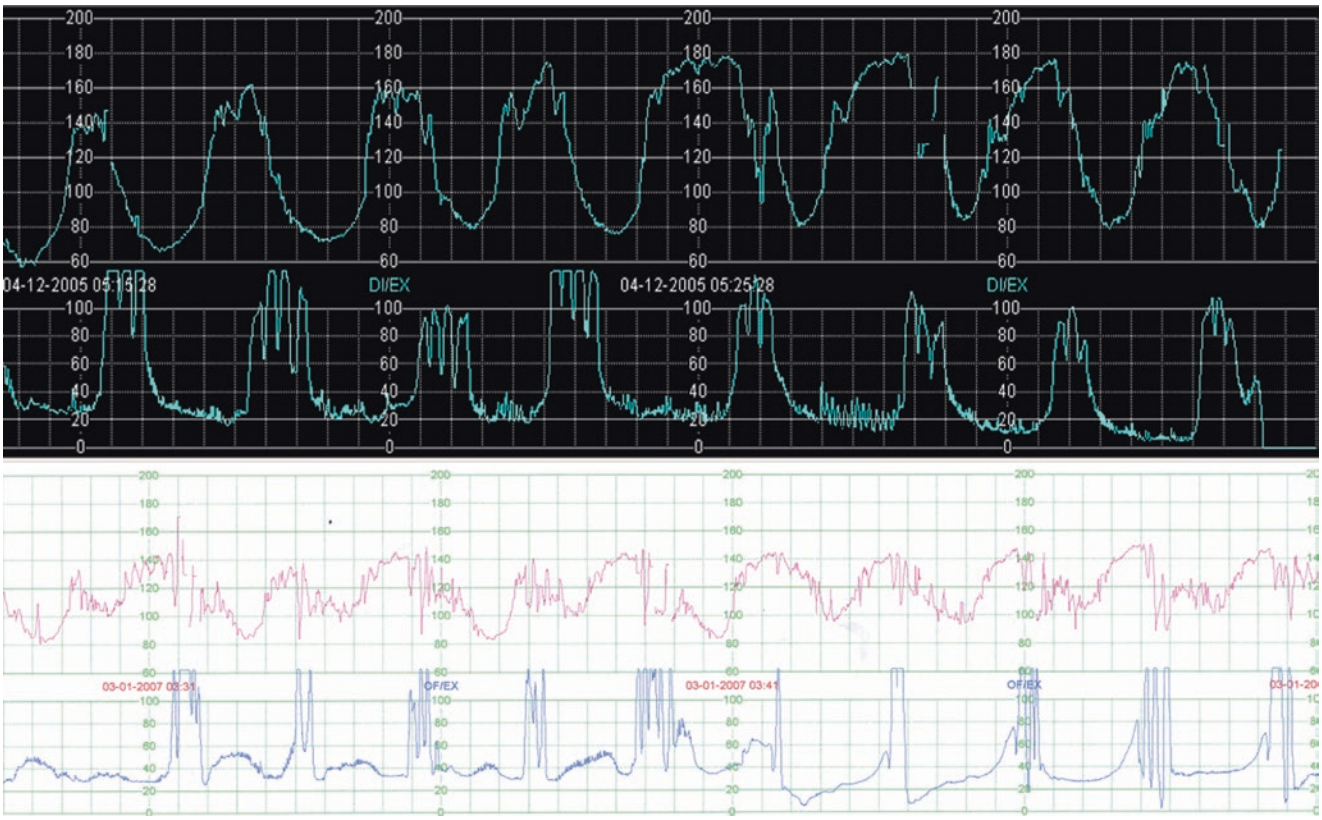

Fig. 5.1 Two CTG traces during the end of the first stage of labor. Both show prolonged decelerations; the *top* one shows an increased basal heart rate and reduced variation. A cesarean section performed directly thereafter revealed a pH in the umbilical artery of the top case of 7.23 BE -6.7 and of the case on the bottom of 6.91, BE -18.3

"suspicious" [9]. Additional information on the fetal condition may be obtained using adjunct technologies, but these are usually forgotten or not implemented locally. Actions that may be taken in case of suspicious or abnormal CTG patterns are:

- Monitor maternal heart rate simultaneously.
- Fetal blood sampling.
- Fetal scalp stimulation.
- Use of ST technology.
- Stop oxytocin.
- Administer a tocolytic drug.
- Amnioinfusion.
- And finally, deliver the baby.
- Moreover, if you do not know what to do, ask your boss for help, especially at night.

In case of external CTG, the Doppler device may record the maternal pulse rate, instead of the fetal heart rate. This may occur especially in case of maternal obesity or positional changes and occurs especially during the second stage of labor, when maternal heart rate may reach fetal values (Fig. 5.2). In this context, it has been found that over two-thirds of accelerations occurring during the second stage are from maternal origin [10]. Insertion of the maternal heart rate occurs also frequently after the birth of the first twin, after which the device may start recording the maternal pulse since the position of fetus-2 is likely to have changed (Fig. 5.2). Modern CTG equipment has the option to monitor the mother simultaneously, and this modus should be used in all cases of external CTG monitoring.

In the recent new FIGO guidelines on intrapartum fetal monitoring, the different adjunct technologies have been summarized [11].

Fetal blood sampling is only being practiced in a few mostly Northern European countries, countries with the lowest CD rates in the Western world. Randomized controlled trials (RCT) in the past have shown that FBS results in a lower incidence of CD and neonatal seizures as compared to the use of CTG monitoring only. However, in these trials, both were randomized against intermittent auscultation and were not compared directly. In the only RCT in which intermittent auscultation and CTG monitoring with or without additional FBS were compared, there were no differences in perinatal outcome [12]. CDs were least frequent in the intermittent auscultation group (6 %), as compared to 18 %

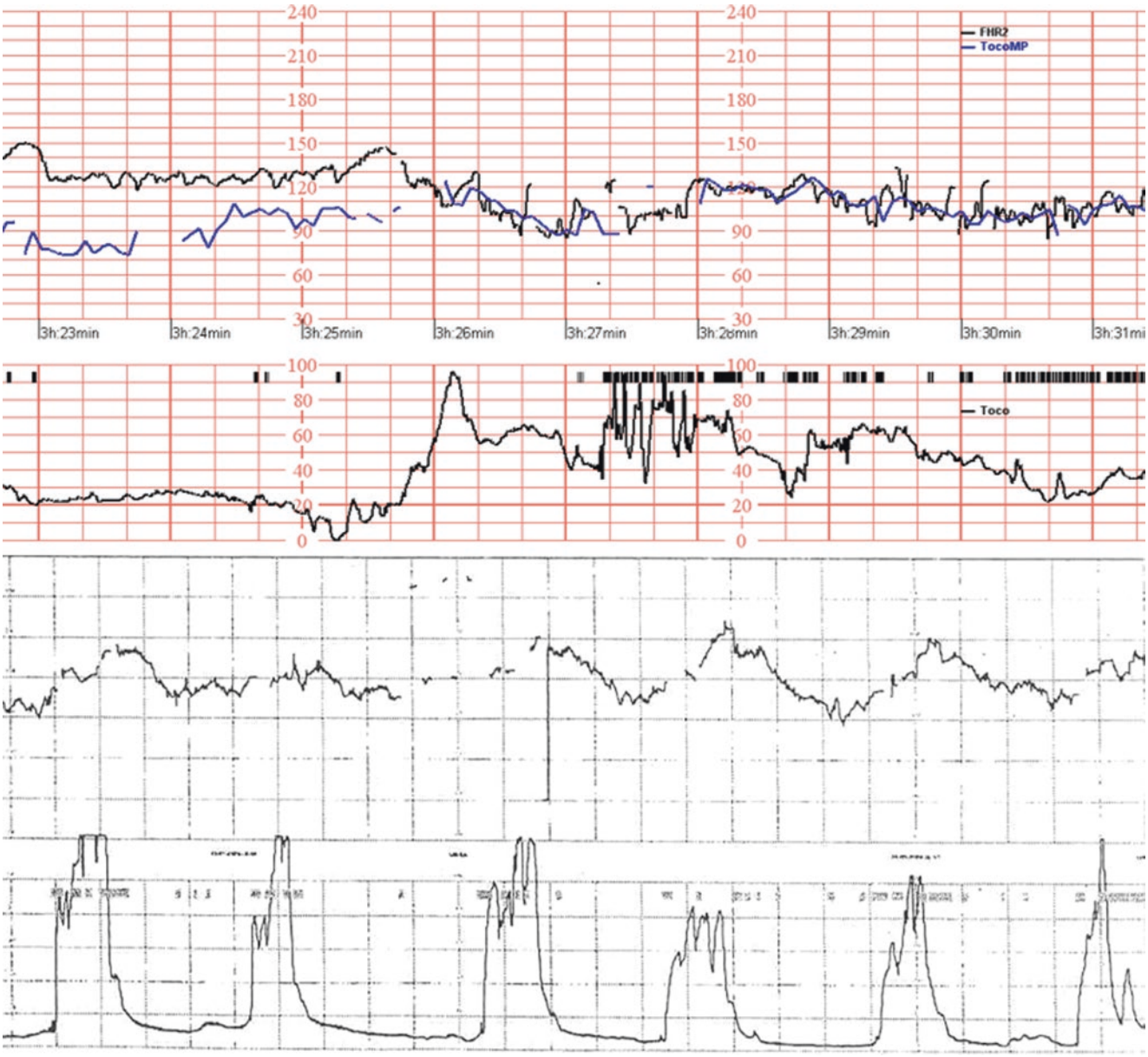

Fig. 5.2 Insertion of the maternal heart rate (*top*; courtesy of Philips Avalon); CTG after the birth of the first child in a twin pregnancy (*bottom*) showing accelerations during every contraction; this baby was born dead 10 min later

in the CTG arm (significantly higher) and 11 % in the CTG/FBS arm. The latter was not significantly different from the CTG-only arm, and therefore, many clinicians have concluded that FBS does not reduce the CD rate. However, in this trial only 690 cases altogether were included. So, there is definitely the need for a large RCT comparing both approaches.

Digital stimulation in case of a suspicious CTG with reduced variability may distinguish between poor or adequate fetal health. A normalization of the pattern is associated with a normal fetal pH, but no additional information is obtained in the absence of a fetal reaction. This simple procedure should be used in all units, since it provides additional information in a considerable number of cases and it reduces the need for FBS with about 50 %.

ST(AN) technology cannot be applied in case of an abnormal CTG, since it has to be started beforehand. European RCTs have shown that STAN results in a lower need for FBS, a lower incidence of instrumental deliveries, and a non-significant reduction of metabolic acidosis at birth.

Many abnormal CTG patterns are due to oxytocin overstimulation [7]. Adequate monitoring of contractions is therefore essential. In case of overstimulation, the first action should be to stop oxytocin (stop and not halving the dose!).

However, oxytocin has a half-life of about 15 min and to stop oxytocin may therefore not be sufficient. The use of a tocolytic drug (beta-mimetic or oxytocin receptor blocker) does significantly reduce contractions within a few minutes ([13]; Fig. 5.3). After normalization of the CTG pattern, the start of spontaneous contractions may be awaited.

Amnioinfusion, the introduction of about 250 ml saline in the amniotic cavity through an intrauterine catheter, significantly reduces the incidence of decelerations and the incidence of CDs ([14]; Fig. 5.4). Such effects may be found in about half of the cases, especially in case of so-called variable decelerations.

So, in case of suspicious/abnormal CTG traces, several actions may be taken before deciding if an instrumental delivery is indicated, provided that there are no emergency situations. The "art" of obstetrics seems to have disappeared in many units and should be revitalized.

5.3 How to Improve the Impact of CTG Monitoring

There are several factors that may improve the results of intrapartum fetal monitoring:

- Structured classification and interpretation and training, training, and training.
- Prioritize the labor ward!!
- Have senior consultants available 24/7.
- New technology.

The new FIGO guidelines on intrapartum monitoring provide important information in which CTG classification and interpretation are combined (Table 5.1; [15]):

Such a systematic approach may well improve standardized classification, interpretation, and actions taken. In this context, it is important to know that several centers have shown a 50–70 % reduction of metabolic acidosis after the introduction of STAN technology [16]. In my hospital there was even an 80 % reduction in acidosis at birth over the course of several years (Landman et al., submitted). The RCTs showed that STAN itself does not significantly reduce acidosis, but the results in favor of ST analysis were more pronounced in the second half of the trials, which suggests a continuing learning process [17]. In these trials, the introduction of STAN technology was accompanied by structured CTG classification and training, which may also explain the better outcome in the convention arms in some of the trials [18]. Therefore, these aspects, structured classification and training, may have been the most important advantage of the introduction of this new technology (Hawthorne effect). The absence of any differences between ST arm and conventionally monitored arm in the recent large US STAN-RCT [19] may, among others, be due to the low inclusion rate per center and therefore lack of training and exposure to the new technology.

Training and feedback are facilitated by the presence of experienced clinicians on the labor ward. The labor ward should be prioritized again and not left to young doctors and midwives only. This also holds for the out-of-office hours. In many countries, senior doctors are at home and not in the

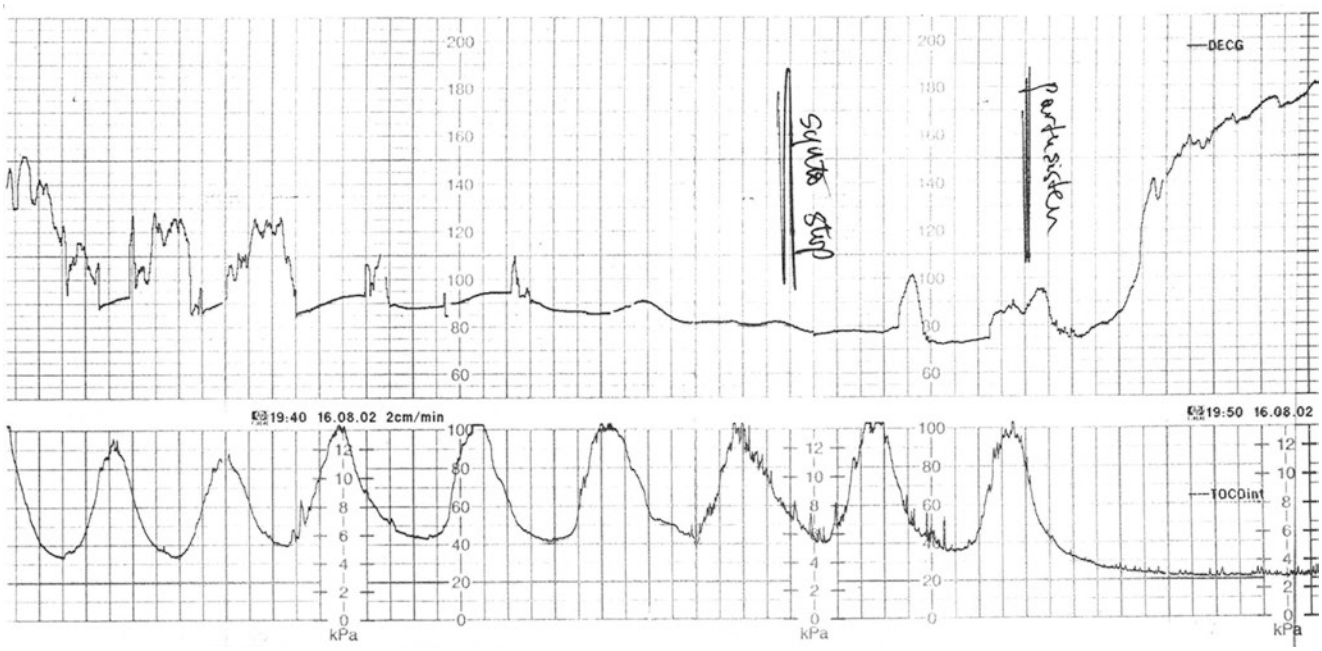

Fig. 5.3 Oxytocin overstimulation. Stopping oxytocin did not have a direct effect; administration of a beta-mimetic drug did

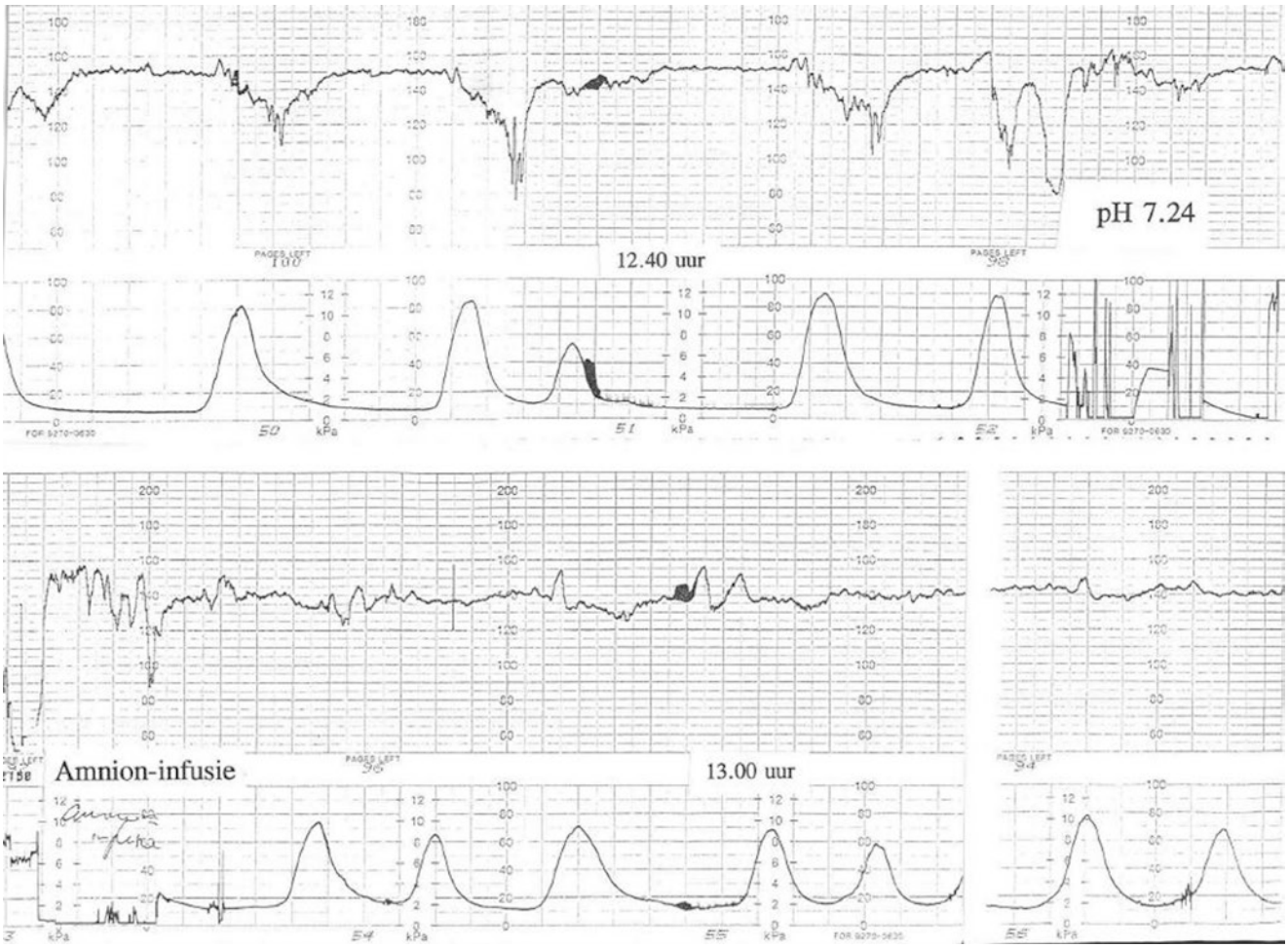

Fig. 5.4 Induction of labor at 38 weeks of gestation, growth-restricted fetus. Recurrent variable decelerations, scalp pH 7.24 at 3 cm dilatation. Amnioinfusion resulted in normalization of the CTG trace. A baby boy of 2.100 g was born 90 min later, with a good start and a pH in the umbilical artery of 7.25, BE -3.8

Table 5.1 The new FIGO guidelines on intrapartum monitoring combining CTG classification and interpretation

CTG classification			
2015 revised FIGO guidelines on intrapartum fetal monitoring			
	Normal	Suspicious	Pathological
Baseline	110–160 bpm	Lacking at least one characteristic of normality, but with no pathological features	<100 bpm
Variability	5–25 bpm		Reduced variability, increased variability, sinusoidal pattern
Decelerations	No repetitive[a] decelerations		Repetitive[a] late or prolonged decelerations for >30 min (or >20 min if reduced variability). Deceleration >5 min
Interpretation	No hypoxia/acidosis	Low probability of hypoxia/acidosis	High probability of hypoxia/acidosis
Clinical management	No intervention necessary to improve fetal oxygenation state	Action to correct reversible causes if identified, close monitoring or adjunctive methods	Immediate action to correct reversible causes, adjunctive methods, or if this is not possible expedite delivery. In acute situations, immediate delivery should be accomplished

Absence of accelerations in labor is of uncertain significance
[a]Decelerations are repetitive when associated with >50 % contractions

hospital at those times, and that is likely to be an important reason for the higher intrapartum and neonatal mortality that occurs during the night. It should not be forgotten that at night a junior doctor will only call the specialist at home, if he/she is rather sure of the presence of fetal asphyxia. In other words, he/she will generally call too late. The time that will cost to reach the hospital will further cause a delay in action to be taken. An adequate 24/7 presence of experienced obstetricians (and of neonatologists and anesthesiologists) is therefore essential in obstetrics.

In my opinion, the aspects discussed before may contribute more to improved outcome, than new technology itself. Items that are of importance include a computerized assessment of CTG traces (standardized assessment, reproducible, no interobserver variation) and some progress being made in that direction [11]. Other aspects may include continuous lactate measurements.

5.4 Flow Diagram of Intrapartum CTG Monitoring and Considerations

The decision to intervene or otherwise is dependent on many variables, such as the underlying fetal condition, maternal disease, and progress of labor. They all play a role in the decisions taken.

A simplified but structured flow diagram of CTG interpretation and considerations regarding intrapartum cardiotocography is shown below:

1. Interpret the CTG tracing in a standardized way (according to the recent FIGO guidelines).
2. Do that in the context of that specific patient (fetal growth restriction? fresh meconium? failure to progress? diabetes and high maternal glucose? blood loss, abdominal pain, hypertonia, prolapse of the cord?).
3. Deliver the fetus immediately in case of an irreversible acute situation.
4. Correct reversible causes (stop oxytocin, use tocolytics, amnioinfusion).
5. Consider available adjunct technologies (scalp stimulation and/or scalp sampling; ST analysis).
6. Base your decision on the items summarized before.
7. And if you do not know what to do, call your boss, also at night.

Conclusions

Intrapartum cardiotocography has not resulted in evident improvements in perinatal outcome and has, on the other hand, resulted in an increase in instrumental deliveries. However, improvements seem possible, especially through prioritizing the labor ward and intensive process-based training in CTG interpretation and competency testing, in other words by focusing on "the human factor." Other factors that may have played a role in the absence of significant effects may be a change in the patient population in the course of the recent decades (older women, more obesity, and other maternal risk factors) and the fact that intrapartum asphyxia seems less important regarding long-term perinatal outcome than thought before.

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Preterm Birth: Risk Factors, Identification and Management

6

Gian Carlo Di Renzo, Elena Pacella, Laura Di Fabrizio, and Irene Giardina

6.1 Introduction

Preterm birth (PTB) is defined as birth before 37 completed weeks of gestation. Spontaneous preterm labour is the precursor of one third of all PTB, a further third following preterm premature rupture of membranes and the rest being medically indicated.

Its incidence can vary depending on the geographical and demographic features of the population studied. The worldwide incidence of PTB ranges between 6 % and 15 %, but it is a percentage rapidly growing in relation to the fact that today some of those cases that in the past hesitated in second trimester 'late' abortions are included. The increase of this trend in industrialised countries is also strongly linked to the rise of maternal age and of the number of pregnancies following assisted reproductive treatments as well as to the introduction of new risk factors related to life style.

The precise role of events linked to an increased risk of PTB is largely unknown, but decidual haemorrhage, mechanical factors, hormonal changes and cervicovaginal infections have been associated with the pathophysiology of PTB. It is nowadays important to investigate epidemiological and environmental factors to identify high-risk women.

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6.2 Risk Factors

The risk of spontaneous PTB correlates to intrinsic characteristics of the mother; in fact it is different between racial and ethnic groups, and it is related to advanced maternal age. In order to identify potential women at risk, it is also important to assess maternal life style, level of education and adequacy of prenatal care, as well as employment-related psychological and physical stress. Furthermore, maternal BMI, nutritional status, chronic diseases (as hypertension, diabetes mellitus), intrauterine malformation or infections, and endocrinological diseases have been linked with an increased risk of PTB (Fig. 6.1).

Aetiology of PTB is multifactorial, and numerous exposures including social, psychological, biological and genetic factors are known to be associated with.

There is consistent evidence that having a history of PTB or second trimester miscarriages is the most strong predicting factor. In literature it is shown that previous abortion, independently from the type (spontaneous or induced), increases the possibility of PTB; moreover, there is an increasing risk of very preterm birth associated with increasing numbers of abortions.

Singleton pregnancies resulting from assisted reproductive treatment (IVF, ICSI) have an increased risk of PTB. Similarly even an invasive diagnostic tool, as amniocentesis or villocentesis, is demonstrated to be a potential risk factor. Other factors that can increase the risk of PTB are history of cervical surgery for CIN disease, late termination of pregnancy, collagen diseases, lupus anticoagulant positivity, current multifoetal gestation, use of recreational drugs and urinary tract infections.

It has been observed that results of studies coming from 'western world' not always are applicable from one situation to another. In a recent multicentre, observational and

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retrospective, cross-sectional study, the Italian Preterm Network Study Group wanted to identify maternal risk factors for spontaneous preterm birth compared to women delivering at term, in order to recognise high-risk women and to provide a global overview of the Italian situation. The study demonstrated that there are peculiar risk factors for spontaneous preterm birth in the Italian population examined. It showed, in fact, an association between preterm delivery and certain maternal factors as BMI, employment, previous abortions, previous preterm births and previous caesarean section (Table 6.1). The increased risk of spontaneous PTB in a woman with a previous caesarean delivery has been substantiated by other studies subsequently, and it has been hypothesised that it can depend by the altered uterine milieu resulting from uterine scar and the more frequent altered placentation.

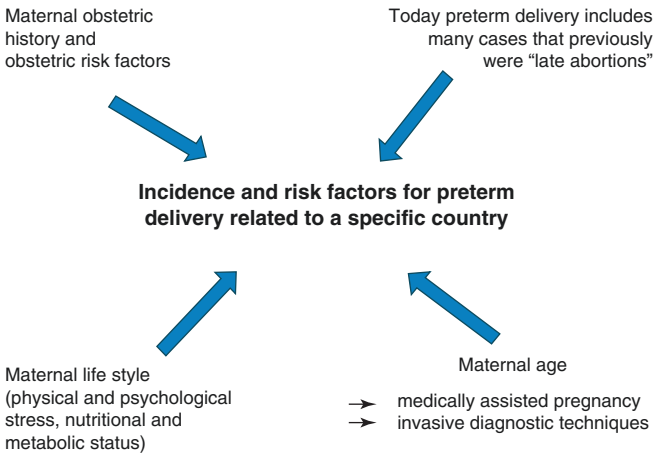

Fig. 6.1 Preterm delivery risk factor in a specific country

6.3 Pathophysiology

Human parturition is the expression of anatomic, biochemical, physiologic and clinical events that occur in the mother and in the foetus in both term and preterm labour (Fig. 6.2). This pathway consists in:

- Decidual/foetal membrane activation
- Increased uterine contractility
- Cervical ripening (dilatation and effacement)

Preterm labour is defined as the presence of uterine contractions between 22 and 36 weeks of gestation at a frequency of at least 6 per hour associated with at least one of the following elements: progressive changes in the cervix or cervical dilation >= 2 cm and/or premature rupture of membranes.

Preterm labour is the consequence of the pathologic premature activation of one or more of these elements (Fig. 6.3). A key hormone regulating the progress of pregnancy and the

Table 6.1 Multivariate logistic analysis of various maternal risk factors for spontaneous preterm birth in Italian population (Italian Preterm Network Study Group)

Covariate	Contrast	Odds ratio estimate	Lower 95 % confidence limit for odds ratio	Upper 95 % confidence limit for odds ratio	*P*-value
Age (cat.)	2. Age ≥35 vs 1. age <35	1.234	0.699	2.177	0.4686
BMI	2. BMI >25 vs 1. BMI ≤25	1.662	1.033	2.676	0.0365
Employment	1. Physical work vs 2. intellectual work	1.947	1.182	3.207	0.0089
Diabetes mellitus	1. Yes vs 2. no	2.286	0.942	5.544	0.0675
Chronic arterial hypertension	1. Yes vs 2. no	2.621	0.746	9.206	0.1327
Asthma	1. Yes vs 2. no	1.555	0.367	6.580	0.5489
Endocrinological diseases	1. Yes vs 2. no	1.420	0.594	3.396	0.4307
Congenital/acquired uterine malformations	1. Yes vs 2. no	2.660	0.602	11.745	0.1967
Previous abortion	1. Yes vs 2. no	1.954	1.162	3.285	0.0116
Previous PTLs	1. Yes vs 2. no	3.412	1.342	8.676	0.0099
Previous caesarean section	1. Yes vs 2. no	2.904	1.066	7.910	0.0371
Previous pregnancies <1 year before current delivery	1. Yes vs 2. no	0.919	0.398	2.124	0.8440
IVF	1. Yes vs 2. no	2.065	0.263	16.223	0.4906
Cigarette smoking	1. Yes vs 2. no	1.340	0.702	2.557	0.3746
Amniocentesis/villocentesis	1. Yes vs 2. no	1.006	0.540	1.875	0.9845

Adapted from [3]

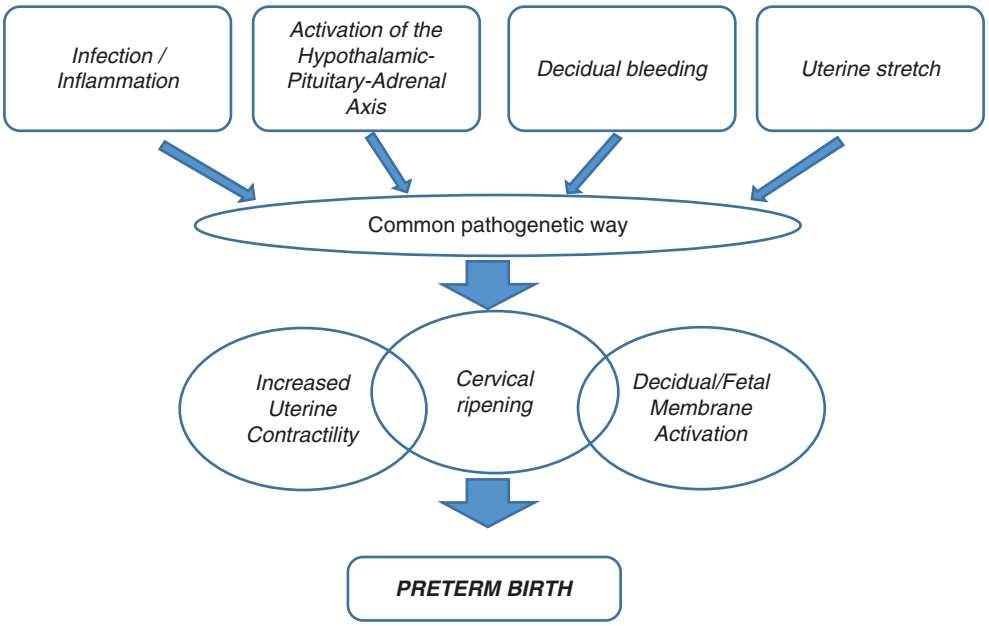

Fig. 6.2 Mechanism of activation of preterm versus term labour

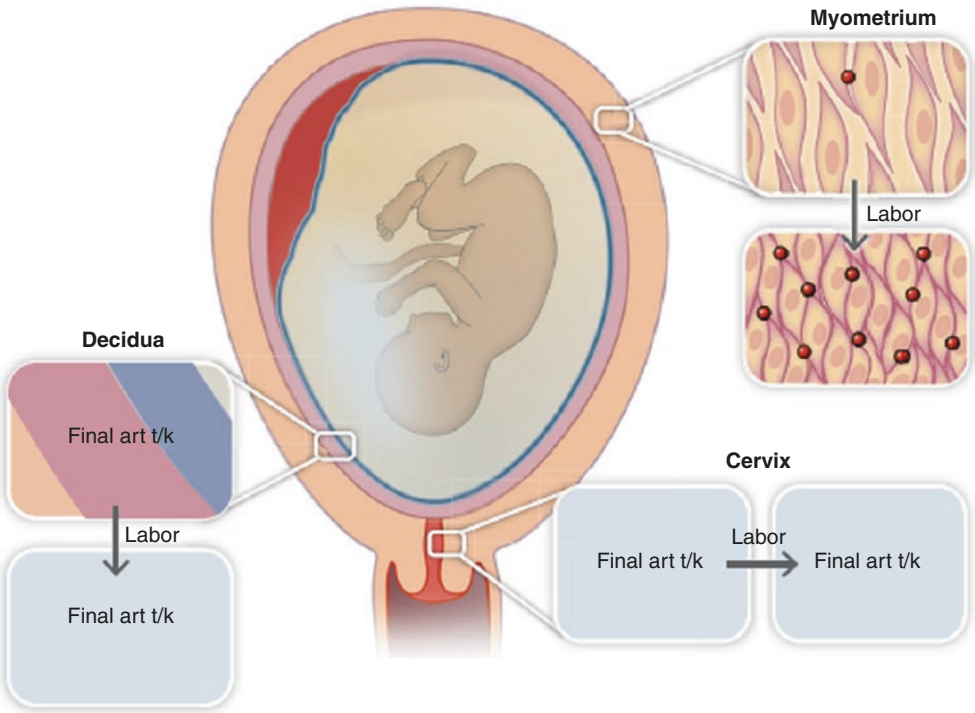

Fig. 6.3 Labour, term and preterm, is characterised by increased myometrial contractility, cervical dilatation and rupture of the chorioamniotic membranes (Adapted from Romero R et al. Science. 2014)

uterine quiescence is progesterone. In many species progesterone withdrawal is a prerequisite for the activation of labour. However, in the human, apparently no decrease of progesterone concentration in blood is demonstrated. However, the apparent loss of progesterone sensitivity and activity at term could be a consequence of several different mechanisms including alterations in progesterone receptors (PR) isoform ratios, the loss of anti-inflammatory function of progesterone, the catabolism of progesterone in the uterus into inactive compounds, changes in cofactor protein levels affecting PR transactivation and the inflammation-induced trans-repression of PR.

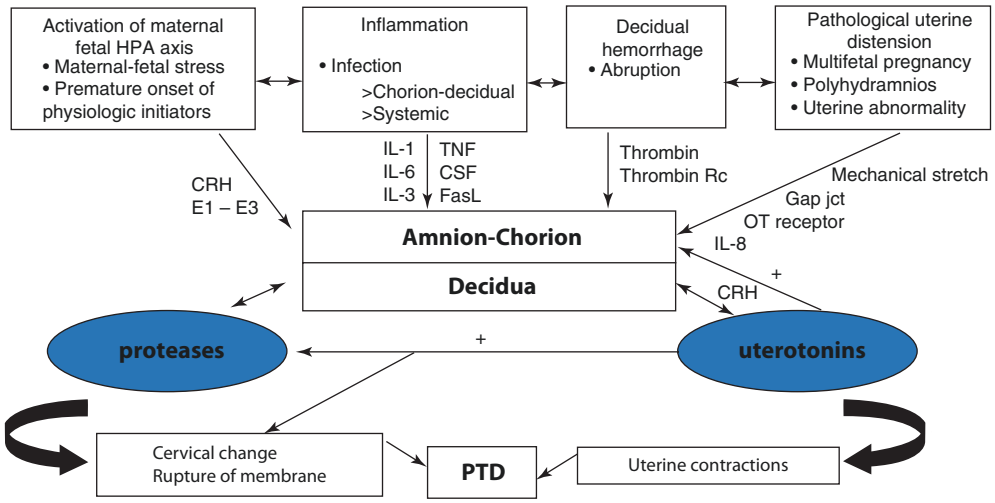

Fig. 6.4 Pathways of preterm delivery

The activation of the mechanisms of labour at term and preterm can be divided into two groups:

1. Infection/inflammation: the route of infection is generally ascending from the vagina through the cervix to membrane's interface, and from there it can move to the amniotic fluid or, in more serious cases, to the foetus (foetal inflammatory syndrome).

Evidence has now shown that at least half of 'idiopathic spontaneous preterm labour' is attributable to subclinical genital tract infections, mostly due to micro-organisms such as *Mycoplasma hominis*, *Ureaplasma urealyticum*, anaerobic species and a host of other sub-pathogenic organisms associated with bacterial vaginosis.

2. Not related to infection/inflammation (Fig. 6.4). Such cases comprise:
   - Uterine over distension, as in the case of multiple pregnancy or polyhydramnios
   - Cervical diseases, due to congenital anomalies or surgical trauma, defined as cervix-isthmic incontinence, a condition that leads to premature ripening and/or dilatation of the cervix
   - Uteroplacental ischaemia, due to abnormal angiogenesis during pregnancy at the level of the spiral arteries, resulting in increased incidence of thrombosis
   - Autoimmunity, as abnormal maternal mechanism of adaptation to the foetal-placental unit
   - Allergies
   - Unknown causes

6.4 Identification

Before undertaking any therapeutic strategy, careful identification is needed, so as to detect manageable conditions and foetal and/or maternal contraindications.

Symptoms reported by patients with suspected preterm labour are pelvic pain, vaginal discharge, back pain and menstrual-like cramps. To improve the accuracy of diagnosis of the nosological entity we still name 'threatened preterm labour', the combination of two methods has been proposed:

- Transvaginal ultrasound cervical length
- Research of foetal fibronectin (fFN) or placental alpha-1 microglobulin (PAMG-1) in cervical-vaginal secretions

6.4.1 Biophysical Marker

Cervical length >2.5 cm has a high negative predictive value in symptomatic women. Cervicometry can be used as a diagnostic tool in two different clinical conditions: (1) Symptomatic patients reporting uterine contractile activity, in order to make differential diagnosis with other conditions that can mimic contractions. Cervicometry <2.5 cm, independently from the presence of funnelling, is able to identify a population at risk of preterm delivery with a sensitivity between 60 and 80 %. (2) Asymptomatic woman, in this case, the method is applied as screening. It is performed at the time of anatomic scan in the second trimester (19–23 weeks of gestation). The finding of a cervicometry <2.5 cm is associated with a subsequent preterm birth with a sensitivity between 30 % and 60 %.

Cervical screening can be undertaken in asymptomatic or symptomatic women, and studies have been performed in both high- and low-risk populations. The role of scanning in low-risk women is less clear, as the interventions to improve outcome are not established. However, more than half of all preterm births come from this group, and prediction remains good. A CL of <15 mm on transvaginal ultrasonography between 14 and 24 weeks' gestation is associated with approximately a 50 % chance of sPTB prior to 32 weeks' gestation (Hassan SS). In 2915 low-risk women at 24 weeks, the CL at 24 weeks averaged 34 ± 7.8 mm and was normally distributed. Only 5 % of women had a CL <20 mm, but the preterm birth rate <35 weeks was 23 % (PPV 25.7, NPV 96.5 %). The authors noted the concept that risk was a continuum across the CL range, rather than a threshold where risks begin. The risk of preterm delivery is greater in high-risk women with a cervical length (CL) less than 25 mm (10th centile) between 14 and 24 weeks' gestation, and the risk is greater as the CL shortens. In a prospective study (183 women), a measurement of CL <25 mm at 16–19 weeks' gestation had a relative risk of 3.3 (CI 2.1–5.0) for preterm delivery <35 weeks' gestation, which increased to 4.5 (2.7–7.6) with serial measures.

6.4.2 Biochemical Markers

Foetal fibronectin (fFn) has proved to be one of the most promising markers among potential new indicators of impending preterm delivery. The test is available in two primary formats (Hologic, Marlborough, MA, USA). fFN is a glycoprotein produced by the chorion, and it functions as a 'glue' between placenta, amnion-chorion membranes and decidua. It is found in cervical-vaginal fluid from 16 to 19 weeks of gestation, it disappears and it is again detectable around term (after 36 weeks) or a week or so before preterm labour. It is believed that fFN is a marker of chorio-decidual interface alteration due to infection or inflammation, placental abruption or mechanical causes. This test is mainly used to exclude a preterm delivery rather than to identify it as its negative predictive power (97 %) has been shown to be significantly greater than its positive predictive value (<50 %) for delivery within 7–14 days. In a recent systematic review of the accuracy of the fFN test to predict preterm delivery in women with symptoms of preterm labour, Deshpande et al. reported pooled sensitivity and specificity from 27 studies for predicting PTB 7–10 days after testing of 76.7 % (70.4–82.0 %) and 82.7 % (79.4–85.5 %), respectively, presented with 95 % confidence intervals. In line with several previous systematic reviews, the authors suggested that the sensitivity of fFN testing may be highest for predicting PTB within 7–10 days of testing.

Most recently, a quantitative bedside foetal fibronectin test has been developed. The value of the test relies on the use of alternative thresholds of fFN detection (10, 50, 200 and 500 ng/mL, respectively) that may allow optimal selection of higher PPV for sPTB (an improved 'rule in' test) within 14 days and before <34 weeks, whilst the NPV remains reasonable as a rule out throughout all thresholds.

The identification of women at high risk of preterm delivery carried out with the fFN test or with transvaginal ultrasound cervicometry is clinically valid, but it has been demonstrated that the contextual use of biochemical and biophysical tests reaches a high negative predictive value (100 %), making it a very useful combined method to identify patients truly at risk and to further reduce the incidence of inappropriate treatment (Fig. 6.5).

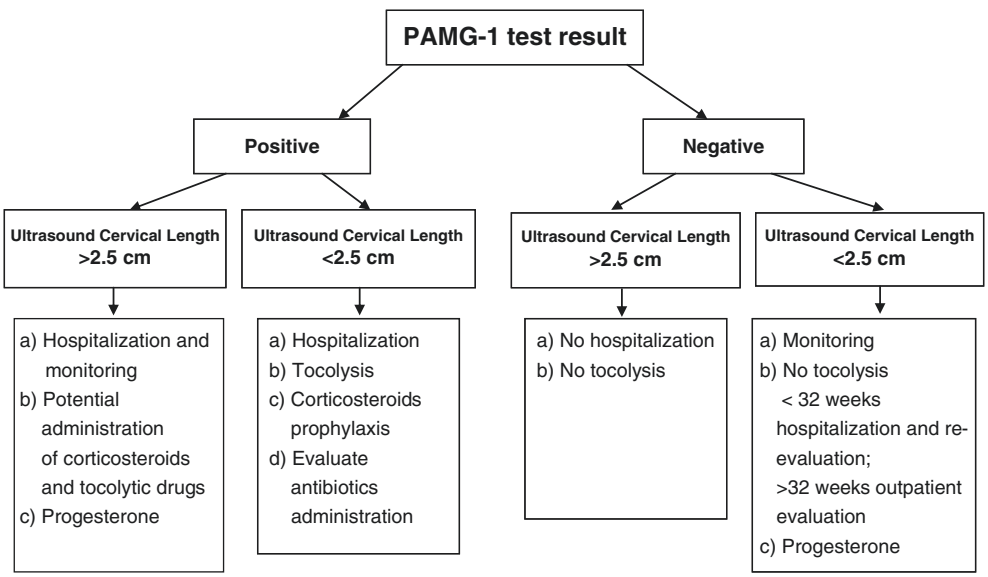

Fig. 6.5 Combined use of PAMG-1 test and ultrasound cervical length for predicting preterm birth in symptomatic patients

Another marker is based on identification of *phosphorylated insulin-like growth factor binding protein (phIGFBP-1)* in vaginal fluid. phIGFBP-1 is produced by the placental decidual cells and thought to be released into the CVF after tissue damage to the choriodecidual interface. A qualitative test, either positive or negative, is measured from a vaginal swab taken with a speculum between 22 and 36 weeks of gestation. An immunochromatography-based dipstick test (Actim Partus, Medix Biochemica, Kauniainen, Finland) is used to obtain the result within 5 min.

Conde-Agudelo and Romero reported pooled sensitivity and specificity from 18 studies for predicting PTB 7 days after testing symptomatic women of 67 % (62–72 %) and 77 % (75–79 %), respectively, presented with 95 % confidence intervals.

A new test, recently introduced, is based on the research of *placental alpha-1 microglobulin (PAMG-1)* in cervical-vaginal secretions. PAMG-1 is another glycoprotein synthesised by the decidua. It is found in the amniotic fluid in high concentrations. Little is found in the cervicovaginal fluid. A vaginal swab can be inserted directly into the vagina, removing the need for a speculum in patients between 20 and 37 weeks of gestation. An immunoassay bedside 'dipstick test' (PartoSure Test, Parsagen Diagnostics, Inc., USA) is used to obtain the result within 5 min. It has been shown that the positive test in patients symptomatic with intact membranes and cervical dilatation <=3 cm indicates the possibility of a spontaneous preterm delivery within 7 days with a high degree of accuracy (>80 %). A negative result indicated that spontaneous preterm delivery within 14 days is highly unlikely (negative predictive value >97 %) (Table 6.2).

Comparing fFN test, PAMG1 test and measuration of cervical length, it has been demonstrated that PAMG1 is the single most accurate test for prediction of imminent spontaneous delivery in patients presenting with signs, symptoms or complaints suggestive of PTL. Therefore, nowadays the identification of the patient at risk of impending preterm delivery is based on the two assumptions:

1. Bearing in mind the excellent NEGATIVE predictive value of such tests, in patients with fFn or PAMG-1 negative and cervical length by ultrasound >2.5 cm, tocolytic therapy and steroid prophylaxis should be withheld, and it is recommended not to admit to hospital.
2. Bearing in mind the excellent POSITIVE predictive value, patients with a positive PAMG-1 test should be admitted to hospital and tocolytic therapy, and steroid prophylaxis should be administered.

Other markers are under evaluation; particularly proinflammatory cytokines have been demonstrated in the second trimester amniotic fluid of pregnancies hesitating in PTB; and maternal salivary oestriol can be detected as early as 3 weeks prior to the onset of spontaneous preterm labour.

The challenge is to develop sensitive and specific tests that reliably detect these pregnancy's changes before they became irreversible and to find effective intervention of arresting the process of preterm labour to enhance the effectiveness of current available interventions (Table 6.3).

Table 6.2 Biochemical marker tests to predict spontaneous preterm delivery within 7 days of testing in women with symptoms of preterm labour

Biomarker	Name of test	Test cutoff (ng/mL)	N	SN (%)	SP (%)	PPV (%)	NPV (%)
fFN (qualitative)	Rapid fFN /QuikCheck	50	4285	76	83	25	98
fFN (quantitative)	Rapid fFN 10Q Analyser	10	350	96	42	29	98
		50	350	91	65	39	97
		200	350	71	84	52	92
		500	350	42	96	71	87
phIGFBP-1	Actim Partus	10	2159	67	79	35	93
PAMG-1	PartoSure	1	353	84	95	77	97

fFN foetal fibronectin, *phIGFBP-1* phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1), *PAMG-1* placental alpha microglobulin-1

Table 6.3 Benefits of identifying patients at real risk of preterm birth

Benefits to the hospital	Benefits to the patient
Reduces unnecessary admissions and transfer to NICU	Unnecessary medical intervention
Cost savings to the hospital	Peace of mind
Reduction in administering medical management	Uninterrupted travel plans
Availability of beds	Employment
	Less burden on spouse and family

6.5 Management

Women who present with signs and symptoms of labour frequently will not deliver in the short term, and many will continue to full term, even in the absence of interventions. Women with risk factors will usually not deliver preterm. Conversely, even women who receive prophylactic interventions may still deliver early. Improved prediction in all these groups would be clinically beneficial, to target preventative interventions, admit to hospital with optimal neonatal facilities and therefore triage the need for in utero transfers as well as instigate in utero therapies to improve outcomes (e.g. steroids and magnesium sulphate).

6.5.1 Pharmacological Aspects

Tocolysis and administration of corticosteroids to induce lung maturation is the first therapeutic tool for the management of threatened preterm labour, in selected patients; also bed rest and hydration are usually recommended in the management of these patients (without evidence of real benefits).

Antenatal corticosteroids given to mothers with anticipated preterm delivery (betamethasone or dexamethasone 12 mg intramuscularly in two doses, 24 h apart) will improve survival and reduce the risk of respiratory distress syndrome (RDS), necrotising enterocolitis and intraventricular haemorrhage, and a single course does not appear to be associated with any significant maternal or short-term foetal adverse effects. The beneficial effects of antenatal steroids were similar in studies conducted in the 1970s as in those conducted more recently implying that they remain beneficial in the presence of modern neonatal care.

Betamethasone is likely to be more effective than dexamethasone, but has also more side effects. It reduces foetal body and breathing movements and foetal heart rate variation for about 1–3 days, without evidence for an impaired foetal condition. Due account for this phenomenon has to be given when monitoring the foetal condition. Betamethasone does not induce heart rate decelerations nor does it affect foetal Doppler.

Although with relative contraindications, accompanying tocolysis is preferable to guarantee the full course of corticosteroids. The current accepted indications for the use of tocolysis, in fact, are delaying delivery for 24–48 h to initiate and/or complete corticosteroid administration or for controlling uterine activity during in utero transfer to maternity units provided with neonatal intensive care especially for gestations <32 weeks.

6.5.1.1 Tocolytic Agents

Therapeutic indications are:

- Gestational age (GA) at 22–34 weeks (advanced GA in exceptional cases)
- Presence of four or more contractions for 30 min, lasting at least 30 s possibly evaluated by cardiotography
- Cervical dilatation of 1–3 cm (0–3 for nulliparous) and cervical shortening >50 % or less than 1.5 cm by ultrasound
- Normal foetal cardiac activity

Inhibitors of Prostaglandin Synthesis (Indomethacin, Naproxen, Ketoprofen, Diclofenac)

This group of drugs interfere with the synthesis of prostaglandins, inhibiting both cyclooxygenases (COX), which catalyse the conversion of arachidonic acid into prostaglandins, precursors of prostaglandins E and F.

Indomethacin is a generic inhibitor of COX, after absorption by oral or rectal administration, which achieves the plasmatic peak in 1–2 h. Several studies have shown tocolytic effects of this drug comparable to β-sympathomimetic and fewer maternal side effects. Prolonged administration may be associated with headache, dizziness and depression, besides it could double the maternal bleeding time.

The major side effects linked to the tocolysis with inhibitors of prostaglandin synthesis are possible closure of the ductus arteriosus (which can resolve within 24 h after drug interruption), neonatal pulmonary hypertension (possibly due to the prolonged deviation of blood from the ductus arteriosus to the pulmonary vascular bed), ventricular haemorrhage (when it is used for prolonged time after failure of the other therapies or in combination with magnesium sulphate) and oligohydramnios (due to foetal urinary production) especially if the drug is administered after 32 weeks of pregnancy. Indomethacin can also increase the risk of necrotising enterocolitis.

The possible dosage used is 50 or 100 mg by suppository; alternatively it could be used 50 mg per os, followed by 25–50 mg per os every 6–8 h.

Tocolysis by indomethacin must be limited for pregnants before 32 weeks, without intrauterine growth restriction and normal amniotic fluid volume. The duration of administration should not exceed 48–72 h.

Calcium Antagonists

Nifedipine acts by inhibiting calcium passage through the plasmatic membrane, particularly interfering with voltage-dependent ion channels. The calcium channel block is reversible with interruption of therapy.

This substance causes vasodilation, so its use is frequently associated with hyperaemia, headache, nausea, tachycardia

and mild reduction of blood pressure. Its use in combination with magnesium may cause neuromuscular toxicity.

The first dose is usually 10 mg of nifedipine per os, to be repeated after 20 min if the contractions persist. Sublingual administration must be avoided in patients at risk of hypotension. Oral therapy may be carried out with 10–20 mg pills every 4–6 h.

β-Sympathomimetics (Ixosuprine, Exoprenaline, Fenoterol, Ritodrine, Salbutamol, Terbutaline)

Substances belonging to this family have a β2-adrenergic effect at the uterine level, with a partial β1-adrenergic activity. Their action is mediated by cyclic adenosine monophosphate, which inhibits the kinase of light chain of myosin, thus avoiding myometrial cell contraction.

Myometrial β-receptors decrease in the pregnant uterus treated with β-sympathomimetic. Although these substances have a maximum effect on the uterus and a minimal effect at the extra uterine level, they may significantly influence the maternal cardiovascular physiology and metabolic system. The most important side effects are hypotension, cardiac arrhythmia, myocardial ischemia and pulmonary oedema, which could regresses by interrupting the therapy and administrating diuretics. A low dose of infusion is not related to major changes in the foetal heart rate, whereas a high dose can provoke foetal tachycardia and reduction of variability.

Initially 0.005–0.10 mg/min of ritodrine is administered intravenously, with an increase of 0.05 mg/min every 10–30 min, up to a maximal dose of 0.350 mg/min. Terbutaline can also be administered endovenously, starting with 0.01 mg/min and increasing by 0.01 mg/min every 10–30 min, up to 0.08 mg/min.

Oxytocin Antagonists

Oxytocin antagonists tend to inhibit oxytocin receptors, inducing uterine contractions in human and animal models. They inhibit the double oxytocin effect on myometrium, which activates channels and indirectly stimulates prostaglandin production by decidual and foetal membranes.

Atosiban (the only compound commercially available) is an analogue to oxytocin, and it is able to block myometrium and decidual receptors of oxytocin competing specifically with the substance. It is characterised by fast action and dose-dependent effect. Atosiban is able to delay preterm delivery. It has uterus-specific action, and it is therefore safer than other tocolytics.

The recommended dosage and administration schedule for Atosiban is a three-step procedure: initial bolus dose of 6.75 mg minute, followed by an infusion of 18 mg/h for 3 h and then 6 mg/h for up to 45 h. The rare maternal side effects are nausea, headache, dizziness, tachycardia, hypertension, hyperglycaemia, allergic reactions.

Nitric Oxide Donors

Nitric oxide (NO) is a myorelaxant gas that mainly acts on vessels, bowel and uterine muscle. Nitroglycerine is a NO donor. The application of nitroglycerine patches seems to be efficacious for treating preterm contractions. The acute treatment is represented by a transdermic patch of 10 mg, initially applied every 6 h, then every 12 h and finally replaced by another patch every 24 h.

NO binds to cyclic guanosine monophosphate, causing relaxation of smooth muscle of vessels and inhibiting platelet aggregation and endothelial adhesion.The major maternal side effects are nausea, vomiting, tachycardia, orthostatic hypotension and cutaneous rash. The foetal adverse effects are determined by variation of feto-placental flow, due to maternal vasodilation. Neonatal hypotension can be observed.

There is no evidence to support the routine administration of NO donors in the treatment of preterm delivery. It might be useful to combine them with other tocolytic drugs (Atosiban and Indomethacin) for a synergistic effect, which may prevent maternal side effects.

Magnesium Sulphate (Used Mainly in American Countries, Not in Europe)

Magnesium sulphate has been widely used for the treatment of pre-eclampsia and as a tocolytic agent over the last 20 years. Its inhibitory activity on the smooth muscle is demonstrated, but its mechanisms of action are still unexplored. A high concentration of magnesium has a central inhibitory effect, interfering with acetylcholine release and then with nervous conduction. Magnesium also suppresses the contractile activity of isolated myometrium and increases cyclic adenosine monophosphate and decreases intracellular calcium.

The recommended starting dose is 4–6 g administered intravenously for more than 20 min, followed by a maintenance dose of 1–4 g/h. The endovenously therapy must be continued for about 12 h, until the reduction of uterine contractions below four to six per hour has been reached.

The main side effects of intravenous way of administration are hot flushes, headaches, nistagmus, lethargy, hypovirus or diplopia. Myometrial contractility is inhibited by maternal serum levels of 5–8 mg/dl. Concentrations of 9–13 mg/dl may provoke deep tendinal reflex, and level above 14 mg/dl may cause respiratory depression.

Treatment with magnesium may also lead to pulmonary oedema, so that strict observation of intake and outtake is needed, daily decreasing the administration of fluids below 1500–2500 ml. It is recommended that constant examination of tendinal reflex and calcium and magnesium serum levels be done so as to avoid toxic effects. In case of toxic effects caused by hypermagnesemia, calcium gluconate should be promptly administered.

Due to the many investigations confirming the poor tocolytic effect of magnesium sulphate and its high incidence of side effects, this drug is scantly used as tocolytic agent.

6.5.1.2 Non-pharmacological Aspects

- *Identification of patients at risk* (combined use of fFN test and ultrasound cervical length) (Fig. 6.3).
- Change in life habits. Work conditions in patient at risk need to be changed; bed rest is advisable, as well as avoiding smoking and use of illicit drugs.
- Study of cervico-vaginal microbial flora. *Gardnerella vaginalis* and anaerobic bacteria colonise 15–20 % of pregnant women's vagina. It has to be corrected because the association between bacterial vaginosis and preterm delivery is particularly striking. Probiotics use is currently under investigation.
- *Cervical cerclage*. In the past years, cervical stitch was widely used in pregnancies considered at high risk of preterm delivery. The literature shows evidence that cerclage provides clear and proven benefits only in circumstances diagnosed with 'cervical incompetence'.

Results of randomised trials have not generally supported this practice, but the absence of benefit may be due to suboptimal patient selection, which was essentially based on obstetric history. Recently it has been demonstrated that cervical cerclage is efficacious only in cases at high risk for early preterm delivery as cases of a previous history of three or more late abortions or three or more preterm delivery, history of preterm labour and an objective decrease in cervical length (patients with cervical shortening, evaluated by transvaginal ultrasound) or increase cervix dilatation in non-symptomatic patients. In cases with advanced cervical dilation and uterine contractions, the use of emergency cerclage associated with the administration of tocolytic agents has shown controversial effects.

In a recent adjusted indirect meta-analysis of randomised controlled trials, it has been demonstrated that methods for indirect comparisons, either vaginal progesterone or cerclage, are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid-trimester, singleton gestation and with previous preterm birth.

Moreover, in a secondary analysis of a multicentre trial, cerclage was shown not to offer additional benefit for the prevention of recurrent preterm birth in women with short cervical length <25 mm receiving 17-α-hydroxyprogesterone caproate, although the sample size was insufficient for a definitive conclusion.

- *Cervical pessary*. Many years ago, the cervical pessary was used for cervical incompetence with very inconsistent results. In recent years, it has been considered the preventive effect on preterm delivery of placing a cervical pessary in a population of appropriately selected at-risk women screened for cervical length assessment at the mid-trimester scan (non-symptomatic patients, with singleton pregnancy and a short cervix, less than 25 mm, at 20–24 weeks' gestation as risk marker), without prior cervical incompetence. Various studies show significant risk reduction without increasing the rate of vaginal infections, but not all authors confirmed these data.

Regarding twin pregnancies, instead, in a recent subanalysis (PREDICT study), cervical pessary has been tested as placebo to evaluate the preventive effect of vaginal progesterone in high-risk twins. Women with twin pregnancies, in fact, have been randomised to daily treatment with progesterone or placebo pessaries from 20 to 24 weeks until 34 weeks' gestation, and it has been demonstrated that in high-risk twin pregnancies, progesterone treatment does not significantly improve outcome compared to pessary.

6.5.2 Preventive Tools

6.5.2.1 Progesterone

Endogenous progesterone and related synthetic compounds such as 17-alpha-hydroxyprogesterone caproate (17-OHPC) as well as other progestogens (dydrogesterone) have been tested in clinical trials to prevent preterm birth.

Adequate progesterone concentrations in myometrium are able to counteract prostaglandin stimulatory activity as well as oxytocin properties that enhance the activity of β-agonists. Moreover, progesterone decreases the concentration of myometrial oxytocin receptors, counteracting the effect of oestrogens; the same is apparent in the number and properties of gap junction. Progesterone also inhibits prostaglandin production by amnion-chorion-decidua, and it has been shown that the decrease in binding of progesterone at the level of foetal membranes at term gestation may justify the predominant effect of oestrogen in promoting prostaglandin production and triggering labour.

The administration of high-dosage progesterone has been advocated as a possible tocolytic agent.

The action of progesterone is slow and can be used for acute tocolysis in conjunction only with other acute tocolytic agents. For example, the combination of natural micronised progesterone and ritodrine has shown synergistic effects by decreasing the need for high concentrations of the β-agonist, which have potentially troublesome side effects (Tables 6.4 and 6.5).

However, the use of progestogens as a maintenance tocolysis requires further studies before being recommended as tertiary prophylaxis of preterm birth.

Table 6.4 Combined use of beta-agonists and progesterone for acute tocolysis

Cases	
47 patients (β-agonists)	42 patients (β-agonists + P)
Mean gest. age: 30.5 (3.2)	Mean gest. age: 30.3 (2.7)
Treatment	
Ritodrine (100 mg in saline 0.1–0.3 mg/min)	Ritodrine (50 mg in saline 0.1–0.3 mg/min) + micronised P (200 mg/die)
Results	
Delivery after 48 h: 87 %	Delivery after 48 h: 85 %
Delivery after 7 days: 65 %	Delivery after 7 days: 68 %

Adapted from Di Renzo et al. (2005)

Table 6.5 Side effects of the use of β-agonists alone or with progesterone for acute tocolysis

Side effects	β-agonists (%)	β-agonists + P (%)
Mat. tachycardia	97	42
Nausea and vomiting	28	6
Tremblings	26	12
Palpitations	32	12
Chest pain	15	8
Hyperglycaemia	92	28
Hypokalaemia	47	23

Adapted from Di Renzo et al. (2005)

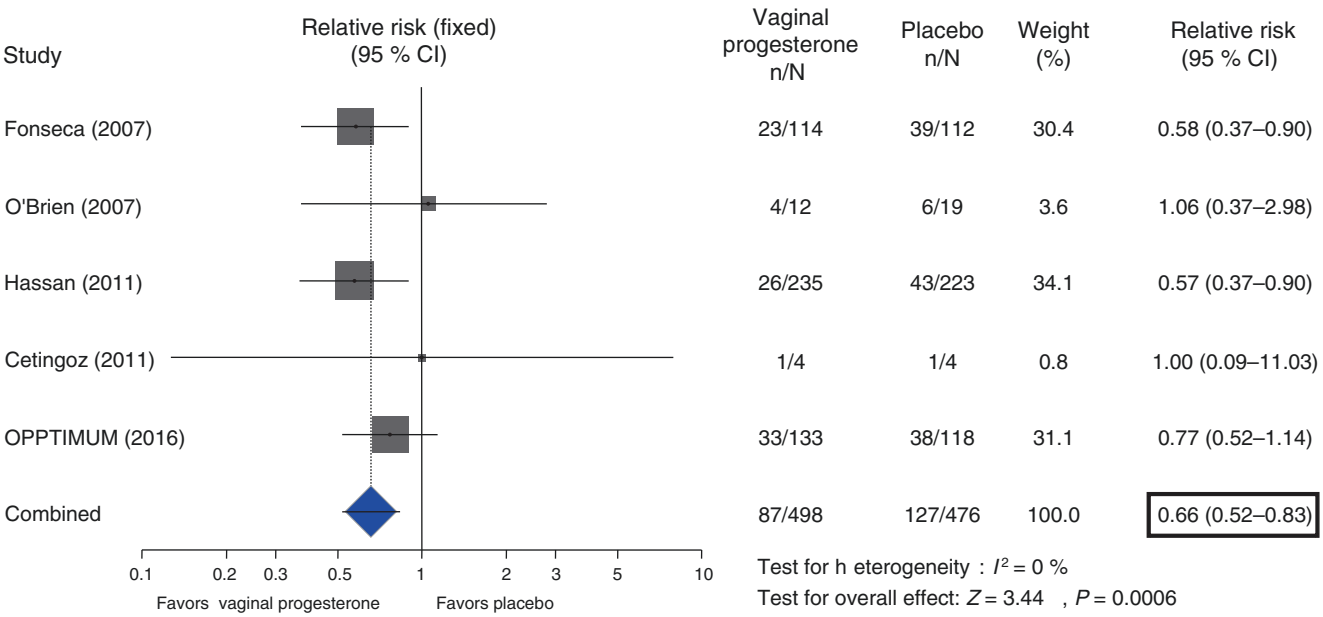

Fig. 6.6 Short cervix and vaginal natural micronised progesterone: a meta-analysis (Reproduced form Romero et al. UOG 2016)

In multiple pregnancies, either twins or triplets, progesterone and progestogens have not been shown to prevent preterm birth, but apparently the administration of natural micronised progesterone is linked with an amelioration of neonatal morbidity.

Women with a sonographically short cervix (≤25 mm) regardless of obstetrical history should be offered vaginal progesterone treatment for the prevention of preterm birth and neonatal morbidity. Two forms of vaginal micronised progesterone can be used daily: 200 mg vaginal soft capsules or 90 mg vaginal gel.

A recent meta-analysis has confirmed the statistical significance of this tool and the cost benefit advantages (Fig. 6.6).

6.5.2.2 Magnesium Sulphate

Many studies have examined the use of magnesium sulphate for neuroprophylaxis and prevention of cerebral palsy. It appears, in fact, that magnesium sulphate could be used to

Table 6.6 Mortality and morbidity in very preterm newborns according to different antenatal treatments for neuroprophylaxis. Group A: betamethasone, aminophylline, magnesium sulphate. Group B: betamethasone alone

	Group A	Group B	Significance
RDS[a]	28 (35.9 %)	26 (38.2 %)	NS
IVH and PVL (total)	4 (5.1 %)	14 (20.6 %)	$p < 0.001$
IVH (3–4 degree)	1 (1.3 %)	7 (10.3 %)	$p < 0.001$
PDA	7 (9.0 %)	5 (7.5 %)	NS
ROP	2 (2.6 %)	4 (5.9 %)	NS
Neonatal death[b]	8 (10.2 %)	7 (10.3 %)	NS

Adapted from Di Renzo et al. (2005)
[a]Severe degree needing surfactant replacement and HPPV
[b]Within 28 days from delivery

prevent neurologic complications of pregnancy in the neonate.

Prevention of neonatal severe neurological morbidity has particularly been studied through a new antenatal-combined pharmacological approach which includes:

- Betamethasone (12 mg twice/24 h apart)
- Aminophylline (480 mg/die min 48 h)
- Magnesium sulphate (8 g/die min 48 h)

It has been demonstrated that the adjunctive administration of aminophylline and magnesium sulphate to mothers at risk for preterm birth can significantly reduce the rate of intraventricular haemorrhage in neonates born at less than 30 weeks of gestation (Table 6.6).

Given the beneficial effects of magnesium sulphate on substantial gross motor function in early childhood, outcomes later in childhood should be evaluated to determine the presence or absence of later potentially important neurological effects, particularly on motor or cognitive function.

In case of preterm labour before 32 weeks, it might be considered to give MgSO4 to reduce the risk of cerebral palsy in the newborn (FIGO good clinical practice advices).

The dosage of magnesium sulphate utilised for neuroprophylaxis is by far less than that proposed in the past for tocolysis (8–12 g a day versus 32–48 g a day for tocolysis).

6.6 Mode of Delivery

Neonatal outcome of preterm neonates depends on many factors; that is why, the mode of delivery of preterm infants is nowadays controversial.

In the 1980s, a policy of elective caesarean delivery (CS) has been recommended, even without medical evidence to support it, with the aim to reduce the incidence of intrapartum hypoxia associated with prematurity and a possible prolonged labour.

6.6.1 Vaginal Delivery in Preterm Labour

In case of low and extremely low birth weight with vertex presentation, it has not been demonstrated a clear correlation between the delivery mode and neonatal complications. Singletons with a birth weight lower than 1500 g have no differences in terms of survival rate and neonatal outcome after CS and vaginal delivery (VD) or are improved after a VD. In addition, the Cochrane review on the mode of delivery in preterm singletons confirms a similar rate of birth injury, asphyxia and perinatal mortality rates after CS and VD. Moreover, maternal morbidity in preterm deliveries is significantly decreased in case of VD compared to CS, confirming that in the absence of foetal and obstetrical indications, vaginal delivery in preterm labour should be chosen.

6.6.2 Caesarean Section in Preterm Labour

In case of intrauterine growth retardation and preterm vertex neonates between 26 and 36 weeks, there is a higher rate of caesarean sections. This mode of delivery, in fact, increases the survival rate of the small for gestational age (SGA) neonates below 31 weeks but not that of SGA >33 weeks and decreases the neonatal mortality rate of the growth-restricted newborns in case of vertex singletons with a birth weight lower than 1500 g.

In predicable infants between 22 and 25 weeks of gestation, independently of the risk cofactors, CS could be associated with a better neonatal outcome.

In breech preterm deliveries, data are conflictual. One retrospective study reports a lower arterial PH after VD but no difference for transfer rate in neonatal intensive care. A recent systematic review concludes that neonatal mortality rate is lower in the CS group than in the VD group.

In very low birth weight twins, the protective effect of CS is unclear [1, 2], and then vaginal delivery could be safely considered in preterm vertex twins. For a non-vertex presenting twin, most guidelines recommend elective CS.

6.6.3 Instrumental Delivery in Preterm Labour

Vacuum delivery in preterm foetuses is associated with an increased risk of intracranial haemorrhage due to venous sinuses fragility. However, there are studies comparing the outcomes of preterm infants delivered by vacuum extraction to normal vaginal delivery that do not show any significant difference in neonatal morbidity. In case of late preterm infants (31 to 34 + 4) delivered by forceps and vacuum delivery, there are studies demonstrating no different outcome between the two groups suggesting that both instruments are a safe option in the hands of experienced obstetricians. A Swedish population-based cohort study reports increased rates of cerebral haemorrhages and Erb's palsy following vacuum delivery in preterm infants compared with CS or normal VD deliveries.

Conclusions

- Proper identification of patients at risk or in true preterm labour is essential.
- Take into consideration new risk factors (age, PMA, foetal sex, psychosocial stress, previous caesarean section, etc.).
- PAMG1 and cervical US measurement are best tests for identifying the true preterm labouring patient or excluding preterm labour.
- Use a safe tocolytic (atosiban) in well-selected cases and for the shortest time.
- Use tocolysis with a clear aim (corticosteroid administration and/or in utero transfer).
- Be aware that not responding to tocolysis may imply presence of infection/inflammation (chorioamnionitis and foetal inflammatory syndrome).
- Use steroids (betamethasone or dexamethasone) only once and when needed.
- Use a combination of drugs (antenatal aminophylline may decrease neonatal IVH).
- Use magnesium sulphate prophylaxis in imminent preterm birth before 32 weeks.
- Prematurity alone is not a valid indication for CS unless if there are obstetrical indications.
- Vaginal delivery appears to be safe and the gold-standard mode of delivery for singleton and twin vertex preterm foetuses.
- Caesarean section should be recommended in preterm labour in the presence of intrauterine growth restriction, breech presentation and in twins with a non-vertex-presenting foetus. CS delivery is not recommended but could be discussed for previable infants.
- Instrumental delivery is not recommended in preterm infants. However, if necessary, a low forceps delivery should be preferred to vacuum extraction below 34 weeks.

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Eclampsia

7

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Eclampsia is defined as the development of convulsions or unexplained coma during pregnancy or postpartum with signs and symptoms of preeclampsia [107]. In eclampsia the occurrence of the seizures cannot be attributed to causes other than preeclampsia. Despite advances in detection and management, preeclampsia/eclampsia remains a common cause of maternal morbidity and mortality.

7.1 Incidence and Epidemiology

The incidence of eclampsia varies worldwide (Table 7.1). The incidence has been estimated to be 2.7 cases per 10,000 births in 2005 in the United Kingdom [51]; 5.7 per 10,000 deliveries in Canada in 2007 [57]; 5.0 per 10,000 deliveries in Denmark, Norway, and Sweden between 1998 and 2000 [5] and 6.0 per 10,000 deliveries in the Netherlands [124]. Wallis et al. reported the incidence of 8.2 per 10,000 deliveries between 1987 and 2004 in the United States [117]. The frequency of eclampsia in less industrialized countries is substantially higher, and estimates range from 16 to 69 per 10,000 births [41].

The rate of eclampsia has decreased in the industrialized countries in recent decades, despite the stable incidence of hypertensive disorders of pregnancy. The rate of eclampsia in the United Kingdom decreased from 4.9/10,000 deliveries (95 % CI 4.5–5.4) in 1992 to 2.7 cases per 10,000 deliveries (95 % CI 2.4–3.1) in 2005 [51]. This 45 % decrease reflects a continued temporal decline over the past century, with reductions of over 90 % observed since the 1920s [57]. In the United States, the age-adjusted frequency of eclampsia decreased nonsignificantly from 10.4 per 10,000 deliveries between 1987 and 1995 to 8.2 per 10,000 deliveries between 1996 and 2004 [117]. This reduction can be attributed to improved access to antenatal care, inpatient management of preeclampsia with severe features and appropriate timing of delivery, and the use of magnesium sulfate ($MgSO_4$) [3].

Eclampsia occurs in 2–3 % of women with preeclampsia with severe features who are not receiving antiseizure prophylaxis and in up to 0.6 % of women with preeclampsia without severe features (previously referred to as "mild" preeclampsia) [106].

7.2 Pathophysiology of Eclampsia

The etiology of eclamptic convulsions is unknown, and there are many unanswered questions regarding the pathogenesis of the cerebral manifestations. Several theories and etiologic mechanisms have been implicated as possible etiologic factors, but none of these have been conclusively proven.

Cerebral autoregulation is a mechanism for maintenance of constant cerebral blood flow during changes in blood pressure; this is hypothesized to be altered in eclampsia. Cerebral blood flow normally remains relatively constant when cerebral perfusion pressure ranges between 60 and 120 mmHg [9]. In this normal range, the elevations in blood pressure result in vasoconstriction of the cerebral vessels, whereas vasodilation occurs as BP decreases.

Studies with Doppler ultrasound have outlined a picture of the cerebral hemodynamics in both normal pregnancy and

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Table 7.1 Incidence of eclampsia in developed countries per 10,000 deliveries

Author	Country	Years	Incidence per 10,000
Wallis et al.	United States	1987–2994	8.2
Zwart et al.	Netherlands	2004–2006	6.2
Liu et al.	Canada	2007	5.7
Andersgaard et al.	Sweden, Norway, Denmark	1998–2000	5
Knight et al.	United Kingdom	2005	2.7

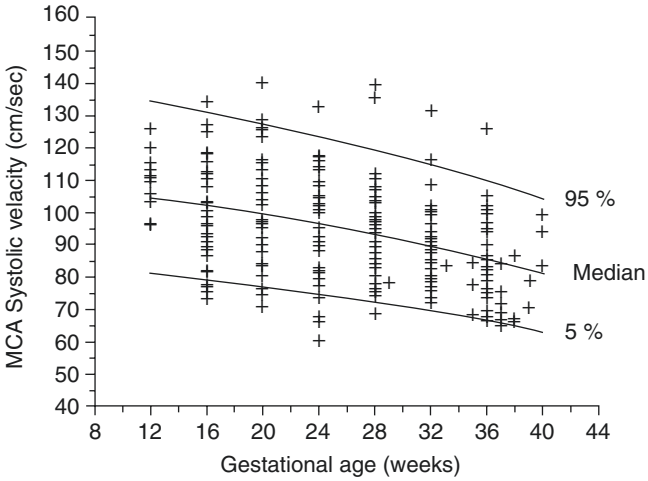

Fig. 7.1 Change in middle cerebral artery (MCA) systolic velocity (cm/sec) during normal gestation. Individual datapoints from each of the patients are depicted by the + symbols (Reproduced from Belfort et al. [9])

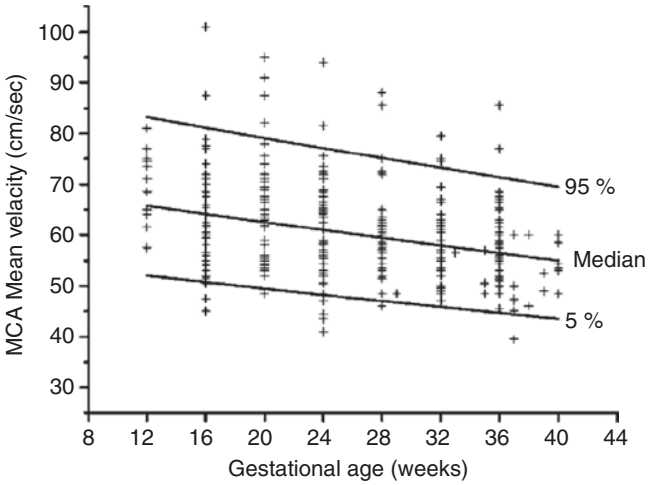

Fig. 7.2 Change in middle cerebral artery (MCA) mean velocity (cm/sec) during normal gestation. Individual datapoints from each of the patients are depicted by the + symbols (Reproduced from Belfort et al. [9])

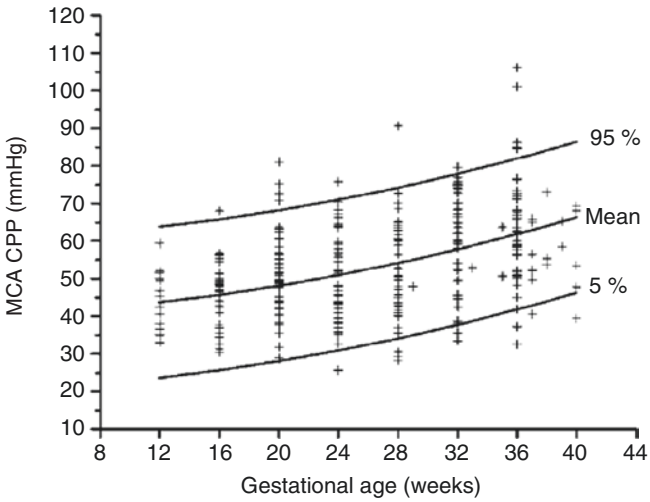

Fig. 7.3 Change in middle cerebral artery (MCA) cerebral perfusion pressure (mmHg) during normal gestation. Individual datapoints from each of the patients are depicted by the + symbols (Reproduced from Belfort et al. [9])

preeclampsia. In normal pregnancy, the systolic velocity and resistance index in the middle cerebral artery both decrease approximately 20 % over gestation [9], whereas the cerebral perfusion pressure (CPP) increases by 50 % from early pregnancy to term (Figs. 7.1, 7.2, 7.3, and 7.4).

The Doppler-derived data have also been confirmed by magnetic resonance imaging studies that show that the middle and posterior cerebral artery diameters remain static during normal late pregnancy, whereas the flow (which in this stance is proportional to the velocity) decreased by approximately 20 % [123]. Cerebral autoregulation is very efficient during pregnancy, and despite a significant increase in perfusion pressure, the cerebral blood flow changes by a much smaller percentage. A small decrease in cerebral resistance is seen in normal pregnancy, as blood pressure increases within the normal range, and this is believed to the result of prostacyclin release as the vessel walls are distended. However, as pressure increases out of the normal range (in preeclamptic women without headache), a physiologic increase in cerebral resistance occurs to limit perfusion and should not be regarded as pathologic change [11, 12] (Fig. 7.5).

Once cerebral perfusion pressure exceeds 130–150 mmHg, the autoregulatory mechanism fails [107]. The normal compensatory vasoconstriction may fail in extreme hypertension resulting in cerebral overperfusion, which may or may not be accompanied by vasospasm and ischemia when vascular integrity is breached [9, 13, 78]. Belfort et al. compared cerebral perfusion in 72 women with preeclampsia without severe features and 120 women with preeclampsia with severe features [13] (Fig. 7.6). A significant proportion of severe preeclamptics have high perfusion pressure (52 %) versus only a minority of preeclamptic patients without severe features. Overall they showed that in preeclampsia with severe features, the resistance is abnormally

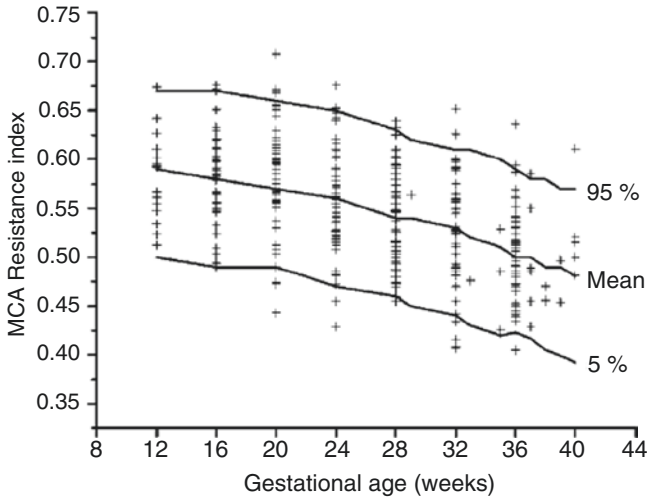

Fig. 7.4 Change in middle cerebral artery (MCA) resistance index (RI) during normal gestation. Individual datapoints from each of the patients are depicted by the + symbols (Reproduced from Belfort et al. [9])

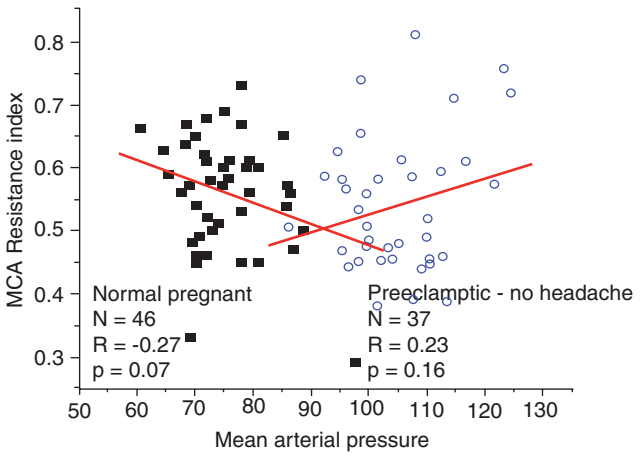

Fig. 7.6 Middle cerebral artery (MCA) perfusion pressure (mmHg) in patients with preeclampsia with severe features versus preeclampsia without severe features (Reproduced from Belfort et al. [9])

high, whereas it is within the normal range in women with mild preeclampsia [13].

As a result of overperfusion, segments of the cerebral vessel are believed to become dilated and increasingly permeable with exudation of plasma, leading to focal cerebral edema, compression of brain tissue and blood vessels, and ultimately decreased cerebral blood flow [107].

Hypertensive encephalopathy and cerebral overperfusion are now believed to be the more likely model for the most cases of eclampsia not associated with hemorrhage, as opposed to cerebral ischemia and vasospasm [9, 106]. Hypertensive encephalopathy is an acute clinical condition resulting from abrupt severe hypertension and subsequent significant increases in intracranial pressure [122, 123]. On the basis of cerebral imaging, hypertensive encephalopathy

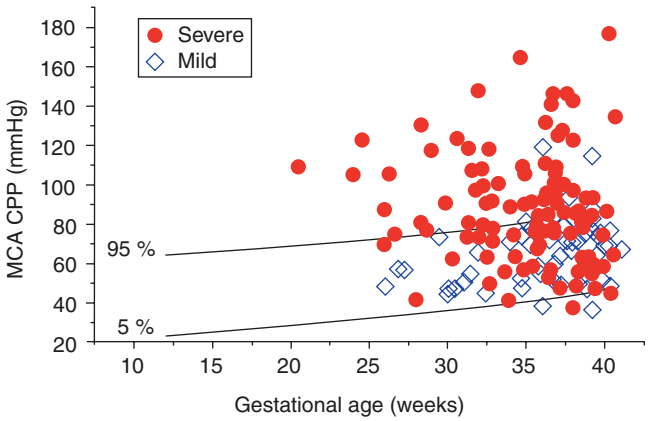

Fig. 7.5 Cerebral flow index and cerebral perfusion index data from women with mild preeclampsia (without headache) (Reproduced from Belfort et al. [11])

and eclampsia share many clinical, radiologic, and pathologic features. In patients with hypertensive encephalopathy and some patients with eclampsia, there is failure of normal cerebral blood flow autoregulation [33, 34, 92]. There are two theories proposed for these cerebral abnormalities: forced dilation and vasospasm [34]. The forced dilation theory suggests that the vasogenic edema frequently seen in eclampsia is caused by a loss of cerebrovascular autoregulation [11, 12, 111]. Normal physiologic cerebral vasoconstriction initially controls downstream pressure and volume flow with increasing blood pressure. When the upper limit of autoregulation is reached, forced vasodilation starts to occur as the capacity of the local artery is overwhelmed (either by the duration or extent of the hypertensive stimulus), allowing for local overperfusion with subsequent interstitial or vasogenic edema [11, 12, 34, 111]. The vasospasm theory proposed that cerebral overregulation occurs in response to acute severe hypertension with resultant cerebral underperfusion, ischemia, cytotoxic edema, and infarction [34, 112, 122]. Recently Van Veen et al. conducted a study comparing dynamic cerebral autoregulation in 20 patients with preeclampsia versus 20 healthy pregnancy women [113]. They showed that impaired dynamic cerebral autoregulation does not correlate with blood pressure (corroborating the same finding for static autoregulation demonstrated by Belfort et al. [9, 11, 12]), which might explain why cerebral complications such as eclampsia can occur without sudden or excessive blood pressure.

Hinchey et al., in 1996, linked eclampsia to a condition that they called reversible posterior leukoencephalopathy syndrome [46]. This syndrome comprised a variety of symptoms and signs including headache, visual disturbances, altered mental status, and seizures, as well as radiologic features of cerebral edema, which was mainly seen in the occipital lobes and posteriorly in the brain. This concept has persisted, but the syndrome itself was renamed as

posterior reversible encephalopathy syndrome (PRES) [44] (Fig. 7.7).

The reason PRES seems to mainly affect the parieto-occipital lobes is not known at present [42, 46, 53, 92]. It is possible that this may be related to decreased sympathetic innervation in the vertebrobasilar arteries (as compared to the internal carotid arteries) [56], leading to overwhelming of the autoregulatory capacity during acute hypertension at a lower pressure than in those areas that have more dense sympathetic innervation [25, 56].

The long-term consequences of eclampsia and preterm preeclampsia (gestational age <37 weeks) have been studied by Aukes et al. who have shown that remote preterm preeclampsia is associated with an increased prevalence of cerebral white matter lesions on MRI when compared to control patients (who had normotensive gestation or term preeclampsia) [6, 7].

It is difficult to make a case that these white matter lesions were caused by PRES, however, since the lesions are mainly found in the frontal part of the brain (not only in the posterior regions) and also occur in patients who did not have seizures. It is more likely that there is an underlying predisposition for preeclamptic women to develop cerebrovascular disease in later life [119].

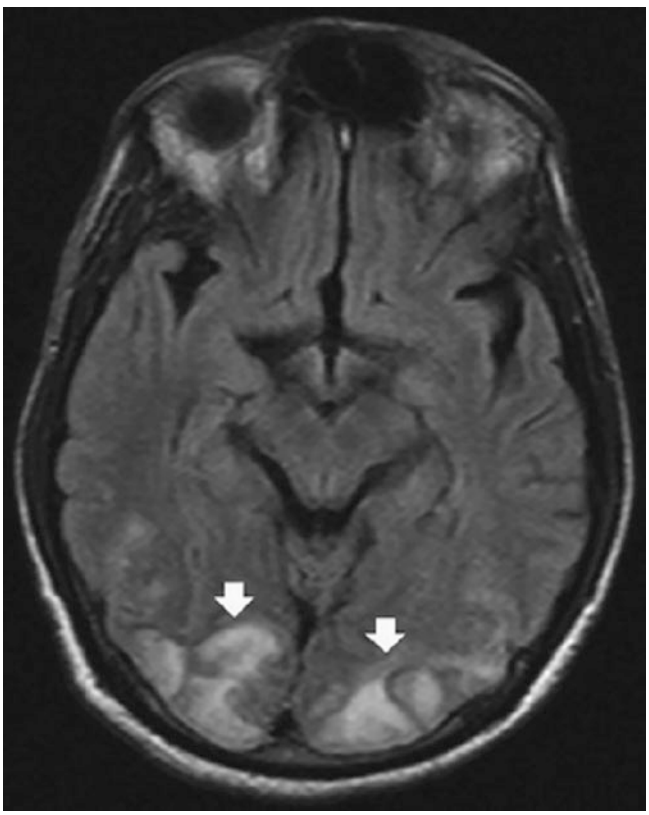

Fig. 7.7 MRI of the brain revealing posterior reversible encephalopathy syndrome (PRES). *Arrows* point at vasogenic edema that is considered reversible

In summary, many women with eclampsia will have evidence of vasogenic edema on brain imaging usually in the occipital and parietal lobes. While not confirmatory, this provides good circumstantial evidence that hypertensive encephalopathy plays a central role in the pathogenesis of eclamptic convulsions. The long-term consequences of eclampsia (and severe preeclampsia) are unclear, but there are data to suggest last effects.

7.3 Clinical Diagnosis

Convulsions in association with hypertension (with or without proteinuria) in a currently, or recently, pregnant woman suggest the diagnosis of eclampsia [107]. The hypertension may not necessarily be in the severe range, and a high level of suspicion is required so as not to overlook this diagnosis. In patients, who develop eclampsia, there is a wide spectrum of signs reported, ranging from no preceding signs to mild to severe hypertension, minimal to severe proteinuria, and absent to generalized edema [104, 107]. Some degree of hypertension is almost always present but may be absent in 16 % of the cases [74]. Hypertension may be severe (systolic ≥160 mmHg and/or diastolic ≥110 mmHg) in 20–54 % of cases [37, 74] or mild (systolic blood pressure between 140 and 160 mmHg and diastolic between 90 and 110 mmHg) in 30–60 % of cases [37, 74]. Severe hypertension is more common in patients who develop eclampsia in the antepartum period (58 %) and especially in cases who develop eclampsia at 32 weeks or earlier (71 %) [74].

Proteinuria (protein to creatinine ratio ≥0.3 or ≥300 mg per 24 h urine collection or dipstick at least +1 only if other quantitative methods are not available) may also be associated with eclampsia [74]. Mattar and Sibai showed in a series of 399 patients with eclampsia that severe proteinuria (equal or greater than 3+ on dipstick) only occurred in 48 % of the cases and that proteinuria was absent in 14 % [74]. Abnormal weight gain (with or without clinical edema) in excess of 2 lbs per week in the third trimester might be the only sign preceding eclampsia. In the same study, edema was absent in 26 % of the 399 eclamptic patients [74].

Most women have premonitory symptoms in the hours before the initial seizure. These include persistent occipital or frontal headaches, blurred vision, photophobia, epigastric or right upper quadrant pain, and altered mental status, and 59–75 % of women who develop eclampsia have at least one of these symptoms (Table 7.2). Patients report headache as their major preceding complaint in 50–75 % of cases, whereas visual changes have been reported in 19–32 % of the patients [23, 37, 50]. In a systematic review that included 59 studies involving more than 21,000 women with eclampsia from 26 countries, the most common antecedent signs and symptoms were hypertension (75 %), headache (66 %), visual disturbances (scotomata, loss of vision [cortical

Table 7.2 Symptoms in women with eclampsia

	Katz et al. (n = 53)	Chamets et al. (n = 89)	Douglas and Redman (n = 325)
Headache	64 %	70 %	50 %
Visual changes	32 %	30 %	19 %
Right upper quadrant, epigastric pain	Not reported	12 %	19 %
At least one	Not reported	75 %	59 %

blindness], blurred vision, diplopia, visual field defect, photophobia) (27 %), and right upper quadrant or epigastric pain (25 %) [14]. In 25 % of cases, the patients were asymptomatic prior to the seizure(s) [14].

Eclampsia is generally manifested by a generalized tonic-clonic seizure or by coma. At the onset, there is usually an abrupt loss of consciousness, often associated with a scream or shriek, and muscle stiffening in the arms, legs, chest, and back [94]. The patient may appear cyanotic during this tonic phase, which may last from a few seconds to approximately a minute. Following the hypertonicity, the patient's muscles will usually begin to jerk or twitch for an additional 1–2 min. During this clonic phase, the patient may bite her tongue and express frothy and bloody sputum. The postictal phase begins once the twitching movements end. This is usually followed by a deep sleep, deep breathing, and gradual return to sentience. On awakening the patient will often complain of a headache. Most patients begin to recover responsiveness within 10–20 min after the generalized convulsion. Focal neurologic deficits are generally absent although there may be memory deficits. On examination there may be increased deep tendon reflexes, visual perception deficits, altered mental status, and cranial nerve deficits [94].

7.4 Time of Onset

Eclamptic convulsion can be antepartum, intrapartum, or postpartum. The frequency of antepartum eclamptic convulsion has been reported to be 38–53 % [23, 37, 50, 74]. Mattar and Sibai reported that most cases of eclampsia develop at or beyond 28 weeks (91 %). The same study showed that 7.5 % of patients who develop eclampsia develop it between 21 and 27 weeks of gestation and that in 1.5 % eclampsia occurs at 20 weeks of gestation or earlier [74].

If eclampsia develops before 20 weeks of gestation, the coexistence of molar pregnancy needs to be ruled out [81, 102]. Although rare, several case reports have described eclampsia during the first trimester without the coexistence of molar pregnancy [74, 81], and for this reason, eclampsia should be ruled out at any gestation in pregnant women who have had a seizure [102]. Women with early eclampsia may be misdiagnosed with a seizure disorder, hypertensive encephalopathy, or thrombotic thrombocytopenia purpura. Women in whom a convulsion(s) is associated with hypertension and/or proteinuria during the first half of pregnancy should thus be considered eclampsia unless proven otherwise [104]. All women with early gestation eclampsia (first half of pregnancy) should have ultrasound examination of the uterus to rule out a molar pregnancy. Also extensive medical evaluation and neurologic examination should be performed for these patients to rule out other etiologies such as meningitis, cerebral abscess, encephalitis, cerebral hemorrhage or thrombosis, cerebral vasculitis, thrombotic thrombocytopenia purpura (TTP), brain tumor, and metabolic disease; it is always wise to rule out chemical and drug (legal and illicit) exposures [104, 107].

The incidence of postpartum eclampsia ranges from 11 to 44 %, and most of the postpartum eclampsia occurs during the first 48 h following delivery [23, 37, 50, 74, 102]. However, eclampsia can and does develop beyond 48 h and has been reported as late as 23 days postpartum [23, 50, 74]. Late postpartum eclampsia is defined as eclampsia that occurs beyond 48 h but within 4 weeks of delivery [62, 102]. Approximately 56 % of these women will demonstrate signs and symptoms of preeclampsia during labor or immediately postpartum, whereas others will show these clinical findings for the first time more than 48 h after delivery (44 %) [62]. Late postpartum eclampsia can develop despite the use of prophylactic intra- and postpartum (at least 24 h) magnesium sulfate in previously diagnosed women with preeclampsia [23, 62]. Therefore, women with convulsion(s) associated with hypertension and/or proteinuria and/or with headaches or visual disturbances 48 or more hours after delivery should be considered to have eclampsia unless otherwise proven and should be treated as for eclampsia [23, 62, 102]. In these cases, an extensive neurological evaluation including CNS examination, cerebrovascular testing, and brain imaging (MRI and/or CT depending on the circumstances) and routine laboratory tests (CBC and platelets, liver function, renal function and electrolytes, and coagulogram) are usually instituted at a minimum, with further more sophisticated testing (lumbar puncture, EEG, and angiography) used as dictated by initial findings [23, 62, 102].

7.5 Neurodiagnostic Study

Several neurodiagnostic tests, such as electroencephalography (EEG), computerized tomography (CT), magnetic resonance imaging (MRI), diffusion-weighted magnetic resonance imaging (DWI), cerebral Doppler velocimetry, and cerebral angiography (both traditional and MRI angiography), have been studied in women with eclampsia.

There is limited information on EEG in eclampsia. In general, despite the fact that the EEG is almost always acutely abnormal in patients with eclampsia, none of the identified patterns are pathognomonic for eclampsia [107].

Review of the EEG literature has shown that postictal EEG abnormalities are common in eclamptic women and the EEG almost always becomes normal with prolonged postpartum follow-up [18]. The reliability of these studies has been questioned given methodological issues, and the fact that all but one were published between 1955 and 1984. There are no more recent EEG studies available in which more modern equipment and practices have been used.

Lumbar puncture is not helpful in the diagnosis and management of patients with eclampsia and may be dangerous if the patient has acutely elevated intracranial pressure. For this reason, such a test should only be ordered when the differential diagnosis absolutely requires it and the benefit outweighs the risk [107].

CT and MRI studies performed following seizure activity in preeclamptic patients usually reveal the presence of edema and infarction within the subcortical white matter and adjacent gray matter (mostly in the parietal and occipital lobes). Other CT and MRI findings have been summarized in Table 7.3.

In uncomplicated eclampsia (i.e., no cerebral hemorrhage, hydrocephalus, or congenital anomaly), cerebral imaging findings are similar to those found in patients with hypertensive encephalopathy. The classic findings are referred to as posterior reversible encephalopathy syndrome (PRES) [53]. In a small series of eclamptic patients studied by Brewer and colleagues, 46 of 47 patients (97.9 %) revealed PRES on CT or MRI with or without contrast [17].

Within the past two decades, magnetic resonance diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping have become more commonly used and reported, and this facilitates the discrimination between vasogenic and cytotoxic forms of cerebral edema [24]. DWI takes advantage of strong diffusion gradients that detect changes in water molecule distribution in cerebral tissue. In the presence of infarction, cytotoxic edema is caused by sodium pump failure, and the resultant reduction in proton diffusion elicits hyperintense ("bright") signal on DWI (Fig. 7.8). Conversely, vasogenic edema is characterized by increased extracellular fluid with enhanced water diffusion, and this may be seen as normal or decreased signal brightness on DWI. While it is generally a reliable way of distinguishing vasogenic from cytotoxic edema, occasionally a hyperintense signal may be seen in DWI in patients who do not have cytotoxic edema, and this has been dubbed "T2 shine-through" (Figs. 7.9 and 7.10). Thus, specialist in radiology expertise may be required to determine whether DWI hyperintensity is due to restricted diffusion or to T2 shine-through, prior to instituting specific therapy or counseling regarding a prognosis.

This issue is usually resolved by estimation of the underlying ADC in the region of interest since ADC map is independent of T2 effects and can be used to determine whether diffusion is restricted or free in the area of interest. A decreased ADC map that corresponds to hyperintense areas on the DWI confirms restricted diffusion, while an elevated ADC results from water molecules with increased diffusional motion and thus represents vasogenic edema.

In two small series [61, 123], the frequency of vasogenic edema and cytotoxic edema in eclamptic patients was estimated. Cerebral edema (mostly vasogenic) was present in up to 93–100 % of these women. Concurrent foci of infarction and cytotoxic edema, as evidenced by reduced apparent diffusion coefficient (restricted diffusion), were present in six of 27 patients studied by Zeeman and colleagues [123] and in three of 17 eclamptic and preeclamptic women studied by Loureiro and associates [61]. In addition five of six women

Table 7.3 Computed tomography scan and magnetic resonance imaging findings in complicated eclampsia

Diffuse white matter low-density areas
Patchy areas of low density
Occipital white matter edema
Loss of normal cortical sulci
Reduced ventricular size
Acute hydrocephalus
Cerebral hemorrhage
Intraventricular hemorrhage
Parenchymal hemorrhage
Cerebral infarction
Low-attenuation areas
Basal ganglia infarction

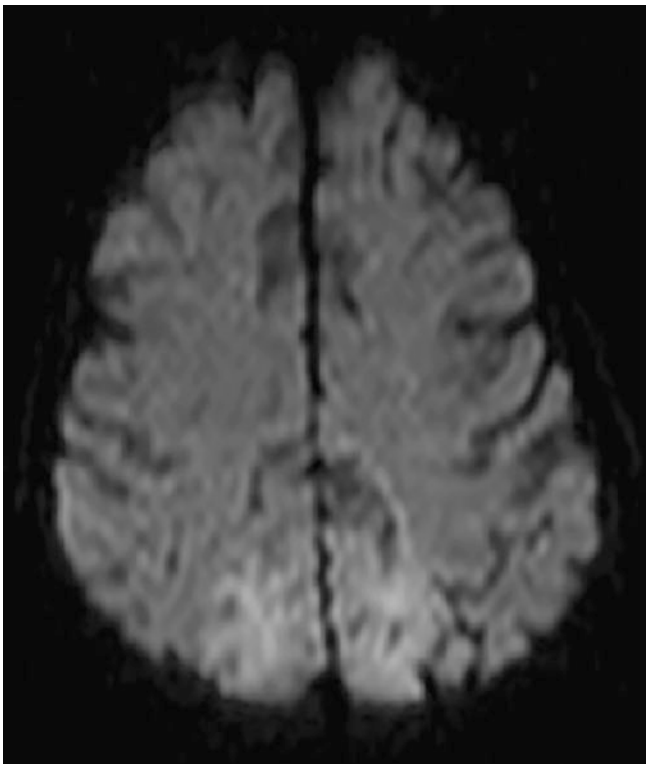

Fig. 7.8 Diffusion-weighted imaging (DWI) – increased signal indicating cytotoxic edema in bilateral parasagittal parietal lobes

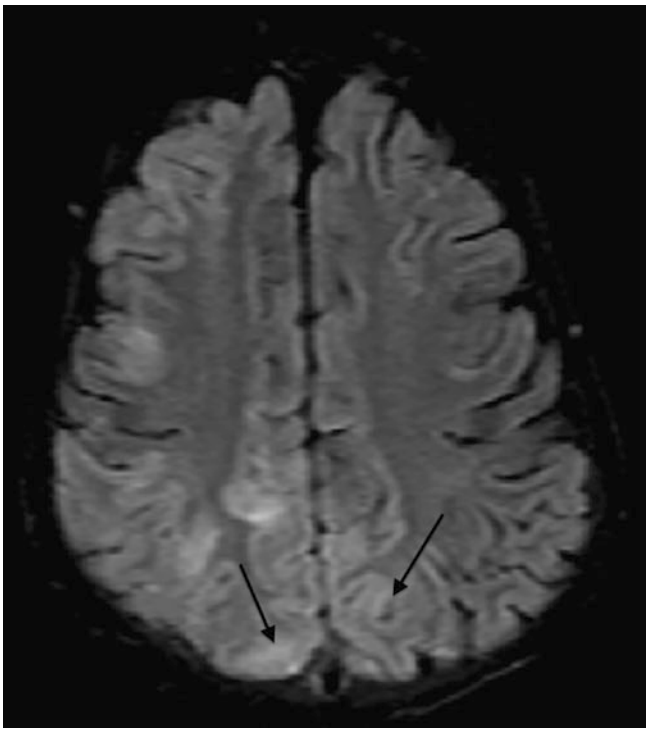

Fig. 7.9 T2 signal – *Arrows* show bilateral occipital-parietal lobe increased signal indicating cytotoxic edema

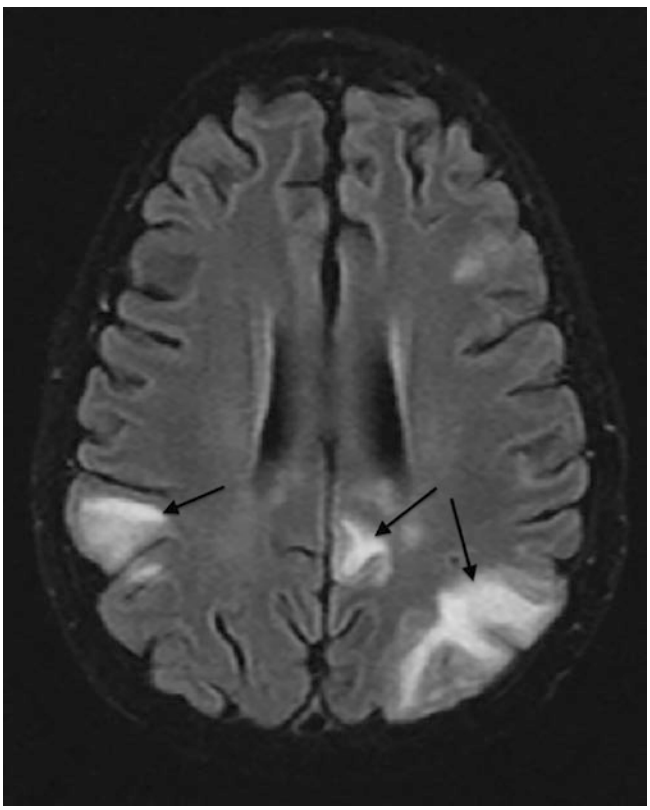

Fig. 7.10 T2 signal – *Arrows* show bilateral parietal lobe increased cortical and subcortical signal demonstrating vasogenic edema

reported by Zeeman and colleagues [123] and four of 17 women reported by Loureira et al. [61] had persistent abnormalities on repeat MRI testing 6–8 weeks later, suggesting that these lesions might not be reversible.

Uncomplicated eclampsia (full recovery) is usually a clinical diagnosis and does not require cerebral imaging diagnosis and management. However, cerebral imaging is indicated for patients with focal neurologic deficits, prolonged coma, fever, suspicion of TTP, or other imitators of preeclampsia and those who develop seizures with a therapeutic $MgSO_4$ level or who are unresponsive to $MgSO_4$ therapy [107]. We also recommend that all postpartum eclampsia be investigated with cerebral imaging.

In these patients, hemorrhage and other serious abnormalities requiring specific pharmacologic therapy or surgery must be excluded. Cerebral imaging also might be helpful in cases of atypical eclampsia including normotensive and/or non-proteinuric eclampsia, onset of eclampsia before 20 weeks of gestation (after excluding molar pregnancy) or after delivery, and in women who may have known antiphospholipid syndrome or autoimmune disease [107]. Advances in MRI and magnetic resonance angiography, as well as in cerebral vascular Doppler velocimetry, may aid our understanding regarding the pathogenesis and improving long-term outcome of this condition [106].

It is important to distinguish PRES (an overperfusion syndrome with forced cerebral vasodilatation) from reversible cerebral vasoconstriction syndrome (RCVS), which is different in etiology (vasospasm) [39]. RCVS is characterized by recurrent thunderclap headaches, seizures, strokes, and nonaneurysmal subarachnoid hemorrhage [39]. RCVS seems to be associated with constriction and/or dilation of large or medium arteries, while PRES does at the level of distal arterioles and capillary. An overlap between these two syndromes represents a continuum in them. Postpartum cerebral angiopathy is another ill-characterized RCVS, usually occurring within 30-day duration of uncomplicated pregnancy and delivery. The diagnosis is confirmed by angiography (Fig. 7.11) [39].

7.6 Differential Diagnosis

As discussed above, a differential diagnosis (Table 7.4) should be considered. The diagnosis and management of these diagnoses are beyond the scope of this chapter.

7.7 Maternal and Perinatal Outcome

7.7.1 Maternal

The overall maternal death rate associated with eclampsia varies from 0.4 % to as high as 7.2 % in developed countries.

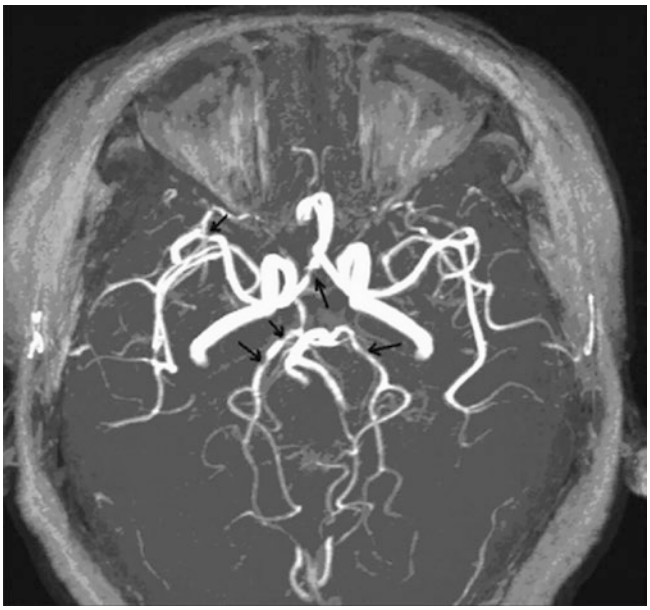

Fig. 7.11 Cerebral arteriogram demonstrating cerebral vasoconstriction. *Arrows* show diffused vasoconstriction in small blood vessels

Table 7.4 Differential diagnosis of eclampsia

Seizure disorders
Hemorrhage
Reversible cerebral vasoconstriction syndrome
Vasculitis, angiopathy
Hypertensive encephalopathy
Thrombotic thrombocytopenia purpura
Amniotic fluid embolism
Hypoglycemia, hyponatremia
Postdural puncture syndrome
Ruptured aneurysm
Arterial embolism, thrombosis
Angiomas
Hypoxic ischemic encephalopathy

In developing nations with limited access to tertiary medical centers and specialist expertise, maternal mortality has been reported to be as high as 14 % [37, 41, 69, 84].

A retrospective analysis of 990 cases of eclampsia in Mexico before 1992 reported a case mortality rate of 13.9 % (138/990). The subgroup of women with eclampsia prior to 28 weeks of gestation had the highest risk of maternal death (12/54 [22 %]). Multiple seizures occurring outside of a hospital setting and lack of prenatal care were important risk factors [59]. In another study by McKay and associates, 790 of 4,024 pregnancy-related deaths (19.6 %) in 1979 and 1992 were considered due to preeclampsia-eclampsia, with 49 % of these 790 considered to be due to preeclampsia-eclampsia, and fully 49 % of those 790 were associated with eclampsia [69]. In this series, the risk for death from preeclampsia or eclampsia was higher for women older than 30 years, for those without prenatal care, and for black women; the greatest risk for death was found among women with pregnancy ≤28 weeks of gestation. In a recent population-based cohort study from Canada that included 1,481 cases of eclampsia between 2003 and 2009, the case mortality rate was reported as being 0.34 % (5/1,481) [58].

The primary drivers of eclampsia-associated maternal morbidity are placental abruption (7–10 %) (Lo'pez-LIera et al. 1992,1993; [59, 60, 74, 104]), disseminated intravascular coagulopathy (7–11 %) (Lo'pez-LIera et al. 1992, 1993; [59, 60, 74, 104]), pulmonary edema (3–5 %), acute renal failure (5–9 %), aspiration pneumonia (2–3 %), and cardiopulmonary arrest (2–5 %) (Lo'pez-LIera et al. 1992, 1993; [59, 60, 74, 104]). Acute respiratory distress syndrome (ARDS) and intracerebral hemorrhage are rarely reported complications of eclampsia in those series from developed countries (Pritchard et al. 1984; [37, 74]).

7.7.2 Fetal and Neonatal

Perinatal mortality and morbidities remain high in eclamptic pregnancies. The reported perinatal death rate in recent series ranged from 5.6 to 11.8 % [37, 55, 104]. A population-based cohort study from Canada reported fetal death rates in eclamptic and non-eclamptic pregnancies of 10.8 and 4.1 per 1,000 total births, respectively; neonatal death rates were 7.5 and 2.2 per 1,000 live births, respectively [58]. Although the perinatal mortality and morbidity rates secondary to eclampsia are large part a reflection of the gestational age and maternal condition, the primary risks to the fetus are placenta abruption, fetal growth restriction (FGR), and complications of prematurity secondary to indicated delivery at the extremes of gestational age and hypoxia secondary to maternal convulsions [29, 84, 96]. The rate of preterm delivery is about 50 %, with about 25 % of cases occurring before 32 weeks of gestation [37, 104]. A number of retrospective and prospective studies have assessed both short- and long-term outcomes of infants of eclamptic mothers. Sibai et al. followed 28 preterm infants and 14 full-term infants for up to 50 months [96]. The majority of the infants were small for gestational age or intrauterine growth restricted; however, by a mean of 20.6 months, nearly all of the infants had appropriate growth velocity with respect to weight, length, and head circumference. In terms of long-term neurologic sequelae, these authors found that observed major deficits mirrored those anticipated in premature or anomalous infants born to non-eclamptic women [96]. In another published cohort from Sweden, similar outcomes were observed. Of note, in these authors' study intervals, there were no differences in either maternal or perinatal outcomes over the time intervals examined (1973–1979, 1980–1989, and 1990–1999) [88].

Similar findings have been observed in other retrospective analyses, with higher perinatal morbidity and mortality at the extremes of gestational age in developing nations [55, 43].

7.8 Management

7.8.1 Prevention and Prophylaxis

Due to our sparse knowledge about the pathogenesis of eclampsia, the strategies for prevention are limited. In addition, the onset of eclampsia is not reliably predicted by maternal characteristic, gestational age, or antepartum status [1]. The management goals in eclampsia involve timely diagnosis and treatment of preeclampsia with appropriate pharmacologic agents to prevent eclampsia and the prevention of intracranial hemorrhage, cerebral edema, stroke, and recurrent seizures in women with established eclampsia [1].

A great deal of effort has been directed at the identification of demographic factors, biochemical analytes, or biophysical findings, alone or in combination, to predict the development of preeclampsia. Although there are some encouraging findings, these tests are not yet ready for clinical use [16, 22, 38]. In addition, even if a test were reliably able to predict the future onset of preeclampsia, we do not yet have any absolute way of preventing the development of preeclampsia. It is clear that the antioxidants vitamin C and vitamin E are not effective interventions to prevent preeclampsia or adverse outcomes from preeclampsia in unselected women at high or low risk of preeclampsia [89, 90]. Calcium supplementation (1.5–2 g/day) may be useful to reduce the severity of preeclampsia in populations with low calcium intake (<600 mg/day), but this finding is not relevant to a population with adequate calcium intake [47]. The administration of low-dose aspirin (60–80 mg) to prevent preeclampsia has been examined in a meta-analysis of more than 30,000 women, and it appears that there is slight effect to reduce preeclampsia and adverse perinatal outcomes. These findings are not relevant to low-risk women but may be relevant to populations at very high risk in whom the number to treat to achieve the desired outcome will be substantially less [21, 28, 91, 116]. In the United States, daily low-dose aspirin (81 mg/day) beginning in the late first trimester is recommended to women with a medical history of early-onset preeclampsia and preterm delivery at less than 34.7 weeks of gestation or preeclampsia and/or for women who have experienced preeclampsia in more than one prior pregnancy [49]. There is no evidence that bed rest or salt restriction reduces preeclampsia risk [40, 75].

Current management to prevent eclampsia is based on early detection of gestational hypertension or preeclampsia and the subsequent use of preventive strategies that include close monitoring (in-hospital or outpatient), use of antihypertensive therapy, timely delivery, and the prophylactic use of magnesium sulfate during labor and immediately postpartum in those considered to have preeclampsia (mostly with severe features) [103]. These management schemes are based on an assumption that the clinical course in the development of eclampsia follows a progressive process that begins with weight gain followed by hypertension and proteinuria, which is followed by the onset of convulsion or coma [95]. This clinical course may be true in some women who develop eclampsia; however, data from large series of eclamptic women from the United States and Europe indicate that approximately 20–40 % of eclamptic women do not have any premonitory signs or symptoms before the onset of convulsion [20, 50, 95, 97, 104]. In a review of 179 consecutive cases of eclampsia by Sibai et al. [98], factors either associated with, or at least partially responsible for, the failure to prevent eclampsia were physician error (36 %), failure of magnesium sulfate to prevent seizure (13 %), late postpartum onset (12 %), early onset (<21 weeks [3 %]), abrupt onset (8 %), and lack of prenatal care (19 %) [98].

The efficacy of in-hospital management of patients with gestational hypertension or preeclampsia for the prevention of eclampsia has not been evaluated in randomized trials. Data from retrospective studies from the developed countries indicate that about 50 % of eclamptic patients develop their first convulsion while in the hospital under “close medical supervision” [20, 50, 98, 104]. Thus, early and prolonged hospitalization of women with mild gestational hypertension or preeclampsia with no severe features may not prevent most cases of eclampsia. These patients may be just as safely managed s an outpatient with weekly laboratory evaluation that includes complete blood count (CBC) with platelet count and liver function test to rule out the development of preeclampsia with severe features. Patients should be familiar with the symptoms and signs of preeclampsia with severe features and know to immediately report these to their provider [49].

There are several randomized trials describing the use of antihypertensive medication versus no treatment or a placebo in the treatment of the patients with mild gestational hypertension or preeclampsia with no severe features. Overall, these trials revealed lower rates of progression to severe disease (Magee et al. 1999). However, the study design and the sample size of these trials are inadequate to evaluate potential benefits regarding prevention of eclampsia (Magee et al. 1999).

Due to our inability to consistently and successfully predict those who might have an eclamptic seizure, it has been the recommendation and practice of many to employ seizure prophylaxis for preeclampsia with severe features (including patients with HELLP [hemolysis, elevated liver enzymes, low platelets]) and patients who have persistently blood pressure in severe range (greater than 160 mmHg systolic or 110 mmHg diastolic) [98, 106, 107]. Over the last decades, there

have been several trials focused on the efficacy and safety of various seizure prophylactic agents.

Following the publication of the landmark $MgSO_4$ for prevention of eclampsia (Magpie) trial, there was international consensus that magnesium sulfate ($MgSO_4$) is the prophylactic agent of choice for preeclamptic women [72]. In brief, 10,141 women with preeclampsia were enrolled in this randomized, controlled trial in 175 secondary and tertiary facilities in 33 countries. The study showed that there were significantly fewer eclamptic convulsions among women allocated $MgSO_4$ than among those allocated placebo (58 % lower relative risk). This reduction represents an overall finding of 11 per 1,000 fewer women had an eclamptic seizure when allocated to the $MgSO_4$ group. Although the Magpie study demonstrated improved efficacy for eclamptic seizure prophylaxis, there was no significant difference in maternal, fetal, or perinatal morbidity [72].

Based on a number of hypothesized mechanisms of action of magnesium sulfate, other agents with perceived similar physiologic or pharmacologic effect have been studies. To date, no alternate therapies have proven to be as effective as $MgSO_4$ with respect to seizure prophylaxis or superior in terms of any reduction in maternal morbidity or mortality.

Given the known cerebral vasodilator effect of magnesium sulfate, Belfort et al. conducted a multicenter randomized trial to compare nimodipine, which is a calcium channel blocker with known selective cerebral vasodilatory effects, to magnesium sulfate in patients with preeclampsia with severe features [10]. Contrary to expectations, $MgSO_4$ was found to be more effective than nimodipine for the prevention of eclampsia. Of interest is that not only was there significantly lower rate of eclampsia in the $MgSO_4$ group, but this effect was primarily exerted in the postpartum interval [10].

With respect to other neuroleptic agents, the work of Lucas et al. has demonstrated an advantage of $MgSO_4$ over phenytoin for the prevention of eclampsia [63]. In their study, 2,138 preeclamptic women were randomized to receive either $MgSO_4$ or phenytoin upon diagnosis and admission [63]. Eclamptic seizures developed significantly less frequently in the group of patients that received magnesium sulfate, with same maternal and neonatal outcome.

7.8.2 Immediate Management of Eclamptic Convulsion

Eclamptic seizures are a life-threatening emergency and require proper care to minimize morbidity and mortality. Key management principles are:

- Prevention of maternal hypoxia and trauma
- Prevention of recurrent seizure
- Treatment of severe hypertension if present
- Evaluation of the need for prompt delivery

We suggest a neurology consultation for these women who do not improve promptly following control of hypertension and seizures and for those who develop localizing neurologic signs.

7.8.2.1 Seizure Supportive Care

The first priority in the management of eclampsia is to prevent maternal injury and to support respiratory and cardiovascular functions. Supportive measures include raising and padding the beds' side rails and inserting a padded tongue blade between the teeth (avoiding inducing gag reflex). To minimize the risk of aspiration, the patient should lie in the lateral decubitus position, and vomitus and oral secretions are suctioned as needed [105, 107]. Aspiration may be caused by forcing the padded tongue blade to the back of the throat, stimulating the gag reflex with resultant vomiting. Consideration of endotracheal intubation for airway protection should be entertained in any patient with a recent history of eating or for patients that remain obtunded or comatose and are at risk for aspiration [105, 107].

During the convulsive episode, hypoventilation and respiratory acidosis often occur. Although the initial seizure lasts only a few minutes, it is important to maintain oxygenation by supplemental oxygen administration via a face mask with or without oxygen reservoir at 8–10 L/min [105, 107]. After the convulsion has ceased, and the patient begins to breathe again, oxygenation is rarely the problem. However, maternal hypoxemia and acidosis may develop in women who have had repetitive convulsions and in those with aspiration pneumonia, pulmonary edema, or a combination of these factors [105, 107]. We recommend the use of transcutaneous pulse oximetry to monitor oxygenation in all eclamptic patients. Arterial blood gas analysis is required if the pulse oximetry results are abnormal (oxygen saturation <92 %).

Additional drugs such as diazepam should not be given as an attempt to stop or shorten the convulsion, especially if the patient does not have an intravenous line in place and someone skilled in intubation is not immediately available. If diazepam is used, no more than 5 mg should be given over a 60-s period. Rapid administration of diazepam may lead to apnea and cardiac arrest or both [105, 107].

7.8.2.2 Prevention of Recurrent Seizure

The next step in the management of eclampsia is to prevent recurrent seizures. Magnesium sulfate is the drug of choice to treat and prevent subsequent convulsions in women with eclampsia [120]. It may be given intravenously by continuous infusion or intramuscularly by intermittent injection. Magnesium sulfate regimens are illustrated in Table 7.5.

Table 7.5 Dosage of $MgSO_4$

Magnesium	Loading dose	Maintenancedose	Therapeutic level (Measured 6 h after load)
Continuousintravenous infusion	4–6 g over 15–30 min; diluted in 100–150 mL of IV fluids	2 g/h	4–8 mEq/L
Intramuscularinjection	10 g of 50 % $MgSO_4$ solution (5 g into each buttock)	5 g every 4 h	4–8 mEq/L
Refractory seizure	Reload with 2 g IV, not to exceed 2 doses, over 10 min in a 20 % solution		

Because a regimen of a 4-g intravenous loading dose followed by a 1–2 g/h IV maintenance dose was deemed to have failed to prevent eclampsia in a significant number of preeclamptic women, Sibai et al. [99] modified this regimen to 4-g IV loading dose followed by a 2–3 g/h IV maintenance dose. Sibai compared Pritchard's regimen of a 4-g IV and 10-mg intramuscular loading dose followed by a 5-g IM maintenance dose every 4 h, with a 4-g IV loading dose followed by a 1–2 g/h continuous IV maintenance infusion [99]. The IV loading dose with maintenance dose of 1 g/h did not produce adequate serum levels of magnesium that were regarded as adequate; thus, they recommended a 2–3 g/h maintenance dose [99]. The Magpie trial, which used a 4-g IV loading dose and 1 g/h infusion rate, did not show any higher rate of eclampsia than that seen in studies where the 6-g loading dose and 2 g/h infusion have been used [72]. The risk of magnesium toxicity is very low, and in those countries where close monitoring is impractical and the determination of blood levels of $MgSO_4$ not available, it is entirely reasonable to use the 4-g loading dose and 1 g/h infusion. In countries and facilities where adequate safety precautions are in place, women treated with magnesium sulfate to prevent or treat eclamptic seizures are generally given an intravenous loading dose of 4–6 g followed by a maintenance dose of 1–2 g/h [49], although no randomized trial has ever proven this to be a better approach. Approximately 10 % of the women with eclampsia will have a second convulsion after receiving magnesium sulfate. In 1995, The Eclampsia Trial Collaborative Group reported their findings from an international, multicenter randomized control trial (The Eclampsia Collaborative Group 1995). In this study, 1,687 eclamptic women were randomly allocated to two treatment categories: (i) $MgSO_4$ versus diazepam and (ii) $MgSO_4$ and phenytoin. The study was designed to look at the recurrence of convulsions and maternal death as its primary outcomes. Women allocated to the $MgSO_4$ group had a 52 % lower incidence of recurrent convulsion as compared to those allocated with diazepam (13.2 % versus 27.9 %) and a 67 % lower risk of recurrent seizures than those receiving phenytoin (5.7 % versus 17.1 %). Maternal mortality was nonsignificantly lower among women allocated magnesium sulfate. There were no significant differences in other measures of serious maternal morbidity or in perinatal morbidity or mortality [110].

Table 7.6 Signs and symptoms of magnesium toxicity

Manifestation	Level (mg/dl)
Loss of patellar reflex	9–12
Double vision	9–12
Feeling of warmth, flushing	9–12
Somnolence	10–12
Slurred speech	10–12
Muscular paralysis	15–17
Respiratory arrest	15–17
Cardiac arrest	30–35

In patients who experience recurrent seizures, another bolus of 2-g $MgSO_4$ can be given intravenously in 3–5 min. Some patients will have recurrent convulsions while receiving adequate doses of magnesium sulfate, and these patients should have imaging to rule out cerebral bleeding and other causes of seizures [107]. In status eclampticus, recurrent seizures can be treated with sodium amobarbital 250 mg intravenously over 3–5 min [107].

Serum magnesium levels are generally not monitored during the infusion because, as mentioned earlier, there is no established serum magnesium level that is considered "therapeutic" [107]. The patient who has received a large dose of $MgSO_4$ should be monitored for signs and symptoms of magnesium toxicity using serial evaluations of reflexes, respiratory rate, and urinary output. The signs and symptoms of magnesium toxicity in relationship to the magnesium level are described in Table 7.6 [107].

If a patient develops signs of magnesium toxicity, the infusion should be stopped immediately (any $MgSO_4$ bags and lines discarded), and the patient should be evaluated for respiratory compromise (pulse oximetry and/or arterial blood gas). In addition, we suggest that in such situations examinations by a provider capable of evaluating and performing endotracheal intubation are mandatory. In any patient who is receiving $MgSO_4$, suspicion of respiratory compromise should prompt immediate administration of oxygen (by whatever means appropriate to maintain adequate oxygenation). A serum magnesium level should be obtained if possible, and treatment with 1-g calcium (either calcium gluconate or calcium chloride solution) over 3 min should be promptly instituted [1].

Eclamptic seizures are almost always self-limiting and seldom last longer than 3–4 min. Although neurology and emergency medicine colleagues may recommend or consider the use of alternative neuroleptic agents, we have to emphasize that the obstetrical literature has shown that in the setting of eclampsia the administration of such agents is seldom necessary or appropriate (Witlin and Sibai 1998; [99, 107]).

7.8.2.3 Contraindication to Magnesium Sulfate

Contraindications to $MgSO_4$ are limited. These include myasthenia gravis and myocardial ischemia or infarct. With respect to the latter, magnesium can interact with other cardiovascular drugs (i.e., calcium channel blockers) to elicit arrhythmias or reduce myocardial contractility. In addition, given its renal excretion, magnesium infusions should be administered cautiously to patients with renal failure because of the risk of magnesium toxicity and resultant cardiorespiratory depression [1]. In patients with renal failure, while the initial 4-g loading dose of magnesium sulfate can be safely administered, continuous infusion thereafter is contraindicated. This is because after distribution, in a patient with renal failure, a 4-g loading dose achieves a therapeutic level, and continuous infusion would rapidly increase the level to the toxic range because of limited glomerular filtration [1]. Whenever plasma creatinine levels are >1.0 mg/mL, caution should be exercised, and serum magnesium levels should be used to adjust the infusion rate [1].

7.8.3 Antihypertensive Therapy

Reduction of blood pressure is a crucial step in the management of eclampsia if the patient presents with severe hypertension. The objectives of treating severe hypertension are to (i) avoid or mitigate the loss of cerebral autoregulation and the associated hypertensive encephalopathy and (ii) to avoid or treat associated left ventricular failure, aortic dissection, and strokes, without compromising cerebral perfusion or jeopardizing uteroplacental blood flow that may already be reduced in eclamptics [107].

Cerebral hemorrhage accounts for 15–20 % of deaths from eclampsia and is often associated with significant elevation in blood pressure (≥160/110) [1]. Current recommendations are for the use of antihypertensive therapy when there is a sustained systolic blood pressure ≥160 or diastolic blood pressure ≥105–110 mmHg [1, 49]. However, the validity of these thresholds has not been tested in prospective studies [80]. It is specifically recommended that treatment include lowering systolic pressures to ≤160 mmHg [80]. Moreover, Martin and associates provided provocative observations that highlight the importance of treating systolic hypertension [73]. They described 28 selected women with severe preeclampsia who suffered an associated stroke. Most of these were hemorrhagic (93 %), and all women had systolic blood pressure >160 mmHg. By contrast, only 20 % of these same women had diastolic pressure >110 mmHg. The goal in extremely hypertensive preeclamptic/eclamptic women is not to normalize BP but through a stable and progressive process that involves no more than a 15–20 % incremental decrease in mean arterial pressure, to ultimately achieve a systolic pressure in the range of 140–150 and diastolic pressure in the range of 90–100 mmHg. This is done to prevent prolonged exposure of the patient to severe systolic hypertension, which is hypothesized to cause loss of cerebral vascular autoregulation. When present, severe range hypertension and maternal stabilization should occur before delivery, even in urgent circumstances [67].

There are several drugs available for the rapid lowering of dangerously elevated blood pressure in women with preeclampsia or eclampsia. Although many different antihypertensive agents are available, we will confine our discussion to those agents most commonly used for acute hypertensive crises in pregnancy (Table 7.7). The three most commonly employed in North America and Europe is labetalol, hydralazine, and nifedipine. For many years, parental hydralazine was the only one of the three available in the United States. When parenteral labetalol was introduced, it was considered by most to be equally effective for obstetrical use, and most governing bodies in our specialty recommended both hydralazine and labetalol as first-line agents. Orally administered nifedipine has now become available, and this has gained popularity as first-line treatment for sever hypertension [114].

7.8.3.1 Hydralazine

Hydralazine has long been the gold standard of antihypertensive therapy for the use by obstetricians in the United States. Hydralazine reduces vascular resistance via directly relaxing arteriolar smooth muscle (believed to be mediated by nitric oxide release), affecting precapillary resistance vessels more than postcapillary capacitance vessels [52]. The administration of hydralazine may result in maternal hypotension and fetal compromise because of shunting of blood away from placenta [108]. For this reason, hydralazine is administered with a 5–10-mg initial dose IV over 2 min, and this is followed by 5–10-mg doses at 20 min intervals until a satisfactory response is achieved [31]. The maximum dose is generally accepted to be 20–30 mg. Hypertension refractory to the preceding approach warrants the use of alternative antihypertensive agents. As with any hypertensive agent, the tendency to give larger initial dose of hydralazine when the blood pressure is higher must be avoided. The response to even 5–10-mg doses cannot be predicted by the level of hypertension. Thus the initial dose of hydralazine should not exceed 10 mg.

Table 7.7 Pharmacologic agents for antihypertensive therapy in preeclampsia-eclampsia

Antihypertensive	Mechanism of action	Dosage	Comment
Hydralazine	Arterial vasodilator	5 mg IV, then 5–10 mg IV/20 min up to total dose of 20 mg; titrated IV infusion 5–10 mg/h	Must wait 20 min for response betweenIV doses; possible maternal hypotension
Labetalol	Selective α- andnonselective β-antagonist	20 mg IV, then 40–80 mg IV/10 min to 220 mg total dose; titrated IV infusion 1–2 mg/min	Less reflex tachycardia and hypotensionthan with hydralazine
Nifedipine	Calcium channelblocker	10 mg PO, may repeat after 20 min oral route only	Possible exaggerated effectif used with $MgSO_4$
Nitroglycerine	Relaxation of venous (and arterial) vascular smooth muscle	5 μg/min infusion; doubleevery 5 min	Requires arterial line for continuous blood pressure monitoring; potential methemoglobinemia
Sodium nitroprusside	Vasodilator	0.25 μg/kg/min infusion; increase by 0.25 μg/kg/min every 5 min	Requires arterial line for continuous blood pressure monitoring; potential cyanide toxicity

7.8.3.2 Labetalol

Another effective antihypertensive agent commonly used is intravenous labetalol – an α_1- and nonselective β-blocker. It causes rapid decrease in BP via decreased SVR in patients with severe hypertension [64]. Reports on the efficacy and safety of labetalol in the treatment of hypertension during pregnancy have been favorable [30, 65, 76]. Mabie et al. [68] compared bolus intravenous labetalol with intravenous hydralazine in the acute treatment of severe hypertension. They found that labetalol had a quicker onset of action and did not result in reflex tachycardia. Belfort et al. conducted a study in eight patients and demonstrated that labetalol reduced the cerebral perfusion pressure as well as the systolic, diastolic, and mean blood pressure significantly at 60–180 min without significantly affecting the heart rate and middle cerebral artery velocities [13] (Fig. 7.12). The recommended dose is 20 mg intravenously initially over 2 min. If the blood pressure has not decreased to the desirable level in 10 min, then 40 mg is given. In the event of inadequate response over the next 10 min, a dose of 80 mg is given which can be followed by a second 80-mg dose if needed. The recommended maximum dose is 220 mg per treatment cycle [31, 107]. Parenteral labetalol may cause neonatal bradycardia and should be avoided in women with asthma, heart disease, or congestive heart failure [31].

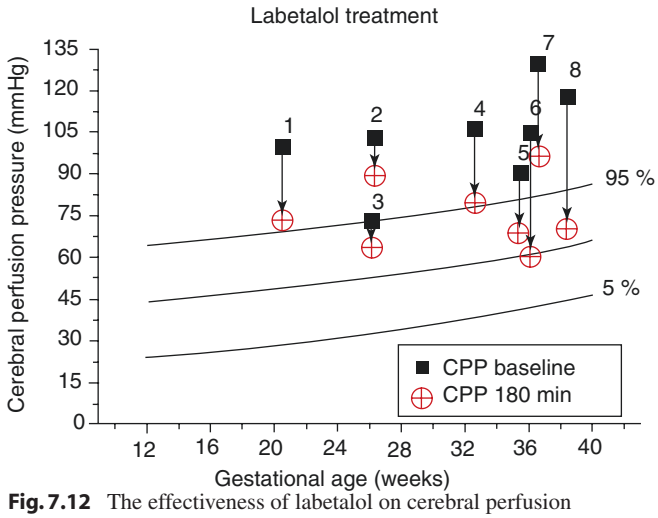

Fig. 7.12 The effectiveness of labetalol on cerebral perfusion pressure (Reproduced from Belfort et al. [13])

7.8.3.3 Nifedipine

Calcium channel blockers such as nifedipine lower BP primarily by relaxing arterial smooth muscle. Nifedipine has become popular because of its efficacy for control of acute pregnancy-related hypertension. Both the NHBPEP Working Group in 2000 and the Royal College of Obstetricians and Gynecologists recommended a 10-mg initial oral dose to be repeated in 30 min if necessary [80, 87]. The American Congress of Obstetricians and Gynecologists has also recommended 10-mg nifedipine orally as initial dose and has further recommended that if the blood pressure does not decrease after 20 min, a 20-mg dose orally be given followed by another 20 mg in 20 min if blood pressure does not decrease in the desired range [31]. Randomized trials that have compared nifedipine with labetalol found neither drug definitely superior to the other [114]. In a recent randomized control trial by Raheem et al. [85], patients with severe hypertension were randomized to receive nifedipine (10 mg tablet, orally, up to five doses) and intravenous placebo saline injection or intravenous labetalol injection (in an escalating dose regimen of 20, 40, 80, 80, and 80 mg) and a placebo tablet every 15 min until the target blood pressure of ≤150/100 mmHg was achieved. They found the oral nifedipine and intravenous labetalol regimens to be similarly effective in the acute control of severe hypertension in pregnancy [85]. In another study conducted by Rezaie et al. [86], IV

hydralazine was compared with oral nifedipine and found to have the same efficacy in reducing severe hypertension in pregnancy.

Nifedipine has been associated with an increase in maternal heart rate and with overshoot hypotension [114]. Concern for neuromuscular blockade and severe hypotension with the contemporaneous use of nifedipine and magnesium sulfate has not been substantiated in a large retrospective review. However, because both drugs are calcium antagonists, careful monitoring is advisable [70].

7.8.3.4 Nitroglycerine and Nitroprusside

Nitroglycerine predominantly relaxes the venous compartment but also has vasodilatory effects on arterial vascular smooth muscle, leading to decrease preload at low doses and afterload at high doses [45]. Nitroprusside causes arterial and venous relaxation by impedance of influx and intracellular release of calcium. Both sodium nitroprusside (initial rate 0.25 mcg/kg/min to a maximum dose of 5 mcg/kg/min) and nitroglycerine (initial IV infusion rate of 5 mcg/min, titrated to effect every 3–5 min to a maximum dose of 100 mcg/min) administration have been used in the management of hypertensive crisis [1]. Each of these drugs because of their specific mechanism of action actually has a preferential clinical application. Thus, given the preferential action of nitroglycerin as a venodilator, it is the agent of choice in preeclampsia associated with pulmonary edema and for control of hypertension associated with tracheal manipulation. Potential adverse effects include headache, tachycardia, and methemoglobinemia. Due to its ability to increase cerebral blood flow and intracranial pressure, it is contraindicated in hypertensive encephalopathy [1]. Sodium nitroprusside is the agent of choice in hypertensive encephalopathy and should be reserved for extreme emergencies [1]. It should be used for the shortest amount of time possible because of concerns about cyanide and thiocyanate toxicity in the mother and fetus/newborn and because it has the potential to increase intracranial pressure with potential worsening of cerebral edema in the mother. Once the hypertensive emergency is treated, a complete and detailed evaluation of maternal and fetal well-being is needed with consideration of, among many issues, the need for subsequent pharmacotherapy and the appropriate timing of delivery [79].

7.8.3.5 Diuretics

Potent diuresis can further compromise placental perfusion. Immediate effects include depletion of intravascular volume, which most often is already reduced in preeclamptic when compared with that of normal pregnancy. Therefore, before delivery, diuretics are not generally used to lower blood pressure [121]. Diuretics use is usually limited to those cases in which there is concomitant pulmonary edema or evidence of significant volume overload [107].

7.8.4 Management of Complications

Once the emergency issues related to seizures have been managed, it is essential to rule out the presence of associated complications of severe preeclampsia/eclampsia, such as disseminated intravascular coagulopathy (DIC) and pulmonary edema. Specific details regarding the management of DIC and pulmonary edema are beyond the scope of this discussion and are dealt with elsewhere in this text. Aspiration of gastric contents should always be excluded after seizures in a pregnant or recently pregnant woman, and any features of pulmonary edema should be followed up with a thorough cardiac evaluation including an ECG and echocardiogram if available to exclude underlying hypertensive cardiomyopathy, ischemic damage, dysrhythmia, and previously undetected valvular disease [107].

7.9 Consideration Regarding Delivery

7.9.1 Intrapartum Management

After stabilization and control of severe hypertension under most circumstances, induction/delivery will be recommended. However, this does not mean emergent cesarean section [1, 49, 107]. In rare cases of extreme prematurity with stable fetal condition, and there have been complete maternal neurologic recovery and blood pressure stabilization, and it may be appropriate to delay delivery for the administration of steroids. These rare cases must be individually managed with the full informed consent of the patient.

Maternal hypoxemia and hypercapnia cause fetal heart rate and uterine activity changes during and immediately after convulsion. The fetal heart rate tracing may reveal bradycardia, transient late decelerations, decreased variability, and compensatory tachycardia. Uterine contraction can increase in frequency and tone [105, 107]. These changes usually resolve spontaneously within 3–10 min after the termination of convulsions and the correction of maternal hypoxemia. With these FHR changes, the patient should not be rushed to emergency cesarean delivery if the maternal condition remains stable. However, if the bradycardia and/or recurrent late decelerations persist beyond 10–15 min despite all resuscitative efforts, then a diagnosis of placenta abruption or non-reassuring fetal status should be considered. Fetal outcome is generally good after an eclamptic convulsion [105, 107]. The mechanism for the transitory fetal bradycardia may be a decrease in uterine blood flow caused by intense vasospasm and uterine hyperactivity [105, 107]. Also hypoxemia caused by hypoventilation and absence of maternal respiration during convulsion may also result in fetal hypoxia and heart rate changes [105, 107].

The decision to perform cesarean section should be based upon fetal and maternal parameters. Expert opinion (level III evidence) favors cesarean delivery for those with eclampsia before 30 weeks of gestation, who are not in labor and whose Bishop score is below 5 [105, 107]. The same experts advise that patients in labor or those who have ruptured their membranes should be allowed to attempt vaginal delivery in the absence of obstetric complications [1, 105, 107]. When indicated, labor is initiated either with prostaglandins or oxytocin in patients at >30 weeks of gestation, irrespective of Bishop score. A similar approach is used for those before 30 weeks of gestation if the cervical Bishop score is at least 5 [105, 107].

7.9.2 Fluid Therapy

Fluid therapy in women who have had seizures should be individualized according to the specific situation. In general, these patients are at risk for pulmonary edema because of capillary permeability, and fluid restriction is initially reasonable [118]. Lactated ringer solution can be administered at a rate of 60–125 mL per hour unless there is unusual fluid loss from vomiting, diarrhea, and diaphoresis or excessive blood loss with delivery in which cases blood products are indicated [118]. Renal failure and oliguria may complicate eclampsia, and prior to any large volume IV infusions, it is important to determine renal status. Given that eclamptics frequently have significant extravascular extravasation of intracellular fluid which appreciably increases their risk of pulmonary and cerebral edema [93, 95], a thoughtful approach to fluid replacement is needed even in those emergency situations where blood products have to be given for life-threatening hemorrhage.

7.9.3 Invasive Monitoring

Much of the knowledge of cardiovascular and hemodynamic alteration associated with preeclampsia-eclampsia has come from studies performed using invasive monitoring and a flow-directed pulmonary artery catheter [4, 26, 27, 32, 35, 36]. There is however no evidence that the use of invasive hemodynamic monitoring is either indicated or helpful under most circumstances. The American Congress of Obstetricians and Gynecologists recommends that such monitoring be reserved for severely preeclamptic women with accompanying cardiac disease, renal disease, or both or for cases of refractory hypertension, oliguria, and pulmonary edema [4].

7.9.4 Analgesia and Anesthesia

There is no contraindication to the use of epidural anesthesia in patients with preeclampsia with severe features or in patients with eclampsia [103]. The development of techniques that use slow induction of epidural analgesia with dilute solutions of anesthetic agents has now decreased the need for rapid infusions of large volumes of crystalloid or colloid to correct maternal hypotension which has decreased the risk of pulmonary complications [48, 115]. Moreover, epidural blockade avoids the need for tracheal intubation, which can cause significant stimulation of the sympathetic nervous system and sudden worsening of already severe hypertension. Sudden massive increases in blood pressure can cause pulmonary edema, cerebral edema, or intracranial hemorrhage [54]. Finally tracheal intubation may be difficult and thus hazardous in women with airway edema due to preeclampsia or eclampsia [4]. Women with airway or laryngeal edema may require awake intubation using a flexible fiberoptic laryngoscope with the availability for immediate tracheostomy [105]. Changes in systemic or cerebral pressure may be attenuated by pretreatment with labetalol or nitroglycerine [105].

Epidural, spinal, or combined techniques of regional anesthesia are generally thought to be safe for cesarean delivery in preeclamptic and/or recently eclamptic patients as long as there is no coagulopathy or severe thrombocytopenia (platelet count <50,000/mm^3) [105].

7.10 Postpartum Management

After delivery, patients with eclampsia should receive close monitoring of vital signs, hematologic and biochemical parameters, urine output, fluid intake, and symptoms for at least 48 h [104]. These women usually receive large amount of intravenous fluid intrapartum and postpartum. During the postpartum period, there is mobilization of extracellular fluid leading to increased intravascular volume. As a result, women with eclampsia, particularly those with any renal function abnormality, those who have received significant blood component transfusion, and those with preexisting chronic hypertension, are at risk to develop pulmonary edema and exacerbation/recurrence of their severe hypertension [74, 100, 105].

It is recommended that parenteral magnesium sulfate be continued for at least 24 h after delivery or 24 h after the convulsion, although data in support of this recommendation are few. If the patient has oliguria (less than 100 cc urine in 4 h), both the rate of fluid administration and the dosage of magnesium sulfate should be reduced [105, 107]. Once delivery has occurred, the oral antihypertensive agents such as nifedipine, labetalol, or even angiotensin inhibitors (ACE inhibitors) can be used to keep systolic blood pressure below 160 mmHg and diastolic less than 110 mmHg. The recommended dose of oral labetalol is 200 mg every 8 h (maximum dose of 2,400 mg/day) and the recommended dose for

nifedipine 10 mg every 6 h (maximum dose of 120 mg/day) [8]. There is no randomized trial to compare the efficacy of labetalol and nifedipine in postpartum period. There are few data supporting the use of ACE inhibitors in postpartum women [109], and this is an area that deserves exploration given the importance of the renin-angiotensin (RA) axis in preeclampsia.

7.11 Subsequent Pregnancy Outcome

Pregnancy complicated by eclampsia may be associated with life-threatening complications for both mother and infant. Women with a history of eclampsia are at increased risk of all form of preeclampsia in subsequent pregnancies [2, 19, 60]. In general the risk of preeclampsia in the subsequent pregnancy is approximately 25 %, with the rate higher if eclampsia occurs before 32 weeks [15, 101, 107]. The risk of recurrent eclampsia in future pregnancy is approximately 2 % [15].

In recent years, observational studies have consistently shown that preeclampsia/eclampsia carries an increased risk for the mother to develop cardiovascular and renal disease later in life. Women with a history of preeclampsia experience a twofold increased risk of long-term cardiovascular disease (CVD) and an approximate five- to 12-fold increased risk of end-stage renal disease (ESRD) [66, 77, 82, 83]. Recognition of preeclampsia/eclampsia as a risk factor for renal disease and CVD allows identification of a young population of women at high risk of developing cardiovascular and renal disease. For this reason, it is recommended for cardiovascular screening and treatment in formerly preeclamptic women. However, these recommendations are based on low levels of evidence due to a lack of studies on screening and prevention in formerly preeclamptic women [83].

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Anomalies of the Umbilical Cord

8

Salvatore Andrea Mastrolia, Matteo Loverro, and Giuseppe Loverro

8.1 The Maternal–Fetal Connection

Every human being has a sign on his body, more precisely on the abdomen. It is the umbilicus, a scar that represents the only visible memory of our close connection with our mother before birth. This is the site of attachment of the umbilical cord to the abdominal wall during antenatal life. Along with the placenta, the umbilical cord plays a crucial role in fetal health and development, providing a communication between the placenta and the fetus and allowing gas and nutrient exchange (Fig. 8.1).

Although it is one of the most intriguing of the human organs, the umbilical cord is also one of the least investigated [1], mainly because of the changes in cord structure occurring after birth and the difficulty to study such an organ by ultrasound (Fig. 8.2) during pregnancy, which has the burden of being highly operator dependent. This is a severe limit in obstetrics since several obstetrical syndromes, including intrauterine growth restriction (IUGR), stillbirth, and preeclampsia, have been associated to cord anomalies [2].

8.1.1 Normal Anatomy of the Umbilical Cord

A normal umbilical cord is made of two arteries and one vein and is included within a homogeneous substance called Wharton's jelly, which is a myxomatous connective tissue that varies in size and may be imaged with high-frequency ultrasound transducers [3] (Fig. 8.3).

The cord is covered by the amniotic membranes (Fig. 8.4), and its diameter usually measures between 1 and 2 cm at term (variations in cord diameter are usually attributed to Wharton's jelly volume, but might also be dependent on the caliber of the vessels), while it has an average length of 55–61 cm at term. Such a length is sufficient to allow a vaginal delivery to be accomplished in the presence of a fundal implantation of the placenta [4].

The umbilical cord develops throughout gestation, although its growth becomes slower after 28 weeks. At 6 weeks postconception, the cord has a mean length of about 0.5 cm (Fig. 8.5); by the fourth month, it averages between 16 and 18 cm (Fig. 8.6); and at the sixth month of gestation, it reaches a length of 33–35 cm [5] (Fig. 8.7).

Standard curves for cord length have been provided from 34 to 43 weeks gestation [4].

The umbilical arteries arise from the fetal internal iliac arteries, course alongside the fetal bladder, and exit the umbilicus to form part of the umbilical cord. The paired umbilical arteries surround the umbilical vein with a helicoidal pattern for the entire length of the cord completing 10–11 coils between the fetal and placental insertion sites [3], and then they branch along the chorionic plate of the placenta.

The umbilical vein is the result of the confluence of the chorionic veins of the placenta. Its primary goal is the transport of oxygenated blood to the fetus. It enters the umbilicus and joins the left portal vein as it courses through the liver. The umbilical vein also presents a connection with the inferior vena cava that is provided through the ductus venosus, that shunts a third of the oxygenated blood directly toward the heart instead of entering the liver circulation [6]. The intra-abdominal portions of the umbilical vessels degenerate after birth; the umbilical arteries become the lateral ligaments of the bladder, while the umbilical vein regresses to be the round ligament of the liver [6].

The umbilical cord is usually twisted or coiled counterclockwise, to the left, with a left-to-right ratio of about 7:1 [5]. The average number of coils in the entire length of cord is about 40, with approximately 0.2 coils per 1 cm of cord. The latter is referred to as the coiling index [7]. Coiling is established early in gestation and can be seen by sonography as early as the ninth week. The origin of umbilical cord coiling has long been debated, but some data suggest that it is due, at least in part, to fetal movements.

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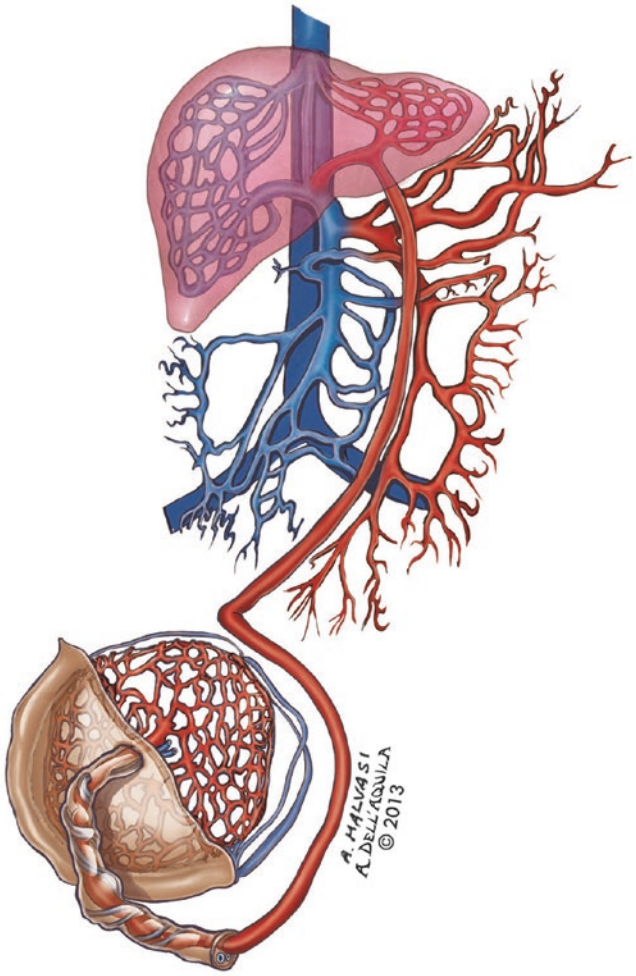

Fig. 8.1 The maternal–fetal vascular system

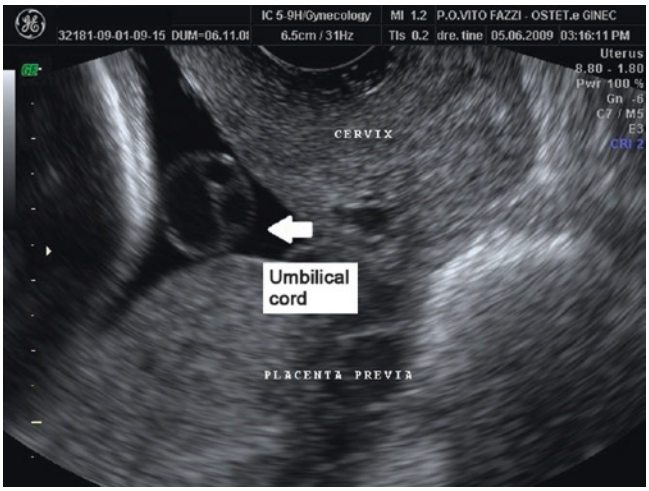

Fig. 8.3 Transvaginal ultrasonographic scan showing an umbilical cord section, in a patient at 28 weeks of pregnancy with placenta previa

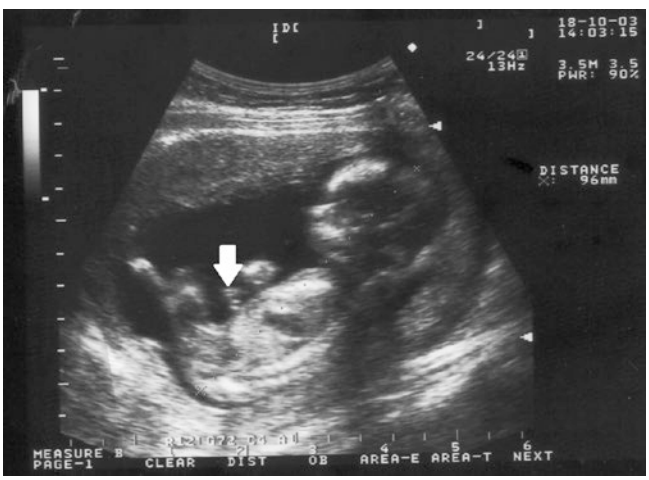

Fig. 8.2 A transabdominal ultrasonographic scan showing, with the *white arrow*, the umbilical cord emerging from the fetus at 14 weeks of pregnancy

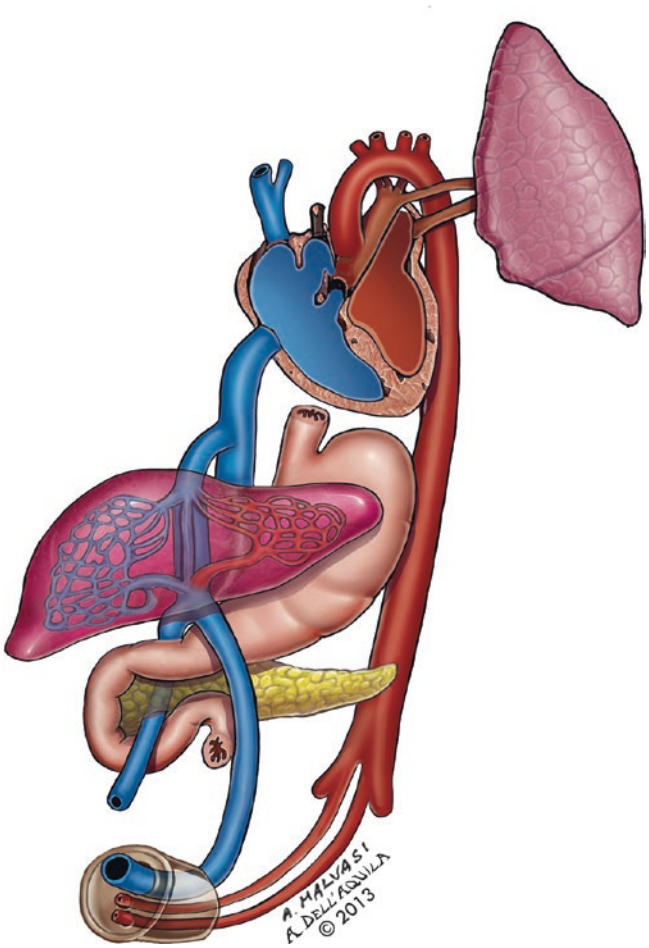

Fig. 8.4 The umbilical cord anatomy (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

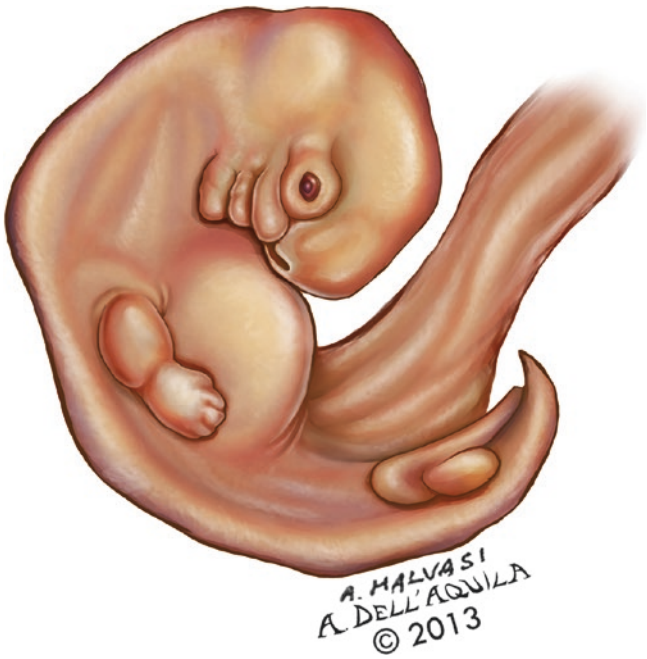

Fig. 8.5 An embryo with the umbilical cord at 6 weeks of pregnancy

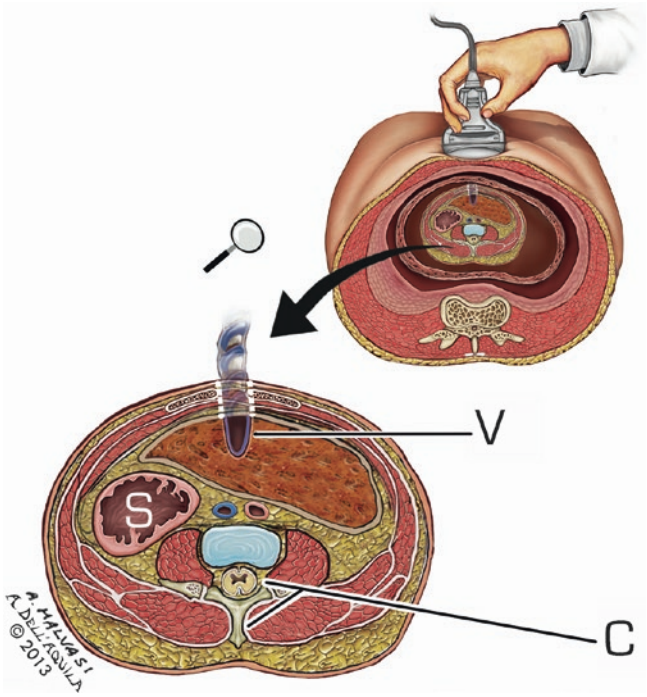

Fig. 8.6 A cross-scan representation of the fetus at 20 weeks of pregnancy, at inset source level of the cord in the fetus (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

8.1.2 Embryology of the Umbilical Cord

The umbilical cord forms during the first 5 weeks of gestation (7 menstrual weeks) as a fusion of the omphalomesenteric yolk stalk and allantoic ducts. An outpouching from the urinary bladder forms the urachus, which projects into the connecting stalk to form the allantois. The allantoic vessels become the definitive umbilical vessels. The umbilical cord acquires its epithelial lining after the enlargement of the amniotic cavity and envelopment of the cord by the amniotic membrane. The intestines grow at a faster rate than the abdomen; they herniate into the proximal umbilical cord at approximately 7 weeks and remain there until approximately 10 weeks. The insertion of the umbilical cord into the ventral abdominal wall is an important sonographic anatomic landmark because the evaluation of this area will reveal abdominal wall defects, such as omphalocele, gastroschisis, or limb–body wall complex [8].

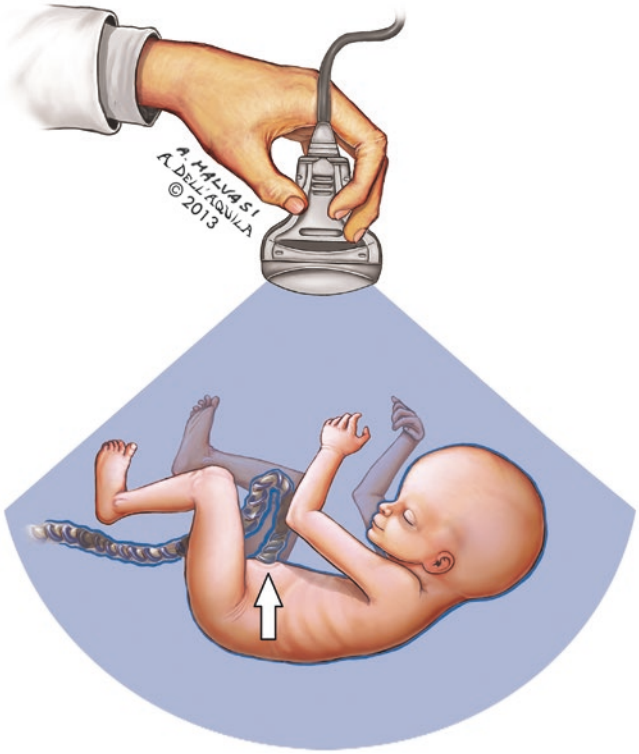

Fig. 8.7 A representation of a fetus at 24 weeks with the complete development of the umbilical cord

8.2 Type of Cord Anomalies

There are several abnormalities that can be recognized in the umbilical cord and may affect pregnancy outcome and especially neonatal outcomes. They can be identified and classified as follows: (1) structural or morphologic anomalies, meaning that either the cord does not have its typical three-vessel structure or that it shows some alterations deviating from the normal anatomy described above; (2) anomalies leading to cord compression within a condition of normal structure, which is the largest group; and (3) conditions of

Table 8.1 Classification of cord anomalies

Class of anomaly	List of anomalies included in the class
Structural or morphologic anomalies	Single umbilical artery
	Persistent right umbilical vein
	Marginal or velamentous insertion of the umbilical vessels
	Vasa previa
	Furcate cord insertion
	Cord varix
	Cysts of the umbilical cord
	Aneurysms and hemangiomas of the umbilical cord
	Abnormal coiling
	Anomalies of cord diameter or length
Anomalies leading to cord compression	Cord entanglements
	Knots of the umbilical cord
	Cord prolapse
Conditions of histological cord pathology	Funisitis (FIRS)
	Meconium-associated damage of the umbilical cord

histological cord pathology, with a normal structure and morphology, which includes obstetrical emergencies involving the umbilical cord during or before labor.

Table 8.1 summarizes the above mentioned classes of cord anomalies, but the reader might take into account that an overlapping of different classes of anomalies is always possible, since the division into groups is only an attempt to provide a clearer description of such a challenging subject. It is indeed absolutely possible that an umbilical cord with an abnormal structure or morphology becomes affected because of compression, or that it acquires histologic changes due to an additional pathologic event.

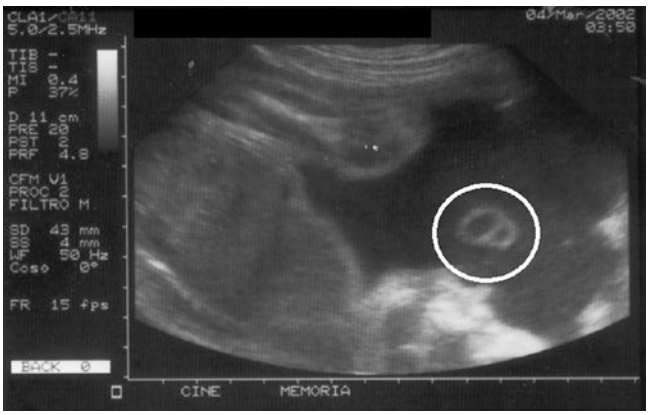

Fig. 8.8 Section of a two-vessel cord

8.3 Structural or Morphologic Anomalies of the Umbilical Cord

8.3.1 Single Umbilical Artery

Single umbilical artery (SUA) refers to a variation of the umbilical cord that presents only one artery instead of the normal number of two (Fig. 8.8). This condition has a reported incidence of 0.2–2 % of pregnancies [9] and is shown to be associated with several fetal structural and chromosomal abnormalities (including cardiac, gastrointestinal, and renal anomalies) leading to fetal and neonatal complications [10].

Thus, the American Institute of Ultrasound in Medicine recommends imaging of the umbilical cord including the number of vessels in the cord during routine prenatal ultrasound examinations and, if a SUA is identified, a targeted ultrasound is warranted to rule out known associated anomalies [11]. In the majority of cases, SUA is an isolated finding with no other apparent abnormality on ultrasound [12–14].

Much of the research conducted on isolated SUA focused on fetal growth. Many studies [9, 10, 15–22] have shown that isolated SUA is associated with fetal growth restriction and SGA infants although other studies [23–26] and a meta-analysis on this topic refuted this claim [27].

Several studies evaluating the significance of isolated SUA revealed associations with preterm delivery [9, 10, 15, 16] and suggested isolated SUA to be an independent risk factor for perinatal mortality [18], although others failed to establish such associations [23, 27, 28] and, therefore, the meaning of this finding is controversial. Recent studies found an increased rate of cesarean deliveries (mainly due to non-reassuring fetal heart rate patterns) and lower umbilical cord blood pH [17] for these fetuses.

With regard to perinatal mortality, data is again inconclusive. The same meta-analysis mentioned above [27] concluded that there was a trend toward higher rates of perinatal mortality in isolated SUA pregnancies, but this did not reach statistical significance.

The contradictory results regarding the relationship between isolated SUA and perinatal outcomes may be explained by the fact that studies in which increased perinatal mortality [10, 16, 18] was demonstrated included in their analysis fetuses with growth restriction or premature deliveries (before 37 weeks), while studies which found no increased risk of perinatal mortality [9, 17, 29] had smaller sample sizes or were conducted only for live-born infants [30].

To overcome this, in a recent report, Gutvirtz et al. [31] evaluated perinatal outcomes of fetuses with isolated SUA and no other risk factors for perinatal complications. They excluded other well-established risk factors for perinatal mortality (multiple gestations, structural and chromosomal abnormalities, prematurity, and growth-restricted fetuses) and controlled for possible confounders (placental abruption, birth weight, gestational age) in an effort to isolate any independent association of this finding with adverse perinatal outcomes.

The cohort studied by this group is the largest reported in the literature with 786 cases of isolated SUA, all reaching 37 weeks of gestation. These authors have demonstrated that isolated SUA at term carries a significant risk of adverse perinatal outcome and increased perinatal mortality [31].

The reason why isolated SUA may lead to adverse perinatal outcomes remains unclear. One possible explanation of the increased rates of perinatal mortality in an otherwise healthy term fetus relates to some structural deviations which may, hypothetically, increase the risk of a cord accident. Lacro et al. [32] found an increased incidence of absent umbilical cord twist in SUA cords, while Raio et al. [33] observed a reduction of Wharton's jelly volume in these cords, and both groups showed an association with an increased incidence of stillbirth.

Currently, isolated SUA is not considered an indication for labor induction according to commonly used formal guidelines. However, due to the available literature, fetuses with isolated SUA should undergo closer monitoring of their well-being in order to prevent possible pregnancy complications and poor outcomes associated with this anomaly.

8.3.2 Persistent Right Umbilical Vein

Persistent right umbilical vein is the consequence of an altered development of the umbilical cord between fourth and seventh weeks of gestation when the left umbilical vein regresses but the right umbilical vein remains patent. This results in an abnormal blood flow in the fetal liver [34]. This anomaly occurs in 0.1–0.3 % of pregnancies and may be isolated or associated with other anomalies, especially in fetuses with situs inversus and heterotaxy, but also with genitourinary, gastrointestinal, cardiac, and skeletal developmental disorders [35].

Several sonographic findings on standard transverse images of the fetal abdominal circumference assist in the diagnosis of persistent right umbilical vein [36]. The fetal portal vein is curved toward the stomach instead of being approximately parallel to it, the fetal gallbladder is medial to the umbilical vein instead of appearing in its normal lateral position and is seen between the umbilical vein and the stomach, and the umbilical vein is connected to the right portal vein instead of the left [34]. Color Doppler is useful to determine the specific type of this anomaly according to the path of its drainage. In the more common intrahepatic persistent right umbilical vein, the isolated right umbilical vein joins the fetal portal system at the sinus venosus and gives rise to the ductus venosus. In extrahepatic persistent right umbilical vein, the right umbilical vein bypasses the liver completely and drains directly into the right atrium, inferior vena cava, or right iliac vein, with the absence of the ductus venosus [35, 37].

8.3.3 Abnormal Insertion of the Cord Vessels

Abnormal cord insertions include conditions in which the umbilical cord does not insert on the fetal surface of the placenta at or near its center (Fig. 8.9). These conditions may be associated with abnormal fetal heart rate tracings, fetal growth restriction, low birth weight, low Apgar scores [5, 38, 39], and adverse perinatal outcome associated to complications, such as disruption, thrombosis, or compression of the abnormally inserted cord vessels.

8.3.3.1 Marginal and Velamentous Insertion of the Umbilical Cord

In about 7 % of term placentas, the cord inserts marginally, and in about 1 %, it inserts within the membranes, and this is known as velamentous insertion [5, 40]. Both marginal and

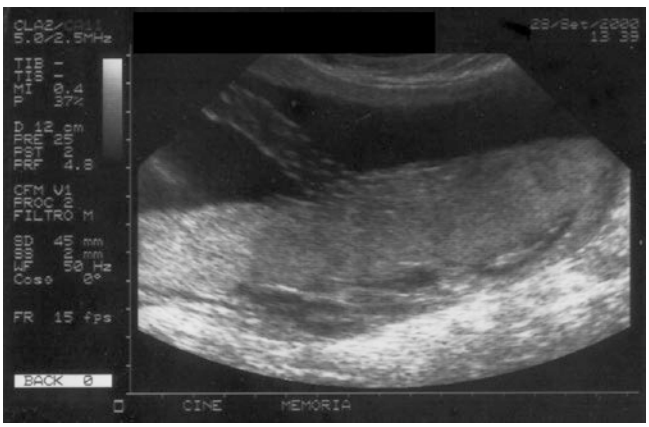

Fig. 8.9 Normal cord insertion

velamentous insertions are more common in twins [41]. Velamentous vessels run within the free membranes without the protection of Wharton's jelly and are thus susceptible to thrombosis, compression, or disruption especially after membrane rupture when the added protection afforded by the amniotic fluid is lost. A velamentous cord may insert within a few centimeters of the placental margin or far away from it. Close insertion is much more common, representing a less severe condition.

Thrombosis of velamentous vessels has been associated with neonatal purpura and fetal death [41].

8.3.3.2 Vasa Previa

Velamentous vessels may cross the cervical os, preceding the presenting fetal part, determining a condition called vasa previa (Fig. 8.10). These vessels may be disrupted if a vaginal delivery is attempted. Hemorrhage from ruptured velamentous vessels is uncommon, occurring in about 1 in 50 velamentous cord insertions, but if rupture does occur, the mortality rate is estimated to be from 58 to 73 % [42]. Other outcomes associated with this condition include fetal distress and hypoxia from compression of the vessels during labor, neonatal thrombocytopenia, or severe neurologic impairment [43].

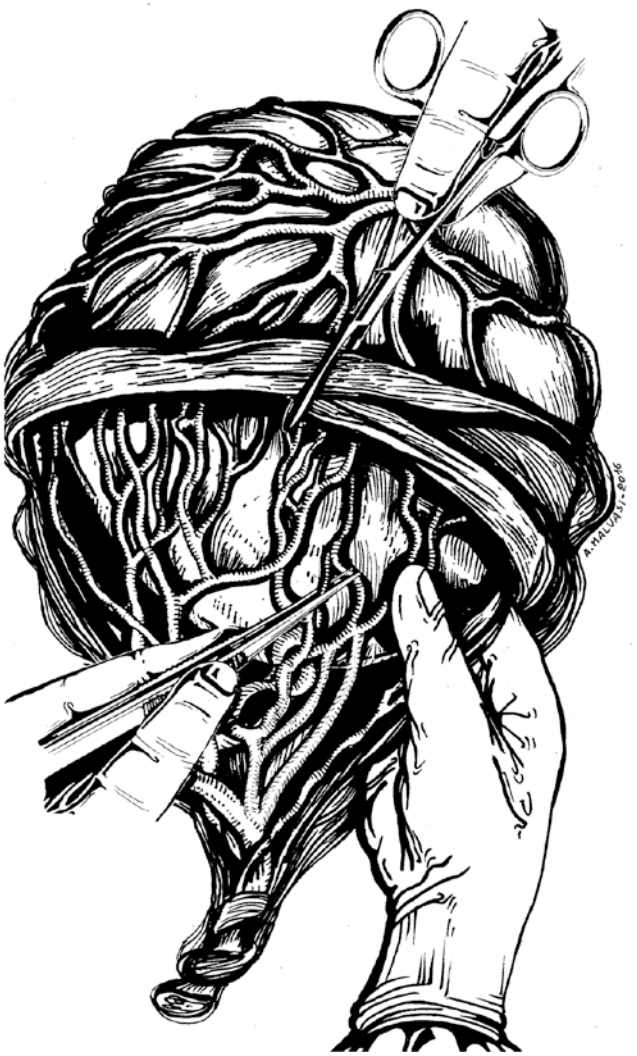

Fig. 8.10 Vasa previa characterized by velamentous vessels may cross the cervical os, preceding the presenting fetal part (the clamp highlights the blood vessels)

8.3.3.3 Furcate Cord Insertion

Furcate cord insertion is a rare abnormality in which the umbilical vessels separate from the cord substance before reaching the surface of the placenta. Like a velamentous insertion, these vessels have lost the protection afforded by Wharton's jelly and are prone to thrombosis and injury [41].

8.3.4 Cord Varix

The diameter of the normal fetal intra-abdominal umbilical vein is approximately 3 mm at 15 weeks of gestation and grows until up to 1 cm at term [44]. Cord varix is a rare condition characterized by focal dilatation of the umbilical vein that can occur in the intrahepatic portion of the vein or with an extrahepatic location [45]. It is associated with a 5.8 % risk for aneuploidy, especially trisomy 21, and a 28 % risk for other fetal anomalies such as hydrops, anemia, and IUGR [46]. The prognosis is worsened by early identification in pregnancy or association with fetal anomalies [46–48]. Although most cases have a favorable outcome, fetal death may occur in case of formation of a thrombus in the dilated segment of the vein obstructing fetal circulation or due to fetal cardiac insufficiency due to volume overload [47].

Although the definite size of cord varix is not well established, some authors consider a vein diameter abnormal if (a) >9 mm, (b) the transverse diameter of the extrahepatic umbilical vein is at least 1.5 times greater than the intrahepatic component, or (c) the vein diameter is more than two standard deviations above the mean diameter appropriate for gestational age [49]. Doppler ultrasound examination is critical in order to diagnose a cord varix. The sonographic appearance of an intra-abdominal varix is of an oblong cystic structure obliquely oriented in a craniocaudal direction between the abdominal wall and the inferior edge of the liver [46]. Weissmann-Brenner et al. [48] suggest that turbulent flow within a varix at color Doppler imaging is associated with a large varix size, premature delivery, and lower birth weights, while Cohen et al. [49] hypothesized that a linear bidirectional flow at color Doppler ultrasound imaging could be related to a tortuous intra-abdominal segment of the umbilical vein rather than to a varix.

A fetus with cord varix should be monitored with serial ultrasound examinations from diagnosis to delivery. If other fetal anomalies are detected, fetal karyotyping should be considered to diagnose or exclude aneuploidy. Fetal echocardiography is usually indicated because cord varix is associated with fetal cardiac abnormalities [50].

This condition should undergo differential diagnosis with other cystic structures that may be observed at sonographic examination of the fetal abdomen and cord, including normal fetal gallbladder and stomach; cystic masses such as a urachal, duplication, mesenteric, or omental cyst; umbilical artery aneurysm; and a cyst of the umbilical cord [47].

8.3.5 Cysts of the Umbilical Cord

Sonographic examination allows the identification of cystic lesions of the umbilical cord at various stages of gestation (Fig. 8.11). During the first trimester, the prevalence of umbilical cord cysts ranges from 0.4 to 3.4 % [51–55]. The prevalence of umbilical cord cysts in the second and third trimesters is unclear and based only on case reports or small series [56–70]. Umbilical cord cysts are usually classified as true cysts or pseudocysts. True cysts are derived from the embryological remnants of either the allantois or the omphalomesenteric duct, are typically located toward the fetal insertion of the cord, and range from 4 to 60 mm in size [71–73].

Pseudocysts are more common than true cysts and can be located anywhere along the cord; they have no epithelial lining and represent localized edema and liquefaction of Wharton's jelly [74]. To differentiate between true cysts and pseudocysts on ultrasound imaging is a challenging task. Histological confirmation of the ultrasound diagnosis has been obtained in only a minority of reported cases, which makes it difficult to define the clinical significance of different types of cord cysts.

In addition, these lesions may be multiple or single and central or located near the fetal or the placental insertion of the cord [75].

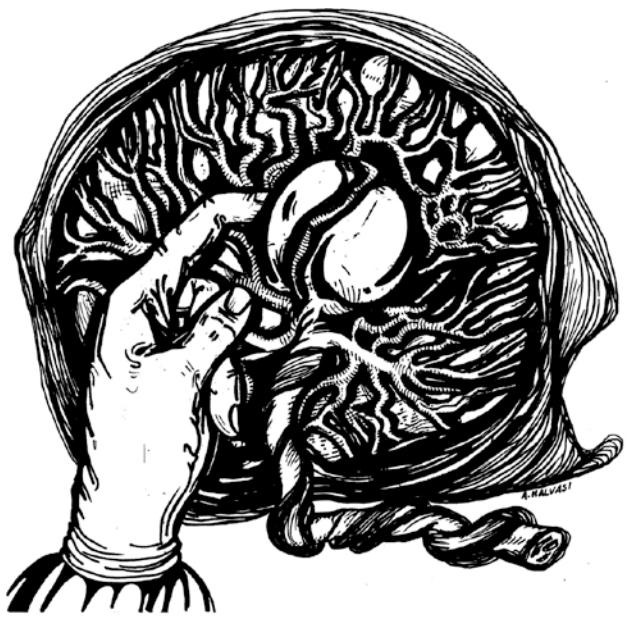

Fig. 8.11 A representation of a cyst of the umbilical cord

8.3.5.1 Outcomes and Additional Anomalies Associated with Cystic Lesions of the Umbilical Cord

The finding of an umbilical cord cyst in a pregnant woman raises some main questions: what is the perinatal outcome of those fetuses with a diagnosis of cord cyst? Is there any association with chromosomal disorders and additional fetal structural defects?

As stated above, there is a paucity of data regarding affected pregnancies, so the answer to these questions remains unclear. However, the literature shows that the majority of first trimester cysts are transient findings that have no adverse effect on pregnancy outcome [51, 52, 54], while a diagnosis of second or third trimester cysts of the umbilical cord may be associated with fetal anomalies. This is described in the reports by Smith et al. and Sepulveda et al. who found that fetal anomalies were associated with cystic lesions of the cord in 80–85 % of the cases. In the study of Ross et al. [53], 100 % correlation was reported between persistent second trimester cysts and anomalies, while Shipp et al. [68] reported fetal anomalies in 38 % of the cases.

Among the structural defects, a remarkable association exists between umbilical cord cysts and abdominal wall anomalies, including omphalocele [56, 58, 76–78] and patent urachus [57, 63, 66, 79–85]. The correct diagnosis is crucial in these cases because the outcome of neonates with patent urachus is usually favorable after surgical closure of the defect, while omphalocele requires complicated serial abdominal wall reconstruction and is highly associated with aneuploidy.

The body of literature regarding the diagnosis of these lesions during the second and third trimester is reported herein:

1. Shipp et al. [68] were the first to present a series of 13 cases of umbilical cord cystic lesions detected during the second and third trimesters. They reported four cases of clear cysts on the umbilical cord, eight cases with complex masses, and one case with complete cystic morphology of the cord throughout its length. The postnatal outcome included eight normal neonates (of them one with omphalitis and chorioamnionitis), one case of trisomy 13, two cases of patent urachus, one case

with multiple vascular anomalies (ventricular septal defect, superior vena cava and innominate vein varicosity, and asymmetric venous dilatation of the left side of the body), and one case with a small umbilical hernia and IUGR, in which the cord pathology revealed multiple syncytial knots adjacent to a complex cyst of the cord. Overall, 12 of the 13 newborns survived and the vast majority had a favorable outcome.

2. Different results are reported by Sepulveda et al. [58] on 13 fetuses with umbilical cord cysts detected during the second and third trimesters of pregnancy but with additional sonographic findings diagnosed in 11 cases. A prenatal karyotype testing was performed in ten of these fetuses, detecting aneuploidy in seven of them. In the three cases with normal karyotype, multiple anomalies were found in two fetuses and isolated omphalocele in one fetus. In a further case with isolated omphalocele, karyotyping was not performed. All chromosomally abnormal fetuses and two chromosomally normal fetuses with associated multiple structural defects died in utero or after birth. There were no perinatal complications in the fetuses with isolated cysts and normal karyotype. Fetuses with omphalocele were born without other defects, and the omphalocele was repaired. In all cases of chromosomal abnormalities, there were additional anomalies detected by ultrasound scans.
3. Smith et al. [56] reported the outcome of three cases with umbilical cord cysts. One, in which a transient cyst was detected at the end of the first trimester, had a normal outcome, and two, in which the cyst was detected at 23 and 39 weeks of gestation, were diagnosed as having trisomy 18. They reviewed the literature and summarized the outcome of their two, and another 21 cases of persistent second and third trimester umbilical cord cystic masses reported in the literature between 1982 and 1996. Nineteen of these cases were associated with either aneuploidy or congenital anomalies. Karyotype testing was performed in 15 cases and found to be abnormal in 13, including 11 with trisomy 18 and two with trisomy 13. A VATER syndrome was diagnosed in one of the cases with a normal karyotype. Among the 19 cases with anomalies, omphalocele was diagnosed in eight, and in two cases it was the only anomaly (and successfully repaired). Only four of the 23 reported cases had a normal fetal outcome. In two cases umbilical cord cyst was the only finding besides IUGR.
4. Ten cases of umbilical cord cysts of the second or third trimester are presented by Zangen et al. [75] In seven of them, the umbilical cord cyst was the only abnormal finding, and in one case the additional findings were polyhydramnios and suspected IUGR without structural anomalies, despite very careful anatomical screening. In all of these cases, normal neonates were born.

Sepulveda et al. [58] showed a correlation between small multiple cysts and aneuploidy, and Ross et al. [53] showed that the risk of fetal anomalies is increased in the presence of cysts located at the fetal or placental insertions. Yet, from this small cohort of cases, it is difficult, if not impossible, to establish a correlation between the appearance of the cyst and the prognosis.

In conclusion, given the apparent association with lethal chromosomal aneuploidy and/or congenital anomalies, the finding of an isolated umbilical cord cystic mass should lead to further detailed sonographic evaluation in a tertiary center. When either IUGR or other anomalies are found, karyotype testing should be recommended.

8.3.6 Aneurysms and Hemangiomas of the Umbilical Cord

Aneurysms of the umbilical vessels, usually the vein, are described. Elastic stains have shown that the elastic fibers of such veins are focally deficient. Aneurysmal dilatations of umbilical vessels may compress the other vessels or cause a cord rupture or hematoma. Fetal death, neurologic impairment [86–88], and fetal growth restriction have been described as associated with these complications. In addition, aneurysms have been associated with abnormal cord insertion, single umbilical artery, and other miscellaneous placental anomalies [5].

Hemangiomas appear histologically similar to those described elsewhere in the body, and those developing within the cord may coexist with similar lesions in the fetus [89]. They are more common at the placental insertion of the cord, arising from one or more umbilical vessels [90]. Prenatal diagnosis may sometimes be performed by sonographic evaluation. These tumors are never malignant, but fetal death is frequent if the tumor is large [41].

The adverse outcomes are mostly dependent on rupture and secondary hemorrhage or formation of a hematoma. Hemangiomas up to 18 cm in length, 14 cm in diameter, and weighing up to 900 g have been described [5]. In some of them, myxoma-like Wharton's jelly is present within the tumor [86], and in these cases, the tumor is designated as angiomyxoma. Unlike chorioangiomas within the placental parenchyma, angiomas of the cord are usually not associated with hydramnios or hydrops. Of interest, elevation in maternal serum alpha-fetoprotein may be observed.

8.3.7 Abnormal Cord Coiling

Since the origin of umbilical cord coiling (Fig. 8.12) is suggested to be, at least in part, the result of fetal rotation and activity, the lack of coiling may partially reflect fetal

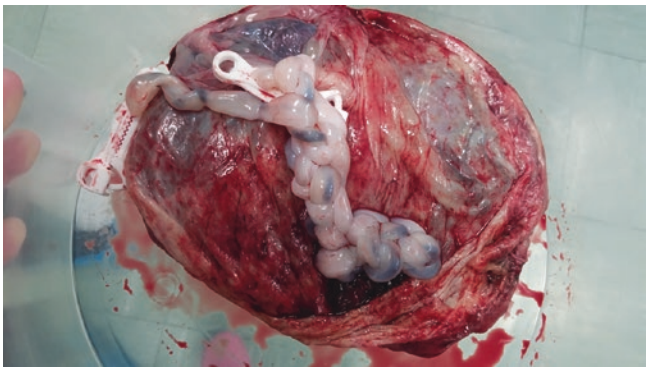

Fig. 8.12 Umbilical cord coiling, as the result of excessive fetal rotation and activity

inactivity or possible neurologic abnormalities [91], whereas marked coiling may reflect fetal hyperactivity [5]. Absent or minimal coiling is uncommon, but, when present, it may be associated with fetal distress, fetal anomalies, chromosomal errors, and increased fetal and perinatal mortality [7, 91–93]. Similarly, excessive coiling has been associated with preterm labor, fetal demise, low umbilical arterial pH, fetal asphyxia, and chronic fetal hypoxia [7, 91–93]. Excessive coiling is also seen more frequently in cords with constrictions and those of excessive length, both of which are also associated with adverse outcome [7, 94, 95]. Regardless of the etiology, excessive coiling has the potential for obstruction of blood flow through the umbilical vessels. As with other types of mechanical obstruction, the presence of associated thrombosis in the umbilical vessels and the fetal circulation may reflect lesions affecting neonatal outcome.

8.3.8 Anomalies of Cord Diameter and Length

8.3.8.1 Lean Umbilical Cord and IUGR

It has been shown that a lean umbilical cord on prenatal sonography poses a risk for small for gestational age at delivery and distress during labor [96]. Moreover, it is reported that umbilical cords of women with early onset preeclampsia and otherwise appropriate fetal growth are more likely to be lean and to have a smaller size in umbilical vein than those of women with an uneventful pregnancy course [97]. In addition, lean umbilical cords with reduced vein caliber are also described in IUGR fetuses with normal umbilical artery Doppler [98, 99].

These findings are confirmed by pathology [100], since computerized microscopic morphometric analysis showed that umbilical cords of IUGR fetuses were significantly smaller and characterized by reduced umbilical vein cross-sectional areas compared with those of healthy fetuses. Inan et al. [101] reported similar findings in umbilical cords of pregnant women with hypertensive disorders. Of interest, biochemical studies showed that, in women with preeclampsia, Wharton's jelly has a high content of sulfated glycosaminoglycans and type III collagen, whereas hyaluronic acid is reduced when compared with that of healthy women [102]. Hyaluronic acid is highly hydrophilic, and its concentration influences the amount of Wharton's jelly, and this is particularly important for the mechanical properties and macroscopic appearance of the cord and may explain, at least in part, the distress developed in some of these fetuses.

Raio et al. [103] assessed the relationship between sonographic morphometric changes of different umbilical cord components (umbilical cord cross-sectional area, vein area, artery area, and Wharton's jelly area) and umbilical artery Doppler abnormalities in IUGR fetuses. They studied 84 intrauterine growth-restricted fetuses and 168 appropriate for gestational age fetuses. All umbilical cord components were reduced in the growth-restricted fetuses. Specifically, the rate of lean umbilical cords, defined as a cross-sectional area <10th percentile for gestational age, was significantly higher in growth-restricted fetuses compared with those appropriate for gestational age (73.8 % versus 11.3 %; $P < 0.0001$). A significant and progressive reduction of the umbilical vein area corresponding to the worsening of umbilical artery Doppler abnormality was found. The umbilical artery area was not related to the hemodynamic changes of the blood flow in the umbilical arteries.

In addition, several anatomic studies investigated the umbilical cord structure in the presence of fetal IUGR [100] and hypertensive disorders [100, 101]. Bruch et al. [100] reported that umbilical cords of IUGR fetuses with normal umbilical artery Doppler parameters were characterized by a reduction of both the total vessel area and the Wharton's jelly area in comparison with healthy fetuses. When IUGR fetuses with normal umbilical artery Doppler parameters were compared to those with abnormal Doppler parameters, a further decrease of the total vessel area was observed, which was mainly due to a reduction of the vessel wall thickness. These findings are in agreement with those reported by Inan et al. [101]. However, a limitation of pathologic studies is that the umbilical cords are analyzed after fixation. Significant variations of its structure may be consequences of physiologic changes after delivery or may be due to the fixation itself [104, 105]. A possible explanation for the reduced umbilical vessel area seen in IUGR fetuses might be vasoconstriction of the umbilical vessels, mediated by an altered function of locally acting factors. Because human umbilical cord vessels are unique in lacking innervation, the action of vasoactive substances might be crucial in the control of their tone [103].

Of interest, structural changes observed in trophoblasts and blood vessels in placentas complicated by fetal growth restriction have been explained as the result of an altered

balance of vasoactive substances, which, in turn, downregulate the production of nitric oxide, a potent vasodilative agent [106–108]. Indeed, nitric oxide has been found not only within the placenta but also in the human umbilical cord vessels and, in particular, in the umbilical vein endothelial cells [109]. This may explain the histologic findings of vasoconstricted umbilical cord vessels observed in IUGR fetuses with normal umbilical artery Doppler parameters [100, 101].

8.3.8.2 Large Cross-Sectional Study of the Umbilical Cord: An Indirect Sign of Fetal Pathology?

Ultrasound examinations are commonly requested when a large fetus is suspected, and these findings are likely to influence obstetric management [110] despite recommendations against changes to medical treatment based on estimated fetal weight. Moreover, several protocols, including the ACOG guidelines [111], use estimated fetal weight as a basis for clinical decision-making, and such recommendations have become standards of care that are difficult to ignore in the current medicolegal scenario.

Unlike ultrasound measurement of conventional biometric parameters that can be technically difficult late in gestation due to the low position of the fetal head, abdominal circumference distortion, and posterior position of the femora, a successful assessment of umbilical cord area seems not to be influenced by gestational age or amniotic fluid volume [112].

Cromi et al. [112] studied consecutive patients >34 weeks' gestation, who presented for sonographic examination and delivered within 4 weeks. These authors analyzed the cross-sectional areas of the umbilical cord, umbilical vessels, and Wharton's jelly, measured in a free loop of the umbilical cord. In addition, they performed a logistic regression analysis to determine significant predictors of macrosomia (actual birth weight >4,000 and >4,500 g). Fetal biometric parameters (biparietal diameter, abdominal circumference, and femur length), sonographic estimated fetal weight, and umbilical cord area >95th percentile for gestational age were used as covariates. They found that, if a cross-sectional area of the umbilical cord >95th centile was detected at ultrasound, only 25 % of newborns actually weighed more than 4,000 g, concluding that a large cross-sectional area of the umbilical cord by itself poorly performs as a predictor of fetal macrosomia.

However, by combining this parameter with an abdominal circumference >95th percentile, 100 % of neonates predicted to be macrosomic were confirmed at birth. The new formula incorporating the umbilical cord area to predict fetal weight appeared to perform marginally better than did the Hadlock formula, although without reaching statistical significance. The authors suggested the possibility that this equation may result in a significant improvement in the prediction of fetal weight in more selected groups or with a larger number of patients [112].

A further finding of this study is the different morphometries of umbilical cords of macrosomic fetuses in the general obstetric population compared with those of diabetic mothers. Fetuses of diabetic women showed to have a larger umbilical cord mainly because of an increased amount of Wharton's jelly, while among women without diabetes but a diagnosis of macrosomia, large umbilical cords did not exhibit the same finding related to Wharton's jelly area [112].

This finding is confirmed by Weissman and Jakobi [113], in a cohort of appropriate for gestational age fetuses of pregnancies complicated by gestational diabetes mellitus, showing that umbilical cord diameter measured by ultrasound was significantly larger than that of the control group. This increased diameter was attributable mainly to a higher content of Wharton's jelly, compared to controls.

Interestingly, when a large umbilical cord is detected by ultrasound, knowing the relative contributions of Wharton's jelly area and that of the umbilical vessels to the whole cross-sectional area of the cord could assist in differentiating between the constitutionally macrosomic fetus and the abnormally large fetus of a diabetic mother.

8.3.8.3 Short Cord

As with umbilical cord coiling, cord length appears to correlate with fetal activity in utero. Thus, short cords develop in conditions where there is an intrauterine constraint of fetal movements, such as uterine anomalies and amniotic bands, or when there is decreased movement of the fetus, such as neurologic conditions, skeletal dysplasia, and other fetal anomalies [40, 114].

The definition of what constitutes an excessively short cord is also not well defined, with reported ranges varying from 32 to 40 cm at term. Moreover, there is a practical reason for defining short cords at this length since it is demonstrated that a cord less than 32 cm in length will not allow vaginal delivery from a vertex presentation. The incidence of short cords is lower than that of long cords, being around 2 % at term [5]. Excessively short cords correlate well with a variety of fetal and neonatal complications and central nervous system impairment [115] as well as with depressed intelligence quotient (IQ) values later in life [5]. The essential question, though, is whether the short length is due to prenatal alteration in the central nervous system or whether these alterations result from complications that ensued from delivery of an infant with a short cord. Short cords, especially those less than 15 cm, have a strong association with fetal anomalies, particularly abdominal wall defects, spinal and limb deformities, and a number of other malformations.

The complications associated with short cords are also associated with "relatively" short cords that are created by cord entanglements. Cord rupture or premature separation of the cord from the placenta during delivery may result in significant fetal bleeding and then serious neurologic sequelae or death. Premature detachment of the placenta (abruption) can also occur due to increased traction on the cord during delivery [116]. Unfortunately, the diagnosis of a short cord is hardly performed on pathologic examination since the length of cord sent for examination is too variable. As a consequence, the clinical history submitted with the specimen may lead to the diagnosis.

8.3.8.4 Excessive Cord Length

The relationship between long cords and excessive fetal movements is more difficult to assess than that of short cord due to the lack of data on prenatal movements and follow-up of infants with long cords to ascertain whether they are "hyperactive" in later life as suggested by some [117]. Experimental studies have supported the association of fetal movement with cord length since animals exposed to physical constraint or drugs that lead to decreased movement developed short cords, whereas those without constraint developed longer cords [118, 119].

Of interest, a genetic contribution has been suggested since women with a history of an excessively long cord in previous pregnancies are at increased risk of a second long cord in subsequent gestations [94]. There is no consensus on the minimum length for a diagnosis of an excessively long cord with definitions ranging from 70 to 90 cm (Fig. 8.13).

This inconsistency is due in part to the lack of accurate measurement of cord length at the time of delivery and to the fact that the entire umbilical cord is not submitted for pathologic examination. Excessively long cords are present in 3.95 % of placentas [94].

Right coiling, excessive coiling, true knots, single umbilical artery, twisting (Fig. 8.14), and cord entanglements are more common in long cords [94]. It has been proposed that excessively long and coiled cords would require greater perfusion pressure due to increased resistance to flow, but this has not been confirmed by direct experiments. This theory is supported by the fact that long cords are associated with histological abnormalities consistent with obstruction of venous return from the placenta such as villous capillary congestion and fetal vascular thrombosis [94, 120] and studies that have shown that cardiac enlargement and hypertrophy are seen in infants with long cords [94, 121]. Evidence of intrauterine hypoxia (chorioangiosis, increased nucleated red blood cells) is also seen with increased frequency in placentas with long cords [94], as well as growth restriction, intrauterine demise, and neonatal coagulation disorders. Long cords have been implicated in cerebral degenerative changes and are associated with a significant increase in brain imaging abnormalities, neurologic injury, and poor neurologic outcome [93–95, 120, 122, 123].

Fig. 8.13 An intrauterine fetal death at term for a true cord knot and excessively long cord (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

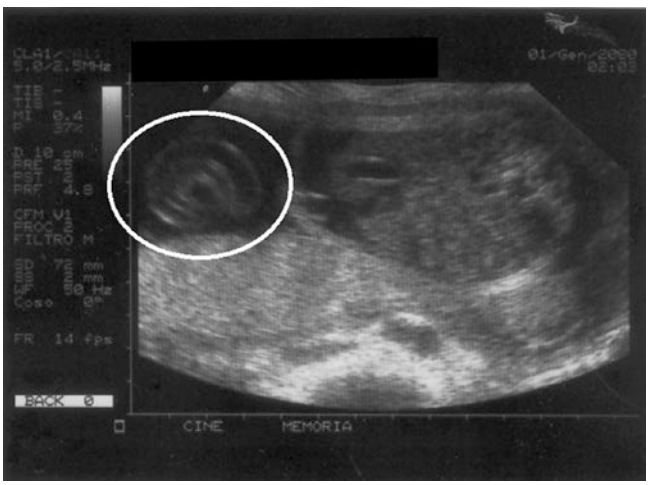

Fig. 8.14 An ultrasonographic scan showing a twisting cord

8.4 Anomalies Leading to Cord Compression Within a Condition of Normal Structure

Mechanical obstruction of blood flow through the umbilical cord may occur secondary to any type of force that compresses umbilical vessels [5, 7, 40, 94, 123, 124].

Compression may arise from knots, abnormal coiling, abnormal length, or constrictions. Often these structural abnormalities are linked; for example, entanglements and knots are frequently seen in long cords, and excessive coiling is often seen with constrictions. These conditions are generally present for many weeks or months and so may cause chronic obstruction to blood flow. However, acute obstruction is also possible when there is an acute progression at or near the time of delivery (Fig. 8.15).

This is the case when a true knot or when entanglement tightens as the fetus progresses through the birth canal or if membranous vessels become compressed after membranes rupture, and there is a loss of the cushioning effect of the amniotic fluid. If the obstruction is complete, fetal death might happen, whereas less severe degrees of obstruction may lead to different degrees of neurologic injury [5, 7, 95, 123, 125–127]. This is consistent with animal studies in which fetal lambs subjected to intermittent partial cord occlusion developed cerebral necrosis and serious fetal neurologic damage [128]. Chronic partial obstruction can also lead to fetal growth restriction. Abnormally coiled cords, abnormally short or long cords, velamentous cord insertions, true knots, cord entanglement, and cord prolapse have all been associated with an increased risk of fetal demise, neurologic injury, or abnormal developmental outcome [5, 7, 40, 95, 123–125, 127].

In acute compression, the umbilical vein, more distensible, will be initially compressed, followed by a compression of the arteries. This leads to vascular congestion of the placenta and, if severe, to hypovolemia and anemia in the fetus. Doppler studies have confirmed that cord obstruction and compression cause impeded venous return [129]. Decreased venous return of oxygenated blood from the placenta will result in distension of the umbilical vessels, particularly the vein, tributaries of the umbilical vein in the chorionic plate, and the villous capillaries.

Chronic cord compression develops from the same mechanical forces that lead to acute compression; however, the pathologic changes are more clearly delineated. Chronic obstruction of blood flow through the venous circulation initially leads to venous stasis and may ultimately lead to endothelial damage and subsequent fetal vascular thrombosis further altering blood supply to the fetus. Thrombi in umbilical vessels and fetal circulation can occur secondary to any process associated with cord compression or decreased venous return [95, 122, 123, 130].

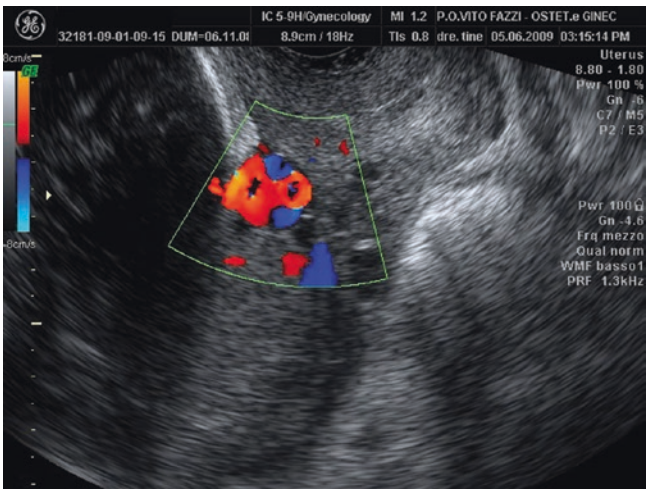

Fig. 8.15 Acute cord compression for an acute fetal progression at or near the time of delivery

8.4.1 Cord Entanglements

The most common type of cord entanglement is a nuchal cord in which the cord is looped around the fetal neck, but entanglements with the extremities or the body also occur. As might be expected, cord entanglements of any kind are more common with long cords [94, 131], and they may lead to cord compression with the changes previously described. Entanglements have been found as early as 10 weeks' gestation by sonography, but some of these early cord entanglements resolve by term [132].

Most cord entanglements do not lead to adverse outcomes, probably because they are somewhat loose. Some of them may become tighter after membrane rupture and during fetal descent in the birth canal. Tight entanglements are associated with low Apgar scores and a higher rate of stillbirths [127].

Nuchal cords are quite common (Fig. 8.6), with an incidence of 15–20 % of all pregnancies. They may encircle the neck in an unlocked or locked pattern, and the latter is considered to have more severe fetal outcome [133]. Infrequently, multiple loops of cord may become wrapped around the neck, and up to eight loops have been reported [5]. Nuchal cords have been associated with fetal growth restriction, suggesting that entanglements and their associated cord compression are long-standing prenatal events [134]. Neonates with nuchal cords are significantly more anemic than controls, presumably because of decreased venous return from compression of the umbilical vein [135], and tight nuchal cords may be so severe as to lead to hypovolemic shock of the neonate [136]. Of interest, a statistically significant correlation between the presence of a tight nuchal cord at delivery and cerebral palsy has been reported [137, 138].

8.4.2 Knots of the Umbilical Cord

Umbilical cord may present true knots (Fig. 8.16) or false knots. False knots, for which the term of knot may be even inappropriate, are anomalies that develop from looping or local redundancies of the umbilical vessels, primarily the umbilical vein. Sometimes focal varicosities of the veins or perivascular accumulations of connective tissue result in a similar gross appearance. Unlike true knots, these structures have absolutely no clinical importance [41]. Like cord entanglements, knots may be tight or loose and may acutely tighten with fetal movement or with fetal descent during delivery. Knots cause compression of Wharton's jelly, and those present for an extended period will retain their curled configuration when untied. Venous distension and vascular congestion distal to the knot are a characteristic finding in tight knots of clinical significance. The associated venous stasis often results in thrombosis of placental surface veins as well.

The incidence of true knots is reported to be from 0.4 to 1.2 % [5], but the frequency is higher with polyhydramnios and with long or excessively coiled cords [5, 94].

Although not all true knots lead to perinatal adverse outcome, they have been associated with signs of fetal distress and fetal hypoxia, perinatal mortality, and long-term neurologic damage [5, 138].

Fig. 8.17 Cord prolapse during vaginal delivery

8.4.3 Cord Prolapse

Cord prolapse is a clinical diagnosis made when the umbilical cord precedes the presenting fetal part during labor and delivery (Fig. 8.17). Hence, the cord may be acutely compressed between the fetal head and the cervix as the fetus descends the birth canal (Fig. 8.18).

Risk factors for cord prolapse include abnormal fetal presentations, preterm labor, multiparity, multiple gestation,

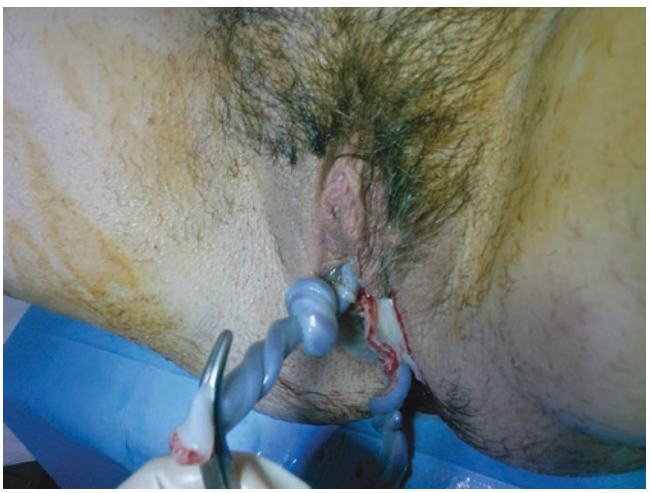

Fig. 8.16 True knot of cord

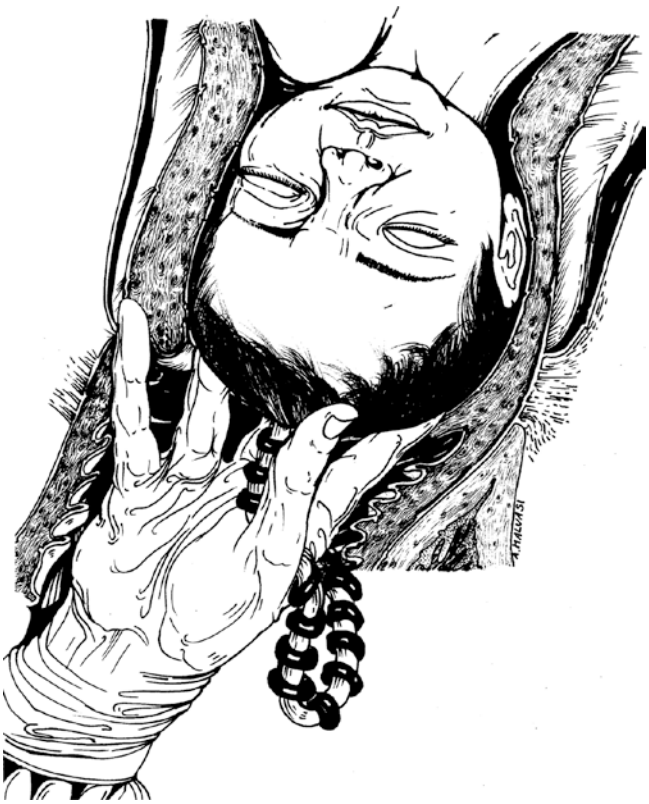

Fig. 8.18 The cord may be acutely compressed between the fetal head and the cervix as the fetus descends the birth canal

low birth weight, obstetric manipulation, polyhydramnios, abruption, placenta previa, and excessively long cords [139].

Although prolapse is relatively uncommon, occurring in less than 1 % of deliveries, the perinatal mortality is estimated to range between 10 and 13 % [5].

Cord prolapse is considered an obstetric emergency as cord obstruction can lead to fetal death or neurologic damage relatively quickly and needs the immediate activation of the obstetric and neonatology team.

8.5 Histological Cord Pathology with a Normal Cord Structure

8.5.1 The Fetal Inflammatory Response Syndrome

The fetal inflammatory response syndrome (FIRS) describes a condition characterized by systemic activation of the fetal immune system accompanied by multiorgan involvement. FIRS was originally reported among patients with preterm labor and intact membranes and in those with preterm prelabor rupture of the membranes [140–142]. The rate of FIRS in pregnancies complicated by preterm parturition is about 39 % and increases to 49.3 % in fetuses delivered within 1 week from cordocentesis [140, 142]. Of interest, FIRS is present in nearly 50 % of fetuses with preterm premature rupture of membranes [140, 141]. This syndrome is associated with a microbial invasion of the amniotic cavity (MIAC) and histological chorioamnionitis (among patients with MIAC alone, 17 % have FIRS, whereas, in those who have MIAC and histological chorioamnionitis, 68 % have FIRS) [143]. Nevertheless, some fetuses of patients with preterm parturition will have FIRS without the presence of MIAC, whereas, in women with MIAC, not all the fetuses will develop FIRS.

Invasive methods such as amniocentesis and cordocentesis were used to establish cutoff values of interleukin-6 to achieve a prenatal diagnosis of fetuses affected by FIRS (a cutoff value of 11 pg/mL was reported). In addition, evidence of umbilical cord inflammation, named funisitis, as well as chorionic vasculitis are regarded as the histologic counterparts and histopathologic hallmarks of FIRS, allowing a postnatal diagnosis [140, 144].

Funisitis is associated with endothelial activation, and this is a key mechanism in the development of organ damage [145].

8.5.2 Meconium-Associated Histologic Changes of the Umbilical Cord

Discharge of meconium, the intestinal content of the fetus, into the amniotic fluid is a relatively common event, especially in term or post-term fetuses. In most cases, it has no clinical importance. In a small number of cases, meconium is aspirated by the fetus, and then meconium aspiration syndrome, associated with significant neonatal morbidity and mortality, may develop [41].

Meconium is a noxious material, containing bile salts, cholic acid, enzymes, and other compounds [146]. If meconium is present in the amniotic fluid for a sustained period, it damages the amnion, the umbilical cord, and the fetal vessels. Initially, within a few hours of meconium exposure, the fetal membranes and surface are stained green on gross examination. Edema is often present as well, giving the membranes a slimy appearance. Microscopically, there is a degenerative change of the amnionic epithelium of the fetal membranes and chorionic plate, manifesting as piling up of the epithelial cells, vacuolation, loss of epithelial cells, and necrosis associated with the presence of pigment-filled macrophages [146, 147].

This myonecrosis most commonly involves the arteries, most probably because they are closer to the surface. The muscle fibers, which are normally spindled, round up, and the cytoplasm takes on a deeper eosinophilia. The nuclei may become pyknotic and might completely disappear. Rarely, umbilical arteries can become completely detached from the cord due to damage to the amnion and Wharton's jelly, or the cord may become ulcerated [148, 149]. Meconium toxicity has been considered responsible for these types of tissue damage, even though the exact mechanism for its toxicity in is not known.

The vasoconstrictive effect of cholic acids, a component of meconium, has been demonstrated as well [149]. It is possible that vasoconstriction may also be mediated by interleukin-1, as the latter has been demonstrated to be present in meconium staining [150], and a similar mechanism is proposed for vasoconstriction due to bacterial products in the setting of an ascending infection [151]. This vasoconstrictive effect is more likely to occur with long-standing meconium exposure.

If the umbilical vein is involved, there may be decreased venous return of oxygenated blood from the placenta or, if the arteries are involved, there may be decreased blood flow to the placenta. All these changes, with special attention to meconium-associated myonecrosis, may lead to a scenario characterized by compromised blood flow, which is associated with fetal distress, cerebral hypoperfusion, and a significant risk of neurologic injury and cerebral palsy [124, 152]. Arterial necrosis with ulceration of the umbilical cord has been described in association with hypoxic ischemic encephalopathy [153].

Conclusions

The umbilical cord plays a critical role in normal fetal development and fetal well-being and requires careful assessment at ultrasound examinations as well as high clinical consideration during pregnancy and delivery. It

may develop several structural, morphologic, compressive, and histological abnormalities that can be associated with other fetal anatomic and chromosomal anomalies. In this scenario, the mother, the fetus, and the newborn can become affected due to the number of poor and adverse outcomes resulting from the above-described anomalies.

Literature does not provide enough evidence regarding this fascinating organ that is the umbilical cord, and this is due to the low incidence of its alterations, the difficulties in pathologic examination of the cord, and the subtle nature of some of the abnormalities involving the umbilical cord, not always easy to diagnose and sometimes misdiagnosed.

There is the need of an effort to produce high-quality studies in order to improve maternal and perinatal outcomes avoiding severe complications arising from cord anomalies.

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Operative Vaginal Birth: A Modern Appraisal

9

Stephen O'Brien, Anna Denereaz, Antonio Malvasi, Andrea Tinelli, and Tim Draycott

9.1 Introduction

For the purposes of this chapter, *operative vaginal birth (OVB)* is any intervention performed by a birth attendant with the aim of expediting a birth vaginally. Ideally, an operative vaginal birth should follow the process of spontaneous vaginal birth. OVB has been performed for many years, by many accoucheurs. Instruments and methods have varied over time, as has understanding of the risks and benefits of OVB. Performed well, OVB is associated with excellent outcomes for women and their babies. Poor performance of OVB is associated with preventable harm to both mothers and infants. A skilled obstetrician should be familiar with the most commonly performed methods of OVB, the rationale for their use and the risks and benefits of each. They should also be aware of the best practice to reduce poor outcomes and the role that structured training can play in this. Clearly, such training is out with the scope of this chapter.

For consistency, British English terms (i.e. Rhodes forceps) will be used throughout the chapter.

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9.2 Worldwide Trends in OVB

Birth attendants have attempted to assist mothers in distress for many centuries, although not until more recently to improve outcomes for infants. One early, and likely ineffective, example from the eleventh century has been attributed to a Salerno doctor: 'When there is a difficult labour with a dead child place the patient in a sheet held at the corners by four strong men, with her head somewhat elevated. Have them shake the sheet vigorously by pulling on the opposite corners, and with God's will she will give birth' [1].

Since then there have been a plethora of different instruments that have been developed and employed by individual practitioners, often in isolation and with limited geographical spread. However, from the nineteenth century, there has been a slow process of standardisation of the instruments that used expedite vaginal birth.

Currently, most worldwide accoucheurs would be familiar with the ventouse (flexible or rigid cup, flexible or rigid stem) and non-rotational forceps (Rhodes forceps). Furthermore, most practitioners would also be familiar with the use of manual rotation to correct fetal malposition and/or ventouse. Some may also use rotational forceps (Kielland forceps).

9.3 The Place of Operative Vaginal Birth

Operative vaginal birth, performed by a suitably competent practitioner, remains the safest mode of birth for both women and their babies for women in the second stage of labour, and OVB is possible and reasonable. An understanding of the anatomy of the birth canal and the fetal head is a prerequisite to becoming skilled in the safe use of forceps or vacuum extractor. The goal of OVB is to mimic spontaneous vaginal birth, thereby expediting delivery with a minimum of maternal or neonatal morbidity. The decision to use an instrument to deliver the fetus balances the maternal, fetal and neonatal impact of the procedure against the alternative options of caesarean birth or expectant management.

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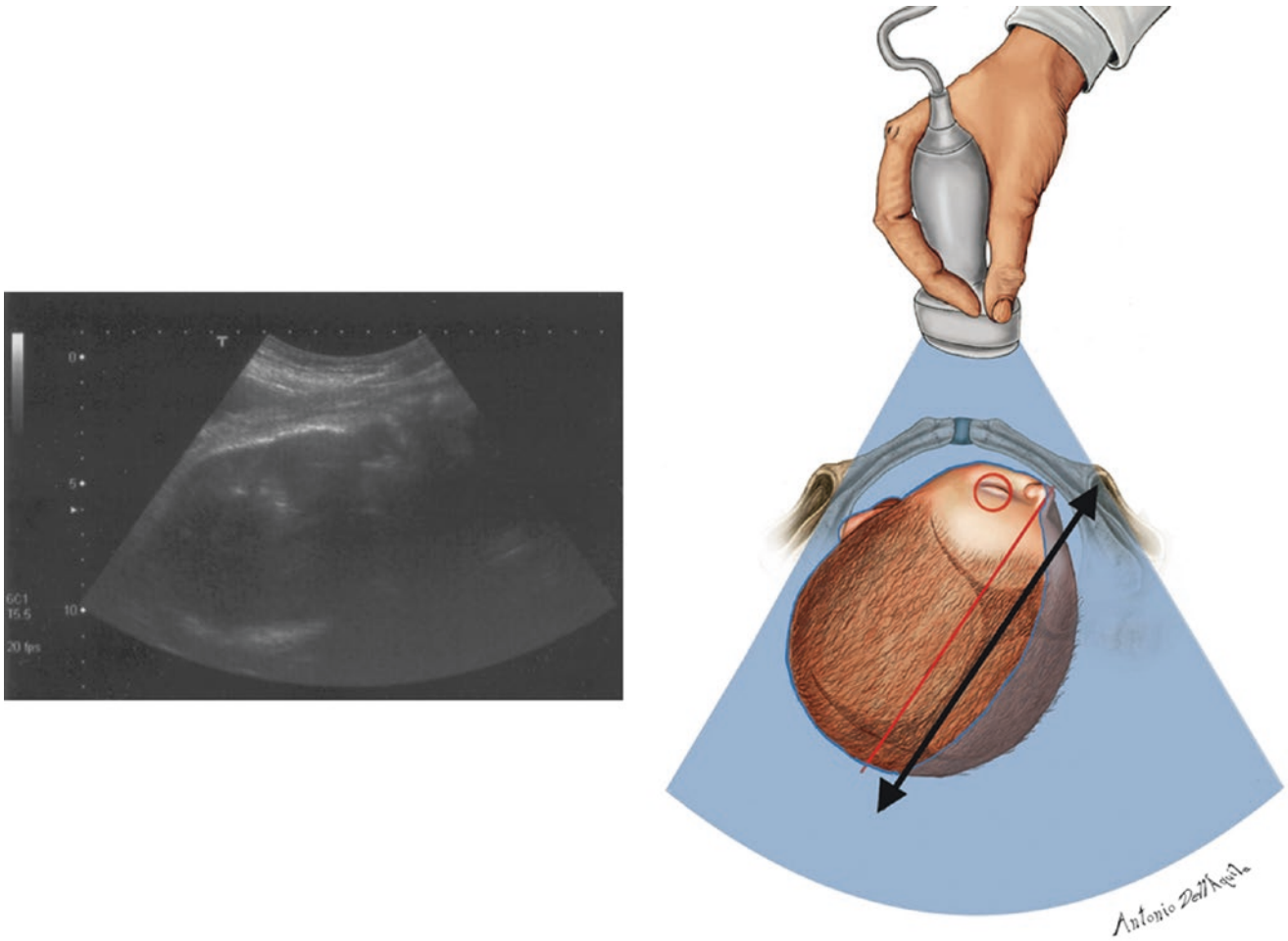

Fig. 9.1 Operative vaginal delivery in a protracted second stage of labour for fetal head in right occiput posterior position: on the left, the ultrasonographic scan showing the left orbit (the squint sign) and anterior asynclitism, and on the right, the corresponding draw

Routinely, a protracted second stage of labour, suspicion of immediate or potential fetal compromise and shortening the second stage for maternal benefit are appropriate indications for operative vaginal delivery (forceps or vacuum) (Fig. 9.1).

Caesarean section at full dilatation (Fig. 9.2) is associated with an increased risk of major obstetric haemorrhage, prolonged hospital stay and neonatal SCBU admission when compared to completed instrumental birth [2]. Moreover, operative vaginal birth, when successful, requires reduced analgesia requirement and can be expedited more quickly [3], and women are much more likely (>80 %) to have a spontaneous vaginal birth in their next pregnancy [4, 5]. In addition, repeat CS may limit maternal choices in future pregnancy and also increases the risk of abnormal placentation that carries significant maternal risks [6].

Therefore, operative vaginal birth may be the best option for the mother and baby in the second stage of labour, but it is essential that the accoucheur performs a careful, accurate and comprehensive clinical assessment to confirm that the prerequisite conditions are met for safe vaginal operative delivery.

9.4 Trends in Operative Vaginal Birth

Worldwide, there has been a general trend for a reduction in OVB and increasing caesarean birth – this is usually seen in an increasing use of caesarean sections in the second stage of labour, a decline in forceps births and a rise (but not compensatory) in ventouse birth.

For example, in the USA, there has been a reduction in all forms of OVB from 9.01 % in 1990 to 3.30 % in 2013. Within this time period, in particular the use of forceps fell sharply from 5.11 to 0.59 %, and ventouse also declined from 3.9 to 2.72 %. There has been a parallel rise in the rate of caesarean section (both elective and emergency) from 20.7 to 32.7 % [2].

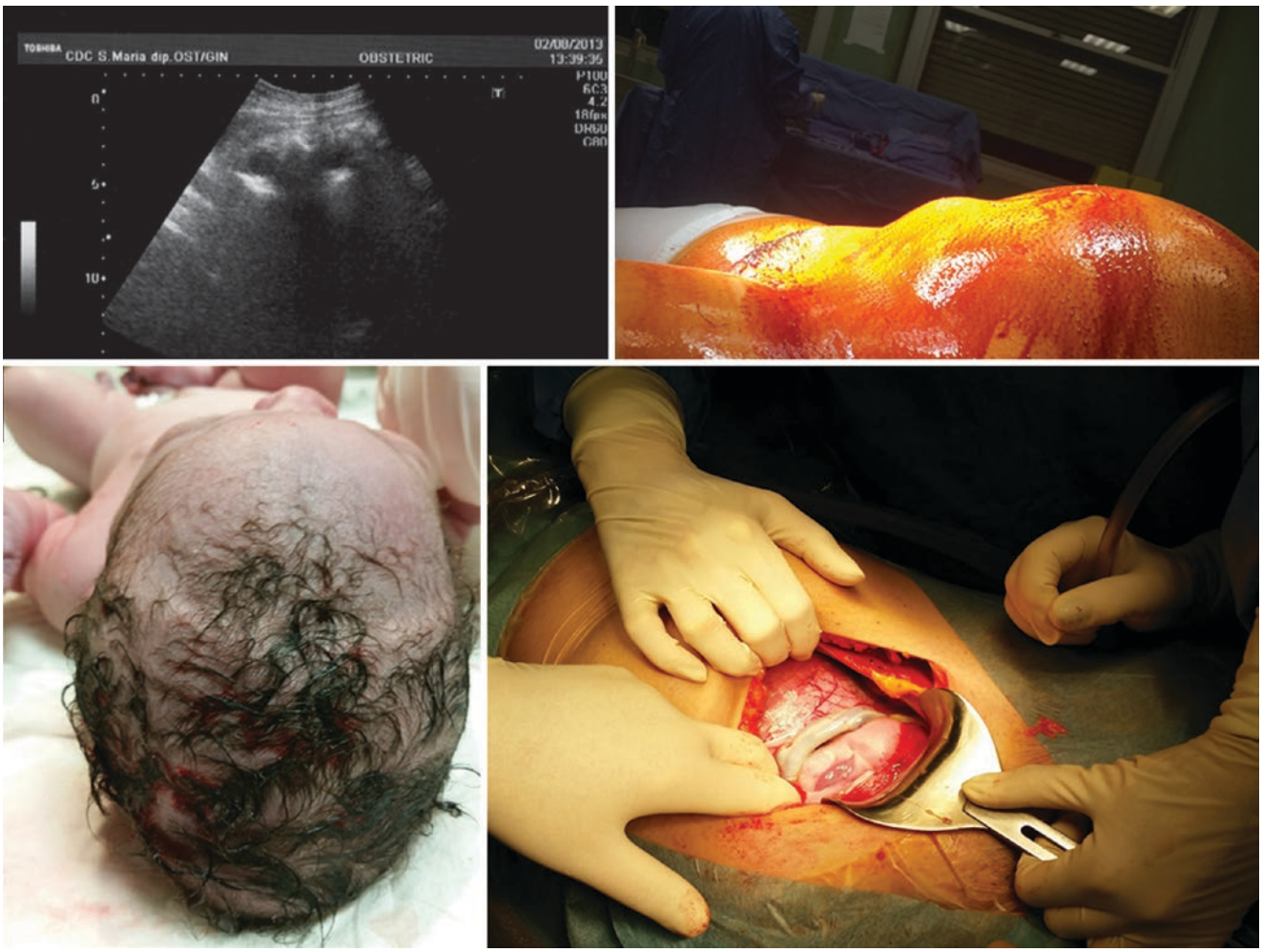

Fig. 9.2 Caesarean section at full dilatation; the image shows, in clockwise fashion: an intrapartum ultrasound image with fetus in medial occiput posterior position, the 'sign of the step' on the mother's pubic bone, the caesarean section with opened abdomen and fetus in sacral rotation and umbilical cord around the neck, the newborn with large caput succedaneum at birth

In England there has been a similar reduction in the use of forceps in particular with a concomitant increase in CS rates: from 1980 to 2014, the rate of forceps declined from 11.3 of births to 7 %, whereas ventouse births increased from 0.7 to 5.8 %, but the rate of caesarean birth still increased from 9 to 26.2 % (within this, the rate of emergency caesarean section, i.e. intrapartum, increased from 5 to 15.2 %) [3].

In Australia the trend of decline of forceps has been less marked, although the rate of caesarean birth has still increased: over the period 1991–2013, forceps deliveries declined from 10 to 7 %, ventouse increased from 2.5 to 11 %, whilst rates of caesarean birth increased from 18 to 33 % [4, 5].

This is despite excellent evidence that caesarean birth significantly increases the risks for any subsequent pregnancy – rates of successful vaginal birth in a subsequent pregnancy are 80 % higher if the woman has had a primary vaginal birth, the increased risk of organ damage in a subsequent caesarean section (1/1,000), the higher rate of placenta accreta and an increase by a factor of two in the rate of stillbirth [6].

There are a number of postulated reasons as to why this has occurred, none of which have been proven.

Firstly, there may be an understandable perception among some women that a vaginal birth will lead to unacceptable risks, and to some extent, this is supported in the evidence. For example, a retrospective cohort study in Sweden of 5,236 women demonstrated that vaginal birth increases women's risk of pelvic floor disorders 20 years after birth compared to caesarean section (functional incontinence 20 years after birth – 40.3 % vs 28.8 %; OR 1.67 [7]).

There have also been changes in women's expectations regarding the mode of birth. Caesarean birth may be becoming more acceptable to women.

In earlier decades, there were barriers to choosing birth by elective caesarean (without an obstetric indication) – however,

rates of CS without an obstetric indication have increased to 2.7 % in the USA [8] and 3 % in the UK [9], and rates are as high as 84 % in some private practices in Brazil [10].

Beyond these factors, there are no proven causes to explain why the use of caesarean section has become more prevalent and the use of OVB has declined.

9.5 Current Issues in Operative Vaginal Birth

9.5.1 Risks of the Use of Sequential Instruments or Failure

There are additional risks associated with the use of sequential instruments during attempted operative vaginal birth.

Althougha failed operative vaginal birth, using a single instrument, such as vacuum extractor, followed by caesarean section, with a normal fetal heart rate trace, does not appear to be associated with poorer neonatal outcomes [11], infants born following the use of second sequential instrument (most commonly forceps following failed ventouse) were more likely to have an umbilical artery pH <7.10 (OR 3.0), and mothers were more likely to sustain an anal sphincter tear (OR 1.8) [12].

Other studies have also demonstrated increased rates of neonatal intracranial haemorrhage following the sequential use of instruments (OR 2.0 in ventouse followed by forceps vs forceps alone) [13].

Rotational births are more likely to fail, particularly using the ventouse cup [14], and this has led to a resurgence in interest in the use of rotational (Kielland) forceps.

Since the publication of the Royal College of Obstetricians and Gynaecologists guideline on Operative Vaginal Birth 2005, there have been a number of publications observing that in UK practice births by Kielland forceps had a rate of adverse maternal and neonatal outcomes comparable to those by rotational ventouse and emergency caesarean section in the second stage for malposition, with a significantly lower failure rate [13].

One recent paper reported: 'There were no cases of forceps-related neonatal trauma or hypoxic–ischemic encephalopathy and therefore contrary to earlier reports, the use of Kiellands forceps is associated with a high successful delivery rate and apparently low maternal and neonatal morbidity' [14].

Another study from Scotland observed that: 'neonatal admission rates after delivery by rotational forceps deliveries (3.3 %) were not significantly different from spontaneous vertex delivery (3.7 %) or ventouse delivery (3.8 %) and lower than emergency caesarean delivery (11.2 %)' [15].

Clearly, all rotational births can be difficult, and it would be interesting to investigate whether an increase in the use of forceps for rotational births outside a small number of UK centres is either feasible or useful.

9.5.2 Training

All practitioners should be adequately trained to safely and efficiently expedite vaginal birth where required and also garner sufficient experience with a range of techniques. Notably in the UK, junior obstetricians have identified training for rotational births as one of their top three training requirements [15]. Surveys of US obstetricians after finishing residency training showed that trainees needed to perform at least 13 forceps procedures in their 4 years of training in order to be likely to use them in independent practice (positive predictive value 0.83) [16].

However, the exposure of junior obstetricians to operative vaginal birth has declined in the most recent generation of graduates. This has partly been driven by a reasonable reduction in working hours for junior obstetricians during their training. In 1991 in the UK, junior doctors were on duty for an average of 90 h a week [17]; by 2014 this had declined to a theoretical average of 48. This change has been mirrored in most other countries. Moreover, there has been an increase in senior obstetrician presence on the labour ward: in the UK there has been a move after 2005 to increase consultant physical presence to 24 h/day in larger units (>6,000 births/year) [18]. This may have the unintended consequence to further reduce the number of operative vaginal births attempted by junior obstetricians, even though the intention was to increase supervision. Although this may be the case, recent studies published in the UK have demonstrated that rates of senior obstetricians performing more complex births are still low – no more than 20 % in one study of rotational forceps births [19], and so this cannot on its own be responsible for the decline in OVB.

There is also an understandable reluctance by woman to have a complex procedure performed by an inexperienced obstetrician, however, well supervised, and an understandable reticence among other delivery ward staff to expose patients to a junior obstetrician's learning curve. Therefore, it is vital that obstetricians use other methodologies, primarily simulation-based training, to shorten this learning curve and improve their familiarity and skills in operative.

Training and experience are likely to be symbiotic. Training can be used to teach both individual skills and more complex techniques such that trainees feel able to safely undertake these techniques on the labour ward.

Individual skills can be taught using repetition and instant feedback models – this has been shown to improve the successful placement rate of forceps blades in simulated births from 32 to 70 % [20].

Table 9.1 Indications for operative vaginal birth

Fetal	Presumed fetal distress
Maternal	To shorten and reduce the effects of the second stage of labour on medical conditions (i.e. cardiac disease class 3 or 4 NYHA, myasthenia gravis, hypertensive crises, proliferative retinopathy, spinal cord injury patients at risk of autonomic dysreflexia, atrioventricular malformation, etc.)
	Lack of continuing progress of the fetal head following a locally recognised time limit of active second stage (in the UK 2 hours for a primiparous woman with no analgesia)
	Maternal fatigue/exhaustion

Adapted from the Royal College of Obstetricians & Gynaecologists 2011

More complex complete procedures can also be effectively taught: the appointment of dedicated operative birth teaching fellows has increased rates of forceps births by 62 % in some US hospitals [21].

There is good evidence that structured obstetric simulation training can improve outcomes – for example, it has been shown to reduce rates of permanent brachial plexus injury following shoulder dystocia [22], low Apgar scores and haemorrhagic ischemic encephalopathy following birth [23].

There are no data investigating changes in clinical outcomes following structured training in operative vaginal birth; however, it is reasonable to extrapolate from other intrapartum training programs that structured simulation-based packages (e.g. RCOG ROBuST training course) could improve outcomes associated with operative birth, but this would be usefully evaluated in a prospective study.

There is a place for operative vaginal birth, performed by well-trained accoucheurs, in selected women.

9.5.2.1 Indications and Requirements

Indications for operative vaginal birth vary between countries. The most important indication is where the benefit outweighs the risks of operative intervention and/or continued pushing (Table 9.1).

This list is not exhaustive, and each woman should be assessed in the context of her individual circumstances, health and labour and the options discussed.

9.5.2.2 Prerequisites for Operative Birth

Before commencing any operative vaginal birth, the obstetrician should fully communicate the situation, risks and benefits to the woman and her partner in order to gain informed consent to perform an OVB. Ideally this should be recorded in written form and the RCOG provides standard consent information for OVB [24].

There are specific requirements that must be fulfilled before any attempt at OVB. These are laid out in the table below, on the Table 9.2.

Table 9.2 Requirements for operative vaginal birth

Full abdominal and vaginal examination	The head is ≤ one-fifth palpable per abdomen
	Vertex presentation
	The cervix is fully dilated and the membranes ruptured
	Exact position of the head can be determined so proper placement of the instrument can be achieved
	Assessment of caput and moulding
	Pelvis is deemed adequate
	Irreducible moulding may indicate cephalopelvic disproportion
	The head is ≤one-fifth palpable per abdomen
	Vertex presentation
Preparation of mother	Clear explanation should be given and informed consent obtained
	Appropriate analgesia is in place for mid-cavity rotational deliveries. This will usually be a regional block. A pudendal block may be appropriate, particularly in the context of urgent delivery
	The maternal bladder has been emptied recently. Indwelling catheter should be removed or balloon deflated
	Aseptic technique
Preparation of staff	Operator must have the knowledge, experience and skill necessary
	Adequate facilities are available (appropriate equipment, bed, lighting)
	Back-up plan in place in case of failure to deliver
	When conducting mid-cavity deliveries, theatre staff should be immediately available to allow a caesarean section to be performed without delay (less than 30 min)
	A senior obstetrician competent in performing mid-cavity deliveries should be present if a junior trainee is performing the delivery
	Anticipation of complications that may arise (e.g. shoulder dystocia, postpartum haemorrhage)
	Personnel present that are trained in neonatal resuscitation

Adapted from the Royal College of Obstetricians & Gynaecologists 2011

9.6 Contraindications to Operative Vaginal Birth

Although every woman and labour should be assessed on an individual basis, there are specific relative, and absolute, contraindications to operative vaginal birth. These are laid out in the Table 9.3.

Table 9.3 Contraindications to operative vaginal birth

Type	Relative	Absolute
Fetal	Suspected cephalopelvic disproportion Brow or mento-anterior face presentation Osteogenesis imperfecta Ventouse only: 34–36 weeks gestation	Fetal bleeding disorder Ventouse only: <34 weeks gestation Face presentation
Maternal	Blood-borne virus (i.e. Hep B/HIV)	Refusal to consent

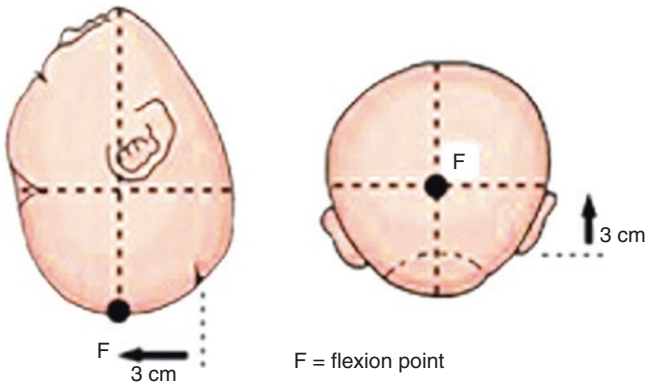

Fig. 9.3 Location of flexion point

9.7 Evidence in Operative Vaginal Birth

9.7.1 Choice of Instrument

Practitioners should use the instrument with which they are most competent and confident will lead to a successful outcome in the particular situation. Different instruments (ventouse and forceps) are associated with different risks and benefits, and practitioners should take these into account when selecting any instrument.

9.7.2 Ventouse or Forceps?

The most recent Cochrane systematic review and meta-analysis on operative vaginal birth demonstrated that the use of any ventouse is associated with a higher likelihood of failure and birth via caesarean section compared to forceps (OR 1.67).

Ventouse birth was however less likely to be associated with the use of episiotomy, vaginal trauma, third/fourth degree tear and flatal/faecal incontinence for the mother and less likely to be associated with facial injury for the baby [14]. There was no significant difference in any other recorded outcomes, including Apgar scores, umbilical cord pH, cephalohaematoma, retinal haemorrhage or rate of admission to neonatal intensive care unit.

It is not possible to say if the increased likelihood of failure seen in the attempted ventouse births reflects any general greater experience of obstetricians using forceps or the intrinsic deficiencies of any ventouse device in assisting birth; however, it is an important finding. The specific advantages and disadvantages of types of device are discussed in the sections below.

9.7.3 Ventouse

The use of a ventouse device, as with all instruments for OVB, is subject to the inclusion/exclusion criteria in the previous section. However, an additional contraindication for ventouse is that they should not be used below 34 weeks gestation and used with caution between 34 and 36 weeks gestation. Ventouse devices are usually grouped as flexible or rigid cup devices. There are separate risks and benefits for each, which are discussed below.

Whilst there are differences between flexible and rigid cups, both work by correcting the angle of the fetal head in the pelvis so that the flexion point (the exit point of the mentovertical diameter) is pointed down the birth canal and the fetal head diameters will be at their most favourable for birth (Fig. 9.3).

Both types of ventouse then apply an element of direct traction force upon the fetal head. In general, a flexible cup would be regarded as less suitable at correcting the position of the fetal head. A rigid cup would be more suitable for correcting malposition but may be more difficult to use. The choice of instrument therefore depends on the specific circumstance of each labour. There are some key differences between flexible and rigid cups which obstetricians should be aware of when selecting an instrument.

9.7.4 Flexible Cup Ventouse

9.7.4.1 Advantages and Benefits

A flexible ventouse cup is most suitable for a birth where the head is in the OA position and low (2 cm or more below the ischial spines).

In general, flexible cups are thought to have a lower rate of failure (Fig. 9.4) and therefore caesarean section than rigid cups. However, this difference, although demonstrated in individual studies [25], was not significant when all available trial data was pooled [14].

Flexible cups are able to generate less traction than rigid cups (11.1 vs 15.8 Kg) [26] but perhaps due to their greater surface area are more successful at generating the traction forces required to assist birth.

Whilst no advantages have been shown over the current generation of rigid (plastic) cups, previous studies have, per-

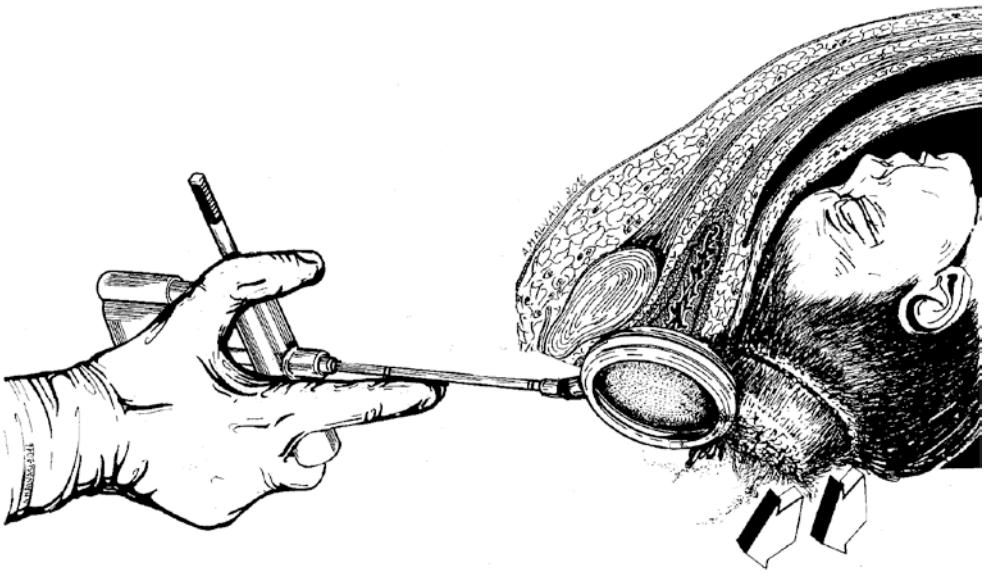

Fig. 9.4 Failure of soft vacuum application in occiput posterior position

haps counter-intuitively, demonstrated that soft cups are less likely to cause cephalohaematoma (RR0.61) and scalp injury (RR0.67) than metal cups [14].

9.7.4.2 Disadvantages and Risks

Flexible cups are not usually recommended for use in rotational births (Fig. 9.5). The large size of the cup and their flexibility means they are difficult to accurately manoeuvre over the flexion point. For this reason they should not be used for any birth where the fetal position is rotated beyond ROA/LOA.

The other major disadvantage of a flexible cup system is that their use is restricted to settings where there is a reliable electricity supply for the suction.

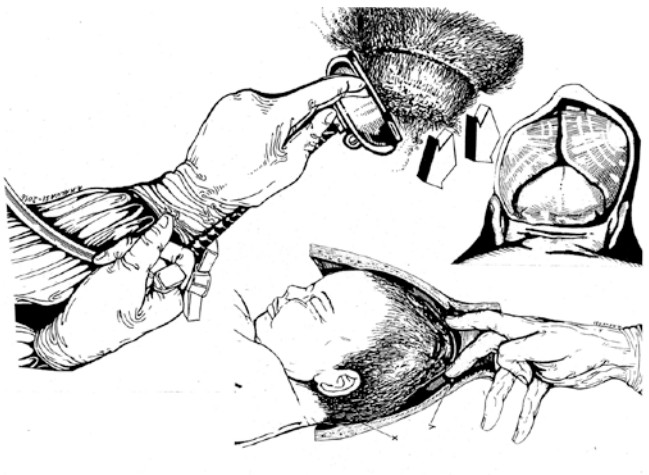

Fig. 9.5 Contraindications in rigid vacuum extractor applications: the caput succedaneum presence

9.7.5 Rigid Cups

For clarity we will discuss the new generation of plastic rigid cups (i.e. Kiwi OmniCup) (Fig. 9.6) in this section and not directly metal cups (Bird, Malström, O'Neil, etc.).

9.7.5.1 Advantages and Benefits

Rigid cups are considered superior to flexible cups where the fetus needs to be rotated to be delivered. Rigid cups are able to be positioned over the flexion point with greater precision than flexible cups, allowing for correction of acynclitism as well as rotation by generating flexion. Therefore they are one of the possible techniques for rotational births along with manual rotation or the use of rotational forceps. Rigid cups may also be manoeuvred further back into the maternal sacral hollow, allowing correct placement over the flexion point for an OP birth, which is often not possible using a flexible cup. Rigid cups are also generally smaller than

Fig. 9.6 Kiwi ventouse a plastic rigid cup

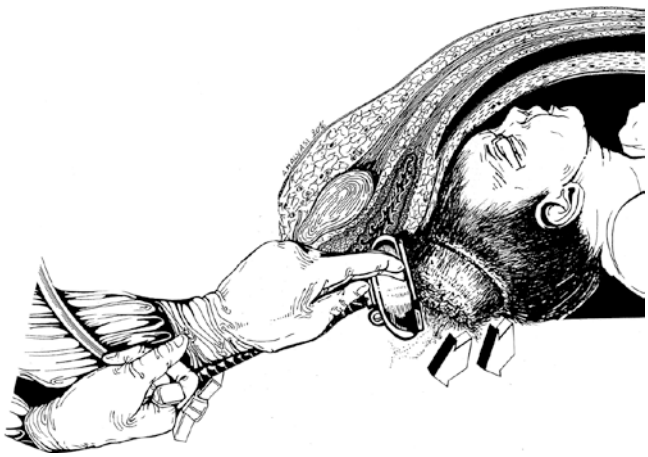

Fig. 9.7 Failure of rigid vacuum application on occiput posterior position

flexible cups and may be more comfortable for the woman during application. Nevertheless, the rigid cup may also be subject to failure (Fig. 9.7).

9.7.5.2 Disadvantages and Risks

They do not appear to be any significant disadvantages from flexible cups when used correctly. However, if a rigid cup is gripped directly by the obstetrician and rotated, this creates significant torque on the fetal scalp, which can create shearing of the cup and chignon from the rest of the scalp. This will result in a permanent 'tonsure' where the hair-bearing scalp is removed.

9.7.6 Forceps

Forceps and their use can be classified into direct or rotational. The use of forceps is again subject to the inclusion/exclusion criteria listed in Table 9.3, but a relative indication for the use of forceps is prematurity, particularly below 34 weeks gestation where ventouse is absolutely contraindicated.

Whilst there has been a general reduction in the use of forceps worldwide, in trained hands they remain the one of the most effective methods of safely expediting birth in the second stage of labour [27].

9.7.7 Direct Forceps

Direct forceps are forceps designed to deliver the fetus without the need for rotation and so are suitable for delivery of a baby in the direct OA or OP position (Fig. 9.8).

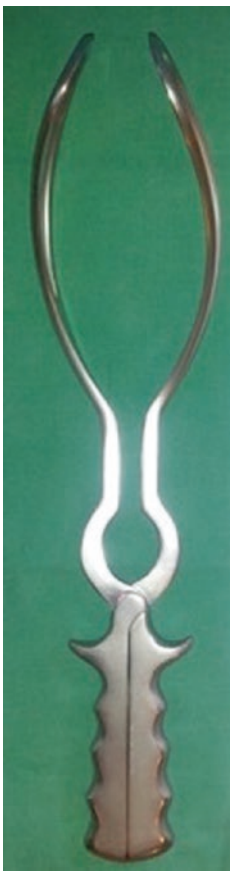

Fig. 9.8 Direct forceps

They are also used following manual rotation to OA or OP. They may also be used to help deliver face-presenting babies, in experienced hands.

Direct forceps come in many varieties, but the most common are those used in low-pelvic births (i.e. Rhodes forceps) and outlet (i.e. Wrigley's forceps). All non-rotational forceps have a pelvic curve (not seen in rotational forceps) to allow accurate application of traction along the J-shaped curve of the pelvis.

9.7.7.1 Advantages and Benefits

As previously discussed, direct forceps have a lower failure rate when compared to ventouse delivery (RR 0.65), thereby reducing the complications of failed operative vaginal birth [14]. The higher rate of a successful vaginal delivery with forceps also means less need for use of sequential instruments and the greater maternal and neonatal risks this entails. Finally, the use of forceps is also associated with a lower rate of cephalohaematoma than ventouse [14].

9.7.7.2 Risks and Disadvantages

However, forceps delivery significantly increases the risk of third or fourth degree tears when compared to ventouse delivery (RR 1.89), and episiotomy does not appear to decrease this risk [28]. This is significant not only in the injury itself but because of the real impact an anal sphincter injury has on future anal function – following an anal sphincter injury; women are more likely to report faecal incontinence at 6 weeks (OR 2.8) and 6 months (OR 1.9) than women who have not [29]. As well as the risk of anal sphincter injury, forceps birth also appears to increase the risk of levator ani avulsion by a factor of two to three times, which may also (although evidence is at a very preliminary stage) independently increase the prevalence of pelvic floor symptoms in later life [30].

The use of forceps is also more likely to result in facial injury for the baby (RR 5.1) [14].

9.7.8 Rotational Forceps (Kielland Forceps)

Rotational forceps (Kielland forceps) are different in design from direct forceps in the presence of a sliding lock and lack of a pelvic curve (Fig. 9.9), allowing an obstetrician to correct both position and acynclitism (Fig. 9.10).

Their use is more complex than other methods of OVB, and although rates of rotational forceps births have been falling for many years, in skilled use they are still associated with the lowest failure rates of all methods of OVB [31].

As well as being utilised in rotational births, the lack of a pelvic curve means they may also be employed in delivering the after-coming head in a breech birth.

Fig. 9.9 Kielland forceps

9.7.8.1 Advantages and Benefits

The main advantage of rotational forceps is their low failure rate and thereby reduced risk of subsequent second stage caesarean section. Failure rates in a pooled meta-analysis of trials comparing rotational forceps to rotational ventouse were reported as 4.4 % vs 16.3 % ($p < 0.009$) [31].

The same meta-analysis demonstrated that rotational forceps had similar outcomes in complex vaginal tears, cervical tears and PPH as rotational ventouse [31].

Again, although previously thought to be raised, rates of anal sphincter injury appear to be lower in rotational forceps (4.15 %) [31] than in all forceps, even when an episiotomy is performed (6.6 %) [32]. Also, despite the rate of injury in rotational forceps is being numerically higher than the anal sphincter injury rate reported following rotational ventouse

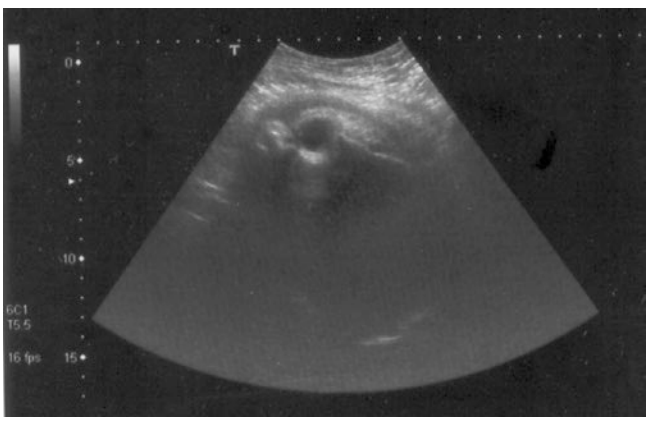

Fig. 9.10 Intrapartum sonography with fetus in left occiput posterior position and posterior asynclitism

(2.2 %), this was not significant after adjusting for confounding ($p = 0.18$) [31].

Rotational forceps should not therefore be seen as being more prone to creating anal sphincter injury than other forms of operative vaginal birth and, given their higher success rates, should be seen as the method of choice by suitably trained accoucheurs.

9.7.8.2 Disadvantages and Risks

Whilst individual studies have found higher rates of some complications, the most recent meta-analysis did not demonstrate any statistically poorer maternal or neonatal outcomes associated with the use of rotational forceps over rotational ventouse [31].

9.7.9 Episiotomy

The role of episiotomy in routine operative vaginal births is debated in current obstetric practice. To date there have been no prospective trials looking at the role of episiotomy in anal sphincter injury or maternal-reported outcomes (incontinence, prolapse and dyspareunia) which have demonstrated an effect. Small trials have however demonstrated a small, non-significant protective effect of episiotomy in preventing anal sphincter injury [33]. However, taken as a whole, these have not shown an overall protective benefit and possible subsequent complications (Fig. 9.11) [34].

However, large retrospective observational studies looking at nationally collected data in both the UK and the Netherlands have shown that use of episiotomy was associated with a lower rate of anal sphincter injury when performed during an operative vaginal birth. For example, in the UK study of all primiparous women in England between 2000 and 2012 (1,035,253 women), women who had a forceps birth with episiotomy had a 6.1 % chance of sustaining an anal sphincter injury compared to 22.7 % in women who had a forceps birth without episiotomy. For women who had a ventouse birth, the rate was 2.3 % when an episiotomy was performed and 6.4 % when an episiotomy was not performed. This is in relation to a rate of anal sphincter injury which varied from 1.8 to 5.6 % during the study period [32]. The study conducted in the Netherlands [35] demonstrated similar outcomes.

Given this disparity of conclusions, the current pragmatic position of the RCOG that restrictive use of episiotomy is supported [24].

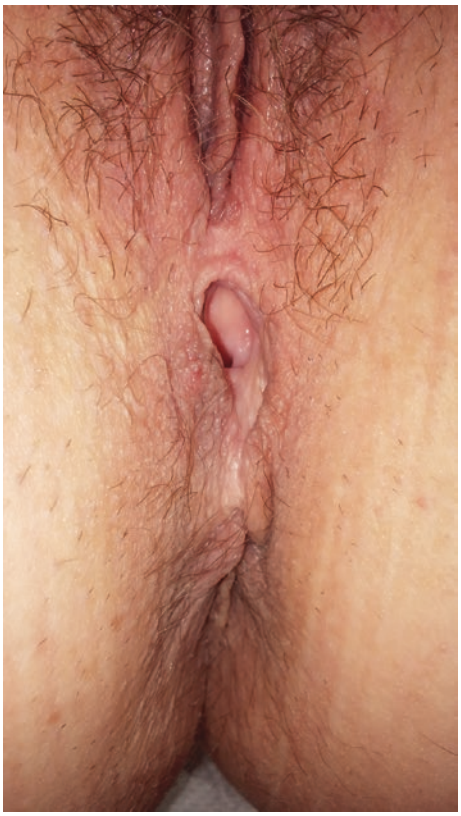

Fig. 9.11 Patient with perianal fistula, positioned between the vulva and anus, subsequent to the application of vacuum extractor and medium lateral episiotomy

9.8 Emerging Instruments for Operative Vaginal Birth

9.8.1 Odon Device

The Odon device is a new instrument for OVB. The Odon device consists of an inflatable circular air chamber attached to a thin circumferential polythene sleeve. Using a semi-rigid plastic applicator, the air chamber and sleeve are inserted into the birth canal and slipped past the widest diameter fetal head. The air chamber is inflated forming a seal around the fetal head and the applicator is then removed. During maternal contractions the accoucheur applies traction to the polythene sleeve, to assist the birth of the baby. It is hoped that it may have lower or comparable failure rate than ventouse and with lower complication rates. In particular, the lack of a negative-pressure generating cup means that it should not be associated with the adverse outcomes generated by negative pressure, such as subgaleal haemorrhage or retinal haemorrhage.

Whilst this is promising, the Odon device needs to be comprehensively evaluated in a robust clinical trial (which is currently in progress and should report by the end of 2017 [36] before it can be considered a viable instrument in the management of operative vaginal birth).

All obstetricians should be familiar with all methods of direct and operative birth but should use the instrument with which they are most expert. Performed well, operative vaginal birth remains safer than any alternative management option. Good operative vaginal birth technique and subsequently practice can be taught, and simulation training should play a role in this for all junior obstetricians going forward.

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Operative Vaginal Delivery

10

Hadar Rosen, Ryan Hodges, Antonio Malvasi, Andrea Tinelli, Dan Farine, and Enrico Marinelli

10.1 Introduction

Instrumental intervention to achieve vaginal delivery dates back to 1500 BC as evident by writings and pictures describing primitive forceps like tools. The first operative deliveries were performed on women who had been in labor for long hours and, thus, at high risk for death. Most of the time, fetuses did not survive these procedures as the priority was preserving maternal life. Nowadays, the goal of the use of forceps or vacuum in vaginal deliveries is to reduce fetal and neonatal morbidity and mortality.

The invention of the precursor to modern forceps is credited to Peter Chamberlin approximately around 1600 AC. The tale of the mystery delivery tool invented by a fugitive French Huguenot has fascinated readers for centuries. Nothing short of a good drama, the trade was passed along secretly for four generations. Forceps were only used with a blanket covering the perineum and operator to keep those in the know scarce [2]. The forceps have been modified and reinvented over the years. Over 700 types of obstetrical forceps have been described throughout history [3] (Fig. 10.1), some invented by leading obstetricians of the time including Simpson, Barnes, and Kejlland. It is astounding, however, what resemblance modern forceps have to the original secretive tools discovered in 1813 hidden under the floorboards of the Chamberlin family attic in their Essex residence, a testament to the family's ingenuity and enterprise [4] (Fig. 10.2).

The vacuum extractor was first described by James Young Simpson in 1848 and was popularized in Europe by Malmstrom in 1954 [5]. This instrument has also undergone many modifications over the years, most notably the evolution of the metal cup to the silastic and rubber cup, to what is now the modern vacuum extractor. In the 1970s, the vacuum extractor had almost completely replaced forceps for assisted vaginal deliveries in most northern European countries, but even its popularity in many English-speaking countries, including the United States and the United Kingdom, was limited. In later years, the number of vacuum-assisted deliveries surpassed the number of forceps deliveries in the United States, and in the year 2000, approximately 66 % of operative vaginal deliveries were by vacuum [6]. The latest modification to the vacuum is that by the late Australian obstetrician named Aldo Vacca. It is a handheld device that has a small cup connected to the body of the vacuum by a tube. This allows for an easier application over the occiput and can be used with any fetal head position. This Australian instrument is oddly named after a New Zealand bird the "Kiwi" [7] (Fig. 10.3).

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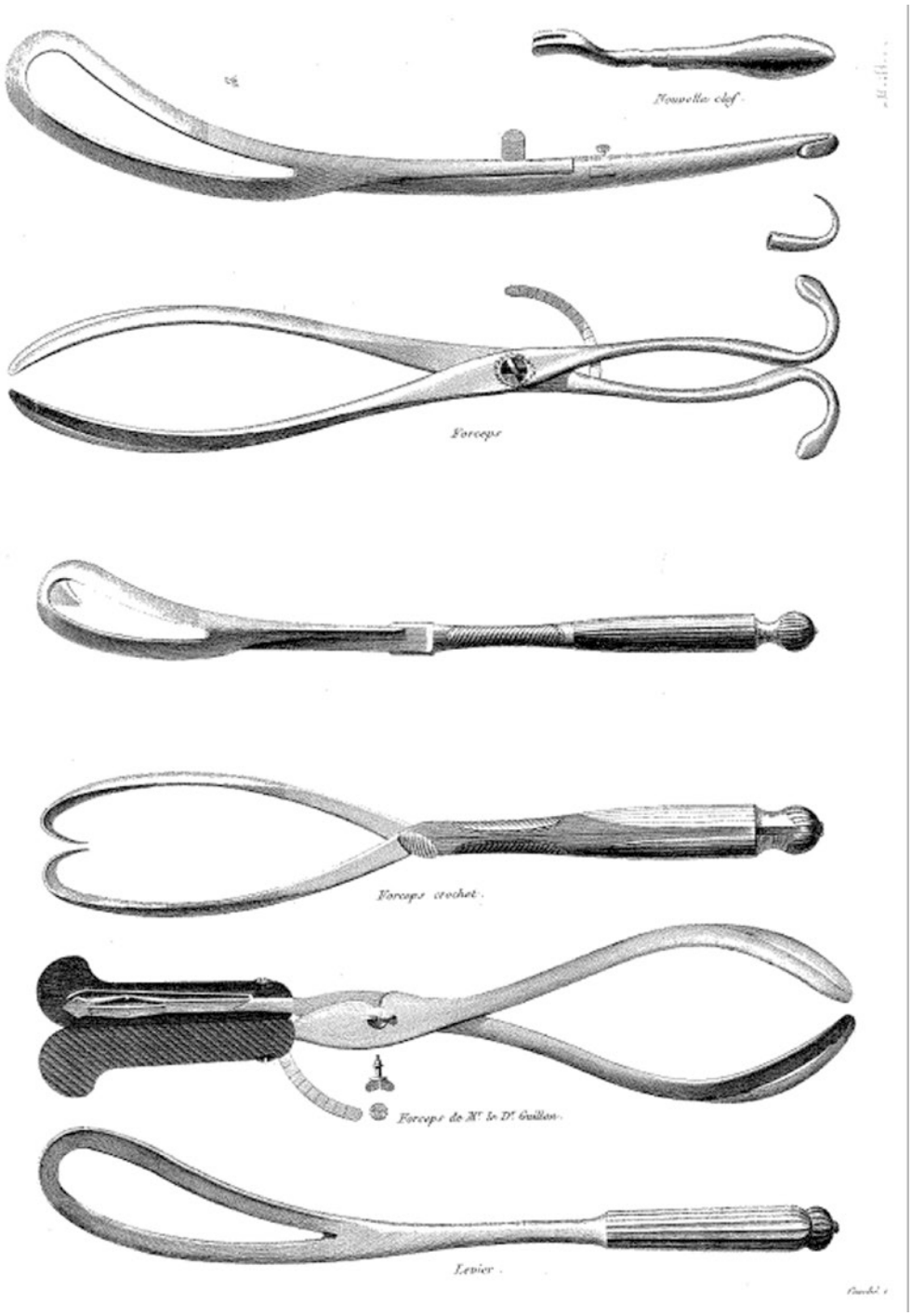


Fig. 10.1 Old diagram of different types of obstetrical forceps

10.2 Incidence

In the Western world, approximately 5–10 % of deliveries are instrumental vaginal deliveries. In the United Kingdom, the rates of instrumental vaginal delivery range between 10 and 13 % [8]. A survey of 37 maternity hospitals in France revealed the rate constituted 11.2 % of all live births in 2002 [9]. In Australia and New Zealand, forceps and vacuum extraction accounted for 7.4–16.4 % of all deliveries in 1999–2000 [10]. Recent figures from the United States are lower. The US rate of operative vaginal delivery decreased from 9.01 % of all deliveries in 1992 to 3.3 % of all deliveries in 2013 [11]. While in some area of the world forceps remains the instrument of choice, in the United States, forceps deliveries accounted for only 0.6 % of vaginal births, and vacuum deliveries accounted for 2.7 % of vaginal births [12] despite good evidence for their efficacy and safety [13]. This reflects a worldwide trend of declining rates of instrumental vaginal

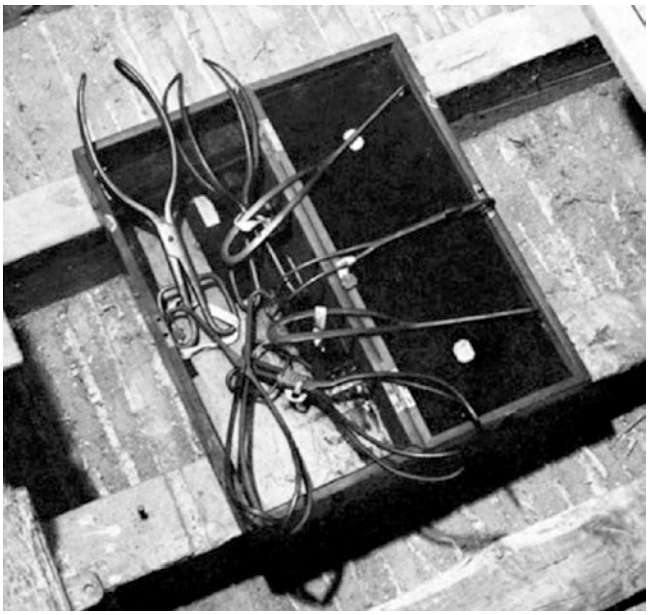


Fig. 10.2 The original Chamberlen forceps found at Woodham Mortimer, Essex (By Sheikh et al. [4])

deliveries along with interrelated rising rates of cesarean deliveries. Between 1996 and 2006, cesarean delivery increased by 50 %, while both spontaneous and operative vaginal births declined [14]. Despite this rising cesarean section rate, there has been no reduction in childhood cerebral palsy attributable to this practice [13, 15]. Rather, the explanation for this decline includes among other reasons lack of adequate training in residency programs and litigation concerns. A survey of graduating obstetricians in the United States reported alarmingly that half did not feel confident performing a forceps delivery [16].

A recent ACOG practice bulletin underscored that operative vaginal delivery, whether that be forceps or vacuum delivery, remains an important part of modern obstetric care and in the appropriate circumstances should be used to safely avoid cesarean delivery, in an effort to decrease first cesarean rates [13].

However, the FDA did publish a Public Health Advisory in 1998 warning about the possible complications of vacuum delivery and a warning about their use. This warning still appeared in the FDA site in 2015.

10.3 Indications

Operative vaginal deliveries are accomplished by applying direct traction on the fetal head either with forceps or a vacuum extractor. Regardless of the instrument chosen to expedite delivery, indications for instrumental deliveries remain the same. An operative vaginal delivery should only be performed if an appropriate indication exists. The clinical decision to proceed with an assisted operative delivery balances the maternal, fetal, and neonatal risks and benefits of the procedure with those of the alternative options, namely, cesarean birth or expectant management. It is also obviously dependent on operator skills, training, and expertise.

Forceps and obstetric vacuums are employed to assist a vaginal delivery for their potential to increase the expelling force (carefully adding to, or replacing, the maternal expelling forces); decrease the resistance force of the maternal birthing canal by modifying the perimeter of the fetal head and correcting fetal head malpositions, asynclitism, and deflection (Figs. 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 10.10, 10.11, 10.12, 10.13, 10.14, 10.15, 10.16, and 10.17); and decrease the resistance of the birthing canal by increasing the perimeter of the soft pelvis (in the case of forceps) [17, 18].

As such, operative delivery may be elective in case of maternal medical comorbidities that a priori dictate refrainment from maternal pushing efforts such as congestive heart failure, cerebral vascular malformations [18], as well as inadequate maternal expulsive efforts as in women with spinal cord injuries or neuromuscular diseases [19].

However, more often operative intervention is performed in an urgent manner when labor does not progress as expected or fetal distress is suspected (Table 10.1).

Another common indication used is maternal exhaustion, yet this clearly is highly subjective and risks should be carefully weighed against benefits prior to proceeding with the above as a single indication. Other less common indications are for instrumental intervention may be the delivery of the after-coming head in an assisted breech delivery as well as during cesarean section to deliver a "floating" fetal head.

10.4 Contraindications

In certain clinical situations, an operative vaginal delivery should not be attempted due to the potential harm to the mother or fetus. Prior to proceeding with an operative vaginal delivery, the operator should ensure no maternal or fetal contraindication to the procedure exists.

Contraindications related to the delivery process include unengaged fetal head or station above the mid-cavity, unknown position of the fetal head, and unruptured membranes and also if cephalopelvic disproportion is suspected or fetal malpresentation exists (such as breech, brow).

Fetal conditions that preclude operative vaginal delivery are known or strongly suspected bone demineralization conditions (e.g., osteogenesis imperfecta) or a bleeding disorder (e.g., alloimmune thrombocytopenia, hemophilia, or von Willebrand disease) [13, 19].

Performance of an operative vaginal delivery in a fetus with suspected macrosomia is supported by ACOG but should be performed with caution given the possible

Fig. 10.3 (**a**) Different types of vacuum extractors; (**b**) Kiwi vacuum extractor

increased risk of fetal injury of shoulder dystocia. Because of the risk of intraventricular hemorrhage, vacuum extraction is not recommended in fetuses with an estimated weight less than 2,500 g (which corresponds to 34 weeks of gestation) [19].

10.5 Nonoperative Practices that Decrease the Need for Operative Birth

Several nonoperative interventions have been shown to decrease the need for operative birth:

1. Involvement of one-to-one birth attendants who provide experienced continuous physical and emotional support care during labor [20].
2. Monitoring progress of labor with partograms and using oxytocin where progress is not adequate [21, 22].
3. Flexibility in the management of the second stage of labor including upright position, adequate analgesia, and delayed pushing if the woman does not have the urge to push [23, 24].
4. Flexibility with regard to time limits for the second stage of labor. Before diagnosing arrest of labor in the second stage, if the maternal and fetal conditions permit, allow for the following: at least 2 h of pushing in multiparous women and at least 3 h of pushing in nulliparous women. Longer durations may be appropriate on an individualized basis (e.g., with the use of epidural analgesia or with fetal malposition) as long as progress is being documented and provided fetal testing is reassuring [25, 26].

10.6 Prerequisites to Operative Delivery

The operator should verify that all criteria are met prior to proceeding with an operative vaginal delivery. The fetal head is engaged, the cervix is fully dilated, the membranes are ruptured, and the bladder is empty. The fetal lie, presentation, head position, and degree of asynclitism must be known (Figs. 10.18, 10.19, and 10.20).

Adequacy of the maternal pelvis by clinical pelvimetry should be evaluated, and adequate anesthesia provided. A recent study of obstetricians in Canada compiled an expert task list to describe the detailed assessment of the second stage of labor that is necessary to perform an operative delivery (Table 10.2).

10.7 Classification of Operative Vaginal Deliveries

Operative vaginal deliveries are classified by the station of the fetal head at application and the degree of rotation necessary for delivery (Table 10.3). The lower the fetal head in the maternal pelvis and the less degree of rotation needed to

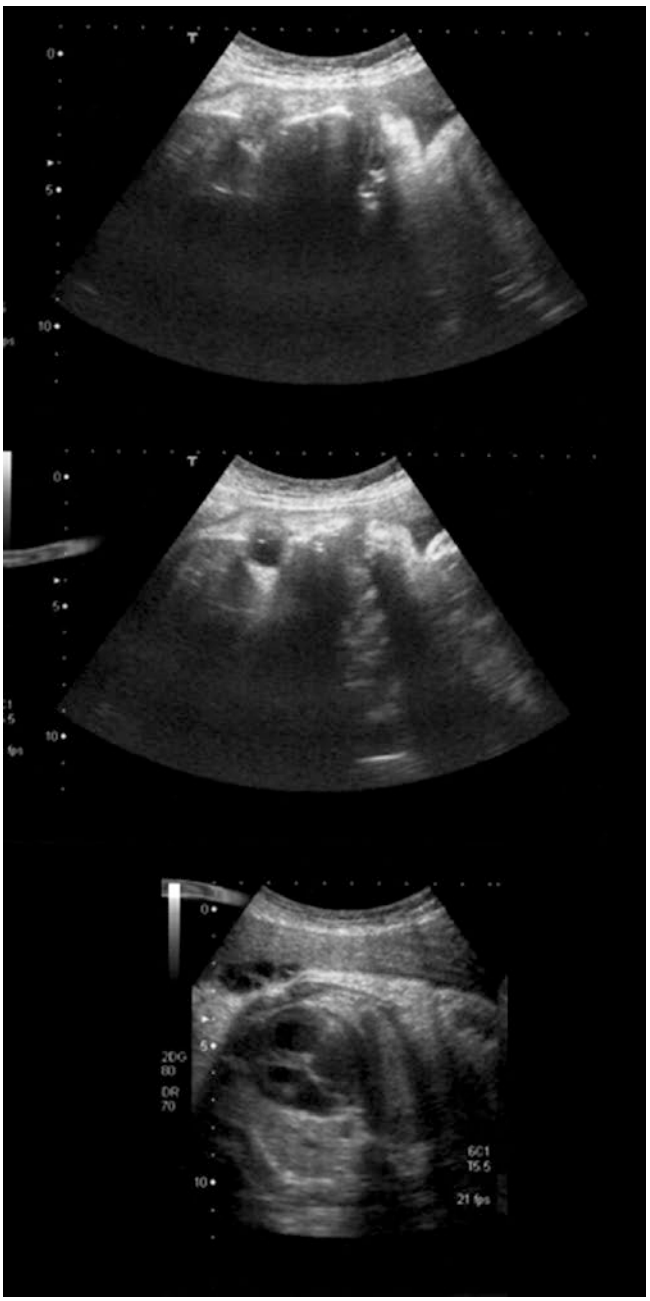


Fig. 10.4 Lateral asynclitism and persistent occiput posterior position ultrasonographic signs: (1) asymmetric fetal profile (sagittal section), on the *top* of the image; (2) squint sign (transversal section), in the medium; (3) four chambers (transverse chest section), the *bottom* image; (4) posterior spine (transverse fetal chest section)

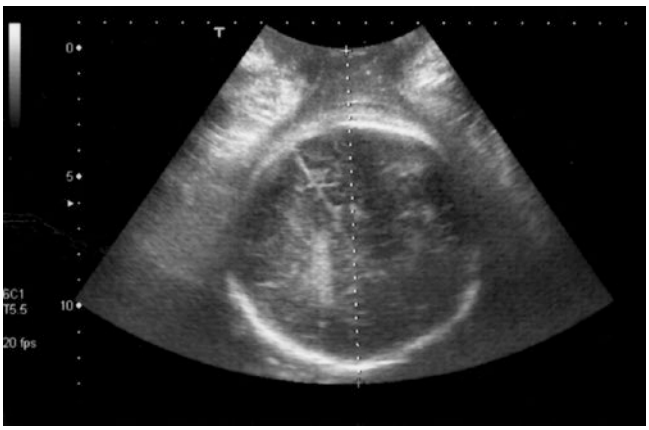


Fig. 10.5 Translabial transverse ultrasonographic section of a malpositioned fetal head, as a consequence of internal rotation failure. In fact in this image, the fetal *midline* shows an angle with the symphysis pubis – sacral line (or anterior posterior pelvis line) >45°. In this case, the fetal head is in occiput posterior position

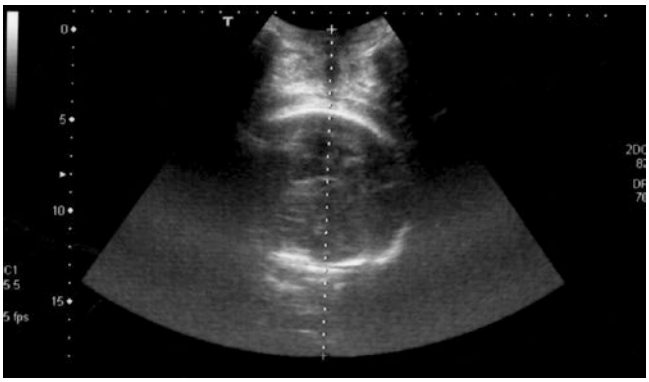


Fig. 10.6 Translabial 2D ultrasonographic section in a dystocic second stage labor. The fetal head has a malrotation and a malposition in the pelvis. The *midline* angle is of 90° (the fetal *midline* crosses at 90° the anterior-posterior diameter, perpendicularly).

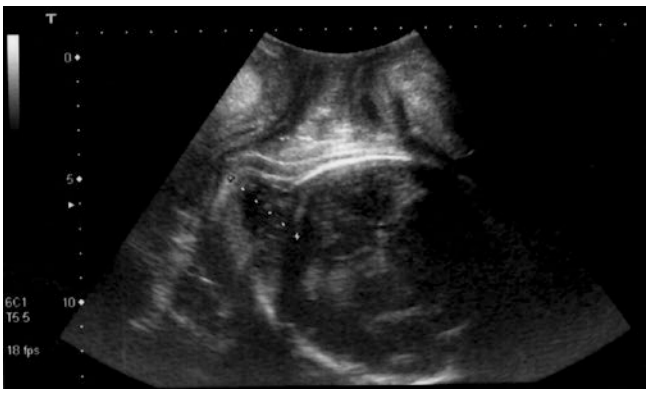


Fig. 10.7 Translabial 2D ultrasonographic scan of a fetal head in persistent occiput posterior position and anterior asynclitism (the midline is anterior and the squint sign not detectable). The caput succedaneum measures 35.7 mm, and it reduces the efficacy of the digital palpation for the diagnosis of sutures and fontanel positions. However, the caput succedaneum dimensions do not have a clinical correlation with the modality of delivery

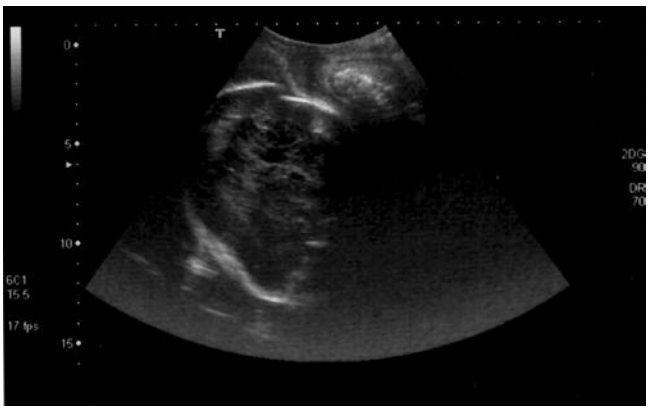


Fig. 10.8 Translabial sagittal ultrasonographic section in the second stage of labor: the fetal head is in occiput posterior position, in upward direction. The image shows the physiologic molding and the caput succedaneum. A molding associated to the caput succedaneum represents a reason of vacuum application failure, during vaginal operative delivery

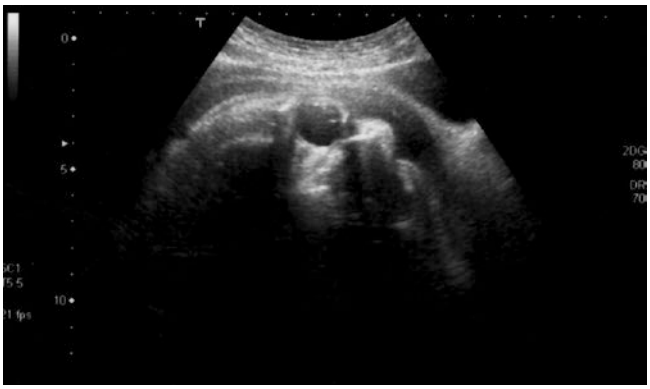
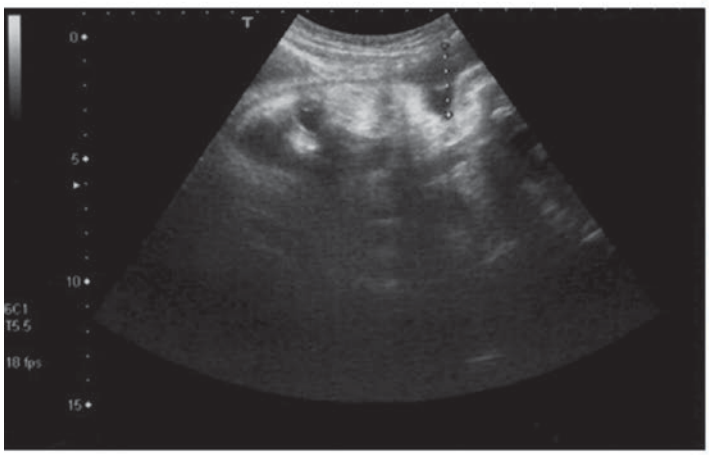


Fig. 10.9 Transverse transabdominal 2D ultrasonographic section of fetal head in second stage dystocic labor. The fetal head is positioned into the pelvis in anterior asynclitism associated to right posterior occiput position



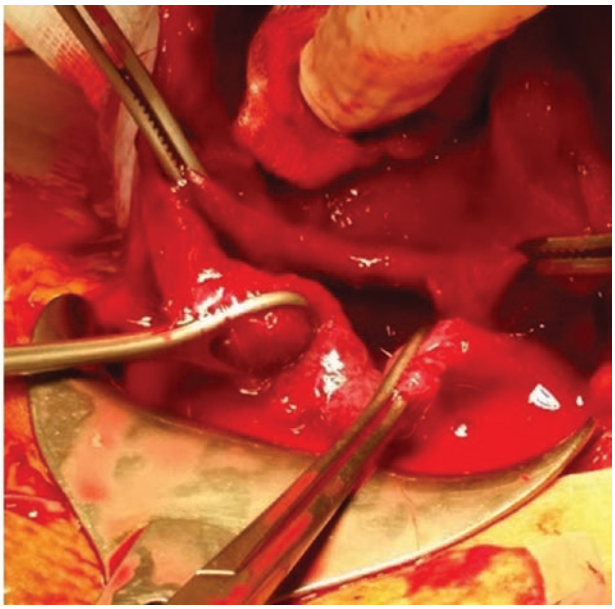


Fig. 10.10 Transabdominal longitudinal ultrasonographic scan of the fetal head in second stage dystocic labor. The fetal head has malrotation and malposition in persistent occiput posterior position and lateral asynclitism. The trace marked the ultrasonographic sign of bundle ring, on the left; on the right, the bundle ring showed during cesarean section

deliver, the less associated risks for the mother and fetus. Operative vaginal delivery is contraindicated if the fetal head is not engaged in the maternal pelvis or if the position of the vertex cannot be determined.

10.8 Consent

There exists no absolute indication for an operative vaginal delivery, and alternative delivery options such as cesarean delivery or continued expectant management with oxytocin augmentation should be communicated to the patient according to the specific case. Operative vaginal delivery is not without risk to the parturient as well as to the fetus as detailed below. Therefore, patient informed consent regarding potential risks, benefits, and alternatives to operative vaginal delivery should be discussed as part of the preparations to an operative delivery. This may not be comprehensive when the intervention is deemed urgent for acute fetal distress, but can still be achieved quickly, and maternal compliance is essential for safe and effective operative delivery. In the absence of emergency, patient consent is paramount. The 2011

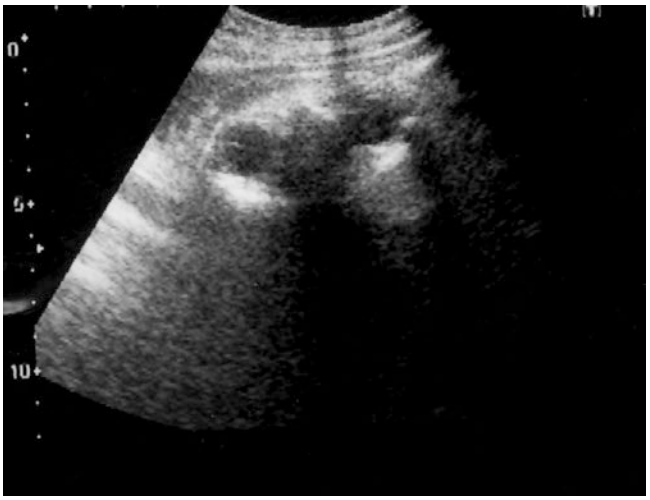


Fig. 10.11 Transabdominal transverse ultrasonographic scan during a dystocic second stage of labor showing the fetal head in left persistent occiput posterior position. This malposition usually provokes the vacuum application failure, especially in case of "soft vacuum" application (i.e., the Kiwi vacuum extractor). To avoid the vacuum application failure, literature suggests to preliminary diagnose the fetal head position and rotation before vacuum application by intrapartum ultrasonography

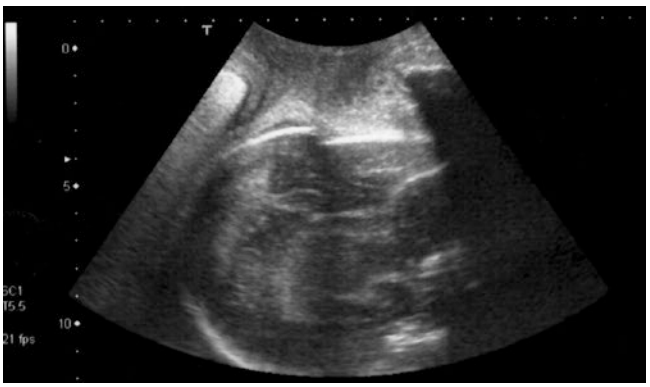


Fig. 10.12 Translabial longitudinal 2D ultrasonographic section of the fetal head with molding in consequence of occiput posterior position and asynclitism (in second stage of labor)

ROGC guidelines refer to the issue of informed consent. It states that women should be informed about operative vaginal delivery ahead of time as part of routine antenatal education.

This information should include the strategies known to be effective in reducing the need for operative vaginal birth as detailed above. The principles of obtaining valid consent during labor should be followed. Where possible, information should be given to women in labor between contractions. Obstetricians must document the decision, the reasons for proceeding to an operative birth, and consent. An accurate record of the operative vaginal delivery must be completed [27].

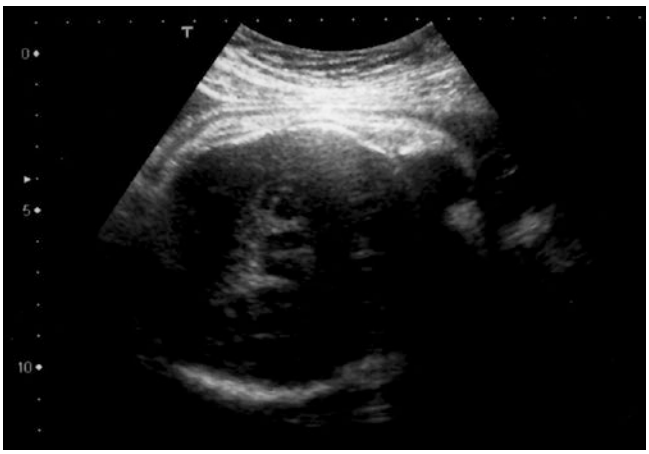


Fig. 10.13 Transabdominal transverse ultrasonographic section of the fetal head in transverse position (with right occiput position) and posterior asynclitism. Transverse midline sign, transverse thalami, and transverse orbits represent the ultrasonographic signs

10.9 Forceps

There are many different designs for forceps, all consist of two separate halves that have four basic components: blade, shank, lock, and handle. More than 700 different types of forceps have been described (Fig. 10.1).

Those could be divided into three categories:

Classical forceps: have cephalic and pelvic curvatures. Usually indicated when no rotation of the fetal head is necessary before delivery. Common types include Simpson, Tucker-McLane, and Elliot forceps. Some further divide these into forceps more appropriate for primipara (e.g., Simpson) and those for multipara (Tucker-McLane).

Rotational forceps: have cephalic curvature but lack a pelvic curvature. Also have a sliding lock to allow forceps to slide to correct asynclitism of the fetal head if present. When rotation of the fetal head is accomplished, classical forceps can be considered to complete the delivery but this is an individual's preference. Types include Kielland, Luikart, Barton (for deep transverse arrest), and Salinas forceps.

Forceps for breech delivery: indicated to help with the after-coming head in a breech delivery. These forceps lack a pelvic curvature and have blades that are beneath the plane of the shank. Types include Piper and Laufe forceps.

10.10 Forceps Application

10.10.1 Phantom Application

The operator holds the forceps in front of the perineum in the same angle and position expected for application.

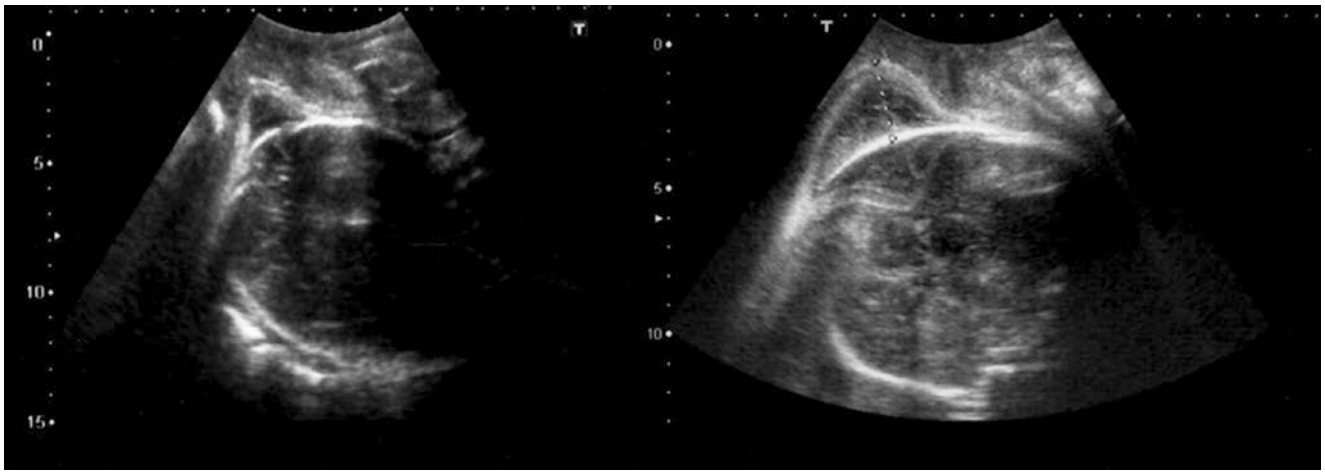


Fig. 10.14 Translabial sagittal ultrasonographic scan of the fetal head in the birth canal with caput succedaneum in dystocic second stage labor. In this case, the fetal head is positioned in left occiput posterior position and posterior asynclitism. The asynclitism and the molding lead to an operative vaginal delivery, with presumable failure of vacuum extraction and urgent cesarean delivery

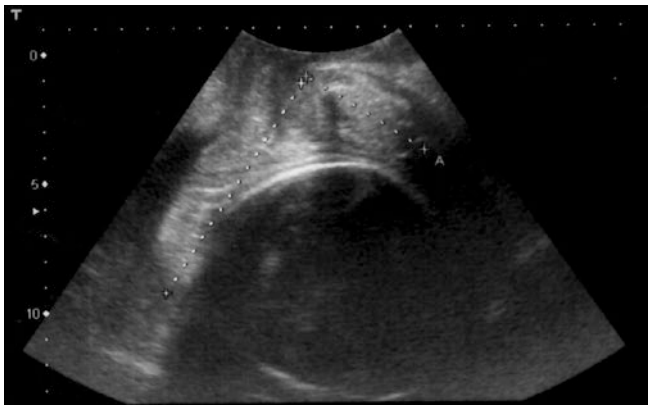


Fig. 10.15 Translabial longitudinal ultrasonographic section during a second stage dystocic labor. Measurement of the angle progression shows the downward direction. The vacuum application, in such case, leads to a failure of fetal extraction (operative delivery failure)

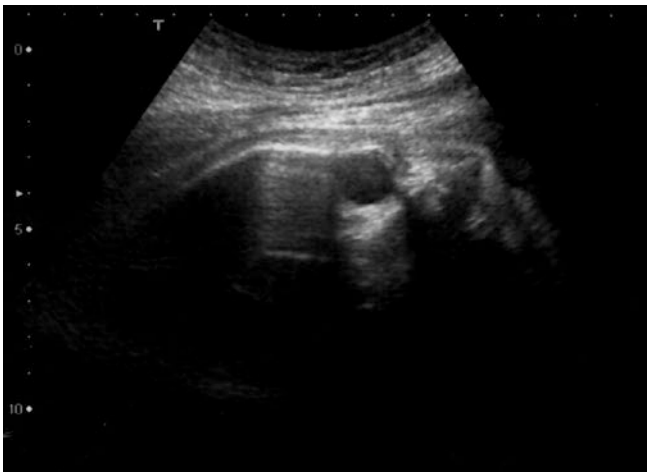


Fig. 10.16 Transabdominal transverse ultrasonographic scan of the fetal head in right occiput posterior position with posterior asynclitism (left squint sign) during a second stage dystocic labor

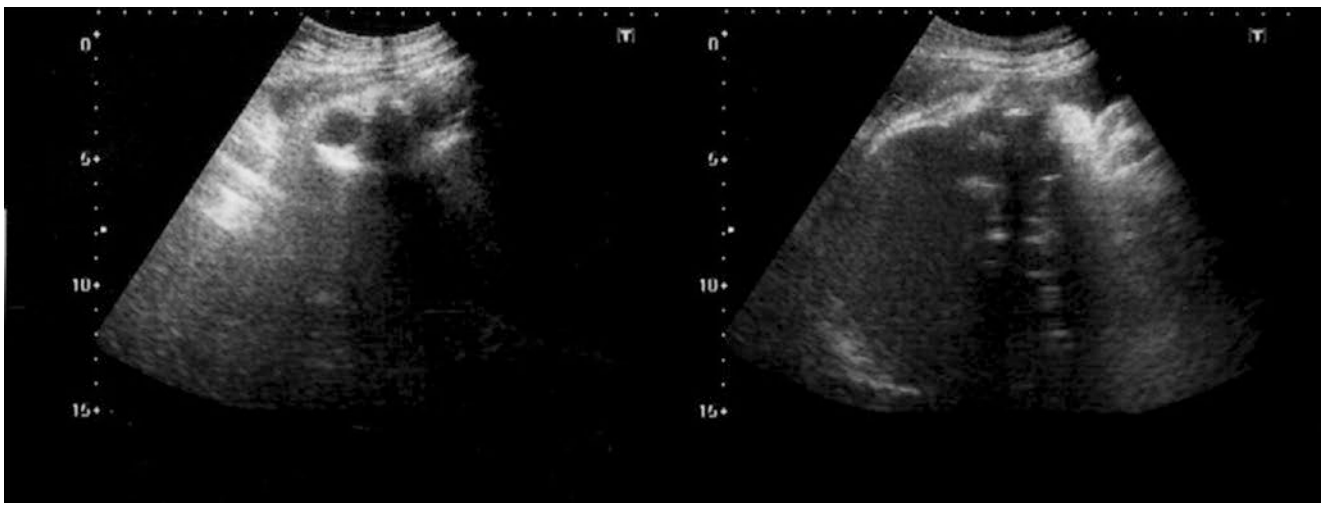


Fig. 10.17 Transabdominal transverse ultrasonographic section of the fetal head in linear occiput posterior position (anterior orbits lens and nasal bridge), on the left. Asymmetric fetal profile in transabdominal sagittal ultrasonographic section, on the right. These signs indicate the lateral asynclitism signs

Table 10.1 Indications of operative vaginal deliveries

Indication	ACOG	RCOG	SOGC	RANZCOG
Fetal	Suspicion of imminent or potential fetal compromise	Presumed fetal compromise	Nonreassuring fetal status	Fetal compromise suspected or anticipated
Maternal/medical	Shortening of the second stage for maternal benefit	Indications to avoid Valsalva Examples: Cardiac disease Class III or IV Hypertensive crises Cerebral vascular disease Myasthenia gravis Spinal cord injury	Medical indications to avoid Valsalva Examples: Cerebral vascular disease Cardiac conditions	Maternal effort contraindicated Examples: Aneurysm Risk of aortic dissection Proliferative retinopathy Severe hypertension, or Cardiac failure
Obstetric	Prolonged second stage: Nulliparous women: lack of continuing progress for 3 h with regional anesthesia, or 2 h without regional anesthesia Multiparous women: lack of continuing progress for 2 h with regional anesthesia, or 1 h without regional anesthesia	Inadequate progress: Nulliparous women: lack of continuing progress for 3 h (total of active and passive second stage of labor) with regional anesthesia, or 2 h without regional anesthesia Multiparous women: lack of continuing progress for 2 h (total of active and passive second-stage labor) with regional anesthesia, or 1 h without regional anesthesia Maternal fatigue/exhaustion	Inadequate progress: Adequate uterine activity documented No evidence of cephalopelvic disproportion Lack of effective maternal effort	Delay in the second stage of labor: There is no clear demarcation as to an appropriate length of time to wait before embarking on instrumental delivery for failure to progress It is a matter for the clinician and patient given the particular circumstance

By Gei and Belfort [17]
Data from Refs. [15, 21, 26, 45]
ACOG American Congress of Obstetricians and Gynecologists, *RANZCOG* Royal Australian and New Zealand College of Obstetricians and Gynecologists, *RCOG* Royal College of Obstetricians and Gynecologists, *SOGC* Society of Obstetricians and Gynecologists of Canada

10.10.2 Application

The forceps blades are applied and checked. The posterior fontanelle should be located midway between the sides of the blades, with the lambdoid sutures in an equal distance from the blades and one finger-breadth above the plane of the shanks. The sagittal suture must be perpendicular to the plane of the shanks throughout its length; the fenestration of the blades should be barely felt, and the amount of fenestration felt on each side should be equal. If the blades have not been applied deeply enough, the palpable fenestration will be more than a fingertip, and the operator is alerted to the risk of facial nerve injury.

10.10.3 Traction

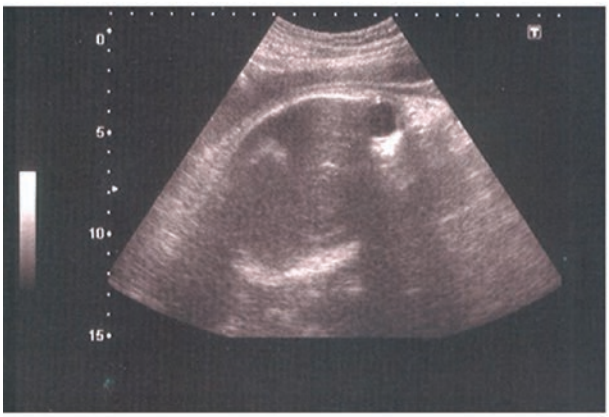
Gentle traction in the direction of the vaginal canal is applied concurrent with contractions and maternal bearing down effort. Between contractions the grip is relieved to reduce compression of the baby's head. Episiotomy should be considered, as discussed below.

If no descent is apparent with three contractions or pulls or if 15 min have elapsed abandoning the procedure and proceeding with a cesarean delivery should be strongly considered. The results of an expert task list developed for forceps and rotational forceps delivery are shown in Tables 10.4 and 10.5.

10.11 Vacuum

10.11.1 Choice of Cup

The original vacuum extractors were rigid and made of metal. There are currently two main types of vacuum cups, rigid and soft. Rigid cups may be made of metal or plastic, while soft cups are made of either plastic, polyethylene, or silicon. The soft cups are gradually replacing the rigid cups as they hold a lower risk of fetal scalp trauma (13 % vs. 24 %). A contrary consideration is that soft cups tend to fail more in achieving vaginal deliveries (16 % vs. 9 %) [6, 28, 29]. Maternal injury, low Apgar scores at 1 or 5 min, umbilical artery pH <7.20, cephalohematoma, hyperbilirubinemia/phototherapy, retinal/intracranial hemorrhage, and perinatal



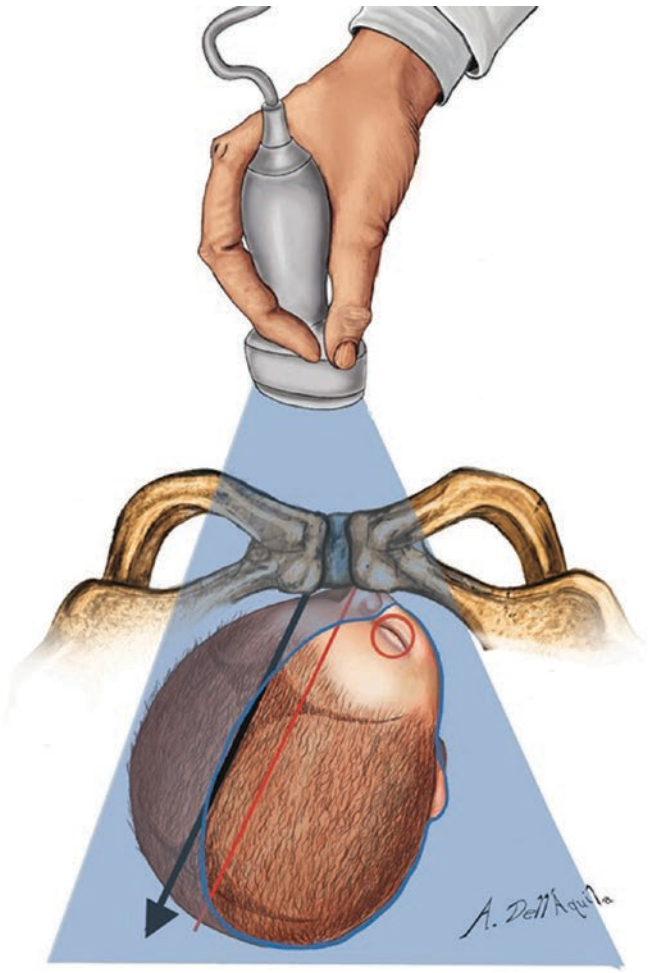


Fig. 10.18 High asynclitism

death do not differ between soft and rigid vacuum cups [28]. Therefore, soft cups should be considered for occiput anterior deliveries, while rigid cups can be reserved for more challenging interventions such as larger infants, significant scalp edema, occiput posterior presentation, or asynclitism. The Kiwi cup is now commonly used in many centers. It has the advantage of being a small, handheld device that can be used for both routine and rotational deliveries [29, 30]. Metal cup is really history and the current consideration is between Kiwi and a silastic one like the Kobayashi; there is a trade-off between better application and force of traction.

10.11.2 Cup Placement

The suction cup should be placed symmetrically on the sagittal suture at the pivot (or flexion) point located 2-cm anterior to the posterior fontanelle or 6-cm posterior to the anterior fontanelle and lies in the midline regardless of fetal position [6] (Fig. 10.21).

Correct placement will facilitate flexion, descent, and rotation of the vertex when traction is applied and will minimize injury to both the fetus and soft tissues of the birth canal [19].

The Kiwi cup, for example, has measurements on the thin tubing so that it is assured that the cup placement is on the flexion point as determined by their detailed vaginal examination. Once the cup is in the correct place, the operator then sweeps their finger around the cup to assure no maternal tissue is entrapped within the cup prior to creating negative pressure within the cup to avoid tissue injury.

Vacuum application begins with low suction and increased to vacuum of about 0.7–0.8 kg/cc2 (500–600 mmHg) if connected to wall suction. A study comparing stepwise versus rapid pressure application demonstrated that the rapid technique was associated with a significant reduction in the duration of vacuum extraction by an average of 6 min without adversely impacting fetal and maternal outcome [31]. Suction is generated with the Kiwi cup by repetitively squeezing the handle and watching the green and red zone color box to ensure correct amount of suction. The dominant hand exerts steady traction in the direction of the vaginal canal and keeping the tubing at 90° to the cup with no rocking motions, while the nondominant hand

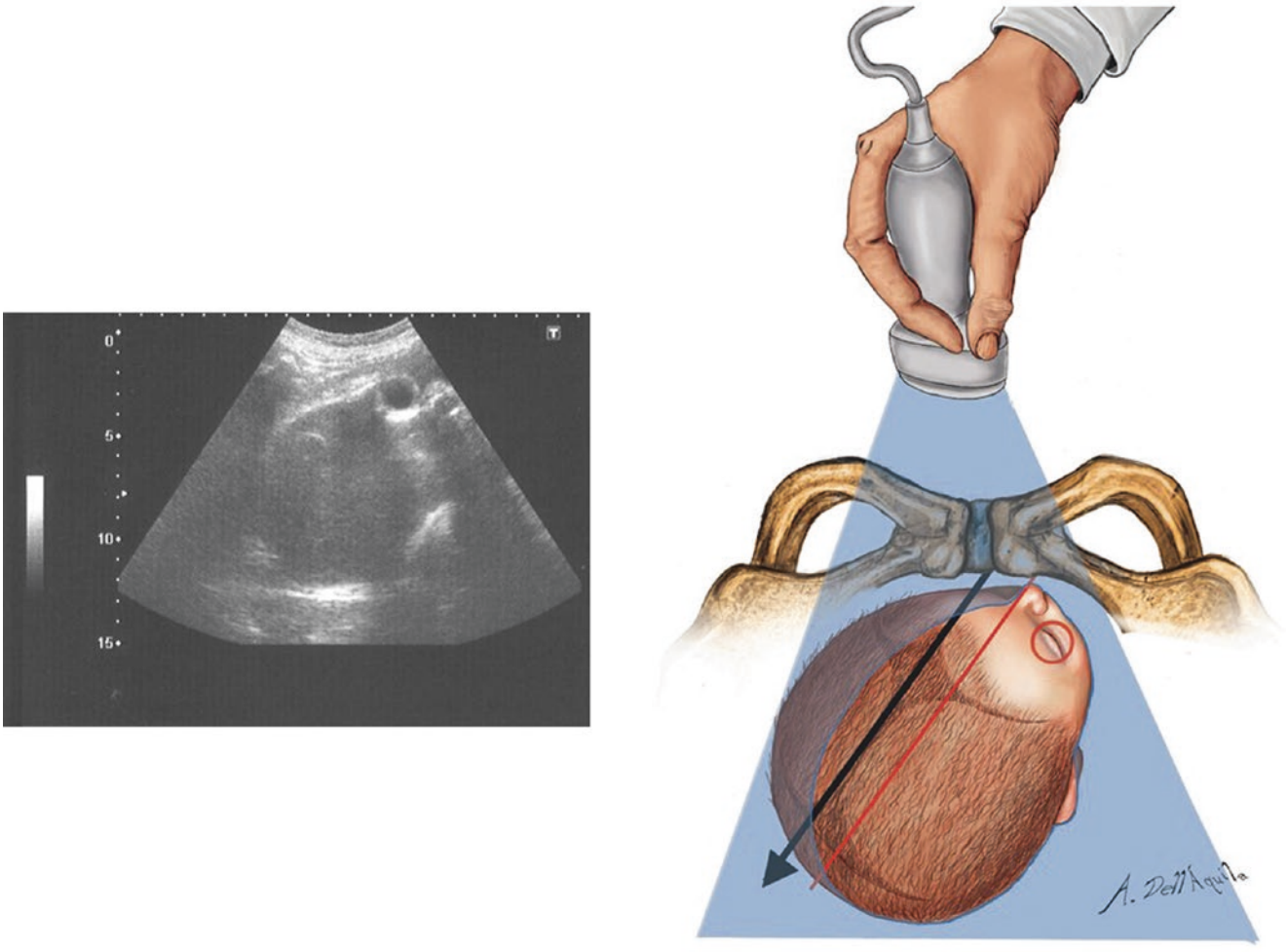


Fig. 10.19 Medium asynclitism

monitors the progress of descent and prevents cup detachment by applying moderate counterpressure directly to the vacuum cup.

The maximum time to safely complete a vacuum extraction and the acceptable number of detachments is unknown. In an observational study of 393 singleton term pregnancies, 82 % of successful deliveries were achieved within one to three pulls, and more than three pulls were associated with a 45 % risk of neonatal trauma [32]. It is generally recommended that vacuum-assisted deliveries be achieved with no more than three sets of pulls and a maximum of two to three cup detachments (pop-offs) [19].

10.11.3 Choice of Instrument

Forceps and vacuum extractors have low risk of complications and are both acceptable for operative vaginal delivery [11, 33]. Both types of instruments are effective in delivering the fetus and shortening the time to delivery. Specific clinical situation and operator preference and comfort level drive the choice of whether to use vacuum or forceps. Candidates should be selected on an individualized basis and counseled accordingly. The different risk profile for each tool may also guide this choice.

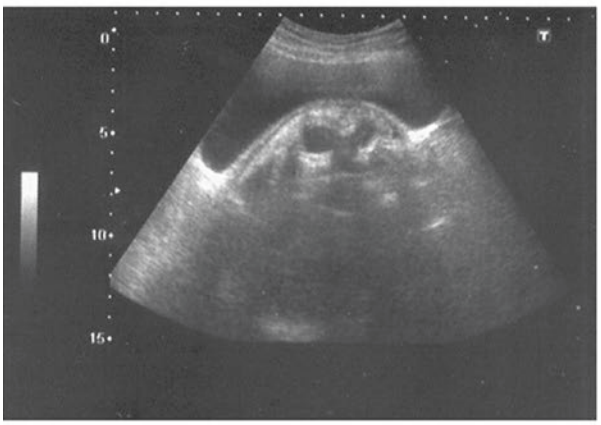
10.12 Vacuum Versus Forceps

10.12.1 Advantages of Vacuum

Vacuum extraction is believed to be easier to learn. Generally, vacuum is better tolerated when analgesia is absent or inadequate and causes less postpartum pain [33].

10.12.2 Advantages of Forceps

A vaginal birth is more likely to be achieved with forceps than with vacuum extractors [33–35] and they are less likely to detach from the fetal head. According to most authorities, forceps are the preferred instrument for operative deliveries



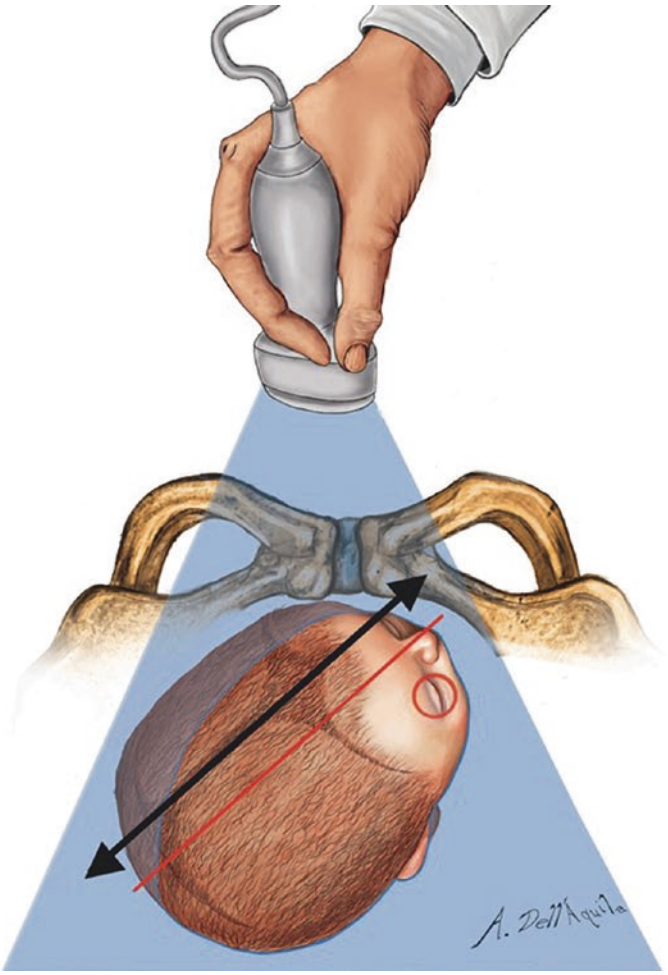


Fig. 10.20 Low asynclitism

performed at less than 34 weeks of gestation to prevent intracranial hemorrhage. For face presentation, and delivery of the breech presentation after-coming head, forceps but not vacuum may be used. The Cochrane review commenting on choice of instrument noted a trend toward fewer cases of cephalhematoma with forceps [36].

10.12.3 Complications of Operative Deliveries

10.12.3.1 Maternal Complications

Instrumental deliveries may increase short- and long-term maternal morbidity, including perineal pain at delivery, pain in the immediate postpartum period, perineal lacerations, hematomas, blood loss and anemia, urinary retention, and long-term problems with urinary and fecal incontinence [19]. However, these risks must be compared to the risks of expectant management and full dilatation cesarean delivery.

10.12.3.2 Short-Term Complications: Obstetric Anal Sphincter Injuries

The quoted rate of third- and fourth-degree tears with forceps from different studies is up to 7 % [37]. Forceps delivery appears to have a higher risk of anal sphincter injury in comparison with vacuum delivery. In a review of 13 randomized trials of forceps delivery versus vacuum delivery, including 3,338 women, forceps use was associated with a higher rate of third- and fourth-degree tears [36]. Another meta-analysis of ten clinical trials concluded that vacuum-assisted deliveries were associated with significantly less maternal trauma than forceps, including a lower rate of severe perineal injury (odds ratio [OR], 0.41; 95 % confidence interval [CI], 0.33–0.50 [33].

Another retrospective study that reviewed 508 operative vaginal deliveries found an increased risk of episiotomy (90.5 vs. 81.8 %; $p = 0.01$) and combined third- and fourth-degree perineal lacerations (44.4 vs. 27.9 %; $p < 0.001$) in the forceps groups compared with the vacuum group. There was no significant difference in the number of third-degree

Table 10.2 The detailed assessment of the second stage of labor, necessary to perform an operative delivery

Summarized expert task list of the assessment of the second stage of labor for operative delivery
1. Focused history
Demographics, medical history, past obstetric and relevant gynecological history, antenatal history, medications, allergies, intrapartum history, use of oxytocin, need for analgesia, fetal wellbeing (EFM, scalp sample, color of liquor)
2. Vital signs (maternal and fetal heart rate monitoring/fetal scalp sample)
3. Abdominal examination (performed first)
Size of the fetus
Position
Room between the breech and the maternal ribs
Amount of head palpable abdominally (coordinate with maternal breathing): 0/5 fingerbreadths above pelvic brim reassuring, 1/5 consider trial of delivery in the OR, more than 1/5 operative delivery contraindicated
4. Vaginal examination
"Sweep" at full cervical dilatation
Strategies to detect fetal position: counting sutures technique, 3-finger technique, peace sign, 10 o'clock to 2 o'clock, fetal ear (tragus and pinna), ultrasound rarely necessary
Confirm station: consistent definition of bony prominence at ischial spines; beware caput; asymmetry of maternal spines; push head up vaginally to abdominal hand; palpable ear usually means low enough for operative delivery; relationship of fetal head and neck (e.g., deflexed); deep transverse arrest may give asynclitism and more room posteriorly with true station higher anteriorly
Caput and molding: degree of relative (or absolute) cephalopelvic disproportion
Adequacy of pelvis: format measurements not required; general feel appropriate; if the fetal head is touching three of five pelvic points (ischial spines, anterior pubic rami, sacrum) there may not be enough room to deliver the fetus vaginally
5. Assessing descent with maternal pushing: does the fetus fill the pelvis?
6. Communication to the mother and her support personnel in detail why the baby is not yet born, strategies to achieve delivery, and obtaining informed consent
7. Documentation

By Hodges et al. [79]

Table 10.3 Operative vaginal delivery

Criteria for the different types of forceps delivery
Outlet forceps ←
Scalp is visible at the introitus without separating the labia
Fetal skull has reached the pelvic floor
Fetal head is at or on perineum
Sagittal suture is in anteroposterior diameter or right or left occiput anterior or posterior position
Rotation does not exceed 45 degrees
Low forceps
Leading point of the fetal skull is at station +2 cm or more and not on the pelvic floor
Without rotation: Rotation is 45 degrees or less (right or left occiput anterior to occiput anterior, or right or left occiput posterior to occiput posterior)
With rotation: Rotation is greater than 45 degrees
Midforceps
Station is above +2 cm but head is engaged

By Practice Bulletin No. 154. American College of Obstetricians and Gynecologists [11]

lacerations between the two groups. Demonstrated was an increase in the number of peri-urethral lacerations in the vacuum group (4.2 vs. 0.5 %; $p = 0.026$) [38].

A review of over 50,000 vaginal deliveries at the University of Miami reported that obstetric anal sphincter injuries were higher in vacuum-assisted (10 %) and forceps deliveries (20 %) compared with spontaneous vaginal deliveries (2 %) [39].

The highest rates of maternal perineal trauma are associated with deliveries involving occiput posterior position, rotations larger than 45°, and with midforceps procedures [40–42].

Table 10.4 Expert task lists developed for forceps

Key points
1. Careful maternal and fetal assessment; ensure analgesia is adequate; and empty bladder
2. Assemble team; one team member to palpate contractions; and check equipment
3. Phantom application of forceps
4. Application: lubrication, apply between contractions, "pencil grip," and check the application
5. Apply traction in a semicircle: angling upward too soon can cause deep sulcal lacerations; angling too late traumatizes the perineal body. Consider episiotomy
6. Prepare for shoulder dystocia and postpartum hemorrhage
7. Debrief with parents, both at the time of delivery and the following day (ideally); and thorough documentation

By Simpson et al. [80]
Red flags: handles of forceps disappear into vagina (head too high); forceps cannot be applied easily: or no descent with contractions (adjust angle and if still no descent after 2 pulls, abandon)

Long-term complications may also be inflicted by operative vaginal deliveries.

The abovementioned Cochrane review concluded that flatus incontinence or altered continence is more common following forceps delivery compared to vacuum deliveries [36].

If no anal sphincter laceration occurs with operative vaginal delivery, anal incontinence rates at 5–10 years after delivery are similar to those in women who had a spontaneous vaginal delivery [43].

10.12.4 Fetal/Neonatal Injuries

The absolute rate of newborn injury with forceps and vacuum deliveries is low [11].

10.12.4.1 Short-Term Complication

When injury does occur, it may range from mild scalp laceration, through different degrees of hemorrhage (Fig. 10.22) including cephalhematomas and subgaleal hematomas, to devastating intracranial hemorrhage as well as facial nerve palsies, hyperbilirubinemia, and retinal hemorrhage [19]. The risk of a fetal complication is estimated at around 5 % [44].

In general, forceps have a lower risk of scalp injury and hematomas than vacuum [45], while neonatal facial injury is more likely with forceps compared to vacuum [36].

Cephalhematomas are more common with vacuum than with forceps deliveries (14–16 % vs. 2 %, respectively) [33, 46] and are usually self-limited and resolve spontaneously.

Neonatal subgaleal and intracranial hemorrhage may be life-threatening complications. The incidence of after vacuum-assisted vaginal delivery ranges from 26 to 45 per 1,000 deliveries [11]. They develop within 1–24 h following delivery and are caused by the rupture of the emissary vein in the loose subaponeurotic tissue. The hematoma spreads in a large space, which extends from the orbit to the nape of the neck, causing a large collection of blood that can lead to hypovolemic shock. It is more common with vacuum rather than forceps delivery. The most dreaded complication is intracranial hemorrhage. A large review of over 580,000 term singleton deliveries reported an incidence of 1 in 860 for vacuum extraction compared with 1 in 1,900 for women who delivered spontaneously. The incidence was the highest (one in 280) in women delivered by combined forceps and vacuum-assisted vaginal deliveries [15].

A cross-sectional study evaluating the incidence of neonatal retinal hemorrhage found that the incidence was higher for vacuum-assisted vaginal deliveries (75 %) compared with spontaneous vaginal (33 %) and cesarean deliveries (7 %) [47]. In 1998 an FDA public health advisory was issued regarding the use of vacuum. The advisory suggested to inform patients that fetal complications including subgaleal hematomas and intracranial hemorrhage had been associated with vacuum extraction [48, 49].

Concerns rose following 12 deaths and 9 serious complications reported among infants exposed to vacuum-assisted devices between 1994 and 1998, a rate that was fivefold increase compared to that reported in the previous 11 years. The FDA advised recommendations for the safe use of vacuum extractor devices, specifically to refrain from rocking movements and from the application rotation but rather a steady traction in the line of the birth canal. They also stressed the importance of involving pediatricians to promote close monitoring closely after delivery.

10.12.4.2 Long-Term Complications

Though scarce data exists, there appears to be little risk of neurodevelopmental deficits in children born by operative vaginal delivery. In 1991, a cohort study evaluated the long-term outcome of neonates delivered by forceps or vacuum extraction. A total of 52,282 young people were subjected to an intelligence test and physical examination at

Table 10.5 Expert task lists developed for forceps

Key factors in a rotational forceps delivery
1. Prevention of fetal malposition
Early assessment and documentation of fetal position
Judicious use of oxytocin
Consider manual rotation
Consider the indication for forceps-assisted delivery carefully
2. Assessment to determine suitability
Careful second stage assessment
Adequate analgesia
Empty maternal bladder
Red flag: assessment of position difficult due to molding/caput
3. Communication and consent
Maternal complications: perineal/cervical trauma (similar to other operative deliveries)
Fetal complications: intracranial hemorrhage, cervical spine injury, entrapment of umbilical cord (similar to other operative deliveries)
Discuss reason for prolonged labor
Discuss timing of procedure
Recommend episiotomy
4. Assemble the multidisciplinary team
Nurse/midwife to palpate contractions
Pediatrician/respiratory technician/anesthetist
Delivery in operating room
Position patient, check equipment
5. Phantom application
Reconfirm fetal position
6. Application by the "wandering technique"
Apply between contractions
Correct asynclitism between contractions
Red flag: difficult application
7. Rotation
Between contractions
Force of one hand only; other hand on maternal abdomen
Ensure OA position after rotation
Red flag: difficult rotation
8. Application of traction
During a contraction
Force of one hand only
Episiotomy
Red flag: force of more than one hand required
9. Delivery of fetus
Remove blades after delivery of head
Prepare for shoulder dystocia and/or postpartum hemorrhage
10. Debrief and document
Examine cervix/vagina/perineum
Examine the baby
Document indications, discussion, timing

By Simpson et al. [81]

17 years of age. After controlling for confounding factors, there were no significant differences in cognitive skills among those delivered spontaneously or by vacuum or forceps assistance [50]. In 2007, a prospective cohort study examined the neurodevelopmental outcomes in children at the age of 5 years born by either instrumental vaginal delivery or cesarean section in the second stage of labor. Outcomes were similar between the two groups and demonstrated only a very low risk of neurodevelopmental abnormality at 5 years of age [51].

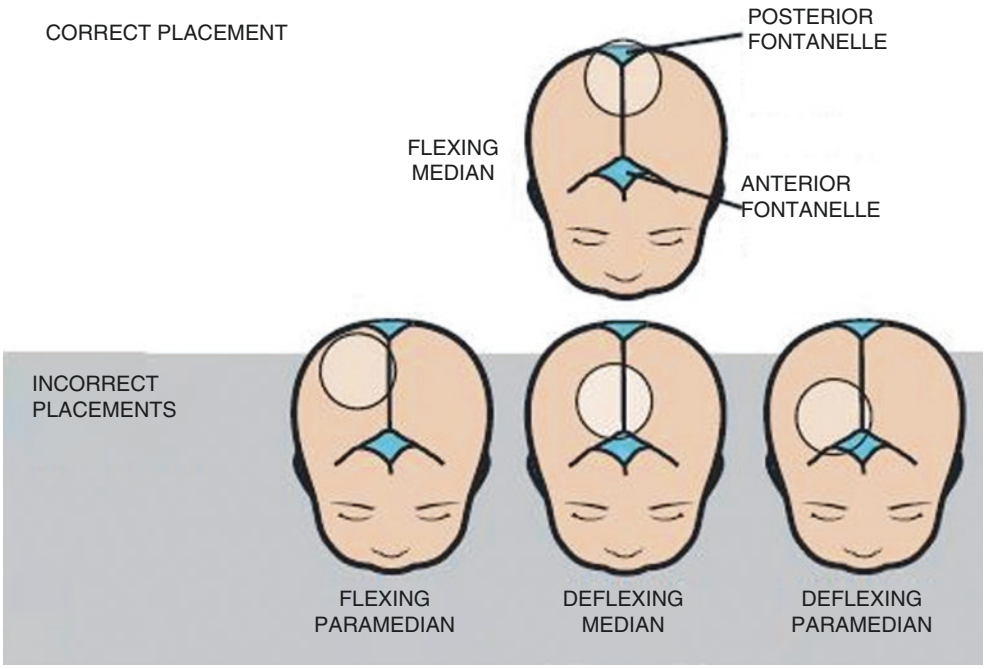


Fig. 10.21 Correct placement of vacuum extractor (By Preventing Maternal and Neonatal Harm during Vacuum-Assisted Vaginal Delivery Pa *Patient Saf Advis* 2009 Dec 16;6(Suppl 1):7–17)

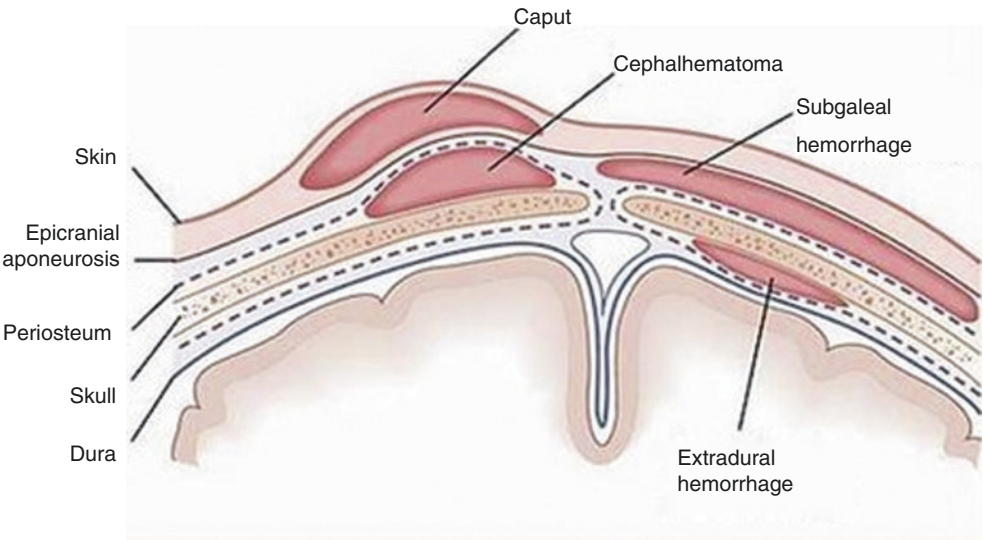


Fig. 10.22 Location of injury in soft tissue planes on the scalp and head

10.12.5 Failed Instrumental Delivery

When use of an instrument fails to achieve delivery, the operator is faced with a clinical dilemma, to either maintain efforts to deliver vaginally by trying the alternative instrument or proceed with a cesarean section. Cesarean section at full dilatation with the head lodged low in the pelvis encompasses significant maternal complications. However, the use of sequential instruments is associated with an increased risk of trauma to the infant, and a baby delivered by two or more operative interventions is more likely to have a serious injury than one delivered by vacuum or forceps alone, specifically significantly higher rates of subdural or cerebral hemorrhage, subarachnoid hemorrhage, facial nerve injury, and brachial plexus injury [15, 52, 53].

The recent ACOG practice bulletin therefore states that the weight of available evidence appears to be against routine use of sequential instruments at operative vaginal delivery [11]. In this regard, a trial of operative delivery in the operating theater is a recommended practice whenever there is concern that delivery may be difficult. This approach has been associated with safe delivery without an increase in

neonatal or maternal morbidity and allows for early recourse to cesarean section if necessary [54].

10.12.6 Predictors of Operative Delivery Failure

Since failed operative vaginal delivery followed by cesarean section is associated with significantly higher rates of some of the more dreaded complications of operative delivery, correct selection of operative delivery candidates is of utmost importance. In a study reviewing 5,120 attempts of operative vaginal delivery, the factors that were associated significantly and independently with failed delivery were the use of vacuum instead of forceps, absence of systemic or regional analgesia, persistent occiput posterior head position, and birthweight 4,000 g [55]. Other studies found that failure was associated with maternal age, increased maternal body mass index, maternal diabetes polyhydramnios, induction of labor, dysfunctional labor, prolonged labor, and birthweight 4,000 g [56], and Sheiner et al. added lack of prenatal care [57]. Fetal weight and head position should be evaluated carefully before a decision is made to proceed with an operative vaginal delivery including considering use of sonographic evaluation where appropriate, and the use of analgesia should be encouraged.

10.12.7 Criteria for Failure of Operative Vaginal Delivery

The ALARM course and the SOGC guidelines call for three pulls without a delivery constituting a criterion for failed forceps and three pop-offs for failed vacuum; some other sources provide similar numbers [29, 56].

10.12.8 Intrapartum Sonographic Predictors of Operative Delivery Success

Intrapartum ultrasound has recently been the focus of investigations evaluating predictors of a successful operative vaginal delivery. Determining fetal head station and position is a cardinal part of patient assessment prior to an intervention. Digital assessment of these parameters is subjective and has been shown to be less than accurate. Recent studies reported that digital examination during instrumental delivery fails to identify the correct fetal head position in 25 % [59] to 65 % [60] of cases. Ultrasound evaluation can assist determining fetal head station and position. Therefore, the accuracy of intrapartum translabial ultrasound may help the evaluation by providing objective information on the fetal head station, direction, and progression of labor. Because birthweight and fetal head position are consistent risk factors of failed OVD, some authors recommended the routine performance of abdominal and translabial ultrasound scanning in the labor room [61].

The main reason for using sonography to define fetal position is to diagnose persistent occiput posterior position (POPP) that occurs in approximately 5 % of deliveries. POPP is associated with about 4- and 13-fold higher rates of operative vaginal and cesarean deliveries, respectively [62, 63].

A recent study showed that not only POPP but also OT position diagnosed by transabdominal ultrasound early in the second stage of labor was an independent risk factor for operative delivery, with an OR of 2.1 compared to OA position.

Another interesting study looked into the relation between fetal spine position and the head position at the second stage of labor. They showed the position of the spine during the second stage of labor can be considered to be a diagnostic sign in predicting the OP position at birth. When the occiput and spine were anterior at the ultrasound examination, none of the infants was born in the OP position; when the occiput was posterior and the spine was anterior at the ultrasound examination, none of the infants was born in the OP position; yet when occiput and spine were posterior at the ultrasound examination, only one out of seven rotated into an OA position at birth [64].

Parameters have been set to predict progression of head descent during the second stage. Of great use to practitioners would be the application of ultrasound to predict the likelihood of operative vaginal delivery success and thus prevent maternal and fetal morbidity and mortality that a failed attempt of instrumental delivery entails. Some definitions of relevant sonographic parameters that have been described are:

- Angle of progression (AoP), the angle between the longitudinal axis of the pubic symphysis the tangent line to fetal skull's contour (Fig. 10.23)
- Head direction (HD), the angle resulting of the union of a perpendicular line to the pubic bone major axis and a perpendicular line to the fetal head widest transverse diameter (Fig. 10.24)

Angles >30 correspond to "upward" directions, angle <0 correspond to "downward" directions, and angles between 0 and 30 correspond to horizontal directions. The presence of an angle of progression ≥120°, a "head-up" direction, and a rotation angle <45° are associated with spontaneous delivery in 90 % of cases.

Henrich et al. reported their experience with a second stage translabial ultrasound approach. They showed that a

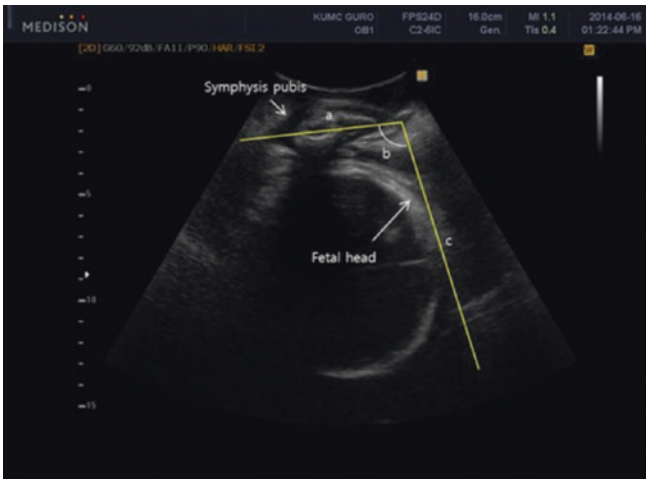


Fig. 10.23 Angle of progression on transperineal ultrasound. Transperineal ultrasound image (sagittal view) depicting the long axis of the pubic symphysis (**a**), angle of progression (**b**), and line extending from the lowermost point of the symphysis tangentially to the fetal skull contour (By Ahn and Oh [78])

"head-up sign" and objective descent of the fetal head under the infrapubic line during maternal pushing efforts result in a successful operative delivery [65]. Cuerva et al. performed intrapartum ultrasound to predict difficulty in forceps deliveries. They compared scans performed at rest and with pushing efforts. Angle of progression and head direction, both with pushing, were the best sonographic predictors for a successful forceps delivery. Furthermore, it was concluded that an angle of progression with pushing >138 is a good indicator of an easy forceps-assisted vaginal delivery [66].

Sainz et al. reported than an angle of progression with pushing >128 gives a probability of an easy vacuum delivery of >85 %, with a false-positive rate of 9.3 %. The same group reported that an AoP with pushing <105, a PD <25 mm, a "head-down" direction, and a MLA>45 are very unfavorable parameters, identifying cases with high probability of leading to unsuccessful attempt at vaginal delivery with vacuum. These techniques remain investigational at present [67].

10.12.9 Antibiotics

The risk of postpartum infection is increased after operative vaginal birth because of higher rates ranging from 3.5 to 16 % [68]. Reasons for this are increased risk of vaginal lacerations, routine bladder catheterization, multiple vaginal examinations, insertion of instruments into the vagina, and contamination [69, 70].

Antibiotics have been shown to reduce postpartum infection following cesarean sections [71], yet there is insufficient evidence to support the routine administration of antibiotic prophylaxis for the indication operative vaginal delivery to prevent postpartum infection.

A retrospective review of 393 women compared the rates of endomyometritis among women delivered by vacuum or forceps and found no statistical difference in the rates of infection or the length of hospitalization among those who received prophylactic antibiotics and those who did not.

Two grams of intravenous cefotetan at the time of vacuum or forceps delivery were shown to be associated with a non-significant decrease (0 vs. 3.5 %) in endometritis [68, 72].

10.12.10 Episiotomy

While episiotomy was once considered an integral part of operative vaginal delivery, cumulative data regarding routine episiotomy during operative delivery is controversial. Episiotomy is done in attempt to prevent anal sphincter trauma, yet evidence exists that episiotomy may in fact be associated with an increased rather than decreased risk of perineal trauma and rectal injuries [73, 74].

A recent randomized trial that compared routine to selective episiotomy showed no significant differences between the groups with regard to anal sphincter tears, neonatal trauma, or urinary or fecal incontinence [75]. When an episiotomy is performed using a selective approach, it was recommended it is mediolateral rather than medial. Although this approach involves longer perineal healing and more pain, it is associated with less anal sphincter injuries and thus is the preferred approach. On the other hand, another large observational study from the Netherlands showed that mediolateral episiotomy protected significantly for anal sphincter damage in both vacuum extraction (OR 0.11, 95 % CI 0.09–0.13) and forceps delivery (OR 0.08, 95 % CI 0.07–0.11). The number of mediolateral episiotomies needed to prevent one sphincter injury in vacuum extractions was 12, whereas 5 mediolateral episiotomies could prevent one sphincter injury in forceps deliveries. The authors concluded that mediolateral episiotomies have a significant protective effect in operative vaginal delivery and advocated its use [76].

10.12.11 The Odon Device

A recent development in the operative delivery field is the Odon device. This instrument has been designed on the basis of a double physical phenomenon consisting of a conveyor

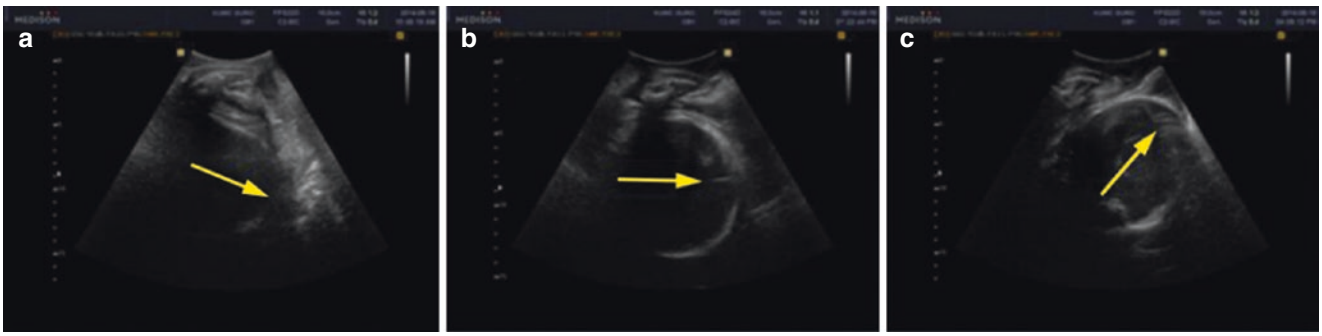


Fig. 10.24 Head direction on intrapartum translabial ultrasound. Categorization of fetal head direction (indicated by arrows) in longitudinal translabial sonograms: (**a**) downward, (**b**) horizontal, and (**c**) upward direction (By Ahn and Oh [78])

belt and air clamp. This phenomenon occurs when a certain object is in contact with a pathway or contained in a plastic bag inside a container, with which it is also in contact. The design originated in Argentina, when Jorge Odon a car mechanic from Buenos Aires, with no medical background, got the idea after watching a video on the Internet that showed how to extract a cork from the inside of a bottle. In 2008, the project had come to the attention of the World Health Organization. To test the device feasibility under preclinical conditions, the WHO allowed trials in 2008 on a simulator at Des Moines University, Iowa, USA, to the approval in 2009 of a World Health Organization study protocol to test the device on human beings, and, finally, to the awarding in 2011 of a "Saving Lives at Birth: A Grand Challenge for Development" grant to further test the potential of the device to save women's and children's lives at the time of birth when the majority of maternal and newborn deaths occur. The device was designed as a cylindrical polyethylene sleeve fitted with a fold on the fetal insertion edge; this fold fits the fetal head diameter. The distal edge of the device has a handle for traction; after applying the device, an amount of air is insufflated and an air clamp that holds the fetal head is achieved. This adds to the effect of conveyor belt or sliding that occurs between the inner parts of the fold upon force exertion. Such force may be either external, i.e., through traction from outside the device, or internal, i.e., arising from the natural forces that bring about uterine contractions and maternal pushing. Once the sleeve is positioned around the fetal head, the air chamber is filled through a cannula, which enters through the interior of the sleeve. Once a minimum of air volume is insufflated, the device should be pulled in order to extract the fetal cephalic pole. The air chamber has a regulating and compensating valve (for the air entrance or another very low pressure fluid), calibrated to work as an automatic safety measure (Fig. 10.25).

If this device, developed to assist vaginal delivery, demonstrates its effectiveness, it will avoid the two greater limitations of forceps and vacuum: the maternal and fetal injuries and the high degree of training needed to master them. The benefits of Odon device are the following:

- Reduces risk of feto-maternal birth-related trauma
- Assists vaginal delivery boosting the effect of uterine contractions and maternal pushing
- Reduces the risk of perineal damage
- Reduces the risk of perinatal infections
- Requires simple training
- Easy application
- Low production cost
- Disposable

In conclusion, operative vaginal deliveries constitute an important obstetrical tool safely aiding parturients achieving vaginal deliveries and preventing complex cesarean sections. The assessment and decision process that leads to operative delivery (or not), and no less the necessary skill and experience to perform the procedure, is the hallmark of the competent obstetrician. The importance of adequate training in residency is underscored and operative vaginal delivery is an essential skill for all obstetricians. Gravid women should be informed of the details of a possible operative delivery in antepartum visits as well as in the delivery suite.

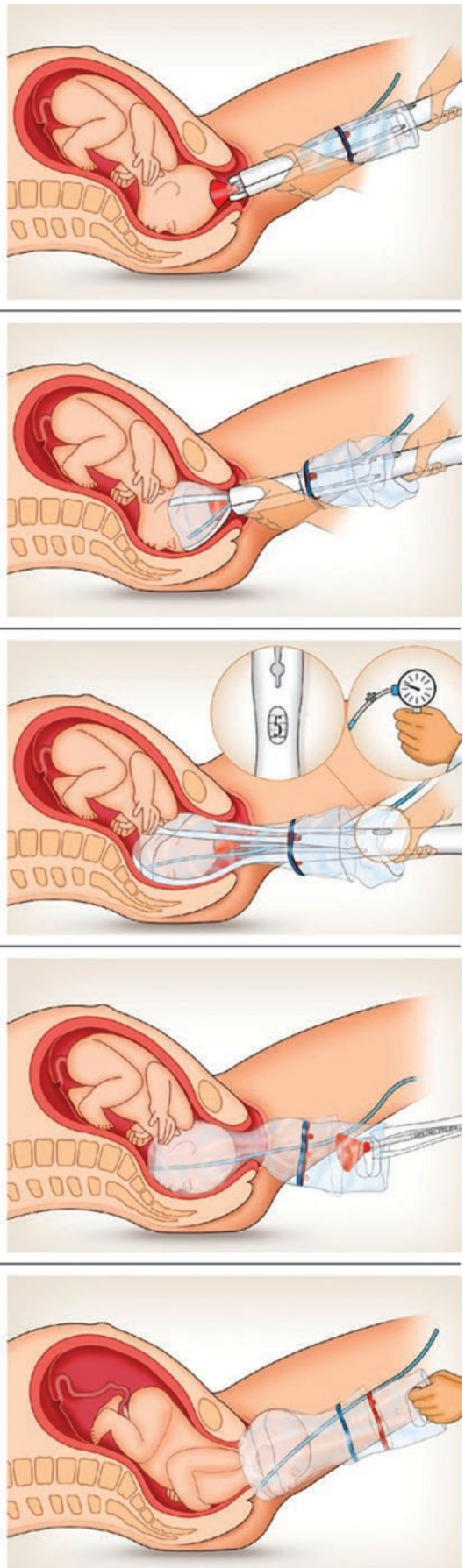


Fig. 10.25 The Odon device (By Carmona and Farine [77])

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Management of Shoulder Dystocia

11

Edith Gurewitsch Allen and Robert H. Allen

The goal of proper management of any complication of labor and delivery is to prevent lasting sequelae for either mother or newborn or both. Shoulder dystocia, first described by Smellie in 1730, is an obstetric emergency that occurs in the final moments of delivery when the fetal head already has emerged through the vaginal introitus, but difficulty is encountered in delivering the aftercoming trunk (Fig. 11.1) [1–3]. If neither recognized nor managed appropriately, shoulder dystocia places the fetus at risk for skeletal fractures, brachial plexus injury, asphyxia, and even death. The mother is at risk for anal sphincter injury, postpartum hemorrhage, uterine rupture, and even death [4–7].

Since shoulder dystocia is as frequently unpredictable as it is potentially anticipated based upon risk factors, every obstetric provider must be able to diagnose and manage shoulder dystocia.

At the conclusion of this chapter, the reader will be able to:

1. Distinguish between prospective and retrospective definitions of shoulder dystocia and their limitations for clinical use
2. Identify and distinguish modifiable and non-modifiable risk factors for shoulder dystocia and resultant injury
3. Understand the pathophysiology of shoulder dystocia and the biomechanical principles of the recommended maneuvers needed to resolve shoulder dystocia and reduce the risk of injury

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11.1 Diagnosis of Shoulder Dystocia

The incidences of shoulder dystocia as promulgated by the American Congress of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) are 0.6–1.4 % and between 0.58 % and 0.70 %, respectively [8, 9]. However, throughout the medical literature, the incidence of shoulder dystocia varies by more than a factor of 50, from 1 in 769 vaginal to 1 in 25 deliveries [8–12]. Rather than a true difference in incidence, the high variation is most directly attributable to inconsistencies in defining shoulder dystocia, as well as the at-risk population from which to calculate incidence. As shoulder dystocia is nonexistent prior to 32 weeks' gestation and is a complication solely of cephalic vaginal delivery, the most appropriate denominator to consider for reporting shoulder dystocia incidence should exclude premature infants <32 week, as well as cesarean and breech vaginal deliveries. Based on a handful of prospective studies, it is likely that the incidence of shoulder dystocia with current mangement techniques among the at-risk population is between 3.35 % and 7 % [13–18].

Biomechanically, shoulder dystocia presents as a bony obstruction to delivery of the trunk resulting from misalignment of the fetus' bisacromial width relative to the anteroposterior dimension of the maternal pelvic outlet (Fig. 11.2). Since the occurrence of shoulder impaction against either the pubic symphysis anteriorly or the sacral promontory posteriorly cannot be visualized, its diagnosis is subjective. Normal descent and delivery of the aftercoming shoulders is facilitated by spontaneous rotation of the bisacromial shoulder width to occupy the oblique diameter of the pelvic outlet, which occurs during spontaneous external rotation (restitution) of the fetal head outside the introitus. Failure of the shoulders to rotate to the normal oblique orientation may result from either insufficient passage of time between head and body rotation prior to the shoulders reaching the level of the pelvic outlet (as may occur during precipitous second stage or with operative

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Fig. 11.1 Schematic of shoulder dystocia. After emergence of the fetal head through the vaginal introitus, the anterior fetal shoulder becomes lodged behind the maternal pubic symphysis (arrow), obstructing spontaneous delivery of the fetal trunk

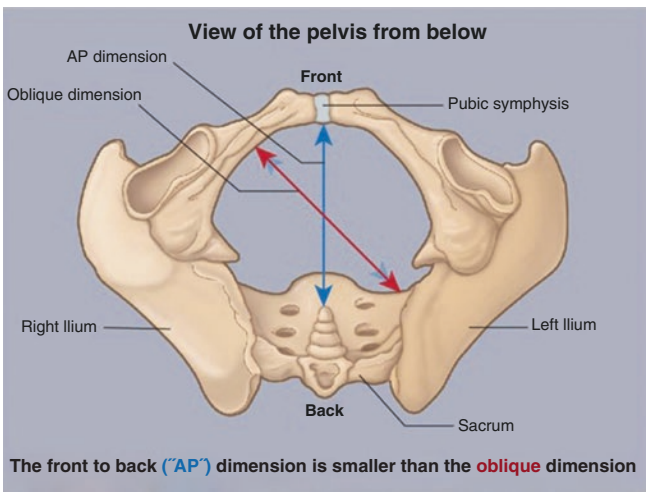


Fig. 11.2 Pelvic dimensions. In the normal gynecoid pelvis, the anteroposterior dimension is smaller than the oblique diameter

intervention) or from relative head-to-body size asymmetry. The persistent anteroposterior position of the fetal shoulders within the pelvis generally is confirmed by digital palpation, although a retraction of the fetal head against the perineum (turtle sign) (Fig. 11.3), which occurs in a minority of cases, is suggestive. Definitive diagnosis is confirmed when an initial attempt with downward axial traction fails to deliver the trunk as it would under normal circumstances.

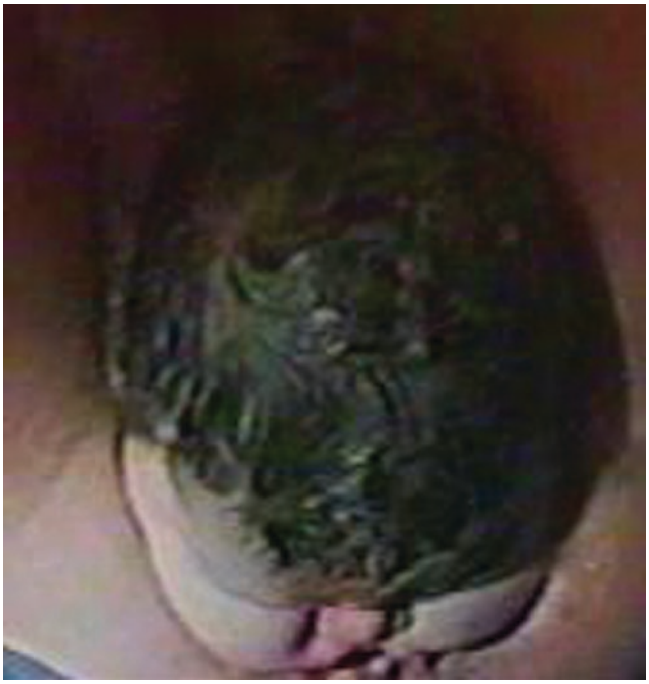


Fig. 11.3 Turtle sign. Fetopelvic disproportion most often caused by fetal macrosomia may present as retraction of the fetal head against the maternal perineum (Reprinted with permission (Medscape, WebMD))

Another commonly accepted definition for shoulder dystocia is the need to use ancillary maneuvers beyond initial downward traction [8, 9, 19]. Such a retrospective definition is problematic for diagnostic use in the clinical setting since it presupposes shoulder dystocia recognition in order for ancillary maneuvers to have been used. It is well established that milder forms of shoulder dystocia are difficult to diagnose [20]. In a prospective study of more than 30,000 vaginal deliveries in which the degree of traction applied to the fetal head was estimated by the delivering clinician and correlated with neonatal outcome, two-thirds of the deliveries were estimated as involving higher than average degree of traction yet were *not* characterized as having shoulder dystocia [21]. The same study proved a direct correlation between the degree of traction used and the occurrence and severity of brachial plexus injury (Fig. 11.4), which was more strongly correlated with injury than the concomitant diagnosis of shoulder dystocia. Thus, to be considered as a complication of vaginal delivery with potential for fetal injury, a clinically more effective and utile definition for shoulder dystocia should be the clinician's perceived need to increase traction above that level he/she would consider "usual." Upon recognizing that "usual" traction is insufficient to deliver the shoulders, the obstetric provider is explicitly advised not to increase traction, despite the natural tendency to do so, but instead to initiate ancillary maneuvers designed to reduce the amount of further traction needed and thereby to minimize the risk of brachial plexus injury [13, 22].

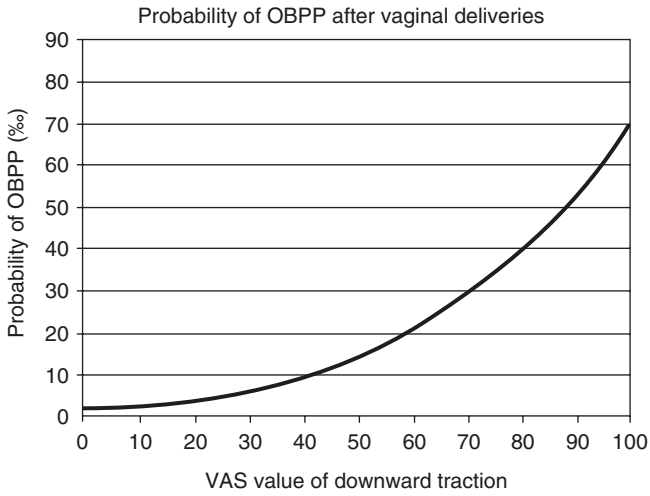


Fig. 11.4 Clinician-applied traction and odds of brachial plexus injury. Regardless of diagnosis of shoulder dystocia, the risk of brachial plexus injury to the newborn increases as a function of the magnitude of clinician-applied traction (Reprinted with permission (Mollberg))

11.2 Risk Factors for Shoulder Dystocia

Before discussing the management of shoulder dystocia once it occurs, a review of epidemiologic considerations is in order. Dynamic causes of shoulder dystocia wherein an otherwise normal-sized fetus' shoulders become misaligned within the maternal pelvis owing to rapid descent will occur only intrapartum; it may be spontaneous and non-modifiable (as with precipitous second stage) or iatrogenic and thus modifiable (as with operative vaginal delivery).

Shoulder dystocia resulting from fetopelvic disproportion is most often the result of macrosomia and accelerated and asymmetric somatic fetal growth relative to head size [23, 24]. Less commonly, short maternal stature and/or contracted maternal pelvic dimensions can lead to obstructed shoulder delivery of a normally grown fetus.

The large-for-gestational-age (LGA) infant potentially is recognizable prior to the onset of labor. Antepartum risk factors for shoulder dystocia are the same as those for fetal macrosomia:

1. History of a prior shoulder dystocia delivery [25]
2. Pregestational or gestational diabetes mellitus [26]
3. Baseline maternal obesity (BMI >25) [4, 27]
4. Excessive weight gain during pregnancy (>15.9 kg) [28]
5. Postdatism [26]
6. Parity [4, 29]

Signs of excessive gestational weight gain, abdominal circumference to head circumference ratio >1.04, and estimated fetal weight >90 % for gestational age in the third trimester should prompt diagnosis and treatment of possible impaired glucose tolerance, even among women with previously normal pregnancy glucose screen. Dietary counseling about elimination of high glycemic index foods should be provided, and such women should be encouraged to limit further weight gain, especially if already obese. The presence of signs of accelerated fetal growth among women demonstrating adequate glycemic control of pregestational or gestational diabetes on diet alone (mild gestational diabetes) favors empiric treatment with medication to prevent or reduce the risk of delivery complications, including shoulder dystocia (Fig. 11.5) [30, 31].

Whereas treatment of impaired glucose metabolism or mild diabetes when manifested as accelerated fetal growth can reduce the risk of shoulder dystocia, deliberate induction of labor for so-called impending macrosomia is associated with a higher incidence of shoulder dystocia compared to those managed expectantly [32]. Indeed, both induction of labor and use of epidural labor analgesia have been associated with an increased risk of shoulder dystocia, albeit a relatively weak correlation. Although unproven, this phenomenon may be the result of interfering with spontaneous fetal descent and oblique shoulder positioning prior to the onset of natural labor.

The strongest predictor of the occurrence of shoulder dystocia in an index delivery is the occurrence of shoulder dystocia at a prior delivery. Unless a fetal injury has occurred, it is possible that a parturient may not be aware that a prior delivery had been complicated by shoulder dystocia. When the history of a previous delivery is otherwise remarkable for a large-for-gestational-age infant (>90 %) or clavicle fracture, a review of delivery records for any difficulty with shoulder delivery is prudent. As with shoulder dystocia in general, the precise risk of recurrence varies with definition and population considered; however, the relative risk is above sixfold compared to women delivering an infant similar in size to the previous child who did not experience shoulder dystocia during the prior delivery [25].

Considerable debate persists concerning the counseling of pregnant women with either a history of shoulder dystocia and/or in whom the estimated fetal weight is in excess of 4 kg. Elective primary cesarean delivery prior to the onset of labor is not a cost-effective approach [33]. However, among the significantly smaller population of women whose prior deliveries complicated by shoulder dystocia resulted in injury or those with estimated fetal weight above 4.5–5 kg counseling about a prelabor, primary cesarean section should be offered. For all other women, a trial of labor remains the appropriate management strategy; anticipation of possible shoulder dystocia in such cases is best managed only by advance coordination of appropriate setting, staffing, and preparation of needed equipment once delivery is imminent.

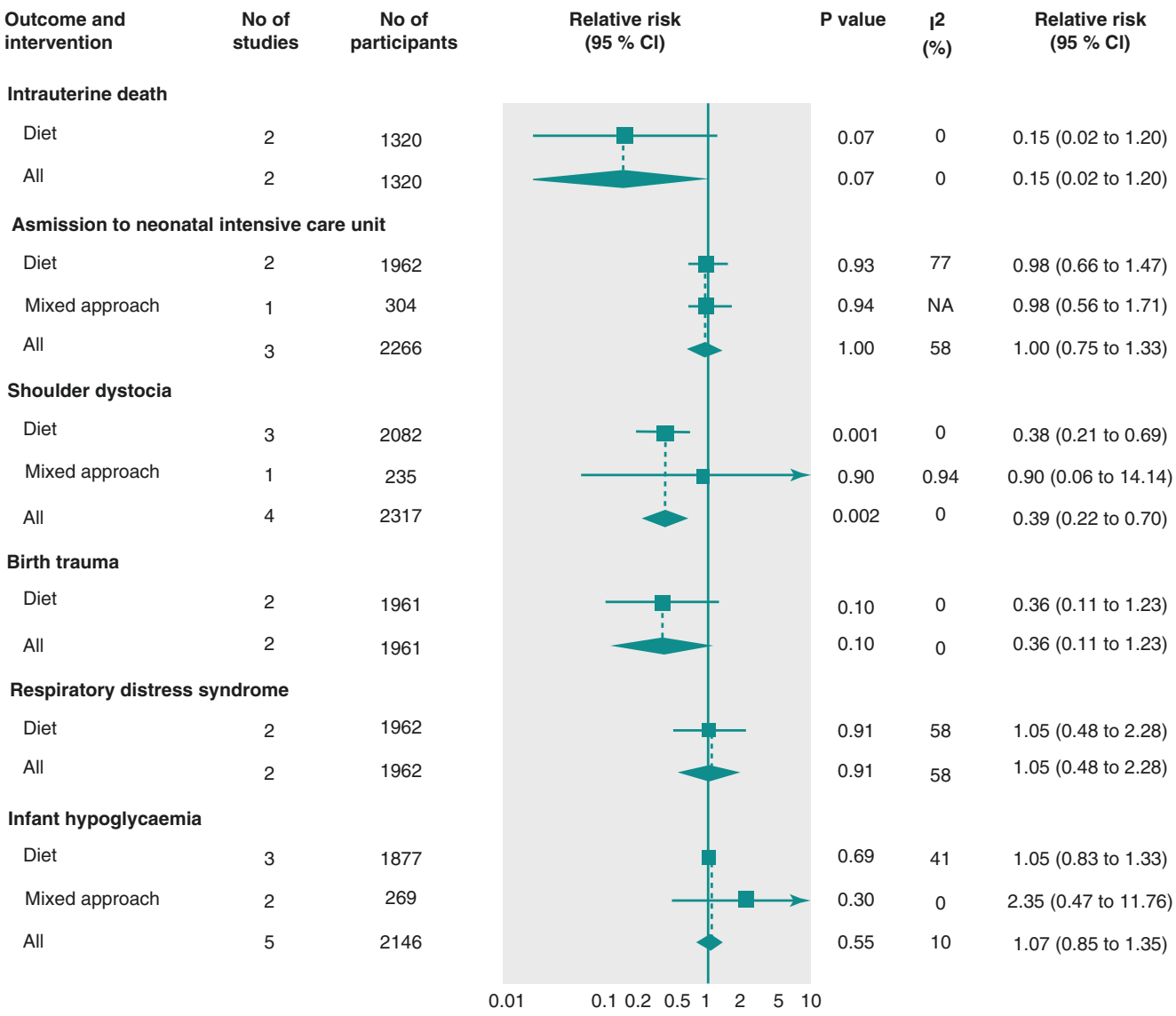


Fig. 11.5 Meta-analysis of intervention for maternal weight gain and impact on neonatal outcome. Most studies of dietary and exercise intervention during pregnancy to curb maternal weight gain and control maternal hyperglycemia result in reduction in delivery-related adverse outcomes for infants (Reprinted with permission (BMJ))

11.3 Shoulder Dystocia Maneuvers

Risk factors for shoulder dystocia correlate poorly with the actual occurrence of shoulder dystocia and do not appear to be cumulative. Even in the presence of risk factors – as well as in the total absence of risk factors – obstetric providers should be cognizant of the potential for occurrence of shoulder dystocia at all cephalic vaginal deliveries occurring beyond 32 weeks' gestation. Given its emergent nature and lack of predictability in any given delivery, development of competence in the proper execution of shoulder dystocia maneuvers should occur before experiencing it in an actual delivery – ideally, with use of regularly repeated rehearsals and drills utilizing mechanical simulators (Fig. 11.6a, b) [34–40].

Compared to other procedures for which simulation-based training is utilized, shoulder dystocia simulation is the most evidence-based in its proven impact on actual clinical outcomes. The "Code D" protocol published by Inglis et al. is noteworthy for its initial steps (Fig. 11.7), which are *required prior to* the initiation of maneuvers: Upon recognition of difficulty delivering the shoulder, a "hands-off" waiting period lasting up to 1 min is observed [36]. This alone can reduce the likelihood and severity of shoulder dystocia [18, 41–44]. Help from additional personnel is summoned during this time, allowing for spontaneous external rotation (restitution) of the

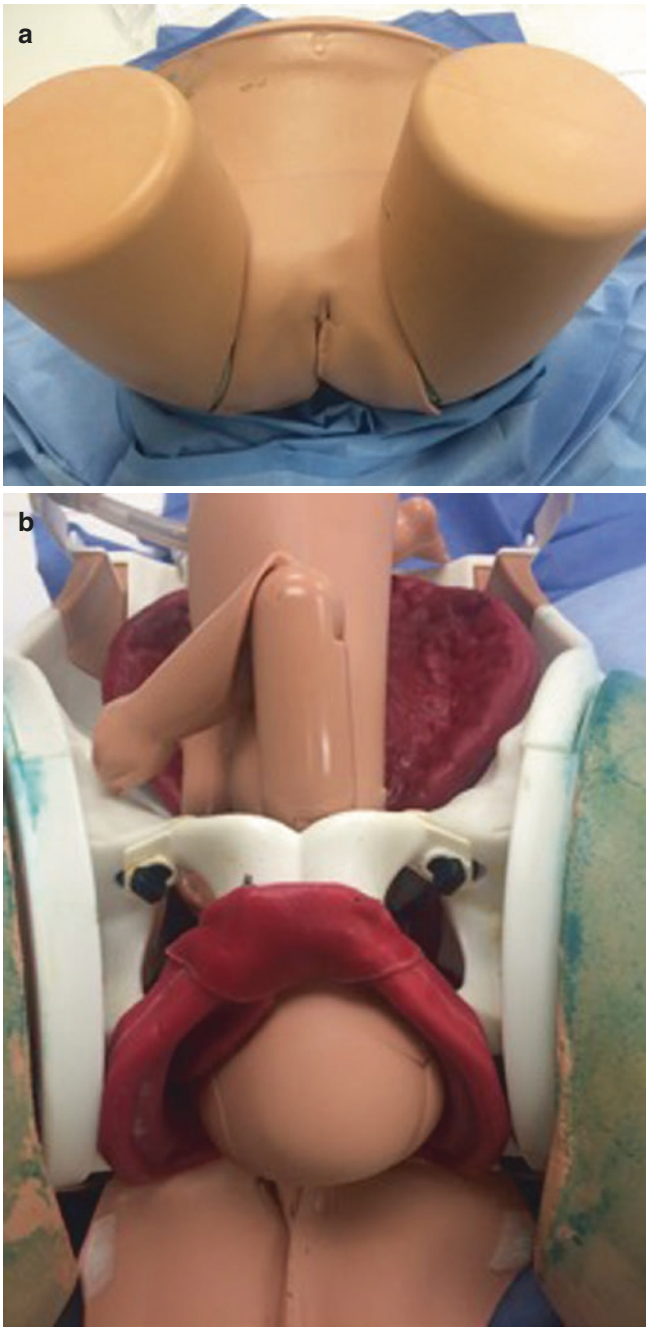


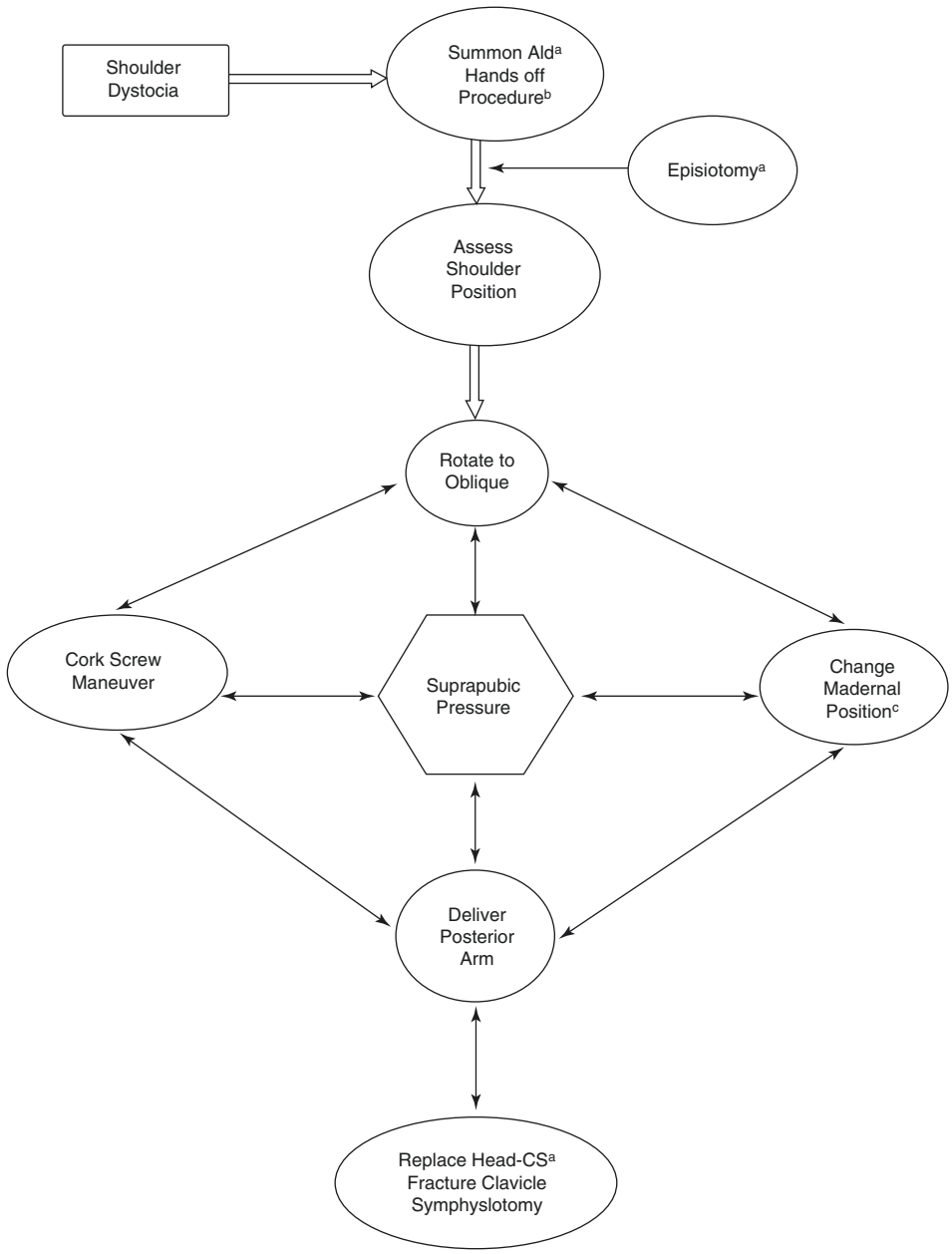
Fig. 11.6 Mechanical birth simulators. Simulators such as Prompt™ by Limbs & Things, Inc. (**a**) can be utilized by obstetric providers to train and rehearse shoulder dystocia maneuvers (**b**). For instructional visualization purposes, the external "skin" can be removed to expose the fetal mannequin in its obstructed position within the maternal pelvis (Reprinted with permission (Limbs & Things, Inc.))

delivered head and additional time for the aftercoming body to rotate within the birth canal. If manual rotation of the shoulders into oblique is needed, pressure should be applied on the posterior aspect of the fetal shoulder (Fig. 11.8) so as to achieve relative adduction and decrease of the bisacromial diameter. On average, an enforced "hands-off" waiting period in the initial moments following recognition of obstructed shoulder delivery increases the subsequent head-to-body delivery interval by only 0.5 min, with minimal effect on fetal cord pH (Fig. 11.9) [36]. Thereafter, the orientation of the fetal shoulders is confirmed with direct digital palpation (Fig. 11.10) and, if needed, is manually adjusted to occupy the oblique dimension of the maternal pelvis. This maneuver, known as Rubin's maneuver, is accomplished before reapplication of any traction to the fetal head [45]. Compared to starting with McRoberts maneuver, Rubin's reduces the magnitude of subsequent traction and the resultant strain on the brachial plexus [46].

With manual assurance that the shoulder position has been restored to oblique orientation, traction can then be reapplied to the head in direction that is aligned with the fetal vertebral column (axially), taking care to support both sides of the head (Fig. 11.11) so as not to increase the lateral flexion of the head away from either the anterior or the posterior shoulder and always limiting the magnitude of the traction to no more than would be used in a normal, unobstructed delivery.

If resistance is still met, the option for McRoberts positioning and/or application of suprapubic pressure by training team assistants may be exercised. From a biomechanical perspective, the performance of McRoberts maneuver – the sharp flexion of the maternal thighs against her abdomen – is intended to result in rotational elevation of the pubic symphysis approximately 1 cm cephalad while simultaneously flattening the lumbosacral angle (Fig. 11.12), allowing the posterior shoulder to descend further into the hollow of the sacrum [47]. Whether the resultant pelvic rotation is sufficient to relieve the obstruction to the anterior shoulder should be readily observable with the first reapplication of traction; if no further descent is achieved, persisting with additional traction attempts will result in increasing magnitude of traction and the risk for brachial plexus injury (Fig. 11.13a, b) [19, 48]. Instead, all further attempts at traction should be redirected to direct manipulation of the fetal trunk.

If attempting to rotate the shoulders into the oblique, and McRoberts maneuver and suprapubic pressure fail, the most effective next option is delivery of the posterior arm [49]. The reason for this is that the maneuver replaces the bisacromial diameter with the axilloacromial diameter, thereby reducing the obstruction by more than 2 cm (Fig. 11.14) [47, 50]. Reliance on posterior arm delivery as an initial maneuver is also associated with better clinical outcomes [17, 38–40, 51–54]. When delivering the posterior arm, care is needed to avoid pulling the arm against resistance. Flexing the infant's elbow and crossing the arm in front of the chest and across the face best achieves this (Fig. 11.15). The arm should not be pulled directly out from underneath the body posteriorly, as this increases the risk of humeral fracture and/or shoulder dislocation [55].



[a]Experienced obstetrician nurse anesthesiologist neonatologist: [b]No fundal pressure, no pushing, no heed traction; [c]Mc Robert, knee chest position, lateral position, squat; [d]Mandatory part of protocol; [e]Option or choice of protocol; [f]Proceed with cesarean delivery.

Fig. 11.7 Schematic of Code D protocol for shoulder dystocia management (Published by Inglis et al. the Code D protocol emphasizes "hands-off" assessment of shoulder position and direct manipulation of the shoulders to the oblique position *prior to* application of traction or other shoulder dystocia maneuvers (Reprinted with permission (AJOG))

If delivery of the posterior arm is unsuccessful because of arm position, the Woods corkscrew maneuver should be employed [56]. A deliberate winding action akin to rotation about the threads of a screw should be kept in mind when executing the corkscrew maneuver. Biomechanically, the goal is to achieve simultaneous rotation and forward advancement of the posterior shoulder such that, in rotating 180° to the anterior position, the previously posterior shoulder will now be positioned in front of the pubic symphysis (Fig. 11.16a, b).

For either posterior arm or Woods screw, episiotomy should be avoided except when needed to facilitate direct access to the fetal trunk [46, 57]. Avoidance of episiotomy does not increase the risk of brachial plexus injury, and in 50 % of cases where McRoberts and suprapubic alone are insufficient to resolve shoulder dystocia, direct fetal manipulation without episiotomy will maintain the mother's perineum intact [7, 58].

The above five maneuvers: Rubin's, McRoberts, suprapubic pressure, delivery of the posterior arm, and Woods

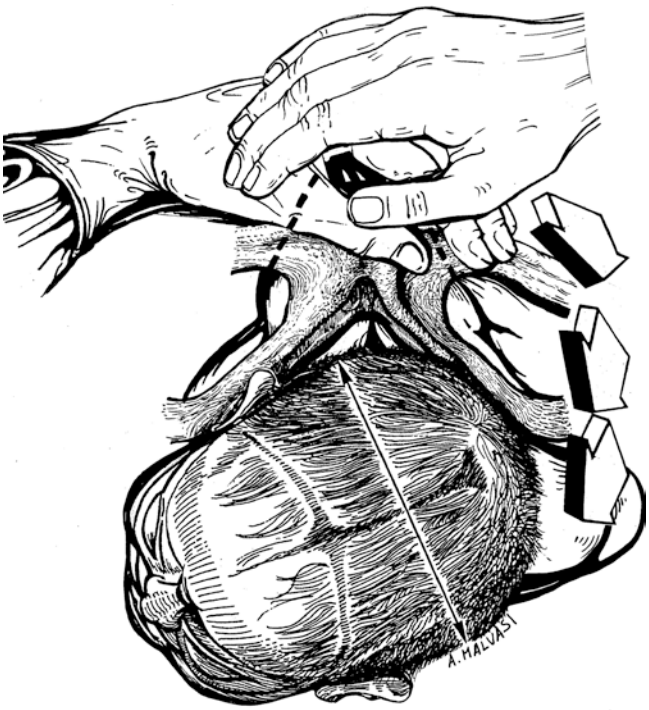


Fig. 11.8 Proper orientation for application of suprapubic pressure. The delivering clinician faced with shoulder dystocia must identify the correct shoulder orientation for the assistant applying suprapubic pressure. Pressure is applied obliquely, just above the pubic symphysis, from the posterior aspect of the fetal shoulder in an attempt to rotate and adduct the anterior fetal shoulder toward the oblique diameter of the pelvis

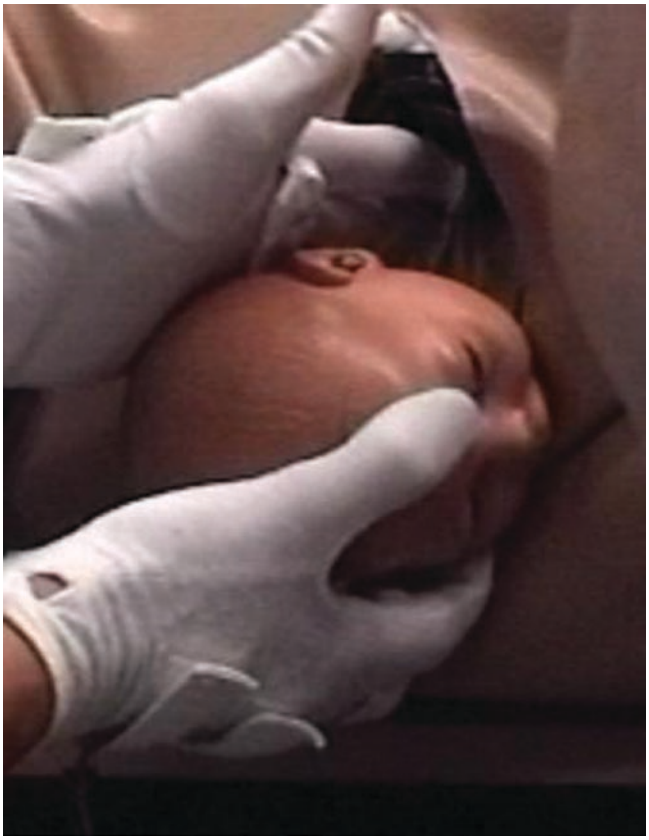


Fig. 11.10 Direct digital palpation of anterior shoulder position. To avoid application of improperly aligned traction or manual rotation of the fetal head, the obstetric provider should always assess the position of the anterior fetal shoulder via direct palpation as shown (Reprinted with permission (Medscape, WebMD))

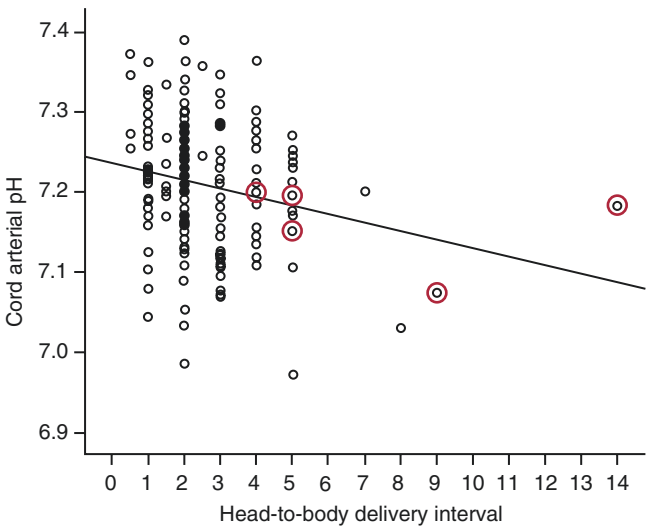


Fig. 11.9 Fetal cord pH as a function of head-to-body delivery interval during shoulder dystocia. The "two-step" approach to vaginal delivery espoused by Locatelli et al. requires a pause between head expulsion and application of delivery traction, awaiting spontaneous maternal contraction. This delay is associated with minimal decrease in fetal pH, even in cases of shoulder dystocia with prolonged head-to-body interval (Reprinted with permission (JOGC))

corkscrew will successfully resolve greater than 99 % of shoulder dystocia emergencies, even if repeated attempts are required. For those women who are capable of it, adoption of knee-chest (Gaskin maneuver) position or even lateral decubitus is often sufficient to reorient the shoulders within the pelvis [59, 60]. As long as care is taken to avoid improperly directed or repeated stronger traction attempts on the fetal head, the risk of permanent sequelae is markedly reduced.

In performing these maneuvers, delivery technique is key to a good outcome. Proper execution of the aforementioned shoulder dystocia maneuvers requires repeated practice, ideally as a full team. The deliberate attempt to slow down, await spontaneous rotation, and manipulate the body directly rather than the head when faced with an actual shoulder dystocia is counterintuitive and thus easily forgotten during an acute emergency. Proficiency should be maintained with regular drills and simulation so that appropriate management is always utilized. The effects of such a program are undeniable in their ability to improve outcomes [35, 38, 40].

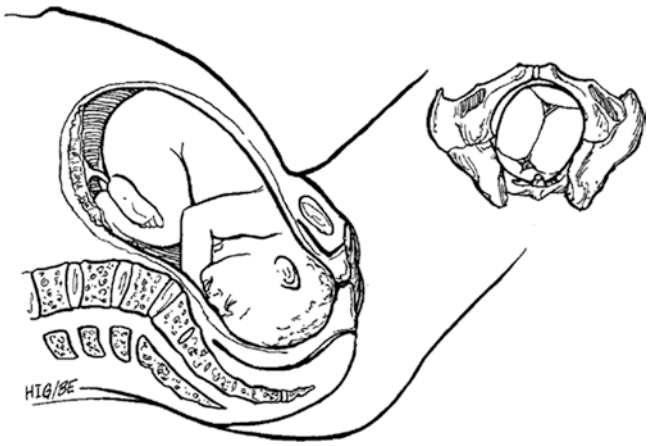


Fig. 11.11 Proper application of axially directed delivery traction.To avoid undue stretch on the anterior brachial plexus, the obstetric provider should apply symmetric pressure to the head, maintaining its neutral position aligned with the fetus' vertebral axis. The goal is to guide the posterior shoulder into the hollow of the sacrum, which in turn results in descent of the anterior shoulder below the pubic symphysis. Lateral flexion of the fetal neck in either a sharp downward or upward direction away from the neutral axial position is improper, as it increases the stretch on the brachial plexus (From J.A. O'Leary (ed.), *Shoulder Dystocia and Birth Injury*, 2009)

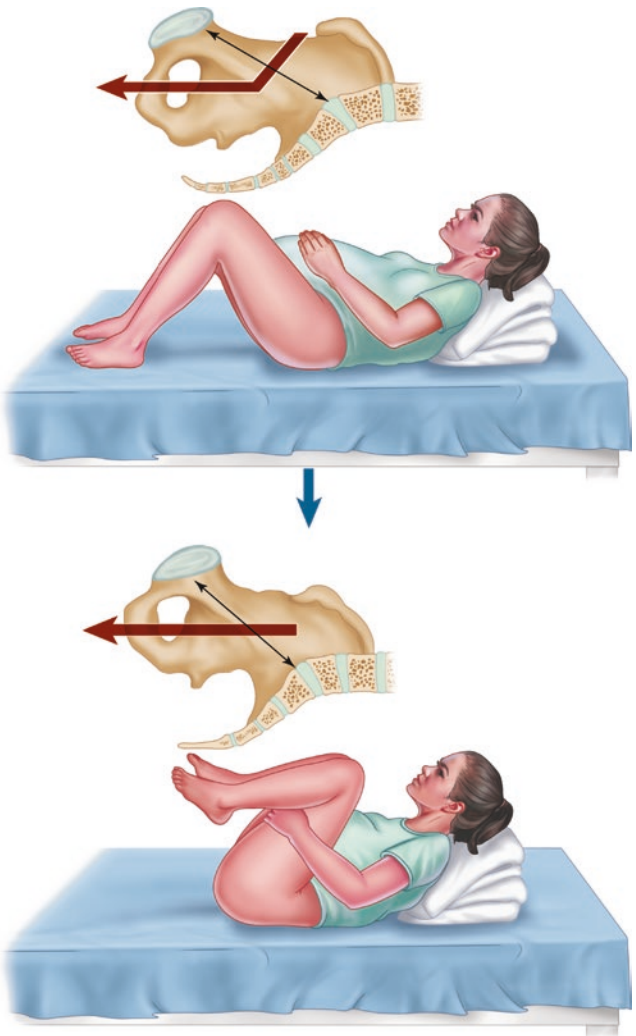


Fig. 11.12 Schematic of McRoberts position and its mechanical effect on pelvic orientation relative to the lumbosacral spine. After removing the maternal legs from stirrups and adducting the hips slightly, the maternal thighs are sharply flexed against the maternal abdomen. This rotates the maternal pelvis, effectively lifting the anterior pubic symphysis cephalad, while flattening lumbosacral spine (From L. Ganti (ed.), *Atlas of Emergency Medicine Procedures,* 2016)

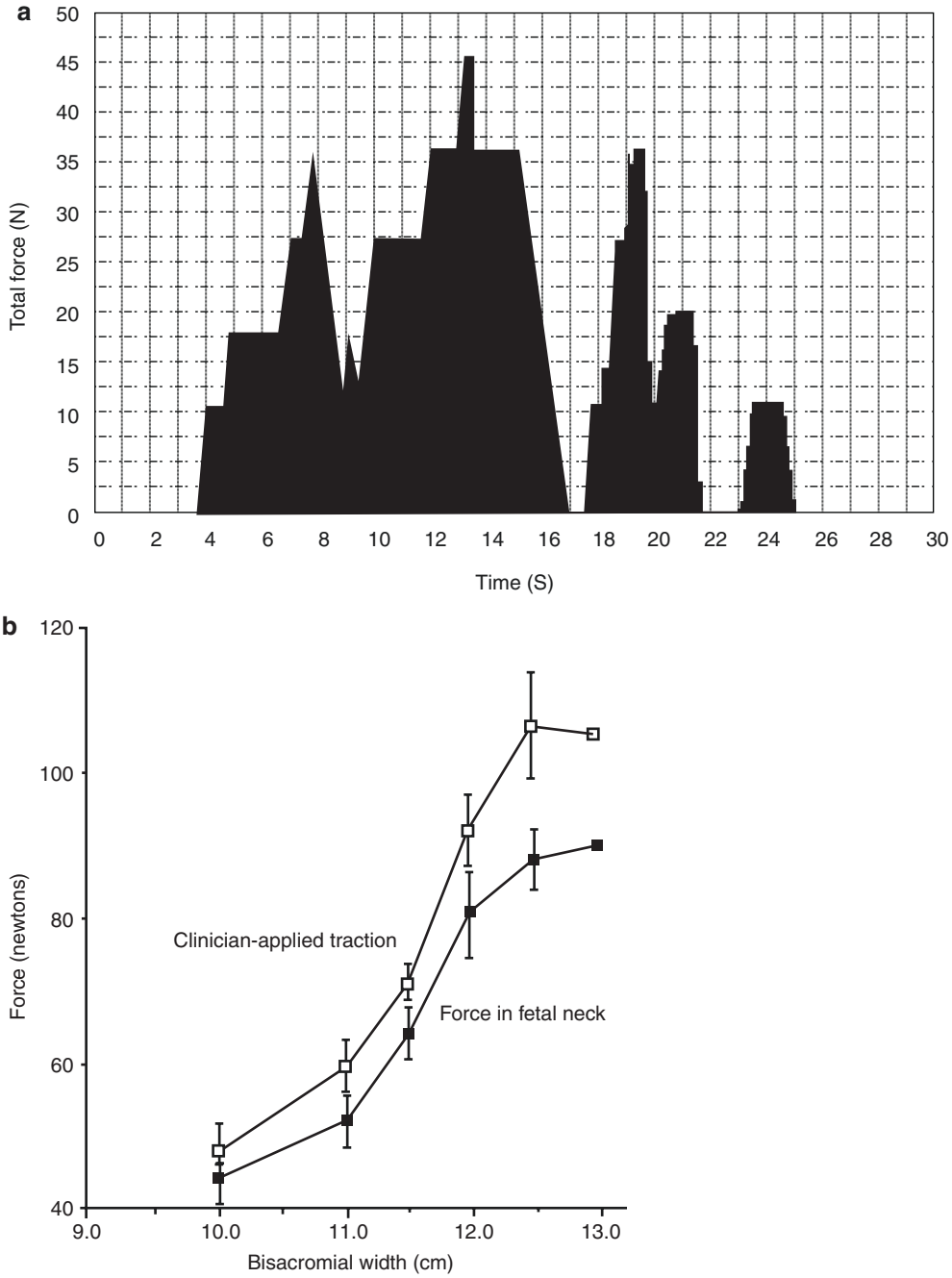


Fig. 11.13 Force-time history and limitation of McRoberts maneuver. Clinician-applied delivery force increases with successive attempts (**a**). In the event the fetal shoulder width is larger than 12.5 cm, McRoberts positioning will fail to clear the anterior shoulder of the pubic symphysis, increasing the risk of injury to the fetal clavicle and brachial plexus with continued traction (**b**) (Reprinted with permission (Gonik))

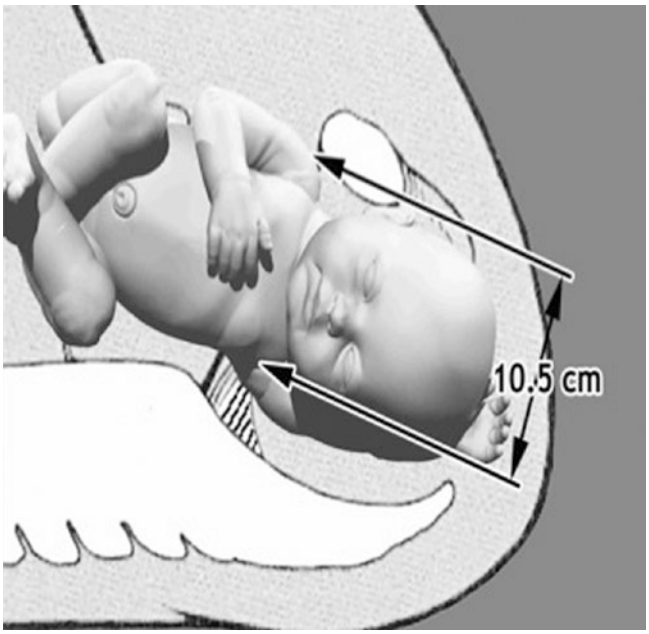
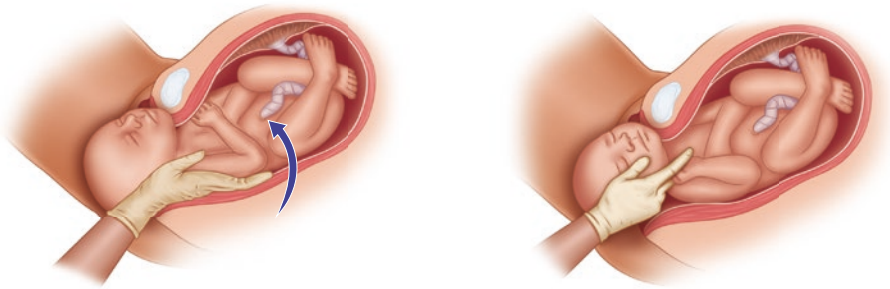


Fig. 11.14 Schematic of acromio-axillary dimension. During delivery of the posterior arm, the bisacromial width is reduced to the acromio-axillary width, typically by 2 cm (Reprinted with permission (Obstet Gynecol))



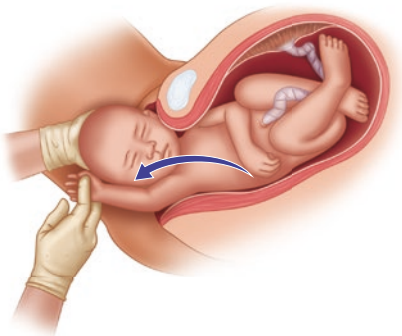


Fig. 11.15 Schematic of technique for delivery of the posterior arm. The obstetric provider's entire hand, including the thumb, should be inserted into the vagina up to the level of the wrist. The fetal elbow is palpated and, if extended, is manually flexed, and the arm is adducted and swept across the fetal chest (From: D. Ayres-de-Campos, *Obstetric Emergencies*, 2017)

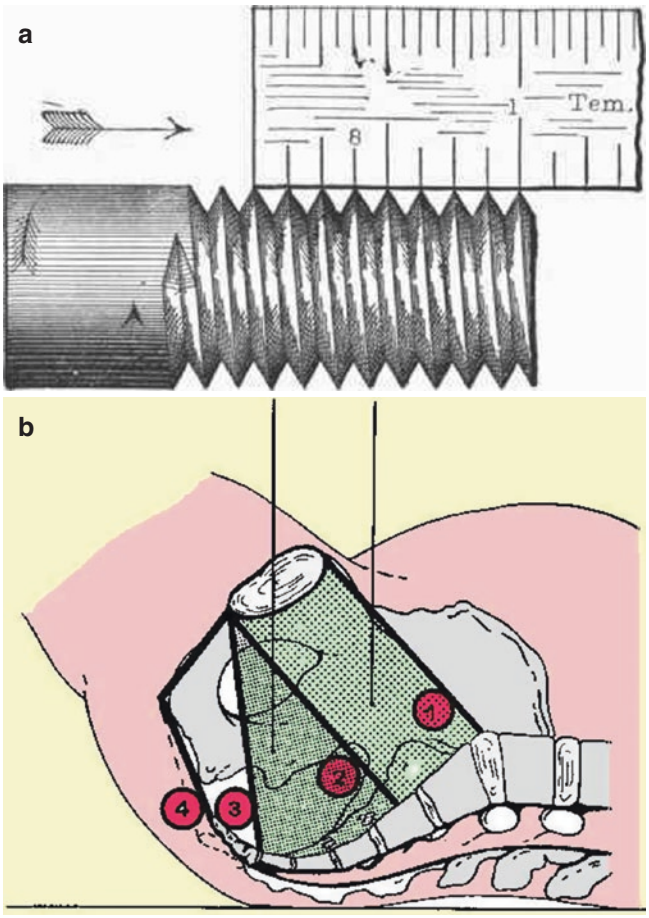


Fig. 11.16 The mechanics of Woods screw maneuver. The mechanical advantage of a screw compared to a steering wheel is that rotation about the threads results in forward motion (**a**) (chestofdrawers.com, Figure 115, accessed 12.8.16). The skew shape of the maternal pelvis successively positions the sacral promontory, pubic symphysis, and coccyx as threads of a screw (**b**). By pulling the posterior shoulder forward as the trunk is being rotated in a winding action during Woods screw maneuver, the obstetric provider will effectively move the posterior shoulder to an anterior position in front of the pubic symphysis anteriorly

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Placenta Previa

12

Filiberto M. Severi, Caterina Bocchi, Silvia Vannuccini, and Felice Petraglia

12.1 Introduction

Placenta previa (PP) is a severe complication of pregnancy where the placenta is abnormally placed and partially or totally covers internal os of the cervix. It is a major cause of painless massive hemorrhage during pregnancy with a high risk of maternal and perinatal morbidity and mortality. In fact, it is associated with potentially life-threatening conditions for the mother such as antepartum and postpartum bleeding, invasive placentation, need for hysterectomy, blood transfusion, septicemia, and thrombophlebitis. Similarly, adverse fetal and neonatal outcome is observed, with a high risk of preterm birth and perinatal death [1].

12.2 Definition

Implantation of the placenta, fully or partially, in the lower uterine segment is considered as placenta previa. Historically, the definition of placenta previa was based on obstetrical criteria, in the setting of vaginal bleeding, when a "double-setup" examination was performed. Over time, sonography has almost completely replaced clinical examination to assess the relationship between the placenta and the cervix; thus, types of placenta previa and their definitions have been changed according to ultrasound findings. However, there are still inconsistencies in placental terminology, and, since the management is different according to types of placenta previa, it would be useful to have a consensus on placental terminology [2].

According to RCOG guidelines [3], placenta previa should be classified by ultrasound imaging according to what is relevant clinically: if the placenta lies over the internal cervical os, it is considered a major previa (Fig. 12.1); if the leading edge of the placenta is in the lower uterine segment but not covering the cervical os, minor or partial previa exists (Fig. 12.2).

Currently, the definition of placenta previa is based on the distance between the placenta and internal os of the cervix. Definitely, there is an agreement that complete placenta previa is one which completely covers the internal cervical os [4–6]. However, when the placental edge just reaches the margin of a closed cervix, not crossing the os, but not a measurable distance away, terminology becomes confusing [2].

Different terms have been used, such as incomplete, partial, or marginal placenta previa, referring to different conditions in each case. When the cervix is visibly dilated and partially covered by the placenta, the term partial previa would seem appropriate, as this parallels the clinical definition of partial previa [4, 7], but this is a rare incidental finding and this term is no longer mentioned in placental terminology [8]. Conversely, the term marginal previa has been commonly used referring to a placenta that either reaches the margin of the internal os or is located a short distance away from the os in the lower uterine segment, typically within 20–25 mm [4, 5, 8]. However, some other authors have made a distinction, defining "low-lying" a placenta that is a short distance from the internal os (≤20 mm) (Fig. 12.3) [6, 9].

Controversies in terminology reflect different recommended managements in a placenta that covers any part of the internal os compared to one that is a short distance from the os. In order to limit confusion, a placenta that reaches the internal os should be simply termed placenta previa, while the term "low-lying placenta" should be used if placenta implants in the lower uterine segment, but does not reach the cervix. In the latter case, vaginal delivery may be achieved, depending on the distance between the lower placental edge and the cervical os [2].

Conversely, if the distance between the internal cervical os and the placental edge is >20 mm, the patients should be managed as per routine, because the majority of studies have

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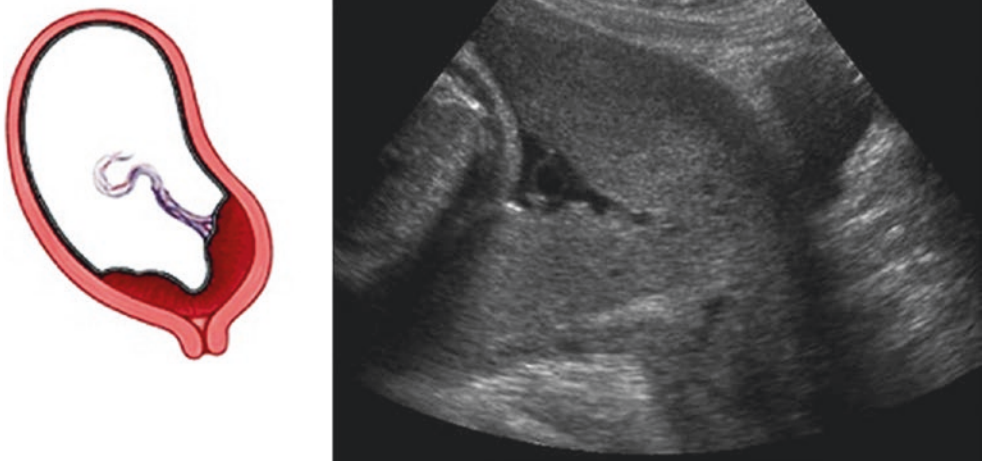

Fig. 12.1 Complete placenta previa (major previa) at transabdominal ultrasound. Placenta lies over the internal cervical os

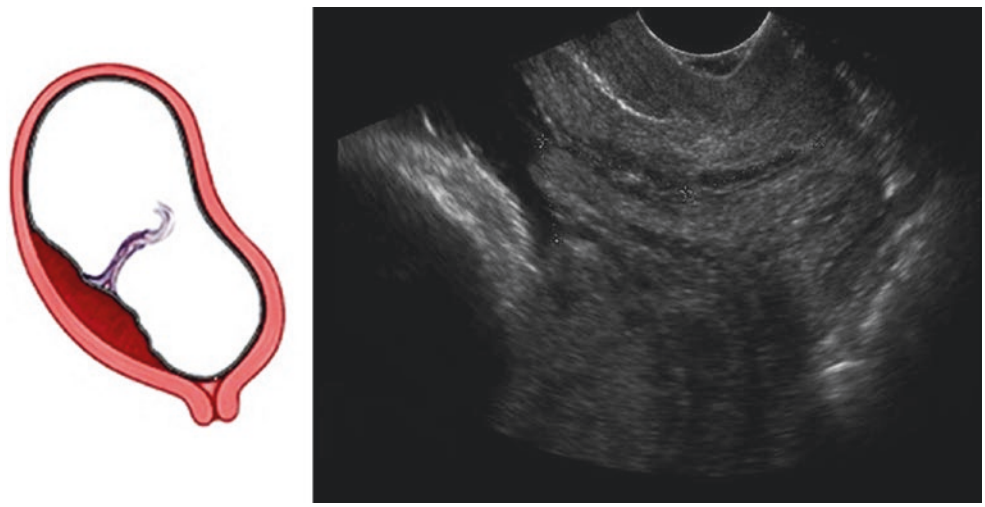

Fig. 12.2 Minor or partial placenta previa at transvaginal ultrasound

not demonstrated an increased risk for caesarean delivery for hemorrhage [10].

12.3 Incidence and Prevalence

The occurrence of placenta previa has increased in the last decades. A systematic review on published studies from 1966 to 2000 showed that the overall prevalence rate of placenta previa was 4.0 per 1000 births [11]. A more recent meta-analysis on placenta previa prevalence on the last 30 years reported a higher prevalence (5.2 per 1000 pregnancies), with a pooled prevalence of major placenta previa of 4.3 per 1000 pregnancies. [12]. According to regional differences, the prevalence of placenta previa was reported to be highest among Asian population (12.2 per 1000) and lower among studies from Europe (3.6 per 1000), North America (2.9 per 1000), and sub-Saharan Africa (2.7 per 1000).

The increasing rate of caesarean deliveries in the past three decades may have contributed to this increase in the prevalence of placenta previa [13, 14]. If primary and secondary caesarean rates continue to rise as they have in recent years, in 2020 the caesarean delivery rate will be 56.2 %, and there will be an additional 6236 placenta previas, 4504 placenta accretas, and 130 maternal deaths annually [15].

12.4 Risk Factors

The etiology of placenta previa remains unclear, but several epidemiological studies reported a panel of predisposing factors [16]. Previous caesarean section and uterine surgery (i.e., previous curettage, previous myomectomy, Asherman's syndrome) represent major risk factors for placenta previa, as uterine scars predispose to a low placental implantation. The occurrence of placenta previa seems to be correlated also with the number of caesarean sections.

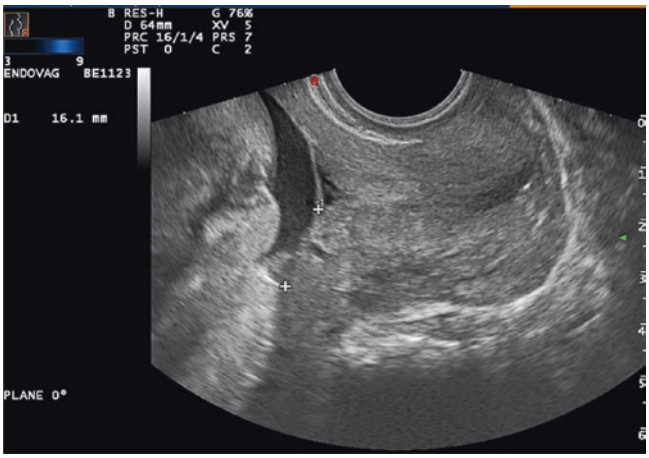

Fig. 12.3 Lower placental edge – internal cervical os distance measuring <20 mm at transvaginal ultrasound

The incidence of placenta previa increased from 10 per 1000 deliveries with one previous caesarean section to 28 per 1000 with more than three caesarean deliveries [17]. Damage and scarring to the endometrial and myometrial lining during caesarean delivery and spontaneous and induced abortion are known to predispose to the low implantation of the placenta in the uterus [18–20].

In addition, advanced maternal age (over 35 years), low socioeconomic status, grand multiparity, smoking, cocaine abuse, recurrent miscarriages, history of induced abortions, submucous myomas, a short caesarean- or curettage-to-conception interval, male fetal gender, and multiple pregnancy are other risk factors associated with the occurrence of placenta previa [16, 21–24] (Table 12.1).

Finally, women with history of placenta previa in a prior pregnancy are at higher risk of developing this condition in a subsequent pregnancy [11]. The increased risk of PP in women aged more than 35 years may be explained by atherosclerotic changes in the uterine blood vessels causing compromised uteroplacental blood flow. In order to maintain optimal blood flow, an increased surface area may be required for placental attachment, and this may result in placental encroachment on the lower uterine segment [25].

The high prevalence of PP in multiparous women may be due to endometrial scarring at the site of prior placental attachments resulting in lower placental implantation; alternatively, changes of blood vessels at the sites of prior placental attachments may lead to decreased uteroplacental blood, resulting in a larger placenta encroaching on the cervical os with repeated pregnancies. The relationship between cigarette smoking during pregnancy and PP risk may be attributed to the vasoactive properties of nicotine and to chronic hypoxia associated with carbon monoxide: chronic hypoxic changes in the uterine vasculature of smokers, resulting in a larger placenta with increased likelihood of placental encroachment on the cervical os [21].

Table 12.1. Risk factors for placenta previa

Risk factors	OR (95 % CI)
Prior caesarean section	2.7 (2.3–3.2)
Advanced maternal age (≥35 years)	1.8 (1.2–2.5)
Spontaneous or induced abortion	1.9 (1.7–2.2)
Cigarette smoking	1.6 (1.4–1.8)
Cocaine abuse	2.9 (1.9–4.3)
Male fetal gender	1.2 (1.1–1.3)

Similarly, maternal cocaine use is known to cause catecholamine-mediated vasoconstriction and vasospasm in blood vessels innervated by the sympathetic nervous system, resulting in underperfusion of the uteroplacental vessels and a larger placenta encroaching on the cervical os [23].

There is an increased frequency of placenta previa among women with preexisting or chronic hypertension. The exact mechanism that leads to lower implantation of the placenta among women with chronic hypertension is not clear. However, it has been suggested that a better blood supply and oxygenation of the placenta in the lower uterine segment prevents the release of vasoactive substances into the bloodstream and thus reduces the risk of pregnancy-induced hypertension and preeclampsia in cases of placenta previa [26].

Furthermore, recent studies indicate that assisted reproductive technology (ART) also constitutes a risk factor for PP [27–29]. Indeed, in a group of 318 patient who consecutively conceived by ART, it was found that endometriosis (OR 15.1) and tubal disease (OR 4.4) increased the risk of PP. Thus, even factors causing infertility may contribute to the pathogenesis of PP because most women who undergo ART have some underlying infertile factors [30]. Besides, a recent study on ART cycles showed that endometrial thickness is directly proportional to the risk of placenta previa, independently of significant risk factors, such as smoking and endometriosis, but related to the endometrial preparation and hormonal stimulating therapy [31].

12.5 Pathophysiology

The pathophysiology of placenta previa is not completely understood [32]. As gestation advances, the relationship between the placental edge and the internal cervical os changes. In fact, a low implanted placenta in the early second trimester of pregnancy would move away from the internal os in the third trimester in most of the cases. This placental "migration" from the lower uterine segment toward the fundus may be explained by a greater vascularization of fundus compared to the rest of the uterus, allowing a better

development of the trophoblastic tissue. This phenomenon would occur because of a process of a degeneration of the trophoblast close to the internal orifice secondary to decreased vascularization rather than a true migration of the placental tissue [33]. Thus, distortion of the normal anatomy of the lower uterine segment induced by a previous uterine scar would prevent this "migration" [20]. Alternatively, defective decidual vascularization and subsequent endometrial hypoxemia may increase the surface area of the placental tissue, predisposing to a lower implantation close to the cervix [34].

12.6 Diagnosis

Placenta previa characteristically presents with painless vaginal bleeding, in late second trimester or in the third trimester. The initial bleed in more than 50 % of cases occurs prior to 36 weeks' gestation. Bleeding episodes can be recurrent in most cases, with a worsening of bleeding. The absence of abdominal pain is regarded as a significant differentiating feature between placenta previa and abruption, although 10 % of women will have a coexisting abruption or the presence of uterine contractions. Alternatively, the condition would remain unknown until labor onset [35]. Even though clinical signs are very important in the initial management of placenta previa suspect, definitive diagnosis is made only by ultrasound [10].

Placental location is usually reported during the routine anomaly scan in the second trimester. A follow-up scan in the third trimester should be scheduled when the placental edge is found to be reaching or overlapping the internal cervical orifice, to confirm this finding and to plan the management of delivery [3, 36] (Fig. 12.4).

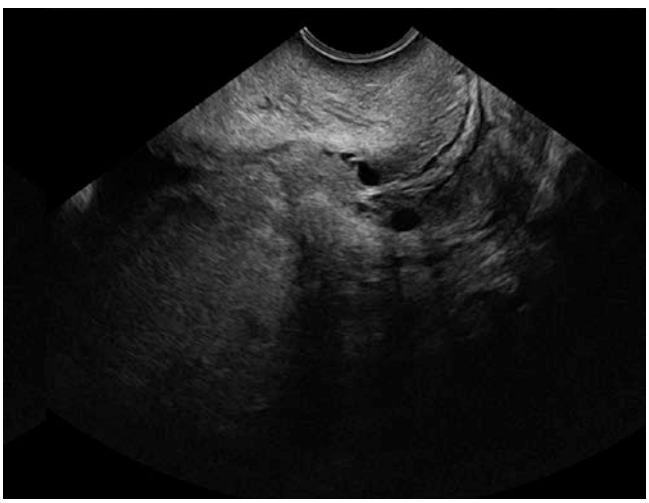

Fig. 12.4 Transvaginal ultrasound at 20 weeks: the placental edge is found to be overlapping the internal cervical orifice

The ultrasound can either be done by transabdominal, transvaginal, or translabial methods (Fig.12.5). Transvaginal ultrasound is considered to be the most accurate, with less risk of false-positive results [37, 38]. This approach allows the sonographer to visualize the relationship between the lower placental edge and the internal cervical orifice with greater clarity because there is no obstruction of visualization caused by the fetus. Transvaginal ultrasound is safe, even in suspected cases of placenta previa, if the sonographer visualizes the placement of the intravaginal probe and avoids close cervical contact [38–43] (Fig. 12.6).

Translabial sonography is an acceptable technique to visualize placental location if there are concerns about the insertion of a transvaginal probe, but it is not as precise as transvaginal ultrasound [8].

The scanner head is placed between the labia majora anterior to the vaginal introitus and oriented along the axis of the vagina [44]. If placenta previa or low-lying placenta is diagnosed early (15–19 weeks' gestation) in pregnancy, repeated sonographic screening performed throughout the pregnancy is critical [45].

The suspected diagnosis of placenta previa at 20 weeks of gestation by abdominal scan should be confirmed by transvaginal scan. In the second trimester, transvaginal sonography will reclassify 26–60 % of cases where the abdominal scan diagnosed a low-lying placenta, meaning fewer women will need follow-up [3, 40, 41] (Fig. 12.7).

Anyhow, a conclusive diagnosis of placenta previa is possible only in the third trimester of pregnancies, because almost 90 % of the placentas defined as low in the second trimester move away out of the lower uterine segment later on in gestation [46, 47]. This occurs as a result of atrophy of the placental tissue in the lower uterine segment, secondary to a poor blood supply combined with the subsequent growth of placental tissue in the areas of increased

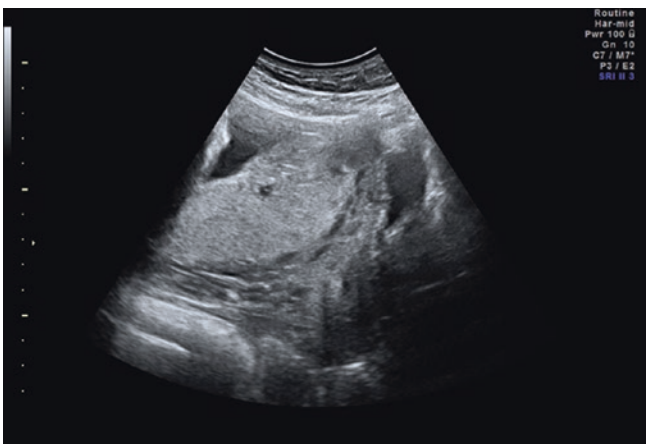

Fig. 12.5 Major placenta previa at transabdominal ultrasound

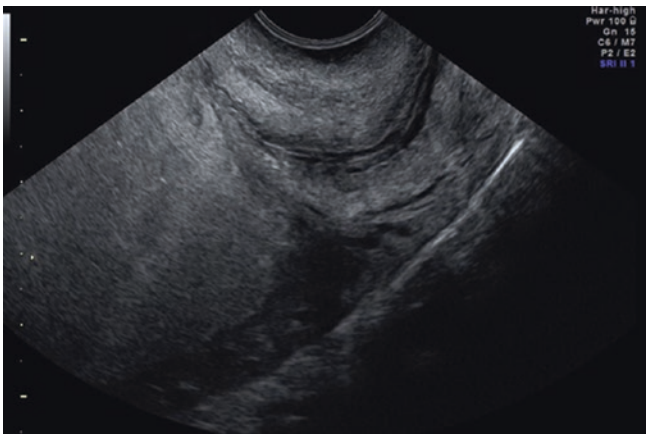

Fig. 12.6 Transvaginal ultrasound: complete placenta previa (major previa)

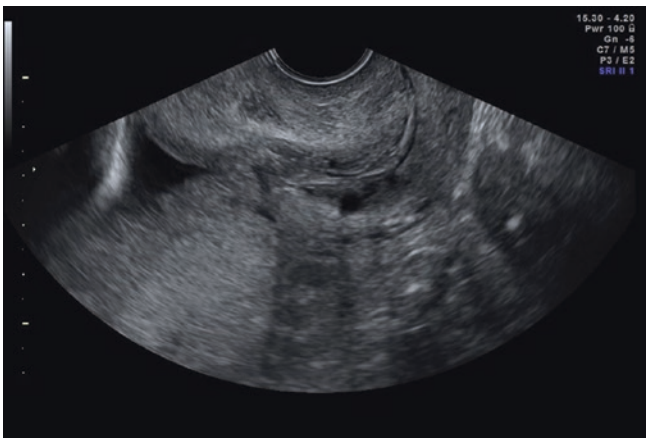

Fig. 12.8 Transvaginal ultrasound: placental edge reaching the internal cervical os at 28 weeks

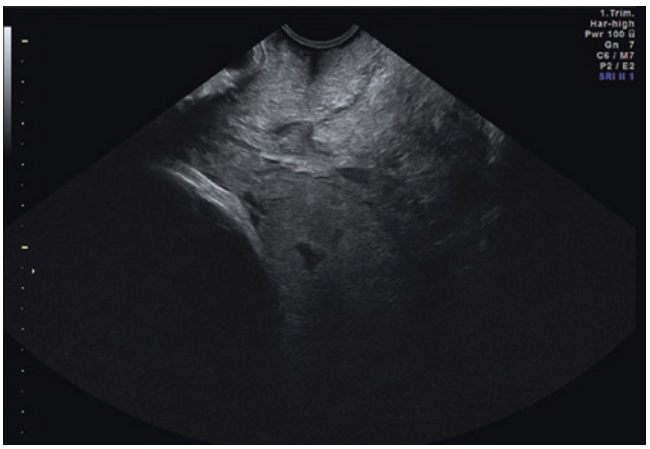

Fig. 12.7 Transvaginal ultrasound: placenta previa in the third trimester

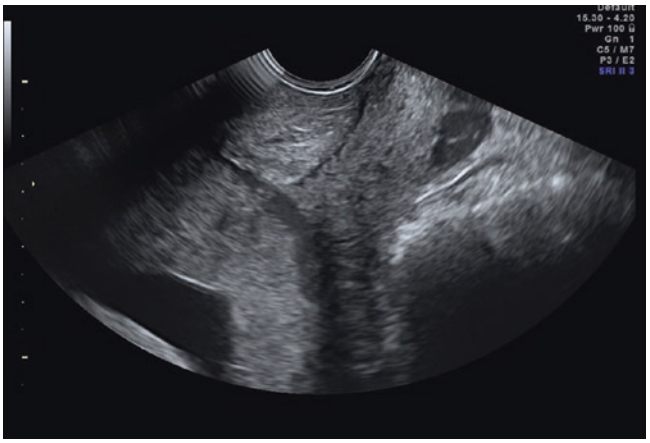

Fig. 12.9 The placental edge overlaps the internal cervical orifice by more than 2 cm at transvaginal ultrasound

vascularity in the fundal area of the uterus. This developmental event is called trophotropism [1].

The study by Heller [48] on second-trimester low-lying placentas demonstrates a very high (>98 %) likelihood of migration of the placenta away from the cervix (>2 cm from the internal os) by the time of delivery. These results can be used to counsel patients and reduce their level of anxiety regarding peripartum complications or the need for caesarean delivery because of the second-trimester finding. Since only 66 % of low-lying placentas resolve by the end of 27 weeks' gestation, whereas almost 90 % of cases will be clear of the cervix by 32 weeks, it would be cost-effective to delay reassessment of the placental location until after 28–30 weeks in those pregnancies uncomplicated by bleeding or preterm labor (Fig. 12.8).

Some investigators have attempted to correlate the position of the placenta in the second trimester, as detected at the scan, with the likelihood of migration in the third trimester of pregnancy. In fact, in some cases of midtrimester low-lying placenta, the placental edge is more likely to "migrate" than others are. Ultrasound may be useful in predicting both the likelihood and extent of placental migration as a function of time. In women with placental edge within 3 cm of the internal cervical orifice at 26 weeks of pregnancy or later, the mean rate of migration was 5.4 mm per week in women in whom placental edge migration did occur. If the placental edge overlapped the internal cervical orifice by more than 2 cm, migration was not observed in any woman, while migration always occurred when the placental edge was more than 2 cm from the internal cervical orifice (Fig. 12.9).

On the contrary, if the distance of the placental edge was less than 2 cm from the internal cervical orifice, placental migration occurred in most cases [49]. The extent to which the placenta overlaps the internal cervical os in the second trimester can be used to determine if the placenta previa will

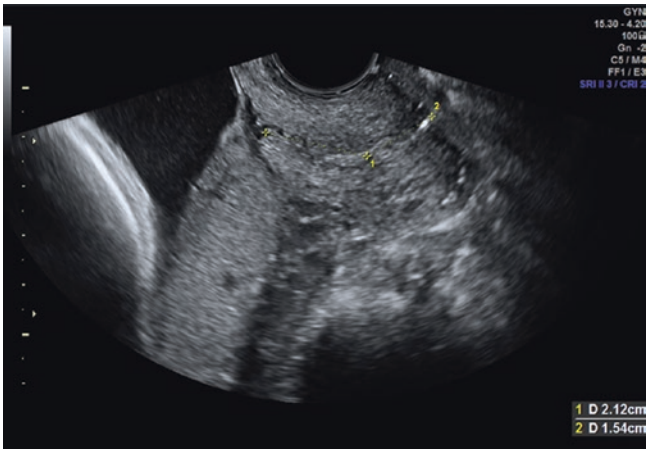

Fig. 12.10 Placental edge shape at transvaginal ultrasound

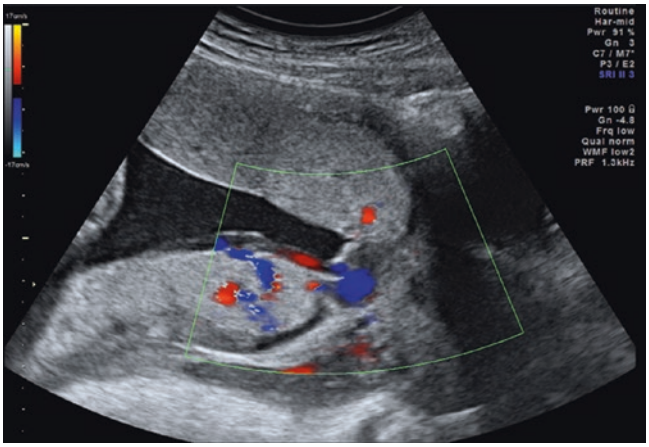

Fig. 12.11 Posterior placenta previa and anterior accessory placental lobe, with vasa previa

persist until term. With complete previas that cover the os at 20 weeks' gestation, 40 % will continue as a complete previa until birth. Women with a history of a prior caesarean are at greater risk for a placenta previa or a low-lying placenta to persist until birth [38]. Scarring from the caesarean birth impairs the ability of a low-lying placenta to migrate as the uterus expands with the advancing pregnancy [38, 50, 51].

The shape of the placental edge detected at 28–32 weeks is another factor in predicting placental migration. Placental migration was seen in 29.6 % where the placental edge was thin, but only in 5.8 % where it was thick (if the thickness was 1 cm or less, within 1 cm from the edge, the angle between the basal and the chorionic plate exceeded 45°, or both). Indeed, a significantly higher rate of antepartum hemorrhage, abdominal delivery, adherent placenta, and low birth weight was found in cases where the placental edge was thick [52] (Fig. 12.10).

In summary, when a low-lying placenta is diagnosed in the second trimester from 16 to 24 weeks, more than 98 % of placentas will no longer approach the cervix by the time of delivery. In almost 90 % of cases, the placenta will be clear of the cervix by 32 weeks' gestation and almost 96 % by 36 weeks. A very small percentage of second-trimester low-lying placentas persist or progress to placenta previa requiring caesarean delivery, and a few will develop into vasa previa. Careful scanning at follow-up is essential for determining whether part of the placenta or a fetal vessel crosses the internal surface of the cervix to plan appropriately for delivery.

A low-lying placenta is a known risk factor for the development of vasa previa [53], and this factor must be kept in mind when following up on an earlier diagnosis of a low-lying placenta. Color Doppler imaging is recommended to assess the internal surface of the cervix to diagnose or exclude vasa previa as well as to identify the umbilical cord insertion to the placenta. [54] (Fig. 12.11).

12.6.1 Vasa Previa

Vasa previa describes fetal blood vessels coursing through the membranes over the internal cervical os and below the fetal presenting part, unprotected by placental tissue or the umbilical cord. [55]. This can be secondary to a velamentous cord insertion in a single or bilobed placenta (vasa previa type 1) or from fetal vessels running between lobes of a placenta with one or more accessory lobes (vasa previa type 2) [56]. The reported incidence varies between 1 in 2000 and 1 in 6000 pregnancies [57]. Unlike placenta previa, vasa previa carries no major maternal risk but is associated with significant risk to the fetus. When the fetal membranes are ruptured, either spontaneously or artificially, the unprotected fetal vessels are at risk of disruption with consequent fetal hemorrhage. Vasa previa therefore often presents with fresh vaginal bleeding at the time of membrane rupture and fetal heart rate abnormalities such as decelerations, bradycardia, a sinusoidal trace, or fetal demise. The mortality rate in this situation is around 60 %, although significantly improved survival rates of up to 97 % have been reported where the diagnosis has been made antenatally. More rarely, bleeding can occur in the absence of membrane rupture. Because the fetal blood volume is around 80–100 ml/kg, the loss of relatively small amounts of blood can have major implications for the fetus. Very rarely, fetal heart rate abnormalities in the absence of bleeding may be present secondary to compression of the fetal vessels by the fetal presenting part.

Risk factors for vasa previa include placental anomalies, such as a bilobed placenta or succenturiate lobes, where the fetal vessels run through the membranes joining the separate lobes together, a history of low-lying placenta in the second trimester, multiple pregnancy, and in vitro fertilization, where the incidence of vasa previa has been reported to be as high as one in 300 [58].

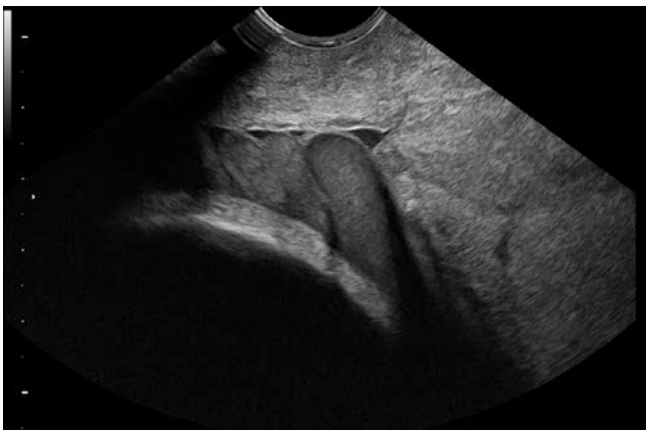

Fig. 12.12 Vasa previa at transvaginal ultrasound

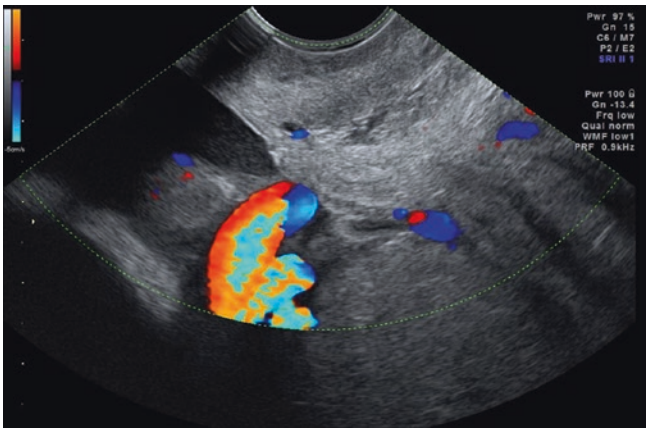

Fig. 12.13 Vasa previa at color Doppler

Vasa previa can be accurately diagnosed with color Doppler ultrasound, by using transvaginal probe and assessing the lower pole of the uterus in the region of the internal cervical os to identify any fetal vessels. The accuracy of ultrasound in the prenatal diagnosis of vasa previa is good with a sensitivity of 100 % and specificity of 99.0–99.8 %, when performed transvaginally with color Doppler [59] (Figs. 12.12, 12.13, 12.14, and 12.15).

A surgical birth is indicated for women diagnosed with vasa previa. Because the exposed blood vessels are not protected by Wharton's jelly or placental tissue, a planned caesarean birth is recommended before the likelihood of spontaneous labor, at approximately 35–36 weeks' gestation.

12.7 Management

Clinicians should determine if a woman has risk factors for placenta previa during the initial prenatal visit. Any episode of painless vaginal bleeding during pregnancy should be evaluated for placenta previa with ultrasound [51]. Placenta previa is responsible for potentially life-threatening conditions

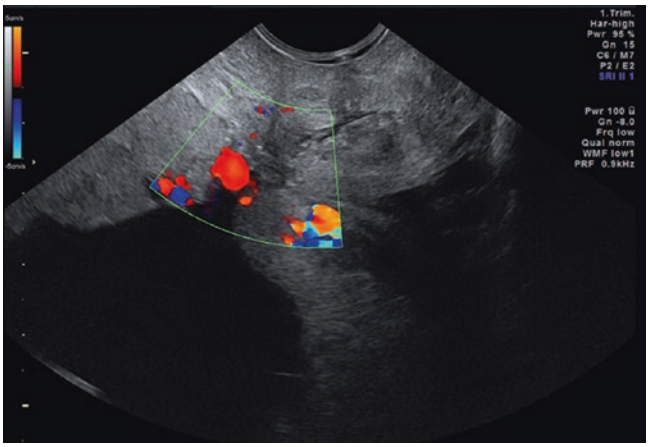

Fig. 12.14 Placenta previa and vasa previa at 30 weeks

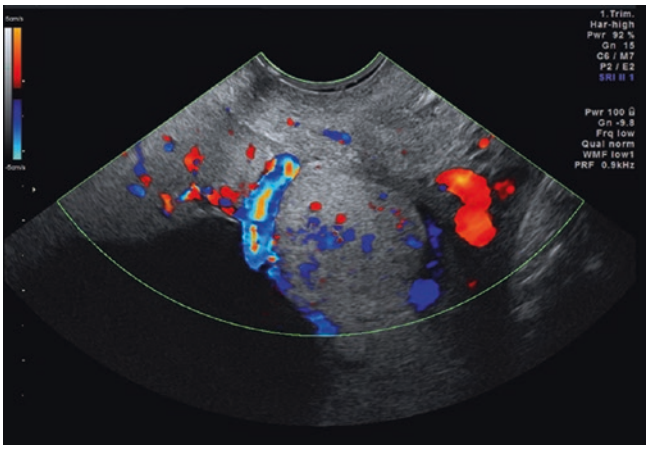

Fig. 12.15 Placenta previa and vasa previa at 32 weeks

for the mother and the fetus, and women with confirmed diagnosis in the third trimester should be counseled about potential risks and their care should be tailored to their individual needs.

Maternal risks [32, 60]:

1. Maternal mortality: from 5 % lo less than 0.1 %
2. Antepartum and postpartum hemorrhage, with need for hysterectomy and/or blood transfusions
3. Placenta accreta (occurring in approximately 15 % of PP)
4. Air embolism: if the sinuses in the placental bed are torn
5. Postpartum sepsis: due to ascending infections
6. Recurrence approximately in 4–8 %

12.7.1 Placenta Previa Accreta

With the rising incidence of caesarean section operations combined with increasing maternal age, the number of cases of placenta previa accreta and its complications is continuing to increase. The risk of placenta previa in a first

pregnancy is 1 in 400, but it rises to 1 in 160 after one caesarean section, 1 in 60 after two, 1 in 30 after three, and 1 in 10 after four caesarean sections. If the placenta is over the lower segment scar, then there is an attendant risk that the placenta will invade into or occasionally through the myometrium. This risk is about 1 in 50 if there has been one caesarean section, 1 in 6 after two, 1 in 4 after three, 1 in 3 after four, and 1 in 2 after five caesarean sections [61]. Indeed, 10 % of placenta accreta are anterior previa, and in patients with previous CS and anterior previa, the incidence of accretism reaches 67 % [62]. Thus, antenatal sonographic imaging can be complemented by magnetic resonance imaging in equivocal cases to distinguish those women at special risk of placenta accreta [63, 64] (Figs. 12.16, 12.17, 12.18, and 12.19).

Adverse fetal and neonatal outcome, such as perinatal death and preterm delivery, is increased in pregnancies complicated by placenta previa.

Fetal risks [65–67]:

1. Perinatal mortality: due to prematurity (OR for PTB 27.7 – NICU 3.4).
2. Fetal growth restriction: among multiparous women, placenta previa was associated with a twofold increased risk of SGA fetuses.
3. Major congenital malformations: reports indicate a doubling in women with placenta previa. The most common are those of central nervous, cardiovascular, respiratory, and gastrointestinal systems.
4. Unexpected fetal death secondary to vasa previa or severe maternal hemorrhage.
5. Fetal malpresentations (35 %).
6. Fetal anemia.
7. Umbilical cord prolapse.
8. Cord compression.

12.7.1.1 Antenatal Management

The clinical outcomes of cases with placenta previa are highly variable and cannot be predicted confidently from antenatal events. Immediate delivery of the fetus may be indicated if it is mature or earlier if the fetus or the mother's condition is at imminent risk. Thus, an initial assessment to determine the status of the mother and fetus is required. Although mothers used to be treated in the hospital from the first bleeding episode until birth, it is considered safe to treat placenta previa on an outpatient basis if the fetus is at less than 30 weeks of gestation and the mother and the fetus are in good health [68].

All women at risk of major antepartum hemorrhage should be encouraged to remain close to the hospital of confinement for the duration of the third trimester of pregnancy. Therefore, any home-based care requires close proximity to the hospital, the constant presence of a companion, and full informed consent by the woman. However, there are still no specific recommendations about antenatal management of women with diagnosis of placenta previa in the third trimester [10]. One retrospective observational review considering the care of 161 women with placenta previa in the third trimester demonstrated that neither the likelihood of bleeding nor the need for rapid delivery was associated with the degree of previa [69]. A potential role may be played by cervical length measurement in the third trimester, for predicting antepartum bleeding and need for emergency caesarean section [70–72]. However, it should be made clear to any woman being managed at home that she should attend immediately experiences such as any bleeding, contractions, or pain (including vague suprapubic period-like aches). The risk of hemorrhage does not appear to be decreased by the avoidance of sexual intercourse, but the woman should avoid vigorous activity. There is no evidence that supports the use of bed rest for a woman who is not bleeding [43].

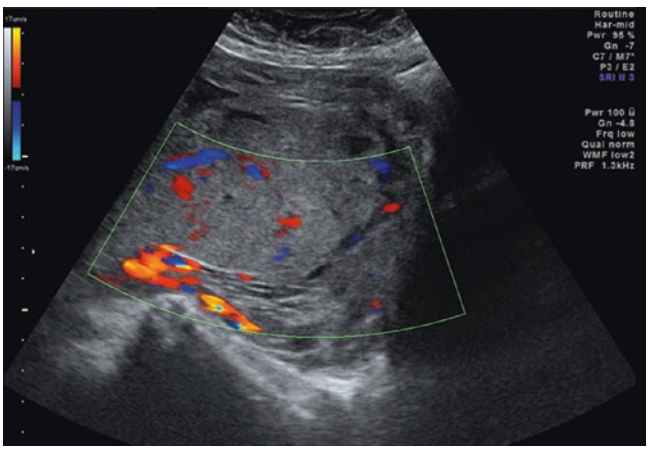

Fig. 12.16 Placenta previa at transabdominal ultrasound: absence of color Doppler signs of accretism

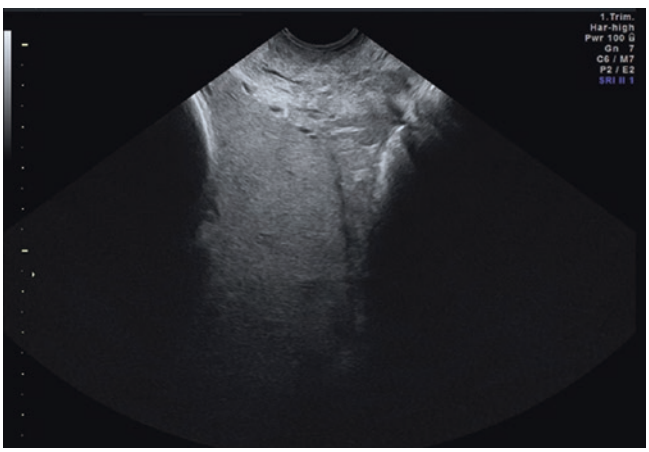

Fig. 12.17 Placenta previa accreta – absence of the hypoechoic retroplacental zone

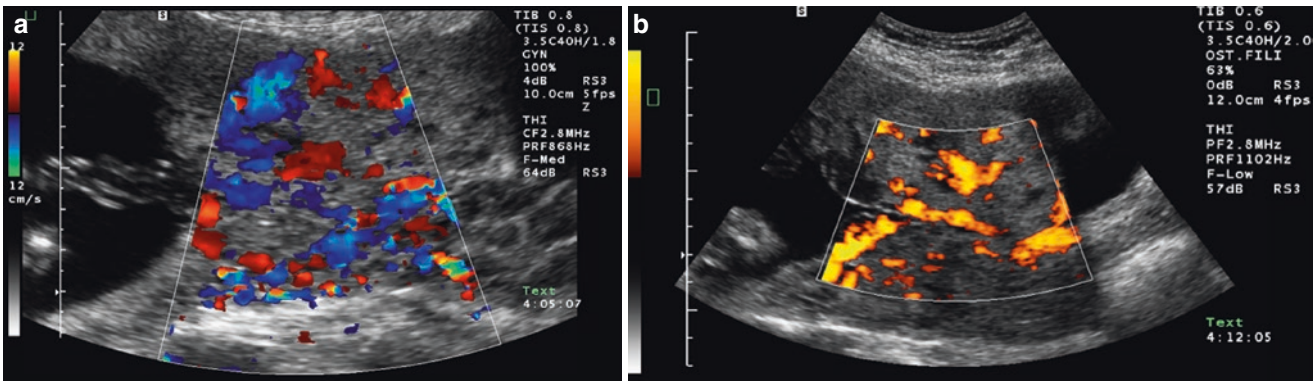

Fig. 12.18 Placenta previa accreta – multiple vascular lacunae at color Doppler

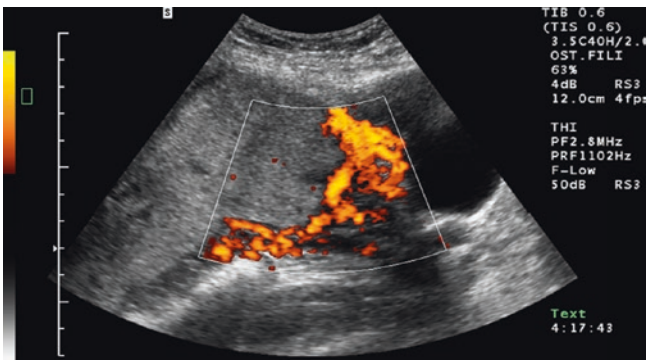

Fig. 12.19 Placenta previa accreta – abnormalities of the uterine serosa–bladder interface with increased vascularity on color Doppler imaging

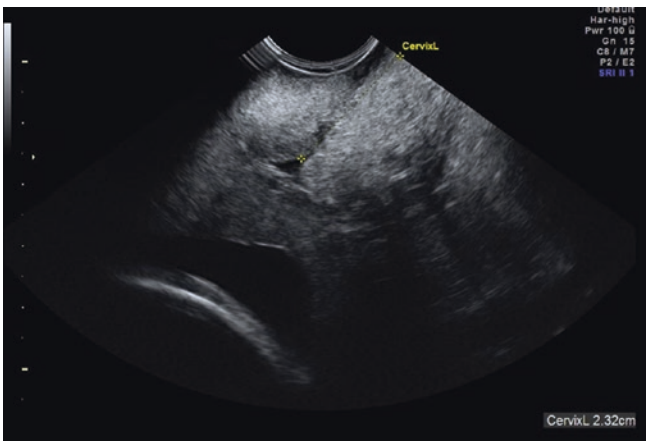

Fig. 12.20 Cervical length measurement in complete placenta previa

Prevention of preterm labor is important to minimize neonatal complications. Regular contractions will cause cervical effacement and dilatation, which will eventually cause bleeding from the placental implantation site. Women being observed for placenta previa should be evaluated sonographically for changes in cervical length (Figs. 12.20 and 12.21). A decrease in cervical length is correlated with an increase in emergent preterm caesarean birth and intrapartum blood loss [73].

Women experiencing cervical length changes should be hospitalized until birth. Because bleeding can occur with uterine contractions, tocolytic medications such as terbutaline, nifedipine, indomethacin, or magnesium sulfate are used to stop the contractions if there are no other contraindications to the use of these drugs [43]. The use of tocolytics has been found to prolong a pregnancy for more than 7 days in women with placenta previa who are experiencing symptoms of preterm labor [74]. This delay allows more time for the fetal lung to mature. No evidence supports the prophylactic use of tocolytics in women with placenta previa who do not have symptoms of preterm labor. Steroids such as betamethasone should be administered to women who are less than 34 weeks' gestation to further accelerate fetal lung maturity [43, 75].

12.7.1.2 Timing and Mode of Delivery

Caesarean section is the recommended mode of delivery for major placenta previa, whereas for minor previa an attempt at vaginal delivery is deemed appropriate. The introduction of ultrasound in clinical practice has raised the issue of which sonographic threshold of distance between the lower placental edge and the cervix should be used to achieve a safe vaginal delivery [76–78]. Oppenheimer et al. [49] found that the mean distance of the placental edge from the internal cervical orifice in women requiring a caesarean section for placenta previa was 1.1 cm (range, 0.0–2.0 cm). In a study of 121 women with placenta previa, all women required a caesarean section when the placental edge was within 1 cm of the internal cervical orifice within 2 weeks of delivery (Fig. 12.22). In contrast, if the placental edge to internal cervical orifice distance was 2 cm or more, the likelihood of achieving a vaginal delivery was at least 63 % [52]. In low-lying placenta, although there is a good chance of a vaginal delivery, the incidence of postpartum hemorrhage remains high

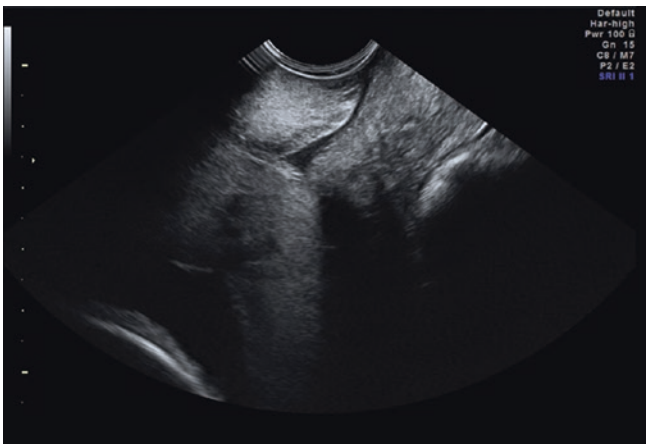

Fig. 12.21 Cervical shortening in pregnant woman with complete placenta previa at 30 weeks

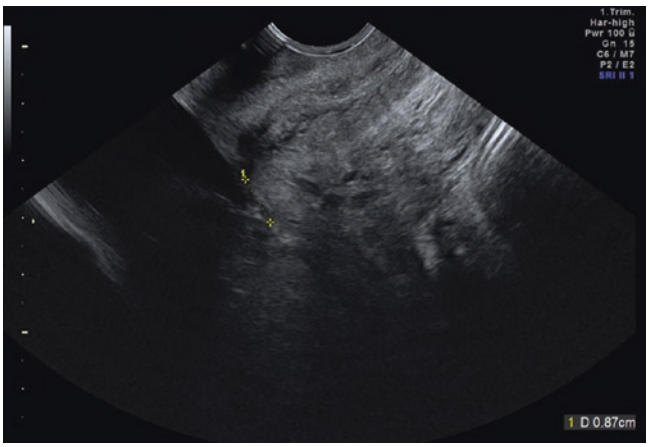

Fig. 12.22 Lower placental edge – internal cervical os distance measuring <20 mm at transvaginal ultrasound

[79]. Therefore, a low-lying placenta deserves an attempt at vaginal delivery but should warn the clinician of the possibility of hemorrhagic complications, so that appropriate precautions can be taken. Whether a caesarean or vaginal birth is planned, the birth should occur in a facility with a blood bank, neonatology support, and experienced practitioners who can manage intrapartum hemorrhage [43].

Concerning gestational age at delivery, no official guidelines address the issue of the optimal timing in placenta previa, but common practice is to conduct delivery between 36 and 37 weeks' gestation. According to RCOG, elective delivery by caesarean section in asymptomatic women is not recommended before 38 weeks of gestation for placenta previa or before 36–37 weeks of gestation for suspected placenta accreta [3]. A recent large study comparing neonatal outcomes among pregnancies complicated by placenta previa delivered at the late-preterm period (35, 36 weeks) relative to the early-term period (37 and 38 weeks) showed that, barring maternal indications, early-term delivery in placenta previa is associated with fewer complications and no greater risk than late-preterm delivery [80].

12.7.1.3 Management of Bleeding

Obstetrical bleeding (intrapartum/postpartum) secondary to placenta previa with variable degrees of accretion is not uncommon. Postpartum bleeding is usually from the placental bed at the lower uterine segment and occurs immediately after the placenta is delivered. Hysterectomy can be an undesirable action to take, especially in the case of a low parity patient. Usually, this step is taken when other traditional measures to stop hemorrhage fail. Various management options are utilized for control of bleeding caused by this clinical abnormality, and conservative approaches are becoming increasingly used instead of hysterectomy [81]. Arterial embolization under fluoroscopic guidance requires expertise in interventional radiology and specialized equipment, although the success rate is high and the procedure has the potential to preserve fertility. This procedure is limited to centers with a high degree of expertise. Nowadays, the use of intrauterine balloons has been well described in the literature for the control of massive postpartum hemorrhage due to atonic uterus not responding to oxytocics such as prostaglandins. Placement of a uterine balloon tamponade (Foley, Bakri balloon, or Sengstaken-Blakemore tube), which may be inserted either after caesarean section or vaginal delivery, is an option with interesting advantages and is thus often preferred to gauze packing [82, 83]. Placement of a uterine balloon can act as a diagnostic test to screen those women who need hysterectomy. In addition, it minimizes the risk of occult bleeding, and removal of the balloon is not a painful procedure. Intrauterine balloon tamponade could successfully control severe hemorrhage from a lower uterine segment of a patient with placenta previa. This technique is simple to use, scarcely invasive, and available at a low cost to all maternity wards and should be considered as one of the first management options to reduce the risk of undesirable hysterectomy [84, 85].

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Abnormal Invasive Placentation: Management and Complications

13

José M. Palacios-Jaraquemada

13.1 Introduction

Under the name of abnormal invasive placentation (AIP) are included known conditions such as placenta accreta, increta, and percreta [1]. In the last few years, experts called AIP to gather all varieties in a clinical way instead of the pathological one. Obstetricians in the USA called the same group of invasions morbid adherent placenta [2] (MAP), which is coincident with the classification previously proposed by European experts.

Due to the increase of cesarean deliveries worldwide, AIP also grows almost equally. Both cesarean and AIP are closely associated, essentially because they are the most frequent cause of uterine damage. The uterine segment is a special area which is developed during pregnancy and is rich in collagens. This characteristic was described in the original work of professor Munro Kerr, and he mentioned that it could be a cause of future damage or dehiscence in future pregnancies, because the cesarean scar is practically inextensible. In developing countries, abortion is one of the most common additional risk factors of uterine damage [3]. Usually in most of these countries, abortion is already illegal and not always practiced in good conditions or by doctors. For shame, religious conflicts and other reasons, this antecedent must be carefully asked about, especially when we suspect AIP in young women without other recognized risk factors.

Diagnosis of AIP is well descripted in textbooks and papers; however, some studies showed that nearly 50 % of cases could be undiagnosed at cesarean [4]. Ultrasound is the election method for diagnosis and can be performed abdominally or transvaginally [5]. From the original description of retrospective signs in 1983, it was in 1992 that sonography criteria already used were established, which included loss of the normal hypoechoic retroplacental myometrial zone, thinning or disruption of the hyperechoic uterine serosa-bladder interface, and presence of focal exophytic masses [6]. Magnetic resonance imaging of the placenta (pMRI) started at the same time, and it is usually indicated in doubtful cases, with suspicion of posterior or parametrial involvement. Although both methods are very sensitive and predictive, their value lies in the operator's experience [7]. Both ultrasound and pMRI have technical details which allow better images. Unlike ultrasound, pMRI is a study of total volume acquisition, which could be reevaluated by many specialists in identical conditions [8].

There is an implicit agreement that AIP must be operated in centers with equipment and qualified team [9]; for this reason, prenatal diagnosis is important. Today, all pregnant patients with a history of cesarean/s, abortion, or any kind of uterine damage associated with low-lying placenta must be correctly evaluated to search signs of AIP. In case of doubt or absence of ultrasonography signs in high-risk patients, it is highly recommended that the patient be reevaluated by an expert in this condition, due to a wide range of variability among observers [10]. Lack of prenatal diagnosis could end up in a catastrophic event at cesarean; for this reason, it is essential that obstetricians make all necessary efforts to confirm or discard the AIP diagnosis.

13.2 Management

There is not only one way to manage or solve AIP, but in all cases it is necessary to pay special attention to reduce blood loss and to minimize the catastrophic consequences of massive bleeding [11]. A resective treatment (hysterectomy or resection of invaded tissues and reconstruction) implies resources and an expertise team. A pure conservative one, such as leaving the placenta in situ, avoids initial dissection or additional maneuvers. However, they need a close clinical control and are not exempted of life-threatening complications. Uterine blood flow at term is about 500–700 ml,

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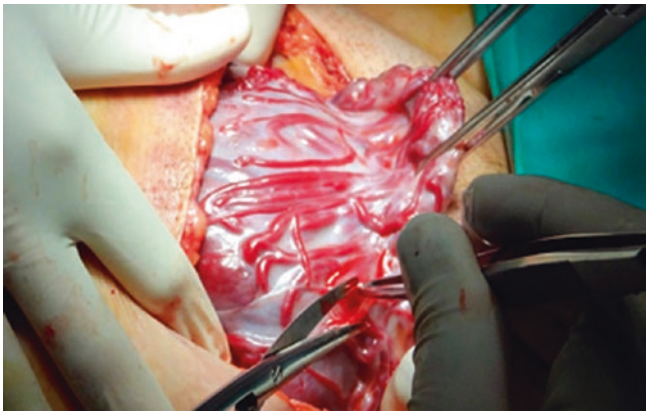

Fig. 13.1 Laparotomy aspect after cesarean. Patient with one cesarean and one cesarean scar pregnancy treated with methotrexate, embolization, and curettage. Spontaneous pregnancy 5 months after second pregnancy. Although clinical aspect is evident, two previous ultrasounds showed neither AIP nor doubt either

a volume which may duplicate in AIP uncontrolled bleeding since newly formed vessels have no possibility of vasoconstriction due to lack of tunica media. Dissection and management of the invaded tissues must be precise, due to the high fragility of the ones involved [12]. Although these features are generally known by most obstetricians, who realize how hard the surgery could be, sometimes they need to solve emergency cases with a few resources. For this reason, the most common scenarios and alternatives for its management are described, paying special attention to reduce complications.

Scenario 1

- No prenatal diagnosis, abnormal
- Abnormal vascularity in the uterine segment
- Placenta previa or low-lying placenta + risk factors (cesarean or other uterine scar)
- No possibility of endovascular control
- No expertise team or blood bank
- Sudden antepartum hemorrhage

When abnormal placentation is suggested or diagnosis is obvious after cesarean laparotomy by Pfannenstiel incision, [13] it is essential to reduce further damage to a maximum, to avoid a potential massive hemorrhage (Fig. 13.1).

13.3 Possibilities

(a) If there is an indication of immediate delivery (acute fetal distress, invasion hemorrhage point or other): T incision surrounding the umbilicus (on the left side), and deliver the baby by fundal incisions on safe uterine area. Avoid touching, cutting, or detaching the placenta. Local hemostasis in uterine borders, low ligature of umbilical cord, and uterine closure in two planes.

(b) When delivery could be delayed: close the incision, perform an accurate study of invaded tissues by ultrasound and pMRI (parametrial, posterior invasions), and transfer the patient to a reference center with resources and an expertise team.

(c) Cross the placenta to deliver the baby: *this is a not recommended option at all*, because it usually ends up in a massive and uncontrollable hemorrhage, which could produce maternal death within minutes.

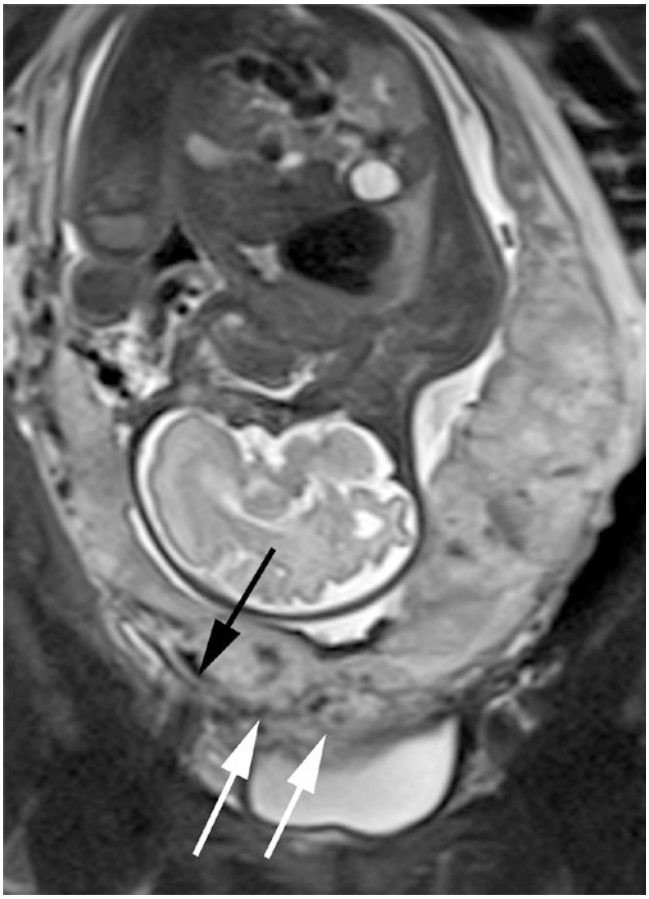

Fig. 13.2 *Black arrow* shows an interruption of anterior myometrium. *White arrows* show an anterior invasion

If the decision for a conservative treatment is made after surgical exploration, is image auxiliary diagnosis absolutely necessary? Yes, some features such as parametrial involvement, degree of lower uterus infiltration, and the presence of posterior invasion must be documented. Massive infiltration of lower uterus has been associated to unexpected and massive bleeding in conservative treatment (Figs. 13.2, 13.3, and 13.4).

If it exists, obstetricians need to consider practicing a planned hysterectomy in controlled conditions or operating

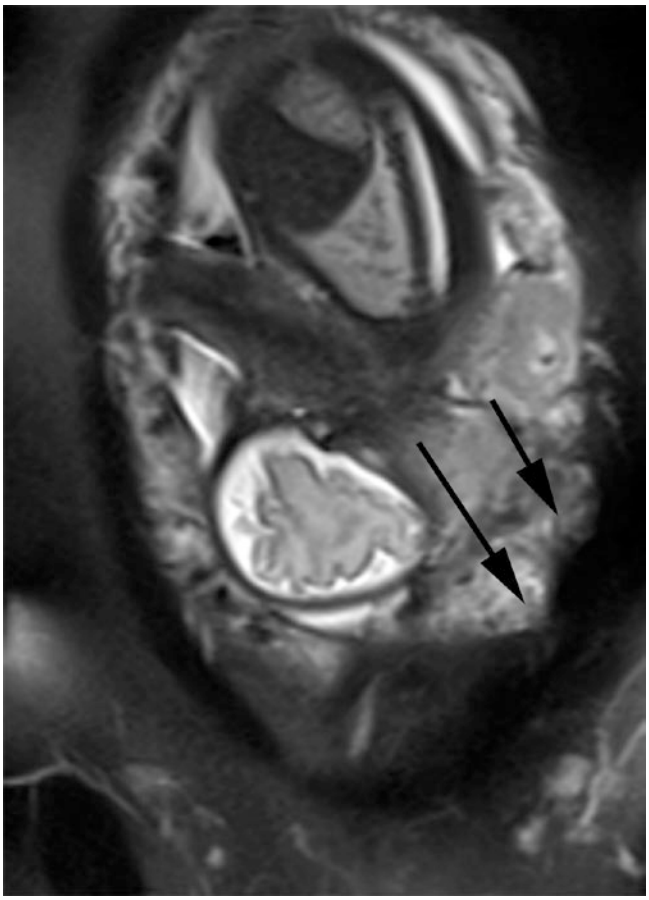

Fig. 13.3 *Right*: a posterior slice of a coronal cut of the same patient shows a right parametrial invasion (*black arrows*), which was undetected in the initial pMRI analysis

on the patient during massive hemorrhage, which could significantly increase morbidity and mortality. Although these cases happened, unfortunately they were not published because of a death event. Other signs of uncommon involvement, such as parametrium [14] or posterior ones, can be analyzed with experts to provide the most accurate diagnosis to make decisions with informed consent.

13.4 AIP (Abnormal Invasive Placentation) and Retained Placenta (Vaginal Birth or Cesarean)

Although retained placenta has many etiologies, the presence of undiagnosed AIP must always be considered [15] (Figs. 13.5 and 13.6a, b). As it was explained before, damage after abortion or curettage should be investigated in all cases [16]. If antecedent of abortion is confirmed and there is a problem to deliver the placenta, it is highly important to take all the measures to avoid additional tissue damage or/and unexpected bleeding.

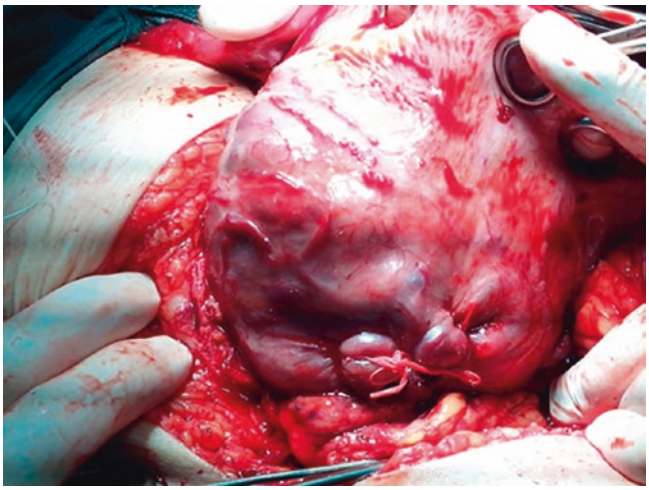

Fig. 13.4 Patient admitted at 39 weeks in labor with intensive left lower pain, pale, and hypovolemic shock in a primary hospital. History of four previous cesarean deliveries and one abortion. No prenatal controls. Surgery: massive hemoperitoneum due to uterine rupture of anterior AIP. Baby was delivered by fundal incision without any attempt for placental detachment. Uteroplacental bleeding point was sutured with two x stitches, and the hysterotomy was closed in two planes. After hemodynamic resuscitation, the patient was transferred to a tertiary hospital to stay in ICU for 3 days. After image study, hysterectomy was planned with full resources and expertise team (5 h). She was discharged after 6 days without complications

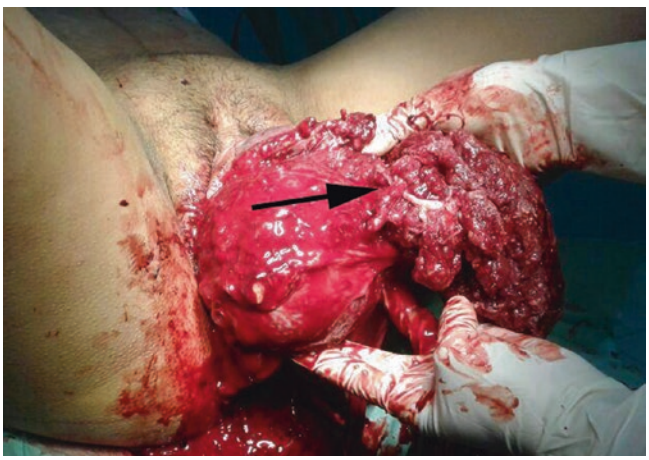

Fig. 13.5 A 26-year-old patient, one previous abortion (at 12 weeks) 2 years before. Vaginal delivery at 39 weeks, retained placenta. The placenta was pulled out until it was realized that the uterus was inverted and a zone of placental attachment was detected in the left uterine horn. The uterus was replaced manually, and a serious postpartum hemorrhage started. During surgery, uterine atony was not solved, and hysterectomy was performed. *Black arrow*: the attached area (left uterine horn) (Courtesy: Dr. Sergio Mendoza, Hospital Dr. Jose Pena, Bahía Blanca, Argentina (with permission))

Scenario 2 AIP with prenatal diagnosis

Prenatal diagnosis of AIP is highly important to plan all the necessary steps to reduce the morbidity and mortality of this condition. After diagnosis, it is possible to choose any of

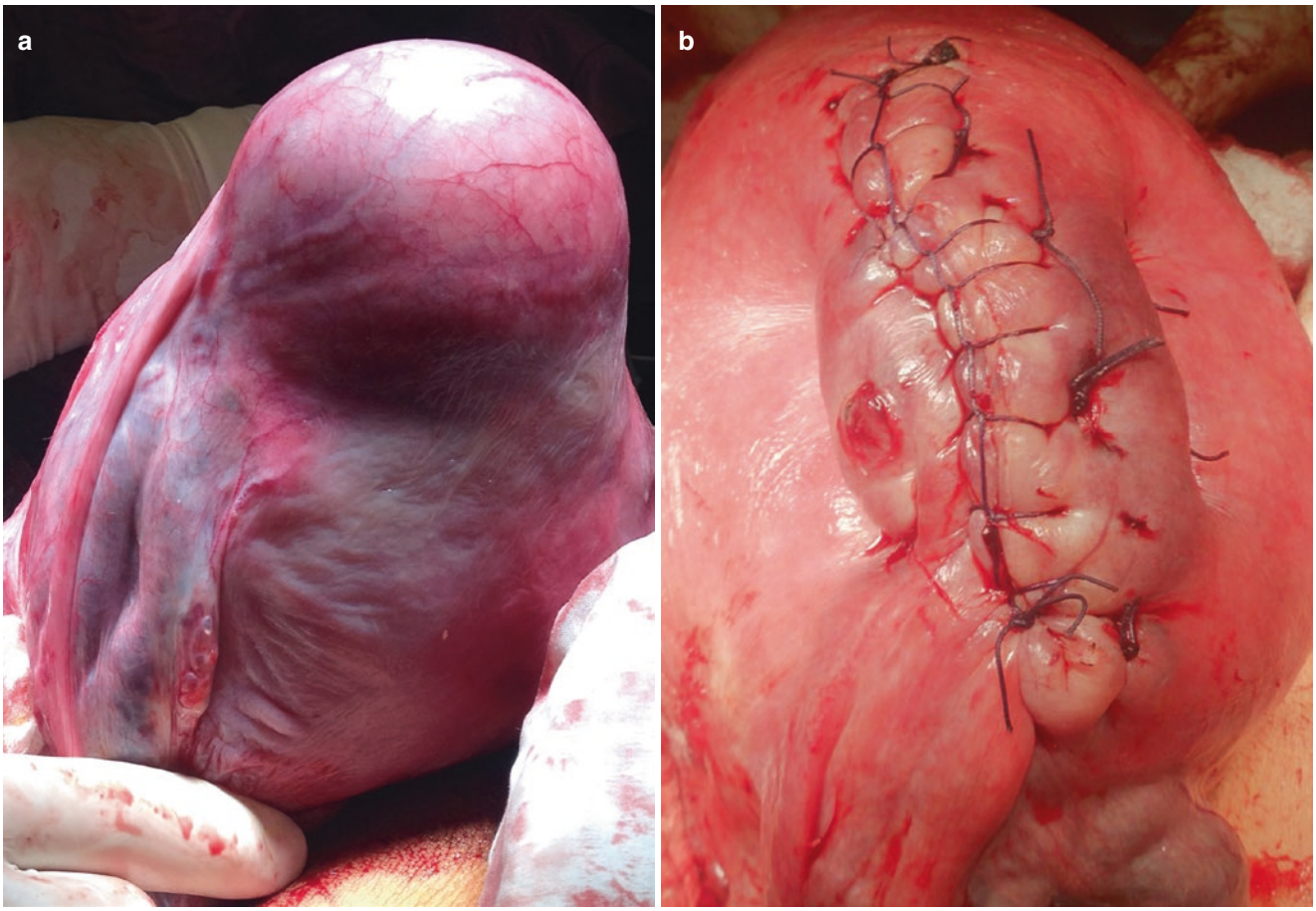

Fig. 13.6 (**a**) Patient: 39 years old, first pregnancy (IVF). Elective cesarean, placenta was strongly attached in the left horn. The obstetrician decided for manual removal, and massive bleeding happened. Abdominal aorta was compressed, and then a tight rubber was placed around the uterine segment and a Bulldog clamp in the left ovarian pedicle to stop the bleeding. (**b**) Invaded tissue was resected with the entire placenta, and the uterus was repaired in two planes. Suture was covered with antiadherent barrier to avoid adhesions

the available treatments according to experience, the patient's decision, and technical possibilities [17]. As it was described before, surgery of AIP implies many technical problems to solve, such as bleeding control, tissue management, and possibility of uterine conservation, among others.

Alternatives for treatment include: the classical ablative hysterectomy, the resective conservative procedures, and the pure conservative one, which leaves the placenta in situ. There is no randomized trial that demonstrates which is the best alternative for all cases, but there is an agreement that decision is made based on technical skills, invasion extension (uterine tissue damage), possibility for an accurate bleeding control, and desire of future pregnancy, among others. While accuracy of AIP prenatal diagnosis by experts is highly reliable, some aspects of the primary analysis may change during surgical exploration. As it happens in other surgical specialities, discrepancies between prenatal diagnosis and surgical exploration could modify a definitive approach or therapeutic decision; however, this concept is not always applied by all therapeutic AIP groups, a fact that may result in definitive loss of capacity for gestation (false positive cases).

13.5 Surgical Exploration

Although accurate prenatal diagnosis made by a skilled ultrasound technician and pMRI studies is highly reliable, it is important to know that there is a possibility of false negative and positive cases [18, 19] (Figs. 13.7, 13.8 and 13.9).

In this respect, and due to the possible consequences of surgical treatment (bleeding, tissue damage, hysterectomy, etc.), we need to be cautious when first seeing that the incision does not agree with the prenatal diagnosis, because placental invasion might not be evident until bladder dissection is performed. Occasionally the baby is delivered through the fundal area, and after the absence of placental bleeding, the obstetrician decides to attempt to

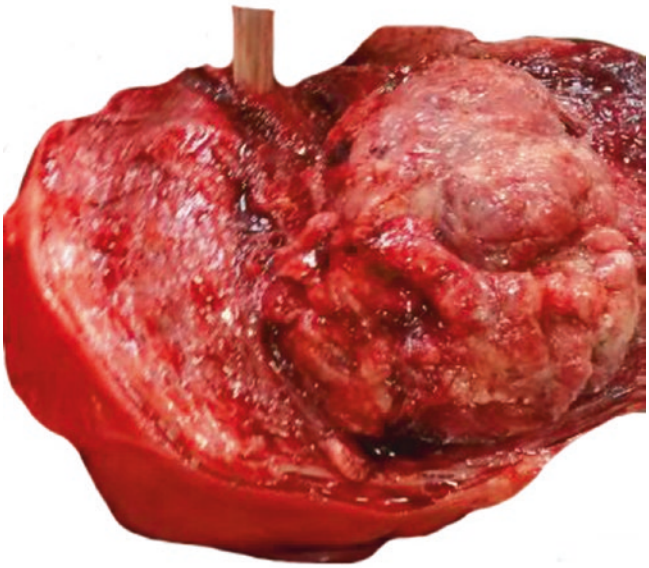

Fig. 13.7 Patient: 26 years old, two abortions. During cesarean, placental detachment was not possible. Attempt to remove the placenta ended in massive bleeding, and hysterectomy was performed (Courtesy: Dr. Martín Roldán. Maternidad de la mujer y el niño. La Rioja, Argentina (with permission))

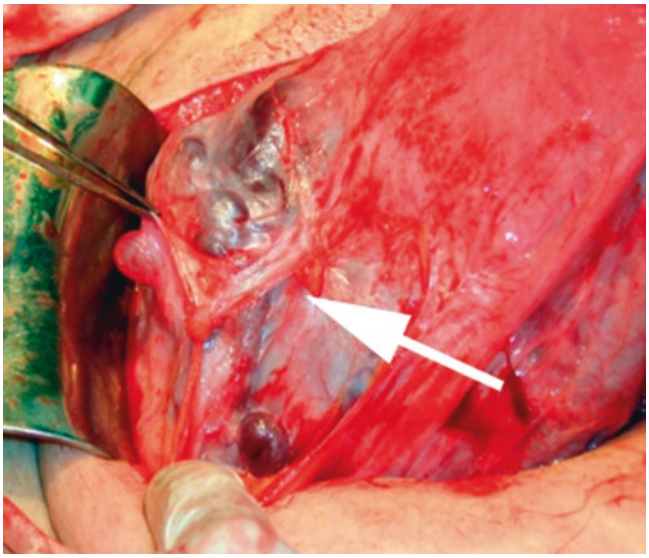

Fig. 13.9 Patient with diagnosis of severe AIP by US and MRI. After delivery, the preoperative diagnosis was in doubt due to surgical image; the placenta was removed, and massive bleeding happened (Courtesy: Dr. Wai Yoong Cheong, North Middlesex University Hospital; London, UK (with permission))

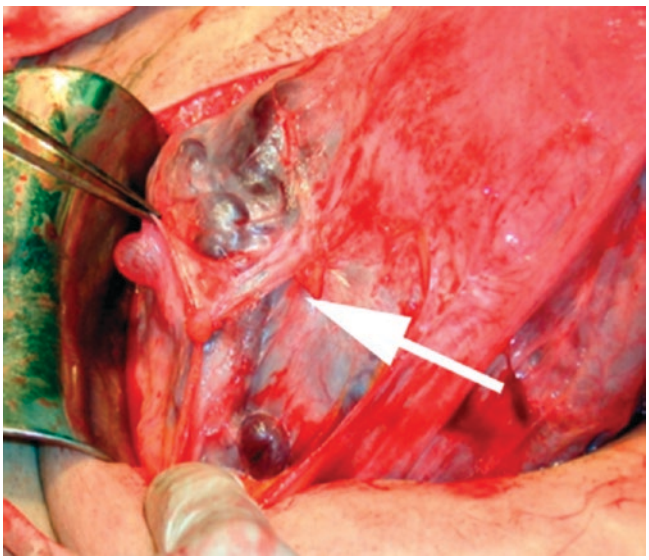

Fig. 13.8 Apparently, this is a severe case of AIP; however, after bladder dissection, most vessels were left on the bladder surface. AIP was located on a 4 × 4-cm anterior wall. *White arrow*: there is a soft plane between the bladder and uterus, which made the dissection maneuvers easy. The invaded area was resected and the uterus was conserved

remove the placenta, because the anterior uterine wall appears to be normal. When the surgical exploration is not complete (posterior bladder wall), this maneuver is particularly dangerous and could end in a catastrophic and massive bleeding.

It is very important not to underestimate the possibility of unmanageable massive bleeding, because in some cases when the placenta is removed, the invaded uterus might break completely into two parts (even using gentle maneuvers), and uncontrollable bleeding may happen within few seconds [20].

It is highly recommendable to confirm the prenatal diagnosis by surgical exploration, especially before performing definitive maneuvers such as hysterectomy. Some experts avoid dissecting the bladder to reduce a possibility of damage and subsequent bleeding on the bulging area. Although the exact number of hysterectomies performed in normal implantation cases is unknown, it might be high when a definitive decision was only taken based on auxiliary diagnosis and on the first surgical view.

From a general point of view, it is not an acceptable practice to cross the placenta in certain or doubtful cases of AIP or to remove a high percentage of uterus with poor prenatal diagnosis or surgical appearance, which after pathological analysis might be normal.

13.6 First Viewing

Initial aspect in diagnosed cases is not always in agreement with the prenatal evaluation; for this reason, apparently normal aspect should never be underestimated [12] (Figs. 13.10,

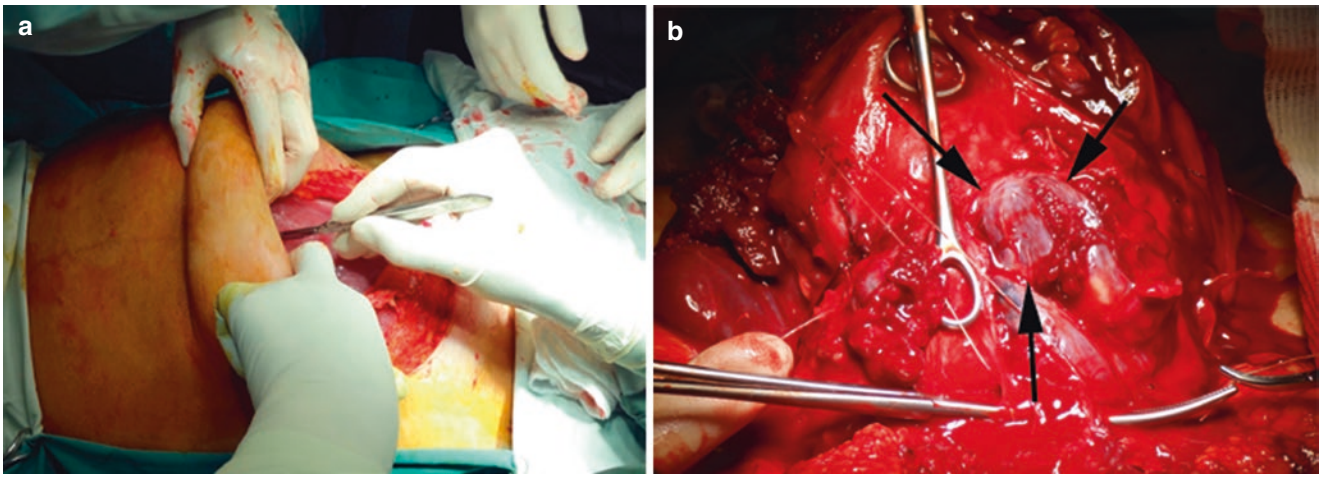

Fig. 13.10 (**a**) Patient: 27 years old, two CS. Diagnosis of AIP by US and pMRI. After cesarean laparotomy, aspect of uterine segment appears normal (false negative case?). But, due to the fact that pMRI located the invasion in the lower uterus (S2), upper body approach was performed. (**b**) (False negative) After delivery, dissection of posterior bladder wall showed the AIP previously described in prenatal studies (*black arrows*)

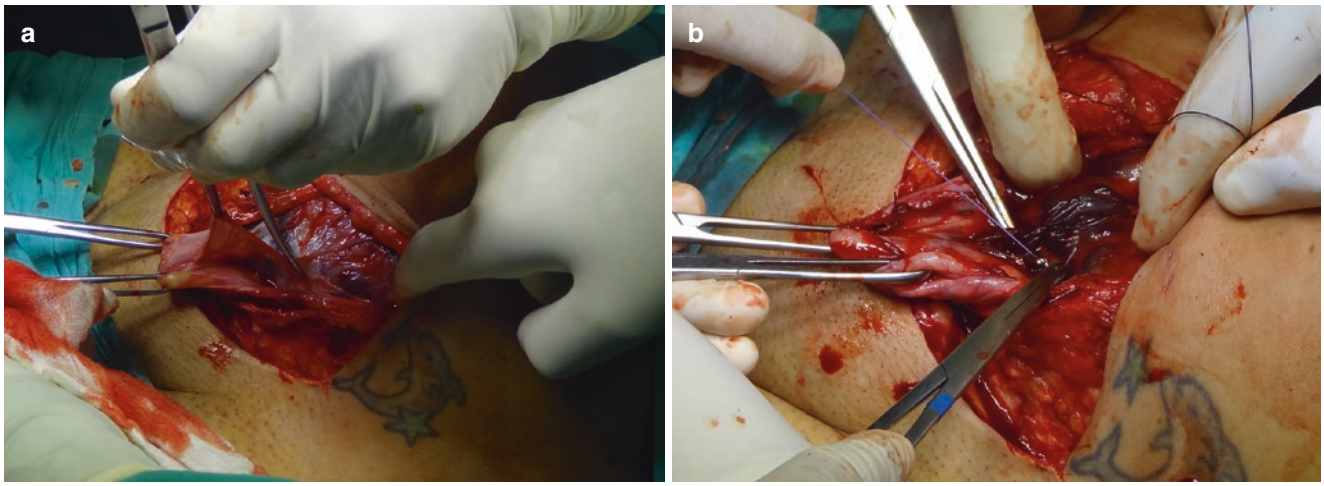

Fig. 13.11 (**a**) Patient: 31 years old, two cesareans, one abortion. AIP diagnosed by US and pMRI. Initial viewing did not show classical AIP described in prenatal studies. Posterior bladder dissection was started. At first viewing it seems a false positive case. *White arrow*: the bladder is pulled out by two Allis clamps. (**b**) After bladder dissection, vessels which connected the bladder, placenta, and damaged myometrium (AIP) are clearly seen (positive diagnosis)

13.11, 13.12, 13.13, 13.14, 13.15, and 13.16). The bladder, some tissue adhesions, or lower invasions (S2) could hide a classical aspect of AIP. When prenatal diagnosis is conclusive (US-pMRI), especially in patients with recognized antecedents of AIP, it is highly recommendable to finish the surgical exploration before confirming that it is a false positive case. It is mandatory to be completely sure that AIP is not present before making any attempt to remove the placenta.

13.6.1 Accuracy of Surgical Exploration

These cases demonstrated that diagnosis of AIP does not finish before the cesarean incision. Initial surgical exploration is needed before making definitive decisions. Both false positives and negatives are possible scenarios, and the team needs to be flexible to change the initial tactic if necessary (Figs. 13.10a, b, 13.11a, b, 13.12, 13.13, 13.14, 13.15a, b,

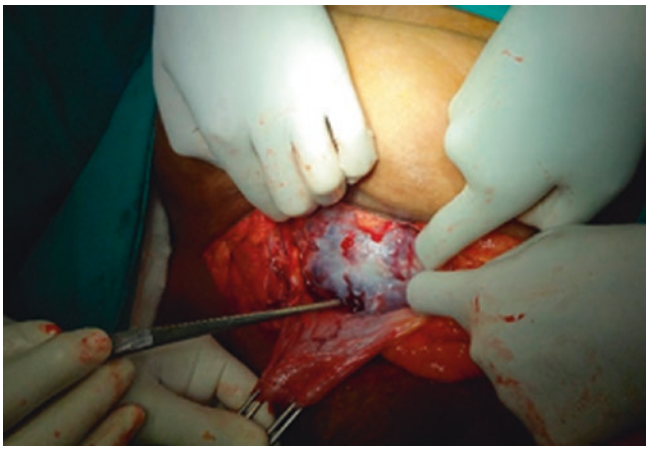

Fig. 13.12 (False positive) patient: 21 years old, primipara, no abortions or other antecedents. Low-lying placenta and AIP was diagnosed by US and hysterectomy was planned. After bladder dissection it was possible to see parallel vessels to the uterine segment, usually seen in placenta previa. The uterus was conserved

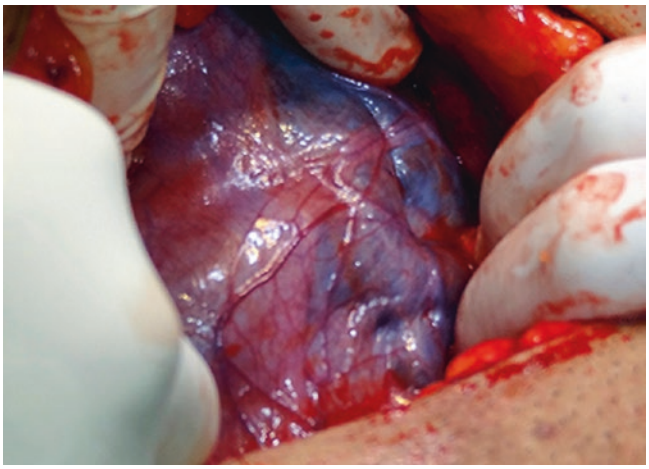

Fig. 13.14 (False positive). Patient: 25 years old, one CS. Diagnosis of anterior placenta percreta by US and Doppler. Cesarean at 35 weeks (planned hysterectomy). After laparotomy, a group of thick and parallel vessels were seen over the uterine segment. The cesarean scar was thin below these vessels, but without placenta adhesion

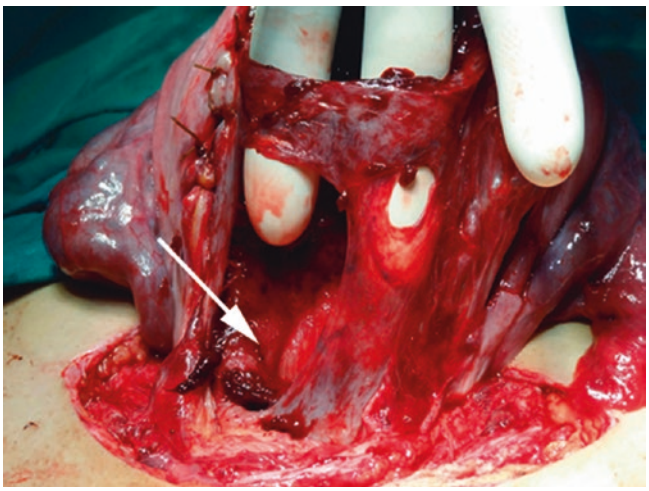

Fig. 13.13 (False positive). Patient: 34 years old, seven CS, low-lying placenta. AIP diagnosis by US. At 34.5 weeks, the patient was admitted with intensive lower pain and in labor. After delivery, posterior bladder was dissected. There were no vessels or other features of placental invasion. The placenta was detached completely without problems; lower anterior wall was disrupted until the cervix (*white arrow*). According to the patient's religious beliefs, the uterus was repaired after resection of disrupted tissues. She refused tubal ligature and became pregnant twice. She delivered the following two babies by cesarean, but in the last pregnancy, she developed a severe preeclampsia, and finally she accepted the tubal ligation

and 13.16a, b). All these cases showed before were operated on without any especial method for proximal vascular control; however, in all of them a dissection of pelvic spaces was performed in order to verify the results of prenatal studies. In other words, diagnosis verification does not imply more bleeding when it is performed carefully [12]. When AIP is discovered in the surgical room, simple measures allow us to make a decision, whether to continue or not. However, in all cases, wide dissection of pelvic fascias and some kind of vascular control are necessary to attempt to move the placenta in specific cases. When there is a doubt or specialists are not available, it is strongly recommended to be cautious.

13.7 Therapeutic Alternatives

Alternative treatments in AIP include resective ablative procedure, such as a hysterectomy, and conservative ones. Within the last group, there is a pure conservative treatment, in which the placenta is left in situ, and the conservative resective, in which the invaded area is resected and the placenta is extracted. All of them present advantages and disadvantages; their main features are presented on the following table.

13.8 Hysterectomy

In some countries, hysterectomy is the *gold standard* treatment for all types of AIP; however, this rule could end in unnecessary and definitive loss of possibility for gestation due to the false positive cases (Table 13.1). Contrary to what many people think, hysterectomy in AIP is not a simple procedure, which has high morbidity and mortality

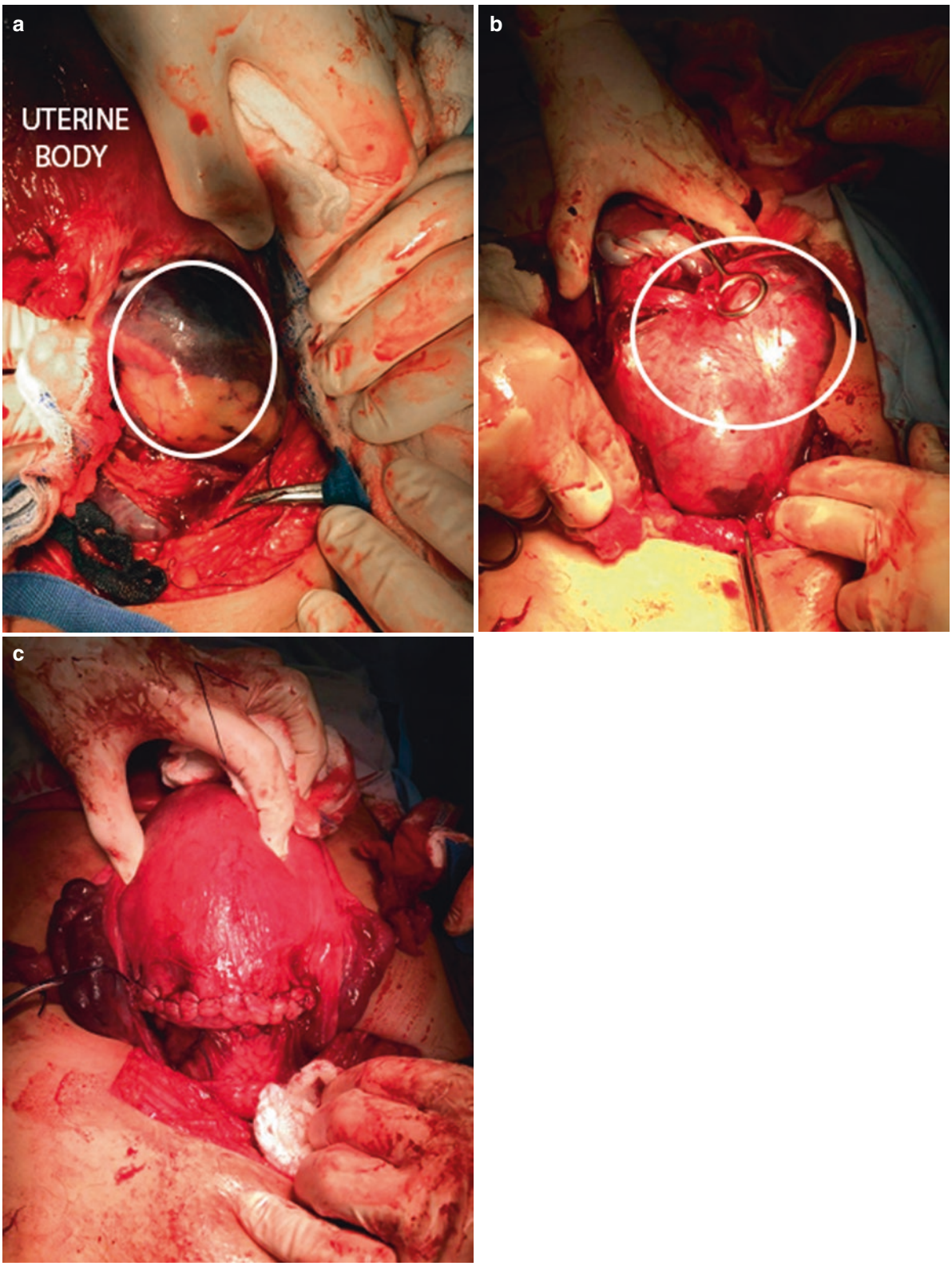

Fig. 13.15 (**a**) Parametrium invasion? Patient: 30 years old, two previous CS. Total placenta previa and diagnosis of AIP by US and MRI. During surgical exploration a circular and purple formation was discovered outwardly of the left round ligament (*LRL*), which was initially interpreted as left parametrial invasion (*white circle*). However, attention was drawn to a presence of fat tissue in that area. After careful dissection tissue was identified as an isolated omentum with a hematoma. There was no connection with the placenta, but it covered a small left uterine scar dehiscence (false positive). (**b**) After dissection and resection of thinning tissues, the uterus was sutured in two planes. The hand takes the uterine body; in *circle*, the thinning anterior uterine area with the attached placenta that was resected. (**c**) Final aspect of the repair

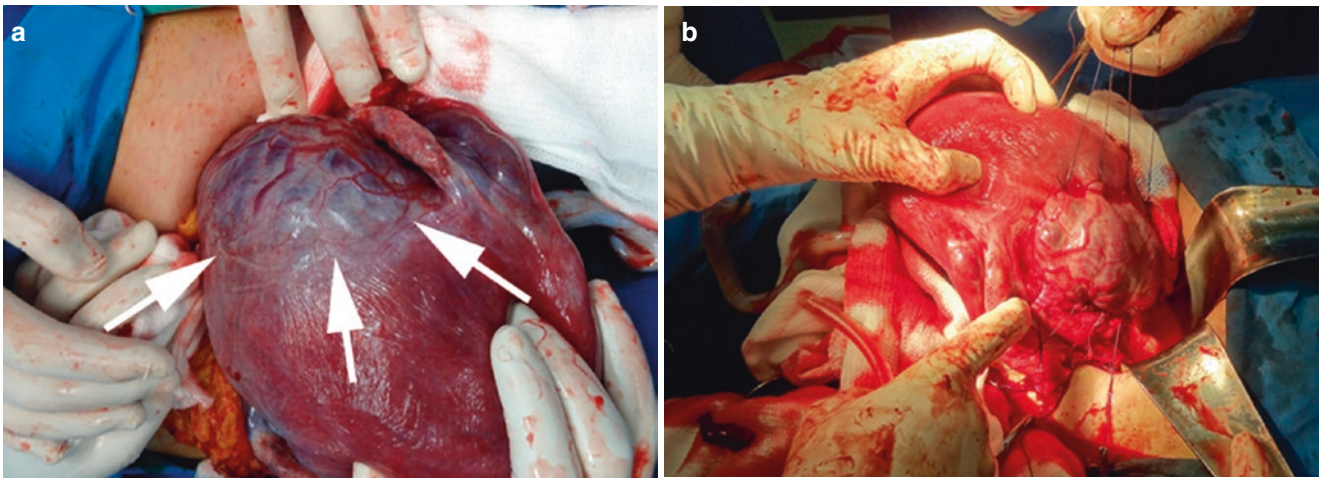

Fig. 13.16 (**a**) 25-year-old patient, programmed cesarean at 39.5 weeks due to fetal weight. After delivery, the placenta did not detach spontaneously from the uterus; after a gentle cord traction, nothing happened. The uterus was exteriorized, and a posterior-lateral AIP was evident (10 cm) (*white arrows*). In this case, forced placental traction implies a risk of massive bleeding. (**b**) All connections to the AIP area were closed by sutures, and then all the invaded tissue was cut with scalpel and removed with the entire placenta. The uterus was closed in two planes without additional bleeding. After surgery, the patient admitted an abortion when she was very young (17 years old)

Table 13.1 Available procedures for AIP (abnormal invasive placentation) treatment

Procedure	Resective	Conservative		
	Hysterectomy	Placenta in situ	One-step conservative procedure	Triple P procedure
Technique introduction	1949	1932	1993	2012
Placenta	Complete extraction without detachment	Not touched	Complete extraction in all cases	Complete or partial extraction
Invaded area	Resected with the uterus	Not touched	Complete resection in block with the entire placenta	Partial resection
	Resected and left attached behind the bladder			
Uterine anterior defect repair	Not necessary	Not performed	Always and using healthy myometrial tissue in two planes	Partial (above the bladder)
Bladder muscular defect repaired	Yes	Not performed	Yes	Not performed
Vascular control	Iliac internal (balloon or embolization), common iliac, or aortic balloon	Uterine artery or iliac internal embolization	Vessels ligature thought fascial dissection. Aortic balloon in vesical trigon invasion cases	Uterine artery or iliac internal embolization
Possibility of recurrence	No	Yes (high) 30–70 % according to different series	Yes (very low) 1–11 % in 180 subsequent pregnancies	No pregnancies after procedure
Possibility of future pregnancy	No	Yes	Yes	Not recommended by author

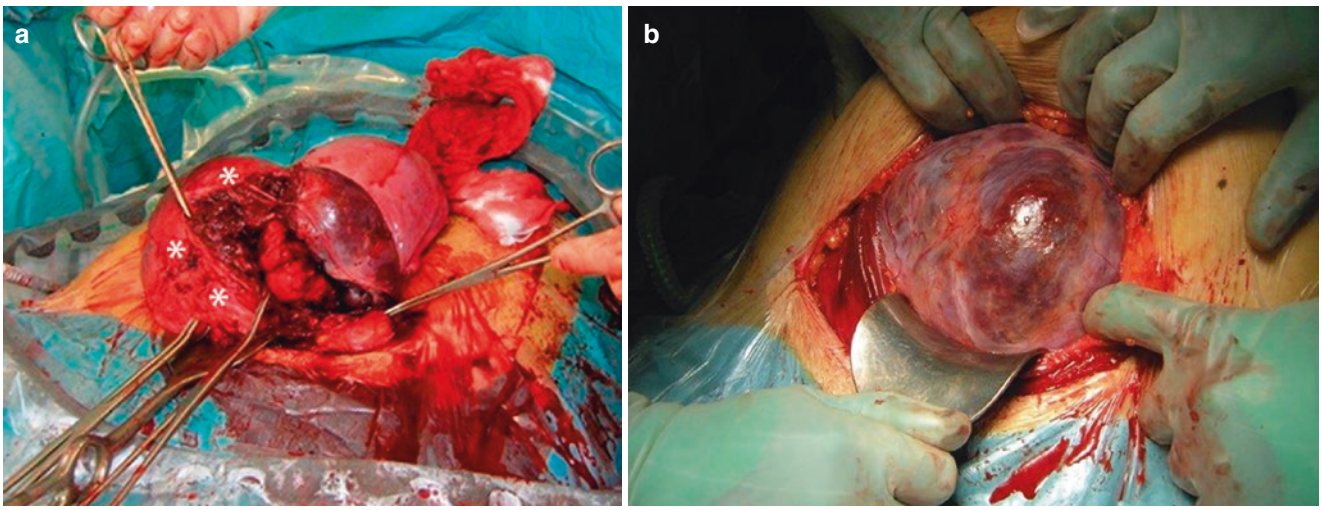

Fig. 13.17 (**a**) Unexpected parametrial invasion (*white asterisks*) in a patient with anterior AIP. US study showed an abnormal, but not very well-defined, image on the lateral side; MRI was unavailable. In order to perform this uncommon hysterectomy, the team asked the presence of a skilled and experienced obstetrician in AIP, who solved this complicated case (Courtesy Dr. Åse Revholt, University Hospital of Northern Norway, Tromsö, Norway). (**b**) First viewing of precedent case. Apart from simple uterine bulging, there is no evidence of newly formed vessels. Parametrial invasion was realized after complete surgical exploration. If hysterectomy is started without a wide management of all possible scenarios, resolution of parametrial invasion could turn quickly into a nightmare (Courtesy Dr. Åse Revholt, University Hospital of Northern Norway, Tromsö, Norway)

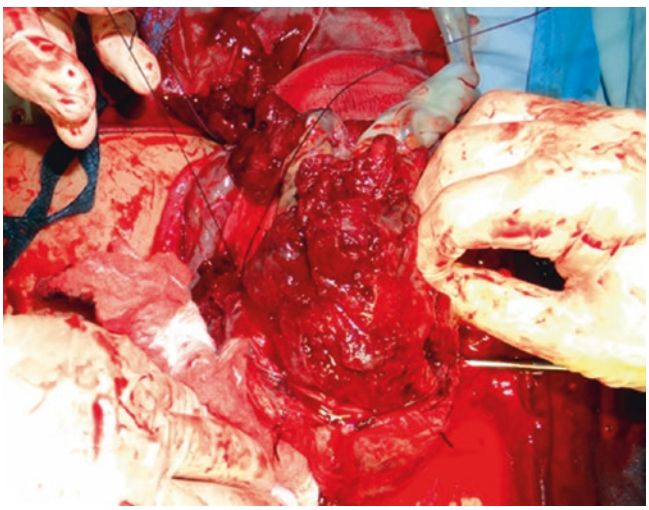

Fig. 13.18 Patient: 34 years old, two CS. US diagnosis of anterior AIP. During hysterectomy it was realized that she had a parametrial invasion with newly formed vessels connected with the ureter and pelvic wall. Hysterectomy was stopped due to technical limitation of original team, who never operated on this kind of patient. A specialist was requested to complete the procedure. The ureter was identified in a crossing with iliac vessels and dissected by the internal face until the bladder. During this procedure thick and thin newly formed vessels were ligated one by one

(Figs. 13.17a, b and 13.18). For this reason, hysterectomy is only recommended in centers with resources and a qualified team. When hysterectomy is started, generally, there is no possibility to turn back, especially because damaged tissue may start bleeding before it is separated from the uterus. Another problem is to find a dense adhesion with other organs, like the bladder. Upper bladder invasion is relatively easy to solve, but not the lower ones which can require special skills to be solved. Finally, undetected parametrial invasion might also be difficult to manage, especially when tissues are fragile or when they have vascular connections with the ureter or the pelvic wall. Most part of placental invasions (AIP) are linked with the uterine scar, so they are usually pelvisubperitoneal. This feature makes it necessary to manage the bladder, especially the posterior wall. Newly formed vessels among the placenta, the uterus, and the surrounding tissues are wide, fragile, and high flow; for this reason, the operator must be familiar with their management to practice the surgery. In summary, operators who perform a hysterectomy must be skilled and be able to manage a wide range of complications and variables [21, 22].

13.9 Vascular Control

Dissection maneuvers may suddenly produce unwanted injuries and massive bleeding. For this reason, some obstetricians use different methods to control bleeding during hysterectomy of partial resections. Uterine blood supply is provided by two main pedicles, the uterine and the ovarian arteries. But lower AIP invasions enlarge a lower anastomotic pedicle, which arises from pelvisubperitoneal trunks like the pudendal internal artery. Uterine blood supply is divided into two areas:

S1, which involves the uterine body and the upper uterine segment (this area is mainly irrigated by the uterine and ovarian arteries), and S2, which involves the lower uterine segment, the upper vagina, and the cervix [23]. This area is mainly irrigated by lower vesical arteries, vaginal arteries (from internal pudendal arteries). Rational vascular control should cover these pedicles according to invasion topography. Originally, internal iliac ligature was described as the best method to control pelvic bleeding, although posterior experiences have demonstrated that it is not true, and the efficacy of this method only reduces pulse pressure with a limited reduction of blood flow, and the method was definitively abandoned by traumatologists, gynecologists, and obstetricians. Some years after that, the procedure was "rediscovered" by interventional radiologists, and they used endovascular balloons instead of ligatures. Experiences with internal iliac artery occlusion were dissimilar as before. The main cause of failure is the presence of thick anastomosis among iliac internal, iliac external, and femoral anastomosis. Due to the fact that most AIPs are located in S2 area, it is understandable to see why this kind of vascular control is not as efficient as it is necessary.

According to this map of the uterine blood supply, iliac common and aortic (infrarenal) balloon occlusion is used to control both uterine sectors (S1-S2). Both have advantages but are not free from complications, which are commonly linked to expertise, quality of materials, and occlusion time. The use of embolization is practical in certain cases, but failure was described in massive low invasions. Nontarget embolization or tissue necrosis may be more common than is reported, especially because complicated cases are not published, although specialists know about them in informal talks in meetings or congresses. This is unfortunate, because complete information is strongly necessary to make decisions. The use of Gelfoam to occlude vessels is effective and cheap, but although foam particles are resorbable, distal occlusion might end in necrosis due to the fact that the average time for complete Gelfoam reabsorption is about 20 days.

The use of opening of pelvic fascias and individual ligature of newly formed vessels is highly effective in skilled operators and minimizes the possibility of complications. This method was used in large series with excellent results.

The use of aortic internal compression in unexpected cases of massive hemorrhage is highly efficient, quick, simple, and inexpensive [24]. To do this, the uterus is exteriorized to the abdomen, intestines are separated cephalically with a surgical field, and then, fist force is applied immediately over the abdominal aorta, which is compressed against the promontory. The pressure instantaneously stops the blood flow to the pelvis. Although this is not a definitive solution for a complicated case of AIP, the method provides time to ask for help or to complete a surgery. Pressure is safe for 60–90 min, and it is possible to alternate pressure and release if necessary. It is proved that infrarenal aortic compression does not produce metabolic acidosis after aortic compression release.

13.10 Conservative Procedures

13.10.1 Pure Conservative Treatment (Placenta Left In Situ)

This approach was originally published in 1932 by Professor E Capecci in the city of Cesenatico, Italy, and it was the best solution to avoid massive hemorrhage in a time in which intensive care therapy, antibiotics, and transfusions were not available. The process includes fetal delivery by fundal area, avoids touching the placenta, and leaves it in situ until a future reabsorption. In spite of medical advances, this treatment is already used, even at tertiary hospitals. However, its practice is not free of minor, moderate, or devastating complications [25–27]. Unfortunately, bad outcomes are not usually published, a fact that makes it difficult to create guides to predict major events. After the baby is delivered, the cord is clamped near the placenta, and the uterus is closed in two planes. According to some units, after that uterine artery embolization is performed to prevent postpartum hemorrhage, experiences have demonstrated that this is not as efficient as doctors believe. Uterine artery embolization may reduce placenta blood flow and bring on an infection due to poor irrigated tissue. Antibiotic combination is provided in order to reduce infection and sepsis; in this respect, it is essential that the patient be aware about incipient symptoms to avoid sepsis which can end in untreated or delayed cases of sepsis or even death. Hemorrhage is another deadly complication, and its occurrence may be sudden, unpredictable, and end up in a life-threatening scenario [28]. For all these reasons, close monitoring in patients with conservative treatment (placenta in situ) is mandatory. A period to complete placenta reabsorption or expelling is variable; these events were described between days and months. Subsequent pregnancy is possible and described but with a variable rate of recurrence [29, 30]. Unfortunately, there is no trustworthy case classification to predict it, but a detailed pMRI study allows to analyze all invaded areas by the placenta with high accuracy. It is important to mention that pMRI is not used as diagnostic method in these cases; unlike the US, the study analyzes all the volume in the three positional planes.

13.10.1.1 Clinical Case

Patient 33 years old, two CS, and known cesarean scar defect prior to current pregnancy (documented by US and pMRI) (Fig. 13.19). Massive infiltration of lower uterus has been

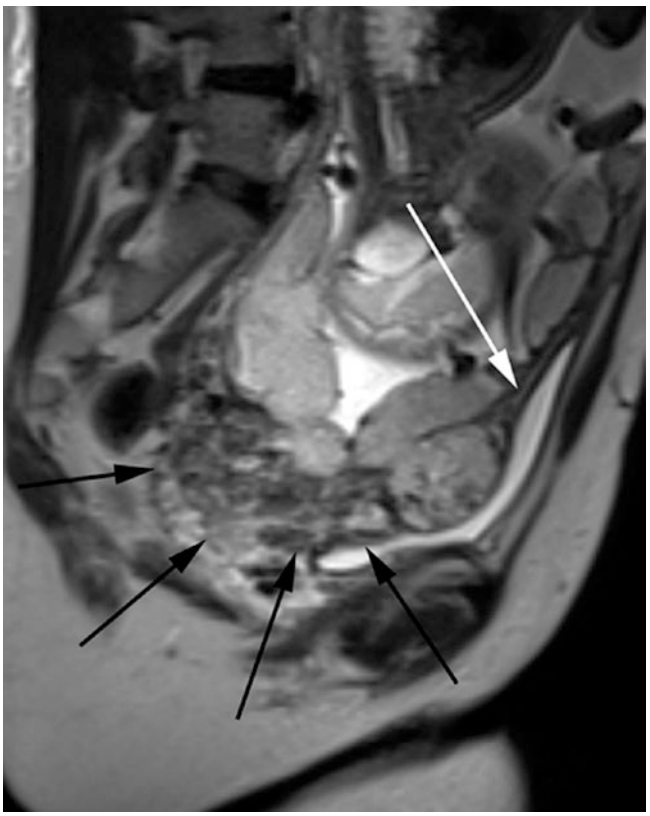

Fig. 13.19 Sagittal T2 pMRI slice: *white arrow* shows an anterior uterine wall interruption adjacent to the bladder. *Black arrows* show a massive lower uterine invasion. There is no recognizable healthy myometrium. Notice the difference in color of upper and lower and infiltrated placenta

linked to increased possibility of bleeding after 30 weeks or even before. Lack of myometrial support, plus invasion, implies the possibility of unexpected and massive bleeding in conservative treatment. This patient started with mild episodes of vaginal bleeding at 29 weeks and also with two episodes of macroscopic hematuria. She developed an intensive bleeding at 30 weeks and was admitted in emergency at primary hospital. Baby was delivered by fundal area, the placenta was left in situ, and the uterus was closed. Two days after that, she was transferred to a tertiary hospital for a planned hysterectomy. She started bleeding massively 2 h before the scheduled surgery (06:00 am). Aortic external compression was performed for 45 min until the team arrived. Protocol for massive transfusion was started; before surgery, an aortic balloon was placed and inflated in the infrarenal aorta. Hysterectomy was particularly difficult due to massive lower and parametrial infiltration. Patient was discharged after 7 days without complications. Although the problem originated in the damaged uterus, primary vascular control is mandatory to avoid the catastrophic consequences of hypovolemic shock, especially metabolic acidosis. When therapy is mainly focused on removing the uterus immediately, results can be devastating within minutes. Lifeguard measures must be taken first to stop the bleeding immediately in an easy way (aortic compression, aortic endovascular balloon, etc.). After hemorrhage is primarily controlled, rigorous resuscitation with blood and solutions must be made by an anesthesiologist or intensivist to restore hemodynamic parameters, metabolic acidosis, and clot state. When clinical parameters are stable, the definitive surgery can start. Please remember that this kind of surgery could be technically difficult, and all specialist help will be welcome. Beware of your ego for another time, and only focus on the patient's life accepting all available specialist help.

13.10.1.2 Arterial Embolization During Massive Hemorrhage

In cases of serious AIP (massive infiltration, parametrial invasion, or bladder involvement) with unexpected bleeding, it is possible to think that arterial embolization could solve the emergency avoiding a complicated surgery, but this decision may be dangerous for many reasons: (1) Time to prepare the equipment and the patient may be inappropriate for a patient with massive bleeding (45–60 min on average). (2) Vasoconstriction could make a catheter arterial passage difficult and be a cause of delay in treatment. (3) AIP hemorrhage for damaged infiltrated tissues includes arterial but also thick vein vessels which can bleed more than the arterial ones and be out of range for arterial embolization. (4) Blood supply of extensive AIP may reach for many arterial sources, which might imply specific vessel catheterization to be effective. Sometimes, it is decided to make a massive introduction of embolic agent to stop the bleeding as soon as possible (usually Gelfoam), which could be a reckless action with unknown results. Unpublished and published cases have resulted in nontarget embolization of the lower limbs, bladder, uterus, rectus, sciatic nerve, muscles, and skin, among others [31–34]. It is perfectly clear that there is no doctor that expects these complications when they try to stop the bleeding. But it is also clear that nobody can solve a rupture of complicated AIP with active and massive bleeding; for this reason, it is necessary to understand that aortic vascular control by balloon can be performed with local anesthesia and ultrasound control within minutes. When it is not available, external aortic compression over 45 kg (90 lbs) occludes a 100 % of aortic blood flow very accurately [35]. Then specific resolution might be complicated and take more time, but first, think simple but do it immediately.

13.10.1.3 Infection

This is probably the most frequent complication of placenta in situ; however, it can be prevented by the use of a wide range of antibiotics and a close clinical control. When infection is not controlled, obstetricians usually decide for a hysterectomy, although conservative alternatives have been published.

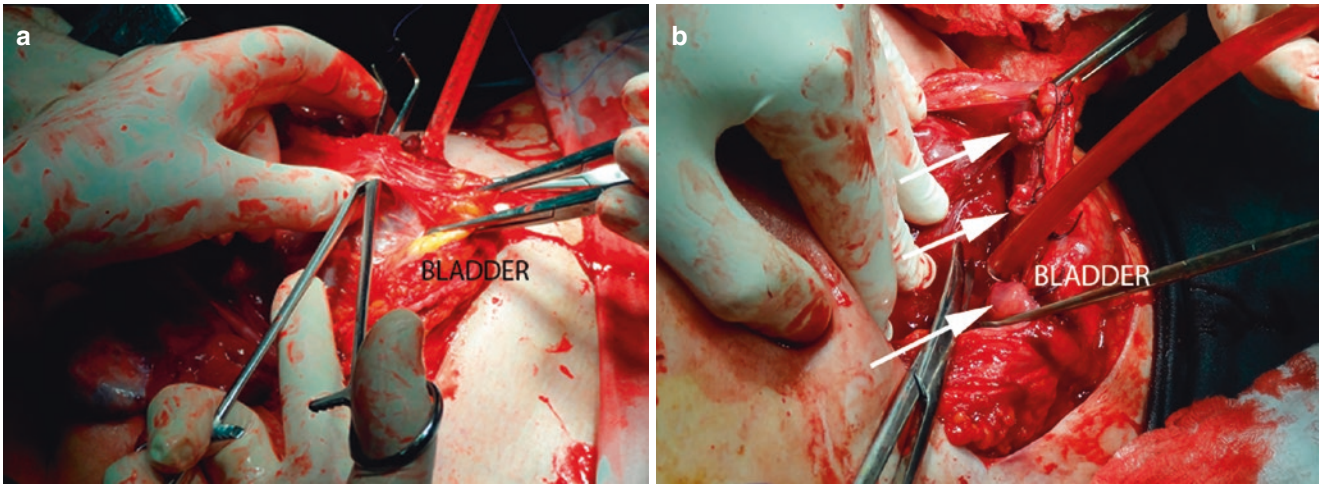

Fig. 13.20 (**a**) Patient: 32 years old, three CS, anterior AIP. Bladder is pulled out by two Allis clamps, and tissue and vessels between the uterus and the bladder are dissected and ligated to separate the space between both organs. (**b**) After initial newly formed vessels are ligated (*white arrows*), dissection between the bladder and uterus is performed

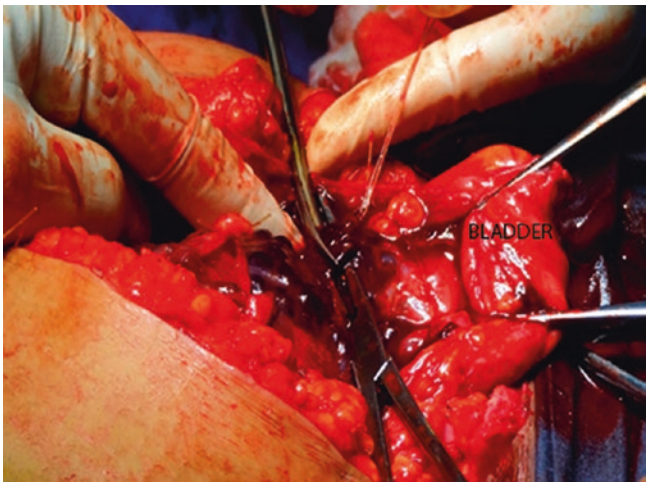

Fig. 13.21 Technique for massive vascular invasion to the bladder is identical to the one described above. Notice that in this case, vascular invasion is especially located in the lower part of the bladder. In these cases, Allis clamps must be relocated while dissection is deeper

13.10.1.4 Future Pregnancy

Subsequent pregnancy is generally possible after a conservative treatment leaving the placenta in situ; however, the possibility of recurrence is high, although variable among authors.

13.10.1.5 Summary

Pure conservative treatments leaving the placenta in situ avoid dissection and hemorrhage during delivery. They are an excellent alternative when resources of expertise team are not available. The surgical key is to avoid touching the placenta or producing additional tissue damage. However, complications such as infection or hemorrhage may happen during placental reabsorption. Future pregnancy is possible but with a high rate of recurrence.

13.10.2 One-Step Conservative Surgery

This approach was designed to solve all the problems associated to AIP in one single surgery and to preserve the uterus in the best condition for a future pregnancy [36]. Prior to surgical design, the uterine and pelvic blood supply and their anastomotic ways were studied in detail. Anterior AIP receives the main blood supply from the branches which arise from the pudendal internal artery, such as the inferior vesical artery and the vaginal arteries; this fact explains why uterine artery embolization has limited action to provide hemostasis in these cases. Laparotomy is usually made with a modified Pfannenstiel incision, in which the skin and fat tissue are cut until the rectus fascia. Then, dissection is made over the fascia until the umbilicus, leaving a flap of skin and fatlike abdominal plastic surgery. Abdominal opening is made with a midline incision of the rectus fascia (alba line) like a classical midline until the peritoneal cavity.

13.10.2.1 Bladder Dissection

After laparotomy is done, the second maneuver is to dissect the posterior bladder wall (Figs. 13.20a, b and 13.21). All the wider tissues between both round ligaments are ligated with 00 Vycril™ in order to close vesical-uterine connections and also to provide a clear access to the upper vagina and cervix. Newly formed vessels between the bladder and the uterus may be evident or not, because they have no tunica media; for this reason, it is not recommendable to use electrocautery. A plane between two organs might be difficult to

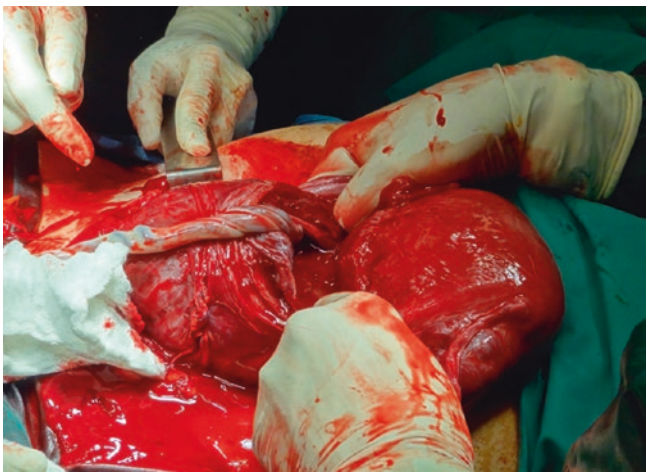

Fig. 13.22 Hysterotomy was made in the upper part of AIP; after the baby was delivered, the uterus was exteriorized. Although the size of uterine bulging was significant, decision for conservative-resective procedure or for hysterectomy was made after a deep dissection of posterior bladder wall

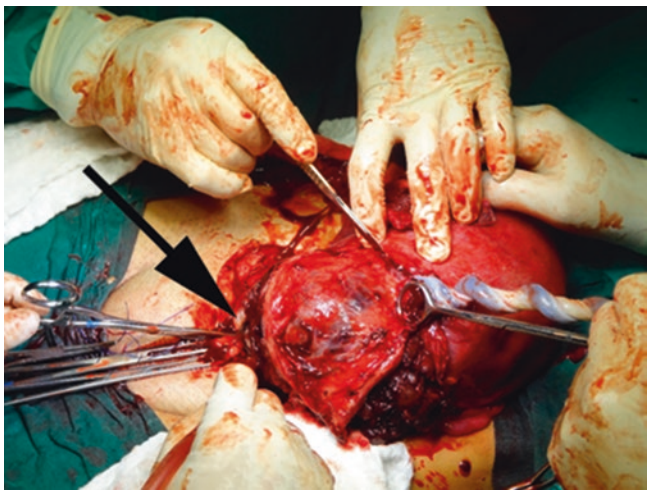

Fig. 13.23 Invaded area is marked with scalpel prior to cutting and removing the entire placenta. U compression suture of uterovaginal anastomotic blood supply was done to avoid bleeding during placental detachment. *Black arrow*: notice that distal myometrium has a thickness of 5 mm. Healthy myometrium is especially seen after a deep dissection of posterior bladder wall. The bladder is taken with Allis clamps

recognize in adhesive cases. When it happens, it is highly useful to use a Pelosi maneuver, which enters through the cervical-vesical plane crossing a finger by side by side. Then, the finger is moved upward, and separation between organs is clearly seen. Usually, the bladder is pulled out with two Allis clamps, but when there are firm adhesions to the uterine scar, it is useful to fill the bladder with water or with methylene blue solution.

13.10.2.2 Hysterotomy

After bladder dissection is done, all newly vascular connections between the bladder and the uterus are closed, so anterior AIP receives an additional blood supply by the uterovaginal anastomotic system. Hysterotomy (Fig. 13.22) is made in the upper part of invaded tissues, the myometrium is cut until the placenta, and then the hand is placed between the myometrium and the placenta (Ward technique) dissecting until the bag of waters is broken. After the baby is delivered, the uterus is exteriorized. Posterior vesical dissection is completed, when it is necessary, until the cervix is seen. Three centimeters of healthy myometrium are needed to perform a plastic procedure.

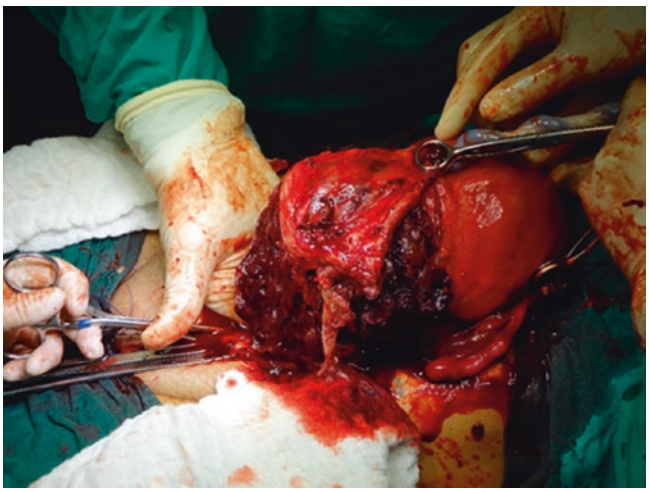

Fig. 13.24 After the invaded myometrium is cut, the entire placenta is removed in one piece with the invaded area

13.10.2.3 Specific Hemostasis

At this moment, the placenta is also attached to the lower segment, and it receives blood supply from uterovaginal vessels [23]. In order to reduce or eliminate bleeding after placental and invaded area removal, U compression sutures are placed in the cervical-segment junction (anterior, lateral left, and lateral right). After that, a complete invasion area with the entire placenta is cut and removed manually (Figs. 13.23, 13.24, 13.25, 13.26, 13.27, and 13.28).

13.10.2.4 Highlights

The one-step surgery for AIP solves all problems of AIP in a single surgical act and rebuilds the uterus as a primary anatomy. The procedure has a very low possibility of recurrence: 2/180 subsequent pregnancies. Although technically it is more complex, there is no secondary concern of infection, hemorrhage, or uterine defect as the purely conservative procedure. Training is available for request, and some European institutions work on it.

13.10.2.5 Triple P Procedure

This technique was developed by Dr. Edwin Chandraharan et al. in 2012; the technique involves perioperative **p**lacental localization and delivery of the fetus via transverse uterine incision above the upper border of the placenta, **p**elvic

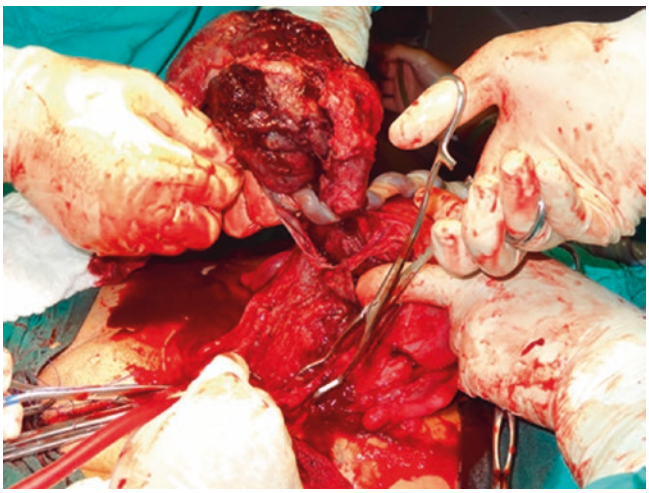

Fig. 13.25 The placenta and the invaded area are removed without further bleeding due to previous occlusion of uterovaginal vessels. There is no action in the uterine arteries, embolization, or arterial balloons. The S2 anastomotic vascular systems to the AIP were occluded (vesical-uterine and uterine-vaginal)

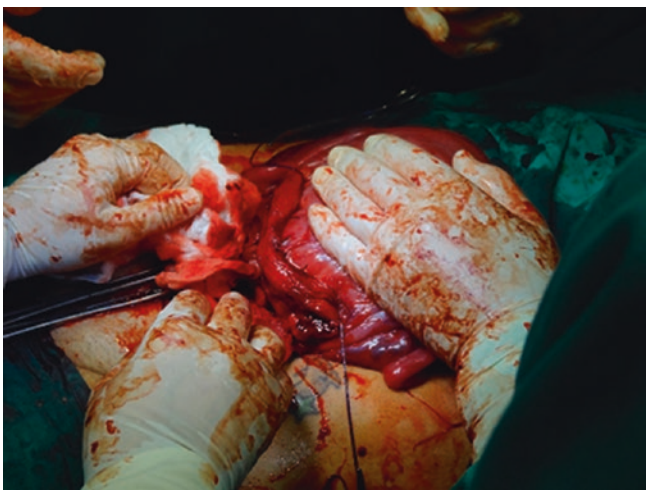

Fig. 13.26 First plane is necessary to approach the uterine borders after a big anterior wall resection. U stitches are performed with 1 Vycril. Irregular borders will be cut before performing a second suture line

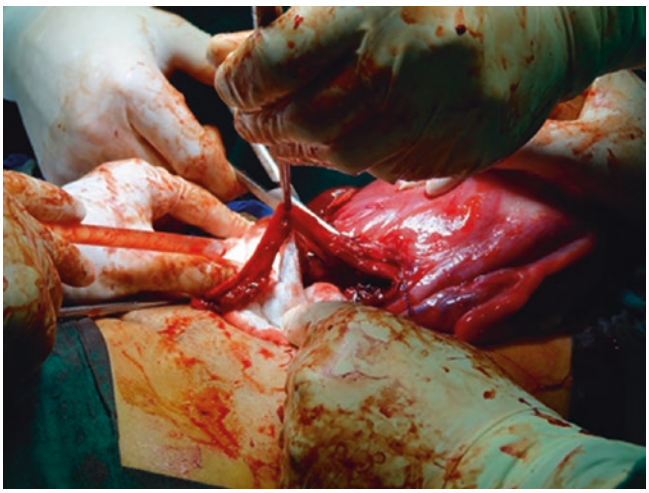

Fig. 13.27 To even the edges and myometrial thickness before definitive suture, redundant tissue in the cephalic border is cut

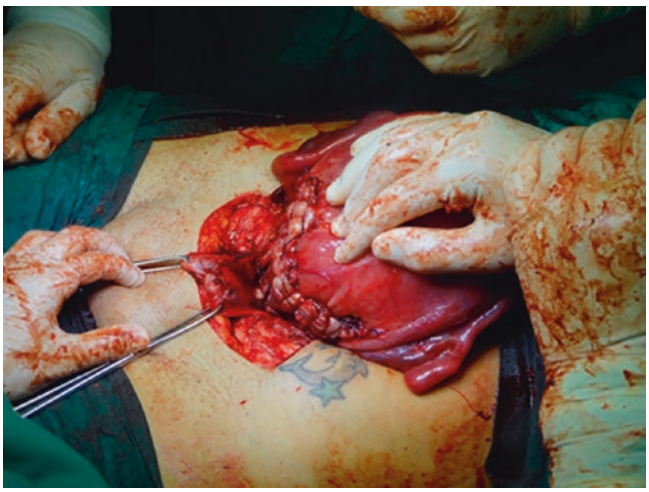

Fig. 13.28 Final aspect after second line of suture. Muscular defects in the detrusor are repaired with 000 Vycril™. After detailed bleeding point check, a sheet of Surgicel™ (Johnson & Johnson, USA) is placed between the suture and the bladder

devascularization, and **p**lacental non-separation with myometrial excision and reconstruction of the uterine wall [37]. Although the procedure is initially comparable to the one-step conservative surgery, resection of invaded myometrium is only limited to the invaded area above the bladder. Another difference is the use of arterial embolization or balloon (uterine artery of iliac internal) instead of selective ligature of pedicles, as a method to stop or control the hemorrhage. During triple P procedure, the uterine artery balloon is left inside the patient and deflated after 4 h of surgery if bleeding is not present. In some cases, compression sutures are used over the line of placental invasion and are placed into the bladder to avoid further bleeding.

Another difference with the one-step conservative surgery is that triple P avoids removing the placenta when it is attached behind the bladder; in these cases, the placenta is cut and left partially in situ (attached behind the bladder). After initial cases, the use of hemostatic powder over the remaining placenta is promoted for hemostasis purposes.

Subsequent pregnancy is not recommended by the author, so the conservative procedure partially fulfills its mission.

13.10.2.6 Unusual Challenges

Although some units have solved an AIP treatment guide, which can be conservative or resective, some particular conditions could change our initial preferences dramatically. Most specialists prefer to avoid bladder dissection when facing massive vascular invasion or in parametrial invasions.

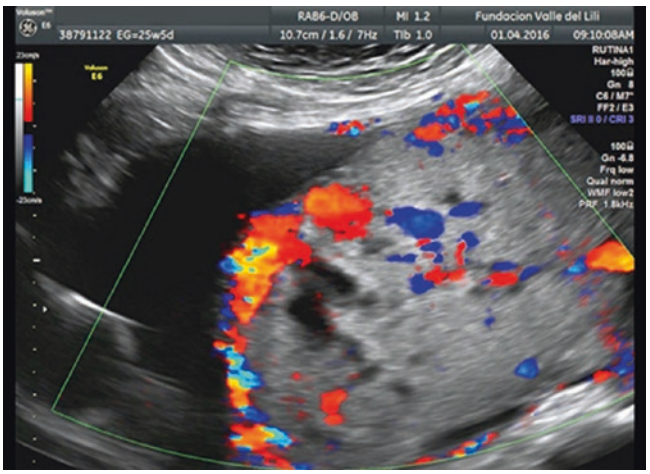

Fig. 13.29 Patient: 39 years old, ten pregnancies, seven cesarean, and two abortions were admitted with active macroscopic hematuria at 25 weeks. US showed a massive bladder vascular invasion with prominent vessels inside the bladder (Courtesy: Dr. Álvaro Jose Nieto Calvache, Fundación valle de Lili, Cali, Colombia (with permission))

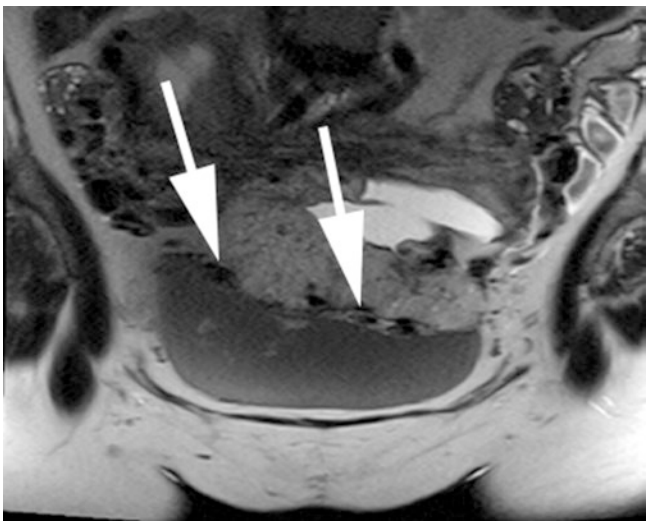

Fig. 13.30 Coronal pMRI: uterine-bladder interphase is completely invaded and irregular by placental invasion (*white arrows*). Notice the presence of a big clot inside the bladder, which changes a normal color in T2 technique (*white*), by gray (Courtesy: Dr. Álvaro Jose Nieto Calvache, Fundación valle de Lili, Cali, Colombia (with permission))

Even the centers which prefer hysterectomy as a rule also prefer to avoid dissection in these cases. But sometimes we do not have the possibility to choose, and severe invasion must be solved if there is no other alternative.

Active bleeding due to parametrial of bladder invasion (Figs. 13.29, 13.30, and 13.31) requires a short period of treatment, which is usually very complicated. But, on these occasions, we have no other alternative, mainly because local hemostasis made by embolization, electrofulguration, or packaging is not efficient and implies a possibility of a life-threatening complication.

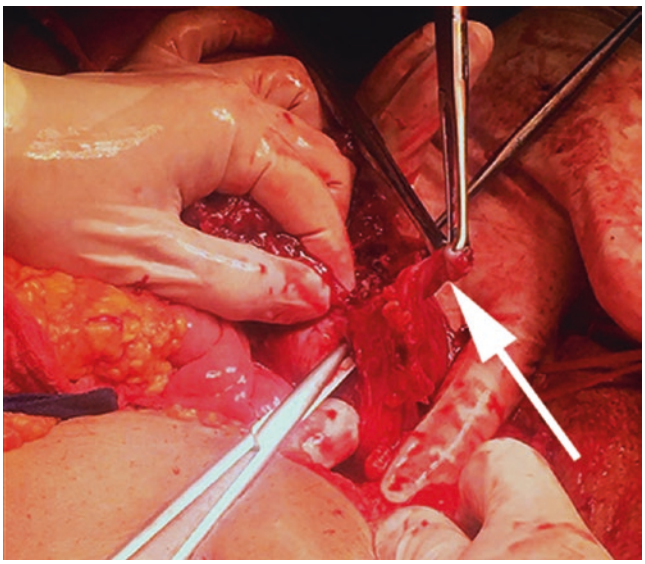

Fig. 13.31 Clinical state was deteriorating fast, because hematuria did not stop and hematocrit dropped every day. Endoluminal electrofulguration was excluded, because there is a reference that contraindicates it. Newly formed vessels do not have tunica media, so fulguration results in the risk of massive hemorrhage. Embolization of these collateral vessels is difficult and does not reach venous component, so surgery was decided. In order to control low anastomotic components, an aortic balloon was placed. After the baby was delivered, a retrovesical dissection was performed; a thick mixed component (artery and vein) was ligated for definitive hematuria control (*white arrow*). Hysterectomy was completed after 40 min of aortic occlusion, blood loss was efficiently controlled, and it was not necessary to transfuse the patient (Courtesy: Dr. Álvaro Jose Nieto Calvache, Fundación valle de Lili, Cali, Colombia (with permission))

13.11 Final Conclusions

Surgical treatment of AIP is a challenge for obstetricians, and they need to be aware that mistakes or bad decisions may end in some catastrophic consequences within minutes. It is highly recommended to avoid touching the placenta without all resources available. To cross the placenta to deliver the baby is almost unacceptable, due to the immediate massive bleeding. Access by fundal area or far away from invaded placenta is highly recommended in emergencies or when team and resources are not available. Resective ablative, resective conservative, or pure conservative alternatives have advantages and disadvantages that must be considered in any particular case to avoid further complications. When it is possible, treatment must be performed by a skilled team and with full resources, because this condition has high morbidity and is always a potentially life-threatening disorder. Training in dissection maneuvers is highly recommended for specialized teams, because in some cases of uncommon complications, skill dissections are needed.

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Cesarean Section: The Evidence-Based Technique, Complications, and Risks

14

Michael Stark, Michel Odent, Andrea Tinelli, Antonio Malvasi, and Eric Jauniaux

14.1 Introduction

At the time when endoscopy prevails as well as new techniques, such as natural orifice surgery and telesurgery, the cesarean section (CS) might become in the future the only indicated laparotomy. Therefore, it is of utmost importance to evaluate its methodology, which should be based on evidence.

In any surgical method, complications do happen, and cesarean section is no different. The most important thing in order to avoid unnecessary complications is the prevention. It means to avoid unnecessary operation, as each operation needs a correct indication. This chapter will deal with different aspects of cesarean section, historical, technical, and physiological aspects which will bring into light not just how to perform but also when to perform in case of correct indication. This knowledge will prevent unnecessary complications and morbidity, both to the mother and to the newborn.

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14.2 Historical Perspective

There is no doubt that cesarean section (CS), together with advances in anesthesia and access to blood transfusions and antibiotics, contributed to declining maternal mortality rates since the Second World War.

Since then, the rising percentage of CS worldwide has been associated with complications such as placenta accreta as rarely seen before [1]. The CS is now the most commonly performed major operation around the world and the first surgical procedure performed independently by residents/trainees in obstetrics-gynecology in the Western world [2]. In most countries, the rise in the frequency of CS is a relatively recent phenomenon. Prior to the 1980s, the rates of CS were generally less than 10 %, but now in most countries this is well above the 10–15 % ideal rates as proposed by the WHO in order to optimize maternal and perinatal health [3–5]. By contrast, in the rural areas of many developing countries, CS remains well below 10 %, and there is no doubt that if substantial reductions in maternal and perinatal mortality are to be achieved, universal availability of life-saving interventions such as CS needs to be matched with comprehensive emergency care and overall improvements in the quality of maternal and neonatal health care [6, 7].

Until the nineteenth century, CS was a surgical procedure of last resort performed to save the baby's life and nearly always resulting in the death of the mother due to intra- and postoperative hemorrhage or secondary infections [8]. It is only when surgeons started to suture the uterus after surgery, using sutures made of silver wire as described by the American gynecologist James Marion Sims (1813–1883), that maternal mortality rates following CS started to improve [3, 5, 6]. In the early 1880s, two German obstetricians, Ferdinand Adolf Kehrer (1837–1914) and Max Saenger (1853–1903), both independently developed a new uterine closure method by advocating a two-layer uterine closure [8]. They also advocated for the first time the use of antisepsis and stressed the importance of not delaying surgery.

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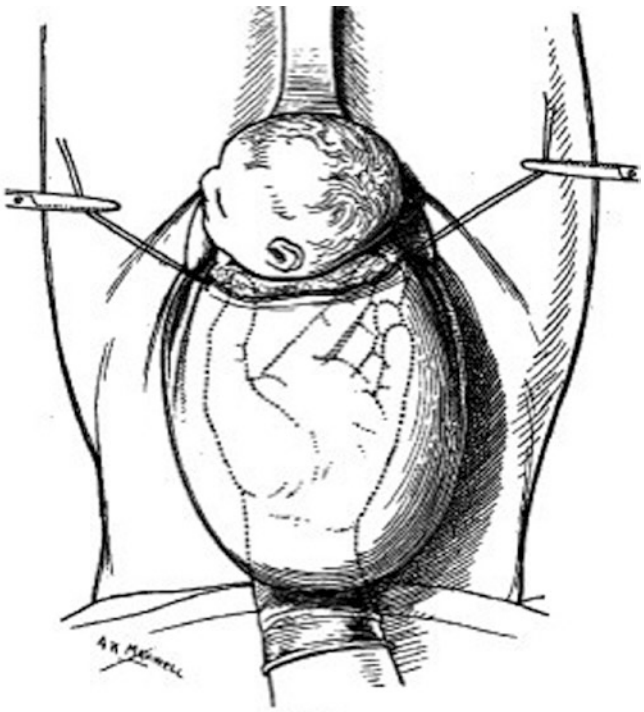


Fig. 14.1 Diagram of a low-segment cesarean delivery based on Munro Kerr description (From Munro Kerr [12])

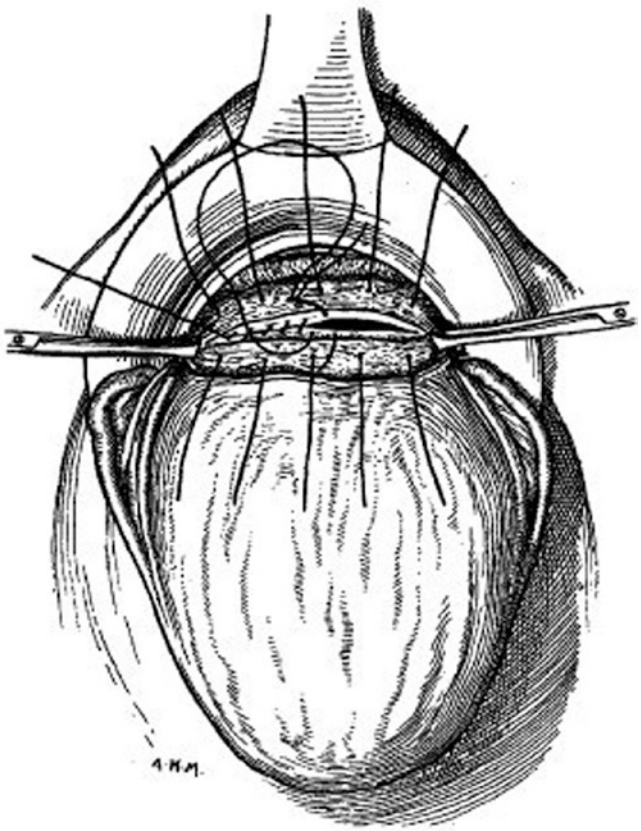


Fig. 14.2 Diagram showing the double-layer closure of the uterine incision based on Munro Kerr [12])

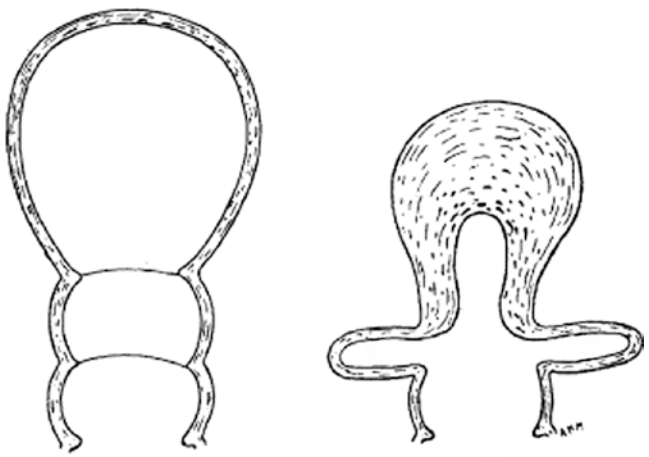


Fig. 14.3 Diagram comparing the uterus during labor [1] and 24 h after delivery. *A* Corpus uteri. *B* Lower segment. *C* Cervix (From Munro Kerr [12])

Significant advances in the twentieth century were marked by the widespread adoption of the transverse low-segment uterine incision over the "classical" vertical corpus uteri approach. Several surgeons including Kehrer had performed the transverse incision in the nineteenth century, but this only became widespread following strong support by John Martin Munro Kerr (1868–1960), who was professor of obstetrics midwifery at the University of Glasgow from 1927 to 1934. Fluent in German and French, Munro Kerr spent a number of years after his graduation in Germany, Austria, and Ireland studying obstetrics and gynecology in Berlin, Vienna, and Dublin. Appointed as visiting surgeon at the Glasgow Royal Maternity Hospital in 1900, he published to great success the book *Operative Midwifery* in 1908, popularizing the lower-segment CS in preference to the classical operation (Figs. 14.1 and 14.2).

The advantages of this "Kehrer-Kerr" technique were less hemorrhage, less infection, and a reduced risk of uterine rupture during subsequent trials of vaginal delivery [9, 10]. These changes made the operation safer, ensuring that most mothers survived the surgical procedure and facilitated its wider use in clinical obstetric practice around the world.

Munro Kerr was also the first to combine the low transverse uterine opening described by Kehrer and the suprapubic transverse skin incision as described by Hermann Johannes Pfannenstiel (Figs. 14.1, 14.2, and 14.3).

Pfannenstiel (1862–1909) was a German gynecologist who, in 1900, described a transverse suprapubic incision method for genitourinary surgery [9] with the aim to decrease the risks of incisional hernia associated with the vertical abdominal incision. In 1921, *The Journal of Obstetrics and Gynaecology of the British Empire* published a special issue on CS, and as we will see later, the transverse incision was modified and improved by Sydney Joel-Cohen. The manuscript entitled "The results of a

collective investigation into caesarean sections performed in Great Britain and Ireland from the year 1911 to 1920 inclusive" is of particular interest [11–13]. This historical audit, the first of its kind, was commissioned by the British Medical Association to Munro Kerr and analyzed by Eardley Lancelot Holland (1880–1967) from the London Hospital. As noted by the authors, "the analysis of the large material is robbed of a certain amount of completeness by the absence of details in many cases." Nevertheless, the data analysis of 4,197 cesarean deliveries indicated that the main indication was "pelvic contraction" (80 %). CS performed for this indication was associated with a 4.1 % maternal mortality mainly due to general peritonitis. Data on fetal and infant mortality were available in 3,378 cases and identified an overall perinatal mortality of 7.5 %.

In 1931, 1,000 deliveries in Germany were evaluated of which 21 (2.1 %) were delivered by CS, most of them due to cephalopelvic disproportion. The mortality rate was 19 % [14].

Most prominent obstetricians and gynecologists at the time opposed the use of the Pfannenstiel abdominal incision because it required more dissection and access to the uterus took more time than using the vertical incision. Overall, surgeons preferred the vertical (midline) abdominal incision because it also enabled a wide space when delivering the baby and better access to the pelvis and lower abdomen. Interestingly, the vertical opening of the abdomen was still the main technique used in the 1970s, although it was known from the beginning of the twentieth century to be associated with higher rates of long-term postoperative complications such as wound dehiscence and abdominal incision hernia and cosmetic issues compared to the transverse skin incision [8, 10]. The midline vertical abdominal incision is still considered faster for entry into the abdomen, and a recent prospective cohort study comparing transverse and vertical skin incision for emergency cesarean delivery found that delivering the baby is 1 min quicker using the vertical incision but that the total median operative time is longer by 3–4 min [15].

Delivering the baby by the Misgav-Ladach CS, which will be described later, is even shorter than the longitudinal incision [16].

Surgeons who are not familiar with this method can still use the longitudinal incision in case of an emergency or in special circumstances. Similarly, the classical vertical uterine incision should only be used in rare cases of very early preterm birth (23–25 weeks) or the delivery of conjoined twins. In developing countries where visibility may not be as optimized and operating time may be more of a pressing concern, the classical vertical incision is still commonly used [3, 6, 7].

There are now scores of possible different methodological variations of performing CS, if one includes the many different ways of opening the skin, the rectus sheath, the peritoneum, and the myometrium and of closing the uterus, the peritoneum, and the subcutaneous tissue [17–19]. In addition for the closure of the different layers, there is the possibility of using different suture materials in a continuous locked or unlocked manner, interrupted sutures, or staples. Although it is now an overall safe procedure, CS can be associated with a variety of immediate and long-term complications for both mother and baby. Considering the rapid increase in the number of CS worldwide, these complications have become an important and often unrecognized iatrogenic issue in obstetrics and gynecology [3]. Some of these anomalies have now become so common that they are reviewed in individualized chapters (see Chaps. 12, 14, 15, and 17).

14.3 The Evidence-Based CS

The method described here is the result of long years' experience, accompanied by comparative, retrospective, and prospective studies. This technique was subject to scores of comparative studies, and without any exception, all showed benefits over different traditional methods which were compared to it.

Local traditions were and continue until today to be the main cause for a surgeon to adhere to one or the other of the described methods, definitely concerning the abdominal incision. It is interesting to note that the first comparative study, showing benefits to the transverse incision concerning scar dehiscence, was done only 74 years after Pfannenstiel's first publication [20].

In 1972, Sydney Joel-Cohen published his book *Abdominal and Vaginal Hysterectomy* [21], in which he suggested cutting the fascia above the plica arcuata. At this level the fascia does not adhere to the muscle and moves freely over it. This is probably the reason that, when this approach was compared to the Pfannenstiel incision, when all other parameters of the operation were similar, significantly lower febrile mobility resulted [22]. This is most likely due to lack of trauma to the tissues, when detaching the fascia from the muscle became superfluous.

As we have seen, the uterine wall continued to be opened longitudinally until John Martin Munro Kerr presented his low-segment transverse CS in September 1921, arguing that in this way less dehiscence would occur in the next pregnancies [23]. The density of the muscular fibers in the body of the uterus is much more abundant than in the lower segment where the connective tissue prevails. Otherwise the cervix would not be able to open when the upper part is contracting. More damage is done to the muscle tissue the higher the uterus is cut open. The mean actomyosin content of the uterus is significantly greater than that of the cervix (7.54 vs. 3.72 mg/gm) ($P = 0.01$) [24].

Embryologically, each Mullerian duct is surrounded by the urogenital ridge mesenchyme that gives rise to the fibromuscular wall of the uterus (endometrial stroma and myometrium) and to comparable connective tissue and muscle layers of the oviduct, cervix, and upper vagina [25], hence

the difference in the histology between the body of the uterus and the cervix. Despite being considered as one organ, the cervix and the uterus have different structures and function. Their histology is different; the endocervix and the endometrium have different characters; the body of the uterus is covered with peritoneum, which is not the case in the cervix; and during labor, the uterus contracts, while the cervix widens and relaxes. We will see later that these differences take part in the decision in where to perform the opening of the uterus.

In the years to come, the prevailing CS contained the following steps: opening the abdominal wall in a longitudinal or transverse incision, opening the peritoneum transversely or longitudinally, packing the abdomen with abdominal towels, opening the uterus above the bladder plica, or separating the bladder, pushing it down, and opening the lower segment transversely, delivering the baby and the placenta, contracting the uterus, suturing the uterus with two layers, suturing the visceral peritoneum when applicable, removing the abdominal towels and cleaning the abdomen, closing the parietal peritoneum, closing the fascia continuously or with single stitches, suturing the subcutaneous tissue, and closing the skin intradermally or with single stitches [26].

At the point where the scalpel touches the skin, all surgical history and culture should be present.

However, each surgical procedure is composed of many, sometimes hundreds, of movements, each one of them has its own history and rationale. Many of these steps are based on local traditions established by opinion leaders in their specialties and countries, and their charismatic influence prevailed in following years. Every single surgical step should be carefully examined for its necessity and, if found so, for the most optimal way to perform it, as even very trivial steps might be significant. It is important to use an evidence-based CS to avoid unnecessary complications.

Therefore, many surgical methods were never subject to comparative studies, and in many hospitals, traditional steps prevail despite the existence of data showing the unnecessity or existing disadvantages. The same applies also to the indications for CS. The very fact that there are such large differences in the rate of CS, even in different hospitals in the same country or even the same city, demonstrates that there are still no standardized indications. It has been shown that with simple measurements the CS rate was reduced dramatically without any ill effects on the outcome of newborns [27].

14.3.1 The Positioning of the Parturient

Today, most CSs are performed using an epidural or spinal anesthesia or combination of both. After anesthesia is administered, the patient should be placed on the operation table with her legs closed. This will prevent tension on the fascia while it is being sutured. The arms of the parturient should not be extended outward in order to prevent neurological damage; this is especially the case when general anesthesia is used [28].

For optimal access to the lower segment of the uterus, and in order to avoid the use of abdominal packs, a Trendelenburg position should be used [29].

After the bladder is emptied with the catheter and the abdomen has been cleaned and covered, the planned site of the incision should be marked. This can be done by pinching or with a pencil, respecting the Langer skin lines [30]. Following these lines will result with an optimal scar. The level of the incision should be drawn in a straight line 3 cm below an imaginary line connecting both spinae iliacae anteriores superiores. The Langer lines become clear when the lateral aspect of the scar is pushed away from the midline. Therefore, marking the planned incision should be done while stretching the skin laterally. In case this line is not clearly marked before stretching the skin, there is a risk that the scar will not be symmetrical and wider on one of the ends.

14.3.2 The Positioning of the Surgeon

For ergonomical reasons the right-handed surgeon should stand on the right side of the parturient. When delivering the baby, the more sensitive right hand can easily estimate the needed force to extract the baby, thereby creating less risk for unnecessary extension of the incision of the uterus, avoiding unnecessary extra bleeding. Later, when stitching the uterus, the tip of the needle will point away from the bladder, thus protecting it.

14.3.3 The Surgical Technique

The first incision is done along the marked Langer lines very superficially, cutting only through the cutis (Fig. 14.4). The

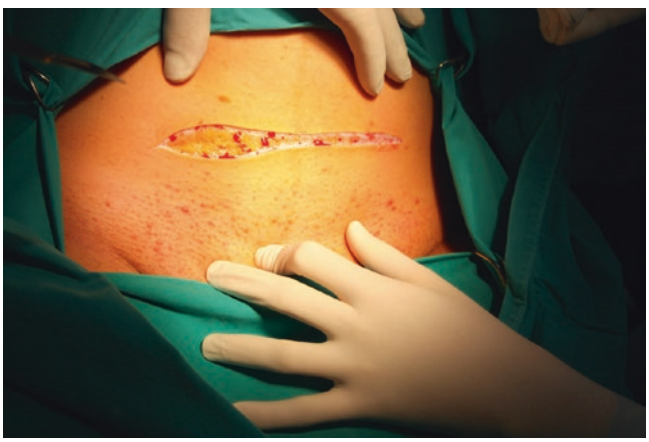


Fig. 14.4 First incision, cutting only through the cutis

location is 3 cm below an imaginary line which connects both spinae iliacae anteriores superiores.

This step usually does not require any hemostasis as there are no large blood vessels close to the cutis.

In the midline, where there are anatomically no significant blood vessels, the incision is deepened transversely until the fascia is reached. Then a transverse incision of 2–3 cm is made in the fascia, exposing the recti muscles underneath (Fig. 14.5).

Now a straight scissor with rounded tips is taken in hand.

One tip of the scissors is placed below and the other above the fascia, while the tips of the scissors are opened to about 3 mm (Fig. 14.6). The scissors are pushed toward the assistant, opening the fascia as much as is necessary as estimated by the size of the baby and then repeating this step backward toward the surgeon.

Following this step, the fascia is now open between the straight blood vessels and the muscles. The surgeon inserts both index fingers below the fascia and stretches its leaflets caudally and cranially (Fig. 14.7).

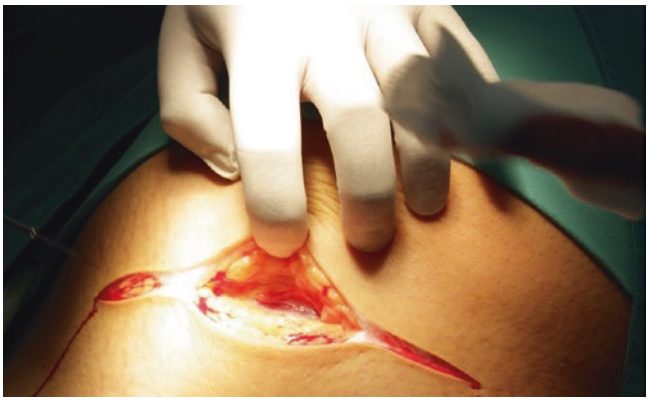


Fig. 14.5 In the midline, the incision is deepened, cutting the fascia, exposing the muscles underneath

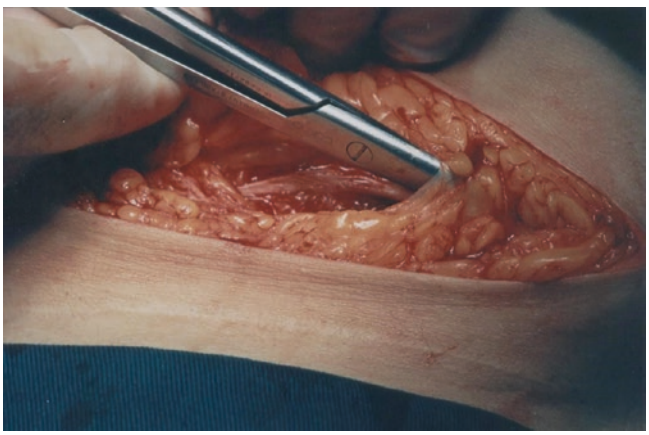


Fig. 14.6 Round-tipped scissors, one tip above and one tip below the fascia pushed laterally as far as necessary

This enables the assistant to insert an index and middle finger below the recti muscles.

The surgeon does the same from his or her side. Now, both, the surgeon and the assistant, pull the muscles laterally, together with the fat tissue and blood vessels as much as needed, again depending on the size of the baby (Fig. 14.8).

Once in a while, more force is needed to pull the muscles laterally, as might happen by repeat operations with fibrosis of the subcutaneous tissues or by overweight women. In this case, four fingers (two fingers from each hand) should be used by both the surgeon and the assistant. The placement of the four fingers should not be next to each other, but one over the other.

Blood vessels have lateral sway, but do not have length elasticity. When both hands are pulling the opening, there is a natural tendency that the hands will move apart, thereby risking blood vessel tearing.

Abdominal packs should not be used, as their usage causes adhesions. The abrasive effect of introducing packs will produce mesothelial trauma which becomes a stimulus for inflammation, followed by adhesions to adjacent surfaces [31, 32].

Not using abdominal packs also ensures that they will not be forgotten inside the abdominal cavity.

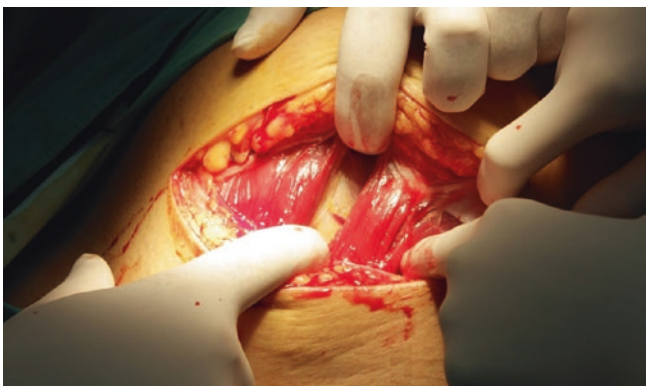


Fig. 14.7 The fascia is pushed up and down which enables both the surgeon and the assistant to place their fingers below the muscles

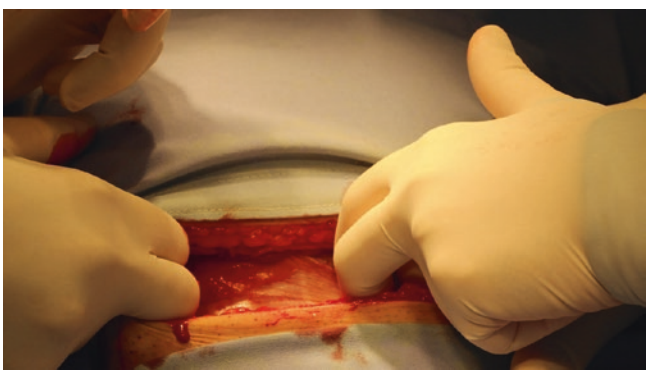


Fig. 14.8 Both the surgeon and the assistant pulling the recti muscles laterally, together with the blood vessels as far as necessary

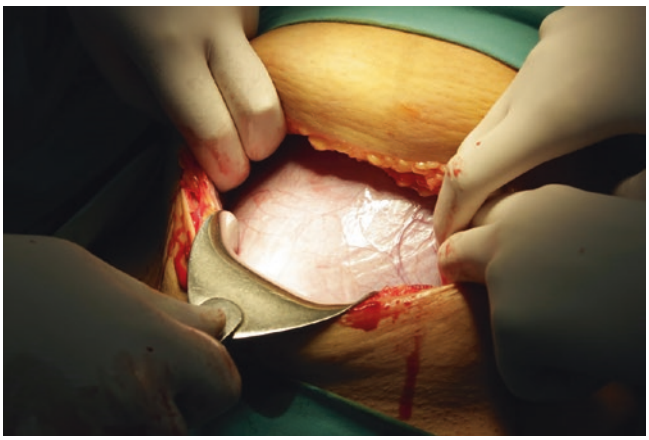


Fig. 14.9 A hand speculum pulls the lower part of the incision to expose the plica

The bladder plica should be cut open using a scalpel; in order to expose the plica, a hand speculum should be used, pulling the lower part of the incision down (Fig. 14.9).

Cutting the visceral peritoneum should always be done from the lateral aspects of one side toward the midline and then from the lateral aspect of the other side toward the midline, until it reaches the point where the other side was reached. The reason is that, if it is done the whole way in one direction, there is a risk of cutting into the intestines, as it is difficult to observe clearly the cutting edge of the scalpel. The plica can now be pushed down using two index fingers.

As mentioned, Munro Kerr suggested opening the uterus in its lower segment [33]. In the lower segment, the amount of the fibrous tissue is more dense than in the uterine body. Therefore, the lower the opening in the uterus, the less damage to the myometrium occurs.

Using a scalpel in the exposed lower segment, a transverse incision of about 2–3 cm is done carefully and gently. It is not necessary to complete the incision to the whole thickness of the cervix as this might cut the head or face of the baby which can happen if the membranes have already ruptured and the woman is in active labor, and therefore the lower segment is thin. The final internal part can be penetrated by pushing with one finger through the cut.

Planned CS should be ideally done after the onset of spontaneous contractions. The initiation of labor starts with the initiative of the baby [34, 35].

In predelivery CS one can find not just a thick lower segment, but also maternal breasts which are not yet ready for breastfeeding. There are also other good reasons to avoid pre-labor CS. A recent large cohort study has found that prior pre-labor cesarean delivery was associated with more than twofold significantly increased risk of placenta previa in the following delivery [36]. By contrast, the 20 % increased risk of placenta previa associated with prior intrapartum cesarean delivery was found to be not significant.

The optimal way to complete the opening of the lower segment of the uterus is to extend the initial opening by extension using two fingers (the thumb of the right hand of a right-handed surgeon pushing away and the index finger pulling toward the surgeon). Doing so, the lower segment will open along its natural fibers, which become transverse when it develops, therefore causing minimal bleeding. Cutting with a sharp instrument, like scissors, does not respect the natural anatomy and results with excessive bleeding.

Delivering the baby in vertex position happens while inserting the right hand of the surgeon into the uterus and encircling the head of the baby and then directing the head upward, while slight fundal pressure is allowed. As the right hand has its sensitivity, usually no overextension of the uterine opening will occur, and therefore no unnecessary bleeding happens.

After clamping, drawing blood, and cutting the umbilical cord, the placenta should ideally be delivered spontaneously by assisting through mild traction of the umbilical cord, rather than by manual extraction [37].

Thereafter the uterus should be exteriorated, as in this position it is easier to suture the uterus, to contract it in order to avoid extra bleeding, and also to easily inspect both ovaries.

There are different ways to suture the lower segment. Many of them originate from the already mentioned local traditions. Some surgeons prefer to suture first the angles, followed by two layers of sutures, usually continuously, but sometimes with single stitches to the first or second layer.

The uterus quickly contracts in the first hours after surgery, and after 6 weeks, the uterus returns to its size before the pregnancy. The quick involution results also in shrinkage of the lower segment of the uterus. The sutures are unable to contract along with the uterus, and in a short time after the surgery, they will begin to loosen over the opening line. The aim of the suture is to secure hemostasis in the first postoperative hours. Suture material creates foreign body reaction, and the more of them used, the more marked and longer the reaction, prolonging the healing process. Therefore the less suture material used, the better the healing.

In order to close the uterine wall with the most minimal amount of suture material possible, it is best to use a big needle which will enable closure of the opening and safe hemostasis (Fig. 14.10).

For this reason, it is recommended to use at least an 80 mm needle with an absorbable 1 m-long suture, PGA USP size 1, done continuously. The reason for using a long suture is that it enables placing the knot not at the most lateral aspect of the opening but allows one to go back one or two times in the direction of the midline. Knots placed at the end of the opening might loosen, which will cause bleeding.

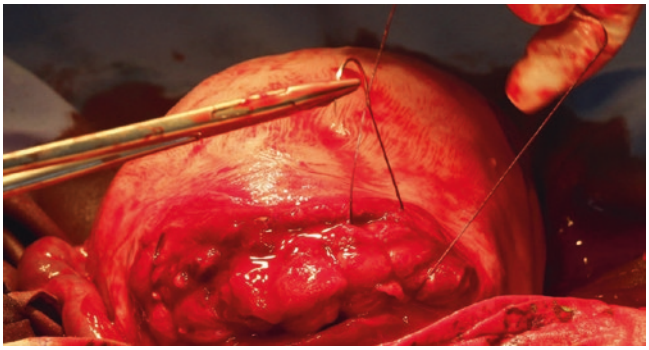


Fig. 14.10 The uterus is closed with one layer only, using a big needle

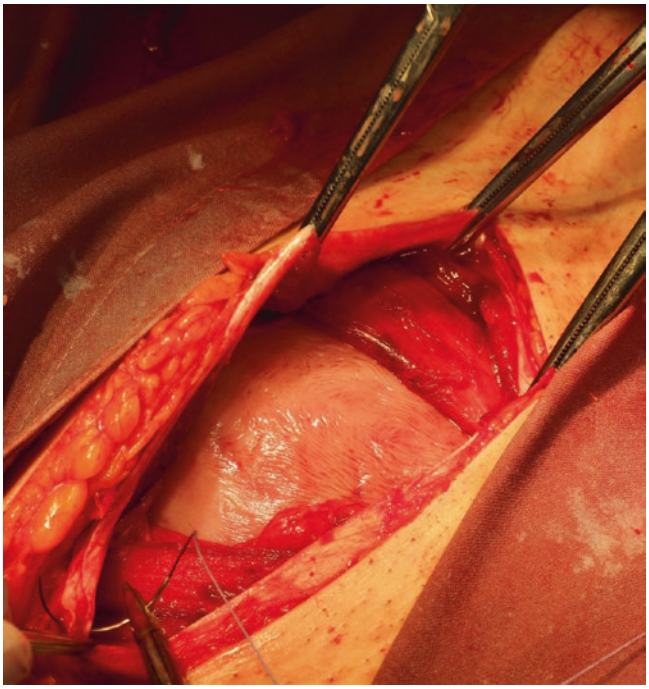


Fig. 14.11 The fascia is closed continuously and the first knot is under the fascia to avoid irritation to the subcutaneous tissue

There is no point whatsoever for a second layer as long as hemostasis is achieved.

It is not surprising that the dehiscence of previous uterine sutured with one layer is less frequent than those with two layers [38], and a double-layer closure of the cesarean uterine incision does not increase residual myometrium thickness compared to single-layer closure [39].

As no abdominal packs are used, blood clots should be removed with the palm of the hand, and fluid blood will anyhow be absorbed naturally by the peritoneum in a short time, as has been known for many years [40].

The uterus is then repositioned into the abdomen. As long as the uterus is exteriorated, the mechanical tension might disguise active bleeding. Therefore, when the uterus is positioned back into the abdomen, the lower segment should be inspected to ensure that there is no bleeding. Bleeders should be treated with targeted single stitches. There is no justification for a second layer in case of single-sight bleeding.

The abdomen should never be closed before checking the blood pressure of the woman as in low blood pressure bleeding cannot be identified and might occur later when the blood pressure rises. As a rule, the abdomen should not be closed unless blood pressure is normal.

In 1980, Harold Ellis from the Westminster Hospital in London demonstrated that when the peritoneum is left open, a new one will form in short time from the coelom cells underlying the muscles [41].

Unlike the skin, the peritoneum cannot heal by end-to-end approximation. If the peritoneum is left open, a new one will be formed without adhesions.

Our group started leaving the peritoneum open already in 1983. Ten years later, we could compare the rate of adhesions in repeated CS in women who were operated on in the first CS, leaving the peritoneum open and with those in which both peritoneum layers were sutured. In the group where the peritoneum was left open, there was significantly less adhesions [42]. The guidelines of the Royal College advise leaving both peritoneal layers open during closure [43]. In 600 repeated operations, adhesions were found in 7 (11.3 %, in women where the peritoneum was left open during the previous operation) and 22 (35.5 %, in cases where the peritoneum was sutured) [44].

As the peritoneum is left open, just the fascia and the skin must be closed.

Similar to the uterus, there are many variations about how to close the fascia; many of them based on local traditions. Anatomically the fascia was opened above the plica arcuata, and therefore we will find two layers in this level on the lateral sides which should be stitched together. In order to facilitate the stitching, a straight Pean is placed in order to laterally hold both layers, and two other Peans are placed three-fourths of the way toward the assistant (Fig. 14.11).

Knots cause local reaction and irritation. Therefore it is advised to place the lateral initial stitch underneath the fascia. This is done by starting the first stitch from inside to outside, taking both layers together, then from outside to inside.

The first knot is placed below the fascia. The suturing now moves with the needle from inside to outside in continuation through the whole layer. It is advised that the suturing will start at the side of the surgeon toward the assistant. If it is done so, the assistant will hold both of the Peans on the side and lift the fascia, thus guiding the surgeon. The Peans should be held close enough to each other in order to enable suturing without tension, but at the same time, open enough to enable the surgeon to see the underlying structure and to

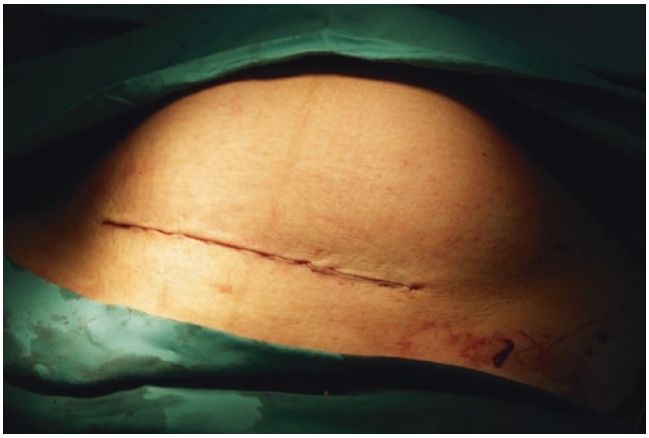


Fig. 14.12 Skin closure, intracuticular

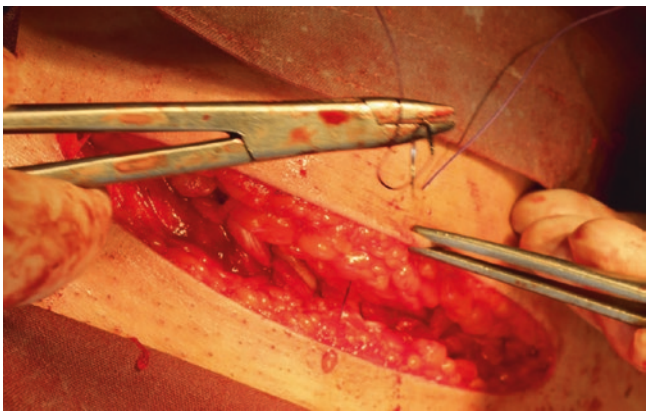


Fig. 14.13 Skin closure, with single Donati stitches, which enables good drainage

avoid damage to intra-abdominal structures. Once the suture reaches the two lateral Peans, the assistant should remove them and elevate the Pean next to his or her side. In this way, the surgeon, holding the suture material with the left hand, is able to control the needed tension.

There is still no convincing evidence concerning the optimal way to close the skin. Some surgeons prefer using intracuticular suturing which looks at first sight more aesthetic (Fig. 14.12).

However to use this method means subcutaneous sutures are needed. Any sutures and knots are reason for foreign body reaction, and therefore we recommend the use of single Donati silk sutures with a cutting skin needle, and the less placed sutures, the less risk for subcutaneous seromas or hematomas (Fig. 14.13).

The amount of the sutures has to do directly with the experience of the surgeon. Well-trained surgeons can achieve excellent results by using three stitches only, provided they use a big skin needle, where the lateral stitches can be removed after 48 h, resulting in immediate disappearance of local abdominal pain, and the midline suture should be removed after 5 days. The reason that the removal of the lateral stitches will immediately reduce the amount of pain is due to the fact that the skin will swell in reaction to the trauma but the sutures cannot expand with it. As a result there is a constant pinching feeling until the removal of the stitch.

Thereafter, the uterus should be contracted again manually, and the abdominal incision should be covered with a pad which should be replaced 3–4 h after surgery as the wide sutures enable blood to drain from the wound.

14.3.4 Postoperative Treatment

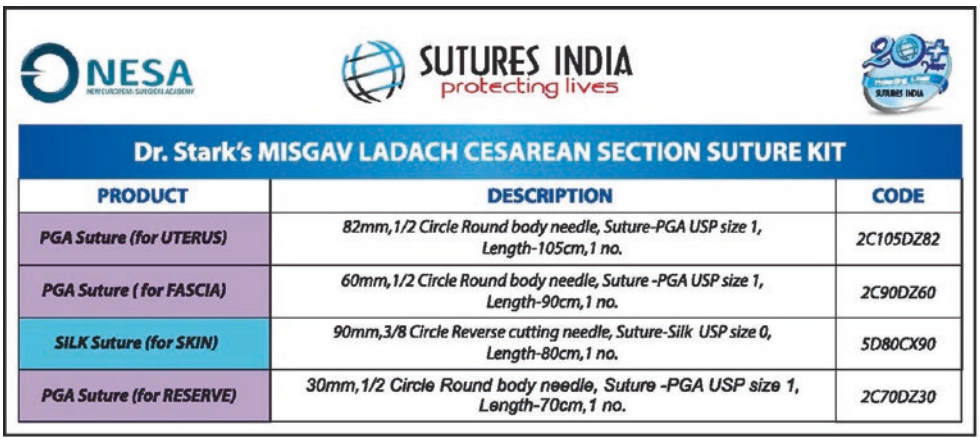
Early mobilization is the most optimal way to avoid the complications of vein thrombosis and therefore should be encouraged. CS is a significant risk factor for thromboembolism [45]. Early mobilization can be enhanced by good postoperative pain treatment and removal of the catheter as early as possible. One should encourage early drinking which helps the self-assurance of the mother and function of her intestines [46].

One of the major problems concerning comparison of different surgical methods is the lack of standardization. Different surgeons, even in the same departments, are often using different variations. Therefore, without standardization of the surgical method in use, it will be impossible to compare the outcomes and standardization is the basis for the ability to compare different methods and even comparison between different surgeons and institutions [47].

14.4 World Literature and Meta-analysis Pitfalls

Since the first publications concerning the evidence-based CS, retrospective and prospective studies have been done extensively. Comparative studies were made concerning febrile mobility, complications, need for painkillers, and cost. Without any exception, all the studies show benefits of the described operation over other methods in use. However, it is interesting to note that nearly each one of these publications finds benefits in different details, sometimes concerning the febrile mobility and at other times concerning the use of painkillers. Obviously the reason for this is that despite the meticulous description of the method [48, 49], local traditions still prevail, and certain variations are used which influence the outcome. Therefore it is of utmost importance to standardize the surgical method and prospective studies, always to compare two methods which will be repeatedly the same [50]. The reason we need a large number of patients in prospective studies is due to the individual variations in the operated mothers. We try to stratify studies according to age,

Fig. 14.14 The designed CS kit



weight, number of previous operations, birth weight of the baby, etc. and are using sophisticated statistical methods to find the significant differences. The surgical steps, however, should not vary, and therefore it is important to define them and to use also the right sequence and way of performance. It is important to use a standardized set of instruments as different instruments might result in variant reaction of the tissues; at the same time, it is important to use standard needles and suture material. The size of the needle, for example, which is used for suturing the uterus, will define the amount of foreign material left behind. Using short sutures will need extra ties and starting again with new suture and a new tie; these are causing local reaction. It is recommended to use an 80 mm round-body needle with 1 m long suture (PGA USP size 1). Same for the suturing of the fascia, a 60 mm half-circle round-body needle with a PGA USP size 1 suture and, for the skin, a 90 mm 3/8 circle reverse cutting needle, suture silk USP size 0, are recommended. This combination of sutures proved to be the most optimal with the least movement needed and in favor of standardization; a CS surgical kit was produced (Fig. 14.14).

Using standardized surgical methods and a standardized set of surgical instruments, as well as suture material, next to standardized routines concerning usage of bladder catheter, antibiotics, painkiller routines and mobilization, and hydration routines, is the only way to enable reliable comparison between different surgical procedures.

14.5 The Future of In-Labor Non-emergency CS

The best way to prevent CS complication is to avoid doing them whenever possible and, in case they have to be done in non-emergency situations, to find their most optimal timing. Even among professionals, it is still frequent to confuse elective and pre-labor CS. It is also frequent to confuse emergency and in-labor CS. Where the responses by the fetal physiological reactions are concerned, it appears today that the main differences are between pre-labor CS and all the other ways of birth. Our objective is to make the concept of "in-labor non-emergency CS" familiar. We will emphasize that it is possible to plan an in-labor CS and also to decide and perform before the stage of emergency "in-labor CS."

14.5.1 Other Reasons to Avoid In-Labor Emergency CS

In order to avoid unnecessary complications, it is important to understand that CS performed in emergency situations are associated with non-favorable short-term outcomes. Many times, such CS are performed when there are already signs of fetal distress, after a long period of pharmacological influence. We must also take into account that emergency CS are often performed in a hurry and very often are associated with non-favorable technical conditions. Furthermore, they are associated with negative long-term complications. According to an American study, women with a full-term second-stage CS have a significant increased rate of subsequent premature births (13.5 %) compared to a first-stage CS (2.3 %) and to the overall national rate (7–8 %) [51]. The same authors have demonstrated that a prolonged second stage of labor alone does not increase the risk of premature birth in following pregnancies. One plausible interpretation is that in case of CS during the second stage of labor, the location of the hysterotomy on the low segment is different from what it is otherwise [52].

This overview of the negative effects of both pre-labor and last-minute emergency CS suggests that the optimal kind of CS is the one performed during labor, before the stage of a real emergency. Until now, the concepts of "planned in-labor CS" and "in-labor non-emergency CS" have not been subject for epidemiological studies. In a multicentered randomized controlled trial about breech presentation at term, only two options were considered: planned pre-labor CS and planned

vaginal route [53]. In the extensive Scottish retrospective cohort study of adverse outcomes in childhood, "planned CS delivery" was in fact synonymous with pre-labor CS. It is noticeable that, in this cohort, children born by planned (pre-labor) CS were more likely to develop type 1 diabetes than those born by "emergency" CS or by the vaginal route. The differences were highly significant, even after adjustment for potential confounders, including maternal type 1 diabetes [54]. This data about an autoimmune disorder indicates the need for further studies of the risks of dysregulations of the immune system in relation to "birth without labor." There is a need, in particular, for a new generation of studies focusing on the risk factors for IgE-mediated atopic syndromes.

14.5.2 Toward New Obstetrical Strategies

On the day when the concept of "in-labor non-emergency CS" becomes familiar, the doors will be opened toward simplified binary strategies, with two basic scenarios: either the birth process is straightforward by the vaginal route or it appears difficult and an in-labor CS before the stage of emergency is considered the best option. Before such simplified strategies become realistic, the history of obstetrics will have to go through several steps. One of these steps will be via studies regarding the long-term side effects of the different medications used during labor. Although there are serious theoretical reasons to reconsider the widespread use of synthetic oxytocin and epidural analgesia, we have not been able to rely, until now, on a large amount of hard data. However, in this new framework, we can already mention valuable studies of the effects of epidural analgesia and synthetic oxytocin, on the initiation and quality of breastfeeding [55, 56]. We can also mention studies looking at risk factors for autism in the perinatal period: while they are based on a great diversity of research protocols in different countries, they all reach similar conclusions about labor induction and labor augmentation [57–61]. The emergence of this new generation of studies (collected in the database "www.primalhealthresearch.com") is already offering reasons to use medications during birth with renewed caution, particularly for labor induction and labor augmentation.

The main step toward the advent of simplified strategies will be an understanding of the process of parturition challenging the effects of thousands of years of tradition and cultural conditioning. This is realistic in the light of modern physiology. From this perspective, the birth process appears as an involuntary process under the control of archaic brain structures. As a general rule, one does not try to help an involuntary process. The point is to identify possible inhibitory factors. From a practical perspective, the key word is *protection*. Several physiological concepts clearly indicate the factors that can negatively interfere with the process of parturition. The concept of adrenaline-oxytocin antagonism is essential where mammals in general are concerned: mammals postpone the delivery when releasing emergency hormones of the adrenaline family. Although this concept is well established, in practice it is not always taken into account, as if it were not perfectly assimilated.

The evolution worked in the direction of continuation of generations with as little complications as possible. Many of the complications which happen during labor or CS are iatrogenic in nature. It is important to stress that each maneuver during childbirth or performance for CS should be well indicated. It seems that the active management of labor did not answer expectations, even if the rate of CS was reduced [62].

14.5.3 The Concept of Neocortical Inhibition

When considering the case of human birth, the focus should be on the concept of neocortical inhibition, a key to understanding human nature in general. We should keep in mind that some human abilities are usually obscured by neocortical activity. There has been until now a lack of interest in this essential particularity of our species. Human parturition is better understood if introduced in the framework of functions usually obscured by neocortical activity. A first example is offered by olfactory abilities. An ingenious experiment has explored the human sense of smell after neocortical disinhibition by alcohol consumption [63]. Another example is offered by the human swimming abilities: the capacity to adapt to immersion and have coordinated swimming movements when submerged disappears around the age of 3 or 4 months, when the neocortex is reaching a certain degree of maturity [64].

When the concept of neocortical inhibition is understood and taken into account, it is easy to challenge the assumption that mechanical factors are the main reasons for difficult births in our species. In fact, the mechanical factors are undoubtedly overestimated, since there are women with no morphological particularities who occasionally give birth quickly without any difficulty. There are anecdotes of women who give birth before realizing that they are in real labor. There are in particular countless anecdotes of teenagers who, at the end of a hidden or undiagnosed pregnancy, just go to the toilet and give birth within minutes. These facts alone suggest that the main reasons for difficult human births are not related to the shape of the body. The best way to clarify the nature of the specifically human handicap during the period surrounding birth is to consider the case of civilized modern women who have given birth through an authentic "fetus ejection reflex" [65]. It is exceptionally rare in the context of socialized birth. The birth is suddenly preceded by a very short series of irresistible, powerful, and highly effective uterine contractions without any room for

voluntary movement. The important point is that when the "fetus ejection reflex" is imminent, women are obviously loosing neocortical control. They become indifferent to what is happening around them. They forget what they have previously learned. They forget their plans. They behave in a way that, in other situations, would be considered unacceptable regarding a civilized woman. For example, they dare to scream or to swear. There are anecdotes of women who have bitten a person perceived as intrusive. Women in hard labor can find unexpected, complex, asymmetrical postures usually involving bending forward. Such scenarios clearly indicate the solution. Nature found to make birth possible in our species: reduced neocortical control. This essential aspect of birth physiology in our species offers an ideal perspective to reach the simple conclusion that a laboring woman needs to be *protected* against all possible stimulants of her neocortex. Since language is a major stimulant, silence appears as a basic need that is culturally ignored or underestimated after thousands of years of socialization of childbirth. In this respect, rational language and language expressing questions have particularly powerful effects.

Light has not been scientifically studied as a powerful cortical stimulant until recent advances regarding the functions of melatonin, the "darkness hormone." However, the long history of blinds and curtains is the confirmation of deep-rooted transcultural empiric knowledge that is pushing us, today, to switch off electric lights in order to reduce neocortical activity during sleeping time. Recent studies of the interactions inside the triad oxytocin-melatonin-GABA offer a promising avenue for research. It is already understood that the GABA(A) receptors mediate the effects of melatonin on neocortical activity [66, 67]. Until now, the interactions between the oxytocin and the GABA systems in the perinatal period have been mostly studied in the framework of the shift of the effects of GABA at the end of fetal life, when this primary excitatory neurotransmitter becomes inhibitory [68]. When considering the effects of melatonin, and therefore light, on human parturition, we have to deviate from the concept of neocortical inhibition and refer to recent advances regarding peripheral effects. It is now established that there are melatonin receptors in the human myometrium and that melatonin is synergistic with oxytocin to enhance contractility of human myometrial smooth muscle cells [69–74]. Today melatonin appears as an important hormonal agent in human parturition. This is confirmed by the significant amount of melatonin in the blood of neonates, except those born by pre-labor CS. The importance of these findings appears clearly when the protective antioxidative properties of melatonin are taken into account. In the age of electric lights, the reasons to improve our understanding of melatonin release and melatonin properties are obvious. It is already well established that short-wavelength light (in practice "blue" light) is the most melatonin suppressive. This is an important fact, since it is the kind of light typically emitted by devices such as televisions, computer screens, cellphones, and even lamps in conventional delivery rooms. It is probable that, when birth physiology is better understood, the practical implications of these recent scientific advances will be seriously considered. Until now preliminary practical implications have been limited to attempts to facilitate shift work and also to facilitate the initiation of sleep through the use of amber glasses that block blue light [75, 76]. Can we imagine a time when it will be considered rational to give birth by candle light? Can we imagine a time when women familiar with the use of amber glasses when in front of computer screens will also use such glasses when in labor? After mentioning language and light, we might summarize the most important points by emphasizing that all attention-enhancing situations are stimulants of neocortical activity. This is the case of feeling observed: it implies that one of the basic needs of a laboring woman is privacy. The perception of a possible danger is another example of an attention-enhancing situations: it implies that a laboring woman needs to feel secure. We can notice that similar conclusions can be reached when using the concept of adrenaline-oxytocin antagonism as a starting point.

14.5.4 Predictive Scores and Tests

As a primary objective, reducing the rates of CS is dangerous. The effect is an increased prevalence of difficult births by the vaginal route with an increased need for pharmacological assistance [77]. The first step should be a renewed understanding of the basic needs of laboring women inspired by the physiological perspective: only this perspective can induce a paradigm shift after thousands of years of socialization of childbirth. According to our deep-rooted dominant cultural conditioning, a woman needs cultural interferences to give birth: this is the "helping-guiding-managing-coaching-supporting paradigm." From the perspective of modern physiology, the keyword is "protection" (of an involuntary process). Such a paradigm shift is the prerequisite for the advent of simplified binary strategies based on the concept of in-labor non-emergency CS. When simplified binary strategies become realistic, there will be new reasons to associate clinical judgements with predictive scores and tests. An American study of predictive scores took into account 11 variables in order to identify, within 2 h after admission, risk factors that place at term nulliparous women in labor at risk for CS. The population was divided into quintiles, in which the lowest risk group had a 5 % incidence and the highest risk group had an 88 % incidence of CS. The objective of this study was clearly to reduce the potential morbidity of long labor or failed operative vaginal delivery [78]. Interestingly it takes also about 2 h to decide, through the "birthing pool test," if an in-labor

non-emergency CS is the optimal option when the first stage is not straightforward. This test is based on the simple fact that when a woman in hard labor enters the birthing pool and is immersed in water at body temperature, a spectacular progress in the dilation is supposed to occur in an hour or two [79]. If the already well-advanced dilation remains stable in spite of water immersion, privacy (no camera!), and dim light, one can conclude that there is no reason for procrastination. It is wiser therefore to perform a CS immediately [80]. In the age of simplified techniques of CS, there are renewed reasons for simplified obstetrical strategies which will reduce, when followed, the rate of neonatal and maternal complications.

14.6 Complications

We have emphasized that the best way to avoid complications related to CS is to avoid unnecessary operations, and understanding the physiology is a key factor. An extremely low percentage of CS is not necessarily an indication for quality, and an extremely high rate is not necessarily a sign of overuse. The population in each hospital is different, not just because of the existence or nonexistence of intensive care units for the mother and newborn, but also due to the population living in the area, their general health, age by first delivery, and many other factors. Therefore, artificially defining an optimal rate of CS will miss the point. It should be individualized, and each single case should be discussed, and the decision to perform CS, except in extreme emergencies, should be consulted with another obstetrician or during the daily staff meeting where applicable.

Even when a CS is indicated for a justified reason, the timing of the operation is critical. We know today that it is optimal to perform an indicated CS after labor has started. The lower segment develops which has influence on the amount of bleeding and easiness to open the uterus; the chance of the baby to be mature is higher, as the baby is the one signaling the mother when to start contractions and the mother is ready to start breastfeeding [81]. There are also surgical aspects which are more favorable when contractions have already started due to fact that when the lower segment develops, it is surgically easier to open the uterus in a location with less muscular tissue and more fibrous tissue. This will secure a stronger scar and lower the risk of dehiscence in following deliveries.

Pre-labor CS is a risk factor for respiratory difficulties during the neonatal period, and the risks are dependent on the gestational age: differences in the quality of the respiratory functions are detectable when comparing pre-labor births at 38 and 39 weeks [82]. The roles of maternal and fetal stress hormones are well known. The effects of maternal corticosteroids on fetal lung maturation are already known and have had practical implications for several decades. Labor implies the action of beta-endorphins (releasers of prolactin, which participate in lung maturation) [83]. Labor also implies the release of the fetal noradrenaline, which is one of the main factors responsible for lung maturation.

The negative effects of stress deprivation of babies born by pre-labor CS are underestimated. For example, it has been demonstrated that, under the effect of noradrenaline, the sense of smell reaches a high degree of maturity at birth among these babies than those delivered naturally. The principle of a Swedish study was to expose babies to an odor for 30 min shortly after birth and then to test them for their response to this odor (and also to other odors) at the age of 3 or 4 days [84].

Since the concentrations of noradrenaline had been evaluated, it was possible to conclude that fetal noradrenaline released during labor is involved in the maturation of the sense of smell. We must emphasize the paramount role of the sense of smell immediately after birth. The fact that the sense of smell is a main guide toward breastfeeding was already recognized in the 1970s [85, 86].

It has also been shown that it is mostly through the sense of smell that the newborn baby can identify its mother (and, to a certain extent, that the mother can identify her baby). There has recently been an accumulation of data multiplying the reasons for waiting, whenever possible, for the onset of labor before performing a CS. Many unexpected differences have been demonstrated through human studies regarding the effects of CS births according to their timing. Among such studies, we must mention the evaluation of adiponectin concentration in cord blood of healthy babies born at term. The concentration of this agent involved in fat metabolism is significantly lower after pre-labor CS compared with in-labor CS or vaginal route [87]. These data suggest a mechanism according to which stress deprivation at birth might be a risk factor for obesity in childhood and adulthood. We must also give great importance to data regarding the milk microbiome. There are significant differences between the milk of mothers who gave birth by pre-labor CS and those who gave birth by in-labor CS or the vaginal route [88]. These results suggest that there are other factors than the operation per se that can alter the process of microbial transmission to milk. Similar differences were found by a Canadian study of the gut flora of 4-month-old babies [89]. Joanna Holbrook and her team, in Singapore, suggest interpretations for these surprising data. They collected fecal samples from 75 babies at the age of 3 days, 3 weeks, 3 months, and 6 months (and they evaluated the degree of adiposity at 18 months). It appears that, apart from the route of birth and exposure to antibiotics, a shortened duration of pregnancy tends to delay the maturation of the gut flora, 1 week more or less in the duration of pregnancy is associated with significant differences, and a pre-labor CS implies the association of all the known factors

that can delay the maturation of the gut flora. This study is all the more important since it also reveals that a delayed maturation of the gut flora is a risk factor for increased adiposity at the age of 18 months [90].

In the framework of human studies, we may include also evaluations of the concentrations of melatonin in the cord blood. Melatonin levels proved to be low after pre-labor births [91]. This is an important point, since melatonin has protective antioxidative properties. Furthermore, it confirms that the "darkness hormone" is involved in the birth process. This is one of the reasons why the role of melatonin during labor is a topical issue, at a time when we are learning about a synergy between its uterine receptors and oxytocin receptors. In general, a baby born after a pre-labor CS is physiologically different from others. For example, babies born before the start of labor tend to have a lower body temperature than others during the first 90 min [92]. In spite of possible interspecies differences, we must learn from animal experiments suggesting that the stress of labor influences brain development. Such is the case of studies demonstrating that the birth process in mice triggers the expression of a protein (uncoupled protein 2) that is important for the hippocampus development [93]. The hippocampus in *Homo sapiens* is a major component of the limbic system. It has been compared to an "orchestra conductor" directing brain activity. It has also been presented as a kind of physiological GPS system, helping to navigate while also storing memories in space and time: the work of three scientists who studied this important function of the hippocampus has been recognized by the award of the 2014 Nobel Prize in physiology and medicine. This is also the case of studies with rats suggesting that oxytocin-induced uterine contractions reverse the effects of the important neurotransmitter gamma-aminobutyric acid (GABA): this primary excitatory neurotransmitter becomes inhibitory [94]. If uterine contractions affect the neurotransmitter systems of rats during an important phase of brain development, it is not improbable that the same happens in humans.

Other reasons to avoid pre-labor CS will present in the future. It seems that the prevalence of lateral (Fig. 14.15) or central placenta previa (Fig. 14.16) is significantly increased only in the case of a pregnancy following a pre-labor CS [95]. There is already an accumulation of data confirming the negative effect of pre-labor CS on breastfeeding, particularly at the phase of initiation of lactation [96, 97]. Toward the end of the pregnancy, major anatomical changes happen. The lower segment of the uterus develops and the wall in the lower aspect of the uterus becomes thinner. Optimally, during CS, the uterus should be open after pushing down the bladder. As we stressed before, the histology of the lower segment is different than the body of the uterus, and one of the differences is the prevalence of more fibrous tissue and less muscle. Therefore, performing CS after the initiation of contractions will enable the opening of the uterus in a segment with less muscle and with a thinner wall. This will result with easy extension of the opening which, as we described, can be done by using two fingers (the thumb of the right hand pushing away and the index finger pulling toward the surgeon). This maneuver results with less bleeding and is much easier than opening the lower segment during pre-labor CS. This enables suturing the uterus with one layer, which proved to be beneficial, not just due to less suture material and therefore less foreign body reaction which could result in a weak scar, but also in avoiding complications related to bleedings and unnecessary extra stitches which might cause damage to the urine bladder (Fig. 14.17) and occasionally even to the ureters and fistulae [98, 99].

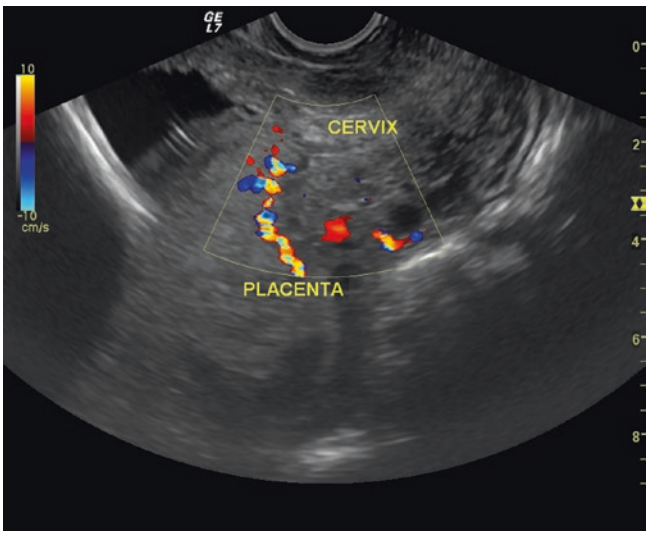


Fig. 14.15 A transvaginal ultrasonographic scan of lateral placenta previa

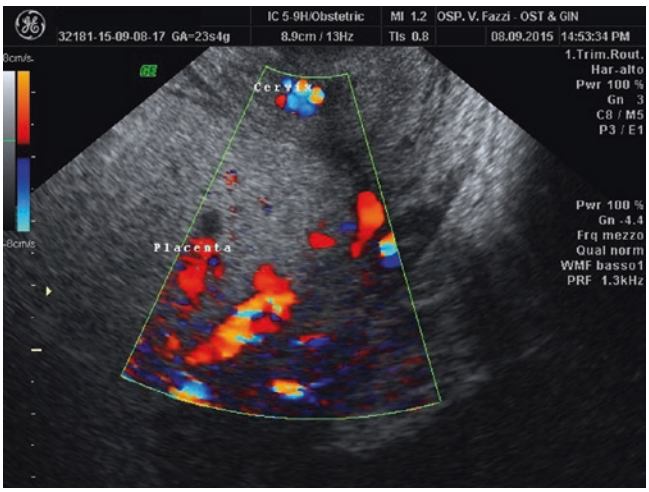


Fig. 14.16 A transvaginal ultrasonographic scan of central placenta previa with accretism

Fig. 14.17 A complication during cesarean section: the accidental damage to the urine bladder, with the leakage of the catheter from the bladder

14.6.1 The Short-Term Complications of CS

Short-term complications of delivery include all maternal or neonatal complications from birth up to 42 days after delivery. Complications such as intra- and postpartum hemorrhage (PPH) are more frequent during and after emergency CS and in women with a preexisting condition such as hypertension and diabetes, women with multiple gestation pregnancy (MGP), or women presenting with a low-lying placenta [17, 100]. These risk factors also increase the need for cesarean delivery [17, 19, 101, 102]. New risks factors such as maternal obesity and advanced maternal age (AMA) are now established risk factors for CS and can explain in part the some of the rapid increase in the CS rates worldwide [103–109]. Obese primiparous women and multiparous women with no previous cesarean delivery have similarly increased adjusted RRs for intrapartum cesarean delivery (relative risk (RR) 1.64 and RR 1.66, respectively) [106]. Induced labor is a significant risk factor for delivery by CS (adjusted odds ratio 2.2) in obese women [104]. A recent retrospective cohort study of all women (n = 1,346,889) delivering singleton births in the state of California between 2007 and 2012 has shown that the CS rates increase from 30.5 % at 20–34 years to 40.5 % at 35–39 years, 47.3 % at 40–44 years, 55.6 % at 45–49 years, and 62.4 % at >50 years [108]. Similar increased rates (35–39 years, 25.9 %, RR = 1.25; 40–44 years, 30.9 %, RR = 1.45; 45–49 years, 35.7 %, RR = 1.59; and ⩾50 years, 60.7 %, RR = 2.44) were also found in a Washington State population-based cohort study of 78,880 births to mothers 25 years and older with singleton births [109]. Nulliparous women age ≥50 years were significantly more likely to experience an intrapartum cesarean delivery (RR, 2.61) [108].

Factors such as obesity combine risks of intrapartum and postpartum complications for both mother and newborn in particular when associated with gestational diabetes and fetal macrosomia [17, 105, 107]. MGP increases the risk of CS due to a higher incidence of fetal malpresentation, also in case of fibroids (Fig. 14.18a, b), and placenta previa and CS in these cases are associated with a higher rate of intra- and postoperative complications [17, 101]. Women requiring cesarean delivery for early preterm births (23–27 weeks) are at higher risks of hemorrhage, infection, and intensive care unit admission, in particular when a classic CS delivery is performed [110].

14.6.1.1 Maternal Complications

Serious maternal complications are defined as hemorrhage leading a blood loss ≥1,500 mL, blood transfusion, or hysterectomy for hemorrhage, infection including endometritis, wound dehiscence, or wound infection requiring antibiotics, reopening, or unexpected procedure, admission to intensive care unit (ICU), or death [100]. The management of PPH is described in other chapters.

Overall excessive bleeding is more common in CS for MGP, placenta previa, placenta previa accreta (Fig. 14.19); in grand multiparous women, following a long and dystocic labor, at full dilation; and in cases of fibroids [17, 100, 101] (Fig. 14.20), and obstetricians need to be prepared to manage potential PPH in these high-risk cases.

Women undergoing CS have a fivefold to 20-fold greater risk for infection and infectious complications compared with a vaginal birth, and infectious complications that occur after cesarean deliveries are an important cause of maternal morbidity and are associated with an increase in hospital stay [111]. Infectious complications following CS include high fever, wound infection, endometritis (most common complications of CS), and urinary tract infection.

Rarely, there can also occasionally be life-threatening infectious complications such as pelvic abscess, septicemia, and septic shock, necrotizing fasciitis, and septic pelvic vein thrombophlebitis. Obese women have a twofold–fourfold increase in infectious postoperative complications, including primary infectious outcome and wound infection [107]. The most important source of microorganisms responsible for

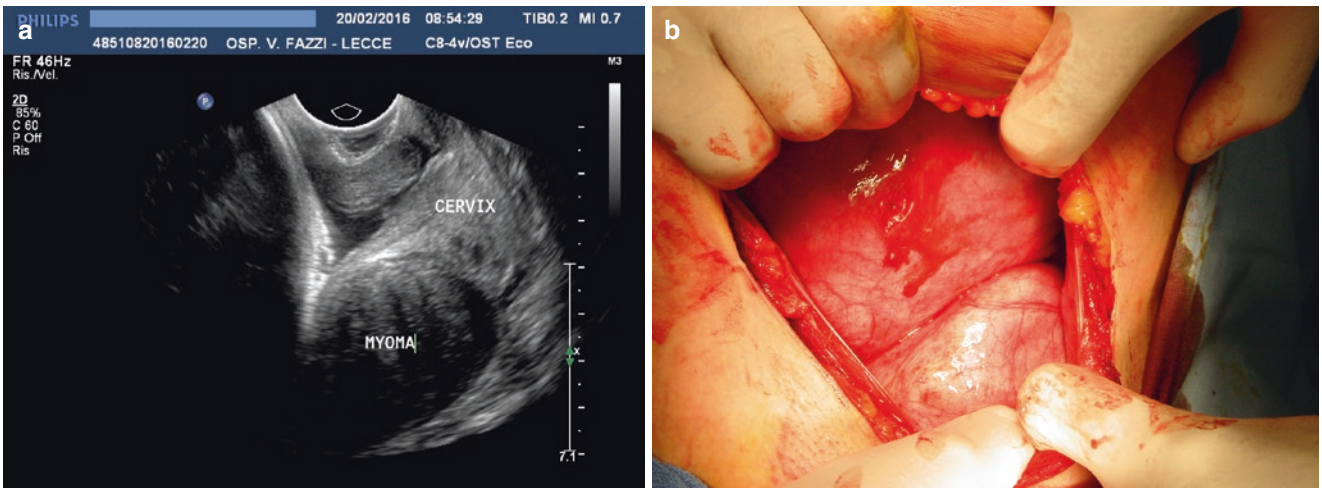


Fig. 14.18 (**a**) Transvaginal ultrasonographic scan showing a posterior cervical fibroid at 36 weeks of pregnancy. (**b**) Intraoperative image of a large cervical fibroid during cesarean section

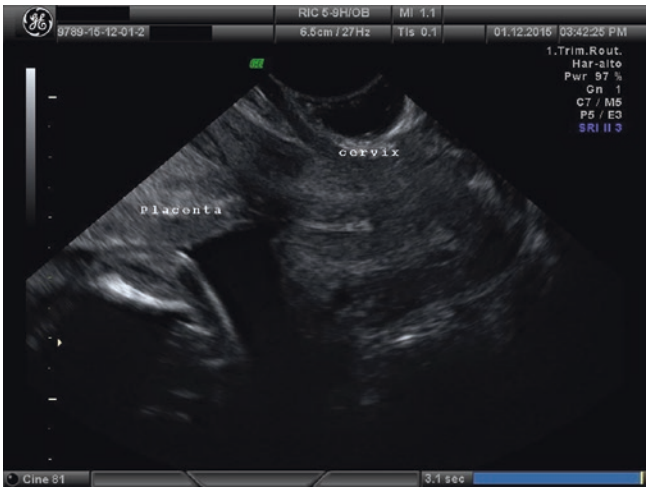


Fig. 14.19 A transvaginal ultrasonographic scan showing an anterior placenta previa in a patient at 31 weeks of gestation, operated by an urgent cesarean section. During operation, patient was hysterectomized for placenta accreta

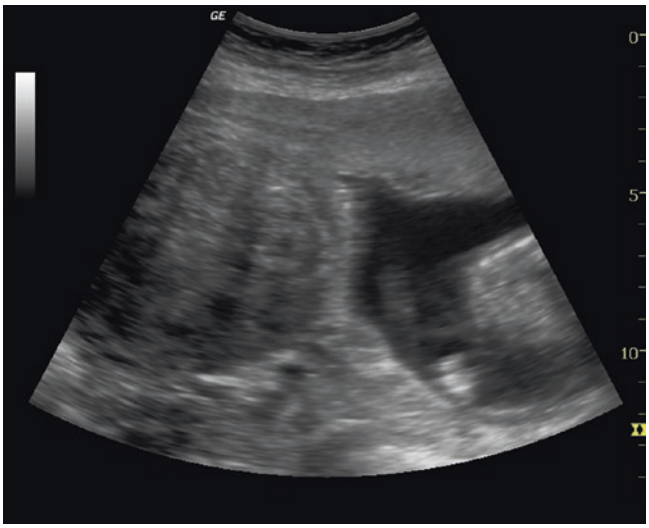


Fig. 14.20 A transabdominal ultrasonographic scan showing a lateral fibroid of 10 cm in diameter in a patient at 26 weeks of pregnancy

post-cesarean section infection is the genital tract, particularly if the membranes are ruptured [111]. Pathogens isolated from infected wounds and the endometrium include *Escherichia coli* and other aerobic gram-negative rods, group B streptococcus and other streptococcus species, *Enterococcus faecalis*, *Staphylococcus aureus* and coagulase-negative staphylococci, anaerobes, *Gardnerella vaginalis*, and genital mycoplasmas. The use of prophylactic antibiotics before skin incision decreases in women undergoing cesarean section reduces the incidence of wound infection, endometritis, and serious infectious complications by 60–70 % [17, 19, 111].

The skin layer can be repaired by subcuticular stitch (immediately below the skin layer) or an interrupted stitch (individual stitches) or with skin staples. In theory, staples are attractive because there is less chance of bacterial migration into the wound, and the capillaries in the subcuticular layer are not damaged during placement of the clips [17]. A recent meta-analysis has shown that closure of the transverse skin incision with suture significantly decreases wound morbidity, specifically wound separation, without significant differences in pain, patient satisfaction, or cosmesis [112].

Vascular thromboembolism (VTE) is the leading cause of maternal death in developed countries. Risk factors are also the puerperal period, CS, immobility, obesity, advanced age, and parity. The incidence of DVT was reported at 0.17 % and that of pulmonary embolism (PE) at 0.12 % in women undergoing cesarean birth [19, 100]. Operative

injuries are uncommon and include uterine lacerations, bladder injury (Fig. 14.21), ureteral injury, and gastrointestinal tract injury (Fig. 14.22) [19].

Multiple repeat CS and cesarean delivery at full dilation increase the risks of serious maternal morbidity, and the risks increase with the number of previous cesarean deliveries [17].

Although CS is the most common operation among obstetricians and gynecologists, it should be considered as a major surgery and should not be done without the presence of an experienced obstetrician. The complications involved are unpredictable and hemorrhages are an extremely actual risk. Complications can happen in any stage of the surgery, starting with the skin incision, injury to the blood vessels and muscles, damage to the intestines and bladder, and injuries to the newborn. Knowledge of anatomy and physiology is of utmost importance, and any complication should be immediately recognized and taken care of. Once in a while, intraoperative consultation with a general surgeon or urologist is necessary. Calling for assistance is not a sign of weakness; on the contrary, it shows responsibility and maturity.

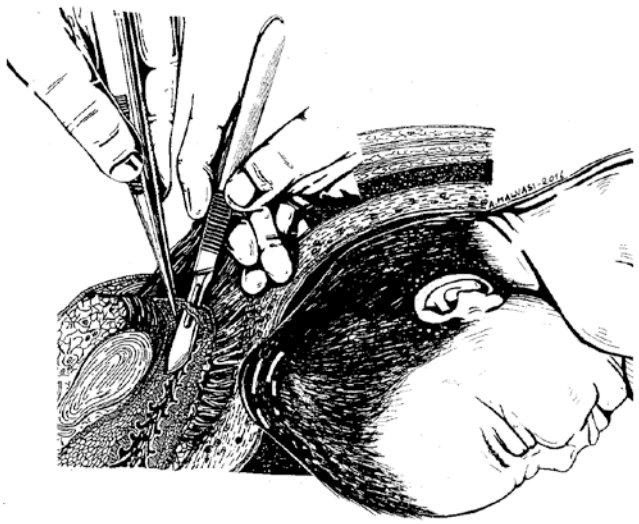


Fig. 14.21 An accidental bladder injury

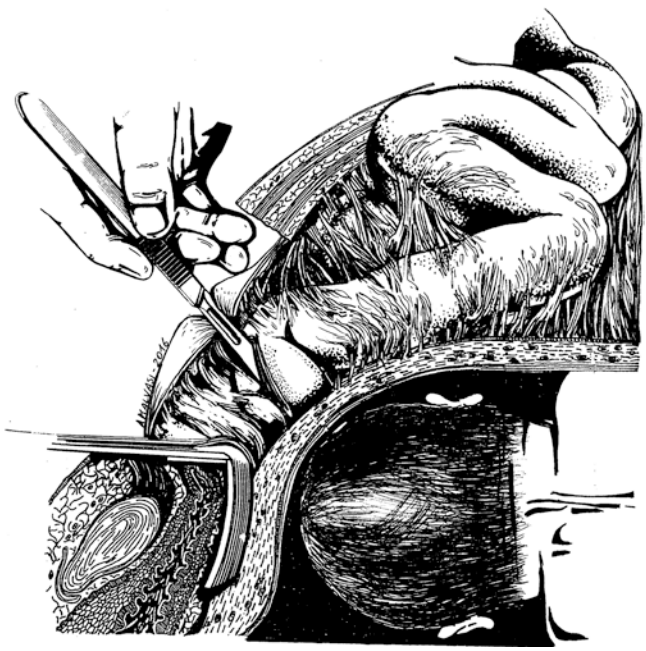


Fig. 14.22 An accidental gastrointestinal tract injury

14.6.1.2 Neonatal Complications

The main complication of preterm CS is a higher rate of neonatal intensive care unit (NICU) admission. Neonatal adverse events are more frequent with elective cesarean delivery performed at 38 than 39 weeks of gestation and at 37 weeks compared to 38 and 39 weeks of gestation [113–115]. The difference between 38 and 39 weeks seems to be significantly smaller than previously anticipated, and a recent randomized controlled multicenter open-label trial found no significant reduction in neonatal admission rate after CS scheduled at 39 weeks compared with 38 weeks of gestation [116].

As shown previously, the maternal skin microbiome, the oral flora, and the breast milk microbiome have also an important role in the development of the human immune system [117]. The physiological changes that occur during pregnancy may disrupt this balanced ecosystem and predispose women to a potentially pathogenic microbiota. Infant colonization sets the stage for the adult microbiome [118]. The intestinal flora of the children born by CS contains less bifidobacteria and is similar to the intestinal flora found in diabetic individuals [117, 119]. Premature and/or very low birth weight (VLBW) neonates are at greater risk for marked dysbiosis of the gut microbiome and are at greater risks of late-onset neonatal sepsis and necrotizing enterocolitis [117]. Maternal obesity and prenatal exposure of antibiotics are additional risk factors for these complications [105, 110, 120, 121]. Prophylactic antibiotics are now routinely given to all women undergoing elective or non-elective CS and are beneficial for women [17, 111] with no obvious consequences for the term newborn. The passage of a single dose of prophylactic antibiotic during a cesarean delivery through the breast milk is thought to be minimal.

Direct injury, i.e., skin cut to the newborn (Fig. 14.23), is uncommon at CS but may be unreported and vary with the experience of the operator and the technique used (Fig. 14.24). There are no epidemiologic data available on accidental cut skin during CS and their short-term impact. Bone fractures in neonates are rare, but can occur during CS, and case of bilateral humerus fracture and other orthopedic complications have been reported [122–124].

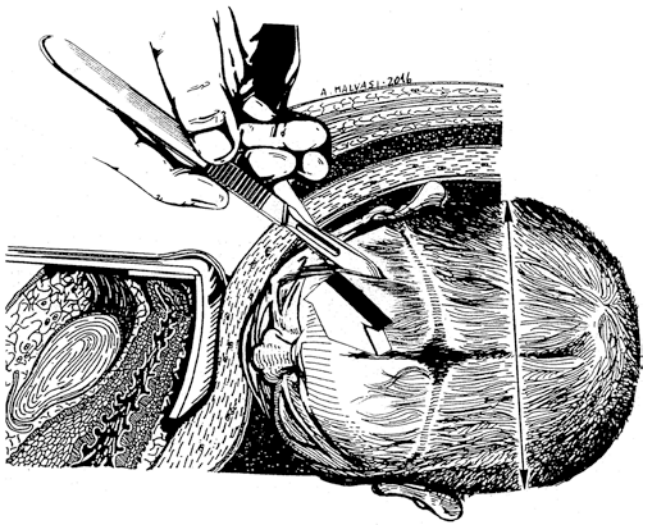


Fig. 14.23 Accidental skin cut to the newborn during cesarean section

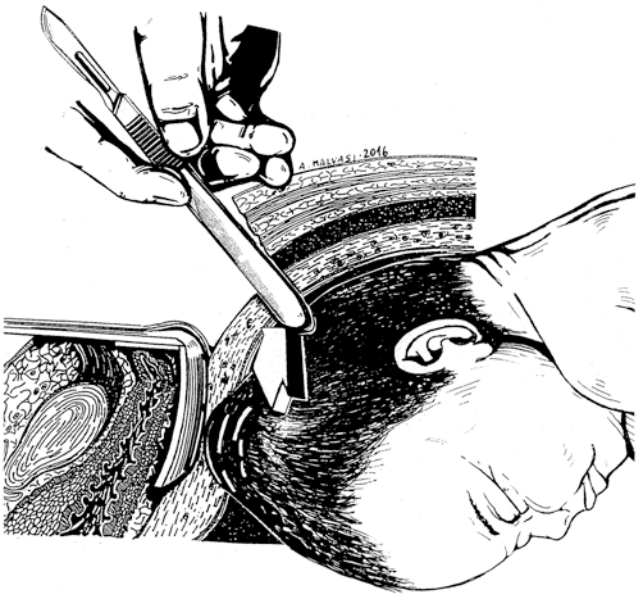


Fig. 14.24 A safety technique used by surgeon during the opening of the myometrium, performed with the scalpel taken from the handle

14.6.2 Long-Term Complications

A cesarean delivery requires cutting and opening of the skin and underlying fat tissue, the muscular sheet, the peritoneum, and the uterine muscle including the myometrial-endometrial junction zone. All these layers need to go through the healing process afterward, which will vary depending on the type of tissue involved and requires hemostasis, inflammation, proliferation, and remodeling. For a wound to heal effectively, these phases should be accomplished fully and in the right sequence. Scarring is considered abnormal when fibrosis is excessive or suboptimal.

14.6.2.1 Keloids

Surgical wounds alter the skin's fibrotic structure, thereby producing scar tissue with significant functional impairments [125]. Keloids and hypertrophic scars are generally characterized by abnormally proliferative scar tissue. Keloids are benign, fibroproliferative lesions that represent abnormal healing resulting in excessive fibrosis, which can occur in all skin types with a higher frequency in black women. Keloids have a different clinical course than do hypertrophic scars. Optimal prevention and treatment of these abnormal wound healing process remain undefined, but they may be surgically corrected. Other measures such as intralesional corticosteroid or verapamil injection, pressure therapy, cryotherapy, and other topical treatments such as topical gel sheeting may be useful [126, 127], but most have not been tested in randomized controlled trials (RCT). Many surgeons remove keloids in subsequent CS; however, mostly the keloids form again. The best way to deal with keloids and at least to minimize their appearance is to remove them, not beyond their borders, but very near to the inner border, leaving minimal keloid tissue and then closing the skin as keloid does not produce another keloid. It will result in a much thinner scar than the previous one.

14.6.2.2 Adhesions

Most of the long-term complications related to CS are related to the development of postoperative adhesions [125]. Recent data suggest that the formation of adhesions is caused by the organization of a fibrin matrix, which takes place during the coagulation process facilitated by suppression of fibrinolysis [128]. Adhesions develop more frequently and with increasing severity with each repeat cesarean. Around 40 % of women develop adhesions following the primary cesarean delivery, and nearly 70 % of those have adhesions at the second surgery [129]. Of those who did not develop adhesions after the primary CS, almost 40 % have adhesions at the third surgery. Overall, a woman presenting with adhesions at her second cesarean has a 1.88-fold risk for adhesions at her third cesarean.

The complications related to adhesions are diverse in nature and clinical consequences, varying from emergency reoperations for small bowel obstruction to chronic pelvic pain. In the context of reproduction, pelvic adhesions are also associated with increasing maternal morbidity for subsequent cesarean deliveries, such as bladder injury and/or the need for hysterectomy and increased delivery interval time [17, 125]. However, the association between CS, adhesions, and infertility has been controversial. A recent retrospective cohort study of 224,024 women delivered by CS has provided strong evidence that there is no or only a slight effect of CS on future fertility [130]. The clinical and social circumstances leading to the CS have a greater effect on future fertility than the CS itself. Similarly a population-based

study of 52,498 women has provided further corroboration of previous studies that have reported reduced childbearing subsequent to cesarean section in comparison with vaginal delivery [131]. However, the authors were unable to measure prepregnancy body mass index, weight gain during pregnancy, and prior infertility, which would have been reduced selection bias. Also, it is unclear whether it is more likely that women could not conceive or whether they actively chose to avoid further childbearing.

It appears that adhesion formation may be reduced with closure of the peritoneum and double-layer closure of the uterine incision, although whether this reduction has clinical significance remains uncertain [17]. Uterine adhesions can now be diagnosed during pelvic ultrasound examination. The typical features include fusion of the uterine tissue with surrounding tissue, acute uterine retroflexion, and lack of uterine mobility. Ultrasound features of pelvic adhesions are found in more than a third of women with a history of CS, and they are associated with chronic pelvic pain [132]. Adhesions in the vesicouterine pouch were the most common, and increasing number of CSs (OR 3.4) and a postoperative wound infection (OR 11.7) increase the likelihood of adhesions developing in the anterior pelvic compartment.

Although adhesions might cause several clinical manifestations, they probably are a group of their own. In a prospective study, women were asked to describe their clinical symptoms prior to the next operation and the surgeons which were not aware of the questionnaire results described the amount and location of the adhesions found. No connection was found between the clinical symptoms presented after CS and with the location and amount and severity of adhesions, as found in the subsequent operation [133].

14.6.2.3 CS Defects

Musculature in mammals cannot be functionally repaired and does not heal by regenerating muscle fibers, but by forming "foreign" substances including collagen [125]. The resulting scar tissue is weaker, less elastic, and more prone to injury than the intact muscle. Experiments in mice have indicated that differences in regenerative ability translate into histological, proliferative, and functional differences in biomechanical properties of the scarred myometrium after CS [134]. These results could explain wide individual variations observed in uterine healing after CS (Fig. 14.25).A uterine CS defect (CSD) or "niche" is a tethering of the endometrium that can serve as a reservoir for intermenstrual blood and fluid and can be associated with clinical gynecological symptoms such as postmenstrual spotting and dysmenorrhea [135]. Approximately 30 % of women with a niche report spotting at 6–12 months after their CS. Other reported symptoms in women with a niche are dysmenorrhea, chronic pelvic pain, and dyspareunia. A CSD may range from a small defect of the superficial myometrium (Fig. 14.26) to clear

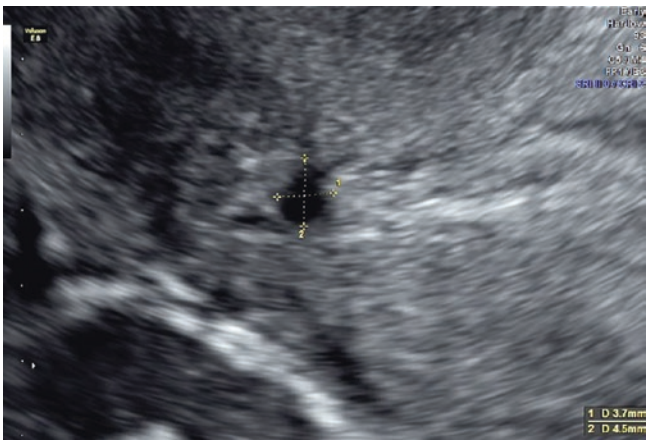


Fig. 14.25 Transvaginal ultrasound view of the of the lower uterine segment in a 7-week pregnant woman 18 months after a previous emergency CS. Note a small scar defect in the superficial myometrium at the junction between the lower segment and the cervix

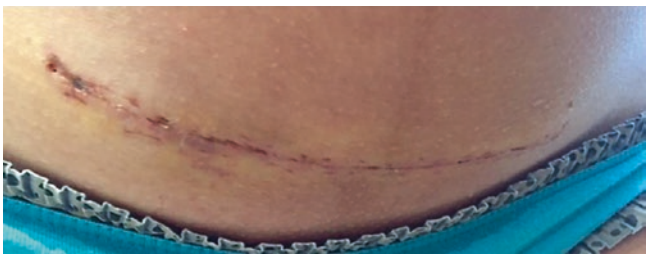


Fig. 14.26 Image of a minor scar dehiscence associated with a skin infection 2 weeks after an emergency CS

loss of substance with a direct communication between the endometrial cavity and the visceral serosa.The relationship between the size of the CSD and the clinical symptoms, uterine position, and number of previous CS has been evaluated in many different studies [136–139]. Possible factors that could play a role in niche development include a very low incision through cervical tissue, inadequate suturing technique during closure of the uterine scar, surgical interventions that increase adhesion formation, or patient-related factors that impair wound healing or increase inflammation or adhesion formation [135].

The main issue of a previous CS scar is the risk of scar deficiency/separation, during the next pregnancy and delivery [140]. This is increased in women with a retroflexed uterus, in those who have undergone multiple CS, and after cesarean delivery in advanced labor [136–139]. A recent retrospective cohort study has shown that uterine scar dehiscence in a previous pregnancy is a potential risk factor for preterm delivery, low birth weight, and peripartum hysterectomy in the following pregnancy [141]. The other and much more serious complications of a previous CS are implantation of clinically detectable pregnancy into a scar (scar ectopic pregnancy) and an abnormally invasive placenta (AIP) or

placenta accreta in a subsequent pregnancy (Chap. 12). Scar ectopic pregnancies are still very rare [142], but the rise in AIP corresponds temporally to rising CS rates with recent US epidemiological studies indicating an overall incidence of PA of 1 in 533 deliveries or an OR of 1.96 after one CS [1, 143]. It has been estimated that if the CS rate continues to rise as it has in recent years, by 2020, there will be an additional 6,236 placentae previae, 4,504 PAs, and 130 maternal deaths annually [144]. As both complications are associated with severe maternal morbidity and significant mortality from very early in pregnancy, an accurate early prenatal diagnosis of this condition is pivotal to avoid catastrophic complications such as uterine rupture, massive vaginal bleeding, and placenta previa/accreta, which might lead to hysterectomy [143]. Uterine scar surgical repair could prevent recurrent cesarean scar ectopic pregnancies [145] and also prevent AIP in subsequent pregnancies, but this concept remains unproven.

14.6.2.4 CS-Induced Disorders of Placentation

The decidual defect following a uterine scar may have an adverse effect on early implantation by creating conditions for preferential attachment of the blastocyst to scar tissue and facilitating abnormally deep invasion of the extravillous trophoblast leading to AIP, but it may also lead to impaired placentation if the uterine tissue around the scar is compromised and does not allow a sufficient blood supply to the placenta. A recent study of the uterine circulation in women with a previous CS has shown that the uterine artery resistance is increased and the volume of uterine blood flow is decreased as a fraction of maternal cardiac output compared to women with a previous vaginal birth [146]. These data suggest a possible relationship between of a poorly vascularized uterine scar area and an increased in the resistance to blood flow in the uterine circulation with a secondary impact on placental implantation.

Large epidemiologic studies have shown that women who have had a previous CS are at increased risk of unexplained stillbirth in the second pregnancy [147, 148]. The etiology behind the higher rates of unexplained stillbirth in subsequent pregnancies after cesarean delivery remains unknown, but it could be explained by the increased prevalence of placenta abruption, which may be, in turn, a consequence of impaired placentation [125].

Epidemiological studies have also indicated that a cesarean delivery is associated with increased risks of placenta previa and abruption in the subsequent pregnancies [36, 149–153]. The risk of previa is higher with increasing number of prior cesarean deliveries [149].

By contrast, the 20 % increased risk of previa associated with prior intrapartum cesarean delivery was found to be not significant. A recent meta-analysis of five cohorts and 11 case-control studies published between 1990 and 2011 has indicated that after a cesarean delivery, the calculated summary odds ratios (OR) are 1.47 for placenta previa and 1.38 for placental abruption [151]. The increased incidence of placenta previa and placenta abruption after a previous CS supports the concept of a biological dysfunction of the lower-segment myometrium secondary to damage of the corresponding uterine area by previous lower-segment CS scar [125].

Conclusion

The aim of this chapter was not just to summarize possible complications, but also to explain our vision toward a reduction in the rate of CS complications by providing insights into the physiology of the late pregnancy, hence the understanding when is the most optimal time to perform the operation, and by introduction of the most reasonable way to conduct the surgery which is based on evidence resulting from several comparative studies. Any CS should follow a solid indication, and in case there is one, a predelivery CS should be avoided unless in an emergency. It is important that the physiological changes occurring to the mother following CS will be as similar as possible to those happening in natural childbirth.

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Postpartum Hemorrhage (PPH) Medical Treatment

15

Rosales-Ortiz Sergio and Ayala Mendez José Antonio

15.1 Introduction

During birth and once the placenta is separated from the uterine wall, a sequence of physiological events occurs in order to quell bleeding from the placental bed; these are changes in myometrial contracture mediated by oxytocin (Fig. 15.1a–d), the most potent endogenous uterotonic as well as hemostatic phenomena. Myometrial contraction occludes blood passage through the blood vessels of the placental bed; it increases platelet activity and the release of coagulation factors while simultaneously fostering fibrinolytic activity; therefore, current management of obstetric hemorrhage includes the complementary use of blood derivatives and antifibrinolytics [1–4].

15.2 Maternal Death and Postpartum Hemorrhage Relevance

Maternal death and postpartum hemorrhage (PPH) management remain controversial subjects in the obstetrician's daily practice and throughout the world. In spite of worldwide efforts coordinated by the WHO, the time period allotted to major coordinated activities that would promote human and social development, "The Millennium Declaration," concluded in 2015. This Declaration included a set of eight objectives with the purpose of fighting extreme poverty and promoting human and social development, based on statistical data obtained during the 1990s; it was launched in the year 2000 with the signature of governments, specialized agencies, civil society, and various worldwide sponsors and was to be completed in the year 2015 (Fig. 15.2).

Specifically, the fifth objective referred to a 75 % decrease in maternal deaths based on the maternal mortality ratio (MMR). The MMR is a strong social marker reflecting women's life conditions, the degree of population development, and the level of health system organization [5–7].

MMR analysis did reveal a significant decrease in maternal deaths, from 532,000 in 1990 to 303,000 in 2015, approximately a 43 % decrease [8, 9]. However, this decline was not sufficient to fulfill the millennium's objective and led to the creation of the "Sustainable Development Goals" agenda whose purpose is to decrease world MMR to under 70 maternal deaths/100,000 live births (LB) between 2016 and 2030.

Not fulfilling the millennium's objective is due to the great and persistent difference between various world regions, ranging from over 1000 maternal deaths per 100,000 LB in some developing countries to less than 10 per 100,000 LB in developed countries; hence, a woman's estimated risk of death due to pregnancy and postpartum complications in high-income countries is 1 in 3,400 compared to 1 in 52 in low-income countries. In summary, 830 daily maternal deaths were recorded in 2015 due to pregnancy and delivery complications, 550 of which occurred in the sub-Saharan region of Africa and 180 in southern Asia; five maternal deaths were reported in developed countries, confirming a 33-fold increased risk of dying in underdeveloped, low-income countries, where 99 % of deaths occurred.

The programmed global MMR should have decreased 5 % annually in order to reach the planned MMR in the year 2015, but its drop was 1.2 % per year, between 1990 and 2000, and 3 % per year between 2000 and 2015, a difference hinging on each government's and society's efforts to implement public policies that would further better health development since the impact of maternal death is reflected in the family's, the community's, and the society's structure. But most disturbing is the fact that most could have been

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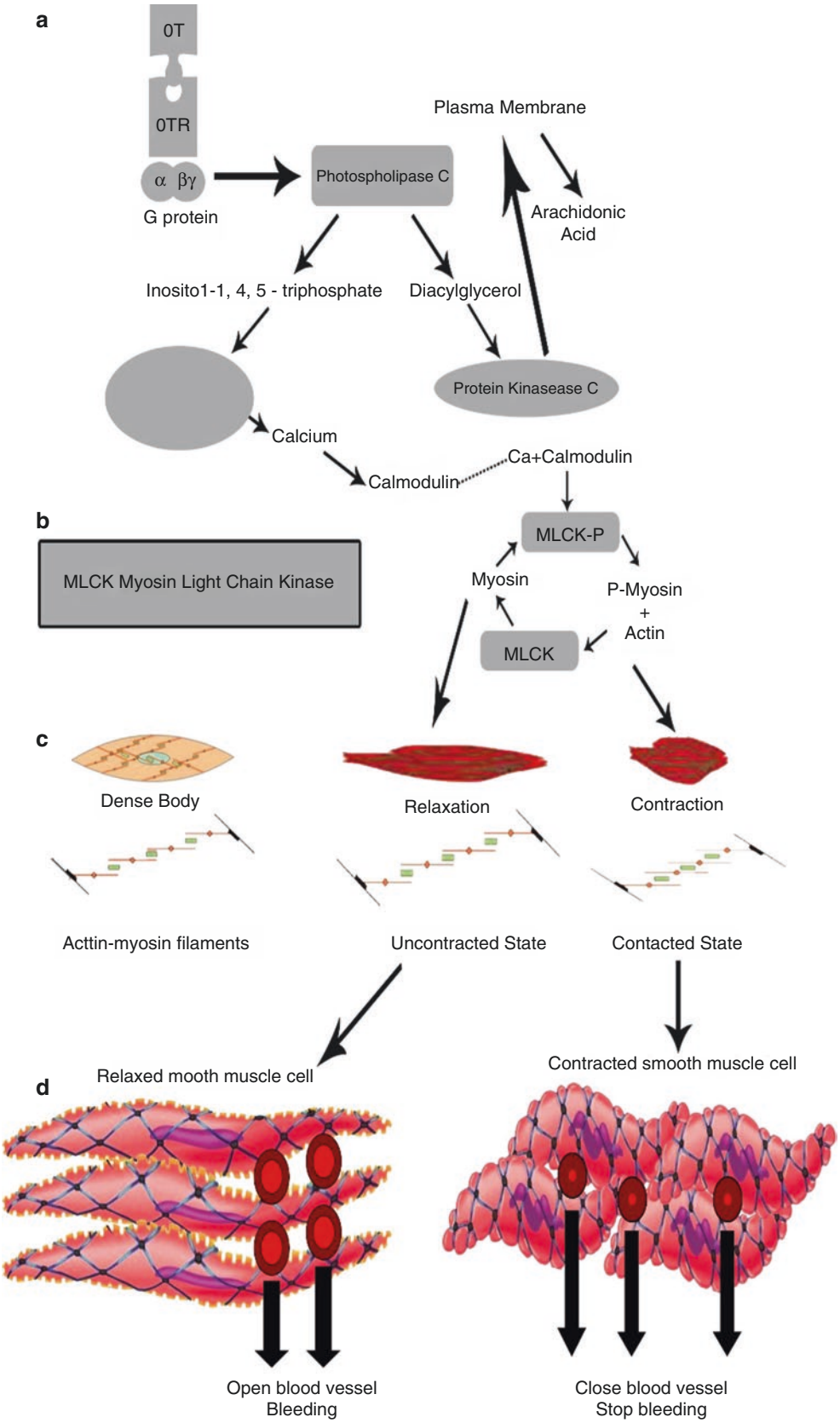


Fig. 15.1 (**a**) After activation of oxytocin receptor, phospholipase C, release intracellular calcium true inositol 1,4,5 triphosphate, who act in sarcoplasmic reticulum releasing calcium. And by the diacylglycerol who act in plasma membrane in two ways: opening calcium channels allowing the entry of extracellular calcium in to the cell and releasing arachidonic acid. (**b**) The union between calmodulin and calcium with MLCK to act in smooth muscle. (**c**) Representation of actin-myosin filaments under the action of MLCK in relaxation and contraction smooth muscle. (**d**) Mechanical mechanism to control the PPH: when the smooth muscle is relaxed, there is blood vessel bleeding, but when the smooth muscle was contracted, it occludes the blood vessels and stops the bleeding

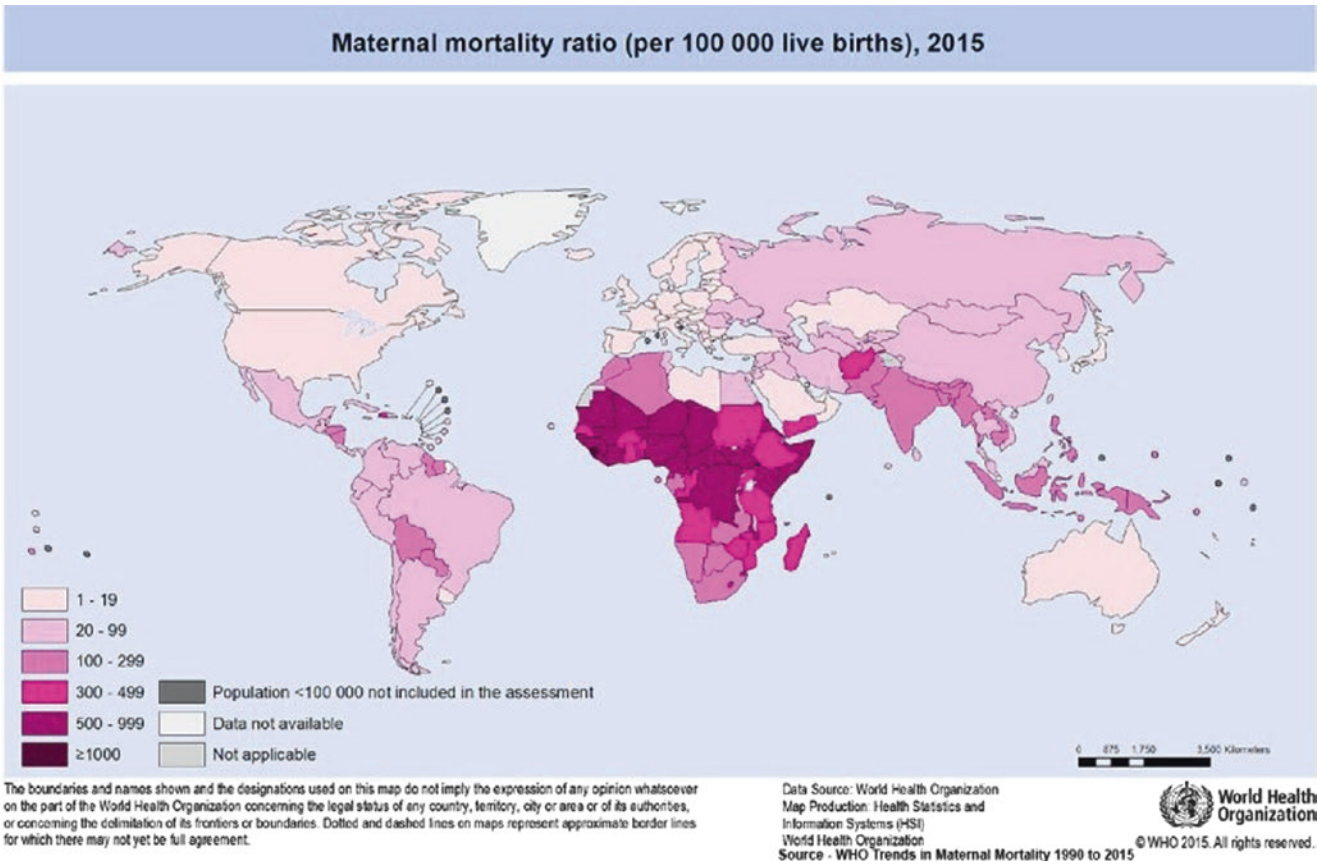


Fig. 15.2 Maternal mortality ratio (per 100,000 live births), 2015

prevented. We must underscore the fact that PPH recurrence can be modified if we count with appropriate health resources, access to health care, and the timely use of uterotonics.

Although a relevant facet of PPH is maternal death, another important aspect is its associated morbidity, including anemia, disseminated intravascular coagulation, the need for blood transfusions, hysterectomy, kidney, and liver failure [10, 11]. Based on these complications, the WHO conducted a survey evaluating PPH, its risks, and maternal outcomes [12]. In a total group of 274,985 women treated in 28 countries, 1.2 % developed PPH, 95 % required prophylactic uterotonics, 35 % required more than one tocolytic, a third was transfused, a fourth required antibiotics, and 17 % of births were associated to severe maternal outcomes (SMO): 14.5 % were classified as near misses due to the development of some form of organic failure, and 3.1 % resulted in maternal death [12].

Every year, 120 million women bear a child, and among these, approximately 12 million will develop PPH: about 200,000 will die and 60 million women will develop a complication leading to some form of medium- or long-term disability in 15–20 million cases. Thus, for every maternal death, 20–30 women will harbor some form of disability [13].

Based on these survey results, the WHO concluded that uterotonic use should be preventive and therapeutic in PPH and should be recommended in all treatment guidelines and obstetric care centers.

15.3 Risk Factors

PPH prevention requires the identification of associated risk factors, but this is only possible in a third of cases.

The described associated risk factors include a past history of PPH (15 % increase in risk) [14, 15], nulliparity [14, 16, 17], uterine overdistension due to fetal causes (OR 1.9, 95 % CI 1.6–2.4) and fluid or tumors [14, 15, 18–20], placental abnormalities such as placenta previa and/or accreta [21], coagulation abnormalities [15, 22], anemia [16, 22], labor induction (OR 1.4, 95 % CI 1.1–1.7), prolonged expulsive phase (OR 1.4, 95 % CI 1.2–1.7), the use of epidural analgesia, retention of placental fragments (OR 3.5, 95 % CI

2.1–5.8), lack of labor progression (OR 3.4, 95 % CI 2.4–4.7), placental morbidity (OR 3.3, 95 % CI 1.7–6.4), lacerations (OR 2.4, 95 % CI 2.0–2.8), instrumented delivery (OR 2.3, 95 % CI 1.6–3.4), hypertensive disorder (OR 1.7, 95 % CI 1.2–2.1), obesity, multiparity, uterine infection, and uterine inversion [20].

Whether any risk factor is predictive of non-response to conventional uterotonic treatment remains unknown [12]. Logistic regression analysis was conducted in an attempt to predict PPH according to the described risk factors, and an increased risk was established for the following variables: age above 35 years (OR 1.42; 95 % CI 1.26–1.60), nulliparity (OR 1.12; 95 % CI 1.01–1.25), parity ≥3 (OR 1.32; 95 % CI 1.09–1.59), gestational age at birth <37 weeks or >41 weeks versus 37–41 weeks (ORs 2.63; 95 % CI 2.28–3.04 and 1.56; 95 % CI 1.02–2.38, respectively), labor induction (OR 1.55; 95 % CI 1.20–2.00), cesarean section (OR 1.46; 95 % CI 1.20–1.79), and residence in the Middle East compared to Africa (OR 1.79; 95 % CI 1.20–2.67, 12). Obstetric hemorrhage remains one of the main causes of worldwide morbidity and mortality, in both developed and developing countries. Hemorrhage before delivery occurs in approximately 6 % of pregnancies, and in half of these cases, its cause is unknown and may lead to postpartum hemorrhage. Postpartum hemorrhage will occur around 10 % of all pregnancies and results from one basic process or the combination of four, known as the four "Ts": uterine atony (tone), placental retention (tissue), genital tract injury (trauma), and coagulation disorders (thrombin) [23].

15.4 Postpartum Hemorrhage Management

Postpartum hemorrhage is defined as the loss of 500 mL or more of blood after delivery or within the first 24 h or the loss of 1,000 mL during a cesarean section [24]; severe postpartum hemorrhage refers to a blood loss greater than 1,000 mL during delivery or cesarean section [25]. PPH has specifically increased in the last decade, ranging between 0.3 and 3.8 % in Africa, 0.7–2.7 % in Asia, and 1.7–5.5 % in Europe [26].

The incidence of PPH could be substantially decreased with the use of prophylactic uterotonics during the third phase of labor if managed in a timely manner [19, 27, 28]. Hence, the active management of the third stage of labor (AMTSL) is pivotal to the decrease in postpartum hemorrhage and should be included in government-sponsored strategies worldwide (Fig. 15.3). It decreases the risk of hemorrhages >500 mL (RR 0.34, 95 % CI 0.27–0.44), the need for maternal transfusion (RR 0.34, 95 % CI 0.22–0.55), and average blood loss by 79 mL or less [29].

AMTSL basically encompasses three elements: the administration of a uterotonic immediately after the delivery of the newborn, controlled traction of the umbilical cord for placental delivery, and early clamping of the umbilical cord. These elements have changed since first proposed as a result of evidence-based findings.

Massage of the uterine fundus after delivery is also often included although the WHO does not consistently recommend it in women who have received oxytocin; however, certification of the uterine tone by abdominal palpation of the uterine fundus is essential to the identification of uterine atony. Early clamping of the umbilical cord has tended to disappear as a result of the positive effects of late clamping on the newborn [30]. However, a recent meta-analysis publish by Heidi Al-Wassia (JAMA Pediatr 2015;169:18) showed that milking the cord has the same effect as delayed cord clamping.

A multicenter study conducted by the WHO and published in 2012 [31] demonstrated that controlled cord traction (CCT) does not significantly reduce hemorrhage and characterizes this measure as optional and it is not included as a recommendation in the last WHO guidelines [33]; however, CCT is the first-choice intervention in the management of placental retention. In accordance with this information, the most important tool in the management of AMTSL in PPH is the use of uterotonics (oxytocin) both prophylactically and therapeutically.

There are many alternatives to the use of uterotonics in the prevention of PPH, but the WHO recommends oxytocin as the gold standard followed by misoprostol and ergot derivatives if oxytocin is unavailable; but its use should not be generalized due to its adverse effects, and in the case of cesarean sections, oxytocin is preferably administered via the intravenous or intramuscular route. The use of carbetocin, an oxytocin analogue, is associated to a decrease in the need for rescue uterotonics and also complements treatment with tranexamic acid, fibrinogen, etc. After an early diagnosis of PPH, uterine massage should be initiated as well as volume replacement with crystalloids and blood products [20, 29].

If bleeding continues, the uterus should be packed with compresses, intrauterine balloons, or inflated condoms or glove. Alternatively the uterine arteries can be embolized if the needed resources are available and/or followed by surgical procedures.

15.5 Uterotonic Drugs

Based on the fact that uterine atony is the main cause of obstetric hemorrhage, uterotonics are the first-line therapy and should be used prophylactically and in the management

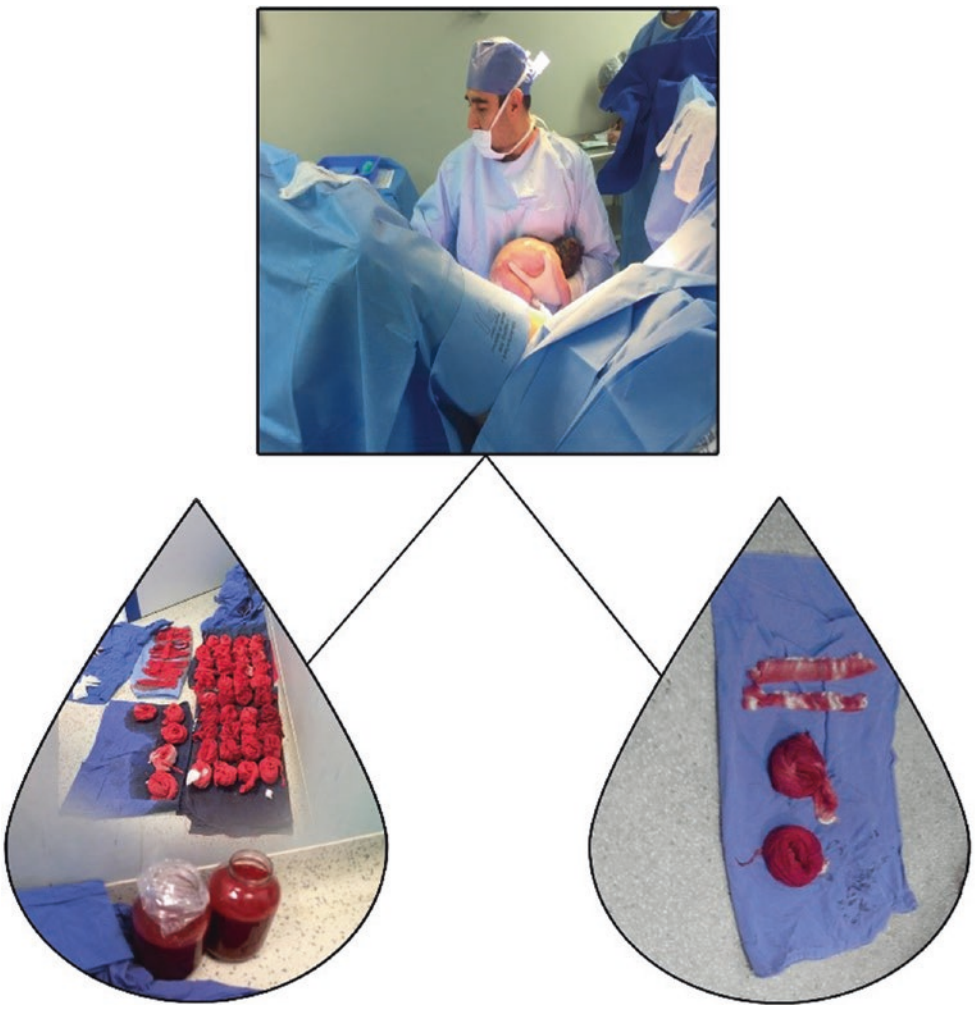


Fig. 15.3 The implementation of AMTSL is one of the best medical interventions, by one side reduces the blood bleeding after delivery and the other side reduces the cost due to less resources used, like uterotonic agents, solution, blood products, recovery time, and surgical interventions, among others

of active hemorrhaging. The questions that usually arise in terms of all existing drugs are: What is the sequence to follow when using uterotonics? When should I use them and how long should I evaluate their effects?

The answer to these questions requires full knowledge of the drugs, their side effects, and their specific use, so no strict sequence can be proposed. Clinical practice guidelines recommend the use of uterotonics during AMTSL and if active hemorrhage is present, as soon as possible; depending on the drug used, continuous evaluation of the response to the uterotonic or uterotonics is needed since the pharmacological response or lack thereof must be determined within the first 30 min after administration; if there is no response, the appropriate measures must be taken to restore the lost volume, request the necessary support, and determine the adequate invasive management in a timely manner.

Worldwide pharmacology includes the following drugs.

15.6 Oxytocin

It is a nonapeptide with eight different amino acids (Figs. 15.4 and 15.5) that act on myometrial receptors and promote uterine contractility; it is perhaps the most frequently used uterotonic, and it is the first-choice drug in many clinical practice guidelines, including the WHO's [32]. There are close to 2013 systematic reviews supporting its use [32]. Its peak action occurs 1 min after administration, but its half-life is very short, between 3 and 5 min, so it requires continuous and well-monitored infusion.

Usually administered as an infusion, it may require a dosage increase. One can begin with 40 units in 1 L of isotonic saline IV or 10 units IM (including the intra-myometrial route). The half-life of oxytocin is 1–5 min so the uterine tone must be continually monitored during the infusion; if it does not respond, 10–20 U may be added

without exceeding 800 units in 500 mL over 30 min [33–35], since a rapid oxytocin bolus may lead to peripheral vasodilation, an increase in cardiac output, tachycardia, and hypotension. Myocardial ischemia has also been reported which is why a slowly administered bolus is recommended [36, 37].

If there is no response, other rescue uterotonics may be used such as methylergonovine, prostaglandins, and even carbetocin. This last drug can only be administered once the oxytocin infusion is stopped in order to free the myometrial receptors and allow it to act as an oxytocin analogue.

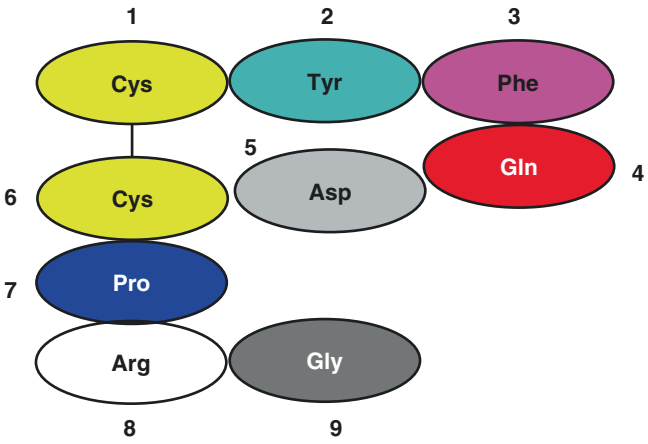


Fig. 15.4 Oxytocin conformation with nine amino acids (each one per circle) but are only eight different amino acids (each amino acid with a different color, Cys is the only repeated amino acid in the sequence)

15.7 Ergot Derivatives (Ergonovine, Methylergonovine, Ergometrine)

Their use was described in 1532 (*Claviceps purpurea*) but was in reality purified from rye in 1932 by Mooir and Dale (Fig. 15.6a, b) that described their mechanism of action on adrenergic receptors and calcium channels, their interaction with actin-myosin, and, hence, their systemic effect on smooth muscle. A 2007 systematic review demonstrated the advantages of their use compared to not using uterotonic drugs [38].

They are frequently used as oxytocin rescue drugs, although they can be a rescue drug for any other uterotonic as long as there are no contraindications.

The recommended administration route is intramuscular or directly into the myometrium; the intravenous route is not currently recommended. The recommended methylergonovine dose is 0.2 mg IM, and it can be repeated every 2–4 h; it leads to strong and sustained myometrial contraction (uterine tetany). If there is no response to the first dose, one must decide whether to switch to a different uterotonic. It may also lead to alpha-adrenergic activity, particularly vasoconstriction, and is thus contraindicated in patients with pregnancy-associated hypertensive states, a previous history of myocardial ischemia, pulmonary hypertension, Raynaud's phenomenon, scleroderma, or a history of migraine headaches [20].

Compared to placebo, it decreases bleeding by an average of 83 mL and limits bleeding to <500 mL (RR 0.38, 95 % CI 0.21–0.69). In spite of its protective effect when compared to

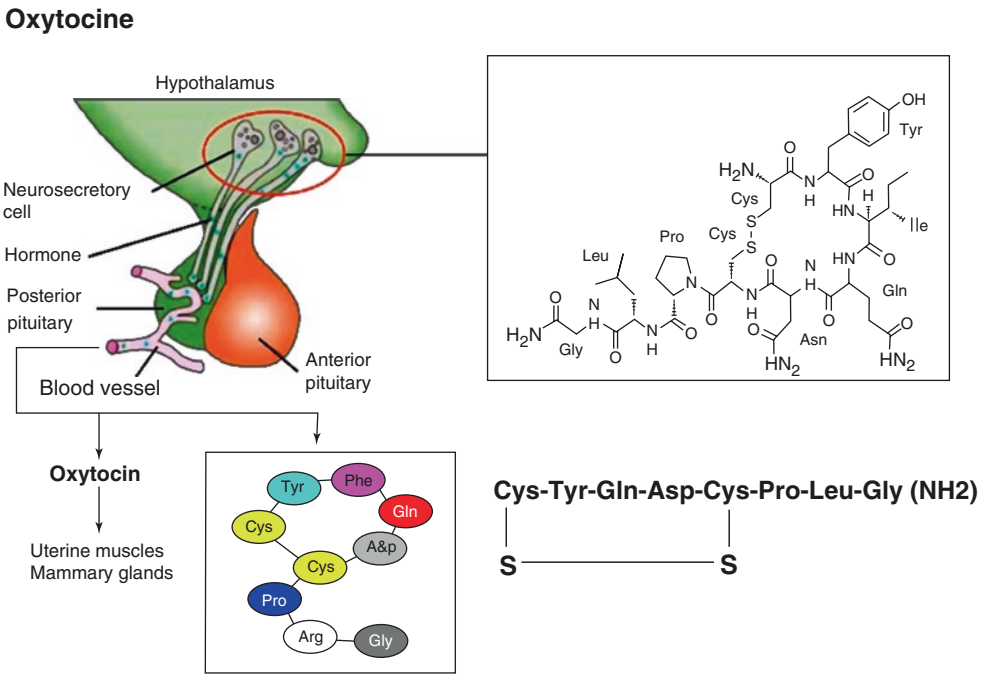


Fig. 15.5 Oxytocin natural release and three different types of molecular formula

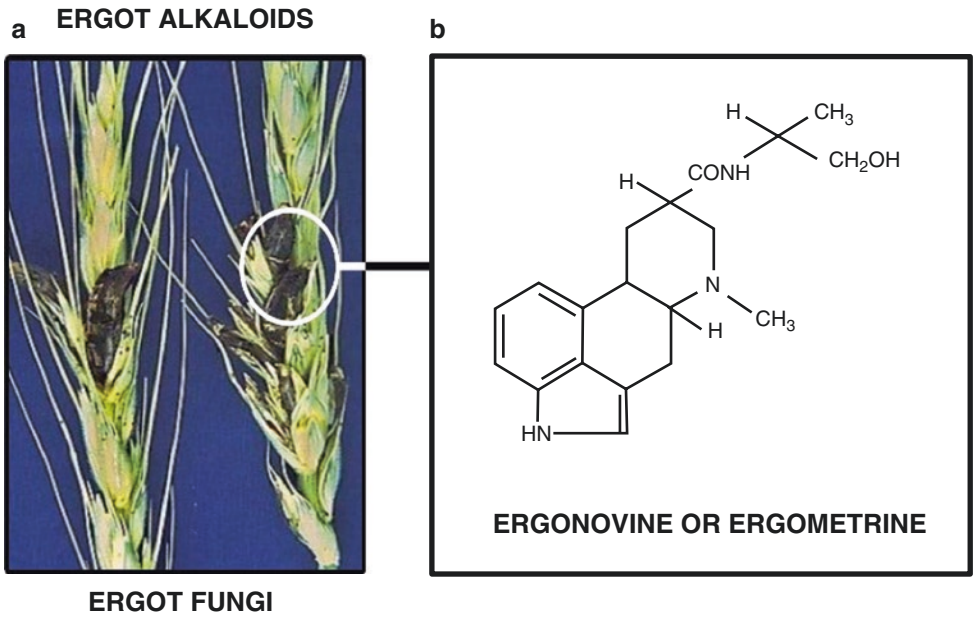


Fig. 15.6 (**a**) An image of Ergot fungi in natural form. (**b**) Ergonovine chemical formula

oxytocin, it did not prove to better prevent postpartum hemorrhage (RR 0.76, 95 % CI 0.61–0.94) [20].

15.8 Syntometrine

This is a drug combining oxytocin's rapid action and the sustained and more prolonged effect of ergonovine and can therefore provide both benefits; it is unfortunately not available in many countries (Fig.15.7).

It is presented as 5 U oxytocin and 0.5 mg ergometrine, for intramuscular or intravenous administration. Its use does not significantly decrease the risk of PPH between 500 and 1,000 mL compared to oxytocin alone (OR 0.82, 95 % CI 0.71–0.95) [39]. It has the same side effects as each individual drug, and these tend to be more frequent when administered intravenously, particularly nausea, vomiting, and hypertension.

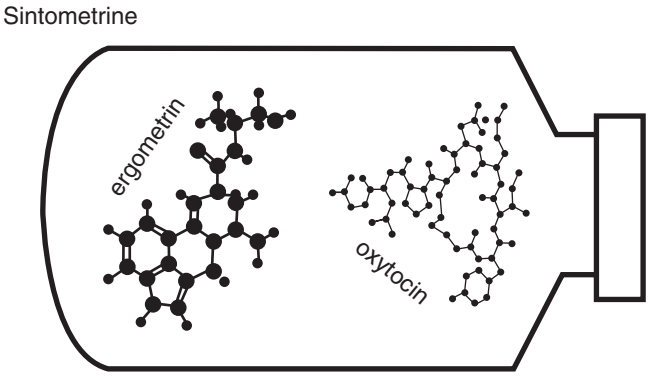


Fig. 15.7 Syntometrine representation, a vial with oxytocin and ergometrine

15.9 Prostaglandins, (Misoprostol, Carboprost, Dinoprostone)

The name *prostaglandin* derives from the prostate gland. When prostaglandins were isolated for the first time from seminal fluid in 1935 by the Swedish physiologist Ulf Von Euler, it was later shown that many other tissues secrete prostaglandins for various functions. The first total syntheses of prostaglandin F2-alpha and E2 were reported by E. J. Corey in 1969.

One of a number of hormonelike substances participates in a wide range of body functions such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, and the modulation of inflammation. Prostaglandins are derived from a chemical called arachidonic acid (Fig. 15.8).

Specific prostaglandins are named with a letter (which indicates the type of ring structure) followed by a number (which indicates the number of double bonds in the hydrocarbon structure). For example, prostaglandin E1 is abbreviated PGE1 or PGE_1, and prostaglandin I2 is abbreviated PGI2 or PGI_2.

Misoprostol (PGE1) (Fig. 15.9) is a drug that has slowly gained acceptance in the field of obstetric hemorrhage treatment; it is useful in decreasing PPH but is particularly recommended when an injectable uterotonic is unavailable or is contraindicated. There is no statistically strong evidence proving that misoprostol is more effective than other injectable uterotonics as first-line PPH therapy [38].

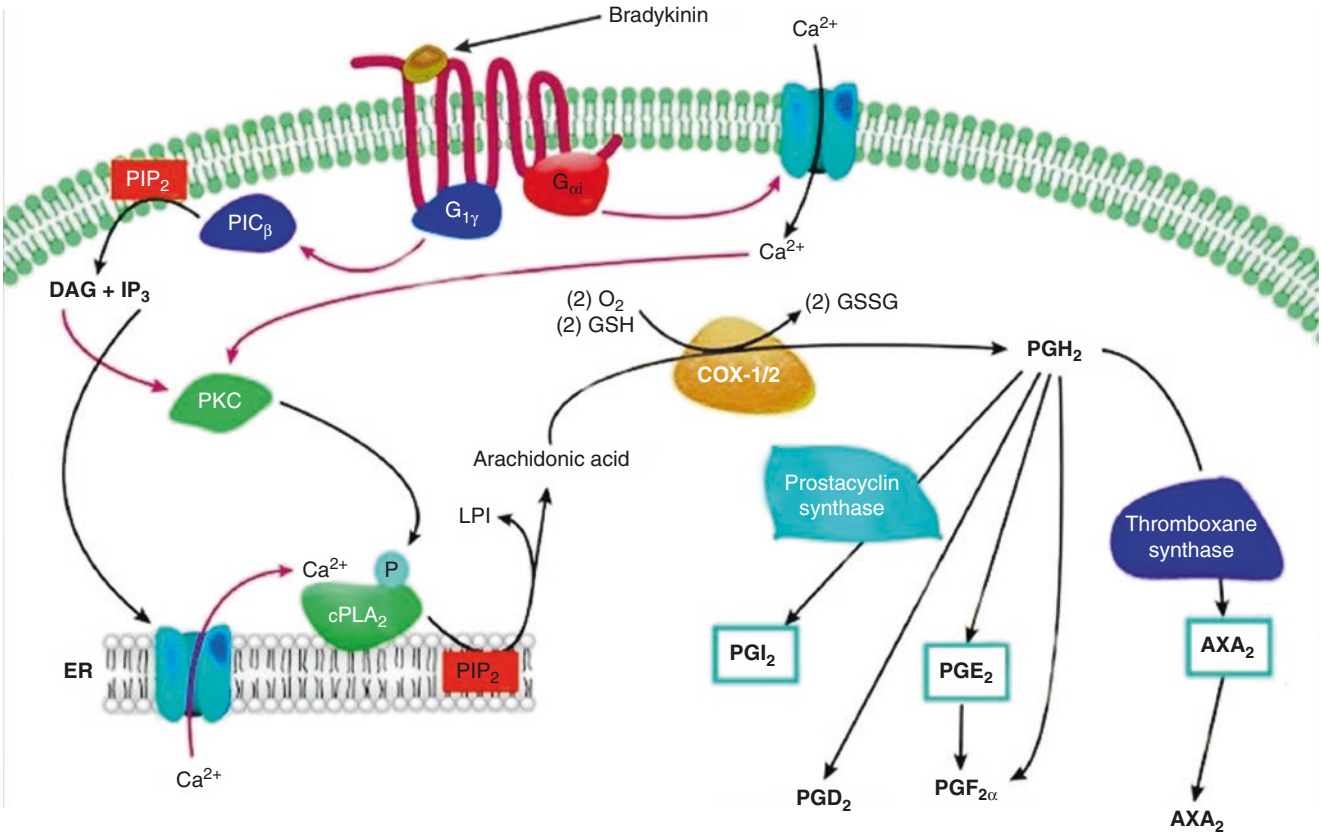
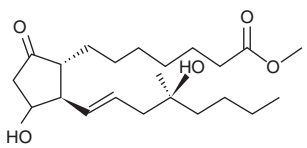


Fig. 15.8 Prostaglandin biosynthesis, an intermediate arachidonic acid is created from diacylglycerol via phospholipase A2 and then brought to either the cyclooxygenase pathway. This pathway produces thromboxane, prostacyclin, and prostaglandins D, E, and F



MISOPROSTOL
PGE1

Fig. 15.9 Misoprostol chemical formula

The ideal dosage and administration route are still uncertain, but the WHO recommends a dose of 800 mcg sublingually, although several systematic reviews recommend 400 mcg sublingually; it is rapidly absorbed, with a peak concentration after 30 min, and its duration is approximately 3 h. Compared to placebo, sublingual administration decreases PPH >1,000 mL (RR 0.31, 95 % CI 0.10–0.94), but compared to injectable uterotonics, no statistical benefit was established [40].

Since the oral route leads to first-pass hepatic metabolism, its duration will be lower than if administered sublingually, absorption is rapid, peak activity is also 30 min, but circulating levels and activity duration decrease to approximately 2 h [39]. Compared to other injectable uterotonics, its use reportedly leads to a greater risk of severe postpartum hemorrhage (RR 1.33, 95 % CI 1.16–1.52).

Rectal administration leads to slower absorption than if oral or sublingual routes are used; maximum peak action is approximately an hour but it can exert its effect for up to 4 h [39]. When comparing this route with injectable uterotonics, it had no favorable effect on severe PPH (RR 1.10, 95 % CI 0.69–1.77) [34, 41].

The vaginal route is not recommended due to the active bleeding that prevents the tablets from being absorbed.

Side effects such as hyperthermia (>39 °C) have been reported with dosages above 400 mcg, the dose that appears to be associated to the least number of adverse events. Fever develops in 45 % of patients treated with a dose of 600 mcg.

Dinoprostone (PGE2) 20 mg in suppository presentation may be an alternative among the rectally administered prostaglandins, and the dose can be repeated every 2 h [41] (Fig. 15.10).

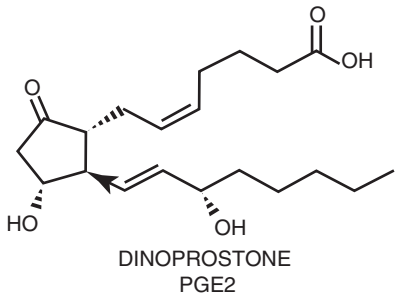


Fig. 15.10 Dinoprostone chemical formula

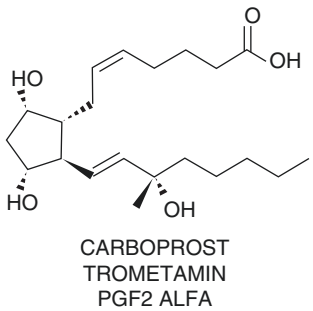


Fig. 15.11 Carboprost tromethamine chemical formula

Carboprost tromethamine (15 methyl-PGF2 alpha, Hemabate) is a methylated analogue of prostaglandin F2 alpha (Fig. 15.11).

It is mainly administered via the intramuscular route but that can also be administered directly in the myometrium or transabdominally; it is injected into the myometrium with or without ultrasound guidance and/or vaginally.

The dosage is 250 mg and can be repeated every 15–30 min, without exceeding 2 mg (eight doses) since it may cause bronchospasm. Two thirds of patients will respond to the first and/or second dose, but if no favorable response is observed after the second dose, the use of another drug should be considered.

It is contraindicated in patients with asthma or respiratory failure. Secondary effects include nausea, vomiting, diarrhea, fever, and flushing [41].

15.10 Carbetocin

This is an oxytocin analogue (Fig. 15.12) that acts on the myometrium's oxytocin membrane receptors, but due to the modifications in the original oxytocin molecular structure, it has greater receptor affinity, it is more slowly degraded, and its effect is evident 1 min after administration with a maximum peak of 3 min and a duration of 45 min [42, 43] (Fig. 15.13).

Since its profile is similar to oxytocin, it is well tolerated and has the same side effects as oxytocin. It has two

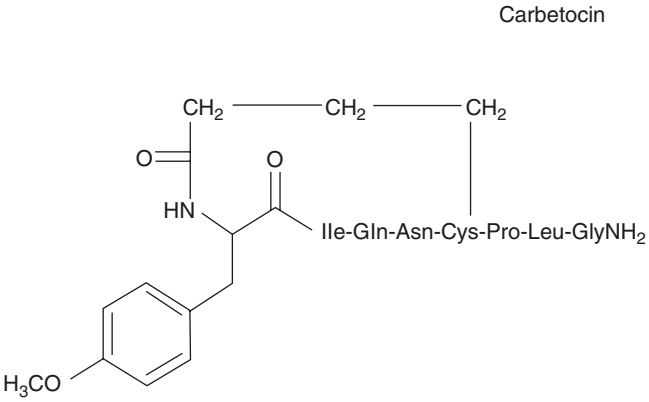


Fig. 15.12 Carbetocin chemical formula

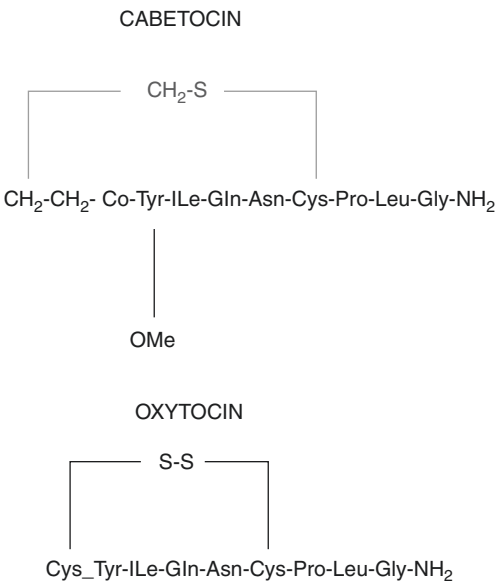


Fig. 15.13 Differences between carbetocin and oxytocin molecule. (*1*) The amino group (NH2) in cysteine has been replaced with a hydrogen atom. (*2*) The disulfide bond has been changed to a thioether bond (CH2S). (*3*) The hydroxyl group (OH) of tyrosine has been substituted by a methyl ether group. These alterations confer more resistant to aminopeptidase (no NH2 group in cysteine) and disulphidase (no disulfide bridge) cleavage and therefore reduce the chance of enzymatic degradation and prolong the half-life of the peptide, thus extending its pharmacological action

mechanisms of action: after binding to the receptor, it activates phospholipase C, yielding diacylglycerol that in turn activates the membrane calcium channels allowing its passage into the intracellular space; likewise, it also activates inositol triphosphate that in turn acts on the sarcoplasmic reticulum releasing calcium. Through both pathways, the cell will have sufficient calcium to trigger a longer and sustained contraction. The sustained contraction also has a greater amplitude and frequency leading to intravascular thrombosis and the formation of a stable clot in the placental bed.

A 100 mcg intravenous injection is administered as a single bolus, without diluting; if there is no effect on the uterine

tone, a second dose should not be administered without first considering a different intervention.

It is indicated in the treatment of PPH. In 2012, the Cochrane Library compared its effect with oxytocin and reported prophylactic benefits in cesarean sections (RR 0.66, 95 % CI 0.42–1.06) but none in vaginal deliveries (RR 0.95, 95 % CI 0.43–2.09); it proved beneficial when a rescue uterotonic was warranted in cesarean sections (RR 0.64, 95 % CI 0.51–0.81) and also decreased the need for uterine massage in cesarean sections (RR 0.64, 95 % CI 0.31–0.53) and vaginal deliveries (RR 0.70, 95% CI 0.51–0.94) [32].

In terms of its prophylactic use, Rosales-Ortiz reported a decrease in bleeding during delivery in women with full-term pregnancies and at least one PPH-associated risk factor (RR 0.67, 95 % CI 0.54–0.83) and a number needed to treat using carbetocin versus oxytocin (NNT 14, 95 % CI 8–37) [44]. In patients delivering vaginally and an associated PPH risk factor, Boucher reported decreased bleeding [45].

The use of uterotonic drugs is pivotal to the control of PPH, but volume management and replacement with fluids and blood product transfusions are indispensable to ensure appropriate tissue perfusion and oxygenation and allow hemostatic factors to form a clot on the placental bed; the use of antifibrinolytic agents also plays a relevant role.

15.11 Tranexamic Acid

This is an antifibrinolytic drug that acts by blocking the binding sites of lysine with plasminogen molecules, thus improving hemostasis by inhibiting fibrinolysis and decreasing bleeding (Fig. 15.14).

Tranexamic acid is used in the prevention and treatment of hemorrhage. It hinders the progression of severe PPH and decreases the need for transfusions as well as that of hemostatic agents and invasive procedures; this is particularly relevant in life-threatening cases of PPH.

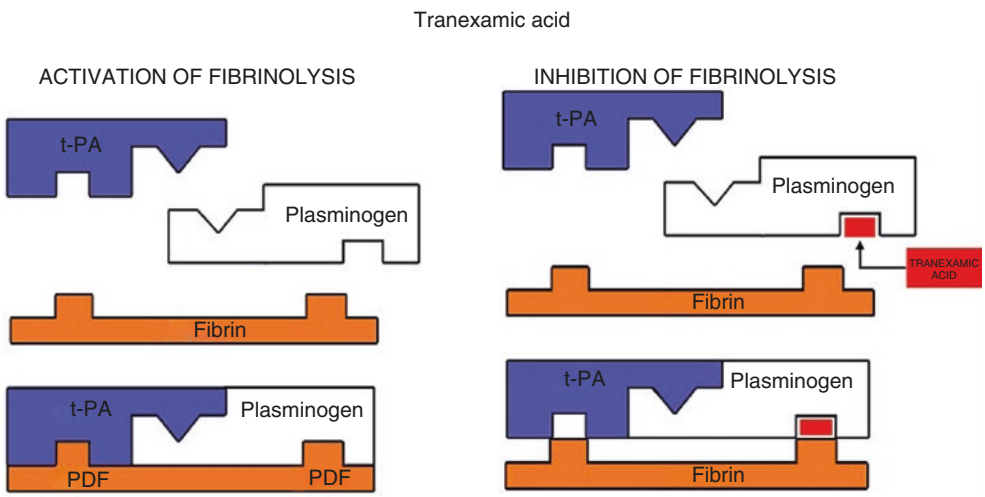
Four grams are administered in 50 mL saline solution IV over 1 h, followed by a maintenance infusion of 1 g/h for 6 h. Its plasma half-life is 2 h and its effects last over 24 h.

The prophylactic administration of tranexamic acid is associated to a decrease in the incidence of PPH (OR 0.32; 95 % CI 0.17–0.59; $p = 0.0006$), decreased bleeding from 149.1 ml (95 % CI 112.9–185.2; $p < 0.00001$) to 400–500 mL (RR 0.52, 95 % CI 0.42–0.63) a decreased need for transfusions (OR 0.28; 95 % CI 0.15–0.49; $p < 0.00001$), as well as a decreased need for additional uterotonic agents [46]; in cesarean sections, it also decreases bleeding during and after surgery [47]. The Cochrane Library concluded that it decreased the incidence in bleeding above 1,000 mL in this group of patients (RR 0.28, 95 % CI 0.23–0.78) [41].

Adverse effects depend on the patient's potential risk for thrombotic events, particularly in cases with a positive history of thrombosis and in pregnant women. The results of systematic reviews suggest that there is no increased risk of myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolism [48].

The TRAAP study's conclusion established that it can be used within 2 min after birth and also after uterotonic administration as complementary treatment acting on the coagulation cascade [49].

Crystalloid isotonic solutions are initially recommended; blood components must also be replaced with red blood cells, platelets, plasma, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate, and/or recombinant factor VIIa.



T-PA Activator of tisular plasminogen
PDF Products of fibrin degradation

Fig. 15.14 Tranexamic acid blocking plasminogen sites inhibiting fibrinolysis

15.12 Recombinant Factor VIIa (rFVIIa)

Due to its relevance in the management of hemorrhage, it is analyzed as part of the pharmacological arsenal, although it is more closely associated to treatment based on blood products. It is used to control hemorrhage in certain circumstances, including that secondary to postpartum atony (Fig. 15.15).

This treatment modality is extremely costly when correcting PPH coagulopathy. Its use is also controversial: Bonnet

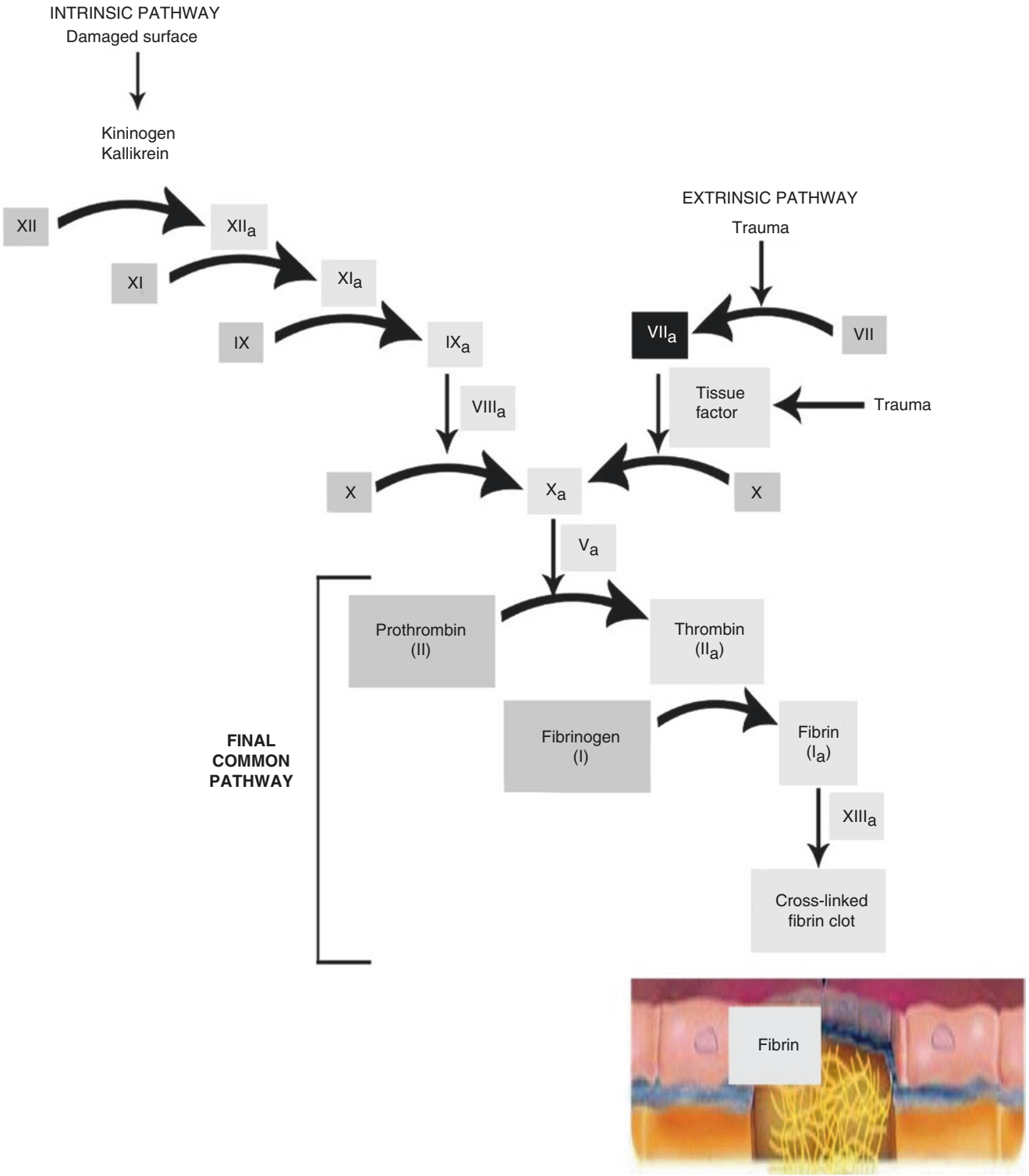


Fig. 15.15 The coagulation cascade, intrinsic and extrinsic pathway. In *black square* we see the fVIIa and its the action place of rFVIIa

and Basso [50] concluded that it is effective in 85 % of patients but also leads to thrombotic complications in 2.5 % of cases. Ahonen [51] agrees with the fact that it decreases blood loss.

rFVIIa is recommended in patients who do not respond to oxytocin, at a dose of 60 mcg/kg; it also decreases the need for complementary invasive procedures such as hysterectomy, uterine artery embolization, or arterial ligation [52] and patients required less transfusions and has less absolute need for blood products.

It is particularly recommended in PPH-associated coagulopathy that does not respond to the usual treatment. The optimal dose is unknown, but it is used as a bolus of 16.7–120 mcg/kg, and in PPH, the suggested dose is 40–90 mcg; the drug should be initiated at low doses to decrease the risk of thrombosis, but it can be repeated every 15–30 min if there is no immediate response [53].

For increased effectiveness, rFVIIa requires the presence of other coagulation factors, normal patient pH and temperature, a platelet count >50,000/mm^3, and fibrinogen levels >50–100 mg/dL. The concomitant administration of fibrinogen and platelets is essential to obtain maximum benefits [54].

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Postpartum Hemorrhage: Mechanical and Surgical Treatment

16

Yakov G. Zhukovskiy, Olga F. Serova, and Sergey V. Barinov

16.1 Introduction

Postpartum hemorrhage (PPH) is regarded as the most dangerous complication of pregnancy for the mother. It is well known that among all obstetric emergencies, PPH has the shortest estimated time to death without proper medical assistance – 2 h only – which means that delay in recognizing the condition and initiating appropriate PPH treatment is the crucial factor leading to adverse outcomes [1].

PPH is not a diagnosis per se, but rather a symptom of multiple postpartum uterine hemostasis disorders where obstetricians cannot determine the cause of complication at once while observing vaginal bleeding. When the clinician recognizes this tense and uncertain situation requiring at the same time immediate action, the only correct, practically proven response necessitates aggressive and vigorous execution of sequential interventions for PPH management without further reflection and hesitation.

Selecting the best and most effective tools and techniques toward treatment is clearly of paramount importance. However, we should not underestimate the significance of adhering to the strict time schedule for implementation of each method and transition to the next one in case of the lack of effect. Armed with the treatment methods of proven validity and powerful instruments, the clinician should know the time point since the onset of PPH for using each one of them, the time span for evaluating its efficacy, and the next treatment step to take in case the time period set for using the previous method runs out [2].

Hence the leading guide for the clinician applying a certain sequence of interventions is not the blood loss volume or the search for PPH cause, but rather the time factor, which is absolutely essential. To avert the fatal outcome, we should proceed to hysterectomy after exhausting the whole treatment armamentarium in accordance with the clearly preestablished time points, simultaneously eschewing massive blood loss.

Despite many medical, mechanical, surgical, and training innovations, hysterectomy remains the option of last resort for arresting PPH and saving the life of the patient even in the high-income countries with their wide availability of effective treatments and guidelines [3]. Emergency hysterectomy is often performed belatedly, in the situation of massive blood loss, when it is associated with serious maternal morbidity and mortality [4]. At the same time hysterectomies continue to be performed in cases of anatomically intact uteri that, in our opinion, could have been preserved [5].

We would regard as a very significant development the opportunity for the physician to reach as soon as possible the "moment of truth" when surgical treatment, most commonly hysterectomy, becomes clearly indicated. Of comparable clinical importance would be the ability to determine the patients whose uteri can be preserved under nonsurgical management.

The moment when immediate surgery becomes essential is reached when (1) the uterine cavity is completely emptied, (2) uterotonics and other pharmaceutical agents have been exhausted, (3) genital tract lacerations are excluded as the source of bleeding (or have been stitched up), (4) the uterine cavity is occupied with the properly placed balloon, (5) the balloon walls are in full and close contact with the whole internal surface of the uterus and apply sufficient direct pressure upon all hemorrhaging blood vessels, and (6) uterine bleeding persists.

Condous et al. (2003) were the first to discover these inherent properties of the balloon tamponade technique. They named it the "tamponade test" [6].

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We, however, have modified this test for a slightly different task. If the tamponade test was geared for the purpose of identifying the patients in need of surgery in general, we set out to identify women in need of hysterectomy in particular. To make the right choice regarding the possibility of uterus preservation at this crucial moment, we have mustered all instruments available to us at the decisive point of the battle. Firstly, we joined the vaginal balloon to the uterine one creating the double-balloon assembly system (DBAS). Secondly, in cases of caesarean delivery (CD), we have used two other conservative surgical approaches alongside DBAS, namely, original hemostatic external uterine supraplacental pleated sutures and uterine artery ligation (most frequently of its descending branches). These two supplementary methods were predominantly utilized in cases of placenta accreta with surgical separation of the abnormally adherent placenta or resection of the affected segment of the uterus.

However, proper DBAS use, sometimes alongside the pleated sutures and arteries ligation, leads to PPH cessation in 95–97 % of cases.

Our histopathological study of uteri removed since the introduction of this integrated test, which was followed by a dramatic decrease in the overall frequency of hysterectomy in our practice, has for the most part demonstrated the presence of pathological structural changes in the uterus such as undiagnosed focal placenta accreta, uterine infection, etc., the cases of hysterectomy owing to isolated uterine atony being practically absent in recent years.

The algorithm in use permits us to make the decision on surgery within the first "golden hour." The sequence of treatment methods and tools is presented below.

We would also like to consider the existing PPH treatment protocols adopted in the leading world countries. Dahlke et al. (2015) reviewed [7] four contemporary national guidelines for the prevention and management of PPH adopted by the American College of Obstetricians and Gynecologists (ACOG), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZOG), the Royal College of Obstetricians and Gynaecologists (RCOG), and the Society of Obstetricians and Gynaecologists of Canada (SOGC) [8–11]. The purpose of their research was not only to elucidate possible differences but also to present the comparative analysis of the guidelines to suggest probable steps for further development and improvement.

The authors noted that "recommendations for nonsurgical treatment strategies such as uterine packing and balloon tamponade varied across all guidelines." The review did not identify specific indications for hysterectomy in any guideline, with RCOG recommending hysterectomy "sooner rather than later." It was concluded that substantial variation existing in PPH prevention and management guidelines among the four national organizations highlighted "the need for better evidence and more consistent synthesis of the available evidence with regard to a leading cause of maternal death."

We would like to add to Dahlke et al.'s remarks that none of the reviewed protocols included the use of the manual exploration of the uterus to follow the administration of uterotonics in cases of atony, a procedure which is extremely useful. Also, the recommendations for balloon tamponade mention devices that are far from optimal in implementing this method.

16.2 Manual Exploration of the Uterus

In our opinion, the full potential of manual exploration of the uterus is underestimated in the existing PPH guidelines.

Thus, the new WHO recommendations on prevention and treatment of postpartum hemorrhage (2013) do not mention this technique at all; in it, administration of uterotonics and uterine massage are immediately followed by intrauterine balloon tamponade and uterine artery embolization [12].

However, we would like to draw attention to the following facts:

1. Inserting the balloon catheter in the uterine cavity not confirmed empty can adversely affect efficacy of the method.
2. Manual exploration of the uterus and removal of blood clots have its own intrinsic therapeutic potential often resulting in PPH cessation, thus obviating the need for balloon tamponade.
3. Balloon tamponade is contraindicated in case of certain pathologies detectable during manual exploration (uterine rupture, intrauterine structural abnormalities, etc.); for example, uterine rupture detected by manual exploration in the presence of PPH requires immediate laparotomy.

It is necessary to emphasize that even when completeness of placenta is not in doubt, blood clots adhering to the placental bed can cause ongoing PPH just as well as retained products of conception. They should always be removed before the tamponade procedure [13]. Thorough cleaning of uterine walls is best achieved when wrapping the examination hand with moist gauze facilitates removal of adhered blood clots or retained amniotic membranes, which prevent effective contraction.

In a correct checklist, PPH when not responsive to uterine massage and uterotonics administration should require immediate exploration of the uterus performed with gauze-covered hand [14].

This should be done even in the case of well-contracted uterus if bleeding persists [15].

Retained products of conception or accessory lobes are surprisingly common, even when the delivered placenta appears macroscopically intact [16].

Moreover, manual exploration of the uterus with uterine wall cleaning sometimes ensures the arrest of bleeding even in the absence of retained placental tissue or noticeable amount of blood clots to be removed.

This manipulation is simultaneously therapeutic (emptying the uterus and aiding its contraction) and diagnostic (in cases of placenta accreta, uterine rupture, cervical and vaginal lacerations, etc.).

In the 1970s, the obstetricians considered the approach, later abandoned, of manual exploration of the uterus in all vaginal deliveries, yet it is interesting that in a study of 100 patients who had elective manual exploration of the uterus at the time of delivery compared with a control group of 100 patients [17], this procedure was associated with decreases in febrile morbidity or blood loss; however, they did not reach statistical significance.

In our opinion, it is important to spotlight an article written more than 40 years ago that has retained its significance for obstetrics with its exemplary study of 1, 219 cases of maternal mortality during an 11-year period in the state of California [18]. On the subject of PPH, the author underscored two striking phenomena, a large number of placenta accreta cases in patients with previous CD and the *lack of manual exploration of the uterus in many lethal cases of PPH* in connection with uterine atony. Failure to explore the uterus after vaginal delivery was noted frequently in the series. We regard this study as very useful in elucidating certain classical obstetrical principles which still hold true nowadays.

16.3 New Approach Toward Intrauterine Balloon Tamponade: "Free Flow" Method

Dynamic process of uterine recovery must be managed by a dynamic intrauterine balloon device.

The idea of intrauterine balloon tamponade (BT) in PPH is undeniably a brilliant one.

The noninvasive approach *per vias naturales*, through the just-vacated birth canal, permits direct access to the PPH source, no matter where on the uterine walls the latter is located. Covering this source with nonwettable film and putting pressure on the bleeding vessels immediately stop the bleeding and create conditions favorable for blood clotting; thereafter the physician can withdraw the balloon with ease, without interfering with the formed blood clots. Once detached from uterine walls, the balloon is removed *per vias naturales* as well, leaving clean, non-bleeding, well-drained uterine cavity behind. What can be more inspiring for a physician to do in case of PPH?

Nonetheless, the efficacy of BT as a method depends on tackling two problems.

Firstly, the size of the uterus and its cavity during recovery from atony and contractile activity restoration should be decreased. There must be no obstacles preventing the uterus from contracting and no interference with its natural hemostasis mechanisms.

Secondly, the cavity occupied by the balloon has a 10–12 cm aperture, the cervix left dilated after the parturition, which creates the possibility of balloon expulsion from the uterus leading to method failure.

In this section we describe our solution for the first problem.

The natural mechanism of uterine postpartum hemostasis comprises two phases. The first one is myometrial contraction and retraction leading to uterine size reduction and, most importantly, to constriction of open placental bed vessels leading to cessation of their blood flow. Only then follows the second phase of uterine hemostasis, blood clotting in the vessels constricted by myometrial fibers.

What happens to the process of uterine hemostasis when any of the existing balloon catheters is installed in the uterine cavity? The pathologically relaxed and enlarged, atonic uterus is occupied by a tight-fitting foreign body that is assumed not to change its size because existing catheters require their inlet pipes to be turned off to keep liquid inside the balloon. Such balloon fixes the uterus for many hours in this pathological expanded state.

Myometrial contraction and uterine size reduction are unlikely, while this balloon remains in the uterine cavity, which makes the first phase of natural uterine hemostasis impossible. The physicians have to count upon the second phase, blood clotting in hemorrhaging vessels, only. Administering uterotonics while the uterus is forcefully distended in the manner described above is senseless and might indeed prove injurious because the uterus is kept strained by the presence of the balloon inside and cannot contract. The sole process taking place there is blood clotting in the uterus that is kept pathologically overstretched without any possibility of contractility restoration.

Thus the balloon has to stay in the uterus for many hours with its inlet pipe turned off, while the physician does not receive any data regarding the condition of the uterus and the tamponade success, which leads to the necessity of antibacterial treatment, indwelling urinary catheters, further stay in a high dependency care or intensive care unit, etc.

Yet another serious problem is associated with using existing balloon catheters. It is unclear when in each case the

balloon has been properly filled due to the difficulty in determining the suitable liquid volume. There can be no universal recommendations when we are in need of an individualized approach. The small, thick-walled obstetrical balloon expands with difficulty; injecting the first 50 ml of solution requires the pressure of 85 mmHg [19]. Therefore the physician injecting the liquid into the balloon with a syringe cannot determine whether it is the rigid balloon wall being stretched or is the uterine wall becoming distended. This indeterminacy in selecting the necessary liquid volume is extremely undesirable in the cases of CD when the balloon overstretches the newly stitched area of hysterotomic incision.

Ten years ago, we developed a highly effective method of arresting PPH with a uterine balloon that not only does not impede uterine contractility but also assists in its speedy (up to 1 h), spontaneous restoration, thus quickly resolving the life-threatening condition of contractile failure of the postpartum uterus.

When using our method, the physician does not have to select the volume of liquid to pour into the balloon; the uterus itself chooses the volume required.

When using our method, the physician does not have to determine when the procedure is over; the uterus itself demonstrates it.

When using our method, the physician does not have to worry that the uterus can be overstretched on the balloon; one is able to select in each case the minimally sufficient force of the balloon–uterus interaction.

Our method of balloon application in the uterus is based upon the principle of communicating vessels. One of these vessels is the uterine balloon itself and the other the tank fixed at a certain height above the intrauterine catheter, the catheter and the tank being connected with a tube. The uterine balloon is being filled by gravity with the liquid from the tank until the balloon walls expand outwardly enough to contact the walls of the uterus. The resulting force of balloon pressure on the uterus is determined by the height of the tank. The connecting tube is being kept open throughout the procedure.

The liquid moves freely between the tank and the uterine balloon via the connecting tube, permitting constant contact of the balloon with the uterine walls when the uterus contracts or relaxes. Its relaxation leads to filling the balloon with an additional liquid volume from the tank. The balloon expands and keeps permanent contact with the uterine wall. Importantly, the contracting uterus expels excess liquid from the balloon into the tank (Figs. 16.1 and 16.2).

Using the principle of communicating vessels in filling the uterine balloon presents numerous crucial clinical benefits for the patient and the clinician. At any given moment of the procedure, the liquid volume is appropriate for maintaining constant pressure in the uterine cavity in spite of its changing dimensions, while the physician receives visual data on uterine activity via observing the changing level of the liquid in the tank, thus knowing precisely when to remove the balloon.

We have abandoned the drainage tube in the catheter design and established liquid volume limits for the balloon capacity, as well as the possibility of leaving any "dead" spaces in the uterine cavity during the balloon use. The cavity must be wholly occupied, the balloon covering all the potentially bleeding vessels without interfering with the spontaneous contractile activity of the uterus.

The existing well-known balloon, which leaves the upper part of the uterine cavity free, cannot reach the placental bed located in the fundus of the uterus.

The application of our system requires three steps only: (1) placing the pre-filled tank approximately 50 cm above the patient, (2) inserting the catheter into the uterus, and (3) connecting the catheter with the tank. Once the system is filled up with sufficient volume of liquid, all the rest is guided by the uterus itself.

We have created an open-circuit system where changes of the level of liquid in the tank serve as the intrauterine manometer registering early indications of the uterine contractility. Looking at the level, the physician observes spontaneous activity and natural might of the uterine forces.

Installing our system immediately after the manual exploration of the uterus when the bleeding continues requires several minutes only.

It is important that activating the uterine balloon system can be performed swiftly and on the spot, even in the emergency room or ambulance car, without any team, but rather by a single trained maternal provider along with any non-trained assistant or a relative of the patient. In the majority cases they result in the arrest of bleeding.

16.4 Preventing Expulsion of the Uterine Balloon

Intrauterine balloon tamponade procedure obviously requires maintaining the proper placement of the balloon in the uterus.

Our experience of BT use in PPH management has demonstrated its effectiveness in 97–98 % of elective CD cases when the cervix is closed and the catheter is introduced retrogradely through the uterine incision; for inflating and deflating of the balloon, its shaft is passed through the closed cervix into the vagina and outside.

BT is highly effective during the elective CD procedure due to the fact that the closed cervix excludes any possibility for an elastic and slippery balloon to be either expelled or displaced.

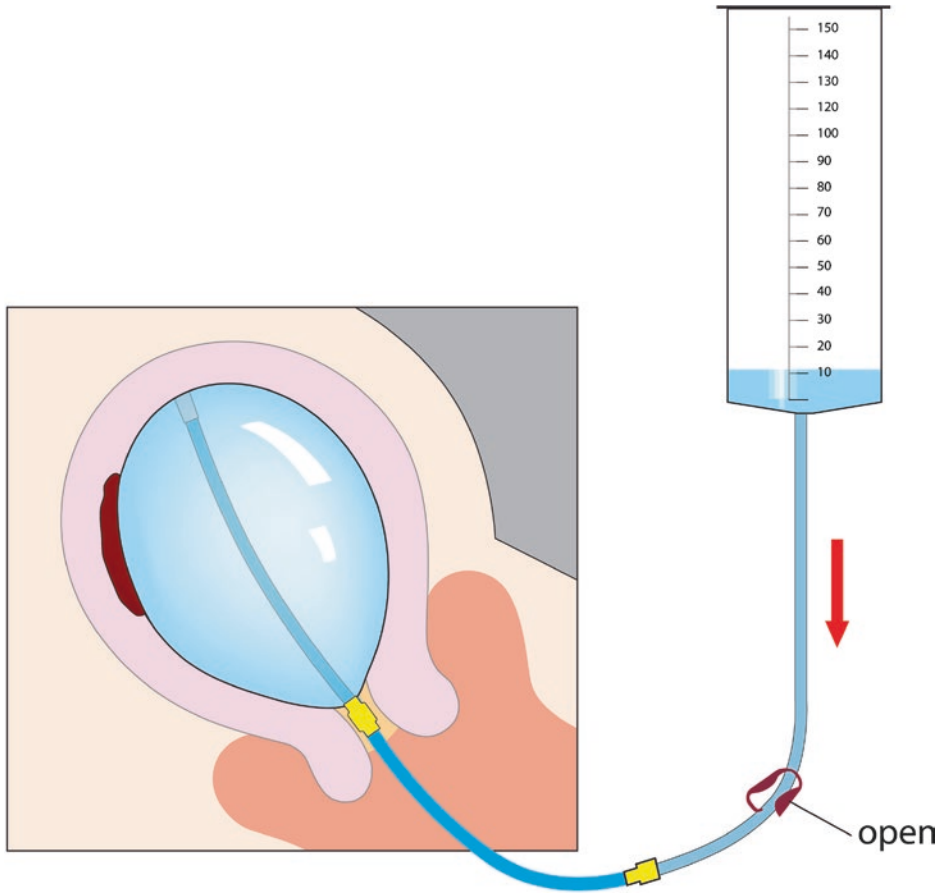

Fig. 16.1 Liquid flowing into balloon on uterine relaxation

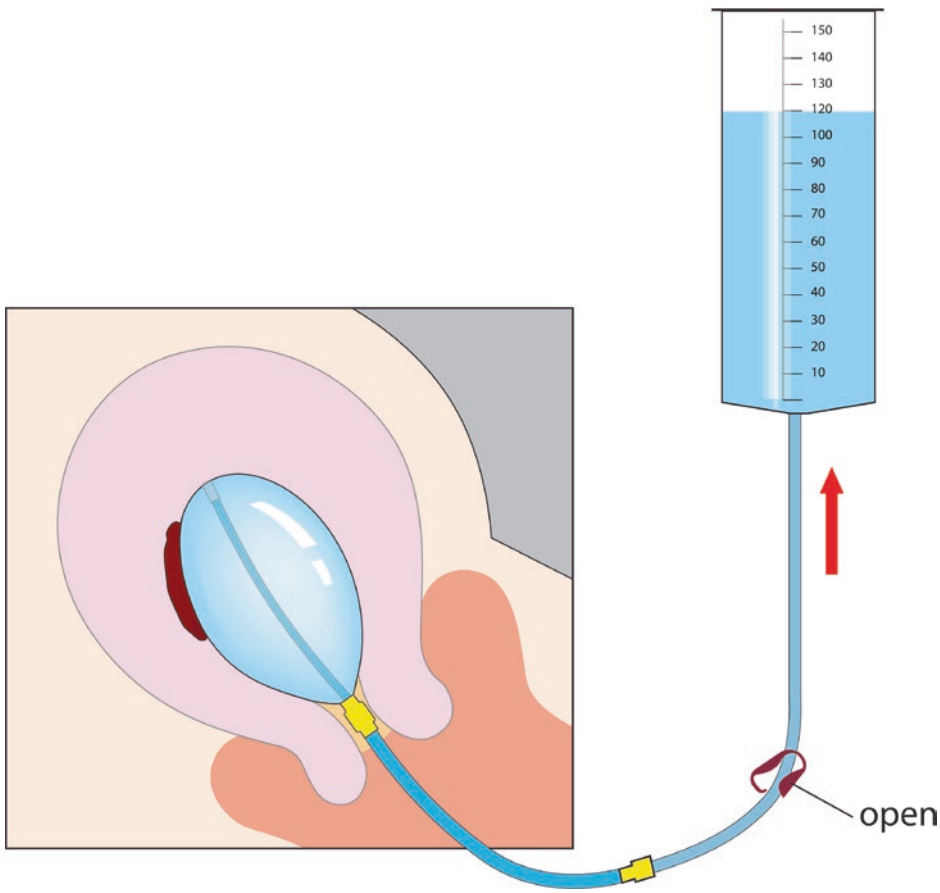

Fig. 16.2 Excess liquid expelled into tank on uterine contraction

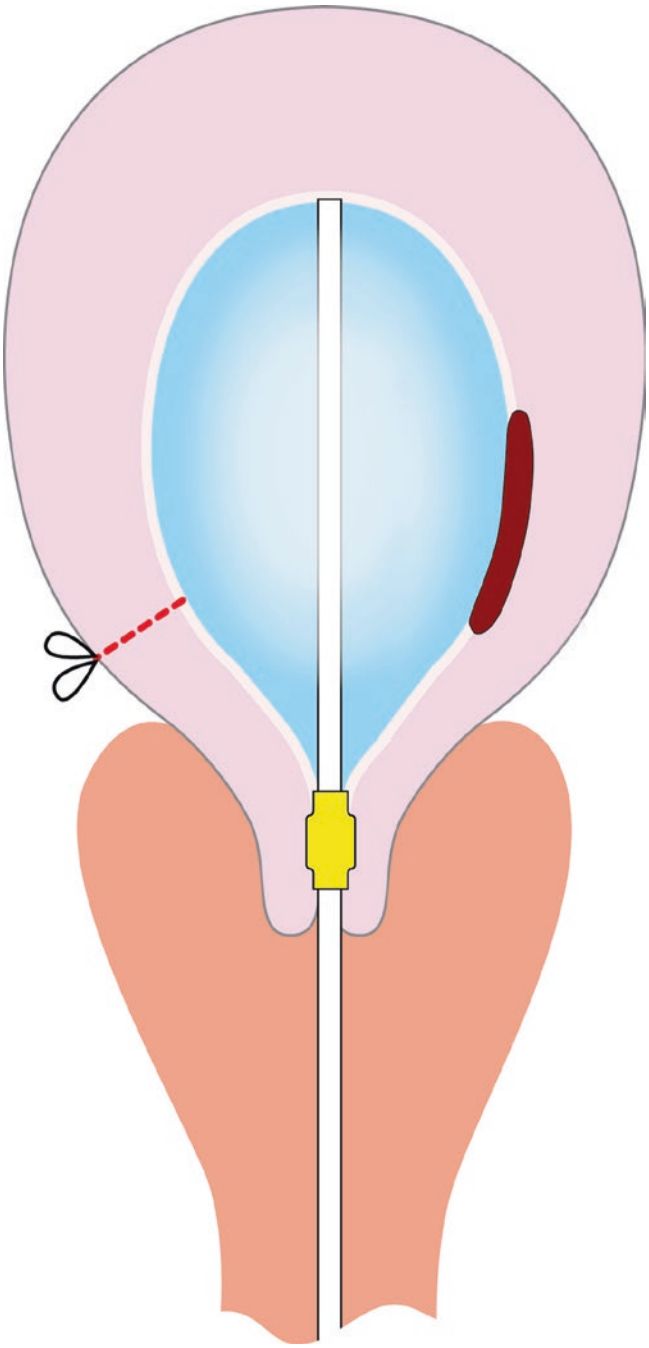

Fig. 16.3 Uterine balloon in place. Maximum method efficacy (Elective CD)

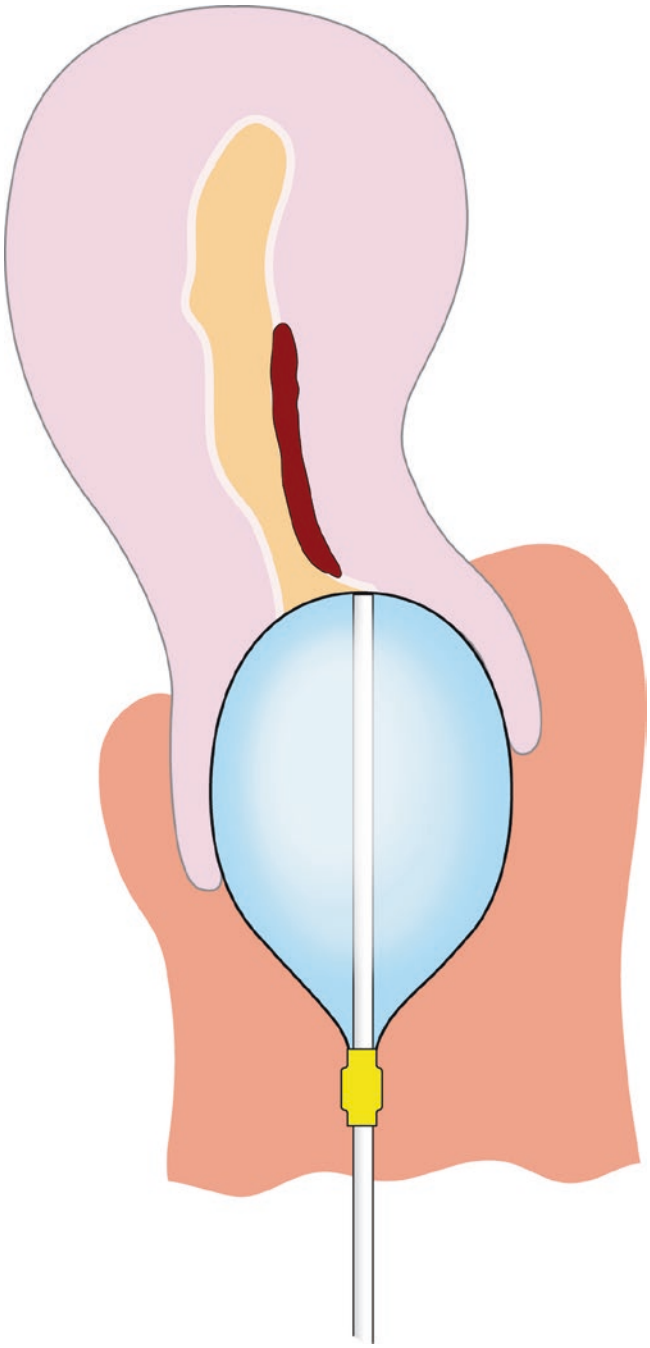

Fig. 16.4 Cervix open. Balloon expulsion

The balloon reliably maintains its position within the uterine cavity when the cervix is closed, and once it is filled with liquid, its contact with the inner surface of the uterus and direct pressure on the bleeding vessels are guaranteed. Thus BT appears to be inherently reliable and effective when the cervix is not open (Fig. 16.3).

However, performing BT when the cervix is dilated has resulted in a quite significant number of clinical cases where balloons were documented as protruding or being expelled.

This displacement of uterine balloon into the vagina through the dilated cervix can virtually be regarded as method failure (Fig. 16.4).

Moreover, balloon expulsion always makes possible the existence of concealed hemorrhage with blood accumulating in the uterine cavity behind the balloon with no

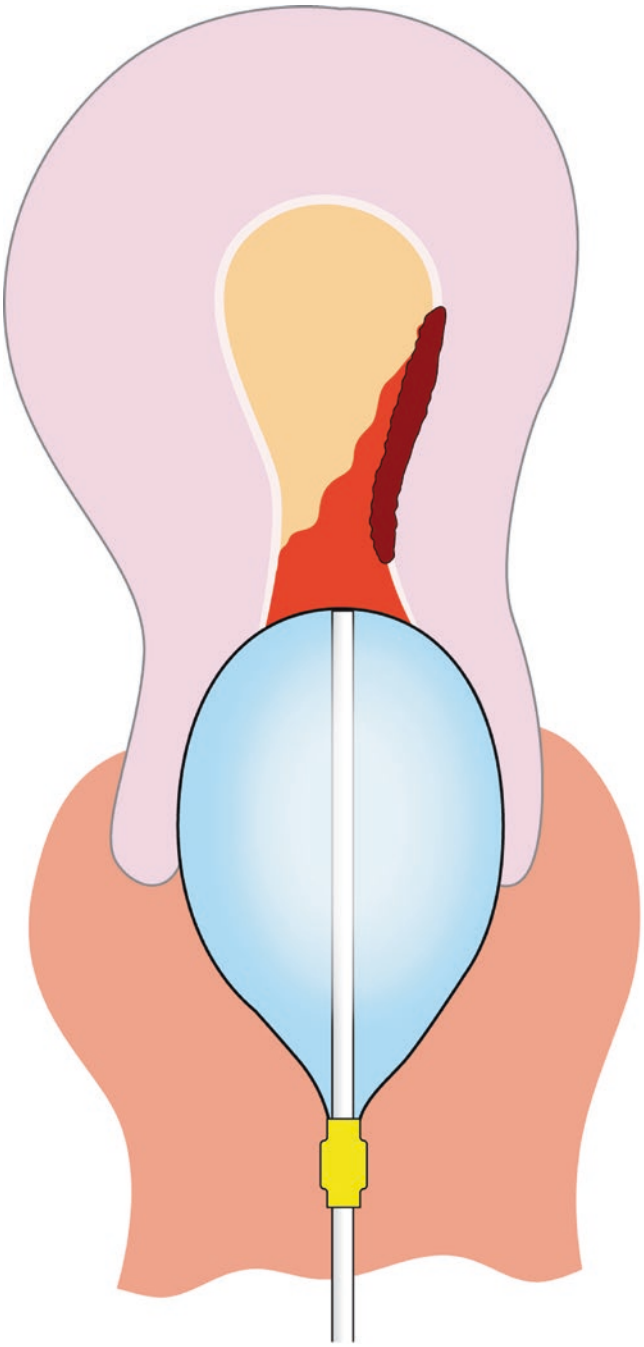

Fig. 16.5 Occult bleeding after balloon expulsion

outflow and remaining unobserved by the physician [20] (Fig. 16.5).

As a consequence of this, there are a number of proposals regarding possible ways of maintaining the inflated balloon inside the uterine cavity.

Vaginal gauze packing was proposed as one of the ways to prevent balloon displacement. Unfortunately this approach can hardly be regarded as acceptable in cases of ongoing PPH due to the difficulties of applying sufficient counterpressure to maintain the balloon in the uterus as well as monitoring the loss of blood. Before using vaginal gauze packing to hold the balloon in place, the tamponade test must be positive. Otherwise there is a danger that the pack will conceal any ongoing bleeding and result in delaying the diagnosis of ineffective tamponade.

If vaginal gauze packing turns out to be unacceptable, then other ways of maintaining the balloon in the uterine cavity are required.

There are a number of different methods to keep the balloon inside via narrowing the dilated cervix, for example, using various kinds of sutures to encircle the opening cervix, such as cervical cerclage, cervical clamp, bilateral cervical lips suturing, etc. [21–24].

We would like to emphasize that the efficacy of arresting PPH with the uterine balloon when the open cervix is surgically narrowed is very high: in almost all cases, the bleeding ceases.

Our idea was to solve the problem of keeping the balloon properly positioned in the uterus without any surgical interventions by using a noninvasive technique. For this purpose, we created a mechanical device emulating the closed cervix, the autonomous vaginal balloon catheter. The device is placed into the vagina during the uterine tamponade procedure when the cervix is dilated.

To accomplish this task, the form, the softness, the external diameter, and the internal lumen of the shaft of the catheter were selected to imitate in the most accurate manner possible the shape of the closed cervix with its canal.

The balloon is mounted on the distal end of the shaft. By this balloon the vaginal catheter is safely and reliably fixed in the upper part of the vagina in direct contact with vaginal fornices.

The vaginal balloon catheter so designed emulates the closed cervix completely, even in the state of its full dilation, thus safely maintaining the uterine balloon inside the uterus immediately after vaginal delivery (Fig. 16.6).

In this manner the new double-balloon assembly system fits the unique anatomy of every patient; in fact, it can be regarded as a personalized dual-balloon catheter.

The important distinctive feature of DBAS is a wide gap between its shafts (Fig. 16.7).

Due to this gap between the shafts of the two joined catheters, the obstetrician is immediately aware when BT is ineffective, as blood can be easily detected leaking outside through the gap between the balloon shafts.

16.5 Double-Balloon Assembly System: New Approach to Lower Segment Uterine Bleeding Management

Placenta previa remains a serious obstetric complication characterized by high morbidity and mortality rates for both the mother and the fetus due to the greater likelihood of

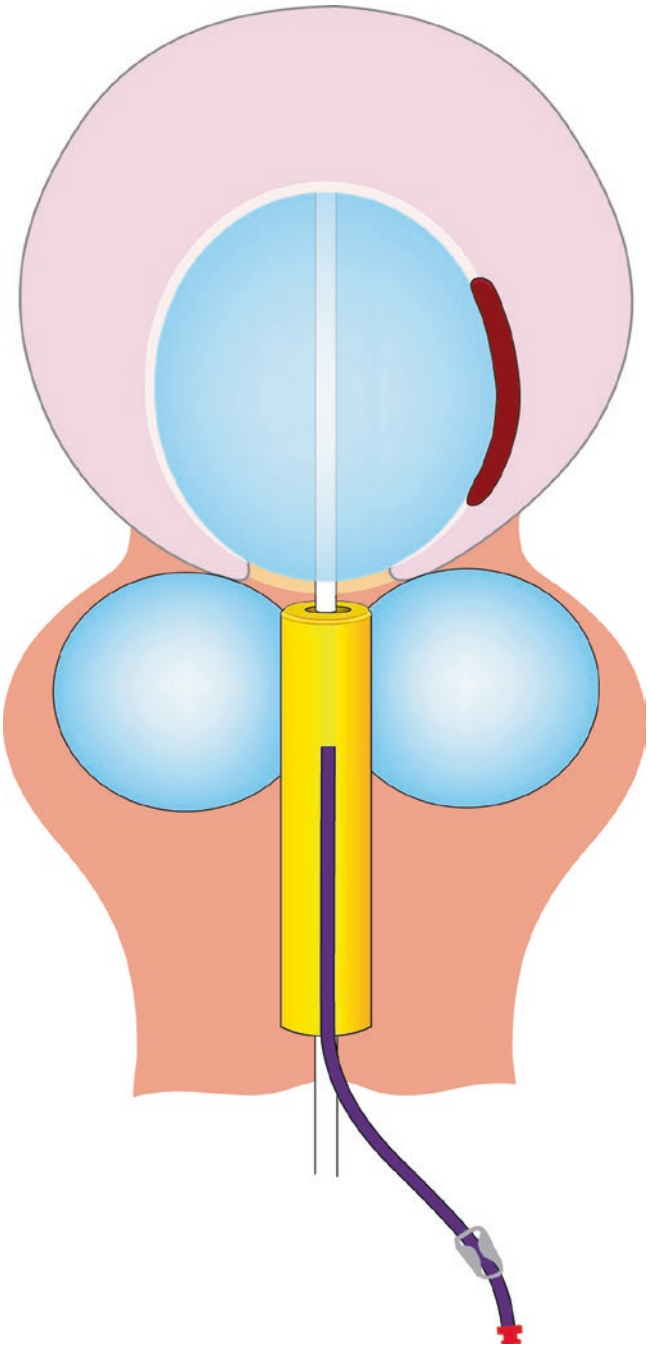

Fig. 16.6 Vaginal balloon keeps uterine balloon in place with cervix open (modified from Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

catastrophic bleeding existing during the CD and in the postpartum period. This type of placentation is associated with significantly greater risks of hysterectomy, massive hemotransfusion, shock, and sepsis. Indeed, the hysterectomy rate in cases of placenta previa is 33-fold higher than in the elective CD control group [25].

Separating the placenta previa often leads to persistent uterine bleeding from the large open vessels at the placental site because the lower uterine segment is often poorly contracted, its myometrium thinner than in the body of the uterus. Also, thinness of the uterine wall often leads to deeper placental invasion in the lower segment.

If uterine body hemorrhages are usually well controlled with the application of ligatures to uterine vessels or the use of compression sutures, the lower uterine segment bleeding is often associated with unsuccessful devascularization, whereas compression sutures of the lower segment are technically challenging and require considerable experience on part of the surgeon; they also might lead to serious ischemic complications.

Uterine artery ligation is of no use in case of lower segment bleeding; those vessels supply the uterine body. On the other hand, internal iliac artery ligation does not interfere with lower uterine segment perfusion via additional blood supply through its well-developed network of arterial collaterals with many subperitoneal anastomoses [26]. It may be concluded that internal iliac artery ligation is not indicated in case of lower segment bleeding because it might prove insufficient or useless; its success rate is low, whereas the risks and complications outweigh the possible benefits. The situations when internal iliac artery ligation might be indicated will be discussed below.

Applying compression sutures in this situation requires good access to the lower uterine segment, the upper part of vagina, and the subperitoneal spaces of the pelvis. This kind of access necessitates wide and deep retrovesical dissection which is rather uncommon in obstetric practice, creates the risks of bladder damage and additional hemorrhage, and must be performed only by senior expert surgeons; only then accurate vascular control and efficacious use of hemostatic compression techniques become possible [27].

Compression square suturing by Cho is an effective method of hemostasis. However, it must be preceded by cannulating the cervical channel with Hegar's dilator in order to provide for the outflow of uterine cavity contents. Also, when tightening the stitches the surgeon should simultaneously achieve sufficient compression of the hemorrhaging vessels and avoid uterine necrosis resulting from excessive ischemization. Overall, this invasive compression approach to lower uterine segment hemostasis involves nothing less than a difficult surgical operation with all its attendant risks [28].

Notwithstanding the foregoing, effective compression of the lower uterine segment, cervix, upper part of the vagina, and their respective parametria can be achieved in a totally noninvasive manner using mechanical means only. This area can be compressed between two voluminous elastic spherical objects and the two inflated balloons, one of which is placed into the uterus and the other one in the vagina. The

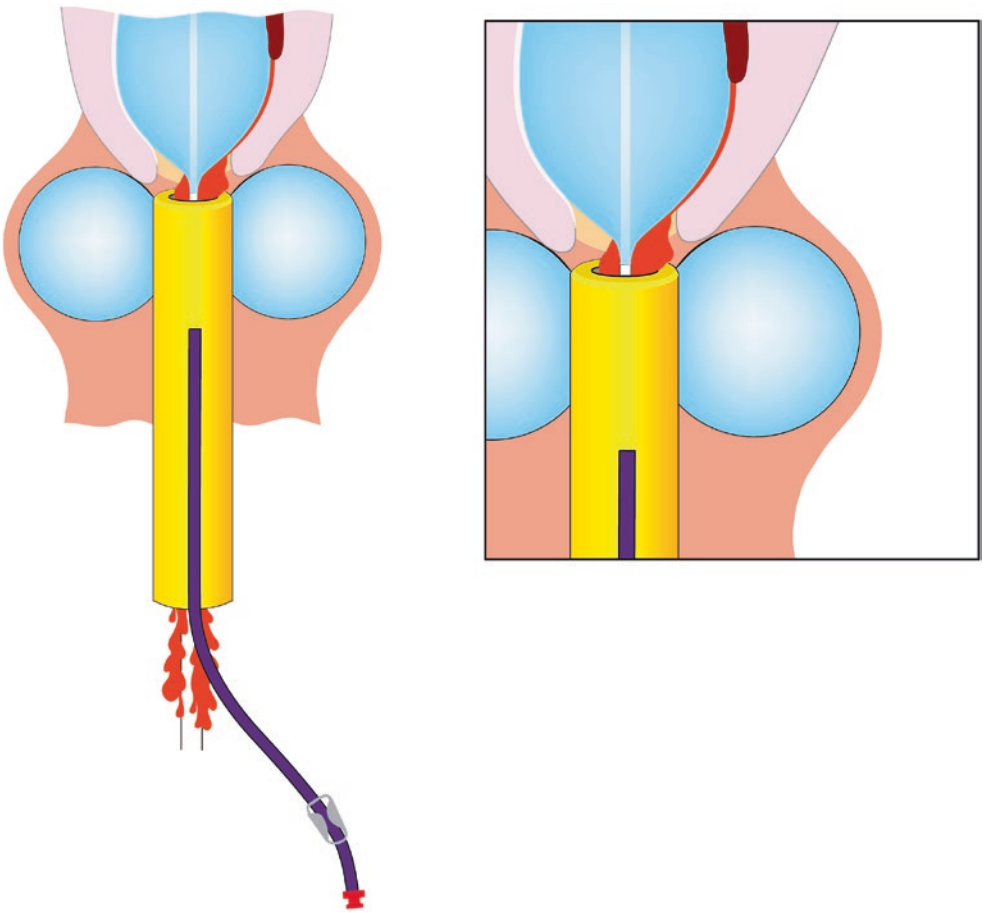

Fig. 16.7 Gap between catheter shafts. Occult bleeding prevented

DBAS assembled in situ, its two catheters moving independently of one another, gives us an opportunity to compress the lower uterine segment along with its attendant blood vessels in a thorough and careful manner.

To maximize the compression effect, we have developed the exact algorithm for installing DBAS. At the core of this technique is fixing the vaginal balloon as high as possible in the vagina in such a way that it contacts and expands vaginal fornices and flattens the cervix over the balloon surface; only thereafter we pour the required liquid volume into the uterine balloon, inserted and partially filled earlier. The expanding uterine balloon moves toward the fixed vaginal balloon and comes in tight contact with it (Fig. 16.8).

DBAS installed in the birth canal creates the necessary pressure on the bleeding lower segment of the uterus and the vessels supplying this area, obviating the need for a dangerous and complicated surgical intervention.

The success of this technique was confirmed by the Doppler ultrasound tests of the lower uterine segment that detected the absence of blood flow in this area, while DBAS was placed in the birth canal [29].

This approach toward stopping PPH is based on a simple, intuitive tool that can be applied easily and quickly by a young, non-experienced doctor. It presents the obstetrician with new opportunities for conservative treatment of hemorrhages, allowing some patients to avoid hysterectomy in the cases where it could otherwise been performed and thus preserve their reproductive function.

The lower uterine segment, heavily vascularized and characterized by minimal muscular contraction, is far from the best site for surgery. The regulated and safe compression provided by the two elastic smooth spheres of DBAS approximates the natural mechanism of hemostasis. Where muscular fibers are too weak to constrict the open vessels, the balloons vectoring their pressure upon the lower segment are optimal for arresting PPH and creating conditions that further the process of blood clotting.

16.6 Emergency Postpartum Hysterectomy

Certain among women giving birth will surely die if hysterectomy is not performed or performed with undue delay.

In spite of a great variety of scientific and practical endeavors directed toward the problem of PPH, hysterectomy remains an unavoidable treatment method. More often

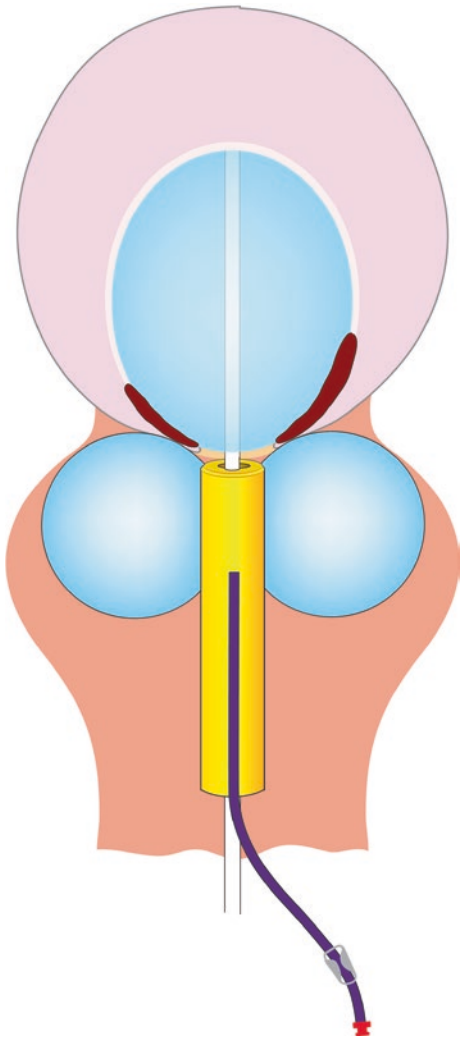

Fig. 16.8 Placenta previa. Inter-balloon compression of lower uterine segment

than not, it does not result from a medical error or substandard care.

In the situation where hysterectomy is a priori a life-saving measure for some patients, it is clear that identifying them as early as possible and performing hysterectomy in optimized conditions when their hemodynamics is stable would be a powerful tool in averting lethal outcomes or serious maternal morbidity, which so far remain formidable problems associated with emergency postpartum hysterectomy.

Elective obstetric hysterectomy in cases when the indications have been formulated during pregnancy and when it immediately follows CD in a preplanned manner, once all necessary preparations have been made and a team of senior obstetricians, anesthesiologists, urologist, oncologists, etc., have been assembled, is obviously less of a problem; it is characterized by greater success rates and a better safety profile [30].

However, the problems remain when hysterectomy is about to perform as the final event of intractable PPH management as an emergency surgical intervention.

How to perform it in the cases when hysterectomy is absolutely indicated – and avoid massive blood loss?

Rossi et al. (2010) have studied 981 cases of emergency postpartum hysterectomy and determined that 44 % of surgeries were performed with no alternative uterus-sparing procedures attempted [31]. In 56 % of cases, conservative procedures were tried but failed. The authors note certain existing problems, e.g., that the time elapsed while the procedures were applied might have contributed to greater maternal morbidity, blood loss volume, and blood transfusion rate. They underscore that there is no set of guidelines for conservative measures to be used before hysterectomy. Selecting the cutoff point for transition to hysterectomy remains a subjective decision.

Cognizant of the aforementioned problems, they suggest that conservative approaches are valid, while the hemodynamics of the woman is stable in the absence of life-threatening PPH.

Other publications put forward certain problems difficult to solve in the emergency situation of PPH. Baskett (2012) wrote that the art of obstetric judgment is necessary for establishing a certain balance between saving the uterus and saving the patient when choosing among extra time spent on uterus-preserving approaches and opting for the hysterectomy [32].

According to Knight (2007), in the UK the proportion of hysterectomy cases when morphologically intact uteri are removed is as high as 39 % [5].

In our opinion, in the clinically urgent acute situation of massive PPH, the obstetrician should have a clear reference point for making the decision to remove the uterus on a sound basis, knowing exactly which alternative procedures are worthy of consideration before transitioning to surgery. Here one cannot put one's trust in the success of one's subjective approach while in a situation of acute stress.

When we started wide use of DBAS in the group of women at the high risk of PPH and analyzed the results, we found that we have a clear reference point for transitioning to hysterectomy.

The sequence of DBAS application in CD cases was as follows: after extracting the fetus and before separating the placenta, we performed bilateral ligation of the descending branches of the uterine artery, and then, immediately after delivery of the placenta, we placed the balloon catheter into the uterus and applied external supraplacental pleated sutures, penetrating one-third of the uterine wall thickness, in two to three transverse rows. After closing the hysterotomy incision, the uterine balloon was immediately filled with liquid using the free flow method, the second balloon then being introduced into the vagina without delay and filled with 120–150 ml of liquid.

In cases of PPH during vaginal delivery when uterotonics were ineffective, after suturing the laceration and performing manual exploration of the uterus, we successively introduced and filled with liquid the uterine and vaginal catheters of DBAS.

The overall efficacy of DBAS application in the manner described above averaged 96 % over the last 2 years, whereas hysterectomy rate in our clinic dropped more than fourfold (3.6 per 1,000 births in 2015).

An important feature of hysterectomies following DBAS application is a significant reduction of blood loss (1,836 ± 108 ml versus 2,502 ± 203 ml, $p = 0.04$). It might be explained by the presence of two liquid-filled balloons, temporarily limiting perfusion of the uterus and upper third of the vagina, in the birth canal of the patient during surgery. Blood transfusion requirements have decreased almost twofold [29].

Our histological study of the uteri removed following DBAS application revealed gross structural changes, caused by suppurative endometritis or by the presence of epidermal scales in uterine arteries in one case and meconium in placental bed vessels in another case of symptomatic amniotic fluid embolism. Thus it is shown that in these cases the indications for hysterectomy were absolute and that the likelihood of arresting PPH using conservative methods was absent.

It should be emphasized that transition to hysterectomy, both in vaginal delivery and caesarean delivery cases, took place at once, without wasting time on any alternative conservative hemostatic techniques; subsequent analysis of clinical data fully justified the chosen tactics.

In other words, we can state that if PPH continues after DBAS use following either method of delivery, then we can assume a highly probable morphological cause of bleeding and transition to hysterectomy with confidence. In our experience, understanding the clinical situation usually comes before massive blood loss develops.

This new approach toward preventing lethal outcomes and PPH-associated serious morbidity can be regarded as the "DBAS test for hysterectomy."

The absence of intact removed uteri shows that DBAS is efficacious in cases of PPH caused by functional uterine contractility impairment.

Such are the results obtained in our clinical practice. Further studies are required to examine DBAS use in more detailed clinical contexts.

16.7 Preventing Main Caesarean Delivery Complications: Our Mechanical Noninvasive Intraoperative Method

The incidence of PPH in cases of CD is double or even triple than in vaginal delivery cases [33–36] due to the presence of hysterotomy incision, which to a great extent damages the muscular layer of the uterus responsible for the first phase of hemostasis – constricting the open blood vessels of the placental bed.

The situation is aggravated when the incision is close to the placental site, the source of PPH.

At the same time, anatomic and physiological features of the uterus as the target of surgery limit the obstetrician's ability to follow the basic rules of wound treatment, such as thorough hemostasis, necrotic tissue removal, and avoidance of dead spaces in the wound.

Even when the hysterotomy incision is perfectly stitched up and the bleeding from the wound has been securely stopped, the second, much more important and more dangerous PPH source, the placental bed, remains inside the uterus.

During the periods of slight, unapparent relaxation of the surgically injured myometrium which cannot be fully countered with uterotonics blood seeps into the uterine cavity out of placental site vessels that have not been fully constricted and not obstructed with blood clots.

It's well known that hematometra is present to a greater or lesser degree in the majority of CD cases. The closed cervix greatly impairs the management of pathological accumulation of blood in the uterine cavity.

Also, the swiftly congealing blood accumulating in the closed cavity becomes the very "necrotic tissue" which serves as the breeding ground for bacterial growth causing uterine infections.

Thus "thorough hemostasis" and the "absence of necrotic tissue" remain unattainable.

We must underscore that the uterine cavity itself serves as the dead space under the just-closed hysterotomy incision.

What can be done with this cavity as the source of hemorrhagic and inflammatory complications in CD?

No structural alteration is possible because this space is a necessary anatomic part of the female reproductive system, responsible for pregnancy, menstruation, etc.; the uterine cavity evidently should not be destroyed. The obstetrician cannot permanently alter the uterine cavity while seeking to resolve temporary problems, limited to the first hours following CD.

Thus the only valid approach is a noninvasive occlusion that is temporary, atraumatic, and fully reversible.

The logical way to achieve those goals is to occupy the whole uterine cavity with an elastic, thin-walled balloon that will cover whole inner surface and compress all potentially bleeding vessels, assisting the process of blood clotting in them.

The obstetrician must consider in the first place the fact of putting direct pressure on the just-closed uterine incision with the expanding balloon.

Thus selecting the minimal sufficient magnitude of balloon–uterus interaction force not overstretching the newly stitched wound is of vital importance. Any overstretch must be avoided, even when the uterus with the balloon inside starts to contract and reduce its size.

Clearly the uterine balloon has to adapt to uterine contractions and size changes, varying its own size and the volume of liquid inside. It is important that the balloon pressure upon the uterine walls should remain constant in spite of the changing uterine size.

This can be achieved by using the free flow method only, the method which is based on the principle of communicating vessels.

When we select the height of the tank filled with liquid and connected with the uterine balloon catheter with the permanently open tube, we know exactly the force of balloon pressure on the uterine walls because we also know the part of total pressure that is expended in stretching the balloon itself.

Thankfully, reliable hemostasis requires the low pressure on the uterine wall, 10 mmHg only. This is the pressure we work with during CD; our physicians often call it "the light touch."

Nonetheless, when we started considering the existing models of balloon catheters, we found none suitable for intraoperative transabdominal insertion into the uterus during CD. For example, one well-known, non-sterile latex catheter is not equipped with shafts. In the situation of acute PPH, it must be truncated, afterward sterilized, and only then introduced into the uterus via the cervix with the assistance of metallic grasping forceps, even while the uterine incision remains open [37].

Therefore we were compelled to design our own uterine balloon. The new balloon is equipped with a shaft that is simultaneously rigid and flexible enough in order to pass in a retrograde manner through the closed cervix, penetrating the unseen internal orifice of the cervix while not injuring the uterus. Our experience with this method over many years has encompassed thousands of CD cases.

There is a short seminal moment during CD, decisive for both the surgeon and the patient – the several minutes between emptying the uterine cavity and closing the hysterotomy incision with stitches. Until the incision is stitched up, the obstetrician has direct access to any source of bleeding inside the uterine cavity.

This is a great gift to the surgeon as the incision is for the purposes of fetus delivery, and this has been done! Now the surgeon can take advantage of this incision for tackling new problems of no less importance that arise immediately after the birth of a child. PPH can be stopped or prevented, efficaciously, safely, and quickly, while the incision remains open.

Yet the standard approach of the surgeons during this decisive moment is to stitch up the uterus as soon as possible. Once the incision is closed, the surgeon loses the opportunity to see uterine bleeding. It becomes a hidden, internal bleeding, which is characterized by belated discovery.

The late recognition of such a bleeding that usually comes after the surgery has been finished makes its management quite challenging, especially when the cervix is closed. In this case one can either approach the source of PPH via the vagina or to return the patient to the operating room for relaparotomy.

Thus when the moment of stitching the wound comes, the obstetrician faces the dilemma: to insert the balloon inside the uterine cavity or not.

Of course, this is not an issue when blood shows through the hysterotomy incision. Intraoperation bleeding leaves no place for doubts. In this clinical situation, the transabdominal application of the uterine balloon is well accepted.

But what is to be done when the surgeon observes no clear signs of PPH once approaching the closure of the incision?

No one can tell for a certainty which patient should get the balloon and which one should not. Often the post-CD period is trouble-free without the use of balloon, yet in a rare case, the obstetrician has to regret profoundly not inserting the balloon catheter before stitching up the uterus when facing a "near-miss" case of PPH.

Remembering that PPH is often unpredictable and that in the majority of PPH cases there are no risk factors to be retrospectively determined, one can think that the balloon catheter should be used during CD as a matter of routine. But today it is an unrealistic statement.

The sober estimate is to insert the balloon during CD in cases of high obstetrical risk of bleeding or in the presence of a serious concomitant illness. In our opinion, this group consists of women with PPH during previous delivery or antepartum hemorrhage in this pregnancy, women with signs of intrauterine infection, women with abnormal placentation, women with uterine scars or overstretched uterus (multiple gestation or polyhydramnios), as well as women with severe gestosis or obesity.

It must be noted that in 2008, Chandraharan and Arulkumaran proposed as research agenda "The role of prophylactic compression sutures in women who are at increased risk of PPH during caesarean section" [38]. Thus the idea of preventive uterine compression during CD is longstanding. Compressing the uterus in a noninvasive, atraumatic manner using the obstetric balloon catheter should be regarded as the next advance. Our method of intraoperative balloon placement in the uterine cavity using the auxiliary probe is demonstrated in Figs. 16.9, 16.10, 16.11, and 16.12.

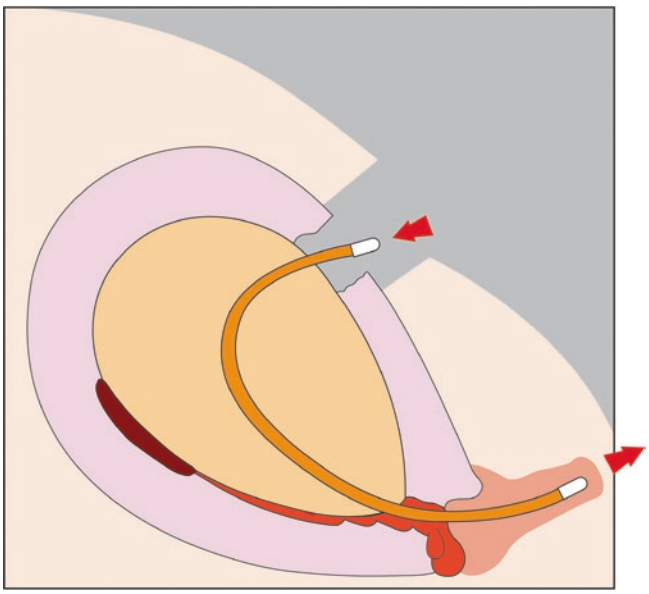

Fig. 16.9 Sequence of actions on transabdominal insertion of uterine balloon catheter

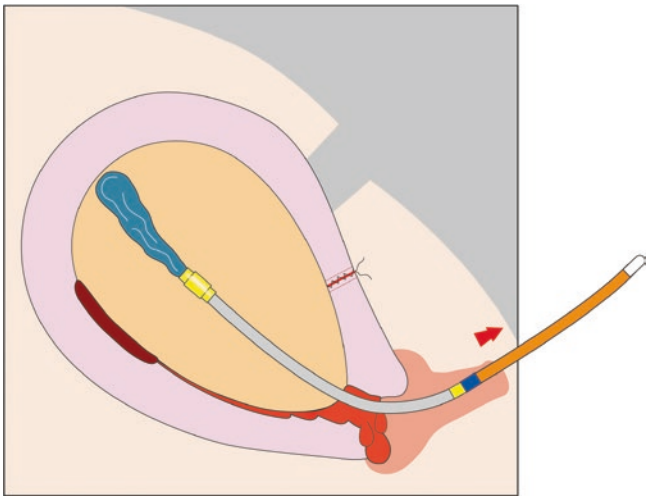

Fig. 16.11 Sequence of actions on transabdominal insertion of uterine balloon catheter

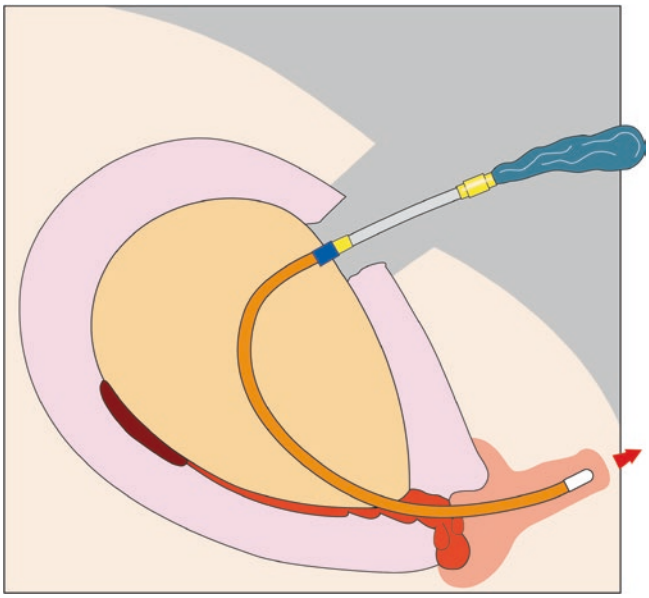

Fig. 16.10 Sequence of actions on transabdominal insertion of uterine balloon catheter

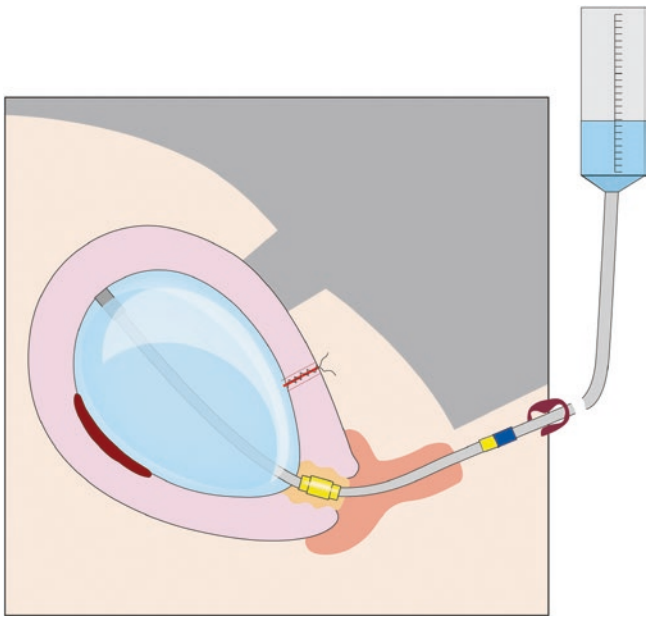

Fig. 16.12 Sequence of actions on transabdominal insertion of uterine balloon catheter

In our experience, in the demanding situation of CD, an average surgeon using the balloon is better than a brilliant surgeon without one due to the causes of CD complications being independent of the obstetrician's skills.

It should be emphasized that the well-drained uterine cavity without PPH and blood clots is the main factor for the uncomplicated postoperative period.

16.8 Vaginal Lacerations and Paravaginal Hematomas

Approximately 20 % of PPH result from lacerations subsequent to delivery [15] that can involve the uterus, cervix, vagina, or vulva and can cause rapid loss of large amounts of blood that requires swift correction of hypovolemia with crystalloid or colloid solutions and red blood cells.

Any vaginal delivery might lead to lacerations, although they most often follow instrumental vaginal delivery of large infants, as well as speedy and/or uncontrolled delivery when the traumas can be substantial and often result in severe disruption of soft tissues and tearing of blood vessels.

Trauma to the genital tract during pregnancy results in greater bleeding than would occur in the nonpregnant state owing to the increased blood supply to the genital tract.

Thus the possibility of lacerations must always be considered when dealing with a PPH that appears unconnected with the perineum, especially when a steady loss of fresh red blood is observed with the uterus appearing to be well contracted. Careful inspection of the lower genital tract often reveals bleeding sites in this area [39].

Also, it must be stressed that the cervix and vagina should be immediately and thoroughly visualized following all instrumental vaginal deliveries.

This visualization must be performed by the obstetrician along with the assistant, preferably in the operating room. The patient must be properly positioned and anesthetized in order to examine her lower genital tract using appropriate instrumentation such as Heaney, Sims, Simpson and lateral vaginal wall retractors, and proper lighting.

When PPH appears to be secondary to vaginal trauma, the treatment method most commonly employed is suturing the lacerations.

However, the suturing might not result in adequate hemostasis in the edematous and friable vaginal mucosa or if there remains any significant dead space. If stitches are placed shallow, a "cheese-wire" effect is a clear threat; if deep, with the ureters located in close proximity to the lateral vaginal fornices and the base of the bladder – to the anterior fornix, the obstetrician should be on alert for such rare yet dangerous complications as ureteral ligation or genitourinary fistulas. These conditions might require vaginal tamponade for arresting the laceration-associated PPH [40, 41].

Lacerations of blood vessels underneath the epithelium of vagina or vulva could lead to hematomas that may cause significant blood loss. While the usual approach toward managing the growing hematomas is incision and drainage, sometimes vaginal packing is indicated in the post-drainage period.

It must be noted that cervical or vaginal lacerations extending into the broad ligament should not be repaired vaginally and require evacuation of hematoma and hemostatic repair during laparotomy; the worst cases might call for hysterectomy.

Internal iliac arteries ligation may be specifically indicated in the absence of any identifiable cause of PPH, in the event of trauma involving vaginal and cervical lacerations, or in case of PPH originating from broad ligament and pelvic side walls. However, it is time-consuming and presents manifold technical challenges, such as the presence of enlarged uterus and operating through a small transverse incision in a pelvis full of blood. This procedure requires careful dissection of the retroperitoneal space and identification of the internal iliac vein and the ureter. It is also possible to mistakenly ligate the external iliac instead of the internal iliac artery, leading to loss of the ipsilateral lower limb unless promptly corrected [42]. Therefore the presence of surgeon familiar with this operation and local anatomy is necessary; the operation is not advised as a first-line technique, especially for a surgeon who rarely operates in the pelvic retroperitoneal space.

Severe and/or prolonged blood loss can interfere with blood clotting processes and lead to a state of disseminated intravascular coagulopathy. In this situation suturing the tears and lacerations is useless and leads to creation of new bleeding points where the stitches are applied. In cases like these physicians must consider vaginal packing as well [43].

Vaginal gauze packing for at least 24 h is a traditional and effective conservative method of tackling PPH associated with lacerations and hematomas; in the latter case it is often used after hemostatic surgical repair.

Nonetheless, the effect of gauze roughness, so useful for the obstetrician during manual exploration of the uterus, might well lead here to sloughing off the edematous vaginal mucosa. The great volume of gauze necessary for packing the vagina can absorb a significant amount of blood and conceal continuing PPH. Gauze packing stops bleeding from a raw or a sutured surface by direct pressure, and gauze might adhere to the vaginal wall. Resulting lesions might lead to vaginal scarring and adhesions associated with postnatal discomfort and dyspareunia. To combat this, a therapeutic approach has been developed where the gauze is moistened with lubricating gel or antiseptic cream [44]. Yet interfering with blood clots which are often situated partially in the vaginal wall and partially in the thickness of the gauze is almost unavoidable and might lead to a possible resumption of bleeding during its removal, which is a clear disadvantage.

An alternative is represented by another conservative method of vaginal laceration management lacking certain disadvantages of gauze packing, the balloon tamponade, which should be considered in case of persisting PPH where the blood loss cannot be readily terminated by appropriate surgical techniques. A great advantage of the balloon is that its silicone wall is nonwettable and does not adhere to wounds. The balloon does not cling to the adjoining tissues and does not slough off superficial layers of vaginal mucosa on withdrawal as can occur with vaginal gauze packing.

In our opinion, vaginal BT along with fulfilling its primary purpose of hemostasis should not impair the profuse early discharge of lochia from the postpartum uterus, quite significant during the first 24 h after birth.

However, existing balloons might act as barriers to free outflow of uterine cavity contents and interfere with the

physiological processes of postpartum period; clearly, a iatrogenic lochiometra might lead to absorption fever and endometritis. There is also a distinct possibility of occult bleeding in case the balloon does not cover the top edge of laceration, when the blood can accumulate unseen behind the balloon. Hence any vaginal balloon must also provide an outlet for the blood and lochia, especially taking into account that it might well remain in the vagina for longer than 24 h.

Our autonomous vaginal balloon catheter has been developed taking those problems into account. Efficacy of hemostasis can be evaluated with ease as the wide lumen of its shaft allows the blood to escape through the internal space of the shaft instead of accumulating behind the balloon (Fig. 16.13).

The wide channel of the balloon shaft creates the conditions necessary for satisfactory drainage of the uterus and makes it possible for the lochia to flow out of the uterine cavity unobstructed, while the balloon remains inside the vagina for many hours. This is important as a prophylaxis of infection-related postpartum complications.

Depending on the severity of lacerations or hematomas, vaginal BT might take 24–36 h. The liquid-filled vaginal balloon requires the indwelling urinary catheter.

16.9 Discussion

Physiologic increase of maternal total blood volume during the course of gestation by approximately 50 % provides a reserve necessary for compensating the blood loss occurring at delivery. It is important to remember that in healthy women giving birth, most commonly reclining on a bed with their legs elevated, their compensatory mechanisms cope very well with acute blood loss of up to 1,000–1,200 ml without significant hemodynamic problems making the vital signs of hypovolemia relatively insensitive. Also, intrapartum blood loss is often underestimated by the obstetricians by as much as 50 %. Yet further increase in blood loss by circa 300–400 ml leads to an often unexpected failure of physiological compensatory mechanisms manifested

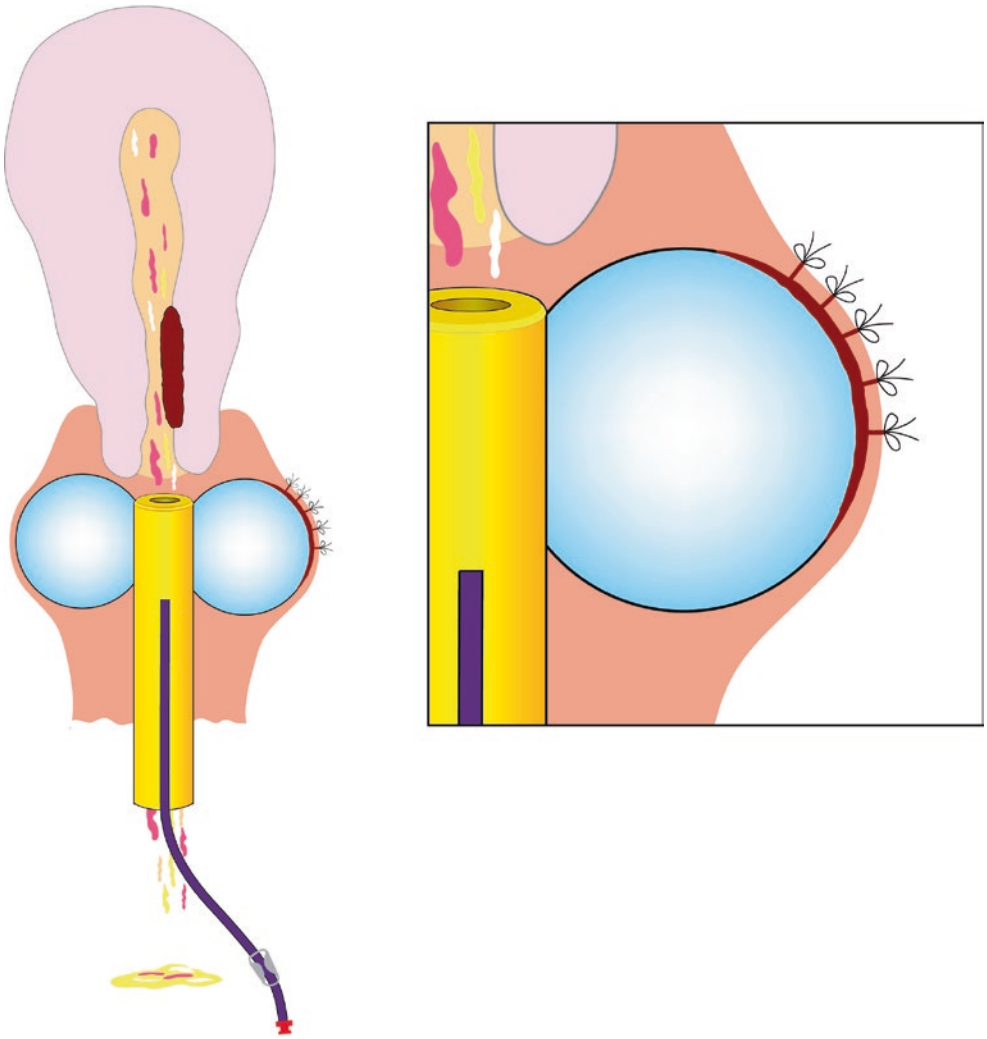

Fig. 16.13 Autonomous vaginal catheter: tamponade of sutured vaginal laceration. Free outflow of lochia

by tachycardia, hypotension, pallor, and other symptoms of hypovolemic shock.

Arresting PPH before the blood loss approaches 1,500 ml and vital signs change is extremely important. Intravenous fluid replacement with crystalloids and colloids at an earlier stage of PPH must assure that intravascular volume remains adequate for perfusion of vital organs and prevention of any permanent damage to them.

Nevertheless, stopping the bleeding by either mechanical or surgical means in time, before massive intrapartum blood loss takes place, remains the absolute priority for the obstetrician. Local hemostatic intervention targeting the bleeding organ, in our case the uterus, remains one of the staples of surgery. Once PPH is stopped, pathophysiological cardiovascular mechanisms immediately lead to rapid abatement of hemodynamic disruption and general improvement in the patient's condition.

Looking at the treatment armamentarium available in case of PPH, one understands that it is very scarce and limited to calling for assistance, fundal massage and bimanual compression, intravenous access with two large-bore catheters, emptying the bladder, uterotonic drugs, fluid replacement, and aortic compression. Subsequent intervention should include a thorough inspection of birth canal and surgical repair of any lacerations. The uterus should then be explored, with any retained products removed manually. In the majority of PPH cases, those methods are sufficient for arresting the bleeding.

If the bleeding continues in spite of uterotonics used, manual exploration performed, and traumatic PPH excluded, the obstetrician must grasp the exceeding severity of this particular clinical case threatening the life of the woman.

Nowadays at this turning point in PPH management, one correct, simple, and quick step by the clinician can swing the situation back to safety, arrest the bleeding, and obviate the need for hysterectomy.

This step is applying the method of *intrauterine balloon tamponade.*

When we consider the features of intrauterine BT, it must be highlighted that we have overcome the main antiphysiological principle of tamponade action: blocking of the uterine contractility restoration by the balloon.

We have stepped away from the classic tamponade method analogous to that in other medical specialties when the bleeding cavity (nasal, esophageal, etc.) is mechanically filled with a rigid plug, to wait until blood clots form in the vessels.

Our method is perhaps best described not as a version of BT but as a dynamic support for the temporary weakened myometrium. We provide the uterus with a rest until it is able to constrict placental vessels by itself.

This support simultaneously stops the bleeding and provides the uterus with priceless time to recover. The obstetrics team may step aside as there is no need to hurry or to goad the uterus on – the bleeding has been arrested by the balloon. The clinician should patiently wait for the uterus to restore its contractility and to demonstrate by the higher fluid level in the tank that myometrium has recovered from atony and is functional again. Once it happens, the balloon gradually diminishes in size while still providing the uterus with assistance when required and not interfering with further restoration of myometrial function. This friendly approach to the uterus permits contractile activity to be restored within 30–40 min.

The method became much more effective once the vaginal balloon catheter was developed to assist the uterine balloon catheter.

The joint use of two catheters has given the obstetrician new capabilities when managing PPH because of (1) secure retention of the uterine balloon inside the uterus with the cervix dilated after delivery and (2) compression of lower uterine segment between the balloons.

The combination of these two catheters has proved most useful in the management of women with placenta previa, with PPH originating in the lower uterine segment characterized by poor contractility and at the same time by rich blood supply from the well-developed subperitoneal vascular network with its many anastomotic connections.

Implementing such compression on the lower segment placental bed in a noninvasive manner using two elastic balloons assembled in place presents obvious advantages over the surgical method of compression suturing where the anterior and posterior walls of the uterus are attached to eliminate cavity space and compress the site of bleeding, the technique which is difficult to perform.

The most complex cases where the surgeons separate placenta accreta or resect the affected segment of the uterus necessitate using certain supplementary techniques along with DBAS, such as hemostatic external uterine supraplacental pleated sutures that leave the uterine cavity free for the balloon and bilateral ligation of the descending branches of the uterine artery.

It is important to emphasize that all the techniques described above must be employed at the same time, immediately after the extraction of the fetus, in order to save precious time and to limit blood loss. Evaluating the performance of each method separately is excluded; the struggle with a massive PPH should be a comprehensive effort involving DBAS, suturing, and artery ligation.

In those extremely rare cases when employing the whole complex of hemostatic techniques fails to stop bleeding, it is clear that the patient is the one to die of exsanguination unless hysterectomy is performed. This understanding comes early enough, before the development of hemorrhagic shock and when the general condition of the woman is satisfactory.

Abdominal delivery is associated with a significantly higher risk of bleeding and hysterectomy in comparison with vaginal delivery. Yet on the other hand existing CD techniques provide for the unique opportunity to perform an unusual procedure, absolutely impossible in a vaginal delivery, and permitting the simple and highly effective prevention of such major CD complications as bleeding and infection.

We have designed an auxiliary tool, a flexible thin plastic probe to make abdominal retrograde insertion of the balloon catheter into the uterine cavity easier (Figs. 16.9, 16.10, 16.11, and 16.12). And if the balloon catheter, a simple, cheap, noninvasive, and safe instrument permitting the surgeon to prevent those complications in view of the complete uncertainty regarding their likelihood, especially in the high-risk group, is available, then the solution is obvious. Surgical damage inflicted upon the uterus must be compensated. The best way to do it is to insert a balloon catheter into the uterine cavity.

The place of vaginal packing in treatment of genital tract lacerations has been significant, as there are certain clinical situations where tamponade is necessary. Perhaps at present we can state that it is time to abandon vaginal gauze packing, just as postpartum uterine gauze packing was superseded.

Among the many shortcomings of gauze as a tamponade medium, we must underscore the real possibility of continuing occult bleeding and blocking of lochia flow from the uterine cavity. Those disadvantages have been overcome with the assistance of our autonomous vaginal catheter.

The large balloon (capacity >300 ml) is mounted at the distal end of the wide shaft of the vaginal catheter. Once the balloon is filled with liquid, the distal pole of the balloon becomes funnel-like; any liquid (blood, lochia) collecting above it freely flows into the wide lumen of its shaft and then outside.

Conclusion

1. Free flow balloon tamponade is a highly effective method of treating PPH of the most common kind, those caused by uterine atony. The method can be used by a single trained caregiver in any setting, even in the ambulance car or at home.
2. Double-balloon assembly system (DBAS) is the mainstay of the complex of hemostatic measures in PPH when bleeding is precipitated by uterine morphological abnormalities compatible with preservation of the uterus (placenta previa/accreta etc.).
3. Joint simultaneous use of DBAS, external supraplacental pleated sutures, and descending uterine artery branch ligation makes possible timely identification of patients in need of hysterectomy, who will otherwise die and represent *the DBAS test for hysterectomy*.
4. Application of DBAS alongside the two conservative surgical techniques described above has been associated with a greater that fourfold drop in hysterectomy rates, practically eliminating hysterectomy in functional uterine atony PPH cases.
5. Preventative intraoperative transabdominal application of intrauterine balloon tamponade is a highly effective mechanical noninvasive method of avoiding hemorrhagic and infectious caesarean delivery complications.
6. Autonomous vaginal balloon catheter ensures reliable vaginal tamponade in cases of trauma, permitting free outflow of lochia and excluding the possibility of PPH remaining occult.
7. Manual exploration of the uterus in PPH is compulsory when uterotonics fail and lacerations are repaired, to be done before the intrauterine balloon tamponade application.

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Complications of Regional Anesthesia

17

Antonella Cotoia, Lucia Mirabella, Pasquale Raimondo, and Gilda Cinnella

17.1 Introduction

17.1.1 History of Regional Anesthesia

"*In dolore paries filios,*" "In pain you will bring forth children" (Gen. 3-16). The biblical citation confirms the association between labor and pain, an unchanged conviction until the era of obstetric anesthesia began with the first administrations of ether or chloroform during childbirth (Snow 1853). Nowadays, there is worldwide agreement that pain, when unrelieved, may have adverse effects on the course of labor and maternal and fetal well-being. Pain relief during labor is safe and helpful, and epidural analgesia (EA) is the only available consistently effective technique of pain control. A joint statement by the American Society of Anesthesiologists and the American College of Obstetricians and Gynecologists asserts that maternal request is a sufficient medical indication for pain relief during childbirth and that pain management should be provided whenever medically indicated [1]. Among the major pioneers of locoregional anesthesia, we can find William Halsted, who performed truncal blocks with cocaine injections but died as cocaine addicted (Fig. 17.1); James Leonard Corning (1855–1923), who was an American neurologist, mainly known for his early experiments on neuraxial blockade (the anatomy of the epidural space was not entirely well studied in the era of Corning) (Fig. 17.2); and Gaston Labat, who together with his colleagues founded the original American Society of Regional Anesthesia in 1923 (Fig. 17.3).

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Regional anesthesia is extremely safe, but, like all of surgical procedures, it is not completely safe and carries risks. However, serious complications related to obstetric neuraxial anesthesia occur rarely but can be devastating when they occur. There have been various case reports, case series, or retrospective studies, but the lack of large comprehensive database makes difficult an accurate estimation of the incidence of complications. In recent decades the development of maternal anesthesia practice, either spinal or epidural block, has improved pregnancy safety, particularly in women undergoing cesarean delivery, living in rural areas, or having preexisting medical comorbidities [2, 3]. The purpose of this chapter is to discuss the complications occurring during regional anesthesia, their diagnosis, and treatment.

Before to start, please remember the correct and pathological anatomy of the column, before and during pregnancy (Figs. 17.4, 17.5, 17.6a, b, and 17.7).

17.2 Cardiovascular Complications During Regional Anesthesia

17.2.1 Hypotension

Hypotension is almost inevitable adverse complication of spinal anesthesia induced by sympathetic block, which causes a significant decrease in the venous return and cardiac output due to systemic vascular resistance reduction and venous capacitance increase.

In the literature there is not one accepted definition of hypotension and the incidence of hypotension varies between 1.9% and 71%, depending on the chosen definition. The most frequently applied definition are systolic arterial blood pressure below 100 mmHg or a decrease below 80% from baseline (Fig. 17.8).

The higher level of block (T4) (Fig. 17.9) required for cesarean delivery, the anatomic and physiologic changes (Fig. 17.10) of parturients, and the reduced sensitivity to the endogenous vasoconstrictors associated with increased

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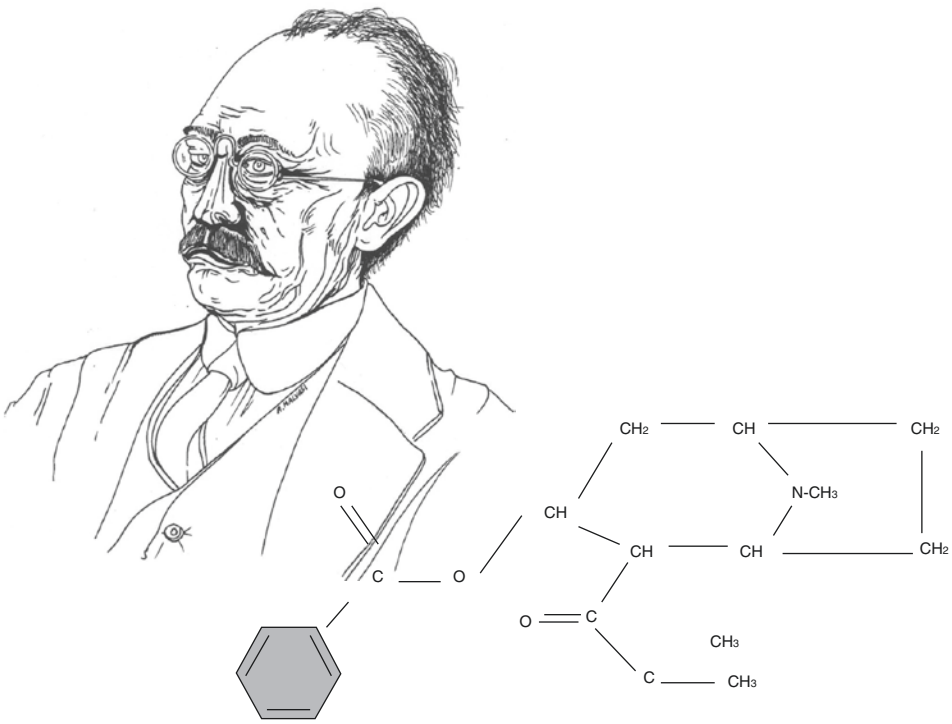


Fig. 17.1 William Halsted, he performed truncal blocks with cocaine injections, but he died as cocaine addicted

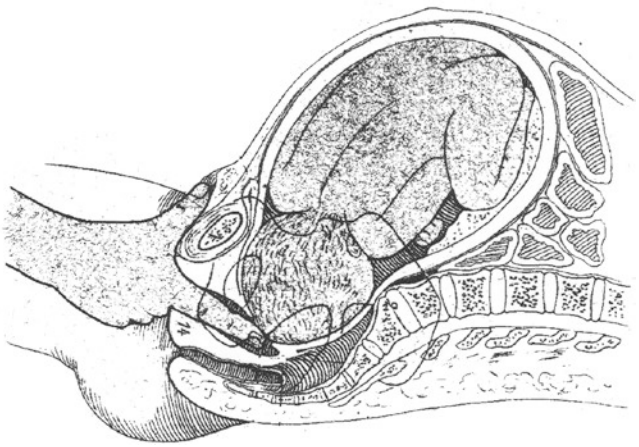


Fig. 17.2 James Leonard Corning (1855–1923), he was an American neurologist, mainly known for his early experiments on neuraxial blockade

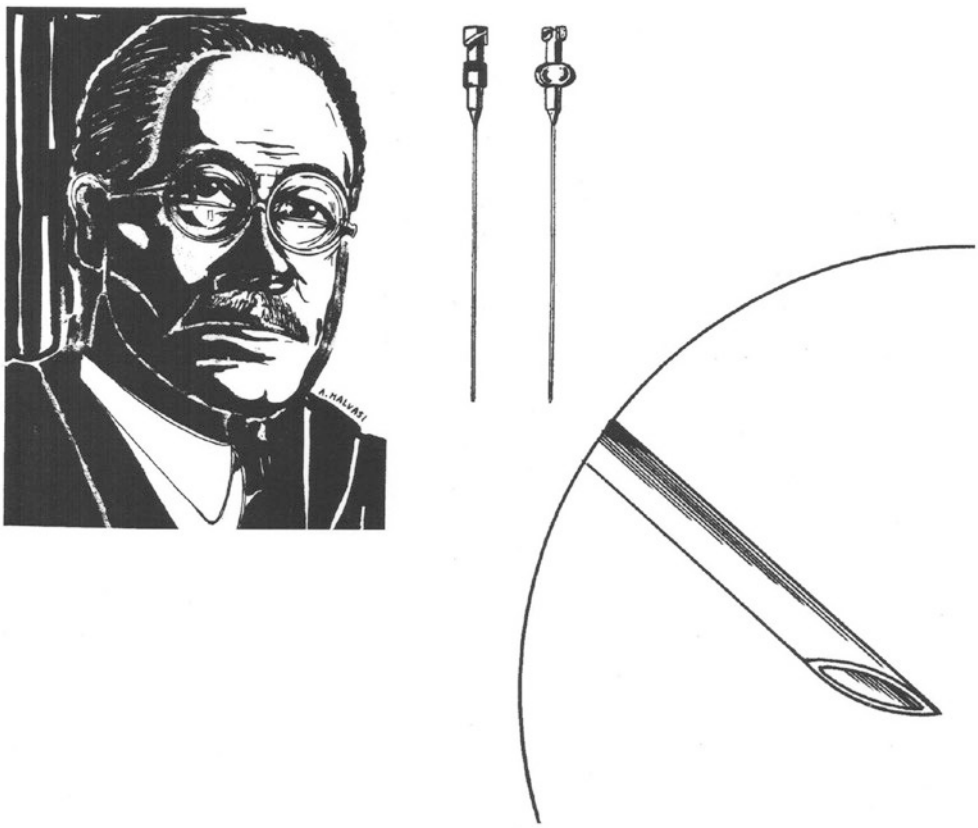


Fig. 17.3 Gaston Labat. Needles for spinal anesthesia employed at the time of Labat

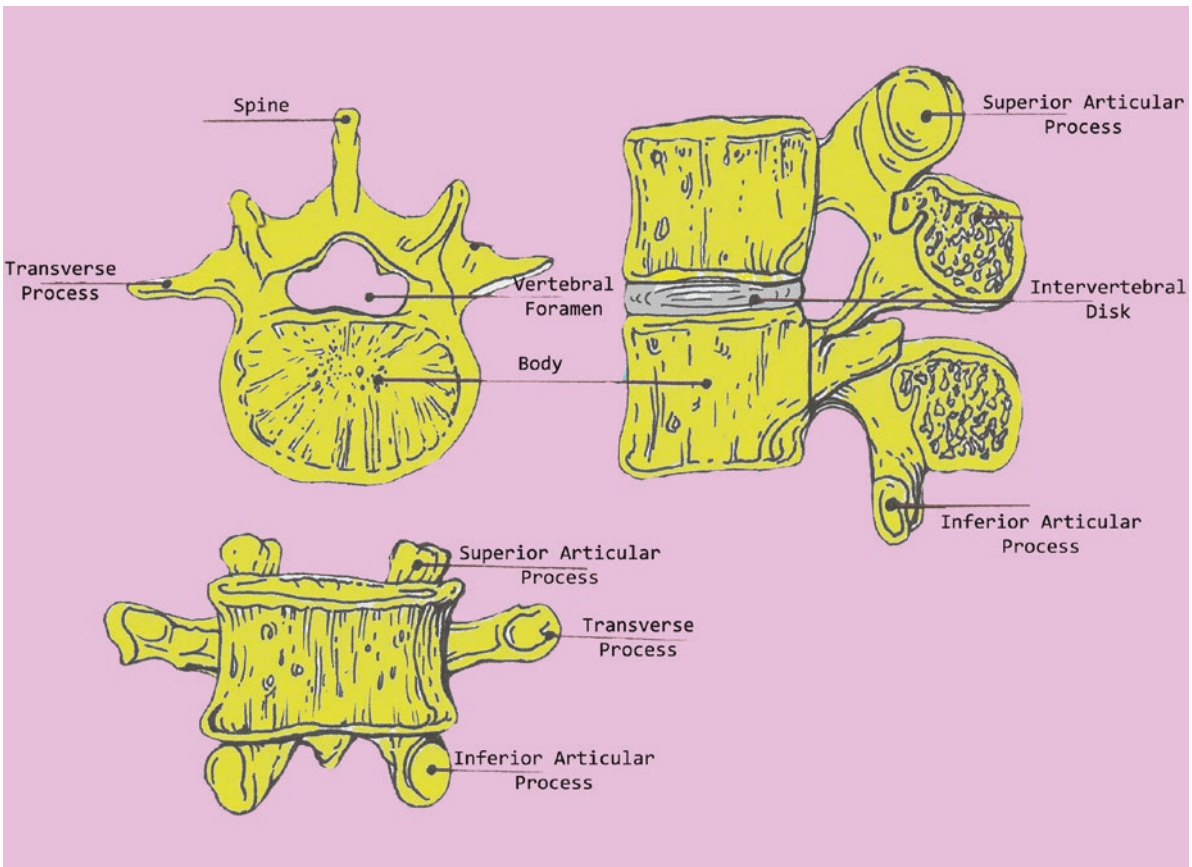


Fig. 17.4 The correct and pathological anatomy of the column: the lumbar vertebrae

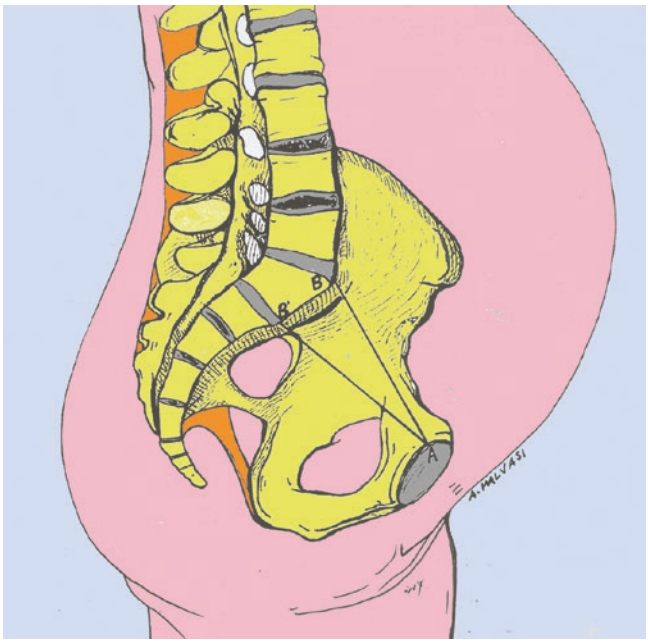


Fig. 17.5 The bones of the vertebral canal and its angle

synthesis of endothelium-derived vasodilators, determining an increased susceptibility to the effects of sympathectomy, expose the parturients to higher risk of hypotension (Fig. 17.11) [4, 5].

Nausea and vomiting (Fig. 17.12) are frequently associated with hemodynamic changes induced by spinal blockade. A decrease in blood pressure at the critical level, compounded by aortocaval compression, may compromise uteroplacental blood flow, leading to fetal hypoxia and acidosis. Risk factors for hypotension are maternal body mass index ≥29 kg/m^2, age ≥35, hypertension, higher fetal weight, associated comorbidities, and local anesthetic injected. Therefore, in the literature local anesthetics dose has been widely studied in order to find out the right matching between hemodynamic changes and perioperative analgesia quality [6–15].

In same cases during cesarean section, the uterine exteriorization, uterine replacement in the abdominal cavity, and other maneuvers on the bowel produce the same nausea and vomiting (Fig. 17.13).

Indicators for predicting alterations of autonomic function, leading to an increased risk of hypotension under spinal anesthesia, are positional blood pressure and heart rate changes between the left lateral to supine position [16]. However, bedside test can be associated to the promising advanced techniques as the assessment of heart rate variability performed on the same day of surgery, although it lacks standardization [14].

Maternal hypotension can be prevented by intravenous fluid preloading (Fig. 17.14) and left uterine displacement to avoid aortocaval compression (Figs. 17.15 and 17.16), associated with vasopressor therapy (Table 17.1) [17].

One of the foremost methodologies is the prophylactic administration of 10–20 ml/kg intravenous fluids over 15 min. Colloid solution would be more effective as compared to crystalloids due to their higher colloid osmotic effect and a longer half-life in the intravascular space, but preloading of colloids is not popular routinely due to risk of anaphylactoid reactions, derangement of coagulation, suppression of platelet activity, and increased costs. On the other hand, large volume of crystalloids may induce the atrial natriuretic peptide secretion contributing to peripheral vasodilatation [18]. According to results from the general population receiving spinal anesthesia and due to studies establishing that maternal hypotension occurs in the period just following the spinal injection, the rapid coloading administration of fluid (15 ml/kg) initiated immediately on induction of spinal anesthesia had also gained a widespread acceptance in obstetric fluid management, especially during emergent conditions [18–19]. However, a slower speed of injection and lower dose of spinal anesthetic resulted in a lower incidence of hypotension or delayed onset [14].

Intravenous vasopressors can be used to treat hypotension in laboring women without adverse effect on the fetus (Table 17.2) [20]. In the absence of maternal bradycardia, phenylephrine may be preferable because it increases systemic vascular resistance more than ephedrine. Conversely, ephedrine raises stroke volume and heart rate more than phenylephrine but impairs fetal acid-base status stimulating fetal beta-adrenergic receptors with consequent fetal tachycardia and increased metabolic demand [21].

Other authors did not observe the difference between the two vasopressors in the incidence of fetal acidosis and confirmed the higher incidence of bradycardia, due to baroreceptor reflex response, in patients receiving phenylephrine which is a selective α1-adrenergic receptor agonist [22]. Since the optimal dosing regimen is unclear, novel closed-loop double pump automated systems are developed to automatically administer vasopressors, based on continuous noninvasive arterial pressure monitoring with remarkable benefits on maternal hemodynamic stability during cesarean delivery [23]. Noninvasive cardiac output monitoring might be indicated for patients with severe cardiac disease, while the decision to perform invasive hemodynamic monitoring

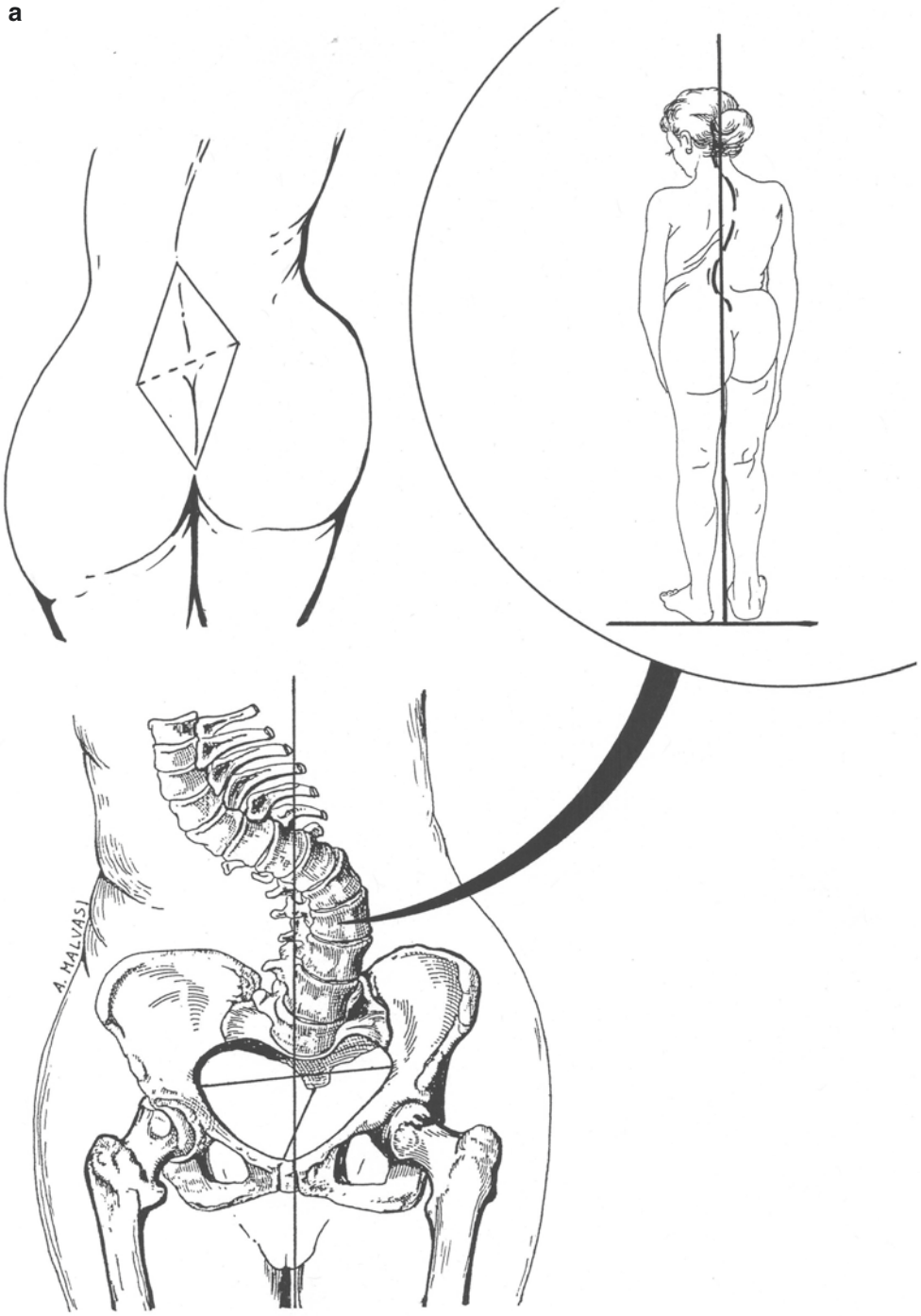


Fig. 17.6 (**a**) Example of adult spine that presents pathological curvatures. (**b**) Example of adult spine that presents pathological curvatures

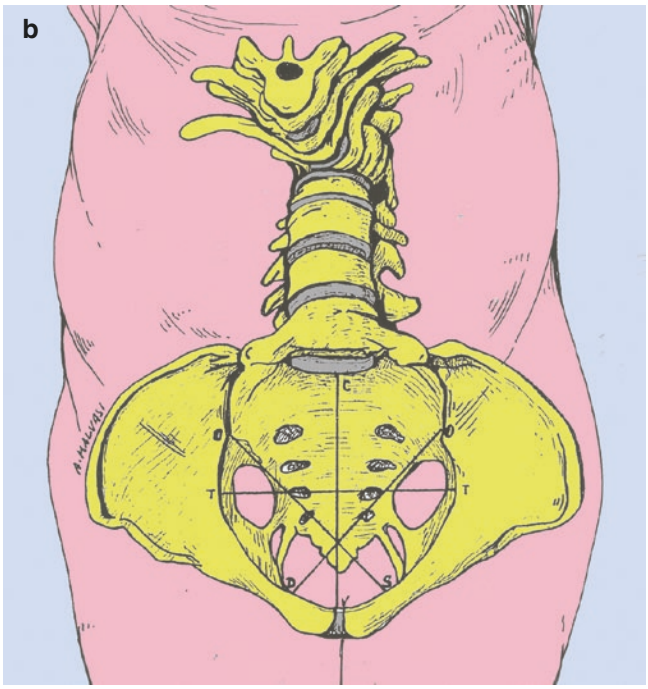


Fig. 17.6 (continued)

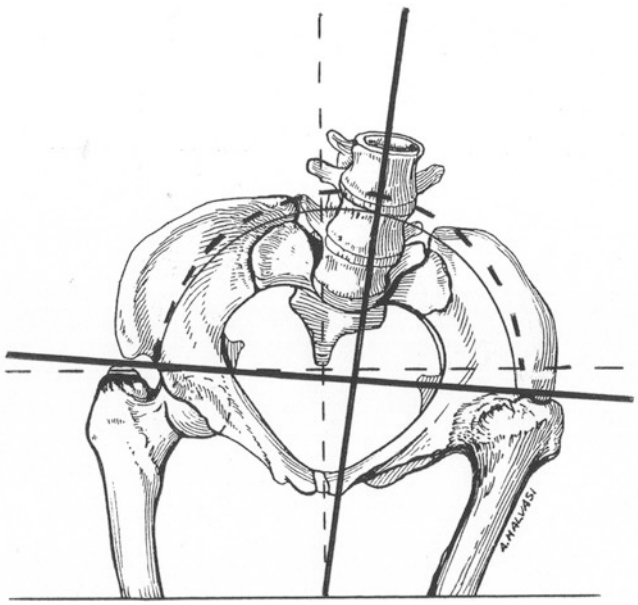


Fig. 17.7 The sacrum in anterior views and its angles

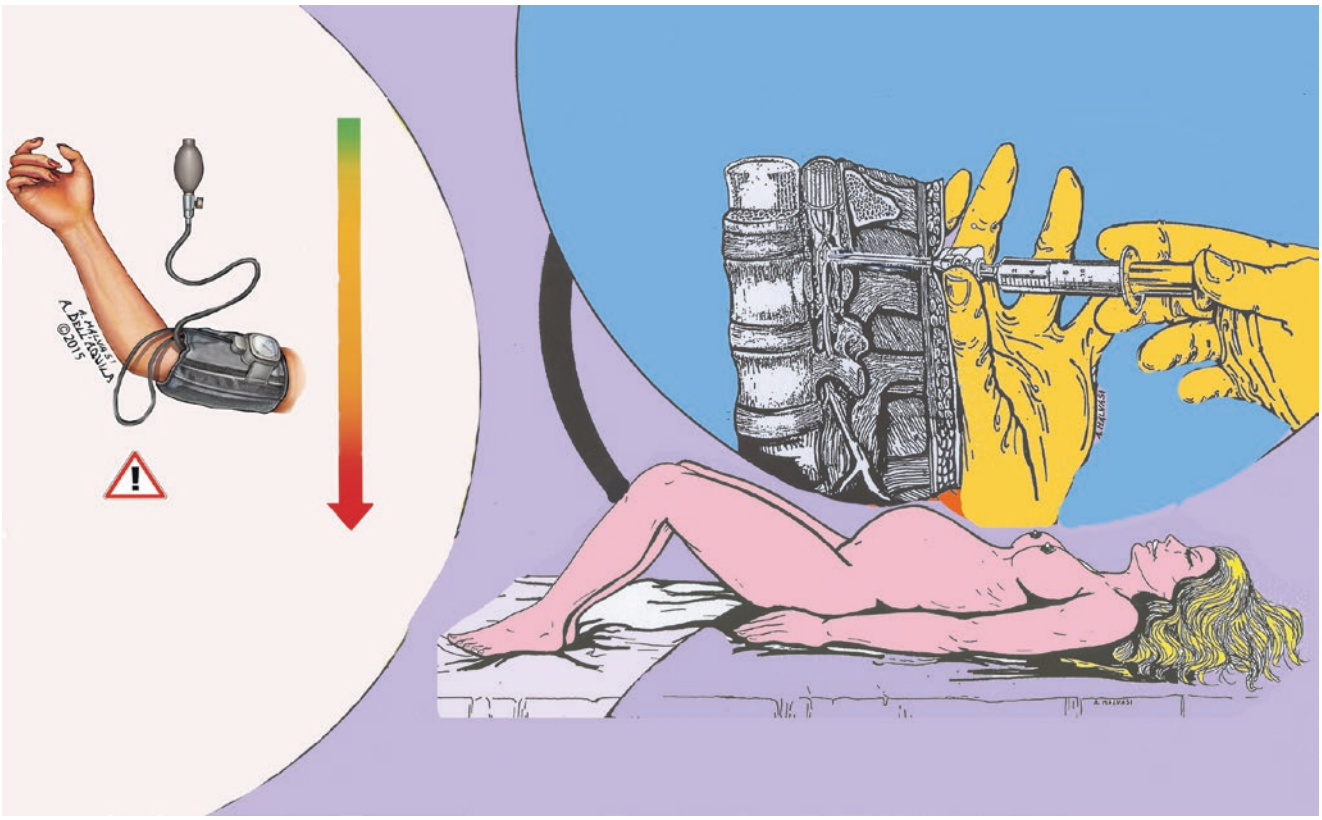


Fig. 17.8 Maternal hypotension (systolic arterial pressure of 100 mmHg or less in the *left*) after spinal anesthesia. The patient is positioned in lateral and safe position to reduce hypotension (in the *right*) (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

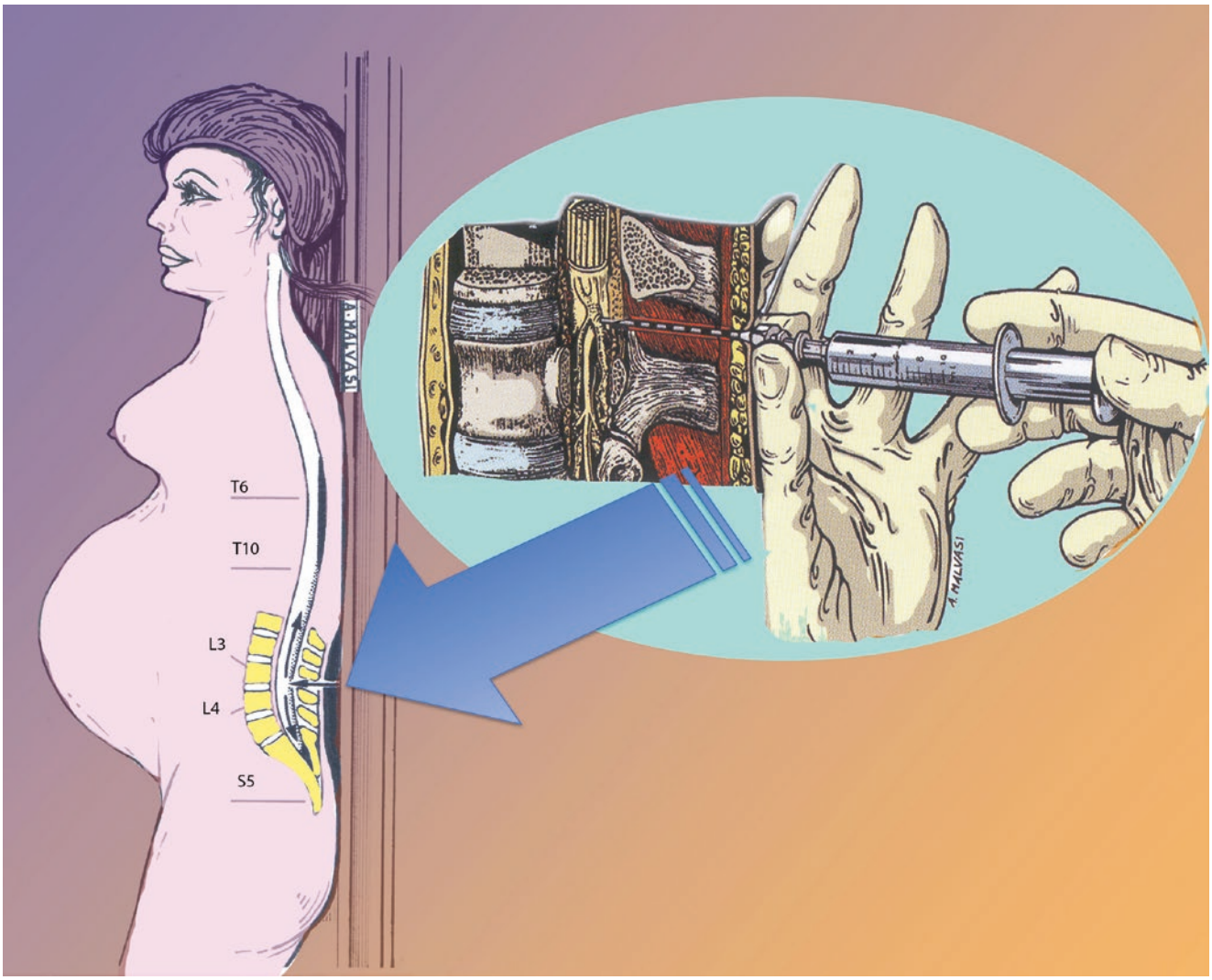


Fig. 17.9 The different level of block after injection of drug in subarachnoid space and different anesthetic drugs distribution in the spinal channel

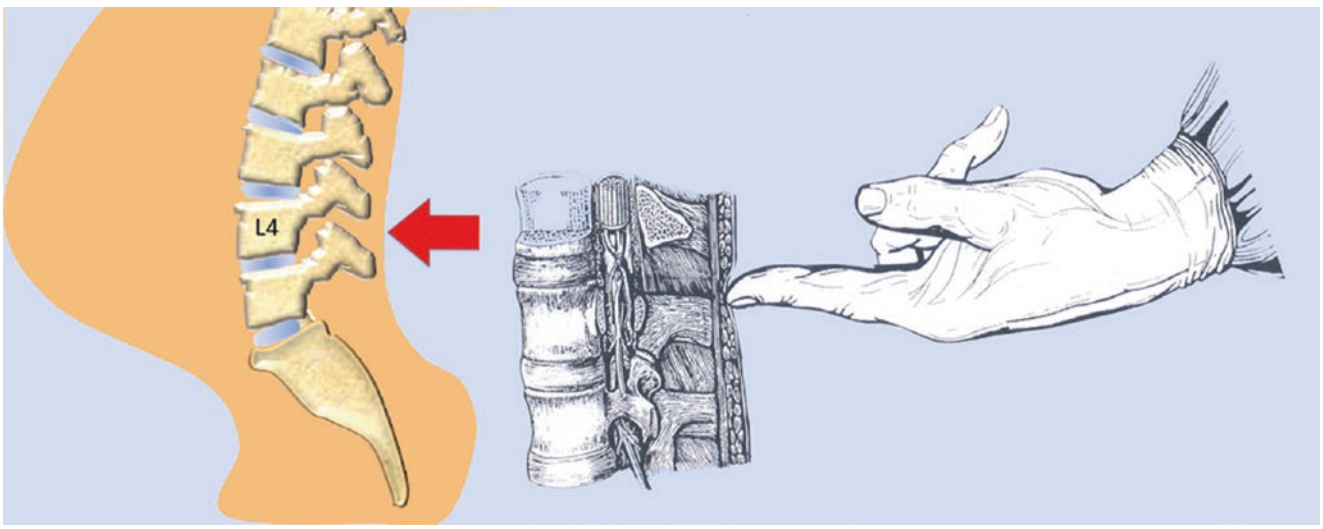


Fig. 17.10 Evaluation of the anatomic and physiologic changes of column

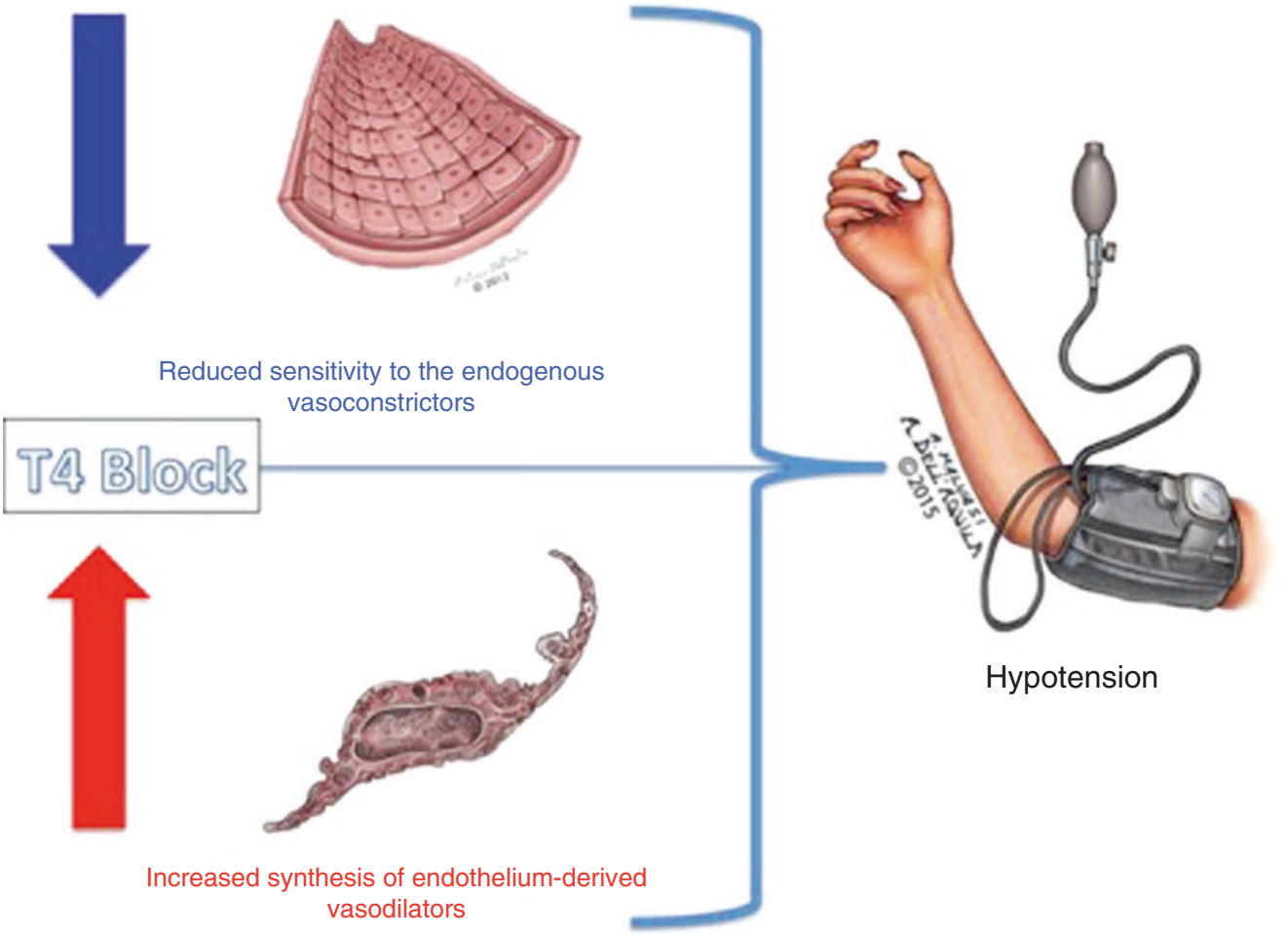


Fig. 17.11 The physiologic changes of parturients post T4 spinal block

Fig. 17.12 Maternal nausea and vomiting are the most common symptoms after spinal block (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

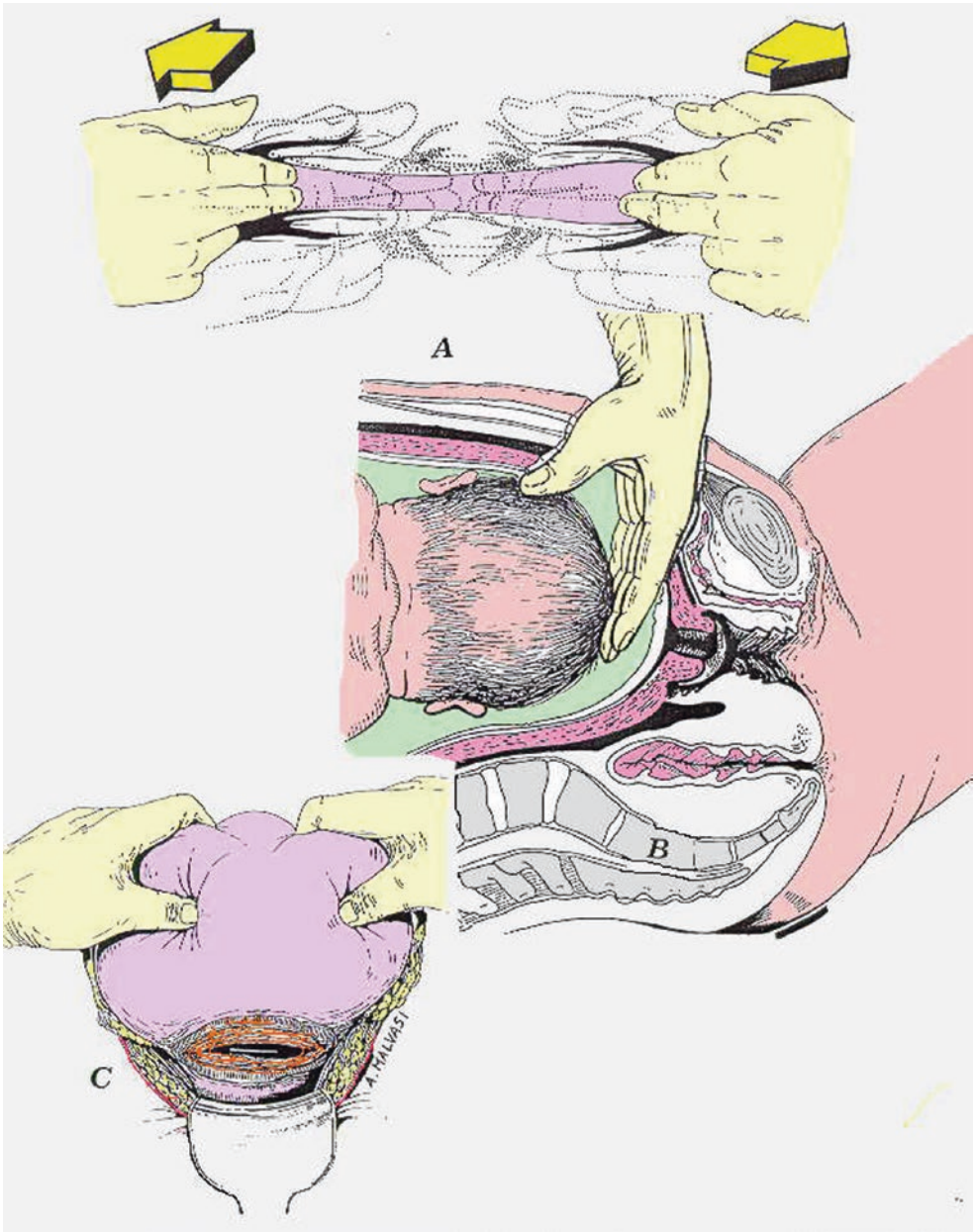


Fig. 17.13 Maternal nausea and vomiting occur during uterine exteriorization, uterine replacement in the abdominal cavity, and other maneuvers on the bowel (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

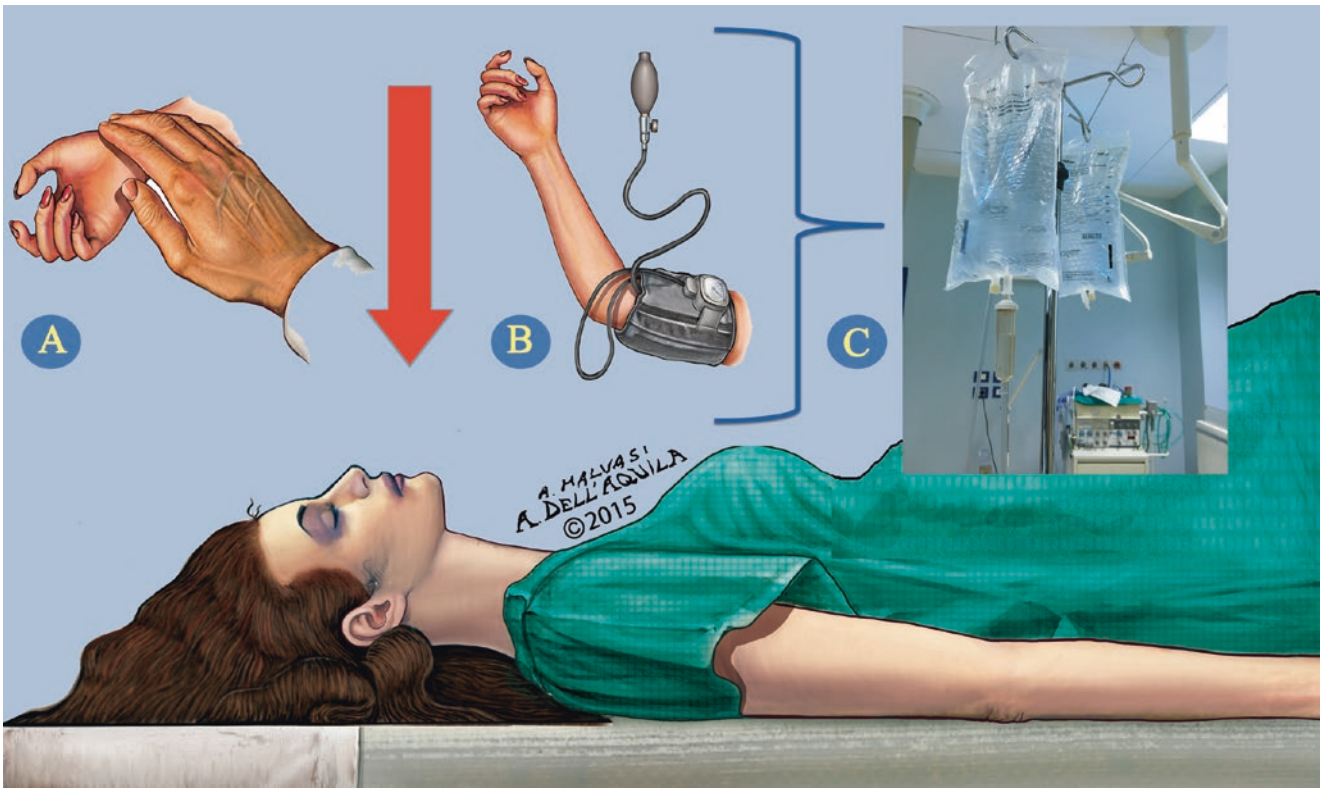


Fig. 17.14 Maternal bradycardia (**a**) and hypotension (**b**) can be prevented by intravenous fluid preloading (**c**)

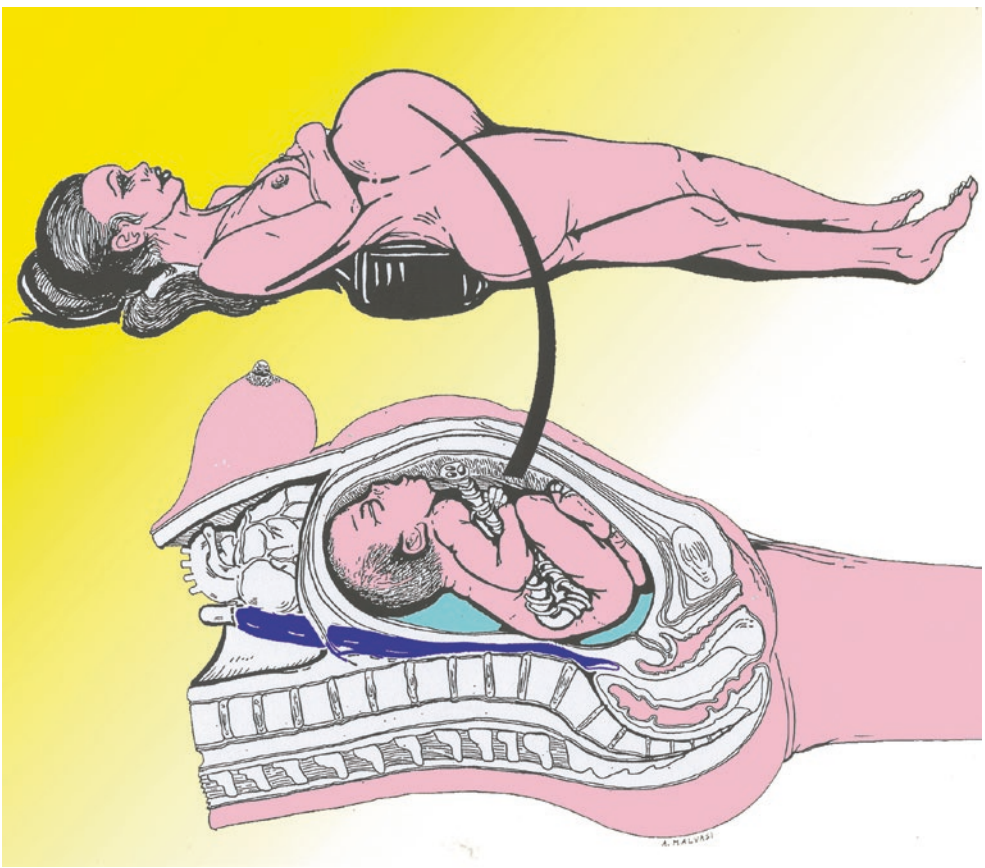


Fig. 17.15 Lateral position of parturient after spinal anesthesia with wedge pillow to displace the uterus on the left (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

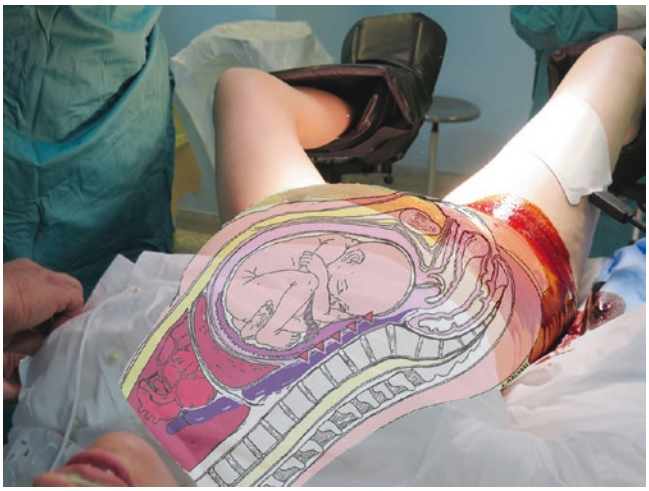


Fig. 17.16 Left uterine displacement to avoid aortocaval compression and prevents maternal hypotension after spinal anesthesia

Table 17.1 Prevention and treatment of hypotension in parturients undergoing elective cesarean delivery with spinal anesthesia

Prevention and treatment of hypotension
Fluid therapy
Timing of administration: preload – coload
Type of fluid: crystalloid, colloid
Vasopressor
Lower anesthetic doses
Leg elevation or wrapping
Elastic stockings
Left uterine displacement

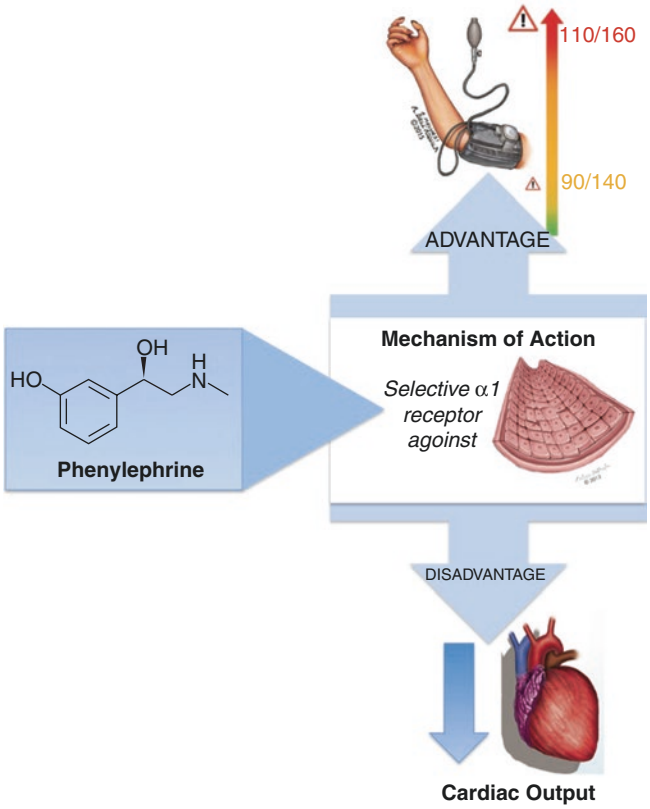


Fig. 17.17 Phenylephrine and its most important effects

Table 17.2 Comparative analysis of vasopressors used in obstetric anesthesia

Drug	Mechanism of action	Advantage	Disadvantage
Phenylephrine (Fig. 17.17)	Selective α1 receptor agonist	Peripheral vasoconstriction, raised systemic vascular resistance, and arterial blood pressure Immediate onset and short duration of action Ideal for continuous infusion No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis Reflex bradycardia can decrease maternal cardiac output
Ephedrine (Fig. 17.18)	α, β receptor agonist. Both direct and indirect effect on the sympathetic nervous system	Increased myocardial contractility (β1 receptor) Peripheral arterial and venous vasoconstriction (α receptor) Release endogenous norepinephrine (indirect effect) Does not need multiple dilutions as compared to phenylephrine	Tachyphylaxis Adverse effect on fetal Acid-base status
Methoxamine (Fig. 17.19)	α1 receptor agonist	Peripheral vasoconstriction No inotropic or chronotropic effect Rare cases of tachyphylaxis	Reflex bradycardia Adverse effect on fetal acid-base status
Mephentermine (Fig. 17.20)	α receptor agonist. Both direct and indirect effect	Peripheral vasoconstriction (α receptor) Release endogenous norepinephrine (indirect effect) Does not need multiple dilutions as compared to phenylephrine	Tachyphylaxis
Metaraminol (Fig. 17.21)	α receptor agonist. Both direct and indirect effect	Peripheral vasoconstriction (α receptor) Release endogenous norepinephrine (indirect effect) No adverse effect on fetal acid-base status as compared to ephedrine	Tachyphylaxis

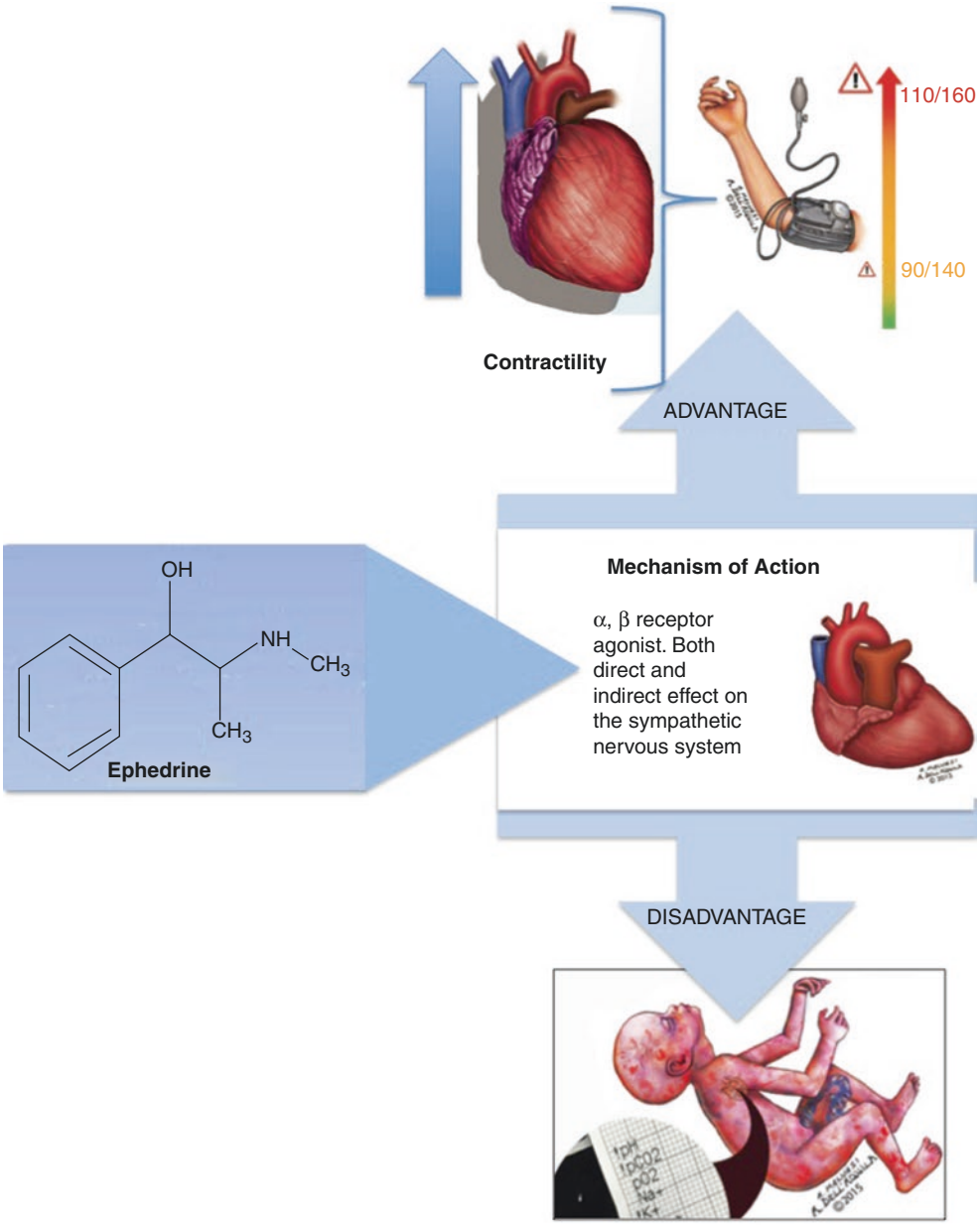


Fig. 17.18 Ephedrine and its most important effects, as cardiac output and blood pressure increasing

should be based on individual patient's medical history and cardiovascular risk factors [14, 19].

Rarely, severe hypotension with bradycardia and cardiovascular collapse can occur after central neuraxial anesthesia, secondary to activation of the cardioinhibitory reflex called Bezold-Jarisch reflex. Prompt treatment with adequate doses of vasopressors is required. If cardiac arrest does occur, cardiopulmonary resuscitation should immediately start, and the fetus should be rapidly delivered in order to improve both maternal by alleviating aortocaval compression and fetal survival prospects. At delivery oxytocin should be administered as uterotonic but must be cautiously administered because of its systemic vasodilatation and coronary vasoconstriction [24].

17.2.2 Bradycardia and Cardiac Arrest

Bradycardia and cardiac arrest are the most feared complications, whose incidence is higher with spinal anesthesia than general anesthesia. The blockade of the preganglionic cardioaccelerator fibers originating between T1 to T4 may progress to complete heart block or asystole (Figs. 17.22, 17.23, and 17.24). It is also aggravated by decreased preload after spinal anesthesia leading to decreased action of right atrial stretch receptors.

Intravenous atropine is typically used as the first line of therapy and also for prophylaxis; ephedrine is used when hypotension is associated with bradycardia or in unresponsive cases to atropine. Cardiovascular side effects are often treated

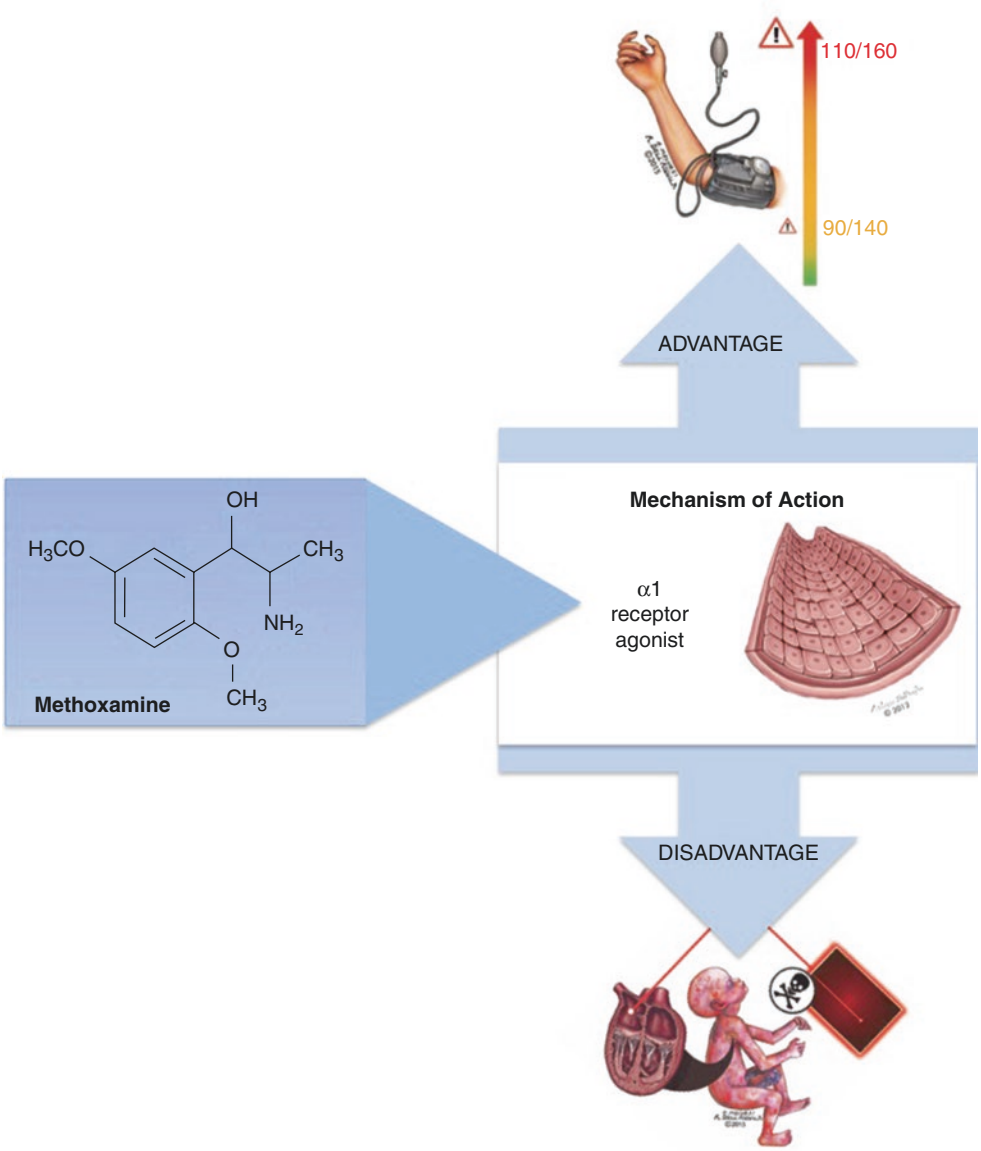


Fig. 17.19 Methoxamine and its most important effect, as augmentation of myocardial contractility and reduction of fetal oxygenation

when the parameters vary more than 20 % from their baseline, if the systolic blood pressure is less than 100 mmHg or if the patient becomes symptomatic (e.g., nausea or faintness) [25].

17.3 Post-dural Puncture Headache

Post-dural puncture headache (PDPH) is troublesome iatrogenic complication of unintended dural puncture during epidural or spinal technique, mostly observed in parturients population with an incidence between 0 and 2.5 % [25]. The depletion of cerebrospinal fluid (CSF) volume, by leaking through the dural hole, causes a decrease in the intracranial pressure, stretching of pain-sensitive cranial structures, and may induce a compensatory cerebral vasodilatation according to the Monro-Kellie doctrine [26]. The experience of the anesthesiologist, patient position, and type and size of needle do not appear to influence the incidence of PDPH as recently observed [27]. PDPH is usually severe, positional, and localized in frontotemporal-occipital regions, radiating to the neck and shoulder. Nausea, vomiting, vertigo, tinnitus and hyperacusis, photophobia, and diplopia (due to traction on the sixth cranial nerve) might be associated with headache (Fig. 17.25). Two cases of thoracic back pain without headache have been described [28].

According to the International Headache Society, the PDPH appears within 7 days following the dural puncture, elicited when moving from the supine position to sitting or standing up [29]. It is usually self-limiting and full recovery can generally be expected within a week. In a small minority of cases, symptoms may persist for weeks, months, or even years, although permanent cases have rarely been reported.

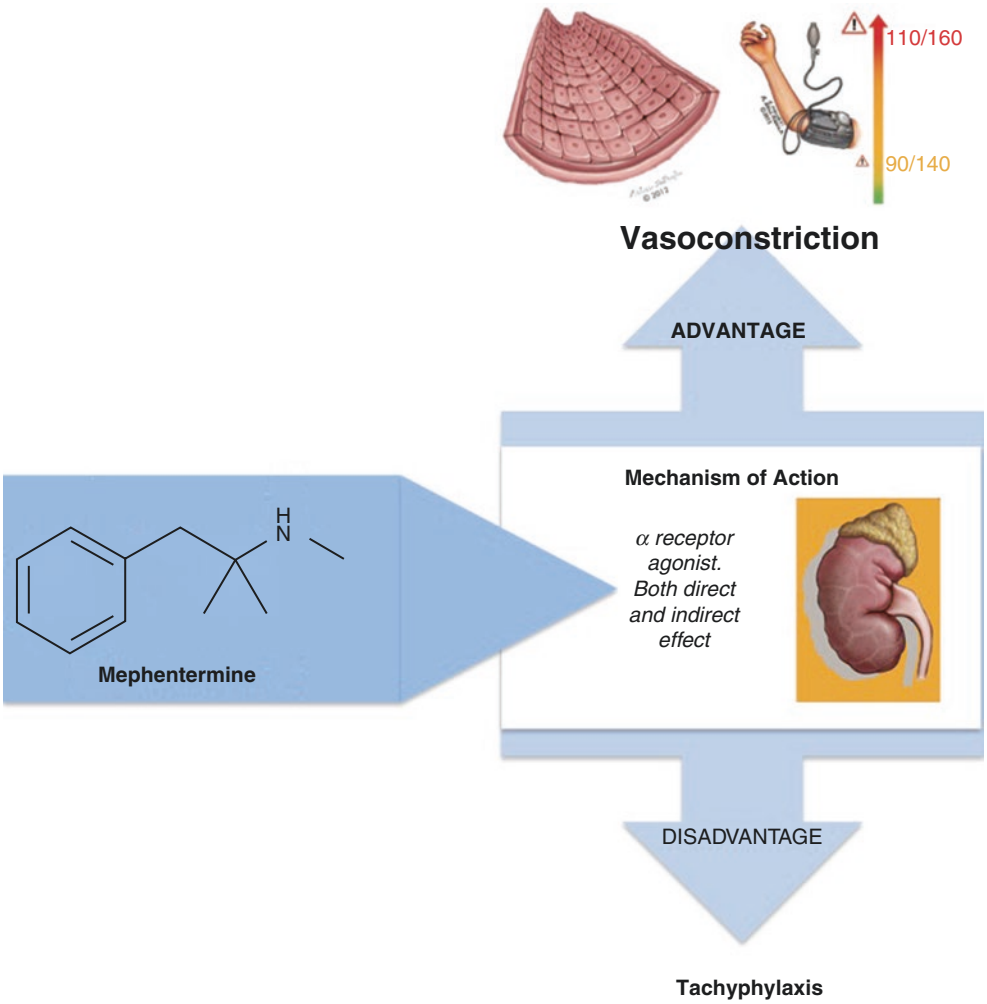


Fig. 17.20 Mephentermine and its most important effects

Tables 17.3 and 17.4 describe other causes of headache for differential diagnosis.

In atypical post-dural puncture symptoms, a cerebral CT scan or magnetic resonance imaging could be performed to exclude the possibility of developing serious complications.

No consensus among anesthesiologists regarding the management algorithm of PDPH to replace the lost CSF seals the puncture site and controls the cerebral vasodilatation. Many physicians recommend approximately 24 h of bed rest and aggressive hydration as a conservative therapy, despite lack of evidence in recent meta-analysis. Bed rest may postpone the occurrence of the headache but does not prevent it, while excessive fluid intake has no preventive or therapeutic benefit, stimulating the mother diuresis and more frequent mobilization [30–32].

Analgesic therapy with acetaminophen, nonsteroidal antirheumatic drugs, and caffeine are traditionally used as conservative treatment (Fig. 17.26).

Caffeine and sumatriptan (Fig. 17.27), a serotonin type 1-d receptor agonist, have cerebral vasoconstriction effects and might be considered in the early treatment of mild PDPH. However, caffeine has transient effect within 48 h of PDPH; it is also found in breast milk and could lead to neonatal irritation, while side effects of sumatriptan include pain at the site of injection and chest tightness [32].

Cosyntropin, a synthetic form of adrenocorticotropic hormone, has been reported to be effective in the treatment of refractory PDPH. Adrenocorticotropic hormone is theorized to work by stimulating the adrenal gland to increase CSF production and producing beta-endorphin effects. Caution should be used in diabetic patients [33].

Oral gabapentin (Fig. 17.28) and pregabalin (Fig. 17.29) are newer therapies studied to provide relief of pain in obstetric patients with PDPH [25, 31].

Autologous epidural blood patch (EBP) has been considered for a long time as "the gold standard" in the treatment of severe PDPH [34]. Although controversies surrounding it remain, prophylactic EBP deserves consideration in cases of accidental dural perforation with a Tuohy needle. This procedure should be avoided immediately after local anesthetic (LA) epidural dose administration, because of the high epidural pressure resultant and interference of LA on blood clot

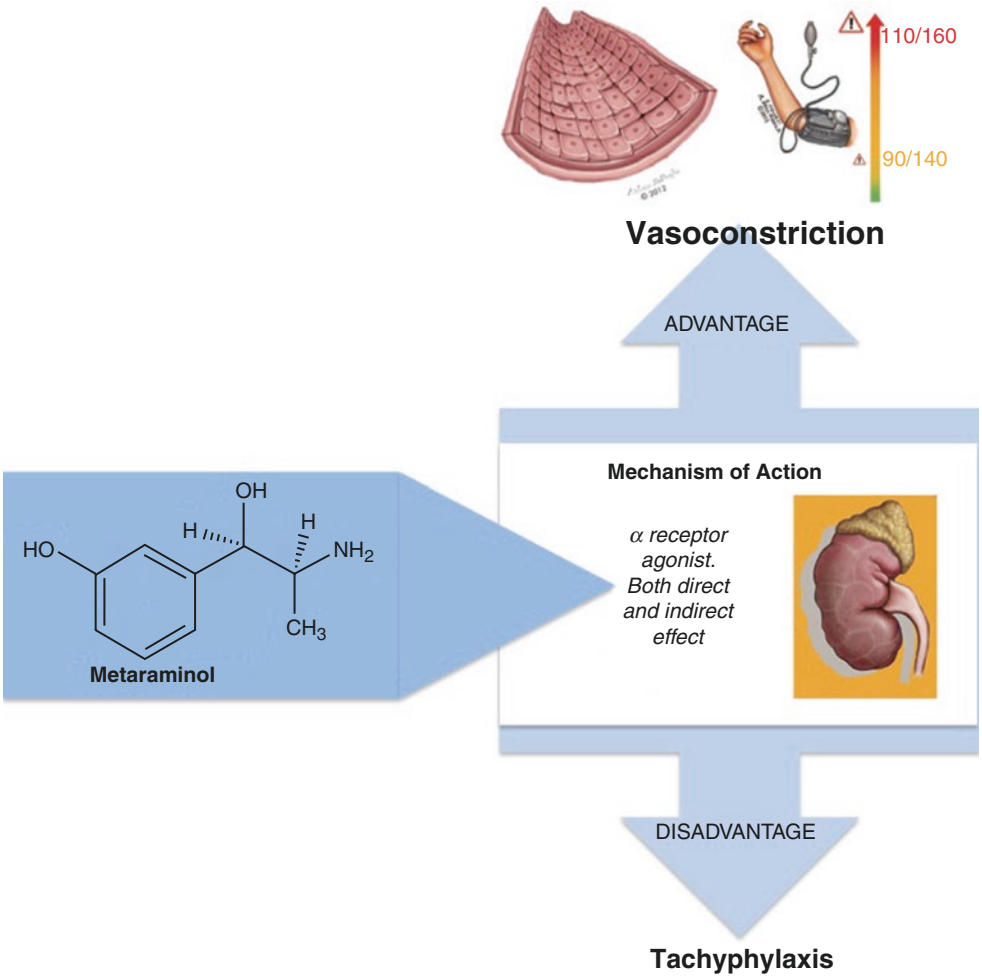


Fig. 17.21 Metaraminol and its most important effects

formation [35]. Contraindications to perform epidural analgesia are those that normally apply to EBP and include refusal by the patients, infection at the site of puncture, coagulopathy, and severe systemic infection. HIV infection is not considered to be a contraindication to EBP. One case has been reported of spontaneous intracranial hypotension in a pregnant patient at 32 weeks of gestation treated with an epidural blood patch. The blood patch produced a transient improvement in symptoms which resolved with conservative therapy.

The autologous blood is not removed quickly from the epidural space and restores intracranial pressure much longer, probably for coagulation around the site of the dural hole which tampons the CSF leakage. Differently, epidural patching with non-blood substances, such as saline or colloid, transiently increases epidural pressure and has higher risk of anaphylaxis when dextran is used [31].

Epidural morphine is also effective in reducing the pain of PDPH but may leak from the dural hole into the intrathecal space and has well-known side effects including pruritus, nausea, and vomiting [36].

Briefly, the EBP procedure should be performed with the patient in the lateral position, as the PDPH renders the sitting position uncomfortable. To avoid blood clotting, one person has to attempt a sterile 20 ml phlebotomy using serial sterile syringes, each with a volume of 5 ml, while the other anesthesiologist identifies the epidural space. The preferred interspace for injection is either at the site of dural tap or one level below the previous insertion. Afterward the anesthesiologist injects the 20 ml withdrawn blood slowly through the epidural needle. He can stop earlier if patient complaints back or neck pain or radicular pain in the leg or worsening headache during the performance of the epidural injection. After the procedure, the patient should rest horizontally in her bed for 2 h.

When headache is persistent or the relief is temporary, the blood patch should be repeated while keeping the patient flat for 24 h afterward to reduce the flow of CSF through the dural rent.

Complications of EBP include the following: backache (35 %), neck pain (0.9 %), and transient temperature elevations (5 %). Potential fatal complications are subdural hematomas and, although rare, need to be followed up closely.

Consider epidural blood patch guided by fluoroscope or computerized tomography (CT) scan and surgical closure of

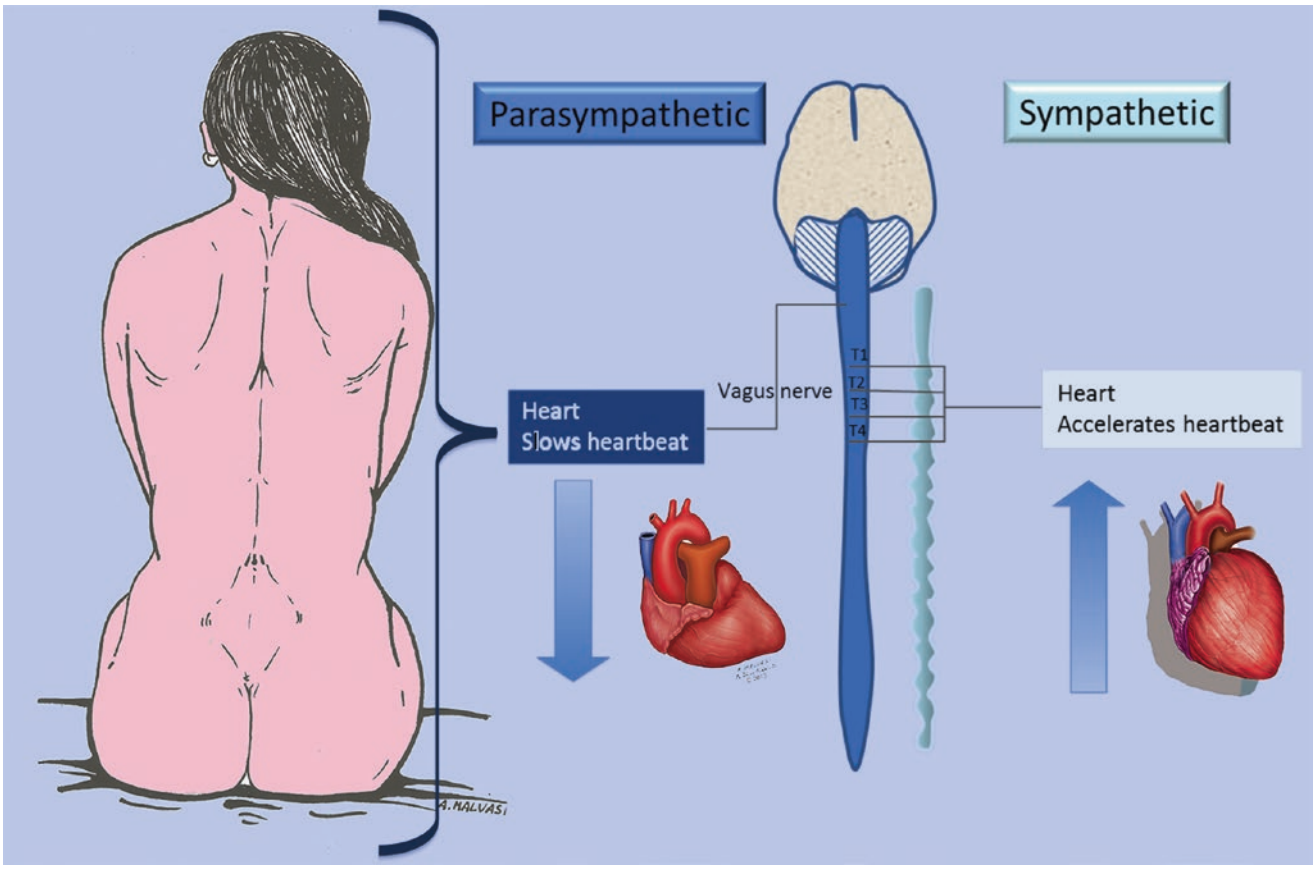


Fig. 17.22 Autonomic cardiac innervation (parasympathetic and sympathetic branches) and the heart effects

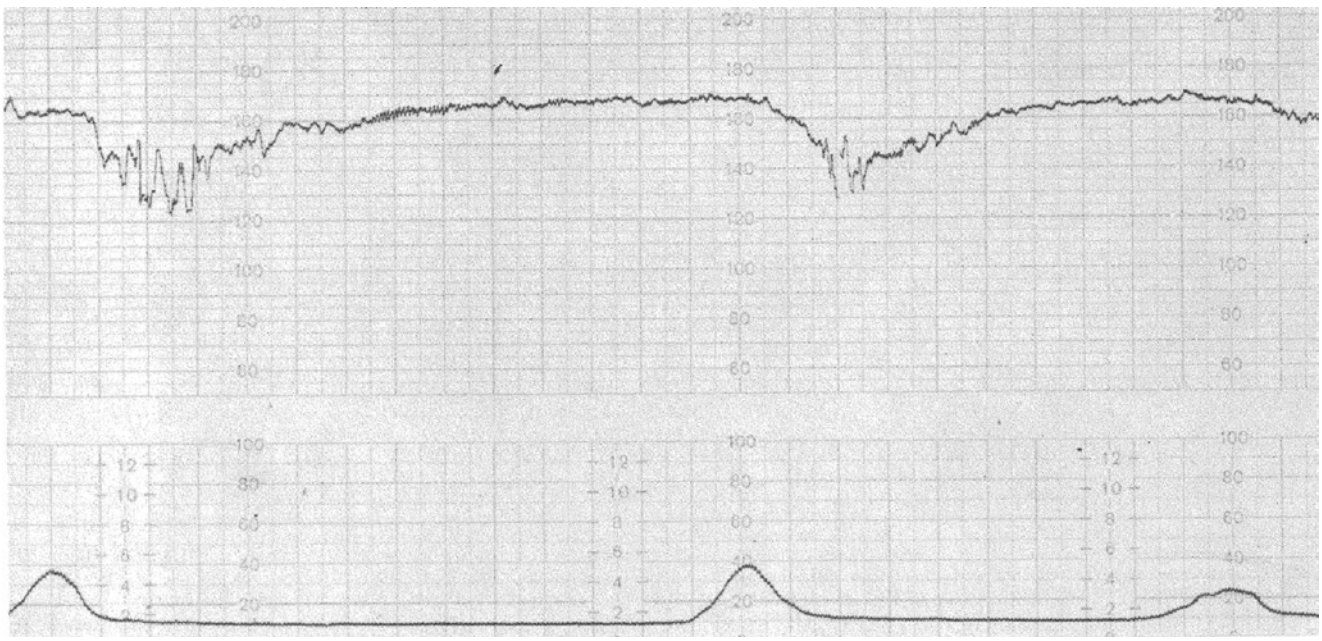


Fig. 17.23 Example of fetal bradycardia

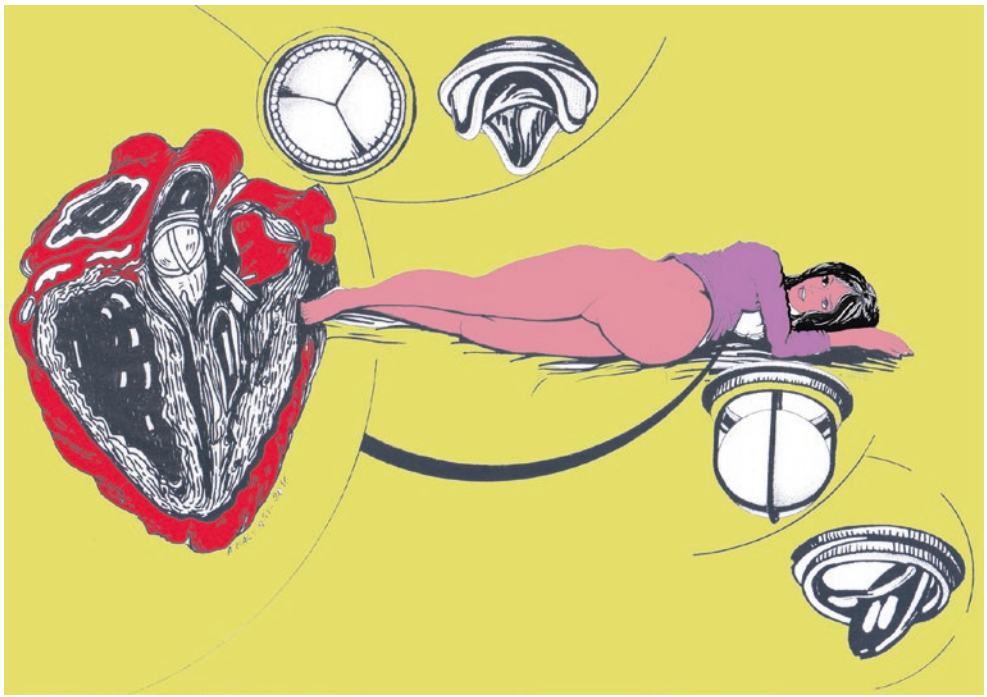


Fig. 17.24 Maternal complications: valvular heart disease and cardiac arrest after hypotension – spinal block related

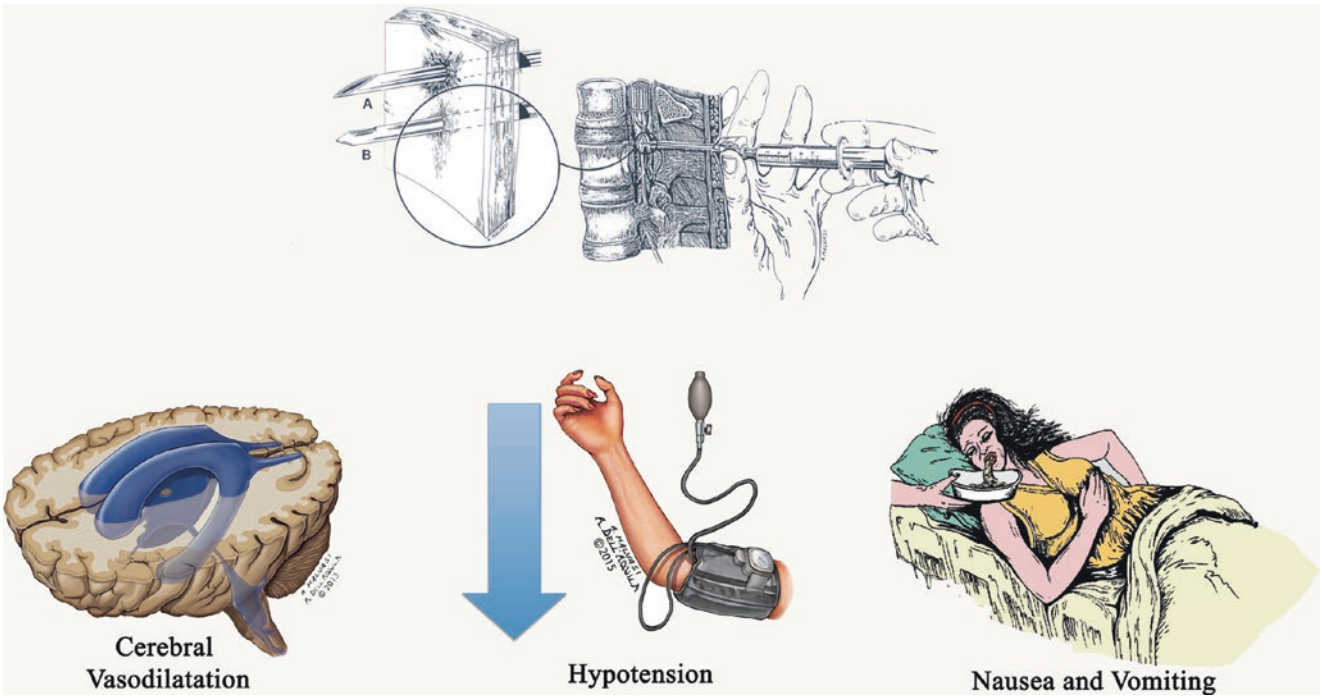


Fig. 17.25 Post-dural puncture headache and other complications

Table 17.3 Differential diagnosis of post-dural headache

Eclampsia
Migraine
Non-specific headache
Viral, chemical, or bacterial meningitis
Pneumocephalus, cerebral aneurysm
Spinal abscess
Subdural hematoma
Myofascial syndrome
Neural toxicity of the drugs
Anterior spinal artery syndrome
Cerebral venous thrombosis
Intracranial tumor

Table 17.4 Neuraxial-related injuries

Injury type	Causes
Spinal cord injury	
Direct damage	Traumatic catheterization
	High puncture level
	Unusually low conus medullaris
Indirect injury	Hematoma (both spinal and epidural)
	Abscess (both spinal and epidural)
Spinal cord ischemia	Mechanical obstruction
	Vasculopathy
	Profound hypotension
	Hemorrhage
	Vasoconstrictor
Cauda equina syndrome	Intrathecal microcatheter
	Intrathecal lidocaine (high concentration)
Meningitis	
Infective	Bacterial
	Viral
	Aseptic
Noninfective	Chemical arachnoiditis
	Anterior spinal cord syndrome
Miscellanea	Lumbosacral pain
	Local anesthetic systemic toxicity
	High neuraxial anesthetics
	Pneumocephalus
	Dural puncture and cerebrospinal fluid leak

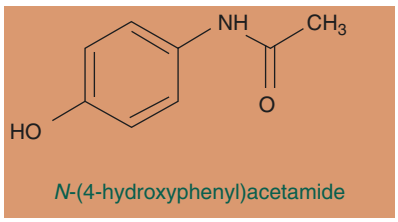


Fig. 17.26 Acetaminophen

the dural perforation if persistent CSF leak is unresponsive to conventional EBP therapy [37–39].

17.4 Infective Complications

Serious infections of the central nervous system such as arachnoiditis, meningitis, and abscess following spinal or epidural anesthesia, though rare, can be lethal. They may be associated with the bacteremia, fever, elevated white blood cells, and neurologic deficits which permit a differential diagnosis with PDPH. The source of the infection is usually the contamination by the anesthesiologist, hematological spread, or maternal immunodeficiency. Meningitis, following post-dural puncture, is typically caused by alpha-hemolytic streptococci, isolated in same cases by nasopharynx of the operating anesthesiologist. Conversely, the skin flora is generally associated with epidural abscess (Fig. 17.30), whose incidence is much higher when epidural catheters are left in place for more than 72 h.

The importance of using and documenting meticulous aseptic technique during all neuraxial block procedures is fundamental, and there is no reason not to follow the aseptic rules of the operating room. Drape and sterile gloves, surgical cap, and face mask while performing neuraxial procedures should be routine (Figs. 17.31, 17.32, 17.33, and 17.34). It is crucial to be aware of the presenting signs and symptoms of meningitis and epidural abscess whose onset could be 4–10 days after the neuraxial procedure. Minimal delay between diagnosis and treatment may result in morbidity and even death. Empirical antibacterial therapy and an appropriate antibiotic treatment can reduce the possibility of hematologic spread through the spinal cord from the site of infectious source. Finally, urgent neurosurgical treatment is necessary to drain the epidural abscess, whose diagnosis is confirmed by magnetic resonance imaging (MRI) [40, 41].

17.5 Hematologic Complications

17.5.1 Hematoma

Hematoma is a rare and well-recognized complication in patients who have received regional anesthesia. It is more frequent following epidural anesthesia or catheter placement rather than spinal anesthesia, because of the increased vascularity of the epidural space, even if it may occur spontaneously (Fig. 17.35). The literature suggests that routine platelet count can predict anesthesia-related complications in parturients with risk factors including preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low

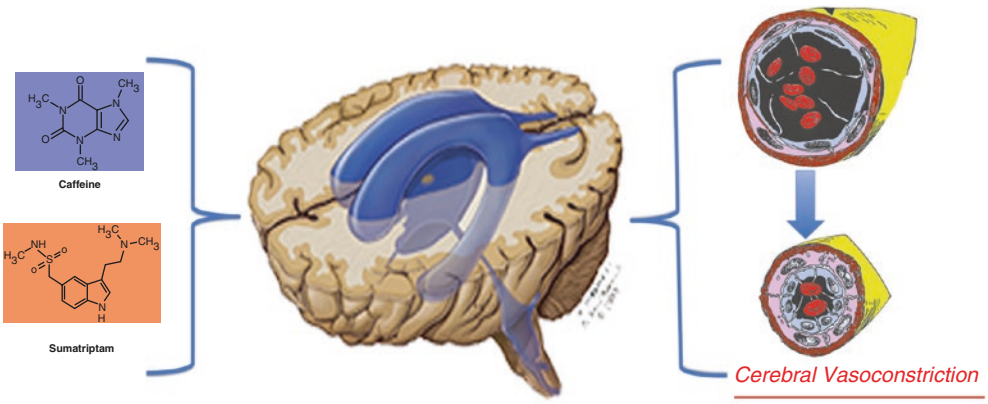


Fig. 17.27 Caffeine and sumatriptan, a serotonin type 1-d receptor agonist, have cerebral vasoconstriction effects

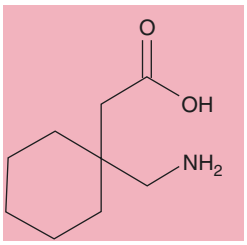


Fig. 17.28 Gabapentin

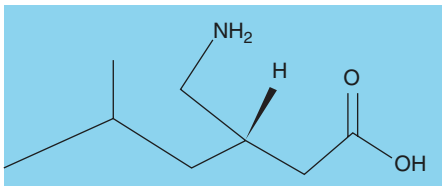


Fig. 17.29 Pregabalin

Fig. 17.31 The importance of using and documenting meticulous aseptic technique

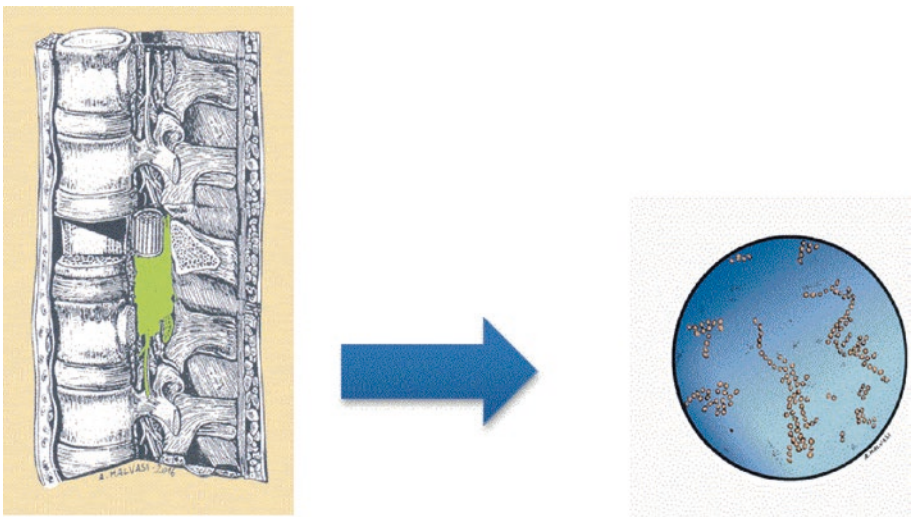


Fig. 17.30 Epidural abscess and microbiological culture

platelets), and other disorders associated with coagulopathy, renal or liver failure, and antithrombotic therapy (heparin, low molecular weight heparin, other factor Xa inhibitors, direct thrombin inhibitor, warfarin, aspirin, GPIIb/IIIa antagonists, ADP P2Y12 receptor inhibitor, etc.) (Figs. 17.36, 17.37, and 17.38). Whereas the routine intrapartum platelet count is not necessary in healthy parturient because it does not reduce parturient anesthetic complications, the guidelines recommend its request in parturients with suspected coagulopathy or at the anesthesiologist's discretion [19, 41].

The British Committee for Standards in Hematology Guidelines recommends that a platelet count of greater than 80,000 mm^{-3} is adequate for the administration of neuraxial blockade [42]. The study of platelet function with thromboelastography may be used to predict the safety of administering neuraxial techniques in parturients with thrombocytopenia. Figure 17.39 is thromboelastography, while Fig. 17.40a, b represents a normal range value for thromboelastography in healthy obstetric patient.

Recently, a study suggested neuraxial technique in parturients whose platelet count was more than 56,000 mm^{-3} with normal thromboelastography value [43].

Early diagnosis of hematoma whose symptoms include both motor and sensory deficits, such as lower extremity weakness, sensory deficit of the lower extremities, severe back pain, and bladder and bowel dysfunction, is key factor for a good evolution, and the MRI is the "gold standard" exam or alternatively CT. Neurosurgery within 8 h after the epidural hematoma is mandatory to avoid permanent neurologic sequelae [25].

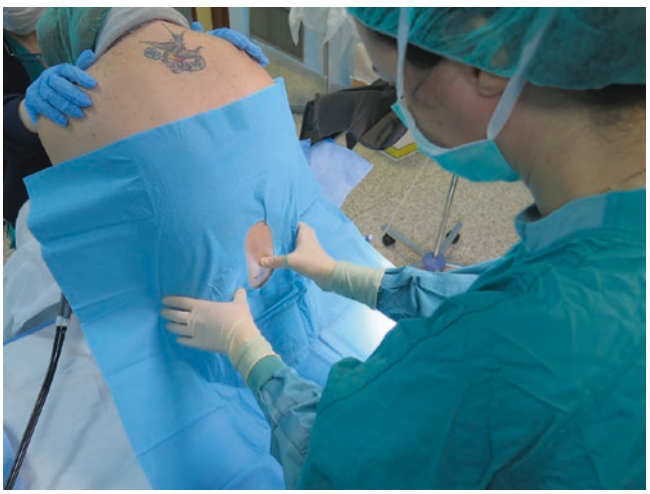


Fig. 17.32 The use of masks, surgical cap, sterile gloves, a sterile gown, and aseptic technique is required for a sterile environment

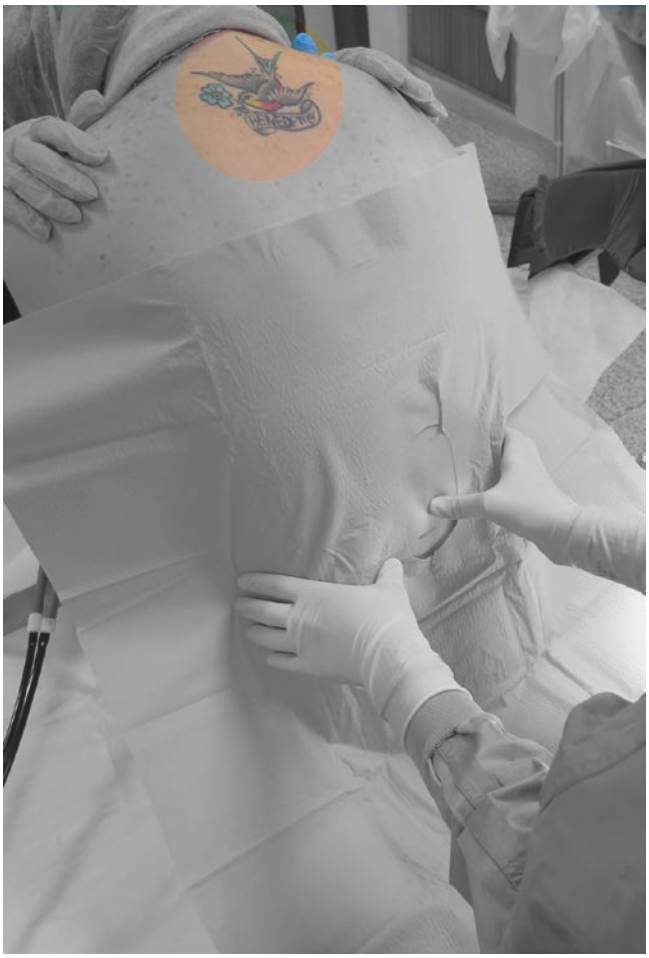
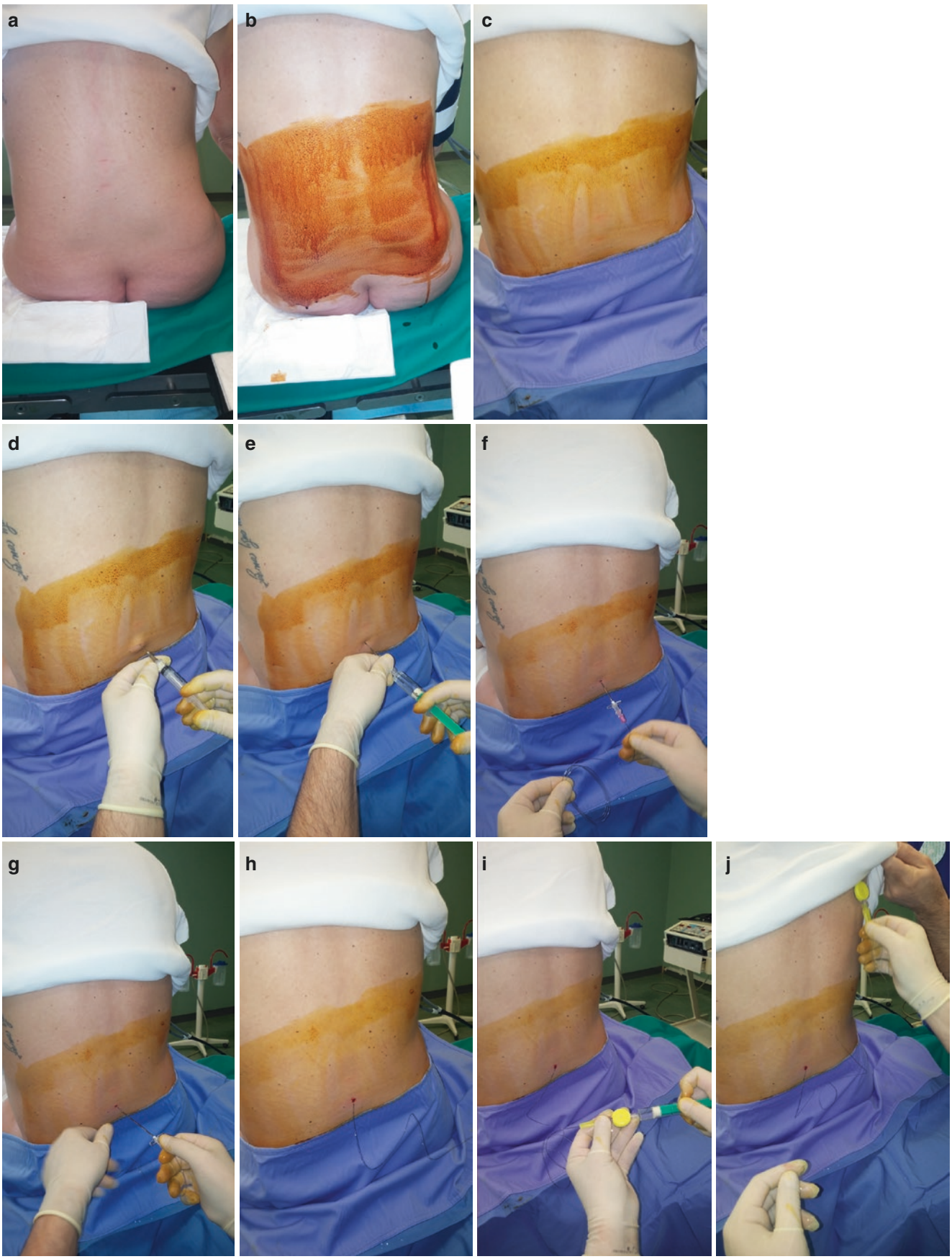


Fig. 17.33 The presence of tattoo as a contraindicated place for insertion of catheter

Fig. 17.34 (**a**–**l**) Epidural catheter placement: under aseptic conditions (**a**–**c**), epidural catheter placement was performed in the sitting position using the midline approach: tissue infiltration to the ligament flavum was performed using 5 ml of 1 % lidocaine (**d**). After, in the sitting position, a 20 G epidural catheter was inserted using an 18-gage Tuohy needle at the L3–L4 level interspace. The epidural space was identified using the loss of resistance technique with saline solution (**e**–**h**). After negative aspiration for cerebrospinal fluid and blood, a 3 ml test dose of 2 % lidocaine with adrenaline was given over 15 s through the catheter. Before insertion, the catheter and bacterial filter were primed with physiologic saline (**i**–**l**), aiming to achieve an air-free column of fluid from the connector to the catheter tip. If no sign of an intravascular or subarachnoid puncture was observed, the catheter was secured and the parturient was placed in the supine position, and after the main dose of fentanyl (100γ) and levobupivacaine (0.0625 %) diluted with isotonic sodium chloride solution to a volume of 15–20 ml was injected. When labor protracted, additional doses of drugs were administered at hourly intervals on the indication of maternal request. Two hours after childbirth, the epidural catheter was removed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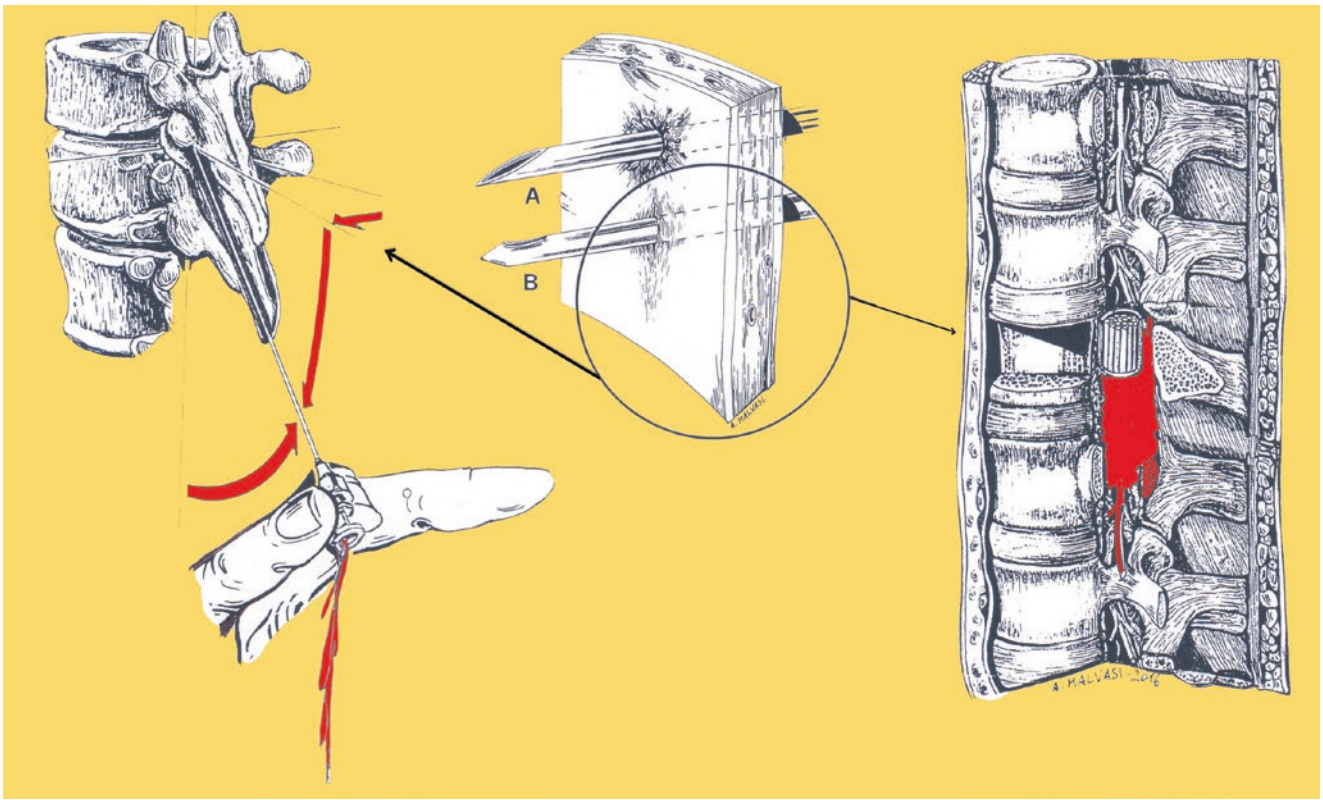

Fig. 17.35 Significant epidural hematoma

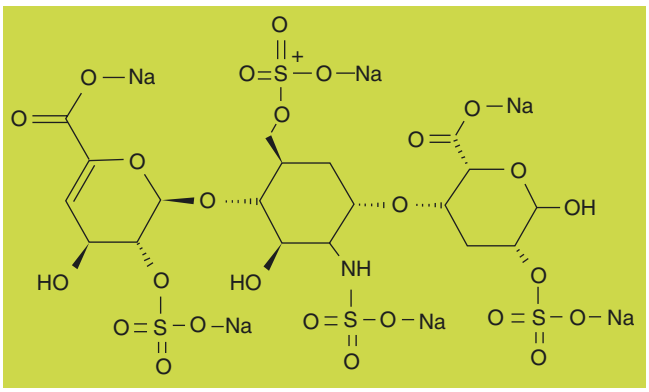

Fig. 17.36 Heparin

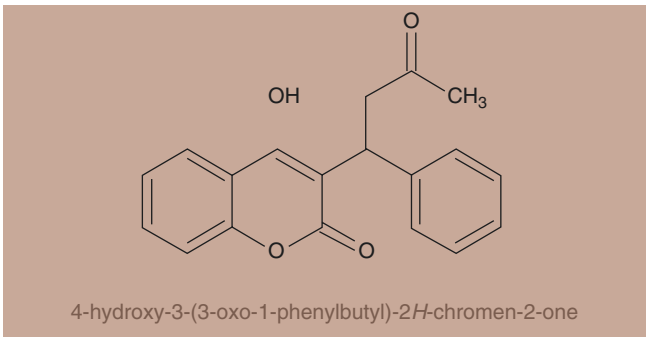

Fig. 17.37 Warfarin

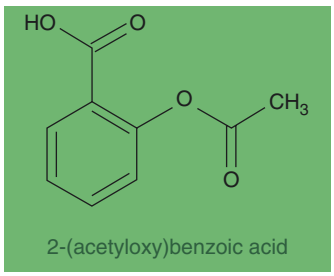

Fig. 17.38 Aspirin

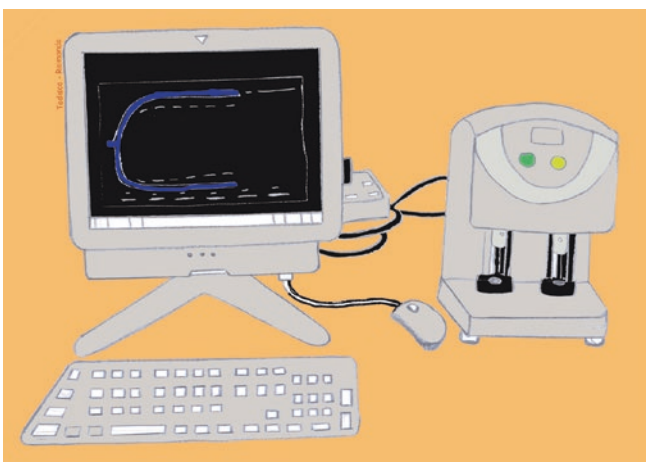

Fig. 17.39 The thromboelastography

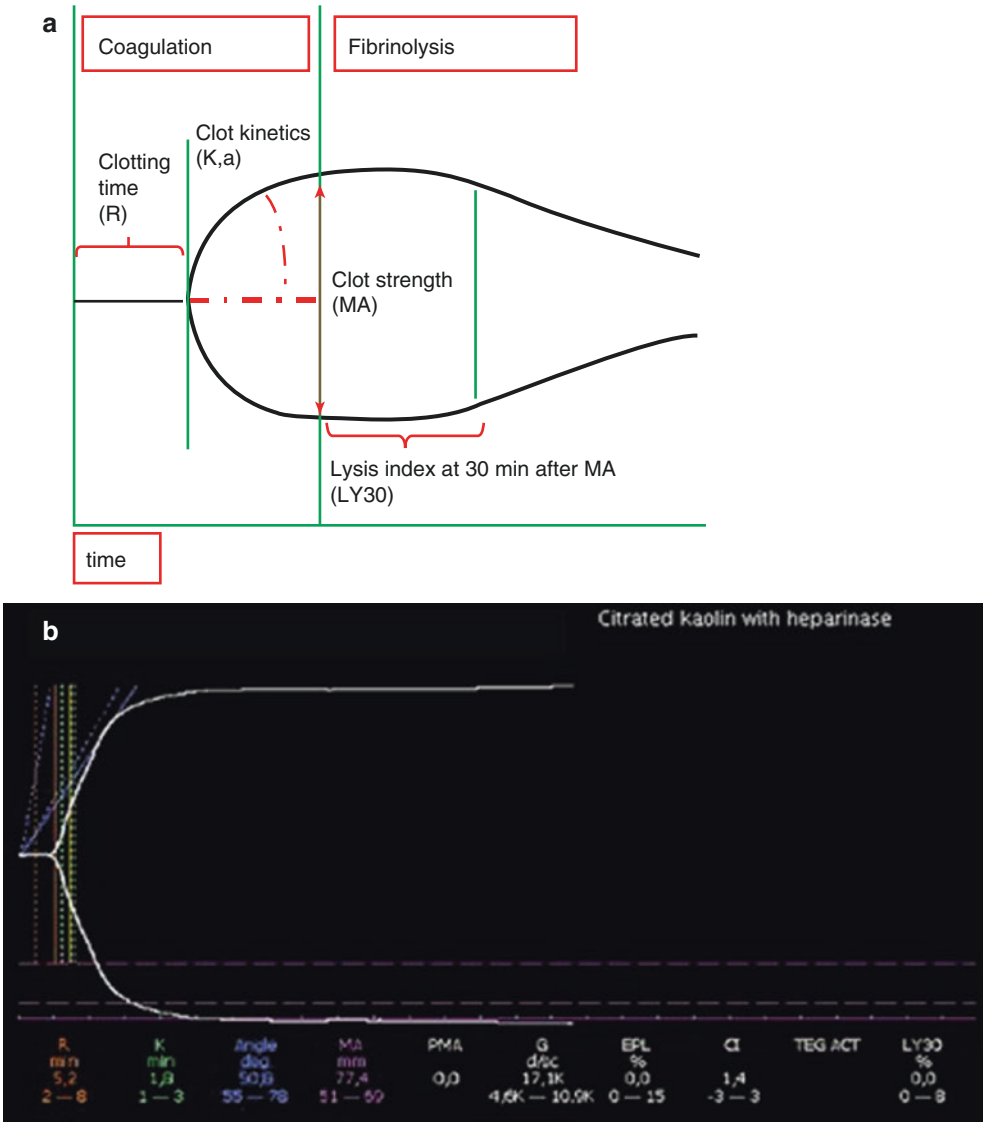

Fig. 17.40 (**a**) Waveform generated by TEG analyzer. (**b**) Normal value of thromboelastography in healthy obstetric patient

Thromboelastography is a method of testing the efficiency of coagulation in the blood by measuring the global viscoelastic properties of whole blood clot formation under low shear stress. Tromboelastography is useful in adult and pediatric populations [44].

Thromboelastography correlates the interaction of platelets with the coagulation profiles (clot aggregation, clot strengthening, platelets function, fibrin cross linking, and fibrinolysis).

It does not necessarily correlate with conventional blood tests such as INR, APTT, and platelet count which have been formally validated and standardized.

17.6 Neurologic Complications

Neuraxial injury may involve the spinal cord, nerve roots, or spinal nerve, other than spinal vasculature. With the exception of compressive lesions such as epidural hematoma or abscess, which are already discussed in this chapter, the neuraxial injuries are typically linked to needle or catheter-related damage, ischemia, or drug neurotoxicity [25, 45] (Table 17.5).

Direct needle or catheter injury can result in misidentification of vertebral level, unrecognized lateral needle placement or deviation, anatomical variation in termination of the spinal cord, or incomplete fusion of ligamentum flavum. In obstetric patients the identification of the puncture site is commonly difficult due to cephalization of the Tuffier's line as they cannot flex their knees on the abdomen and the altered horizontal spine line since their hips are wider than their shoulders, in addition to increased subcutaneous tissue pregnancy related. The conus medullaris ends at the levels of the first lumbar vertebra (L1) but extends to the level of the second lumbar vertebra (L2) in the 20 % of adult population [46] (Fig. 17.41).

To avoid the spinal cord injury complications, it is suggested to never puncture above L1–L2. The spinal cord has no sensory receptors and sensory input from the meninges is inconsistent [47, 48]. A painful response is elicited mostly by

Table 17.5 Factor affecting local anesthetic toxicity

Site of injection	Local anesthetic	Patient factors
Regional blood flow	Physicochemical properties	Age
	Lipid solubility	Genetics
	Protein binding	Neurological/cardiac disease
	pKa	Pregnancy
	Vasodilatory activity	Drug interactions
	Dose (volume × concentration)	Acid-base balance (acidosis, hypoxia, hypercarbia)

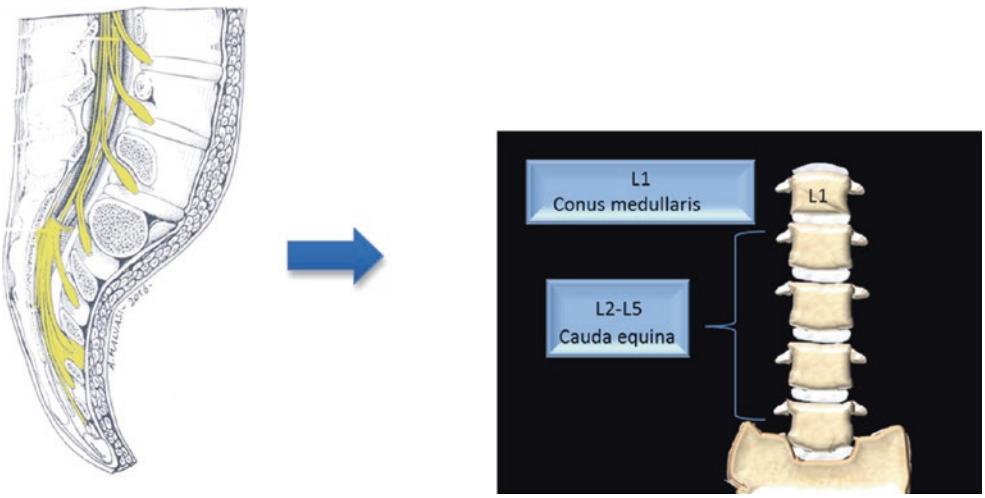

Fig. 17.41 Normally the conus medullaris ends near lumbar vertebral levels 1 (L1), occasionally lower. At the level of L1, the spinal nerves continue to branch out diagonally, forming the cauda equina

drug injection into the spinal cord which stimulates afferent neurons with pressure-related mechanism. Additionally, the insertion of the catheter can elicit transient or persistent paresthesia or pain in the lower limbs. If the patient experiences transient symptoms during the neuraxial block, the anesthesiologist may proceed with the procedure, otherwise it is advisable to stop and reposition the needle or catheter. Local anesthetic injection into the epidural or intrathecal space should never be attempted in any patient who experiences persistent sensory and motor block symptoms to avoid a later detection of nerve injury masked by local anesthetic block.

Cauda equina syndrome is a rare but devastating complication of epidural and spinal anesthesia, usually described after high concentration of intrathecal lidocaine or continuous spinal block through microcatheters, both of which are not currently recommended in obstetric anesthesia. Non-iatrogenic causes are herniation or bulging of L4-S1 intervertebral disks. The dysfunction of lumbosacral nerve roots can cause various symptoms, impairment of bladder, bowel, or sensory and motor function in both lower limbs [49–52].

Catheter-induced vasospasm or epidural space compression, rather than a prolonged hypotension and vasoconstrictors, may be potentially associated to vascular injury and thrombosis of the anterior spinal artery, although it is very rare complication. The anterior cord is more vulnerable to ischemic insult because it is irrorated by a single spinal artery which supplies the anterior two thirds of the spinal cord and subserves motor and sensory functions. Anterior spinal artery syndrome is clinically characterized by bilateral loss of motor function, bladder dysfunction, and sensory loss to pain and temperature, with relative sparing of proprioception and vibratory senses below the level of the lesion. When neurologic injury is suspected, diagnosis and treatment with high dose steroids for vasculitis or anticoagulants and antiplatelets for embolic phenomena must proceed without delay to avoid adverse or incomplete recovery [53–56].

MRI is the diagnostic choice for suspected neuraxial lesions. If MRI is not immediately available, CT should be used for rapid diagnosis, especially in suspected neuraxial compression injury which demands immediately to neurosurgical consultation. Suspected peripheral nerve injury is guided by symptoms, history, and physical examination. Neurological investigation, neurophysiologic test (nerve conduction and electromyography), and MRI of nerves are urgently indicated when symptoms are progressive and non-self-limiting [19, 25].

17.6.1 Transient Neurological Symptoms

Transient neurological symptoms are described as symmetrical bilateral pain in the lumbar or gluteal area and can extend to the

lower extremities without sensory or motor deficits after recovery from uncomplicated spinal anesthesia, which resolved spontaneously. The pain may worsen at nights and improves with ambulation; dysesthesia and paresthesia may be observed. Local anesthetic toxic effect, related more to intrathecal lidocaine rather than bupivacaine, may increase the incidence of transient neurological symptoms. Other risk factors are trauma after multiple attempts at lumbar puncture, the use of cutting spinal needle (Quincke). Transient neurological symptoms incidence is lower in obstetric patients comparing to the general surgical population (0–7 % versus 10–30 %, respectively). The neurological examination is normal, and radiographs, CT, or MRI are usually negatives, although a local inflammatory process has been reported on an MRI of a patient with transient neurological symptoms after spinal lidocaine.

> It is important to note that lumbosacral pain in obstetric patients is rarely linked to regional anesthesia. Many studies, indeed, have demonstrated that the obstetric population without any neuraxial intervention have a 63 % risk of developing back pain during the first-year postpartum pads and may provide an additional measure of patients' comfort.

Most patients have a complete resolution between the second and fifth postoperative day. Nonsteroidal anti-inflammatory drugs have been used successfully, while the muscle relaxants are indicated to relieve significant muscle spasm. Symptomatic therapy, such as leg elevation on pillows and heating pads, may provide additional comfort [57–65].

17.6.2 Chemical Injury

The anesthetist should accurately vigilate to minimize accidental injection of drugs which can cause permanent neurologic injury, although rare. The dramatic report of a parturient rended paraplegic after accidental injection of chlorhexidine in epidural space is an isolated case of irreversible injury, but a wide variety of drugs, such as ondansetron and neuromuscular blockers, have been erroneously administered in the epidural space. Lidocaine (Fig.17.42) toxicity has already been described, and its use in obstetric spinal and epidural anesthesia is no longer justified [66–70].

17.6.3 Total Spinal Anesthesia

Total spinal block can happen when local anesthetic interferes with the normal neuronal function in the cervical spinal cord and brain stem if epidural catheter is accidentally in the subarachnoid space (Fig. 17.43). The onset is usually rapid and severe hypotension, bradycardia, and respiratory arrest will occur. Careful aspiration, a test dose, and incremental local anesthetic dosing can avoid this complication.

Management of total spinal anesthesia is mainly supportive: fluid administration, inotropes or vasopressors to raise

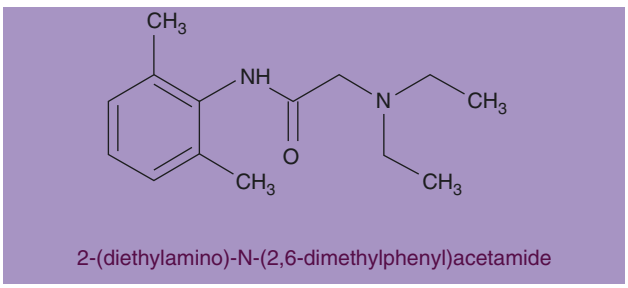

Fig. 17.42 Lidocaine

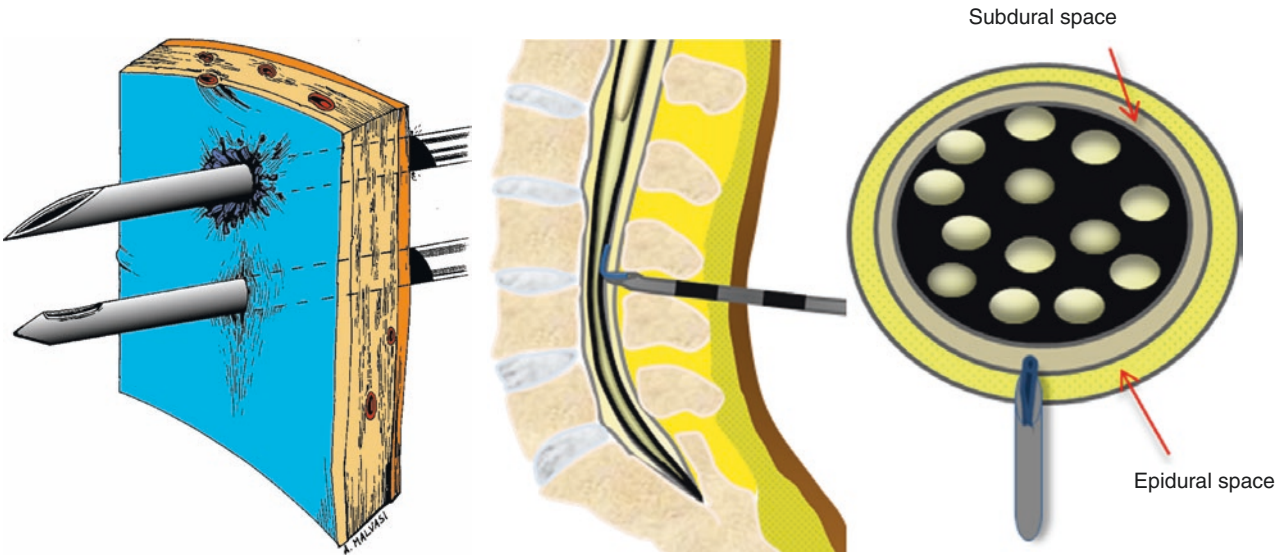

Fig. 17.43 Epidural catheter erroneously inserted in the subarachnoid space (modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012)

blood pressure, and atropine to treat the bradycardia. Respiratory insufficiency may need tracheal intubation and mechanical ventilation to support ventilation [71].

17.6.4 Systemic Toxicity of Local Anesthetics

Local anesthetic (LA) in clinical use rarely produces systemic toxicity, local tissue ischemic toxicity, and nerve toxicities or allergic reactions.

Local anesthetic systemic toxicity (LAST) occurs after inadvertent intravascular injection of LA especially during epidural anesthesia rather than spinal anesthesia. Local anesthetics differ with regard to the central nervous system (CNS) and the cardiovascular system (CVS) toxicity due to different physicochemical properties, including the stereoselectivity, but their common mechanism of action can be summarized into inhibition of Na channels, inhibition of mitochondrial metabolism, and oxidative phosphorylation which affect above all the organs less tolerant of anaerobic metabolism (the brain and heart). Systemic toxicity has typically "biphasic" effect on CNS and CVS. The CNS excitation includes disorientation, agitation, metallic taste in the mouth, visual and auditory impairment, and convulsions. Subsequently, local anesthetics have a dose-dependent depressant effects culminating in coma and respiratory and cardiac arrest (Fig. 17.44).

Bupivacaine has been a cause of several cardiac arrest in pregnant women, and the degree of toxicity is dependent on plasma levels of LA. In pregnancy, the higher cardiac output will speed up LA absorption, while the reduced plasma proteins increase the plasmatic-free fraction of LA, responsible for its effect on CNS and CVS. Other factors affecting LA toxicity are summarized in Table 17.5.

Precautions when administering LA during neuraxial techniques would include aspiration to exclude an intravascular administration; lowest effective dose, resuscitation equipment, and drugs should be available.

The treatment of LAST may include airway management, oxygenation, ventilation to avoid hypoxemia, and metabolic acidosis. Early seizure suppression with benzodiazepines is more preferable than propofol (Fig. 17.45a, b) because these drugs have limited potential for causing cardiac depression. Refractory seizures may require neuromuscular blockade.

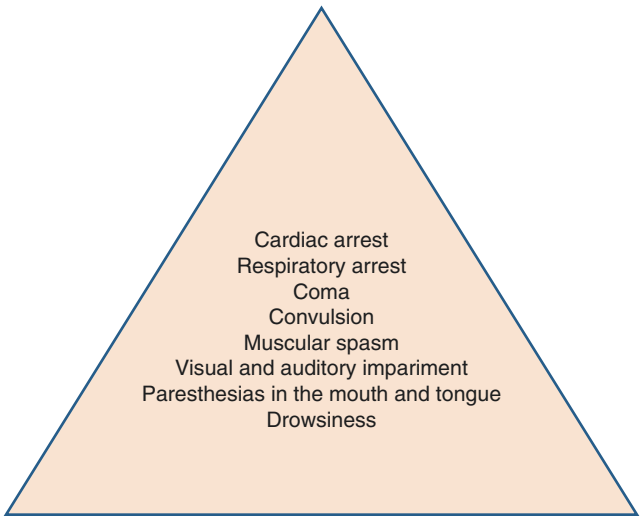

Fig. 17.44 Progression of local anesthetic systemic toxicity

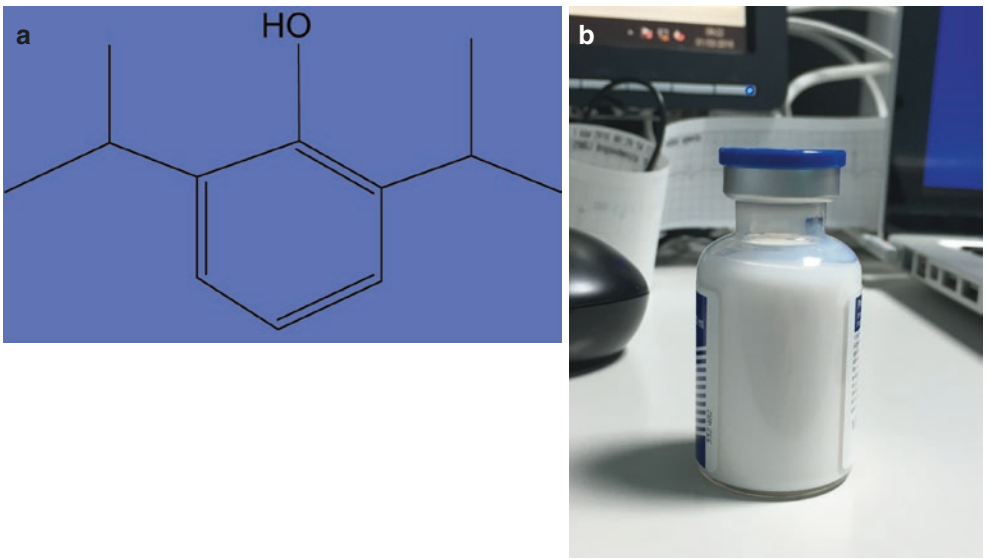

Fig. 17.45 Propofol: chemical formula (**a**) and commercial presentation (**b**)

Table 17.6 Lipid emulsion treatment

Lipid emulsion (20%) therapy		
Intravenous bolus 1.5 ml/kg (over 1 min)	⇨	*Continuous infusion 15 ml/kg/h*
After 5 min if persistent cardiovascular instability		
Repeat bolus once or twice (leave 5 min between boluses)	⇨	*Double the infusion rate to 30 ml/kg/h* Continue infusion for at least 10 min after attaining circulatory stability
Do not exceed 10 ml/kg lipid emulsion over the first 30 min		

Management of cardiac dysrhythmias supporting the patient with intravenous fluids and vasopressors is required. Vasopressin is not recommended and small bolus doses of epinephrine are preferred. Increasing evidence has shown favorable results with early intravenous infusion of lipid emulsions to reverse or prevent the cardiac and neurologic effects of local anesthetic toxicity (Table 17.6).

Indeed, case reports support the early use of lipid emulsion, prolonged seizure activity, or rapid progression of toxic manifestations in patients with suspected local anesthetic toxicity. If available, cardiopulmonary bypass should be considered in situations where the response to early treatment is not favorable.

Infrequently, local anesthetics may provoke an allergic or hematologic reaction. Severe allergic reactions remain a rare event, and the management does not differ from the treatment algorithms for other more common allergic reactions. Methemoglobinemia is a unique side effect of some local anesthetics. It should initially be treated symptomatically guided by blood levels of methemoglobin. Intravenous administration of methylene blue (Fig. 17.46) and hyperbaric oxygen may be required in severe cases [72, 73].

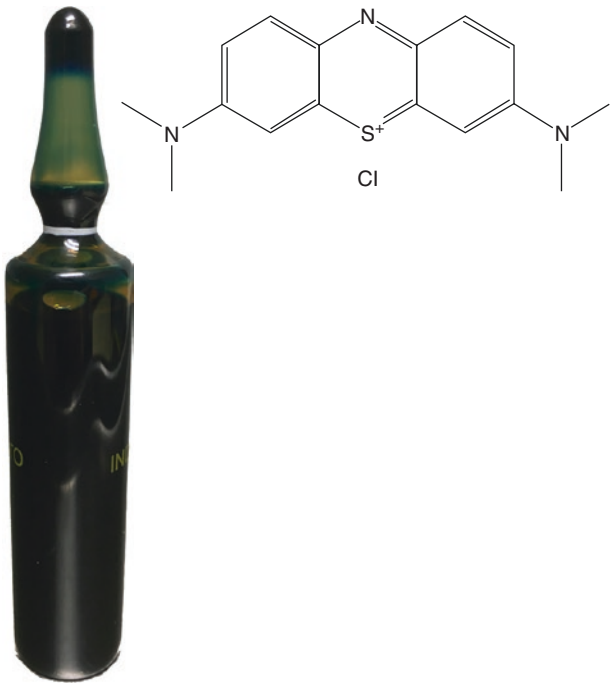

Fig. 17.46 Methylene blue

17.7 Locoregional Anesthesia and Occiput Posterior Position

The literature reports that the most common epidural analgesia complication is the dystocia. However, an optimal epidural analgesia through the CSE technique, low dose drugs and top up use are required.

In fact the examination of the spinal column in the parturients shows the pathological anatomy of the spine and the pelvis. When the spine is not normal, the pelvis is asymmetric, and in this case dystocia occurs in labor (Fig. 17.47). Recent study demonstrated with intrapartum sonography that dystocia is mechanic and not pharmacological. However, an optimal epidural analgesia through the CSE technique, low dose drugs and top up use are required. [74–76].

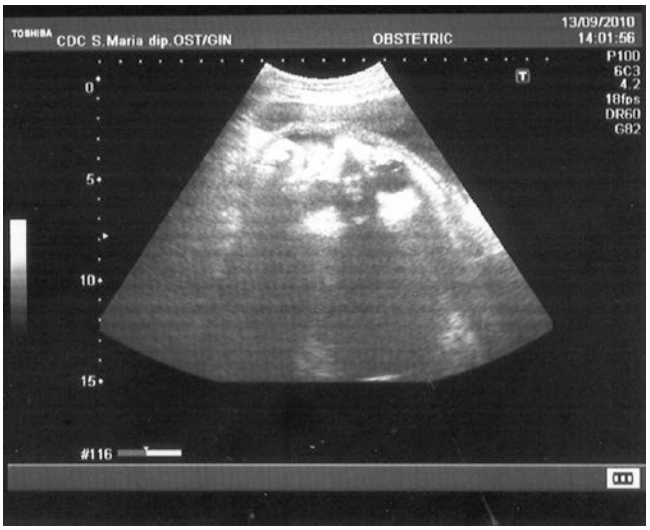

Fig. 17.47 Transabdominal transversal sonographic scan of the fetal head in left occiput posterior position during the second labor stage in epidural analgesia. The picture shows the fetal orbits, the lens, the nasal bridge, and the occipital bone in the left pelvis

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Complication of General Anaesthesia in Obstetrics

18

Lucia Mirabella, Antonella Cotoia, Matteo Melchionda, and Gilda Cinnella

18.1 History of General Anaesthesia During Labour

In 400 BC Plato used the term anaesthesia to indicate the absence of emotions, and in the first century AD, Dioscorides uses this term to indicate the absence of physical sensations. Hippocrates described a soporific *Spongia* soaked in opium, hemlock and mandrake capable to put to sleep.

Before the advent of diethyl ether, many surgeons believed that the pain was unavoidable consequence of surgery.

In the nineteenth century, there is a turning point for the history of anaesthesia: William Morton, a pioneer of ethereal anaesthesia, made a glass sphere containing a sponge soaked in ether which was breathing vapours coming from the sphere to the patient drift off to sleep. He was the first to discover the nitrous oxide.

John Snow made about 4,000 anaesthesia with chloroform and gave a strong boost obstetric anaesthesia with chloroform (also used by Houzelot of Meux for analgesia of pregnant women).

Chloroform anaesthesia was performed with devices created by The Fort, Junker, Galante, Budin, Nicaise, Ombredanne and Ricard. Robert Macintosh is the one who developed techniques for laryngoscopy and tracheal intubation of the surgical patient (1897–1989) (Figs. 18.1, 18.2, 18.3 and 18.4).

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18.2 Introduction

Obstetric anaesthesia is considered by many to be a high-risk subspecialty of anaesthesia practice that is laden with clinical challenges and medicolegal liability [1]. Evidence-based practice guidelines and reviews of mortality and morbidity, including closed malpractice claims, have been used to foster continual improvement in maternal safety and perioperative outcomes [2–5]. However, the effectiveness of these efforts in improving maternal outcomes has not been evaluated. First is because the incidences of serious complications related to obstetric anaesthesia remain largely unknown primary of the lack of large obstetric anaesthesia database, and second the incidences of complications reported in the literature are highly variable as they typically represent estimates from case reports, case series or limited institutional cohort [6].

Caesarean section is the most commonly performed surgical procedure in obstetrics, and although the operation has become very safe over the years, it is still associated with greater maternal mortality and morbidity [7, 8]. Compared with vaginal delivery, caesarean section is associated with a significantly increased risk of anaesthesia-related adverse events and with a four times risk of maternal death [7]. It is known that there is a greater risk of neonatal respiratory distress with caesarean section than vaginal delivery, regardless of gestational age [7]. Caesarean section is often described as elective (when it is planned) or emergency. The risk of anaesthesia-related adverse events during caesarean delivery is especially high when the procedure is unplanned, when it is performed under general anaesthesia and in women with pre-existing comorbidities [9–11]. The American Society of Anesthesiologists recommends neuraxial anaesthetic techniques for caesarean delivery, whenever possible [3]; however, general anaesthesia may be the most appropriate choice for urgent and emergent caesarean section, especially in such circumstances as foetal distress (Fig. 18.5), ruptured uterus (Fig. 18.6), severe haemorrhage and severe placental abruption (Fig. 18.7) [12–14]. One

A. Malvasi et al. (eds.), *Management and Therapy of Late Pregnancy Complications*, DOI 10.1007/978-3-319-48732-8_18

Fig. 18.1 Junker inhaler

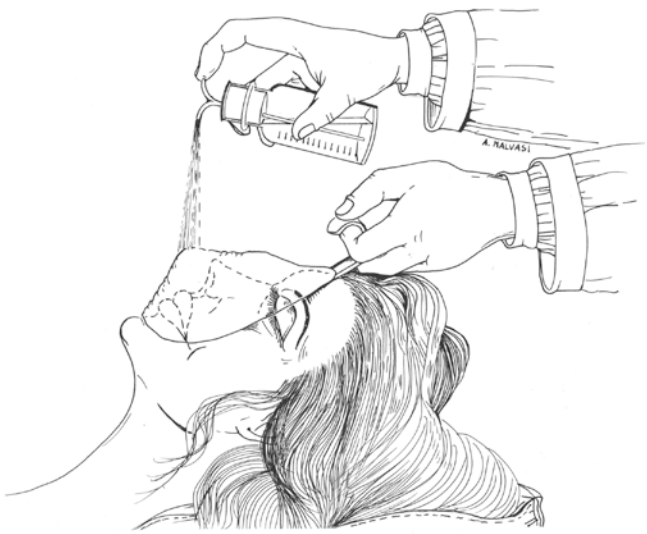


Fig. 18.2 Nicaise. Chloroform anaesthesia

major reason is that the decision-to-delivery intervals with general anaesthesia can be significantly shorter than that with neuraxial anaesthesia [15].

This factor is especially important for urgent and emergent caesarean section due to foetal distress, as shorter decision-to-delivery intervals (e.g. less than 30 min) have been shown to be critical and correlate well with better foetal outcomes [16, 17] (Fig. 18.8).

18.2.1 General Anaesthesia Indications

The Royal College of Anaesthetists audit book suggests that fewer than 15 % of emergency and fewer than 5 % of elective caesarean sections should be performed under general anaesthesia.

When general anaesthesia is used, the most common indications are urgency (≈35 % of cases in a non-teaching hospital), maternal refusal of regional techniques (20 %) (Fig. 18.8), inadequate or failed regional attempts (22 %) and regional contraindications including coagulation or spinal abnormalities (Fig. 18.9) (6 %) [18, 19]. Obstetric indications, such as placenta praevia, were in the past considered absolute indications for general anaesthesia (Fig. 18.10). However, published departmental audits have reported rates

of 9–23 %, although other journals have quoted rates of 2–10 %. Of the caesarean sections performed due to immediate threat to the life of the mother or foetus, 41 % were performed with general anaesthesia [20]. A classification for the urgency of caesarean section is described in Table 18.1.

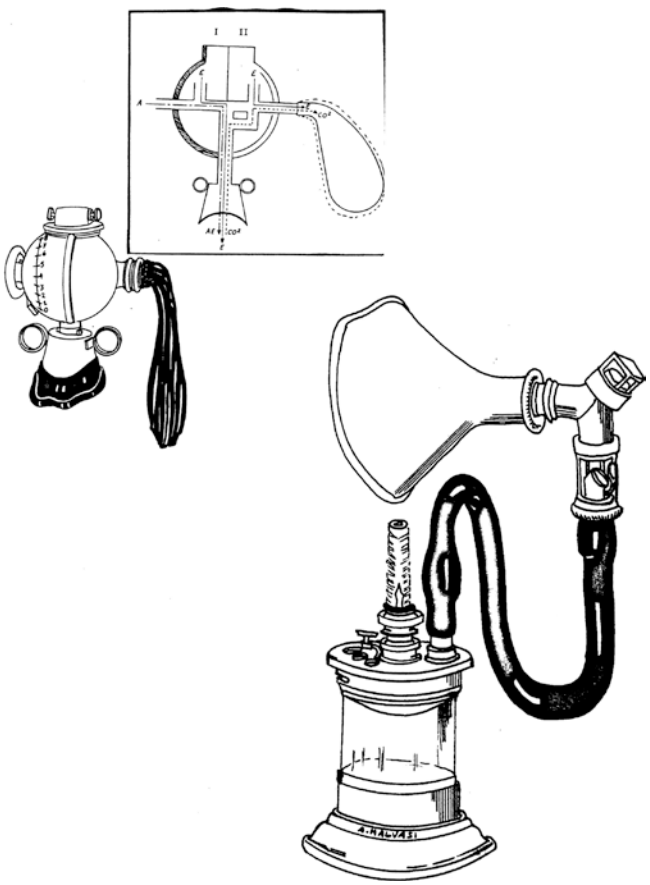


Fig. 18.3 Ombredanne inhaler and Ricard inhaler

The 2007 American Society of Anesthesiologists Practice Guidelines for Obstetric Anaesthesia states that 'neuraxial techniques are preferred to general anaesthesia for most caesareans deliveries' [3]. This evidence-based, guideline-supported change in anaesthesia practice may explain the decrease in the proportion of general anaesthesia for unplanned (but not planned) caesarean deliveries. Although the proportion of general anaesthesia in obstetric practice decreased over the last two decades, the actual number given for caesarean sections is largely unchanged because of the increased section rate. The prevalence of advanced maternal age and pre-existing maternal chronic comorbidities, however, continue to increase, as indicated in the proportion of women older than 40 years [21–23].

Advantages of general anaesthesia include the ability to manipulate respiratory and cardiovascular parameters and the avoidance of sharp drops in systemic vascular resistance. General anaesthesia also negates the problem of having an insufficient block, particularly pertinent in cases where surgery is prolonged or complex. The major concerns in providing general anaesthesia for caesarean section are potential difficulty with airway management, the risk of awareness and the possible effects of anaesthetic agents on uterine tone and the newborn. Concern has also been raised about the sympathetic stimulation from direct laryngoscopy and intubation. The effect of positive pressure ventilation with a reduction in venous return, hypotension and raised pulmonary artery pressures must also be considered [24, 25].

Little evidence supports a particular general anaesthetic technique. Standard practice in obstetrics is to carry out a rapid sequence induction (RSI) with intravenous anaesthetics and a depolarising muscle relaxant such as suxamethonium. Suxamethonium or succinylcholine has a number of well-known disadvantages, but no other neuro-

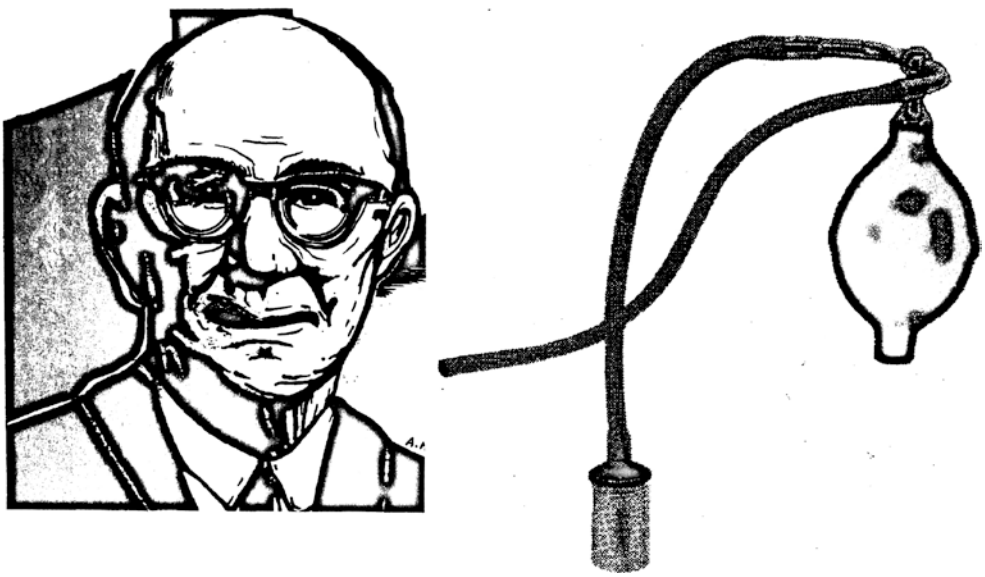


Fig. 18.4 Robert Macintosh

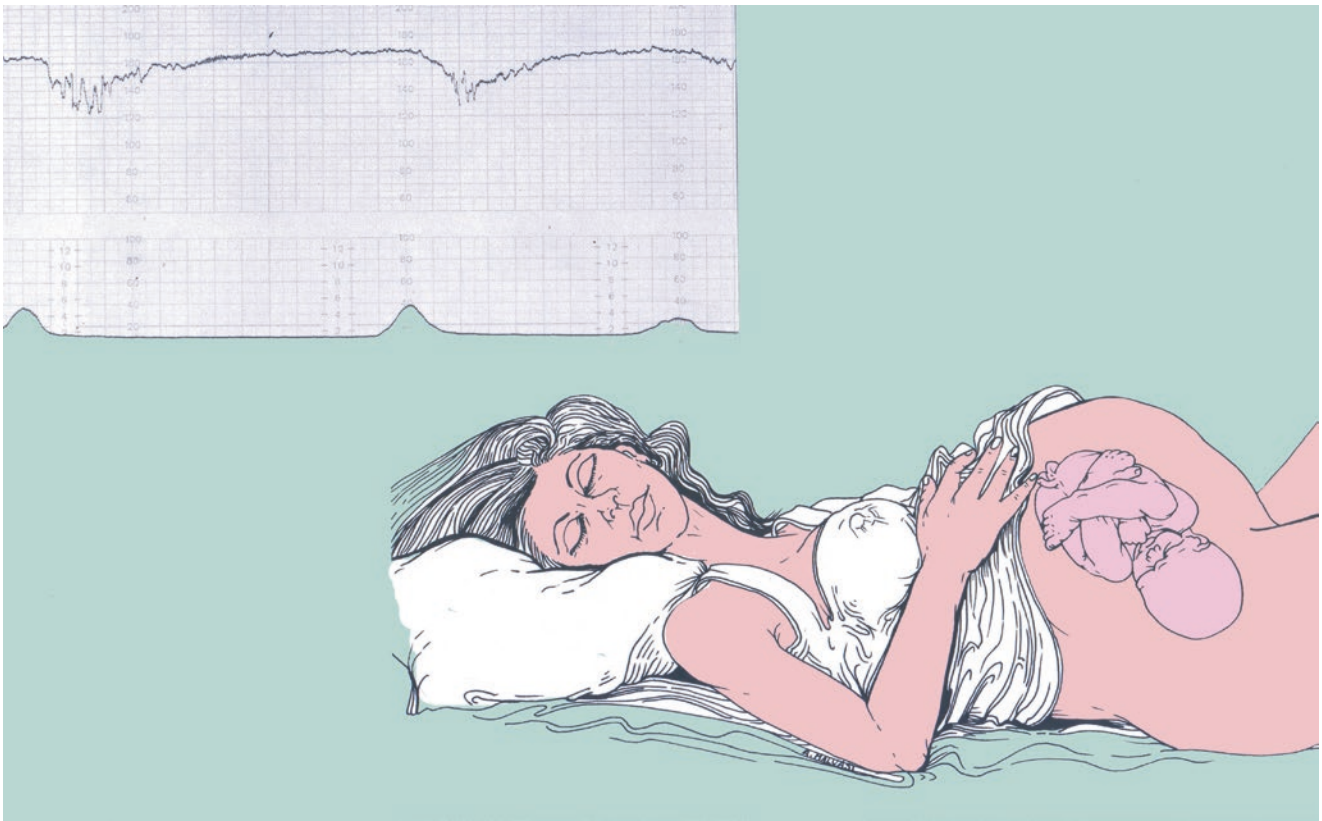


Fig. 18.5 Foetal distress

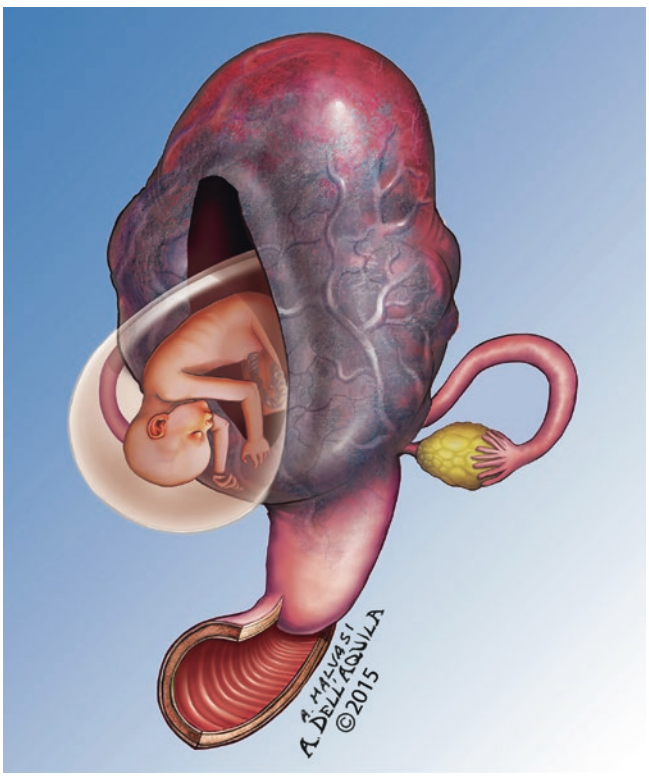


Fig. 18.6 Ruptured uterus

muscular blocker has such favourable onset and offset characteristics. There is an increasing interest in the use of rocuronium, an aminosteroid non-depolarising neuromuscular blocking drug, in place of suxamethonium for RSI in the general and obstetric population. This is less common in obstetric anaesthesia as the duration of action of an effective dose of rocuronium exceeds most obstetric procedures. Sugammadex, a specifically designed γ-cyclodextrin, affects the possibility of rapidly reversing profound rocuronium neuromuscular blockade at the end of surgery [26].

Most anaesthetists 'modify' the standard RSI with the addition of an opioid [27]. The addition of an opioid obtunds the sympathetic response to laryngoscopy but risks respiratory depression in the neonate. The successful use of ultrashort-acting opioids such as remifentanil and alfentanil, with minimal neonatal respiratory depression, has been described [28]. Maintenance of anaesthesia is generally with inhalational agents, such as isoflurane and sevoflurane. Inhalational agents are negatively inotropic, reduce systemic vascular resistance and impair the pulmonary vascular response to hypotension, so must be used with care (Fig. 18.11).

General anaesthesia for caesarean section appears to be associated with higher rates of serious and life-threatening

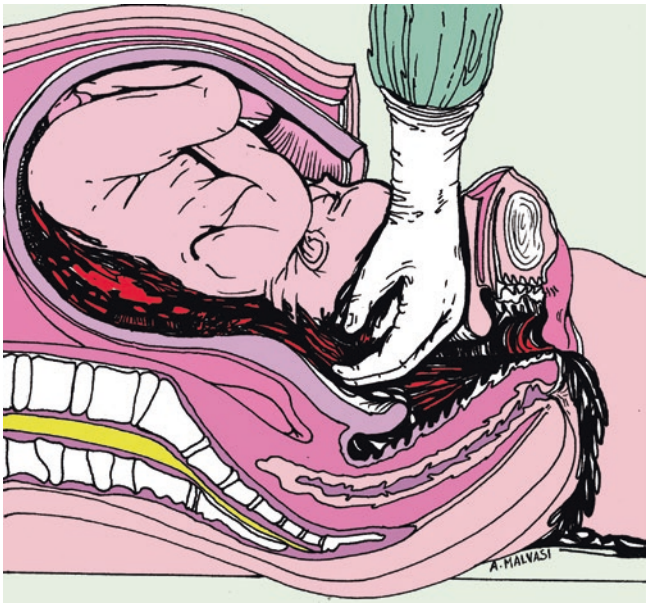


Fig. 18.7 Severe placental abruption

Fig. 18.8 Woman does not want epidural analgesia

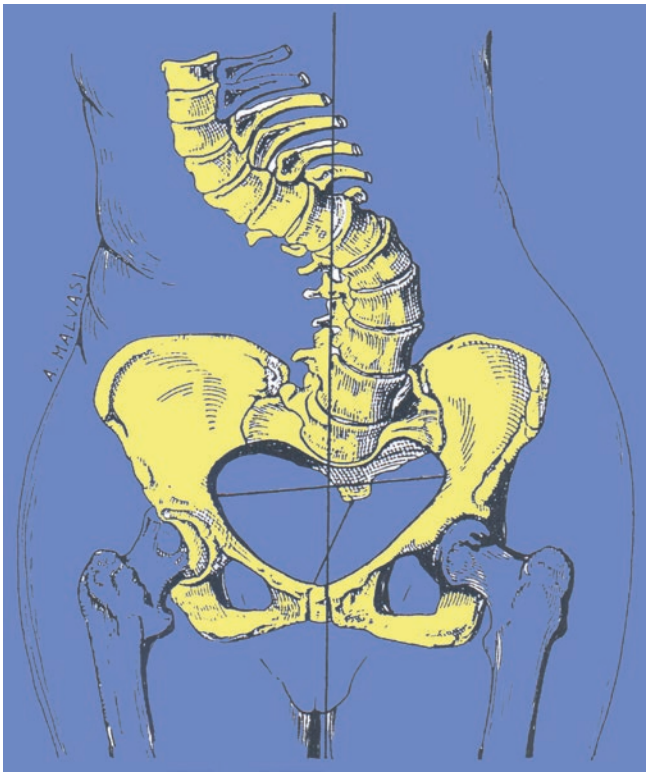


Fig. 18.9 Spinal abnormalities are important contraindication to regional anaesthesia

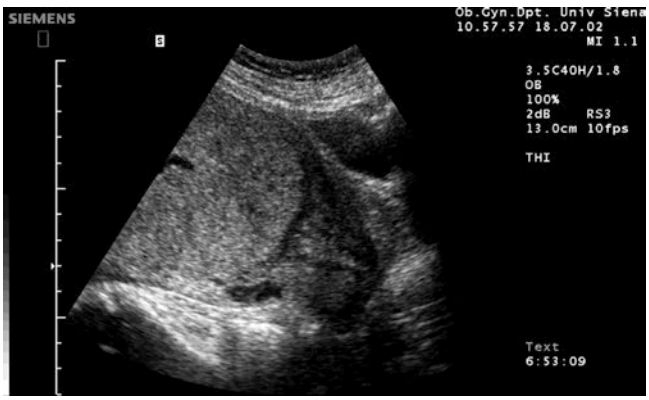


Fig. 18.10 Placenta praevia

complications than regional anaesthesia, and most anaesthetic-related maternal deaths still result from complications during general anaesthesia [29–31]. The major concerns in providing general anaesthesia for caesarean section are potentially difficulty with airway management, the risk of awareness and the possible effects of anaesthetic agents on uterine tone and the newborn.

Complications associated with general anaesthesia are listed in Table 18.2.

18.2.2 Airway Problems for the Obstetric Patients

Airway disasters are the leading cause of anaesthesia-associated maternal morbidity [32–35]. The risk of failed intubation is higher in pregnant women than in the general surgical population [36, 37].

Anatomical and physiologic factors that place the pregnant patient at increased risk for airway management complications and difficult intubation include pregnancy-induced generalized weight gain and increase in breast size, respiratory

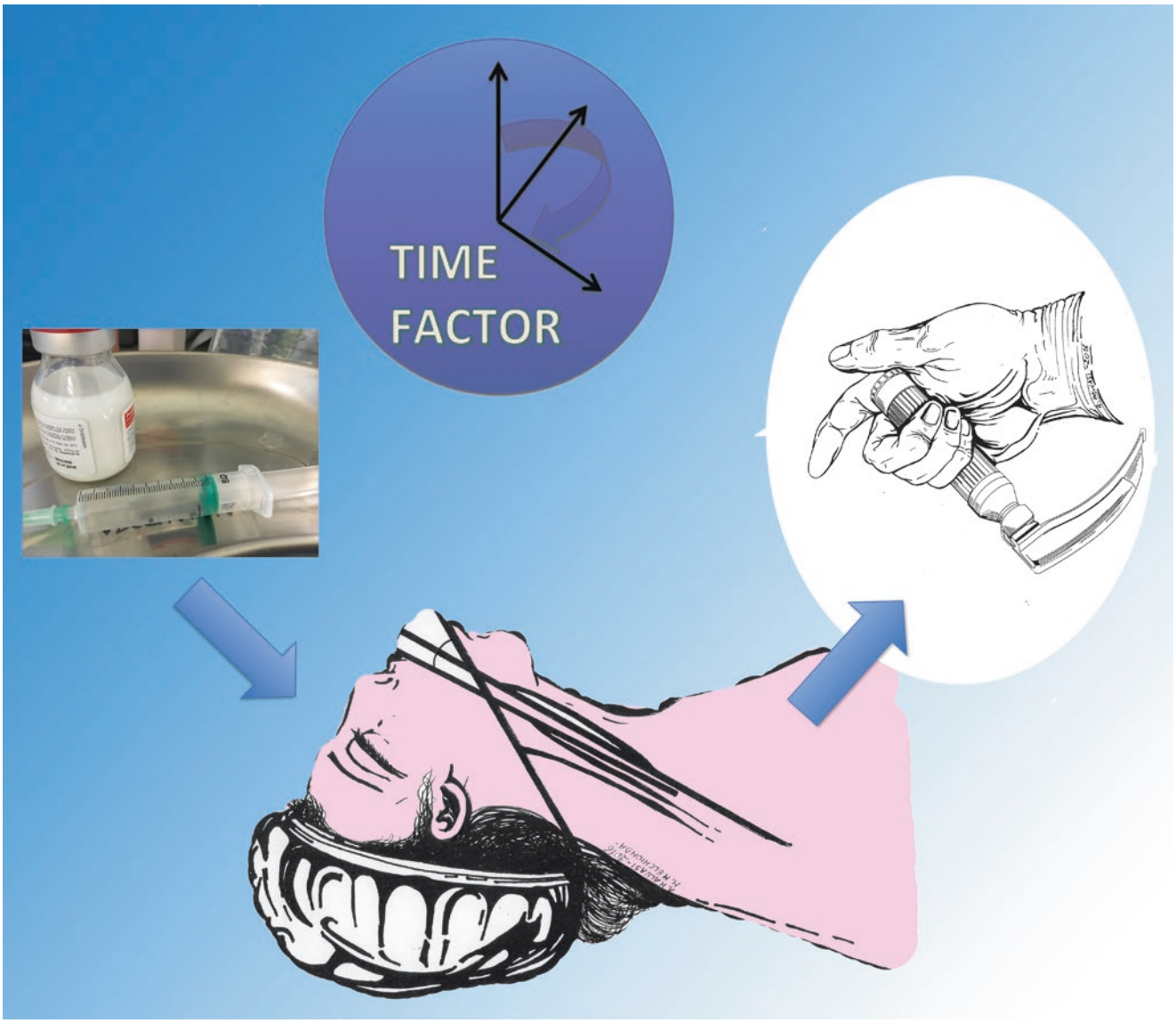


Fig. 18.11 Rapid sequence induction

Table 18.1 Indications to general anaesthesia for caesarean section

Non-reassuring foetal heart tracing	
Massive haemorrhage	Placental abruption
	Uterine rupture – placenta accreta/percreta
Cord prolapse with non-reassuring FH tracing	
Maternal disease	Severe pre-eclampsia
	Eclampsia
	HELLP
C/I to regional anaesthesia	Coagulopathy/low platelet count
	Anticoagulants
Perceived lack of time for RA	
Failed regional	
Patient refusal	

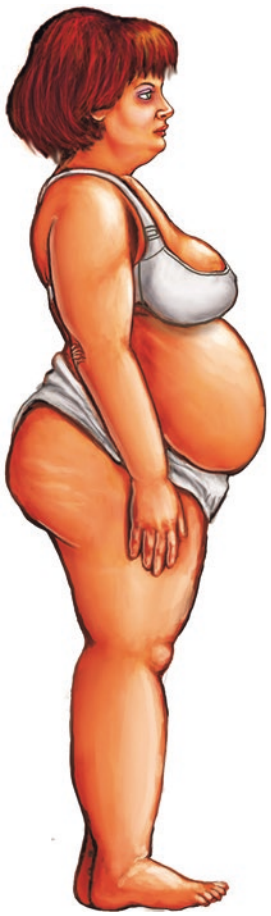


Fig. 18.12 Obesity

tract mucosal oedema, decreased functional residual capacity (FRC) and increased oxygen consumption (Table 18.3).

Pregnancy results in significant increase in breast size. In the supine position, the enlarged breasts tend to fall back against the neck, which can interfere with insertion of the laryngoscope and intubation. Furthermore, it is not uncommon for the parturient to gain 20 kg or more during pregnancy. Obesity (Fig. 18.12) has been reported to further increase the risk of anaesthetic complications in parturients [38, 39]. A high body mass index (BMI) has been associated with an increased risk of airway management problems including difficult intubation [40]. Additionally, the obstetric literature indicates that parturients with a high BMI are at increased risk for caesarean section.

Healthy parturients typically have generalized body oedema due to the effect of increased progesterone levels and accumulation of adipose tissue around the airway, although this oedema is not clinically significant in the majority of these patients. Vascular engorgement of the respiratory tract during pregnancy leads to oedema of the nasal and oral pharynx, larynx and trachea [40–42].

Laryngeal oedema may inhibit the passage of standard size endotracheal tube (ETT), despite adequate vocal cord visualization at laryngoscopy, and requires a smaller internal diameter tube size. Furthermore, tongue enlargement may make it difficult to retract the tongue into the mandibular space during direct laryngoscopy (Fig. 18.13).

Pregnant women, additionally, have reduced tolerance for apnoea and become hypoxaemic faster after failed intubation because of an increased metabolic rate and decreased functional residual capacity (FRC).

Thus, it is essential for the anaesthesiologist to perform a proper preanaesthetic evaluation and identify the factors predictive of difficult intubation. There is a subset of patients who have certain anatomical features that should indicate that endotracheal intubation via conventional means is very likely to be difficult if not impossible. Certain anatomical features (very large breasts and heavy chest wall, large tongue, no teeth and sunken cheeks, fixed head or neck flexion, massive jaw, upper airway mass) may also render mask

Table 18.2 Risks associated with general anaesthesia in obstetric patients

Risks of general anaesthesia
Difficult and failed intubation
Aspiration
Awareness
Nausea and vomiting
Postoperative analgesia
Uterine atony blood loss
Development of chronic pain
Postoperative thromboembolic disease
Foetal asphyxiation
Early neonatal depression
Adverse effects on breast-feeding
Parents' experience of the delivery
Oxygen toxicity

Table 18.3 Physiologic changes of respiratory system during pregnancy

System	Changes
Respiratory system	Increased alveolar ventilation (70 %)
	Relative hypocarbia ($PaCO_2$ of 25–32 mmHg)
	Reduced functional residual capacity (20 %)
	Increase O_2 consumption
	Reduced venous oxygen saturation (SvO_2)
	Accumulation of adipose tissue around the airway
	Vascular engorgement of the respiratory tract
Cardiovascular system	Increased cardiac output (40 %) – increased stroke volume 25 % and heart rate 25 %
	Reduced total peripheral resistance
	Generalized body oedema
	Normal CVP in superior vena cava distribution
	Elevated CVP in inferior vena cava distribution (aorto-caval compression)
	Increased circulating volume
	Increased plasma volume (40–50 %)
	Increased red cell mass (20 %) with a physiologic anaemia
Gastrointestinal	Reduced lower oesophageal sphincter tone
	Enlarging uterus with increasing intra-abdominal pressure
	Higher gastric volumes
	Lower gastric pH
	Delayed gastric emptying

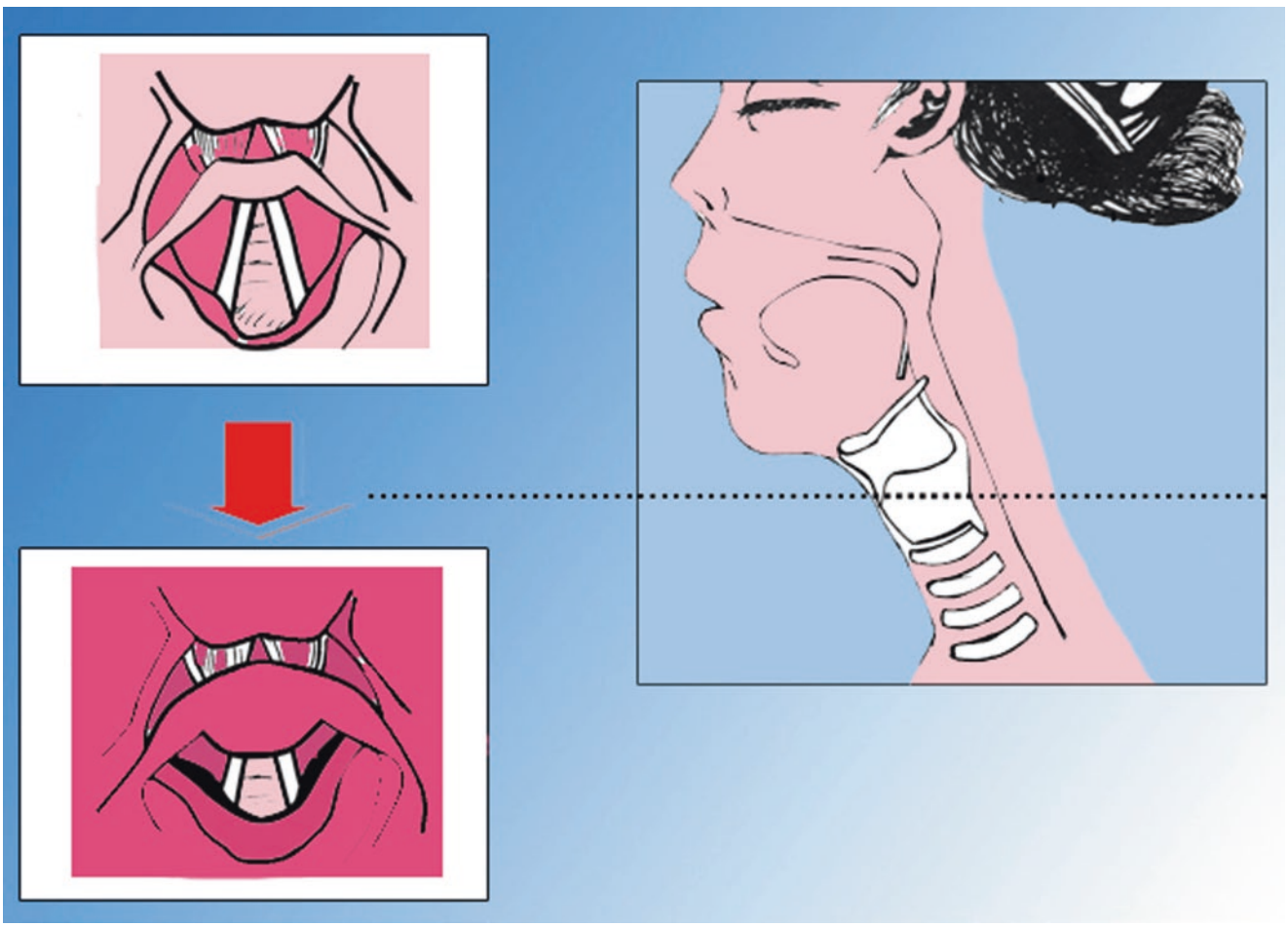


Fig. 18.13 Laryngeal oedema

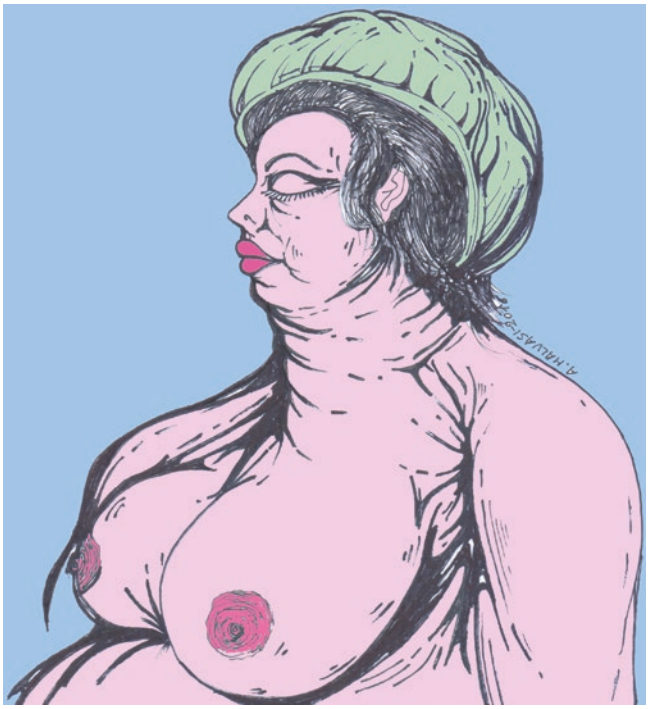


Fig. 18.14. Large breast

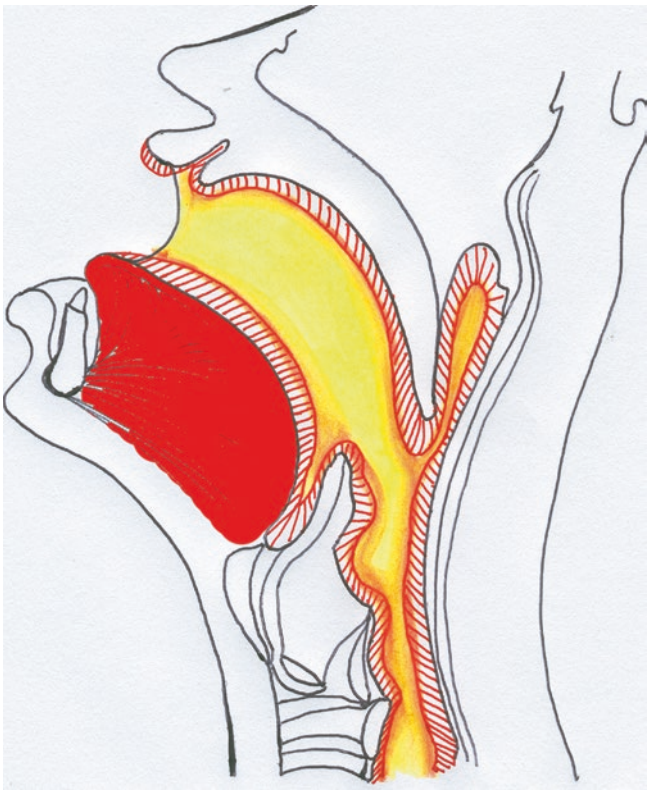


Fig. 18.16 Large tongue

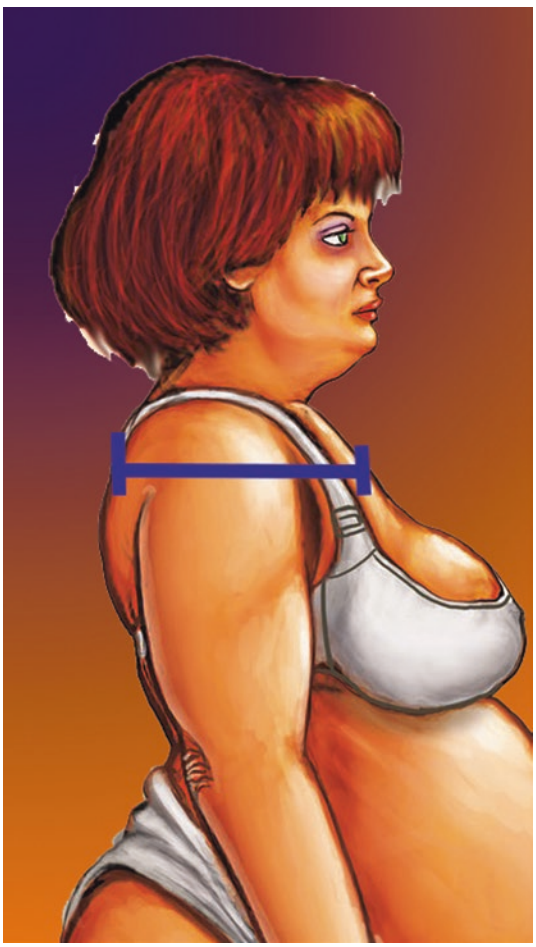


Fig. 18.15 Heavy chest wall

Fig. 18.17 No teeth and sunken cheeks

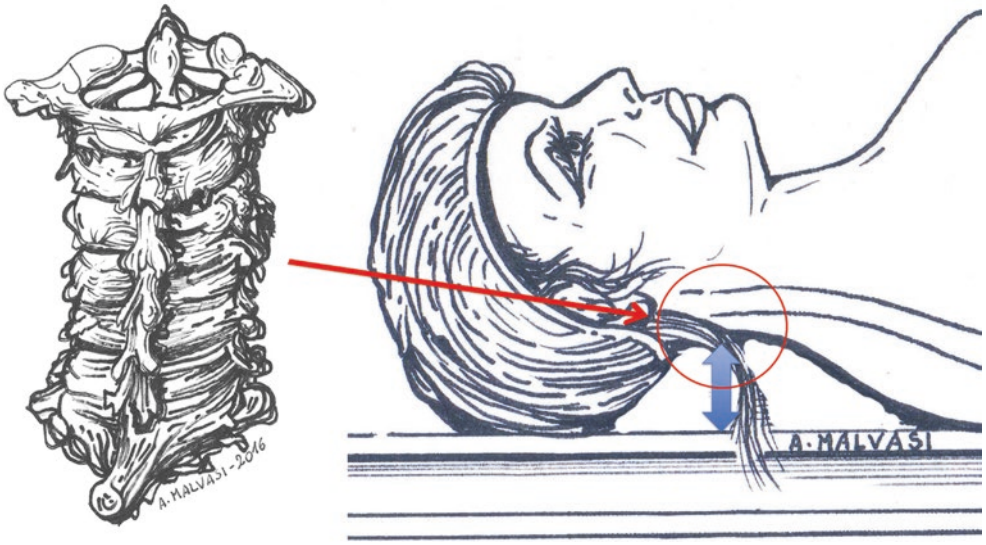


Fig. 18.18 Fixed head or neck flexion

Fig. 18.19 Massive jaw

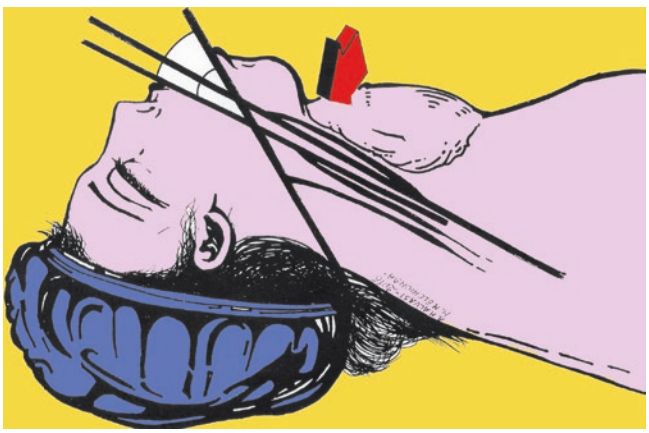


Fig. 18.20 Upper airway mass

ventilation difficult or impossible (Figs. 18.14, 18.15, 18.16, 18.17, 18.18, 18.19 and 18.20).

If there is any doubt regarding the ability to maintain airway patency during general anaesthesia, alternative methods of anaesthesia should be considered [40]. Options include the use of regional anaesthesia, local infiltration anaesthesia, or, if there is adequate time, an awake intubation followed by induction of general anaesthesia.

Regional anaesthesia is the best choice for caesarean section in most cases of anticipated difficulty with endotracheal intubation [43]. If a patient with a difficult airway requires urgent caesarean section, and if there is a contraindication to the use of spinal or epidural anaesthesia, local anaesthetic infiltration can be used as the primary anaesthetic technique [44, 45]. When the anaesthesiologist anticipates that management of the airway will be difficult, a very safe option is to secure the airway with an ETT, while the patient remains awake [39, 40, 43, 46, 47].

Successful awake endotracheal intubation requires proper preparation of the patients, ideal preparation results in a quiet and cooperative patient and a larynx that is nonreactive to physical stimuli. Topical anaesthesia is the primary anaesthetic for awake intubation [39, 40]. In some patients, topical anaesthesia provided sufficient time to anaesthetize all portions of the airway adequately. If the nasal route is chosen, the nasal mucosae should be sprayed. The pressure receptors that elicit the gag reflex at the root of the tongue are submucosal in location, and topical anaesthesia may not uniformly provide adequate blockade of these pressure receptors, and bilateral blockade of the lingual branch of the glossopharyngeal nerve may be required.

Judicious use of intravenous sedation helps relieve anxiety and increase the pain threshold in awake patients that should remain rational, alert and responsive to commands.

There is some controversy as to the appropriate use and extent of local anaesthesia for awake intubation in a patient with a presumed full stomach. The key to avoiding aspiration is to avoid oversedation; there is a low risk of aspiration of gastric contents in an awake, alert and rationale patient regardless of the extent of topical anaesthesia [40].

Once upper airway has been anaesthetized, adequately, there are numerous ways to intubate the trachea:

- Direct laryngoscopy (Fig. 18.21)
- Blind nasal intubation (Fig. 18.22)
- Retrograde intubation (Fig. 18.23)
- Fibre-optic laryngoscopy (Fig. 18.24)

Direct laryngoscopy results in the most noxious stimulation for the patient; thus, it requires the best patient preparation.

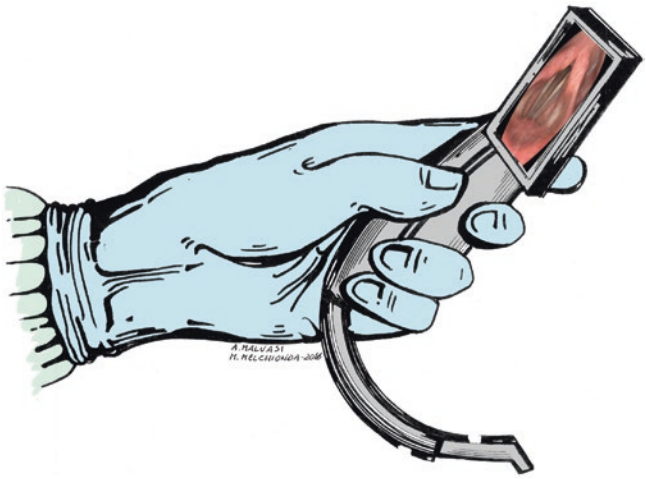


Fig. 18.21 Direct laryngoscopy

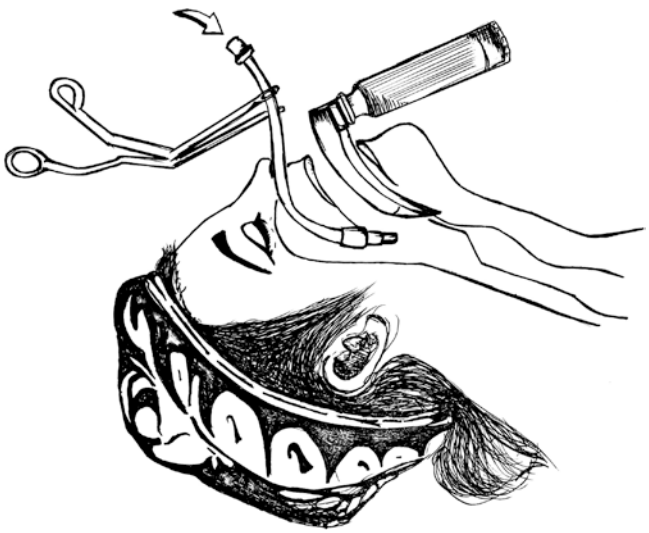


Fig. 18.22 Blind nasal intubation (tube Ø 6 mm)

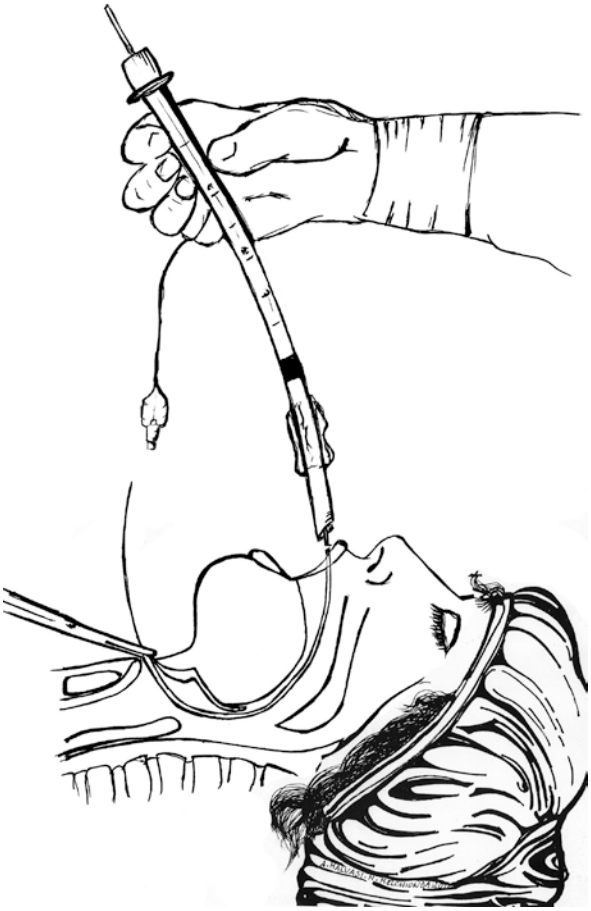


Fig. 18.23 The retrograde intubation

Blind nasal intubation is much less stimulating than direct laryngoscopy, but a small endotracheal tube should be used (6.0 mm). Unfortunately, pregnant women have hyperaemic nasal mucosae, and instrumentation of the nose entails the risk of bleeding [40].

The retrograde intubation has been of value in the management of difficult airway in the past; today it has any value for the obstetric patient (Fig. 18.23).

The flexible fibre-optic intubation has become the 'gold standard' for airway management and the most useful aid to awake intubation in the parturient with known difficult airway [48, 49].

Fibre-optic laryngoscopy is much less stimulating than direct laryngoscopy and/or blind nasal intubation, and it can be performed either per os or nasally. It is also considered safer and less traumatic than nasal intubation. Insufflation of oxygen through the suction port also serves as a defogging mechanism, and it provides supplemental oxygen, which results in a higher FIO_2 for the patient. An appropriately sized, well-lubricated ETT is placed on the bronchoscope before its insertion. Once the fibre-optic bronchoscope is passed into the trachea, the ETT is threaded off the fibre-optic

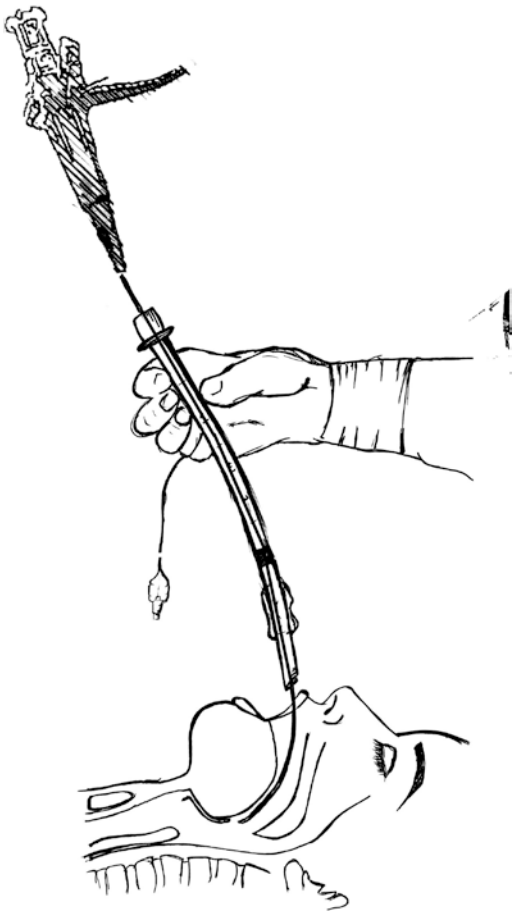


Fig. 18.24 The fibre-optic bronchoscope

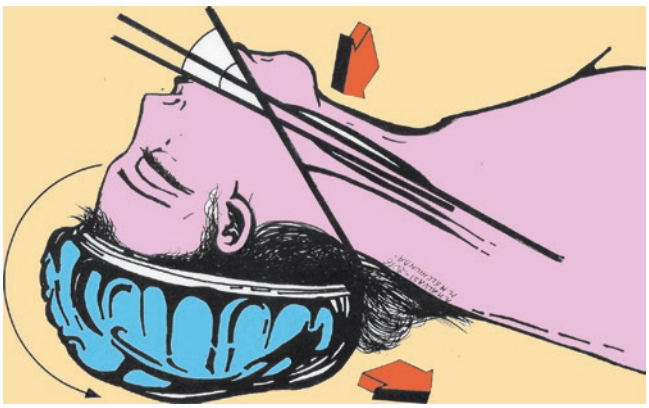


Fig. 18.25 Sniffing position

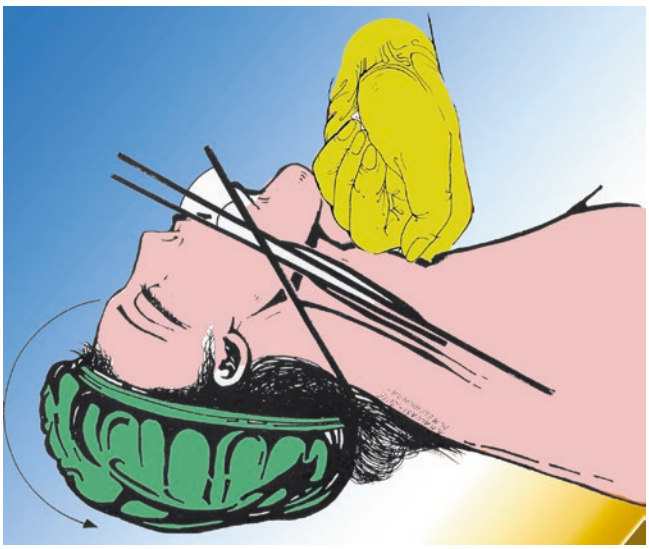


Fig. 18.26 Applying external laryngeal pressure (over the thyroid cartilage)

bronchoscope, the bronchoscope is withdrawn, the ETT adaptor is reattached, and the ETT is connected to the breathing circuit [50].

In the event that intubation is not successful, the anaesthesiologist should have a well-formulated plan in mind, and appropriate equipment and supplies should be immediately available to implement that plan. Hence, it is important for institutions to provide obstetric anaesthesia to have appropriate unanticipated difficult airway and failed intubation protocols.

If the anaesthesiologist is confronted with an unexpected difficult intubation and if there is no foetal distress, the patient is hemodynamically stable, there is adequate gas exchange via mask, and only one anaesthesiologist has attempted intubation, time permits optimizing the chances of successful intubation:

- Repositioning the patient position (better sniffing position) (Fig. 18.25)
- Applying external laryngeal pressure (over the thyroid cartilage) (Fig. 18.26)
- Using a different laryngoscope blade (length and/or type) (Fig. 18.27)
- Another anaesthetist attempt intubation

When the anaesthesiologist is unable to intubate the trachea of an anaesthetized patient, it is essential to try to maintain gas exchange by mask ventilation between intubation attempts. During positive pressure mask ventilation, maintenance of cricoids' pressure is mandatory. Failure to intubate the obstetric patient is often followed by difficulty with mask ventilation and by possible pulmonary aspiration. Either of these conditions rapidly leads to hypoxaemia for both the mother and the foetus. The adequacy of mask ventilation and the presence or absence of foetal distress are extremely important factors that must be taken into account in these situations.

In the presence of foetal and mother distress or hemodynamic instability, aggressive airway control may be achieved.

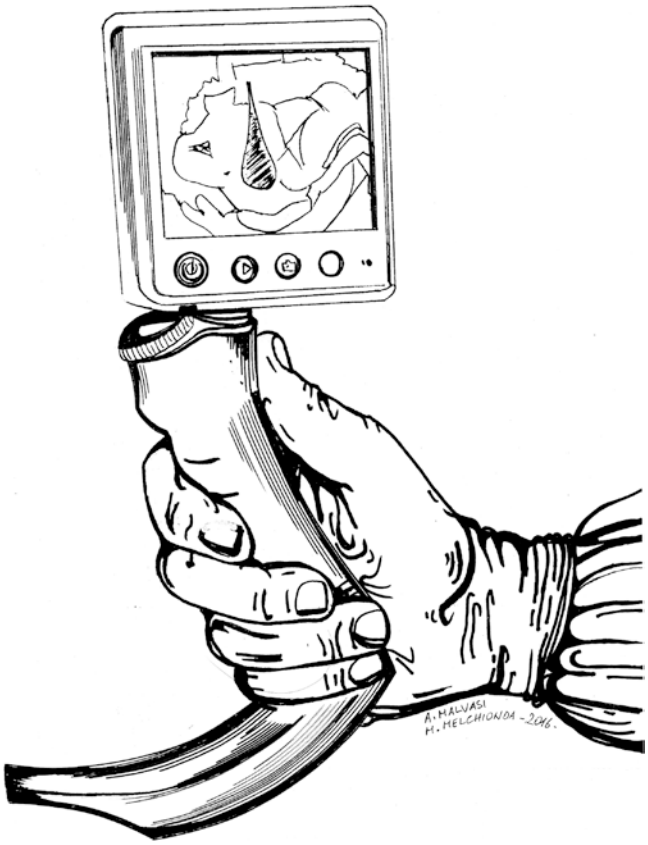


Fig. 18.27 Using a different type of laryngoscope

The difficult airway algorithm proposes the use of laryngeal mask airway (LMA) as a rescue in the event of a failed intubation (Table 18.4).

The laryngeal mask airway (LMA) is a supraglottic airway device developed by British anaesthesiologist Dr. Archi Brain [52] (Figs. 18.28 and 18.29).

Initially designed for use in the operating room as a method of elective ventilation, it is a good alternative to bag-valve-mask ventilation. The LMA is shaped like a large endotracheal tube on the proximal end that connects to an elliptical mask on the distal end. It is designed to sit in the patient's hypopharynx and covers the supraglottic structures, thereby allowing relative isolation of the trachea. The success of the LMA is probably due to two salient features: it performs adequately even when it is used poorly and allows for airway control and ventilation without affecting the function of the larynx [53]. This is due in part to the large area of the airway, which allows gas exchange even if airway alignment is poor. These two points make the LMA particularly useful in the management of the difficult airway (Table 18.5).

The routine use of the LMA for airway management can be associated with a number of problems. These problems consist of a clinically unacceptable non-patent airway, the requirement for multiple insertion attempts in a small percentage of patients, aspiration of gastric contents and suboptimal positive pressure ventilation [1].

Inadequate anaesthesia may cause all of these problems, and therefore a basic requirement for the safe use of the LMA is an adequate depth of anaesthesia.

There have been no reports of failure to correctly place or ventilate through the LMA in patients requiring this device in a cannot-ventilate/cannot-intubate situation [10]. Consequently, in such a situation, a quick, first try insertion of the LMA is an acceptable manoeuvre. Han et al. prospectively studied the use of LMA for elective caesarean section in 1,067 consecutive ASA physical status I and II patients preferring general anaesthesia. The authors concluded that the LMA is effective and probably safe for elective caesarean section in healthy, selected patients when managed by experienced LMA users [54] (Fig. 18.30).

The LMA SupreMe™ Second SeAL is a new laryngeal mask device with a modified cuff and a drainage tube designed to isolate the airway from the digestive tract [55]. The design should also improve the seal with the larynx. The LMA has been used successfully in parturients after failed intubation during rapid sequence induction and allows positive pressure ventilation at much higher pressures (Fig. 18.31).

The Combitube is another airway device that can be used when mask ventilation and intubation have failed. Combitube can be placed easily either in the trachea or oesophagus, allowing ventilation and protecting against regurgitation (Fig. 18.32).

The LMA can be used as a conduit for intubation, particularly when direct laryngoscopy is unsuccessful. The LMA acts as an insertion tool for the endotracheal tube to allow atraumatic intubation when the mask aperture is in alignment with the glottic opening. LMA can be used for blind passage of endotracheal tube, or an intubating stylet, or for the passage of a flexible fibre-optic bronchoscope [56, 57]. The passage of a fibre-optic bronchoscope through the LMA has a much greater chance of success and is nearly 100 % successful in most series [58]. A 6-mm internal diameter (ID) cuffed ETT is most suitable because of both very adequate length and widespread availability (Fig. 18.33).

As an alternative the video-laryngoscopic devices provide to be a very useful tool in patients with difficult airways. This device utilizes a video camera embedded into a plastic laryngoscope blade. The configuration of the laryngoscope blade provides a less obstructed view of the glottis compared to that obtained with conventional laryngoscope, allowing the users to see around the corner of the tongue. The video-laryngoscopic devices have also been shown to either shorten the time to tracheal intubation or improve the quality of oxygenation when compared with the traditional direct laryngoscope, although that there is a significant learning curve involved and experience is limited in maternity patients (Fig. 18.34a–c).

Table 18.4 ASA algorithm for difficult airway management, reproduced with permission

DIFFICULT AIRWAY ALGORITHM

1. Assess the likelihood and clinical impact of basic management problems:

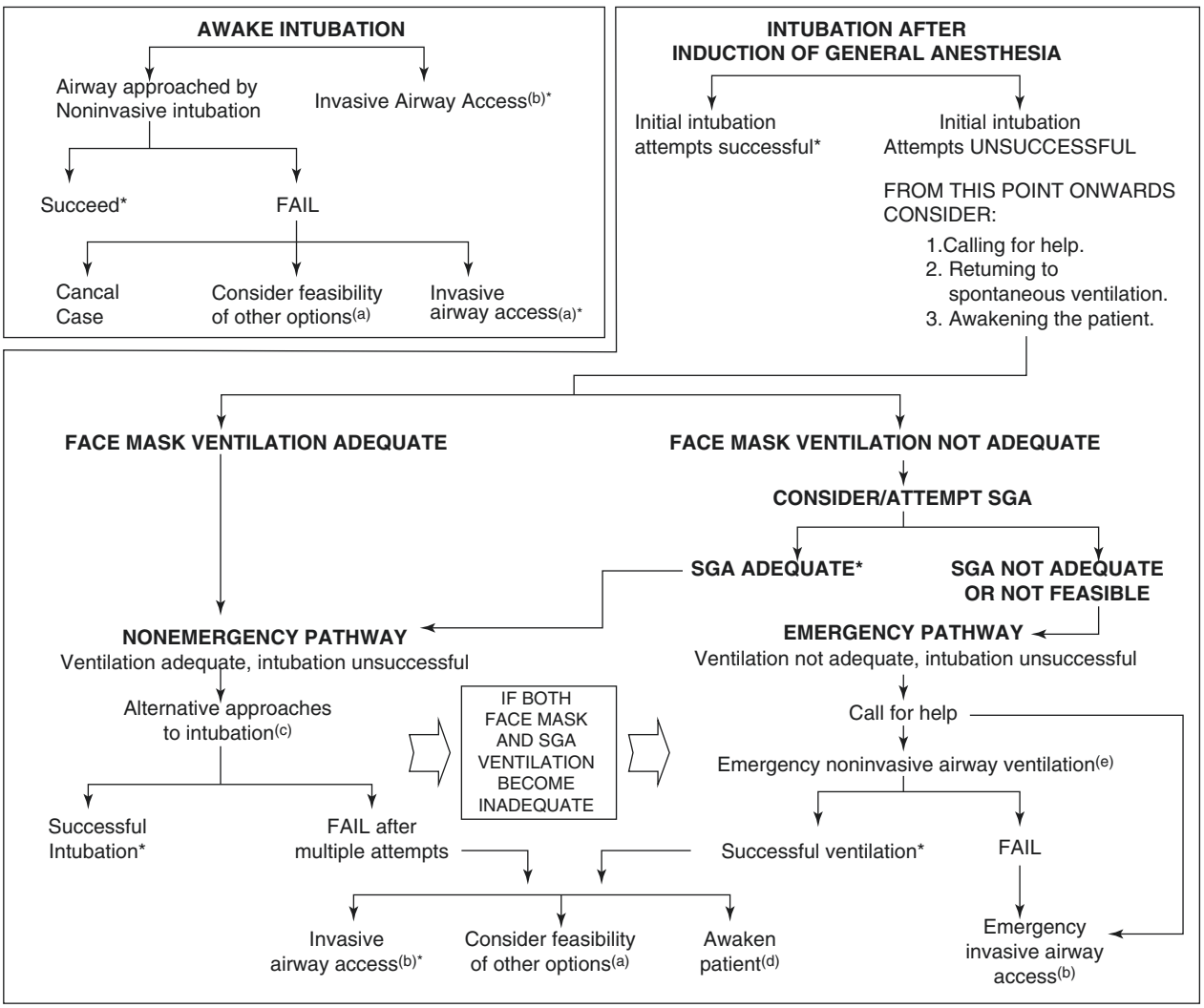
- Difficulty with patient cooperation or consent
- Difficult mask ventilation
- Difficult supraglottic airway placement
- Difficult laryngoscopy
- Difficult intubation
- Difficult surgical airway access

2. Actively pursur opportunities to deliver supplemental oxygen throughout the process of difficult airway management.

3. Consider the relative merits and feasibility of basic management choices:

- Awake intuvation *vs.* intubation after induction of general anesthesia
- Non-invasive technique *vs.* invasive techniques for the initial approach to intubation
- Video-assisted laryngoscopy as an initial approach to intubation
- Preservation *vs.* ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



*Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_{2*}

From Practice Guidelines for Management of the Difficult Airway. A report by the ASA Task Force on the Management of the Difficult Airway. Anaesthesiology 2007

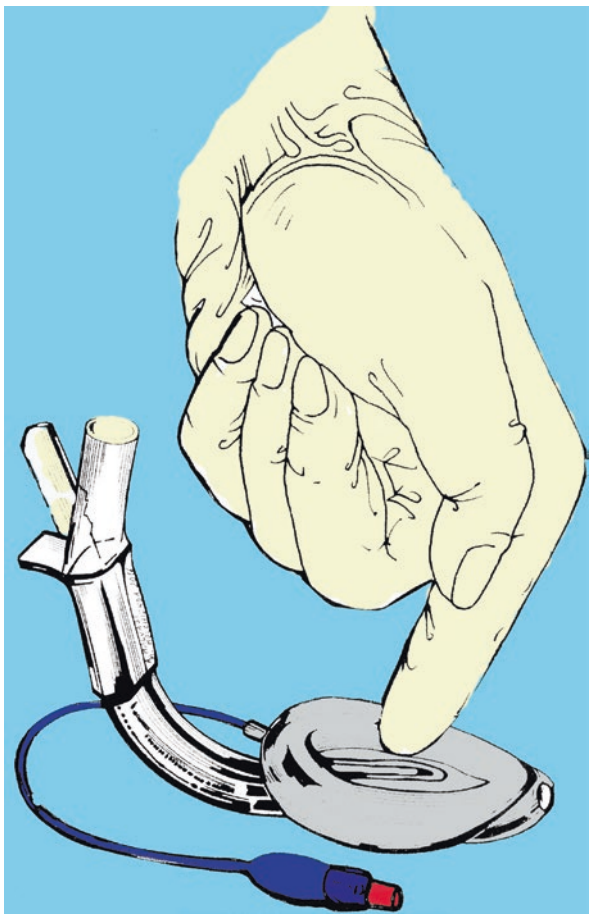


Fig. 18.28 The laryngeal mask airway (LMA)

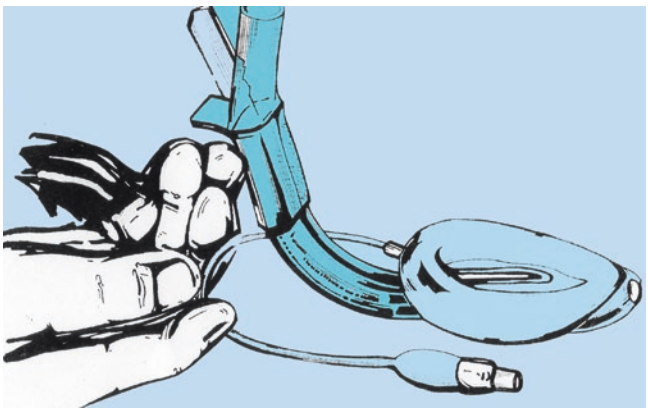


Fig. 18.29 The laryngeal mask airway (LMA)

18.2.3 Aspiration

Pregnant women are considered at increate risk of aspiration while undergoing general anaesthesia because of physiological anatomic and hormonal changes that occur in the gastrointestinal tract and that increase gastroesophageal reflux, particularly when nonelective caesarean section is required [34].

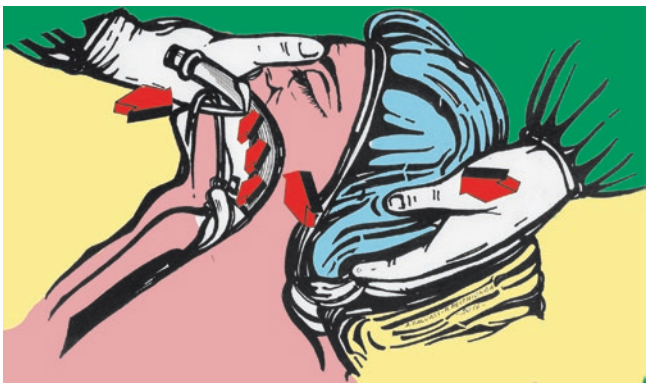


Fig. 18.30 The laryngeal mask airway (LMA)

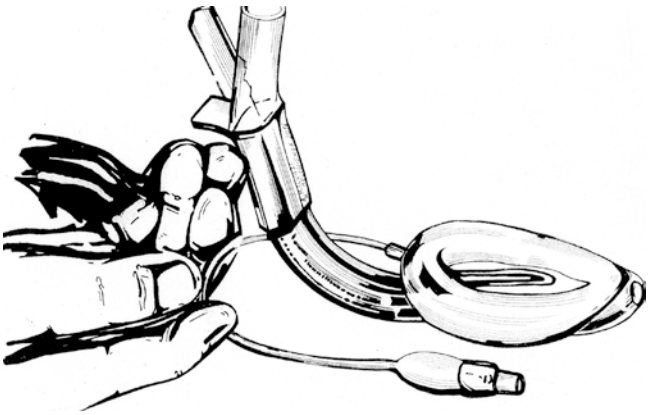


Fig. 18.31 LMA SupreMe™ Second SeAL

The progesterone-mediated reduction in lower oesophageal sphincter tone, the enlarging uterus increasing intra-abdominal pressure and higher gastric volumes and lower pH all contribute to this risk. Additionally, gastric emptying is delayed during labour, especially following the administration of opioids. Aspiration during obstetric anaesthesia was classically described by Mendelson in the 1940s [59, 60].

Mendelson attributed to immediate asphyxiation from solid material and later respiratory failure from adult respiratory distress syndrome secondary to aspiration of liquid material, the cause of death under general anaesthesia. Mendelson observed and described a reaction to aspiration that was characterized by dyspnoea and cardiac failure. Chest X-ray revealed fluffy densities throughout the lungs that differed significantly from the classic syndrome of solid aspiration. The aspiration resembling those of an acute asthmatic attach. The author then concluded that the incidence of aspiration could be reduced by withholding oral feeding in labour, preferring regional anaesthesia, using alkalization of stomach contents before anaesthesia and emptying the stomach prior to general anesthesia. [60].

Prolonged labour can result in dehydration and ketosis, and the reduction of caesarean section under general anaes-

Table 18.5 Technique for the correct insertion of laryngeal mask airway (LMA)

Preoxygenate the patient with 100 % oxygen via a nonrebreather mask, as time allows
Choose the appropriate size of laryngeal mask airway (LMA)
Check the LMA cuff for leaks
Deflate the cuff of the LMA completely against a flat surface
Apply a water-soluble lubricant generously to the posterior surface of the mask
Administer sedation when indicated
Position the patient
Cricoid pressure is intended to reduce the risk of aspiration and should be maintained, especially in patients who have not fasted, until the airway is secured

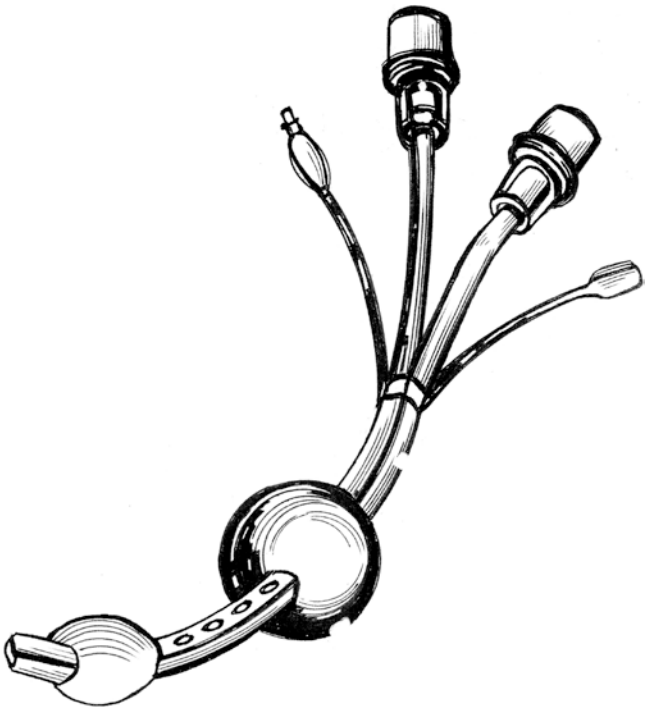


Fig. 18.32 Combitube

thesia suggests a more liberal approach allowing eating and drinking during labour. Feeding appeared to prevent the development of ketosis, but gastric volumes measured is higher, and the risk of vomit and pulmonary aspiration is augmented especially if general anaesthesia is required [61]. Another study proposed to give mothers, in early labour, isotonic sports drinks compared with water, and this appeared to prevent ketosis but without increasing residual gastric volume [62, 63].

However, pulmonary aspiration is frequently associated with difficulty with airway management, and patients undergoing general anaesthesia with full stomach should be intubated with a cuffed endotracheal tube quickly and smoothly.

Aspiration prophylaxis for caesarean section is commonly recommended, and the combination of sodium citrate, ranitidine and metoclopramide has been suggested [29].

Antacids to reduce the volume and acidity of gastric contents have a role to play in preventing aspiration or reducing its severity if it occurs. Gastric volume of 0.4–0.8 mL/kg and pH of less than 2.5 are classically quoted as being the critical values concerned [64–66]. Sodium citrate, 30 mL 0.3 M, before induction of anaesthesia increases

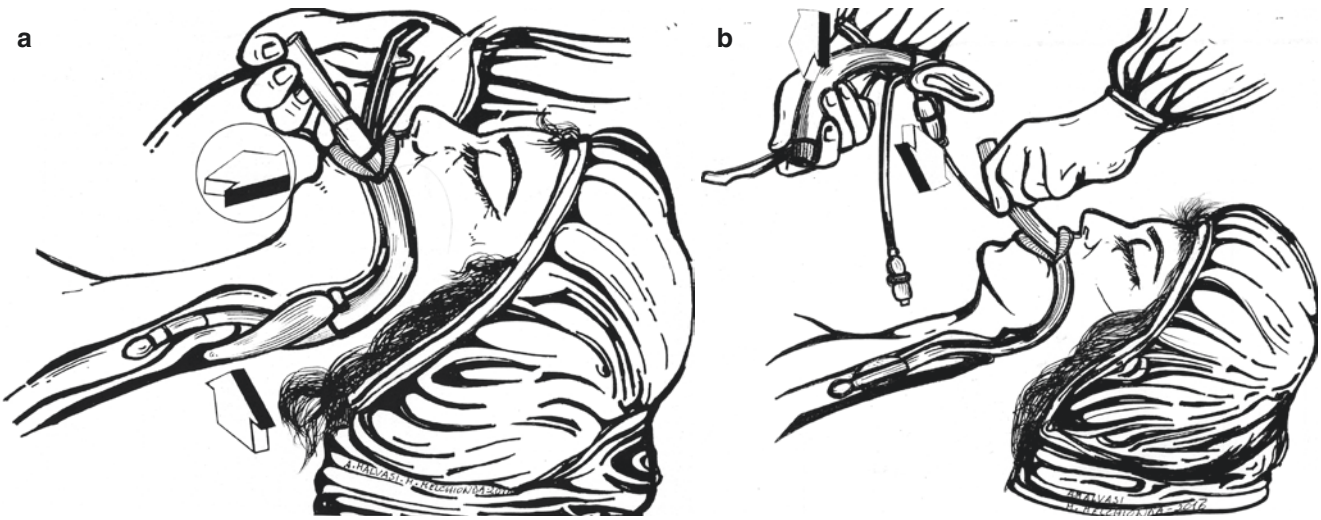


Fig. 18.33 (**a**, **b**) Intubating through the LMA

gastric pH but not the volume. Ranitidine, histamine type 2 receptor antagonists (H2), 150 mg orally 1 h preoperatively, reduces gastric volume and acidity, especially in combination with sodium citrate. Ranitidine can also be given in an emergency intravenously at induction and will provide aspiration prophylaxis [21]. Metoclopramide is a procainamide derivative that is a cholinergic agonist peripherally and a dopamine receptor antagonist centrally, increases lower oesophageal sphincter tone and reduces gastric volume by increasing gastric peristalsis. Metoclopramide can have a significant effect on gastric volume in as little as 15 min and crosses the placenta but without significant effects on the foetus.

An audit on acid prophylaxis in obstetric anaesthetic units in the UK revealed that 99 % of delivery suites routinely use drugs to reduce the gastric volume and acidity for elective caesarean section and 98 % for emergency. H2 receptor antagonists ranitidine and sodium citrate are the most commonly used agents. Only a minority of units used proton pump inhibitors, such as omeprazole, that increase gastric pH effectively but tend to be more expensive [22].

Increased use of regional anaesthesia has played an important role in the reduction of maternal deaths from aspiration, but it must be remembered that aspiration can occur with very high blocks and the loss of laryngeal reflexes. Rapid sequence induction also plays an important role but introduces with it other risks such as failed intubation and oesophageal rupture if vomiting occurs.

The management of aspiration during anaesthesia is outlined in Table 18.6.

18.2.4 Awareness

General anaesthesia for caesarean section is considered a high-risk procedure for awareness. The studies reported an incidence of 0.4 % and is higher than the incidence of general surgical population (0.1–0.2 %), confirming that pregnant women remain at increased risk. Awareness with recall of intraoperative events is highly likely to cause patients dissatisfaction and can result in prolonged psychological disturbance with anxiety, mood and sleep disturbance and phobic behaviour (peach 2009, [1–3]). The higher risk of awareness in the obstetric population compared to the general surgical population may stem from a number of factors; these include physiological changes (Table 18.7).

Changes in the cardiovascular system during pregnancy are designed to meet the increasing metabolic demands of the mother and foetus. By 24 weeks' gestation, plasma volume has increased by 40 %, with a 30–50 % increase in cardiac output. In early pregnancy, the rise in cardiac output is driven by an increase in stroke volume. As pregnancy advances, an increase in heart rate becomes the main contributor, peaking around 32 weeks and remaining high up to 5 days after delivery. Initially, both systolic and diastolic blood pressure drop because of vasodilatation and a fall in systemic vascular resistance (SVR). This is thought to be a result of local mediators such as nitric oxide and prostacyclin. By term, diastolic blood pressure may have reached pre-pregnancy values [68, 69].

Particularly the high cardiac output of pregnancy accelerates the redistribution of intravenous anaesthetic agents and slows the establishment of an adequate partial pressure of volatile anaesthetic agent. Same thing applies to an intravenous induction agent that is redistributed rapidly from the cerebral circulation, potentially leaving a period of light anaesthesia before the volatile anaesthetic agent reaches the effect site. This can be exacerbated if more than one attempt at intubation is required.

To reduce the risk of awareness during these procedures, conscious state monitoring, such as the bispectral index monitor (BIS, Aspect Medical Systems® or the entropy monitor (GE Healthcare)), should be used (Fig. 18.35a, b).

There has been little research into the use of these monitors in obstetric anaesthesia, but across a cohort of high-risk patients, BIS monitoring reduced the risk of awareness by 82 % [67].

Compared with the techniques used in the past, the more generous administration of intravenous induction agent and volatile anaesthetic may decrease the incidence of awarness from 1.3% to 0.4%. Sevoflurane has been shown to have comparable intraoperative maternal and neonatal effects to isoflurane and has attractive properties such as a lower blood gas partition coefficient than isoflurane and fewer sympathetic and airway-related side effects than desflurane. For these reasons the sevoflurane is the most commonly used volatile agent during general anesthesia for caesarian section. [67–70].

The obesity during pregnancy favours higher initial dose requirements and more rapid drug redistribution. In this case propofol has been associated with lighter levels of anaesthesia.

18.2.5 Other Possible Risks of General Anaesthesia

18.2.5.1 Foetal Asphyxiation and Early Neonatal Depression

The anaesthetic agent systemically administered to the mother crosses the placenta and causes foetal and neonatal depression. General anaesthesia for caesarean delivery was associated with lower 1-min Apgar scores compared to neuraxial anaesthesia, suggesting that these differences are a result of transient sedation secondary to anaesthetic agents [71, 72].

It should be also highlighted that postnatal adaptation of the newborn is affected by previous intrauterine foetal condition, concurrent administration of thiopentone and volatile anaesthetics, as well as by induction-to-delivery interval and

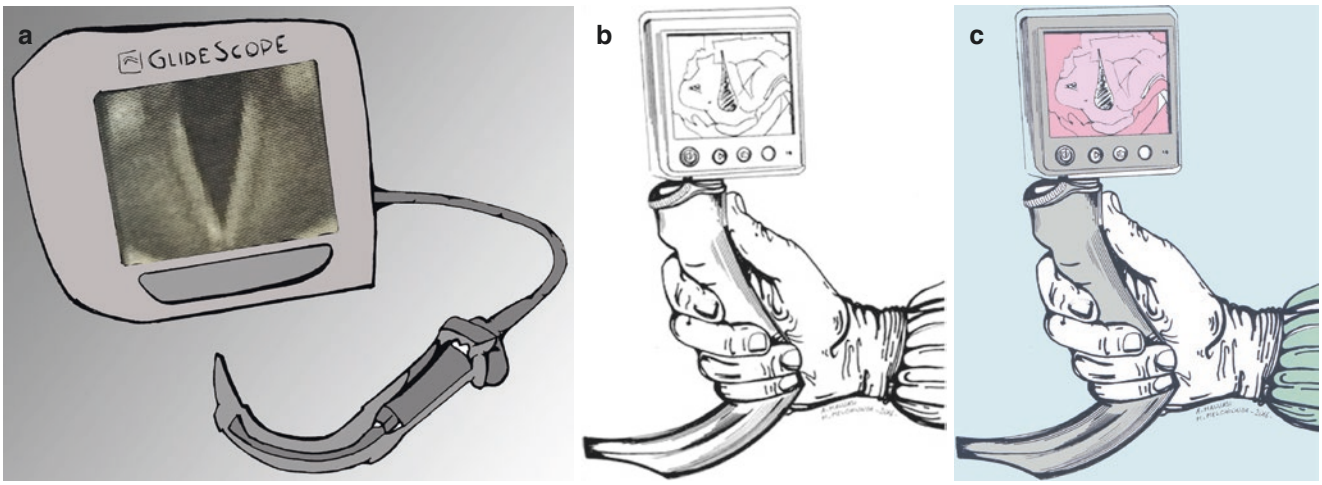


Fig. 18.34 Video-laryngoscopic devices, (**a**) GlideScope, (**b**) Ambu, (**c**) Storz

Fig. 18.35 (**a**) BIS®, (**b**) BIS® monitor

Table 18.6 Management of aspiration during general anaesthesia

100 % oxygen
Head down position and turn to lateral
Suction oropharynx
If no endotracheal tube in situ, apply cricoid pressure and intubate
Endotracheal intubation with a cuffed tube
Suction and lavage tracheobronchial tree (preferably endoscopically)
Bronchodilators for wheezing
PEEP for hypoxaemia
Postoperative chest X-ray
Ventilation on ICU if severe hypoxaemia
Antibiotics if infected material aspirated

Table 18.7 Patients' awareness risk factors

Previous awareness
Known or predicted difficult intubation
Obesity
Drug dependence
Risk of intraoperative hypotension

technique of caesarean section. There are different opinions about the ideal time at which the foetus should be delivered after induction of anaesthesia. Barter was the first to emphasize that parturient women should be prepped and draped before induction of general anaesthesia. Many workers have recommended that delivery is best completed 6 ± 8 min after induction of general anaesthesia. Datta et al. observed that in the absence of hypotension, there is no change in Apgar scores or acid base status with prolonged induction-to delivery interval in spinal anaesthesia. Morgan described that long skin incision-to-delivery time more than 8 min and uterine incision-to-delivery time more than 180 s have been associated with foetal hypoxia and acidosis regardless of the type of anaesthesia [73–77].

18.2.5.2 Uterine Atony Blood Loss

Volatile anaesthetic agents cause dose-dependent myometrial relaxation. Therefore, increasing the dose of volatile agent (to decrease the risk of awareness) may be associated with an increased risk of uterine atony and haemorrhage. Lastly, uterine contraction may vary in different types of anaesthesia. Guay mentioned that in the process of caesarean section, inhalation anaesthetics caused uterine contractions that are closely related to postpartum haemorrhage [78]. Various studies have been conducted on this, and the results have showed that not only previous anaesthetics such as halothane but recent ones such as desflurane and sevoflurane hinder uterine contraction [79, 80]. Turner et al. extracted uterine muscles after caesarean section and investigated how much sevoflurane and desflurane would hinder uterine contractions. They hinder the contractions of uterine muscles at 0.5 MAC, 1 MAC and 1.5 MAC, respectively, and they were similar in extent to each other [81].

18.2.5.3 Postoperative Analgesia and Development of Chronic Pain

Effective pain therapy after caesarean delivery is important for comfort and to allow early ambulation to facilitate care of the newborn. In addition, optimization of postoperative pain treatment could allow early return to a regular diet and normal bladder and bowel function, thus facilitating early discharge from hospital. Post-caesarean neuraxial analgesia is more effective than systemic analgesia and is associated with increased functional ability, earlier ambulation and earlier return of bowel function.

Poor postoperative analgesia is a predictor for the development of chronic pain and postpartum depression after caesarean delivery. The incidence of chronic pain after caesarean delivery may be as high as 10 %. The development of chronic pain is more likely in women who receive general compared to neuraxial anaesthesia and is more likely in women who reported severe acute postoperative pain. Therefore, it is possible that neuraxial anaesthesia and better post-caesarean analgesia using multimodal techniques, in which neuraxial analgesia is one component, may decrease the risk of developing chronic postpartum pelvic pain [82, 83].

18.2.5.4 Postoperative Thromboembolic Disease

Venous thromboembolism is a leading cause of maternal death in both the USA and the UK. Women are at highest risk for thromboembolism in the postpartum period and are at higher risk after caesarean than vaginal delivery [84, 85].

18.2.5.5 Adverse Effects on Breast-Feeding

In a retrospective study, the percentage of women who were still breast-feeding at 6 months was less in those who received general anaesthesia than epidural anaesthesia. Systemic opioid analgesia, more likely in women who receive general anaesthesia, is associated with a decreased rate of successful lactation [38]. In any case, women who have undergone general anaesthesia are less alert in the early recovery period and, therefore, less likely to effectively nurse their newborns [86].

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The Cesarean Scar Complications

19

Luis Alonso Pacheco, Leonardo Resta, Andrea Tinelli, Antonio Malvasi, Sergio Haimovich, and Jose Carugno

The cesarean delivery rate has been raising nonstop for over three decades [1]. In the United States, in the year 2011, one-third of women who gave birth had a cesarean delivery [2]. This trend has been verified not only in the United States but also worldwide. The steady increase number of cesarean deliveries is due to multiple factors including the relative perceived safety of cesarean delivery operation in modern medicine [3]. Other important factors that resulted in a higher cesarean section rate are that there has been a constant decrease rate of operative vaginal deliveries, vaginal delivery of twin with cephalic presentation, vaginal breech deliveries, vaginal birth after cesarean section (VBAC), and medicolegal concerns for possible complications as a result of bad outcomes in patients attempting VBAC [3]. Unfortunately, this rapid increase of cesarean births has not resulted in decreased neonatal morbidity or mortality, which raises significant attention on the possible overuse of cesarean birth [4]. A concern about the uncontrolled raise of cesarean sections was recognized in the early 1970s [5]. An epidemiologic study revealed that "severe" maternal complications such as hemorrhage that required hysterectomy or massive blood transfusion, uterine rupture, anesthetic complications, shock, venous thromboembolism, cardiac arrest, acute renal failure, assisted ventilation, major infection, and wound disruption were threefold increased for cesarean delivery as compared with vaginal delivery [6]. Also, well-known long-term effects of cesarean deliveries such as infertility, pelvic adhesions, and pelvic pain have been described in many textbooks [1]. Subsequent pregnancies have a documented higher rate of perinatal complications not only maternal but also neonatal complications such as prematurity, low Apgar scores, neonatal intensive care unit (NICU) admissions, and higher perinatal death.

There are maternal and fetal long-term deleterious consequences of a previous cesarean section scar. Maternal consequences could be divided in obstetrical complications (in subsequent pregnancies) and non-obstetrical complications (not related to future pregnancies).

19.1 Niche in the Scar

The healing process of the cesarean section scar can in occasions be incomplete. In that situation, there is a disruption of the myometrium at the site of the uterine scar. This "gap" in the anterior lower uterine segment receives different names, being the terms "niche" [7] or isthmocele [8] the most commonly used (Fig. 19.1). This defect and its relation with some clinical symptoms such as menorrhagia, abdominal pain, dyspareunia, and dysmenorrhea were first described by Morris [9] using the term "cesarean scar syndrome."

The estimated incidence of cesarean scar defect (CSD) ranges between 24 and 56 % [10]. This incidence varies considerably depending on the reports. This is due to variation

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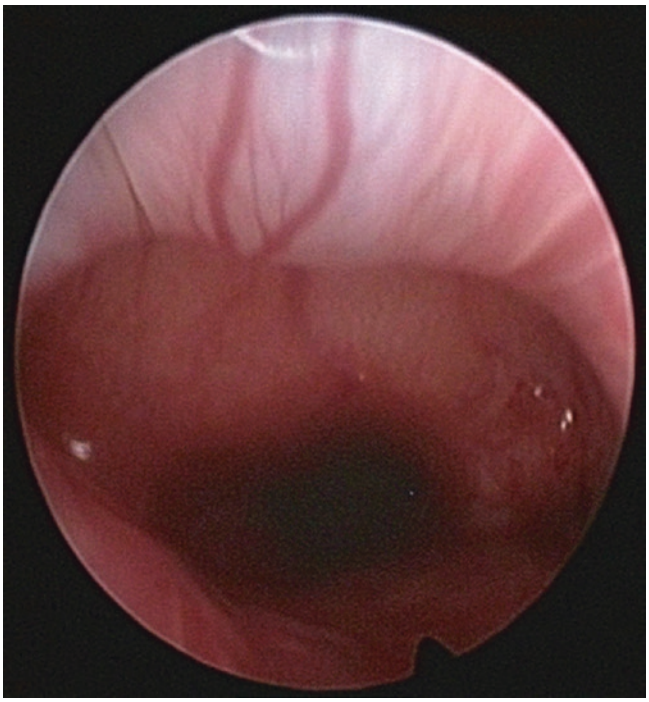


Fig. 19.1 Hysteroscopic appearance of cesarean scar defect

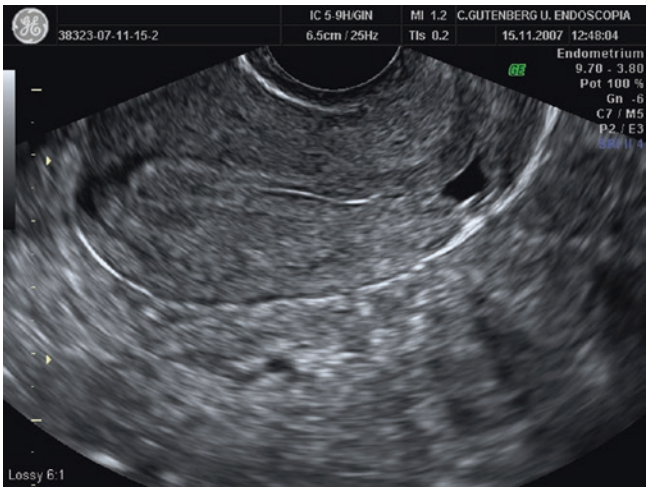


Fig. 19.2 View of the cesarean scar defect in a retroverted uterus

on definitions and the differences in the methods used for the diagnosis of the defect.

There is a clear relationship between the anatomic defect and the presence of different degrees of postmenstrual bleeding and other gynecological symptoms such as dysmenorrhea, chronic pelvic pain, and infertility.

The diagnosis of this condition is based on the clinical symptoms, ultrasound evaluation, and hysteroscopy. There is a high correlation between transvaginal ultrasound and hysteroscopy in the diagnosis of CSD.

Different treatments have been proposed: medical therapy with the use of oral contraceptives to reduce menstrual blood, hysteroscopy surgery to facilitate the drainage of blood and to reduce the local production, and laparoscopic or vaginal surgery to correct the defect.

19.2 Etiopathogenesis

The reason why the defect does not appear in all women undergoing cesarean section is unknown, and the pathogenesis of the scar defect remains unknown. Different factors have been described as a possible cause of a cesarean scar defect (CSD). One possible factor related with the CSD is the difference in myometrial contraction between the thicker superior edge of the incision and the inferior one. This difference in thickness is usually more evident as the number of cesarean increases. The approximation of incision edges with different thickness can contribute to the development of the CSD [11].

Another possible factor suggested is the surgical technique used to close the hysterotomy; it is argued that the presence of a CSD can be in relation with the suture material used, with the suture technique, or both. Furthermore the combination of an ischemic suturing technique and a slow absorbable suture material can produce an abnormal healing [12]. Regarding the technique, Yazicioglu found that the frequency of incomplete healing was significantly lower in the group treated by full-thickness suturing [13]. A recently published meta-analysis found no significant difference in the risk of uterine scar defect with single-layer closure compared to double-layer closure [14].

Ofili-Yebovi found a relationship between multiple previous cesarean section and CSD and also noted that uterine retroflexion was another variable that was clearly associated (Fig. 19.2). In a retroflexed uterus, the lower segment is under a degree of tension, which may affect to the healing of the cesarean section scar [15].

There is an association between the degree of cervical dilatation and the duration of labor with an increase in the risk of CSD if the duration of labor is ≥5 h or the cervical dilatation is ≥5 cm [16]. In late labor, the modified cervix becomes part of the lower uterine segment. Low incisions are more common if cesarean section is performed late in labor and cervical tissue may be included in the closing sutures, interfering with the healing of the scar.

19.3 Clinical Manifestation

It is well documented that some late complications are present after a previous cesarean section. As well as the obstetrical complications, some gynecological disturbances have been described in patients who have a CSD. Postmenstrual abnormal bleeding, chronic pelvic pain, and secondary infertility are linked to this pathology.

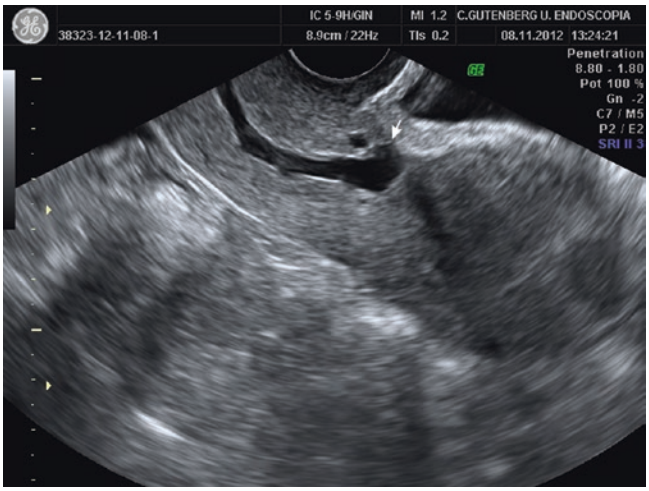


Fig. 19.3 Debris accumulated in the cesarean scar defect and in the cervical canal

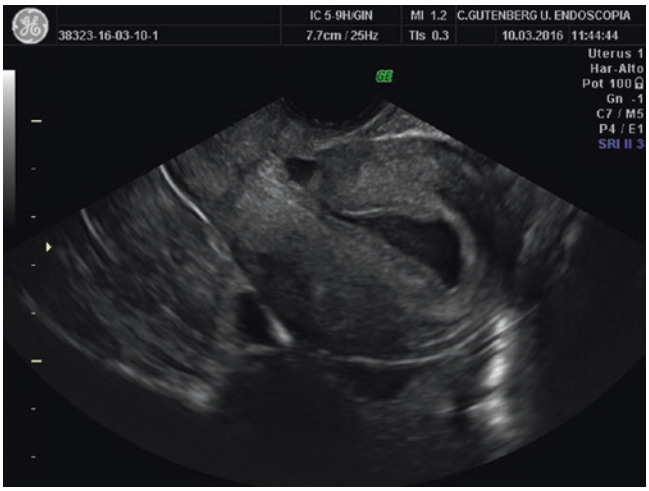


Fig. 19.5 Hematometra due to retrograde passage of blood

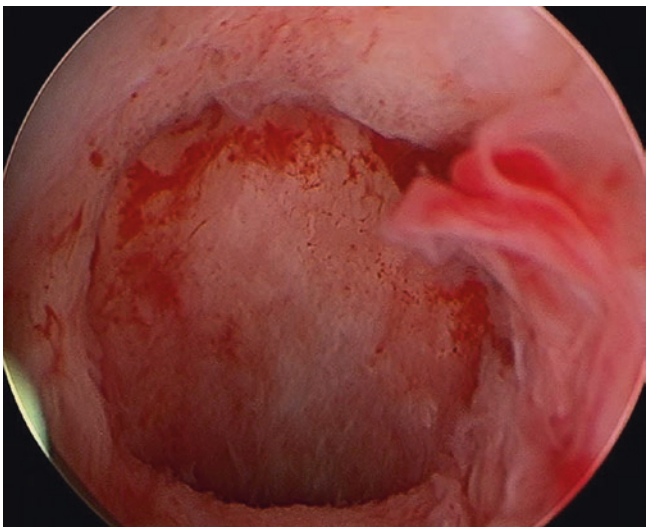


Fig. 19.4 Congested endometrium above the scar

The classic symptom in those patients is the presence of postmenstrual abnormal bleeding, of about 2–12 days of duration, usually scarce and dark in color. Morris [9] was the first to describe a relation between this postmenstrual bleeding and the presence of anatomic and histologic changes at the site of the cesarean scar.

Postmenstrual bleeding (PB) is estimated to occur in one in three (33.6 %) of women with a niche in the scar. There is a direct relation between the size of the defect and the quantity and duration of the bleeding, mainly in retroverted uteri. Probably a triple mechanism is involved in this postmenstrual bleeding. On the one hand, the disruption in the continuity of the endometrium acts as a reservoir pouch, in which some menstrual blood and debris are accumulated (Fig. 19.3); the slow outflow of this retained blood is linked to the PB. Another related mechanism is poor contractility of the uterine muscle around the scar, due to the existence of fibrotic tissue, which prevents normal myometrial contractions [10]. Last but not least, there is minimal production in situ due to local changes that take place in the niche as congested endometrium above the scar, lymphocytic infiltration, and the presence of small polyps [9] (Fig. 19.4).

The presence of a disruption in the myometrium at the site of the cesarean scar is associated with different clinical symptoms as dysmenorrhea, chronic pelvic pain, and dyspareunia. Among these symptoms, dysmenorrhea is the most common with an incidence of 53 %, followed by chronic pelvic pain in 39.6 % and dyspareunia in 18.3 % [17].

All those symptoms are probably caused by chronic inflammation and the lymphocytic infiltration present in the scar.

Secondary infertility has also been related to CSD. The accumulation of blood in the niche can affect the normal characteristics of the mucus and interfere with sperm transportation through this mucus. There is also minimal retrograde passage of blood, to the uterine cavity, especially in retroverted uteri, that can affect the quality of the endometrium with consequences during embryo implantation (Fig. 19.5).

19.4 Diagnosis

The diagnosis of cesarean scar defect is based on a previous history of cesarean section, clinical symptoms, and diagnostic tools as ultrasound and hysteroscopy.

Currently, there is lack of consensus on the definition of cesarean scar defect. Ultrasound is usually the first diagnostic modality used in women with postmenstrual bleeding. The ultrasound study can be performed with conventional 2D ultrasound, 3D or saline infusion sonohysterogram (SIS),

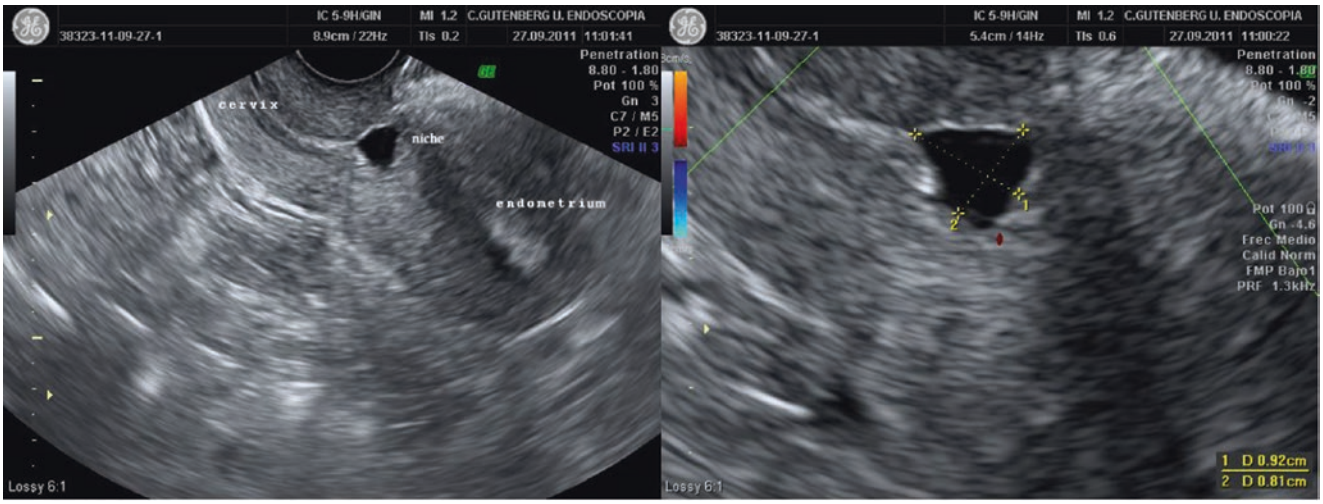
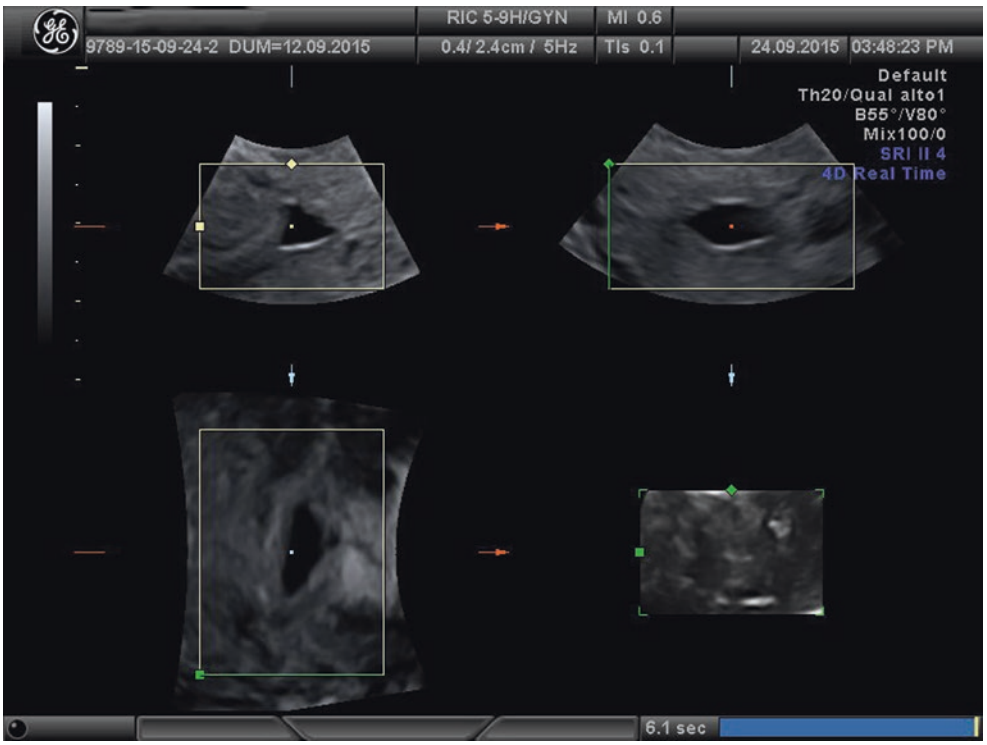


Fig. 19.6 Anechoic area at the site of a previous cesarean section. This niche is usually *triangular-shaped*

Fig. 19.7 3D view of the niche



or gel (GIS) to fill the niche and to create a better image. Hysterosalpingography, hysteroscopy, and RMN can be also used to diagnose this defect.

19.5 Ultrasound

Transvaginal ultrasound is accurate in detecting cesarean scar defects. The niche is defined by the presence of an anechoic area at the site of a previous cesarean section (Fig. 19.6). This niche is usually triangular in shape with the vertex toward the isthmus. Another proposed diagnostic criterion is the presence of fluid within the incision site [18]. The prevalence of a niche on evaluation with conventional 2D ultrasound is 24 % [16]. The best time to perform ultrasonography diagnosis of CSD is during the late proliferative phase in which the cervical mucus can fill the niche. The use of 3D ultrasound facilitates the study of the defect in multiple planes and offers more information than conventional ultrasonography (Fig. 19.7).

19.6 Hysterosalpingography

Cesarean scar defects can also be diagnosed by hysterosalpingography, usually as an incidental finding. The presence of anatomic defect as a diverticulum or thin linear defects at the lower uterine cavity is a common finding in patients with a previous cesarean section, and these defects can be found at around 60 % of patients [19].

19.7 Sonohysterography

The use of SIS or GIS provides a clear visualization of the CSD due to the filling of the niche with liquid, facilitating the diagnosis. Moreover, more defects are detected using sonohysterography and more defects are classified as large than with the use of conventional 2D ultrasound [20]. The instillation of liquid inside this defect allows us to find different shapes and sizes. The prevalence of a niche on evaluation with gel is around 56 % [16]. The main advantage of the use of gel is that remains longer time filling the disruption; this allows performing a better evaluation of the defect.

19.8 Hysteroscopy

Hysteroscopy allows a direct visualization of the scar defect. During hysteroscopy, a pseudo-cavity is visualized in the anterior wall of the low uterine segment or in the upper third of the cervical canal. Hysteroscopically, a *double arch* of fibrous tissue is identified and a dome between those archs (Fig. 19.8). The dome of the isthmocele is covered by a congestive endometrium with different grades of inflammation. In the early proliferative phase, blood and some clots are usually visualized filling the anatomical defect and the cervical canal.

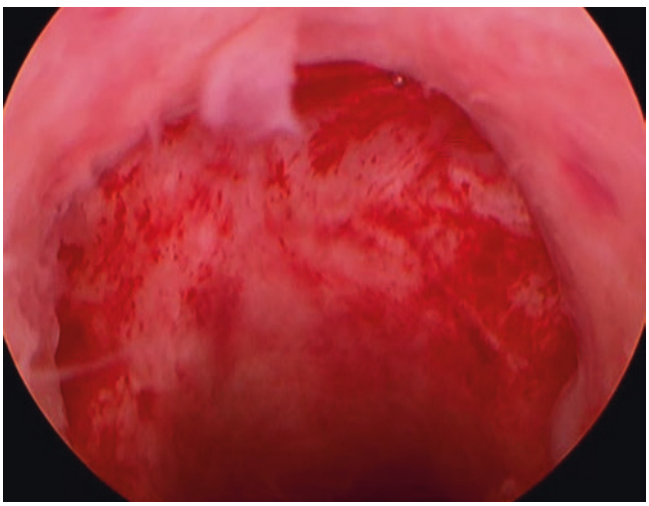


Fig. 19.8 A pseudo-cavity is visualized in the anterior wall of the low uterine segment

19.9 MRI

Magnetic resonance imaging (MRI) can also detect myometrial defect located at the lower uterine segment. The MRI displays a linear low signal niche, sometimes filled with fluid (Fig. 19.9). The use of MRI can be useful to planning the corrective surgery and to rule out other conditions.

19.10 Classification of CSDs

There are two main classifications used for the CSD. The one proposed by Gubbini [21] in which the depth and the base of the isthmocele are measured and the surface of the isthmocele is calculated. According to the result of the surface, the isthmocele is classified into three grades: grade 1 with less than 15 mm³, grade 2 with a surface between 16 and 25 mm³, and grade 3 with more than 26 mm³. In his review, he found that more than 55 % of cases were grade 1.

Yebovi focused the other classification of the CSD on the measurement of the endometrial thinning at the cesarean defect; he defined the degree of thickness by the ratio between the myometrial thickness at the level of the defect and the thickness of the adjacent myometrium and defined a severe defect a ratio >50 % [14] and dehiscence a ratio equal or superior to 80 %.

Other authors have defined CSD as severe when the remaining myometrium at the level of the niche is less than 2.2 mm visualized with ultrasound examination or 2.5 mm in women who underwent hydrosonography for the diagnosis of the CSD [22] (Fig. 19.10).

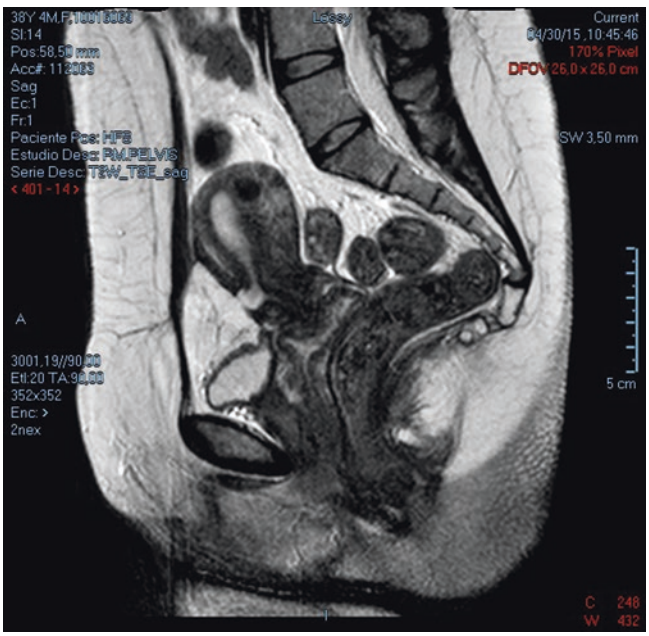


Fig. 19.9 Visualization of the defect with MRI

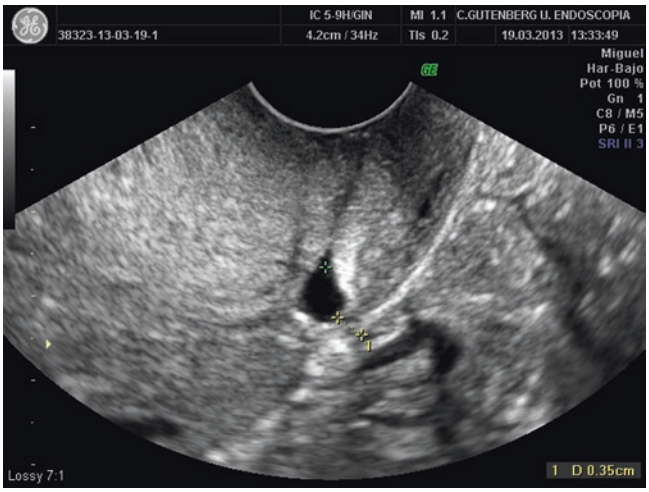


Fig. 19.10 Measurement of the endometrial remaining myometrium

19.11 Treatment

Various surgical options have been proposed to treat the CSD: on one hand, a reparative treatment with laparoscopic repair of the dehiscence and, on the other, the resectoscopy correction in order to improve the symptoms. Other alternatives are the vaginal repair of the CSD and the use of oral contraceptives to reduce menstrual blood. The surgical treatment should only be reserved for symptomatic patients with postmenstrual bleeding, chronic pelvic pain, or secondary infertility. The first two options are the commonly used, and the election of any of them is usually related with anatomical conditions of the CSD.

19.12 Resectoscopic Surgery

The first reference about the use of the resectoscope in the treatment of a CSD was made by Fernandez [23] who performed the resection of the fibrotic tissue of the inferior part of the scar to facilitate the drainage of the menstrual blood collected in the scar, improving the postmenstrual bleeding. Since then, multiple articles have been published, and the resectoscopy has become the most reported approach for the treatment of symptomatics CSD. Fabres in addition to the resection of the fibrotic tissue underneath the pouch defect used the local fulguration of the dilated blood vessels and endometrial glands in the CSD, responsible of the in situ production [24] (Fig. 19.11). The main risk associated with the resectoscopy surgery is the possibility of uterine perforation and secondary bladder injury; in order to prevent this complication, some authors recommend to avoid the resectoscopic surgery if the remaining myometrium at the level of the niche is less than 2 mm [25].

19.13 Laparoscopic Surgery

The purpose of the laparoscopic management is to restore the myometrial continuity at the site of the CSD which leads to a reduction of the niche and consequently to an improvement of the related symptoms. The main advantage of the laparoscopic approach is that we can consider this as a reparative surgery which leads to an increase in the thickness of the uterine wall, something that can't be done with the hysteroscopic approach [26]. Klemm firstly used a combined laparoscopic-vaginal approach to repair the defect [27]. Donnez described a totally laparoscopic approach with excision of the fibrotic tissue around the scar and laparoscopic suture to approximate the healthy myometrium of each side of the opened scar [28]. The laparoscopy surgery offers a clear visualization of the surgical area after the dissection of the bladder with low risk of damage (Fig. 19.12).

19.14 Vaginal Surgery

The vaginal approach of the cesarean section defect is also considered a reparative surgery, which corrects the defect and increases the thickness of the uterine wall. As we referred before, this was firstly used in combination with laparoscopy approach. A new vaginal repair technique has been recently proposed in which after the opening of the cervico-vesical space and the dissection of the bladder, the scar is opened and the fibrotic tissue removed. The opened scar is secondary closed with two layers of suture [29]. The approach that uses the vaginal route is a minimally invasive way of repairing the myometrial continuity.

19.15 Medical Treatment

The use of oral contraceptives can be a conservative alternative for the management of the postmenstrual bleeding. The published results on effectiveness are conflicting. While different studies have concluded that the medical therapy fails to eliminate the bleeding [10], others support the use of oral contraceptives for treating intermenstrual bleeding in patients with defects at the previous cesarean uterine to reduce the menstrual blood [30]. There are no consistent studies about the use of the hormonal intrauterine device.

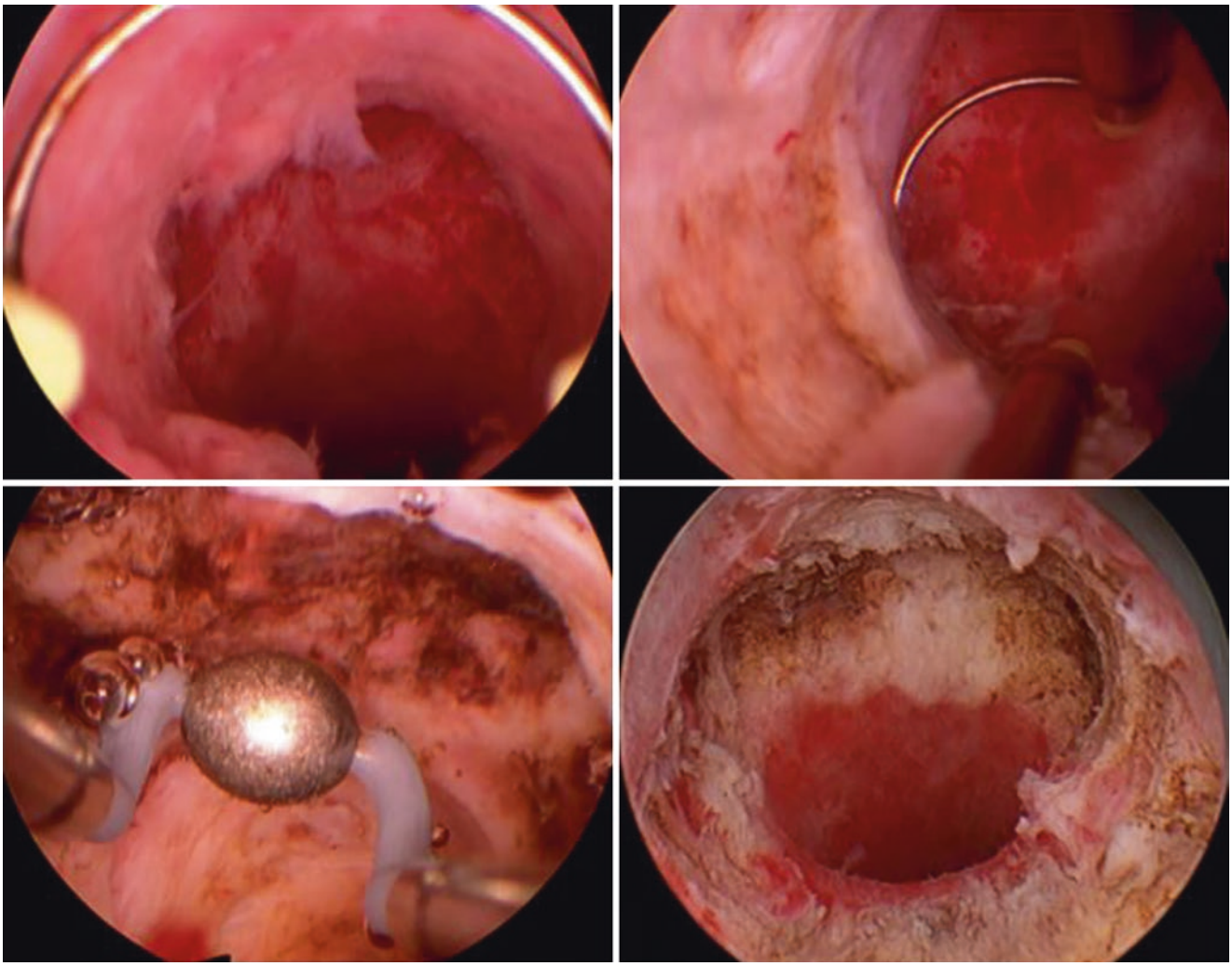


Fig. 19.11 Hysteroscopy surgery: (*1*) view of the cesarean scar defect; (*2*) resection of the fibrotic tissue of the inferior part of the scar; (*3*) local fulguration of the dilated blood vessels and endometrial glands; (*4*) final view

19.16 Surgical Outcomes

The surgical outcomes are different depending on the surgical procedure. After hysteroscopy surgery, between 59.6 [8] and 64 % [25] of patients reported a postoperative improvement of postmenstrual bleeding. This improvement was more evident in patients with anteflexed uterus.

19.16.1 Cesarean Scar Pregnancy

A cesarean scar (ectopic) pregnancy occurs when a pregnancy implants on a cesarean delivery scar (Fig. 19.13). Although it has also been referred to as a cesarean delivery scar ectopic pregnancy in the literature, a more appropriate term may be cesarean delivery scar pregnancy or cesarean scar pregnancy.

The first case of a cesarean scar ectopic pregnancy was reported in English medical literature in 1978 [31]. Since then, there are only 19 cases published until 2001 [32]. But over the past 5 years, there has been a substantial increase in the number of cesarean scar pregnancy (CSP) published in the English language literature.

Cesarean scar pregnancy is a rare entity, incidence being reported between 1:800 and 1:2,216 and a rate of only 6.1 % in women with ectopic pregnancy and at least one previous cesarean section [33, 34–38]. It is the least common form of ectopic pregnancy.

However, the incidence is rising with the increased incidence of cesarean deliveries (Table 19.1), and the diagnosis

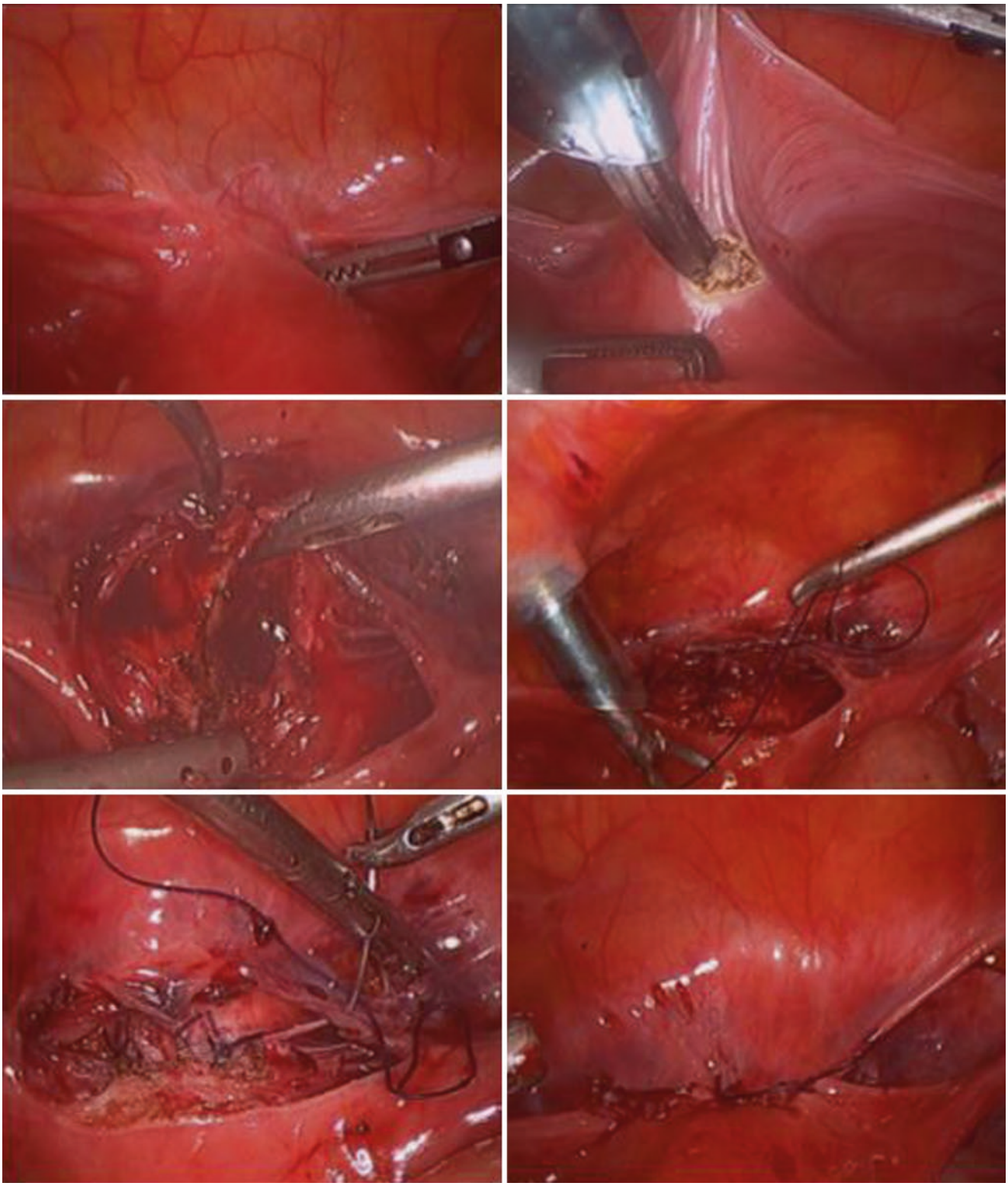


Fig. 19.12 Laparoscopic repair of cesarean scar defect: (*1*) identification of the affected area; (*2*) bladder dissection; (*3*) opening of the scar; (*4*) first-layer suture; (*5*) second-layer suture; (*6*) final view

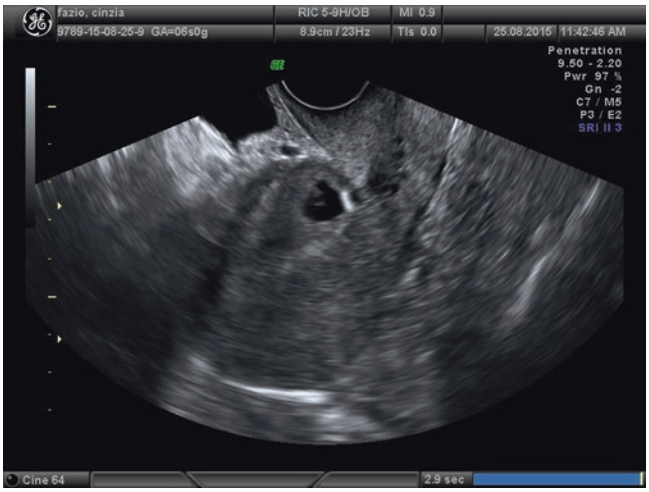


Fig. 19.13 Presence of the gestation sac in the anterior part of the uterine isthmus

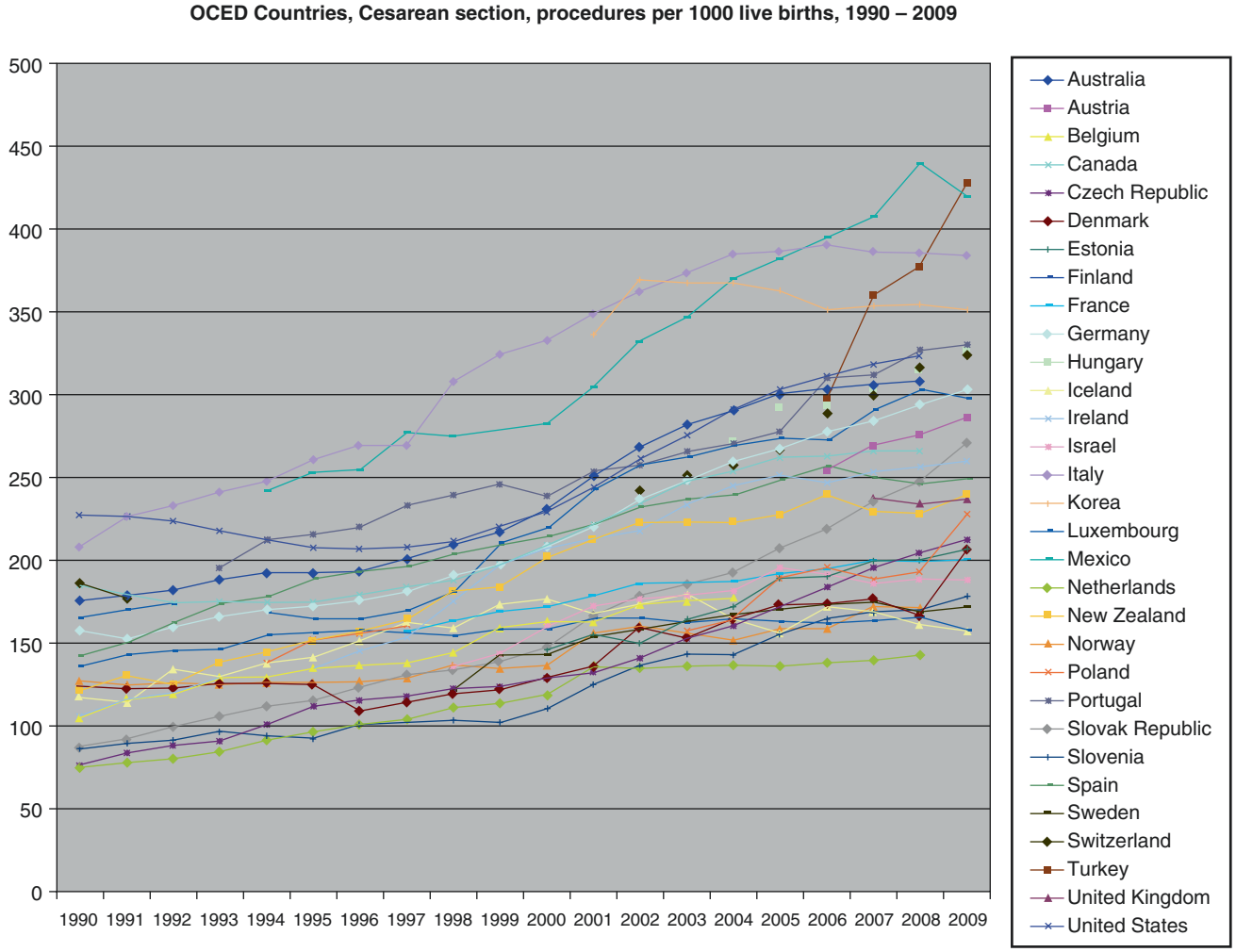
is being made earlier because of the increased use of transvaginal sonography [34, 35, 37, 32, 39].

Up to 72 % of cesarean scar pregnancies occur in women who have had two or more cesarean deliveries [33, 34, 36].

The exact cause and mechanism are not well understood, but it is generally thought that a cesarean scar pregnancy occurs when a blastocyst implants on fibrous scar tissue within a wedge-shaped myometrial defect in the anterior lower uterine segment at the site of a prior cesarean scar. The possible etiology could be a trophoblastic invasion of the myometrium through a microscopic tract.

The myometrial defect most commonly develops after cesarean deliveries, but scar pregnancies have also been reported after other uterine surgeries such as dilatation and curettage, myomectomy, metroplasty, hysteroscopy, and manual removal of the placenta [32, 33, 35, 39]. The dehiscent myometrial defect may be related to incomplete healing or increased fibrosis along the uterine scar.

Table 19.1 Cesarean rate 1990–2009 (Source OECD Health Data 2011)



Fibrosis occurring after multiple cesarean deliveries leads to poor vascularity, which impairs healing. Multiple cesarean deliveries also increase the risk of implantation on the scar, likely due to an increased scar surface area [34, 36, 37, 39, 40].

19.17 Natural History

Very few of these pregnancies reported in the literature progressed beyond the first trimester [36, 41] as almost all are terminated during this period. It is likely that if a developing pregnancy in a cesarean section scar were to continue to the second or third trimesters, there would be a substantial risk of uterine rupture with catastrophic hemorrhage, with a high risk of hysterectomy causing serious maternal morbidity and loss of future fertility. There is also a danger of invasion of the bladder by the growing placenta. A pregnancy that protrudes through the scar, if viable, can implant on other abdominal organs and continue to grow as a secondary abdominal pregnancy [32, 42].

However, if the pregnancy continues within the uterus, the risk of placenta accreta is significantly increased, up to three- to fivefold [43, 44]. CSP progressing to 35 weeks of gestation has been described, but this case was complicated by massive hemorrhage and disseminated intravascular coagulopathy at CS, requiring a lifesaving hysterectomy [41]. There are very few cases reported in the literature of ectopic pregnancy within a cesarean scar resulting in live birth [45].

CSP may present from as early as 5–6 weeks [40] to as late as 16 weeks [46]. A light, painless vaginal bleeding is usually the early presenting symptom in 39 %. Approximately 16 % of women complain of accompanying mild to moderate pain and 9 % complain of only abdominal pain [46]. It can be an incidental finding in an asymptomatic woman (37 %). Severe acute pain with profuse bleeding implies an impending rupture.

Collapse or hemodynamic instability strongly indicates a ruptured CSP. Clinical examination in stable women is usually unremarkable. The uterus may be tender if the CSP is in the process of rupture.

19.18 Diagnosis of CSP

Transvaginal ultrasound (TVUS): TVUS on its own has a diagnostic sensitivity of 86.4 % (95 % CI 0.763–0.9050) [48]. TVUS is the first line to diagnosis or to confirm CSP (Fig. 19.14). The criteria are:

- No fetal parts in the uterine cavity or cervix
- Thin or absence of myometrial layer between the bladder and gestational sac

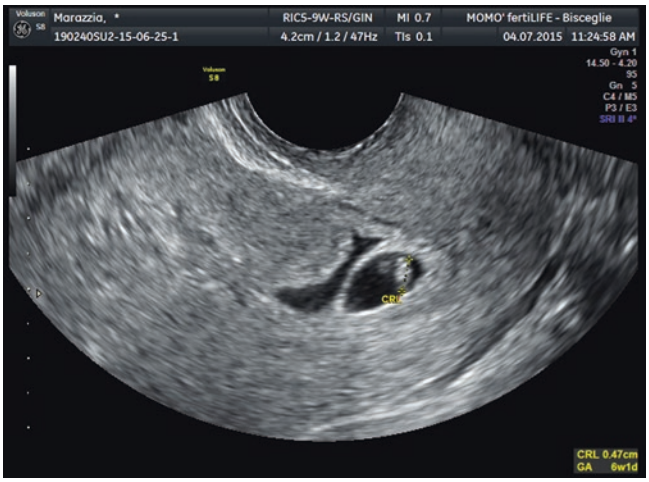


Fig. 19.14 TVUS is the first line to diagnosis or to confirm CSP

- Presence of the gestation sac with or without a fetal pole with or without fetal cardiac activity (depending on the gestation age) in the anterior part of the uterine isthmus with a triangular-"shaped gestational sac" image

The thickness of the intervening myometrium between the gestation sac and the bladder has been shown to be less than 5 mm in two-thirds of the cases [47].

In order to reduce the risk of a false diagnosis, a combined approach is recommended: a TVUS to obtain the fine details of the gestation sac and its relation to the scar followed by a meticulous abdominal scan with a full bladder [34, 48]. The abdominal scan provides a *panoramic view* of the uterus and an accurate measurement of the distance between the gestation sac and the bladder.

19.19 Doppler

The color flow Doppler shows a circular peritrophoblastic perfusion surrounding the gestational sac that helps to reach a diagnosis [49] and to delineate the CSP sac location of the placenta in relation to the scar and the bladder [36] (Fig. 19.15).

19.20 3D Ultrasound

3D US has been used to enhance the diagnostic accuracy of a CSP [23, 24, 50, 51] (Fig. 19.16).

Combination of the multiplanar views and surface-rendered images helps identify subtle anatomical details of a well-developed trophoblastic shell around the gestational sac [50]. The thin myometrium between the gestational sac and the bladder wall can be recognized with confidence.

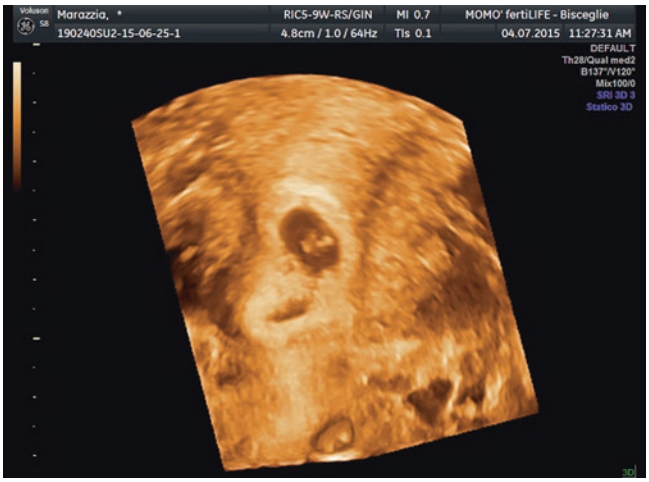


Fig. 19.15 Detailed 3D vision of a cesarean scar pregnancy

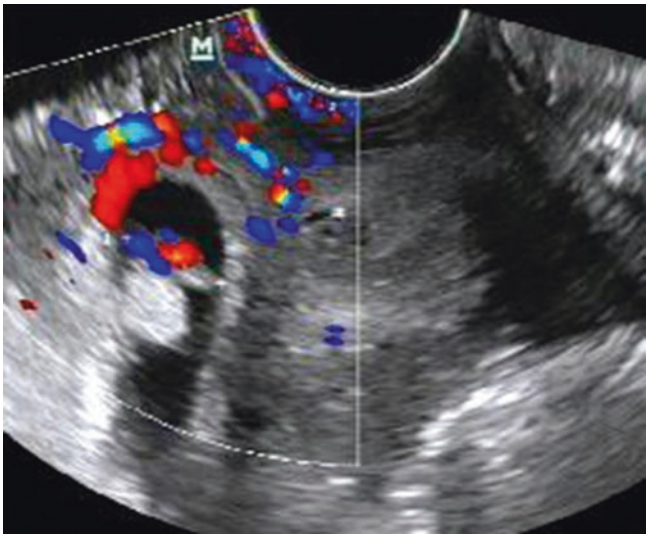


Fig. 19.16 Gestational sac surrounded by rich blood flow signal

Furthermore, peritrophoblastic flow surrounding the CSP may be illustrated by 3D power Doppler.

19.21 MRI

The superior soft tissue characterization and anatomical information provided by MRI allows patients and clinicians to consider conservative management as initial therapy, especially with the increasing availability of minimally invasive uterine artery embolization [52]. MRI can accurately detect the exact location of pregnancy, thus confirming the diagnosis [53, 54].

Huang et al. [55] performed a study regarding the use of intravenous contrast in MRI done for patients with CSP; this study concluded that contrast-enhanced MRI could be used as a reliable adjunct and initial imaging modality for diagnosing CSP in selected cases. The imaging features of contrast-enhanced MRI may result in a more accurate diagnosis before specific treatment for CSP.

19.22 Diagnostic Hysteroscopy

Diagnostic hysteroscopy only helps to confirm the finding of a normal and empty uterine cavity together with the pregnancy tissues at the lower corpus [56].

Hysteroscopic removal of conceptive tissues implanted in a cesarean section scar seems to be a feasible and safe procedure that might be considered as a treatment option [57].

19.23 Diagnostic Laparoscopy

Another diagnostic option for CSP is laparoscopy [58–60]. The uterus size is usually seen normal or bulky (depending on the gestation age) with the CSP arising as a hillock with a "salmon red" ecchymotic aspect, bulging the uterine serosa from the previous cesarean section scar behind the bladder [61].

The fallopian tubes and the ovaries are seen normal.

19.24 Management of CSP

Generally, termination of pregnancy in the first trimester is strongly recommended, as there a high risk of subsequent uterine rupture, massive bleeding, and life-threatening complications as with any ectopic pregnancy.

Treatment objectives should be to perform feticide prior to rupture, to remove the gestational sac, and to retain patient's future fertility.

Treatment can be divided to medical or surgical approach or an association between both.

19.25 Medical Treatment

The administration of methotrexate (MTX) is a standard treatment for tubal ectopic pregnancy, and it is also effective with CSP. The administration can be systemic or local.

19.26 Systemic MTX

CSPs have been shown to respond well to it (dose of 50 mg/m2), especially in those with b-hCG levels <5,000 miu/ml [62]. Conservative medical treatment is appropriate for a woman who is pain-free and hemodynamically stable with an unruptured CSP of <8 weeks of gestation and a myometrial

thickness <2 mm between the CSP and the bladder. All women considered suitable for MTX treatment should have prior baseline full blood count and liver and renal function tests performed. They must be agreeable to surgery if medical treatment fails or if the CSP ruptures.

Systemic treatment alone is not the best treatment option due to 62 % complication rate. IM MTX injection has a slow action and the pregnancy continues to grow. It is recommended to use more than one injection and to associate it with other treatments.

19.27 Local MTX

MTX can be injected locally with ultrasound guidance, to the gestational sac via transabdominal or via transvaginal route. Transabdominal route requires a longer needle, used with caution not to penetrate the bladder wall, and does not require any anesthesia. The transvaginal approach allows for a shorter distance to the gestation sac with minimal risk of bladder injury.

19.28 Surgical Treatment

19.28.1 Uterine Artery Embolization

It has been described as a treatment option alone or in combination with dilatation and curettage [63]. It has a complication rate of about 47 %.

19.29 Dilatation and Curettage (D&C)

A review of the literature by Arslan et al. [64] shows that uterine curettage was either unsuccessful or caused complications in eight out of nine women, requiring surgical treatment, and in a case series of eight CSPs, Wang et al. [59] had four secondary referrals after failed curettage, thus indicating a failure rate of 70 % [12, 17].

The gestation sac of a CSP is not actually within the uterine cavity and the chorionic villi implant into the cesarean section scar of the lower segment. Therefore, not only the trophoblastic tissue is unreachable by the curette but also such attempts can potentially rupture the uterine scar leading to severe hemorrhage and cause more harm. Profuse bleeding during the procedure and absence of chorionic villi in the specimen obtained by curettage must prompt immediate laparoscopy/laparotomy.

19.30 Laparoscopic Removal

Operative laparoscopy should be performed only after a prior TVS confirms the diagnosis (Fig. 19.17). The CSP mass is incised and the pregnancy tissue removed in an endobag. Bleeding can be minimized by local injection of vasopressin (1 unit/ml, 5–10 ml), hemostasis achieved by bipolar diathermy and the uterine defect closed with endoscopic suturing (Fig. 19.18).

19.31 Open Laparotomy Removal

Laparotomy followed by wedge resection of the lesion (hysterotomy) should be considered in women who do not respond to conservative medical and/or surgical treatments, present too late or if facilities and expertise for operative endoscopy are not available. Laparotomy is mandatory when uterine rupture is confirmed or strongly suspected (Fig. 19.19).

This conventional low-tech surgery, which is available in all hospitals, has the advantage of complete removal of the CSP and simultaneous repair of the scar (Fig. 19.20).

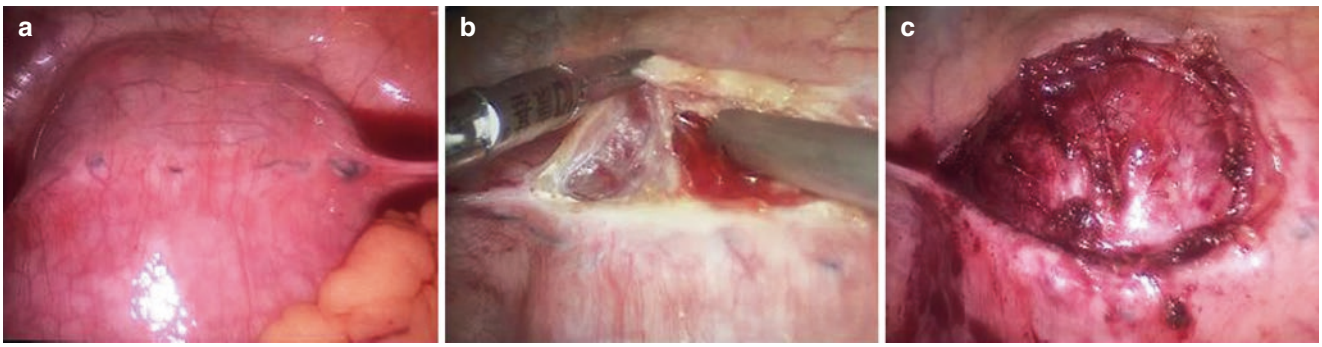


Fig. 19.17 In laparoscopy, we found (**a**) the violet lesion in the lower segment of the uterus. (**b**) Partial bladder reflex of the uterus peritoneum was detached. (**c**) The bladder reflex of the uterus peritoneum was completely detached (Pictures are courtesy of Dr. Xin Luo. Department of Obstetrics and Gynecology, The First Affiliated Hospital of Jinan University, HuangPu Road West, Guangzhou, People's Republic of China)

This approach, however, inflicts a larger surgical wound, longer hospital stay, and longer recovery time, with a possible higher risk of a future placenta previa/accreta.

19.32 Hysteroscopic Evacuation

In 2005, Wang et al. [65] have described a successful treatment of CSP by operative hysteroscopy and suction curettage. At a 4-week follow-up, serum b-hCG level became normal, with restoration of normal echotexture of the uterus on ultrasound scan. Clinical follow-up at 3 months did not reveal any complication. The authors have since reported hysteroscopic management of six more cases with success in all of them, with no complication and no blood transfusion [58]. They conclude that this procedure offers an important alterative treatment for CSP, with a short operative time (mean 36.7 ± 20.8 min), less blood loss (mean 50.0 ± 0.0 ml), short postoperative stay (mean 1.1 ± 0.9 days), and a rapid return of the pregnancy test to negative (<4 weeks, mean 22 days). Most importantly, the fertility is conserved after the surgery. The procedure requires general anesthesia, operative skill, and facilities. Direct visualization of the CSP with meticulous coagulation of the blood vessels at the implantation site is crucial to prevent severe intraoperative hemorrhage.

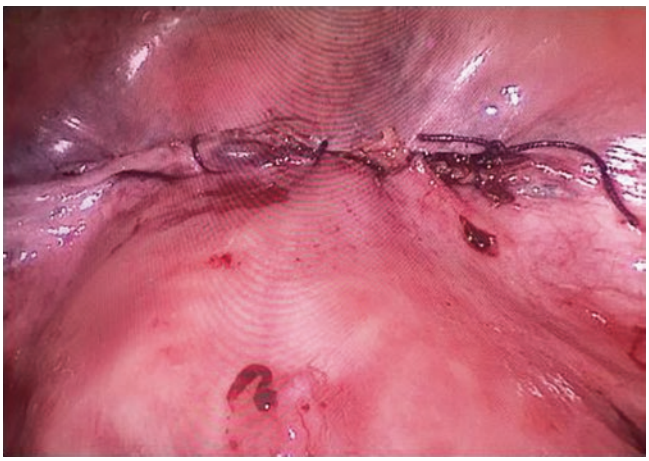


Fig. 19.18 Final view (Pictures are courtesy of Dr. Xin Luo. Department of Obstetrics and Gynecology, The First Affiliated Hospital of Jinan University, HuangPu Road West, Guangzhou, People's Republic of China)

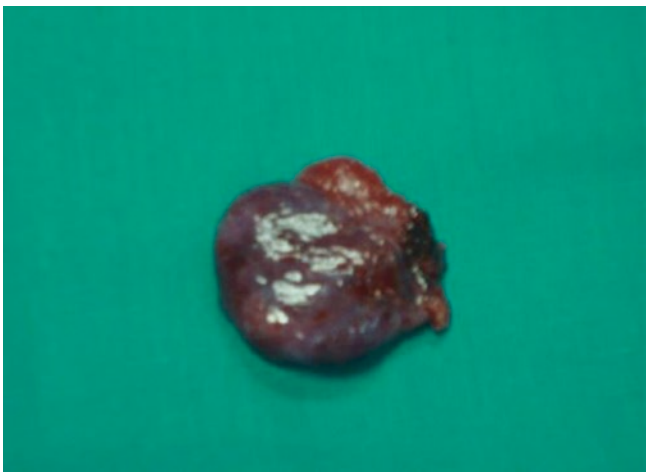


Fig. 19.20 Detailed view of the complete removal of the CSP (Pictures are courtesy of Dr. Gabriel Fiol Ruiz. Servicio de Ginecología y Obstetricia. Hospital Torrecárdenas, Almería, Spain)

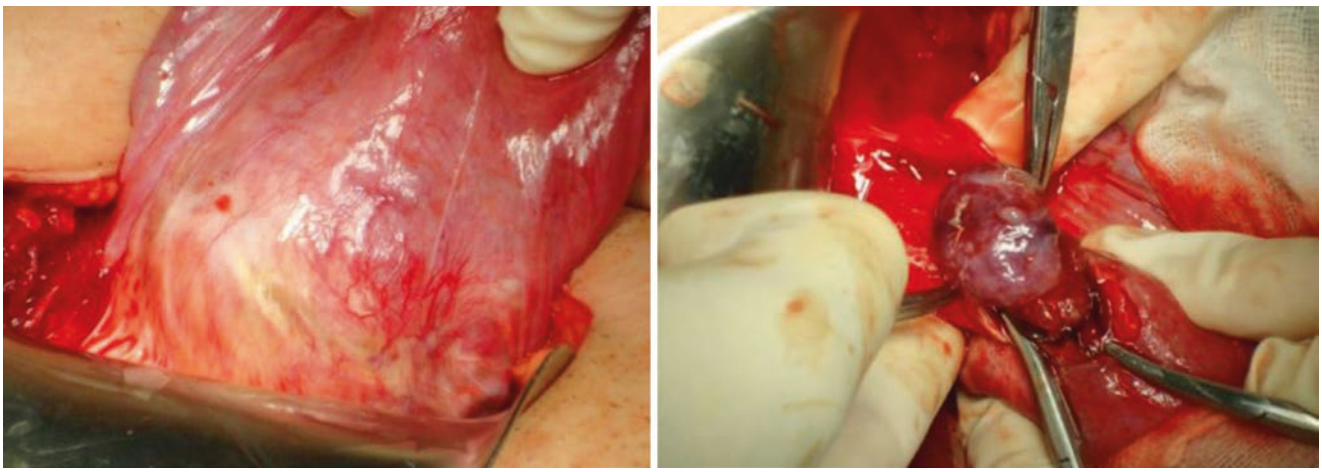


Fig. 19.19 Laparotomy followed by wedge resection of the lesion (Pictures are courtesy of Dr. Gabriel Fiol Ruiz. Servicio de Ginecología y Obstetricia, Hospital Torrecárdenas, Almería, España)

19.33 Which Is the Best Treatment Option?

Timor-Tritsch et al. [1] published a review where all the first-line treatment choices for CSP were analyzed. The results of the review expressed as the rate of complications based on the different first-line treatment options are shown in Table 19.2: alone or in any combination, D&C, dilatation and curettage; MTX, methotrexate; TAUS, transabdominal; TVUS, transvaginal; and UAE, uterine artery embolization.

The review concluded that transvaginal- or transabdominal-guided local and ultrasound-directed methotrexate injection with or without additional intramuscular methotrexate administration as well as surgical excision by hysteroscopic guidance carried the lowest complication rate.

There is no universal agreement on the best or most preferred treatment modality. It is therefore difficult to decide on the optimal management. Patient counseling and briefing, although vital, may be limited by this lack of reliable data.

19.34 Uterine Rupture

Uterine rupture during pregnancy is a catastrophic life-threatening complication; fortunately, the incidence is low, but when it occurs, it could lead to devastating consequences for both the mother and the fetus. Uterine rupture refers to a complete disruption of all uterine layers, including the serosa. It often leads to maternal hemorrhage and adverse fetal outcomes. By comparison, uterine dehiscence generally refers to an incomplete, and frequently clinically occult, uterine scar separation where the serosa remains intact and is not usually associated with adverse outcomes.

Accurate prediction of uterine rupture is important to better counsel patient regarding route of delivery. A large number of studies have been conducted looking at predictive factors of uterine rupture [66]. It is not clear how to define uterine scar defect. Some authors have described scar defects as concavities with a depth of more than 1–6 mm [67]. Osser et al. [20] proposed the evaluation of the uterine scar defect according to the ratio between the remaining myometrium over the defect and myometrium thickness at the cesarean scar site. With the aim to accurately predict the patient at risk of uterine rupture, different imaging modalities have been proposed.

19.35 Ultrasound

Ultrasound with both transabdominal (TAS) and vaginal (TVS) approach is widely used to visualize the cervix and low uterine segment (LUS) during pregnancy (Fig. 19.21). A well-designed prospective observational study of lower uterine segment measurement in women who have had one prior cesarean revealed that by utilizing 3.5 mm of uterine thickness as the cut off, they were able to distinguish the patient who have a 99.3 % negative predictive value for uterine rupture or dehiscence. Although it has a high sensitivity (88 %) and specificity (73.2 %), the positive predictive value was low (11.8 %), suggesting that not all uterine segment thinner than 3.5 mm were clinically abnormal [68]. In an effort to compare the accuracy of transabdominal and transvaginal ultrasound to measure the thickness of the lower uterine segment, Prasanga et al. [69] measured the low uterine segment using both transvaginal and transabdominal ultrasound of 83 pregnant women with a prior cesarean delivery admitted for

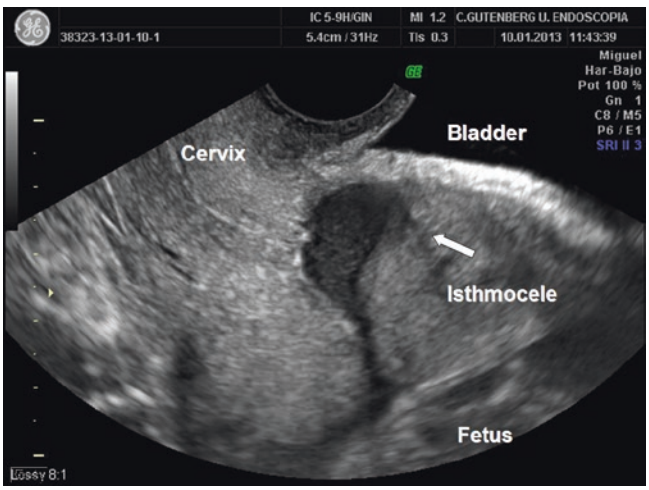


Fig. 19.21 Ultrasound view of the cervix and low uterine segment

Table 19.2 The table resuming the Timor-Tritsch et al. [1] review, with the first-line treatment choices for CSP

First-line treatment choices for cesarean scar pregnancy with the most and the least complication rates			
Treatment	Cases	Complications	%
MTX alone	87	54	62.1
D&C	305	189	61.9
UA embolization	64	30	40.9
Hysteroscopy	119	22	18.4
Local intragestational injection of MTX/KCL	81	8	9.6

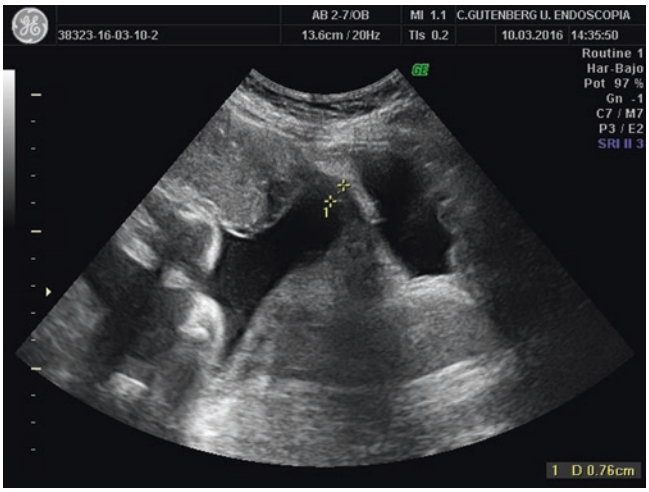


Fig. 19.22 TVS is a more accurate method of assessing the thickness of the lower uterine segment

an elective repeat cesarean delivery at term. The actual low uterine thickness was measured during the cesarean delivery using a sterile ruler after the neonate had been delivered. They concluded that TVS is a more accurate method of assessing the thickness of the LUS compared with TAS (Fig. 19.22).

19.36 3D Ultrasound

A comparison between 2D and 3D transabdominal and transvaginal ultrasound measurement of the lower uterine segment in late pregnant women with a history of one cesarean delivery reported that 3D ultrasound had lower interobserver and intra-observer variability, noting that vaginal ultrasound measurements were more reproducible than using transabdominal approach [70].

Unfortunately, the absence of solid evidence using 3D ultrasound resulting in meaningful clinical outcomes precludes the use 3D ultrasound outside of a research setting.

19.37 Magnetic Resonance Imaging (MRI)

The use of MRI for visualization of previous cesarean hysterotomy incision site in the nonpregnant state has been reported for over 20 years [71].

This technology is currently used more often in attempts to diagnose placenta accreta.

The incidence of uterine rupture in women with history of cesarean delivery is estimated between 0.3 and 1 %, being 0.78 % in patients attempting VBAC and 0.22 % with elective repeat cesarean delivery [72].

The most important predictive factor of uterine rupture is the location of the prior uterine incision. After a previous classical cesarean delivery, the risk of uterine rupture escalates exponentially to up to 12 % [73]. Other described known factors are the use of prostaglandins and oxytocin for labor induction or augmentation, labor dystocia, advanced maternal age, short inter-pregnancy interval, and single-layer uterine closure [74]. On the other hand, a prior successful vaginal delivery significantly reduces the likelihood of uterine rupture [72, 75].

19.38 Clinical Course in Patients with Uterine Rupture

Different clinical signs should alert the clinician of uterine rupture including non-reassuring fetal heart rate (FHR) abnormalities, abdominal pain, uterine contraction abnormalities, loss of the presenting part, and vaginal bleeding. FHR patterns associated with uterine rupture are consistently reported to be non-reassuring, but there is no FHR pattern pathognomonic of rupture. The diagnosis is often suspected clinically, and confirmation occurs at the time of emergency cesarean section with the finding of hemoperitoneum and fetus partially or totally located outside the uterus.

19.39 Management

Suspected uterine rupture represents a life-threatening obstetrical emergency. The entire staff should be notified and an emergency protocol should be activated. The patient should be stabilized and taken for emergency cesarean section. An expedite intervention could prevent devastating consequences for both the mother and the fetus.

In the presence of uterine rupture, the uterine defect should be closed assuring adequate hemostasis. In cases where the uterine rupture is too large or irregular that prevents a safe hemostatic closure, hysterectomy should be strongly considered as a lifesaving measure. Attention should be placed to surrounding organs to identify possible damage. The use of uterotonics is recommended.

Maternal morbidity was assessed in a literature review of 880 cases of uterine rupture during 142,075 trials of labor after cesarean delivery (TOLACs, 6.2 ruptures per 1,000 trials of labor) [76]. For every 1,000 trials of labor, the rate of uterine rupture-related complications was 1.8 for packed red blood cell transfusion, 1.5 for pathologic fetal acidosis (cord pH<7.00), 0.9 for hysterectomy, 0.8 for genitourinary injury, 0.4 for perinatal death, and 0.02 for maternal death.

In a large review of over 140,000 patients undergoing VBAC, the most common serious maternal complication

was the need to undergo hysterectomy, which was reported in 14 to 33 % of women with uterine rupture. Other complications included urinary tract or bowel lacerations, need for blood transfusion, and postoperative infection [76].

It is unclear how to counsel a patient who had uterine rupture regarding future fertility. The risk of recurrence is high and difficult to predict and can occur at any time including the second trimester [77]. There is no consensus on the optimum timing of delivery. It is a common practice to deliver by elective cesarean section at 37 weeks to decrease the risk of recurrence.

A less morbid variant of uterine rupture is dehiscence of the low uterine segment, also known as "uterine window" which refers to an incomplete uterine scar separation in which the uterine serosa is intact. Most uterine dehiscence are subclinical and only diagnosed as an incidental finding at the time of cesarean section. There is insufficient data on management of "uterine windows" to make evidence-based management recommendations. If diagnosed during the antepartum period, the patient should be thoroughly counseled about potential risks and recommended to alert the physician if symptoms of possible uterine rupture are present.

19.40 Pathological Findings of Cesarean Scar Pregnancy

The morphological appearance of ultrasound in the diagnosis of cesarean scar pregnancy is a consideration in the pathological examination of the scar.

The more frequent aspects are shown in the following figures (Figs. 19.23, 19.24, 19.25, 19.26, 19.27, 19.28, and 19.29).

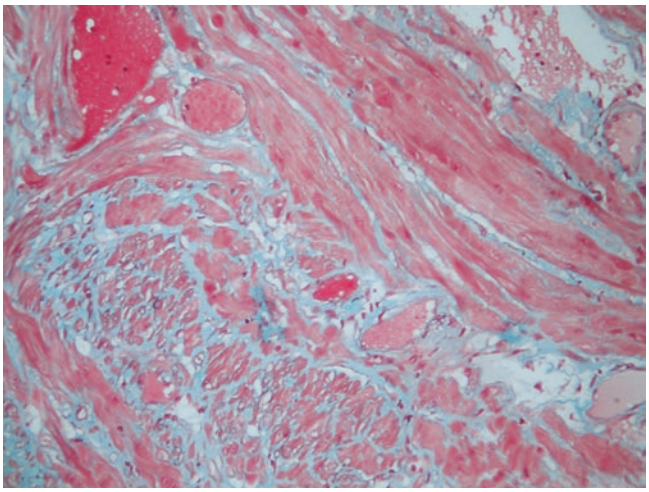


Fig. 19.23 Histological slide of a scar of cesarean section, stained with the Masson' trichromic stain. The muscular fibers, in red, are arranged on orthogonal planes. Single fibers or thin bundles are circumscribed by a small amount of collagen (in *green*). This kind of scar is present in 44 % of cases in our series

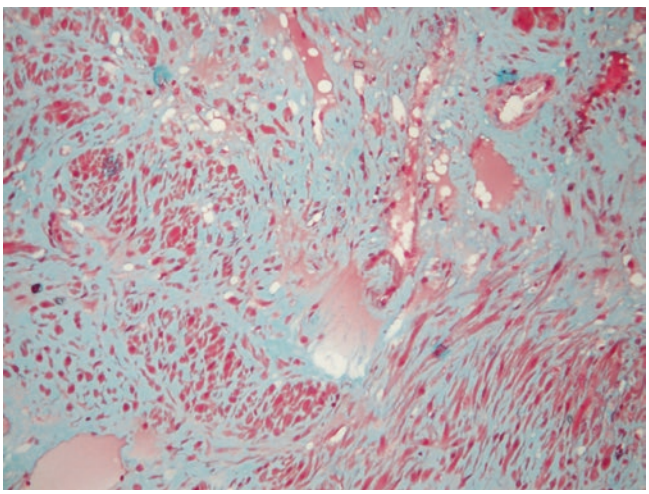


Fig. 19.24 A case of irregular distribution of the muscular fibers in a scar of cesarean section. The fibers missed a dynamic architectural disposition; they are mainly single and surrounded by a rich collagen stroma. This picture is present in the 17 % of our cases

19.41 Other Long-Term Complications

19.41.1 Chronic Pain

An unfortunate complication of any surgical intervention is chronic pain on surgical site. It has been described after thoracic, breast, and abdominal surgery [78]. The persistence of pain on the incision site is not an uncommon complication after cesarean delivery. Nikolajsen et al. [79] surveyed via questionnaire 244 consecutive patients who were delivered by cesarean section. The response rate was 92 % and the mean follow-up time was 10.2 months. Forty-one patients (18.6 %) reported pain 3 months after the cesarean, and 27 (12.3 %) had unresolved persistent pain at the time of the survey, with 13 patients (5.9 %) characterized their pain as present daily or almost daily. Factors associated with persistent pain after cesarean include pain in other locations, severe postoperative acute pain, and the type of skin incision performed [79]. The Pfannenstiel incision, commonly used in the United States for cesarean deliveries, has numerous benefits including a low incidence of incisional hernia and accepted cosmesis. However, a possible complication of this incision is iliohypogastric or ilioinguinal nerve entrapment [80–82]. Branches of the ilioinguinal nerve and the iliohypogastric nerve are commonly severed when performing transverse abdominal incisions. This often results in persistent numbness around the scar. Less commonly, patients have persistent, radiating pain due to nerve entrapment. The diagnostic triad of nerve entrapment after surgery includes burning or

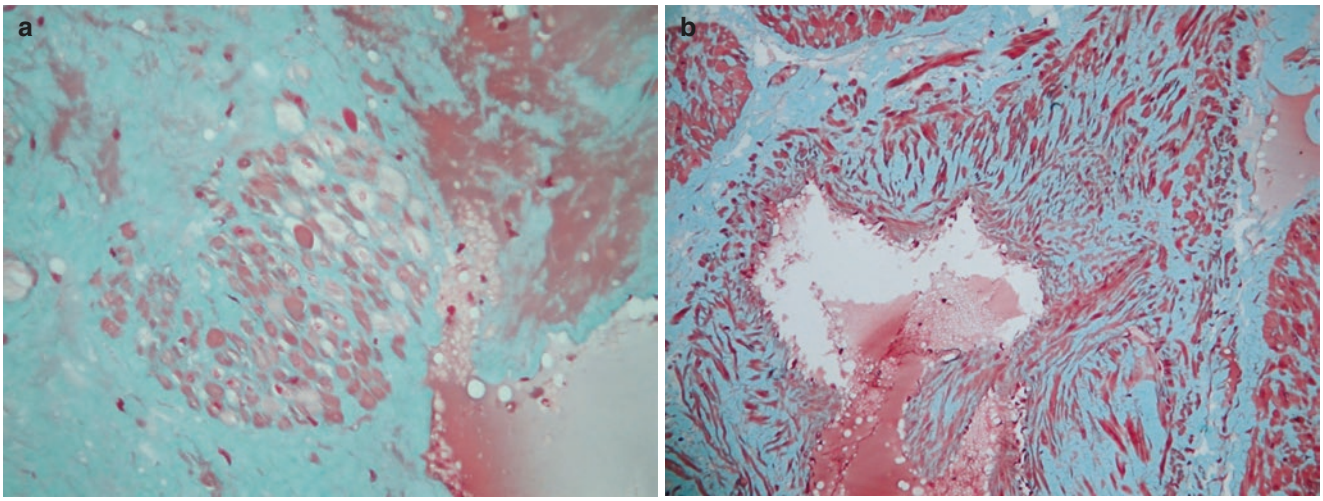


Fig. 19.25 Different histological features in the residual muscular fibers. In (**a**) the fibers are different in size, with homogeneous cytoplasm and scanty nuclei (predominance of regressive phenomena). In (**b**) the regenerative muscular fibers seem to originate from the muscular wall of a vein (predominance of proliferative phenomena)

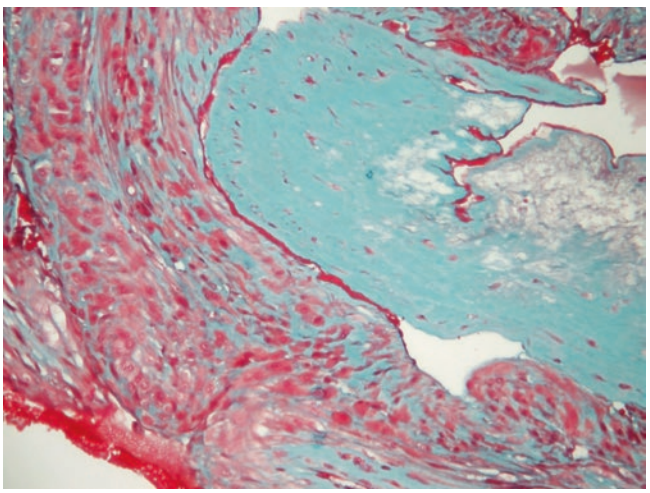


Fig. 19.26 Evident thick fibrous scar immediately under the mesothelium. The pattern of the collagen fibers, of longitudinal type in the figure, is crossed with the prevalent arrangement of the muscular fibers (in *red*, in the *bottom left*). This kind of cesarean section scar is a clear mechanical obstacle in an attempt of vaginal delivery in a subsequent pregnancy

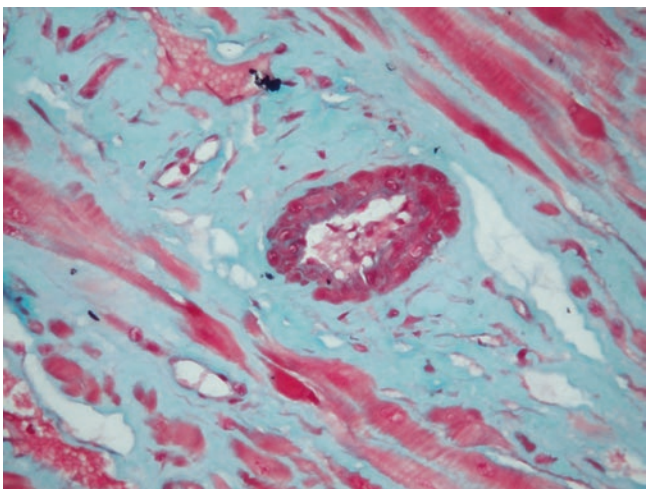


Fig. 19.27 A small artery in a scar of cesarean section shows a proliferation of the myocytes of the median layer. The latter have a polygonal epithelioid shape, a scanty cytoplasm, and a large nucleus with evident nucleolus. This aspect may be the sign of a different hemodynamic stress on the arterial flow or the effect of a hormonal stimulation

lancinating pain near the incision that radiates to the area supplied by the nerve, evidence of impaired sensory perception of the nerve, and pain relieved by local infiltration with an anesthetic [83]. Treatment involves surgical repair of the scar with resection of the compromised nerve or nerve block.

Surgical technique and number of previous skin incisions with increased fibrosis as a result of multiple surgeries on the same surgical site may also increase the risk of developing nerve entrapment and chronic incisional pain. Other factors also associated with increased risk of chronic pain are length of the incision, closure of the peritoneum, and emergency cesarean section [80].

An infrequent cause of chronic cyclic pain reported in 0.1 % of patients delivered by cesarean section is the presence of incisional scar endometriosis [84]. It presents as a tender palpable mass that increases in size during menstruation.

Another potential source of pain and abnormal vaginal bleeding most commonly postmenstrual spotting is the presence of a uterine "niche" (a defect on the endometrial side of the uterine wall). There has been an association between the number of previous cesarean and the size of the defect, with several reports of resolution of symptoms after laparoscopic or hysteroscopic repair of the defect [85].

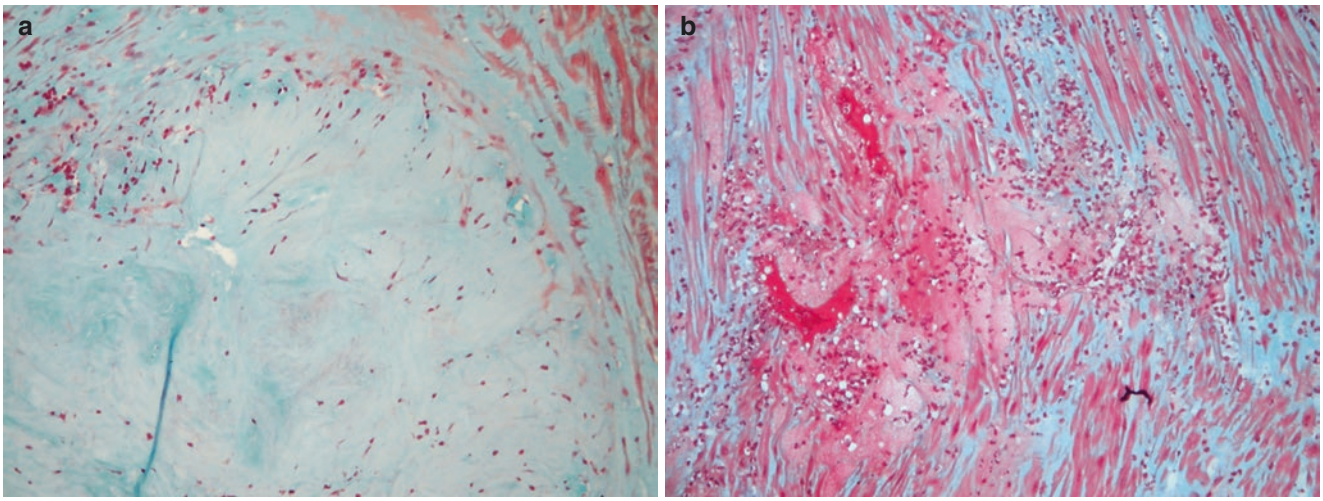


Fig. 19.28 Residual signs of inflammation are also present after several years since the cesarean delivery. The inflammatory cells may be scantly present in sclerotic scary areas (**a**) or in areas with regression of the muscular fibers, with initial fibrotic substitution (**b**). These aspects, a long time after the surgery, may suggest that the scar of the cesarean section is a dynamic situation and the contraction of the myometrium should produce a continuous stimulus able to modify the nature and the function of the scar

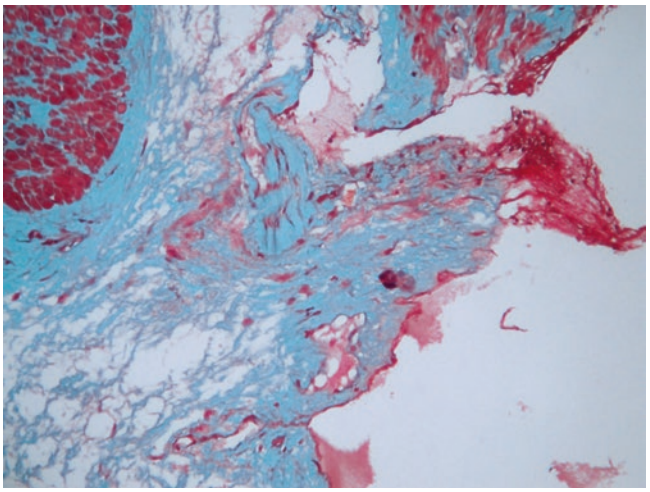


Fig. 19.29 In a scar of cesarean section, the overlying mesothelium (*arrow*) shows proliferative phenomena in a patient in which a surgical suture has been performed during the intervention

19.41.2 Pelvic Adhesions

Abdominal surgery is a well-accepted risk factor for development of adhesions. The most common location is between the uterus and surrounding organs. The incidence and severity of adhesions increase with increasing number of cesarean. Tulandi et al. [86] reviewed more than 1,200 charts of patient who underwent cesarean section and found no adhesions in primary cesarean, 24.4 % in patient undergoing their second cesarean and 42.8 % on their third cesarean delivery. It has been speculated that the risk of adhesion formation may also be determined by surgical technique [87]. The presence of pelvic adhesions has been associated with perioperative complications such as increased operative and delivery time, increased blood loss, and increased risk of bladder injury [88].

19.42 Fertility

There is evidence indicating subsequent subfertility after cesarean delivery. A recent systematic review reported that women who delivered by cesarean section had 10 % fewer subsequent pregnancies than women who delivered vaginally [89]. It is suggested that surgery involving the uterus may compromise local vasculature or produce intrauterine scarring resulting in subsequent decreased fertility. Moreover, the presence of adhesions could decrease fertility by obstructing the tubal patency.

19.42.1 Fetal/Neonatal Complications

19.42.1.1 Unexplained Stillbirth

The effect of cesarean delivery on future stillbirth is controversial. Studies of the risk of stillbirth following prior cesarean delivery have reported mixed results. Large epidemiologic studies demonstrated that cesarean delivery is associated with an increased risk of stillbirth in subsequent pregnancies [90, 91].

Others have reported no association [92, 93].

Although the exact cause is unknown, the association may be due to scar tissue from prior cesarean that may lead to placenta malfunction in the following pregnancy leading to stillbirth. The conflicting results may be due to several

factors such as different study populations, variable definitions of unexplained stillbirth, and different adjustments for potential confounders.

19.43 Small for Gestational Age

Another long-term reported complication of cesarean delivery is an increased risk of small for gestational age fetuses (less than fifth percentile). This could be due to placenta dysfunction as a result of intrauterine scarring produced during the first cesarean.

19.44 Preterm Birth

A South Australian cohort study [94] demonstrated that previous cesarean section is associated with an increased risk of preterm birth (OR 1.17; 95 % CI 1.04–1.31). These findings were also confirmed by Smith et al. [95] who reported the adjusted OR of 1.45 (95 % CI 1.21–1.74) for preterm birth between 24 and 32 weeks of gestation.

19.45 Summary

As the rate of cesarean delivery continues to increase, the resulting negative consequences are a growing concern. Although it is often difficult to establish causality, it is well known that the morbidity increases with the number of cesarean deliveries. The spectrum of complication could be from as severe as massive maternal hemorrhage with both maternal and fetal demise up to only cosmetic concerns as a result of the abdominal scar. Pregnancies following a previous cesarean delivery are at increased risk of complications. These risks are higher with a higher number of previous pregnancies. Cesarean delivery may also increase the risk of adverse reproductive outcomes, including decreased future fertility and increased rate of spontaneous abortion and ectopic pregnancies. It is important for both clinicians and patients to be aware of this increased risk of complications associated with cesarean deliveries. Both short- and long-term complications as a result of having a cesarean should be considered when discussing mode of delivery.

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Clinical Management of Infections in Pregnancy: Update in Congenital Cytomegalovirus and Toxoplasmosis

20

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Infections in pregnancy represent a unique medical challenge as there is the management of both the infected woman and the developing fetus to consider. In pregnant women, most infections are no more serious than in nonpregnant women of similar age, but some of them can be transmitted to the fetus in utero or to the infant during or immediately after delivery, with potentially serious sequelae. Pregnancy is often thought to be associated with increased susceptibility to infection, due to maternal immune system changes, characterized by a shift from cell-mediated immunity (Th1) toward humoral immunity (Th2), which may alter susceptibility and severity of infectious diseases. The management of infections in pregnancy aims mainly at improving the diagnosis and prognosis of congenital infections. The three important levels to approach fetal infections are epidemiology, the interpretation of maternal serology, and therefore dating of maternal infection, prenatal diagnostic and prognostic assessment, and therapeutic possibilities [1, 2].

Investigation and management are often difficult and associated with potential ethical and medicolegal implications; moreover placental histopathological abnormalities related to the infection (calcifications, villitis, immature villi, thrombotic vasculopathy, neutrophil infiltration, placental infarct, increased perivillous fibrin) and molecular testing and immunohistochemistry can be very useful in stillbirths to determine the real contribution of infection.

In the same way, when an infection is diagnosed during pregnancy it is important to supply perinatal counseling about the risks of vertical transmission in utero and about all diagnostic, prognostic, and therapeutic approaches, emphasizing also the risks for both the possible infection related foetal disease and the long-term sequelae in the newborn.

It is therefore really important in managing the infections in pregnancy to organize reference centers with "multidisciplinary team" that gets involved such as expert gynecologists, neonatologists, virologists, microbiologists, infectious disease specialists, and pathologists in order to provide the best information when pregnant woman has to make difficult decisions about whether she wishes to continue her pregnancy, simplifying and speeding up the diagnostic pathway.

Recently, the most investigated maternal infections that may affect foetal development are cytomegalovirus (CMV) and toxoplasmosis, as detectable by a medline search for congenital infection in the last 5 years of literature. The focus, therefore, remains largely on viral and parasitic infections: the prevalence of CMV infection appears stable, the prediction of vertical infections becoming more accurate, as well as promising preventive and therapeutic options are investigated, including the development of a vaccine in the near future; the prevalence of toxoplasmosis in pregnancy is decreasing markedly in Europe thus weakening the effect of preventive measures and questioning the rationale for a routinary screening [1].

20.1 CMV Infection in Pregnancy

Human cytomegalovirus (CMV) is the most common cause of intrauterine infection, occurring in 0.2–2.2 % of all live births, and is a common cause of sensorineural hearing loss (SNHL) and mental retardation [2]. CMV is a highly ubiquitous pathogen, with a 45–100 % adult seroprevalence rate worldwide. Most healthy children and adults infected with CMV have no

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symptoms and may therefore be unaware they have been infected. Others may develop a mild illness when they get infected and experienced nonspecific symptoms, such as: fever, sore throat, fatigue, and lymphadenopathy. Once acquired by symptomatic or asymptomatic primary infection, CMV persists indefinitely in the host, usually as a latent infection [3].

Human cytomegalovirus (CMV) is a DNA virus belonging to the *Herpesviridae* family. After coming in contact with CMV-containing fluids such as blood, saliva, urine, breast milk, or genital secretions, the virus invades mucosal surface and replicates in permissive cells (myeloid cells, hepatocytes, endothelia, cytotrophoblast, etc.). After repeated waves of viremia, the virus established lifelong latency in myeloid cells [4]. After the *primary* infection, defined as CMV infection in a previously seronegative person, the virus becomes dormant and remains in a latent state, from which it can be reactivated. A recurrent (secundary) infection may be due to either reactivation of an endogenous latent virus or to the exposure to a new virus strain from an exogenous source; when a secondary or recurrent infection occurs, episodes of viral shedding via bodily fluids occur [2]. The severity of CMV infection depends on the status of the immune system of the person exposed to the virus. The intact immune system is able to deal with a CMV infection, whereas in immunocompromised persons, the situation is different. The same applies to the fetus during pregnancy, where the immune system is immature and thus functionally resembles that of an immunocompromised person. *Congenital infections* are the result of transplacental transmission of CMV. Transmission to the fetus may occur because of primary or secondary maternal infection. The median frequency of intrauterine transmission following primary infection during pregnancy is 30–40 % compared with only 1 % following secondary infection (Fig. 20.1). Gestational age influences the risk of intrauterine transmission, as the probability of transmission is 5.2 % in the preconception period (3–8 weeks before the date of conception), 16.4 % in the periconceptional period (3 weeks before to 3 weeks after the date of conception), 36.5 % in the first trimester, 40 % in the second trimester, and 65 % in the third trimester. The clinical consequences for the infected offspring appears to be worse when infection takes place during the first 20 weeks of gestation [5].

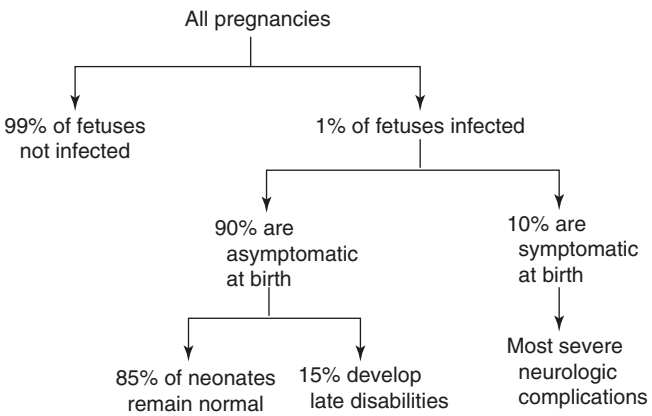

Fig. 20.1 Rates of maternal-fetal CMV transmission: risk of fetal infection and development of disabilities

While the majority of affected infants are asymptomatic at birth, 10–15 % exhibit signs of CMV-associated sequelae including thrombocytopenia, hepatitis, chorioretinitis, sensorineural hearing loss (SNHL), intrauterine growth restriction, and mental retardation. An additional 5–15 % of asymptomatic CMV-infected infants will develop late-onset sequelae, most commonly SNHL, within the first 2 years of life [6, 7]. The frequency of symptomatic newborns following non primary CMV infection is not defined. In fact, reported data are limited to case reports and small case series of symptomatic newborns of mothers with known preconceptional immunity, not proven reactivation or reinfection during pregnancy. Nonetheless, these data suggest that the risk for non-severe symptomatic infection at birth and sequelae, mainly hearing loss, are similar following non-primary maternal CMV infection as compared to primary infection.

20.1.1 Prevention of Infection During Pregnancy

There are two main sources of maternal CMV infection: sexual activity and contact with young children. However, the latter is considered the most important one as the high circulation rate of CMV in infants and children of preschool age puts seronegative pregnant women caring for young children at high risk for CMV infection [6]. Transmission occurs through direct contact with infectious bodily fluids such as saliva and urine; children who excrete CMV may spread infection to a parent and to other adults in the household [6]. CMV educational and hygienic measures have the potential to prevent primary maternal infection. A recent study provides evidence that a primary prevention strategy based on the identification and provision of adequate information to seronegative susceptible pregnant women at risk for primary infection is highly effective in reducing the rate of maternal primary CMV infection and, ultimately, congenital CMV infection. Specifically, women are invited to frequently wash their hands after exposure to young children's bodily fluids as well as surfaces touched by children (toys, high chair, stroller, etc.), to avoid kissing children on the mouth/cheeks, and not to share utensils, food, drinks, washcloths, etc. The use of gloves and avoidance of sleeping in the same bed were not suggested.

Recent onset of sexual activity (last 2 years) in young women increases the risk for congenital CMV infection in their offspring; this finding suggests that recent sexual exposure to CMV may have occurred in the months or years before conception and also during pregnancy. The risk for congenital CMV infection remains elevated even when primary maternal infection occurs months before conception so it is preferable to wait at least 6 months after primary CMV infection before pregnancy. Another important aspect to underline is the relation between sexually transmitted infections during pregnancy (such as gonorrhea, chlamydia, genital warts, syphilis, and trichomoniasis) and primary CMV infection that could enhance the transmission of CMV from mother to fetus. In

addition, because of the possibility of CMV transmission through sexual intercourse, pregnant women should be urged to adopt safe sexual practices if they are not engaged in a mutually faithful monogamous relationship.

Numerous reports have analyzed how to prevent primary maternal infection, and they have shown that CMV educational and hygienic measures have this prevention potential. In the first time, woman seronegative should be informed about CMV and prevention measures and hygiene recommendations to be adopted [8].

Future prospectives are based on development of an effective vaccine for prevention of CMV infection that could be of high epidemiological impact in this regard.

20.1.2 Prenatal Diagnosis

The first step in the prenatal diagnosis of congenital CMV infection is determination of maternal primary and secondary infection by serological testing (Fig. 20.2).

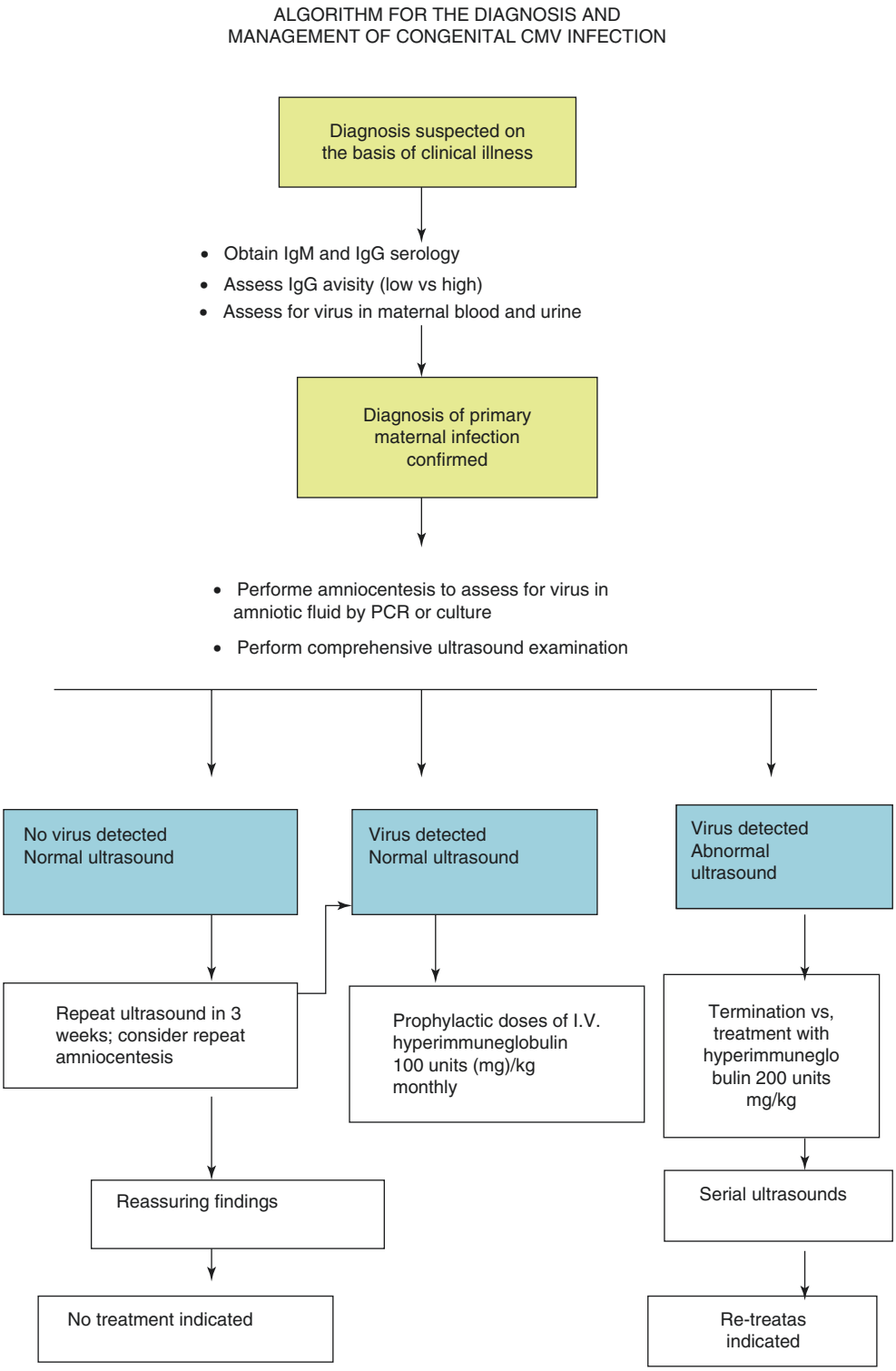

Fig. 20.2 Algorithm for the diagnosis and management of congenital CMV infection

In women with a proven or highly suspected, recent primary CMV infection, the second step is to propose the diagnosis of fetal infection by noninvasive (ultrasound examination) and invasive (amniocentesis) prenatal tests [9].

20.1.2.1 Diagnosis of Maternal Infection

The diagnosis of primary CMV infection in pregnant women is based on serological tests with detection of specific immunoglobulins type G (IgG) and type M (IgM). Seroconversion confirms primary infection but is usually difficult to identify in the absence of any available preconceptional serum specimen. Detection of specific IgM does not always indicate a recent primary infection because they may persist for months after primary infection, be detected during secondary infection, be the consequence of cross-reactivity with IgM elicited by a primary infection with another virus (e.g., Epstein-Barr), and be observed through polyclonal stimulation of the immune system [10].

However, such an approach is feasible only when a screening program is adopted and seronegative women are identified and prospectively monitored.

The *IgG avidity* assay can assist in determining the time of CMV infection, thus helping in distinguishing a recent, primary infection from one remote or recurrent. This assay is based on the observation that virus-specific IgG of low avidity is produced during the first months after onset of infection, whereas subsequently a maturation process occurs by which IgG antibody of increasingly higher avidity is generated. IgG antibody of high avidity is detected only in subjects with remote or recurrent CMV infection [11]. Avidity levels are reported as the avidity index, expressing the percentage of IgG bound to the antigen following treatment with denaturing agents.

An avidity index >60 % is highly suggestive of past or secondary infection, while an avidity index <30 % is highly suggestive of a recent primary infection (duration <3–4 months). Therefore, detection of a low avidity index indicates a primary infection within the 3–4 previous months, while a high avidity index excludes a primary infection within the 3–4 previous months. The avidity results should be interpreted accordingly with gestational age.

Hence serologic diagnosis of primary CMV infection during pregnancy is documented by either seroconversion (the appearance of CMV-specific IgG antibody in a previously seronegative woman) or detection of specific IgM antibody associated with low IgG avidity. A non-primary CMV infection is difficult to diagnose, and can be suggested by a significant rise of specific IgG antibody title and/or a detection of IgM in women who had detectable, high avidity specific IgG antibodies without IgM antibodies before pregnancy [12].

20.1.2.2 Diagnosis of Fetal Infection

Since intrauterine transmission of the virus occurs in only 30–40 % of pregnancies in women with primary infection and at a significantly lower rate in women with secondary infection, it is important in cases of proven maternal infection to find out if the fetus is infected (Fig. 20.2). When a pregnant woman has had a confirmed infection with CMV, a prenatal diagnosis of infection may be required to evaluate the fetal risks [13].

20.1.2.3 Amniocentesis

Isolation of the virus or the viral genome (DNA) in the amniotic fluid (AF) is the method of choice for the diagnosis of fetal infection.

To achieve the highest sensitivity, the amniocentesis should be performed at least 6–8 weeks after the onset of maternal infection and after 21 weeks of gestation, when fetal urination is well established. Some cases of false-positive results have also been reported when the neonate was not infected. These false-positive diagnoses may be explained by contamination of the AF with maternal blood during amniocentesis if the mother had a positive viral genome at the time of sampling. Even when the timing of amniocentesis is the best, some cases of false negative are shown: this situation could be an expression of a late transmission of CMV (>8 weeks after maternal seroconversion) [14].

Actually, it is possible to isolate CMV by conventional culture on fibroblasts or by the shell vial technique, which uses monoclonal antibodies to the major immediate early protein p72 and enables detection of the virus 16–24 h after amniotic fluid collection. However, PCR testing represents to date the main way to detect if the fetus is infected and has largely replaced the conventional culture.

A lot of studies have analyzed the relationship between viral load in amniotic fluid and symptomatic infection. Whereas a low viral load in amniotic fluid was consistently found to be associated with asymptomatic congenital infection, it was observed that high viral load in amniotic fluid was associated with either symptomatic or asymptomatic congenital infection. Only one study (Guerra et al.) reported that a DNA level >105 copies/ml amniotic fluid was a possible predictor of symptomatic congenital infection. The lack of a close association between CMV DNA quantification in amniotic fluid and fetal prognosis may be the result of different variables such as gestational age at maternal infection, timing of intrauterine transmission of infection, timing of amniocentesis, and particularly the unfeasibility of follow-up of infection during fetal life [15]. Hence, once primary CMV infection is diagnosed in a pregnant woman, amniocentesis should be offered to diagnose intrauterine CMV transmission, and in the case of a positive result, cordocentesis should be discussed for prognostic purposes,

according to a recent report by Fabbri et al. This study has indicated that certain hematological, biochemical, and virological markers measured in fetal blood seem significantly related not only to infection but also to organ damage caused by HCMV infection and symptomatic postpartum sequelae. A panel of nonviral and viral assays were performed on fetal blood samples to integrate multiple markers of fetal organ damage caused by CMV infection. In particular, b2-microglobulin and a low platelet count were the best nonviral predictive markers from symptomatic infection, whereas immunoglobulin M (IgM) antibody and DNAemia represent the best virological markers. B2-Microglobulin alone or the combination of these four markers reached the optimal diagnostic efficacy [15].

20.1.2.4 The Role of Ultrasound (US)

When a fetal CMV infection is diagnosed during pregnancy, a close ultrasound (US) survey must be done because it will disclose structural and/or growth abnormalities related to CMV infection (Fig. 20.3). The ultrasound has another important role: if the woman is not serologically tested during the first trimester of pregnancy, sonographic examinations performed during pregnancy may be the only tool available to identify an affected fetus. Ultrasonographic findings are helpful but not diagnostic because CMV has features in common with other intrauterine infections and with other fetal diseases [16]. Moreover, ultrasound examination has a low sensitivity; in fact these abnormalities are observed in less than 25 % of infected fetuses [17].

Authors have described different kinds of prenatal ultrasound findings in fetuses with CMV infection that are subdivided into extracerebral and cerebral anomalies.

The most frequent extracerebral ultrasound abnormalities are hyperechogenic bowel and hepatomegaly [18]. But other types are described such as intrauterine growth retardation (IUGR), oligohydramnios, ascites, liver calcifications, pericardial effusion, and hyperechogenic kidneys.

Given the particular neurotropism of CMV, congenital infection can cause a wide range of brain anomalies. Hydrocephaly and brain calcifications are the most common abnormalities. Other signs of fetal infection are intraventricular adhesions, periventricular pseudocysts, sulcation and gyral abnormal patterns, hypoplastic corpus callosum, cerebellar and cisterna magna abnormalities, and signs of striatal artery vasculopathy [19] (Figs. 20.4 and 20.5).

Magnetic resonance imaging (MRI) could be performed in cases of abnormal US findings or if a specific evaluation of the fetal brain is not technically possible by US. MRI has a greater sensibility than US, but it should not be performed when fetal US examination is strictly normal or when the brain lesions are so severe that it would not change the management of the pregnancy. MRI provides additional information and better results than US in detecting polar temporal lesions, microencephaly, and cortical anomalies [20].

Another aspect of the use of ultrasonography in the management of CMV infection is the study of placenta which seems to be related with the incidence of fetal infection. Numerous reports indicate that placentas from these births contain viral proteins, suggesting that placental infection and virus transmission to the infant are related causally. Placental histopathological abnormalities more frequently found in congenital CMV are calcifications, villitis, immature villi, thrombotic vasculopathy, neutrophil infiltration, placental infarct, and increased perivillous fibrin; CMV DNA and protein are also detectable by molecular testing as polymerase chain reaction and immunohistochemistry. Iwasengo examined CMV infection in stillbirths, showing that molecular testing during postmortem investigation has an important role to determine the contribution of CMV infection (CMV DNA was detected in 15 % of fetal or placental tissue). Moreover, fetal thrombotic vasculopathy was the only abnormality associated with CMV infection.

US placental evaluation includes size, localization, placental echostructure, and placental maximal vertical thickness [21]. Therefore, some authors have investigated ultrasound placental size (as measured by maximal placental vertical thickness) following maternal primary CMV infection to determine if it correlates with infection of the fetus.

The placental thickness of women with vertical transmission of infection seems to be larger than the placental thickness of mothers with fetuses or neonates without disease. Placental enlargement could result from placental vascular ramification, which compensate for hypoxia in utero. Sonographically thickened placentas (Fig. 20.6) have been previously associated with increased fetal and perinatal mortality, abnormally high birth weights, fetal hydrops, maternal diabetes, chromosomal abnormalities, maternal and fetal anemia, fetal heart failure, and congenital nephrotic syndrome. Although a thickened placenta is a nonspecific marker of fetal disease, it could be considered a valid prognostic index to suspect the fetal infection [22].

20.1.3 Postnatal Diagnosis

Congenital CMV occurs transplacentally and may result in symptomatic or asymptomatic infection in the neonate.

Diagnosis in the neonate is made by viral detection in body fluids via PCR, culture, or antigen testing (pp65 antigen) within the first 3 weeks of life. The finding of CMV antibodies

FETUS

Symptomatic

- Hyperechogenic bowel
- In uterogrowth restriction
- Ascites or hydrops
- Oligohydramnios or polyhydramnios
- Plancenta enlargement
- Hepatosplenomegly or hepatic calcifications
- Abnormalities os brain development, enlarge ventricles, calcifications
- Fetal thrombocytopenia
- Fetal demise

Asymptomatic

- No abnormal findings on fetal ultrasound
- Placenta enlargment

NEWBORN

Symptomatic

- Small size for gestational age
- Petechiae or purpura
- Hepatosplenomegaly
- Jaundice at birth
- Lethargy, hypotonia, poor feeding
- Microcephaly
- Ascites
- Myocarditis
- Enterocolitis
- Pneumonitis
- Chorioretinitis, retinal scars, optic atrophy, central vision loss
- Sensorineural hearing loss
- Abnormalities of brain development, ventriculomegaly, intracranial calcifications
- Viral sepsis
- Thrombocytopenia, neutropenia, lymphopenia, hemolytic anemia, lymphocytosis
- Elevated liver enzymes
- Direct hyperbilrubinemia
- Seizures
- Neonatal death

Fig. 20.3 Clinical manifestations and laboratory findings associated with congenital CMV infection in the fetus and newborn

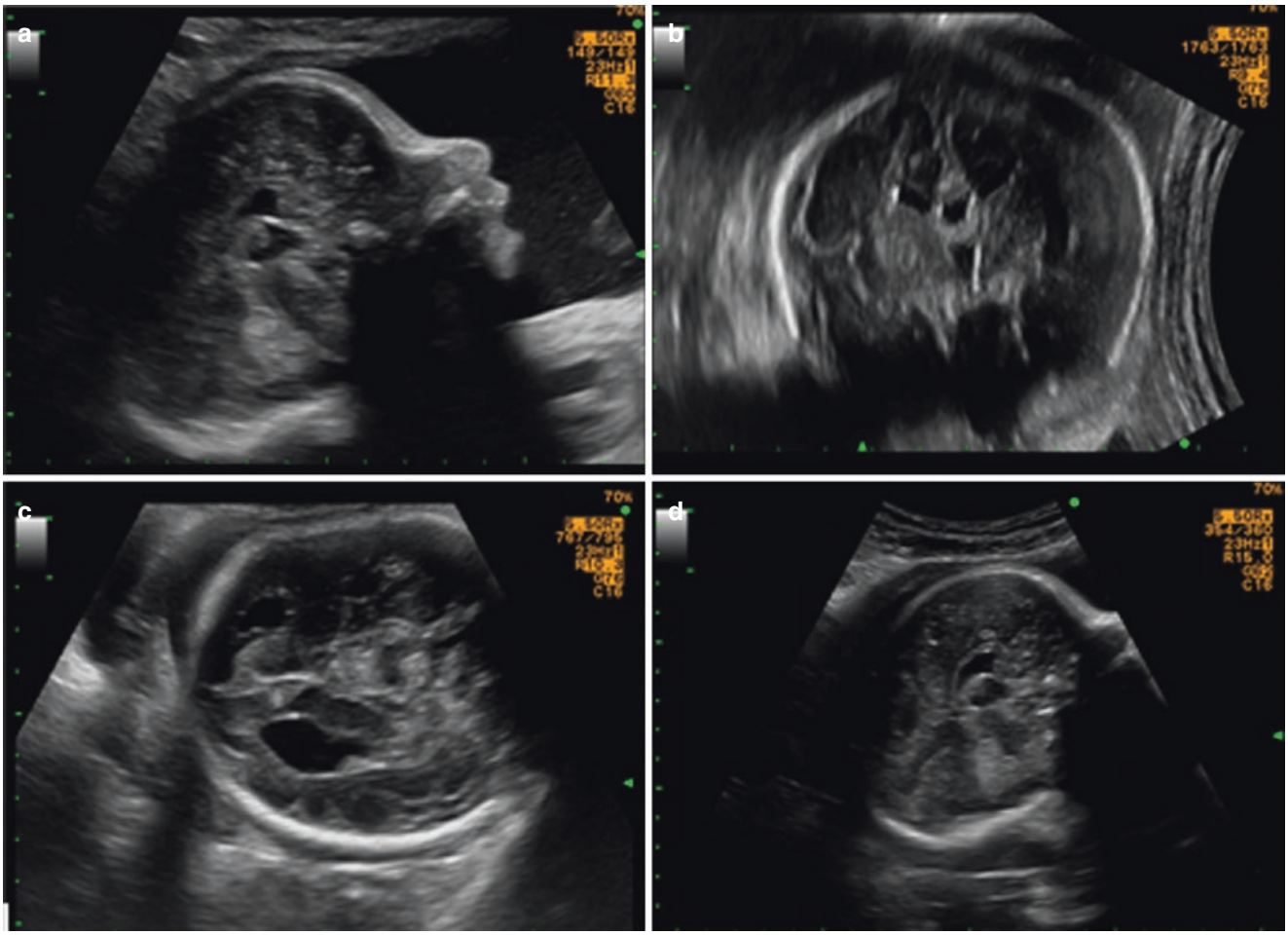

Fig. 20.4 (**a**–**d**) US cerebral features at 32 weeks of gestation after CMV primary infection at first trimester: (**a**, **b**) corpus callosum hypoplasia in sagittal and coronal view; (**c**) mild ventriculomegaly (atrium of 13 mms); (**d**) hyperechogenic spot of subcortical white matter

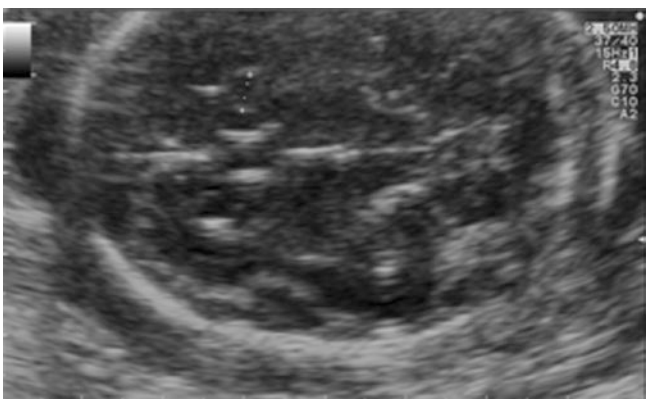

Fig. 20.5 Example of subependymal cyst at 22 weeks' gestation after primary CMV infection

or viral DNA after this point makes congenital versus postnatally acquired infection (from cervical secretions, breastfeeding, or blood products) difficult to distinguish. Antibody titers cannot reliably make the diagnosis as maternal CMV IgG crosses the placenta, and neonates mount weak IgM responses. The preferred specimens are saliva and urine as newborns shed high levels of the virus from these fluids. Thus far, urine has been considered the gold standard [15].

However, difficulties in urine collection documented in some studies have led to a suggestion that saliva analysis may represent an easier, more practical, and less expensive approach, so some propose that saliva PCR should be considered the investigation of choice, although it is susceptible to contamination by maternal milk [10].

20.1.4 Prognosis of Infected Fetus

After the evidence of the infection of fetuses, the main issue is to predict which of them will be symptomatic at birth or later in life. A symptomatic infection was defined as the presence of an abnormal ultrasound and/or magnetic resonance imaging findings and/or histopathological findings of disseminated infection for fetuses terminated or dead in

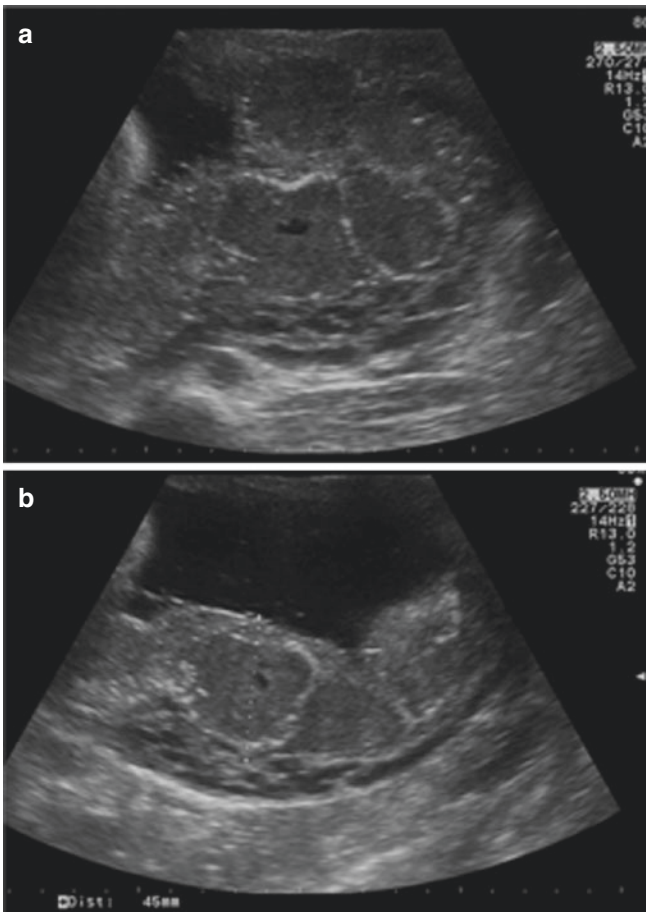

Fig. 20.6 (**a**, **b**) Placental characteristic in a case of CMV fetal infection at term of gestation: placental thickness above 45 mms and dishomogeneous echogenicity

utero or as the presence of clinical symptoms up to 6 months of age for delivered newborns [23]. A lot of studies have shown that a single test or examination cannot predict the collective events that might lead to permanent damage. Although the role of ultrasound examination in predicting the presence of symptoms at birth has been emphasized by some authors, this has been questioned by other groups who find an ultrasound sensitivity of only 21 % in predicting symptomatic newborns.

New approaches have been proposed based on CMV DNA quantification in amniotic fluid or combined assessment of ultrasound findings and prognostic markers evaluated in the fetal blood.

Approximately 10 % of the infants born with congenital CMV infection have signs and symptoms at birth. Only half of these symptomatic infants have disseminated multiorgan involvement named cytomegalic inclusion disease (CID). Other infants have mild or subclinical manifestations of the disease [24]. In the typical form of CID, many organs are involved, mainly the reticuloendothelial system and the CNS. The main clinical abnormalities observed are hepatomegaly, splenomegaly, microcephaly, jaundice, petechiae, hypotonia/lethargy, or seizures. Elevated alanine aminotransferase, conjugated hyperbilirubinemia, and thrombocytopenia are the main laboratory abnormalities. Other manifestations occasionally present in symptomatic newborns include pneumonitis, dental defects, ocular defects (chorioretinitis, strabismus and optic atrophy, cataracts, microphthalmos, necrosis, calcifications, blindness, anterior chamber and optic disk malformations, and papillary membrane vestiges), and hearing loss, intrauterine growth retardation (IUGR), and prematurity (Fig. 20.3). Overall, in this symptomatic subgroup of congenitally infected infants, the mortality rate is around 15–30 %. Death is often due to multiorgan involvement with severe hepatic dysfunction, bleeding, disseminated intravascular coagulation, and secondary bacterial infection. In this condition, death mainly occurs in the first weeks of life. Around 90 % of the symptomatic infected newborns who survive will develop some degree of disability including psychomotor retardation usually associated with microcephaly and other neurological impairments, SNHL, visual impairment, and expressive language delays [25].

At the other extreme of the spectrum of CMV congenital infection are the asymptomatic forms of the disease. Without any systematic screening policy at birth, these infected newborns are most frequently left undiagnosed. Approximately 15 % of asymptomatic children will develop some degree of hearing loss following congenital CMV infection. Globally, CMV causes around 10 % of congenital SNHL, his deficit may be present at birth or develop later in childhood usually during the first year of life, with a great variability in the severity range. Development of new diagnostic tools such as dried blood spots (DNA detection in Guthrie cards) helps to retrospectively attribute SNHL to congenital CMV infection [26].

20.1.5 Therapy

The possibility to treat CMV infection is limited due to toxicity of drugs available. After ultrasound detection of fetus abnormalities and confirmation of the primary CMV infection in the mother and fetus (by amniocentesis), the only "therapeutic" option available to avoid the birth of a severely damaged infant is to terminate pregnancy [27, 28]. Many studies have been done to investigate how it is possible to prevent and treat fetal infection.

In particular, several studies have been developed to analyze the possibility to administrate human immunoglobulins with a double role: prophylactic and therapeutic. Before analyzing which are the actual approach with immunoglobulin, it's important to explain the function of maternal immune system to protect the fetus. An important aspect to be analyzed is the role of maternal immune system to prevent virus transfer across the decidual-placental interface. Recent report suggests that CMV utilizes the fetal Fc receptor for its passage across the placenta. Physiologically, these receptors are used to transport maternal IgG from the intervillous

space to the syncytiotrophoblast. In this way, IgG antibodies seem to have a protective role with regard to vertical transmission rates [4]. Due to their mechanism of action, CMV-specific immunoglobulins could be useful for the prevention of congenital CMV infection following primary CMV infection. In the absence of maternal CMV-specific antibodies, the administration of human cytomegalovirus immunoglobulins is thought to prevent the transmission of CMV from the mother with no specific immunity against CMV to the fetus. These immunoglobulins, known as hyperimmune globulins (HIG), are drawn only from selected donors with high-titer IgG antibodies after CMV infection. Therefore immunoglobulins could reduce the viral load and could thus decrease the probability of severe fetal disabilities. Besides infection of the fetus, active CMV infection of the pregnant women can also lead to impairment of placental function – which may be followed by spontaneous abortion (mainly at the beginning of pregnancy) or restriction of fetal growth [20]. In fact, it seems that the partial reduction in placental size after treatment with HIG provides further evidence that treatment with HIG could resolve fetal disease by neutralizing virus and reducing placental inflammation and insufficiency. The placenta is likely to be one site of action of HIG, and many of the manifestations of congenital CMV infection at birth, including intrauterine growth restriction or neurological damage, may be due to placental insufficiency. CMV modifies maternal immunity through an inflammatory process leading to abortion or immune-mediated disease, most commonly in the brain resulting from neurotoxicity of overexpressed cytokines [29]. Since an efficacious vaccine for CMV disease is still lacking, immunoglobulins are used to treat a large number of transplant patients. Currently, the only approved indication for cytomegalovirus hyperimmune globulins (CMV-HIG) in Europe is for patients who have undergone solid organ transplantation to prevent CMV reactivation and reinfection [30]. Although CMV-HIG are not approved for the prevention or therapy of congenital CMV infections, some authors have used this therapeutic option as so-called "off-label" mode, and results are very questionable, mainly because of the lack of serious large randomized controlled studies (Tables 20.1 and 20.2).

Some studies on HIG administration suggest that there is a possible association between the treatment and both birth weight and duration of pregnancy; CMV may also cause low birth weight due to placental dysfunction with intrauterine hypoxia and malnutrition, even in asymptomatic infants [31]. Multiple doses of HIG seem to improve features of placenta and are correlated with both increasing birth weight and longer gestation, but only for infants born asymptomatic.

Finally, a recent randomized placebo-controlled trial of virus-specific hyperimmune globulin [32] has showed no significant reduction in the rate of transmission of CMV infection among women receiving hyperimmune globulin as compared with women receiving placebo. Moreover, from the cost-effectiveness point of view, results of that trial (related to reduction of vertical infection) are less than the threshold identified as the optimum for a screening program and treatment of primary maternal infection in pregnancy (CHIP study 2014).

Another therapeutic option recently proposed (always "off label") is *standard intravenous immunoglobulins* (IVIG), obtained from unselected donor pools, including a varying proportion of donors previously exposed to CMV that seems to be a less expensive alternative to HIG [33].

Such experience has started since 2010 at the Infectious Disease Unit of Pescara General Hospital, Italy, and it is based on the monthly infusion of IVIG (0.5 g/kg of body weight). CMV IgG and IgM antibodies and IgG avidity indexes are assayed both before and after each IVIG infusion. Preliminary evaluation demonstrates that infusion of IVIG in woman with primary CMV infection significantly increases CMV IgG titers and avidity indexes on blood samples. Moreover, several study have suggested a possible efficacy of HIG administered either to the mother or the foetus in cases of proven foetal infection, in reducing the frequency and severity of foetal and newborn sequelae.

Finally, in a very recent study by Leruez-Ville et al. [34], experimental use of valacyclovir for pregnant women infected by CMV has been proposed. It is a multicenter open-label phase 2 study with one arm. The aim of this study was to evaluate the efficacy of oral valacyclovir, 8 g daily, for pregnant women carrying a symptomatic cytomegalovirus-infected fetus, defined by the presence of measurable extracerebral or mild cerebral

Table 20.1 Clinical studies that have investigated the effect of HIG treatment for the prophylaxis of vertical CMV transmission [4]

Author and design	Number of patients	Dosing regimen (PEIU/kg/dose)	Newborn follow-up (years)	Outcome parameter	Result HIG group	Control group	*p*
Nigro et al. (2005) Props. nrd	84	100 q4w 2–7 doses	2	Percentage of congenitally infected live births	6/37 (16 %)	19/47 (40 %)	$p = 0.02$
Buxmann et al. (2012) Retrosp.	38	100–200 1–3 doses	1-3	Percentage of congenitally infected neonates/fetus	9/38 (24 %)	—	—
Revello et al. (2014) Prosp. rd	123	100 q4w 3–6 doses	0	Percentage of congenitally infected neonates/fetus	18/61 (30 %)	27/62 (44 %)	$p = 0.13$

Table 20.2 Clinical studies that have investigated the therapeutic effect of HIG on CMV-related fetal anomalies and clinical outcome of evidently infected newborns [4]

Author and design	Number of patients	Dosing regimen (PEIU/kg/dose)	Newborn follow-up (years)	Outcome parameter	Result HIG group	Control group	*p*
Nigro et al. (2005) Prosp. nrd	45	200 (plus 400 i.a. or i.u. in 9 subjects)	2	Resolution or regress of fetal sonographic anomalies	14/15 (93 %)	0/7	$p < 0.001$
		1–3 doses		Percentage of symptomatic newborns	1/31 (3 %)	7/14 (50 %)	
Buxmann (2012) Retrosp.	3	180-200 (plus 500 i.a. or i.u.) 1–3 doses	1–3	Percentage of symptomatic newborns	0/3	—	—
Nigro et al. (2012) Retrosp.	64	200	1–5	Resolution or regress of fetal sonographic anomalies	9/14 (64 %)	5/17 (29 %)	$p < 0.001$
		1–4 doses		Percentage of symptomatic newborns	4/31 (13 %)	28/33 (85 %)	
Nigro et al. (2012) Prosp. Ndr	16	200	2–8	Resolution of hyperechogenic bowel	7/9 (78 %)	3/8 (38 %)	$p < 0.0004$
		1–3 doses		Percentage of infans with sequelae	1/9 (11 %)	8/8 (100 %)	
Visentin et al. (2012) Prosp. Ndr.	68	200	1	Resolution or regress of fetalsonographic/MRI anomalies	0/4	0/5	$p < 0.001$
		1 dose		Percentage of infans with sequelae	4/31 (13 %)	16/37 (43 %)	
JCCIIFTSG (2012) Prosp. Unc.	12	100–200 1–5 doses and/or 500–1800 2–6 doses	2–6	Resolution or regress of fetalsonographic/MRI anomalies	9/12 (75 %)	—	—
				Percentage of infans with sequelae	9/12 (75 %)	—	

ultrasound symptoms. Although results of this study indicate that high-dosage valacyclovir given in pregnancy is effective for improving the outcome of moderately symptomatic infected fetuses, it is not a randomized controlled trial. Other trials might be made in the future to improve the knowledge about new emerging and more potent anti-cytomegalovirus drugs that have not currently been tested in pregnancy.

20.2 *Toxoplasma gondii* Infection in Pregnant Women

Toxoplasmosis is a worldwide zoonosis caused by protozoan *Toxoplasma gondii*, whose acute stage is most frequently asymptomatic.

Infection occurs worldwide and the percentage of seropositive persons ranges from 5 % to 90 % [35]. These extreme variations are due to the different level of both exposure to the main sources of infection and hygienic standards between geographic areas. The sources of infection are ubiquitous.

Symptomatic infections usually cause a mononucleosis-like illness with low-grade fever, malaise, headache, and cervical lymphadenopathy. Other manifestations such as encephalitis, myocarditis, hepatitis, and pneumonia can rarely complicate acute disease. Primary infection in pregnant women, when is transmitted transplacentally, can cause congenital toxoplasmosis. Congenital toxoplasmosis can then lead to a wide array of manifestations, ranging from mild chorioretinitis, which can present many years after birth, to miscarriage, mental retardation, microcephaly, hydrocephalus, and seizures.

Prenatal care must include education about the prevention of toxoplasmosis infection in seronegative pregnant women, who – along with their primary care physicians and obstetricians – need to be informed about the risk factors for toxoplasmosis in order to lower the risk of congenital infection.

20.2.1 *Toxoplasma gondii*: Main Microbiologic Characteristics

Toxoplasma gondii is an obligate intracellular protozoan parasite which belongs to the subclass of Coccidia (order Eucoccidiorida, Family Sarcocystidae).

It has a complex life cycle with asexual reproduction taking place in diverse tissues of mammals and birds (secondary hosts) and sexual reproduction taking place in digestive epithelium of cats (primary host). Cats mainly become contaminated by ingesting animal flesh (mouse, bird) encysted with *Toxoplasma gondii* and rarely by ingesting oocysts directly from the feces of other cats. Infected cats are usually asymp-

tomatic and begin to shed unsporulated oocysts in their feces 1–2 weeks after exposure. Within days to weeks, the oocysts sporulate and become infectious. Oocysts survive best in warm and humid conditions (garden, sand box, litter) and can remain infectious for many months. Oocysts withstand exposure to freezing for up to 18 months, especially if they are covered and out of direct sunlight. After ingestion by a secondary host (human, bird, rodent, domestic animal) oocysts release sporozoites, which change into tachyzoites. Tachyzoites are present during acute infection and are capable of invading cells and replicating. They are disseminated widely and circulate from 3 to 10 days in the immunocompetent host before changing into bradyzoites and forming cysts in various tissues, including the lymph nodes, muscle, brain, retina, myocardium, lungs, and liver. These cysts remain present during latent infection [36, 37]. Once infected, humans are believed to remain infected for life. Unless immunosuppression occurs and the organism reactivates, human hosts usually remain asymptomatic. If immunity wanes, such as with the use of immunosuppressive therapy or the acquired immunodeficiency syndrome, bradyzoites can resume rapid division and hematogenously disseminate as tachyzoites again [38, 39].

Toxoplasma gondii has a clonal population of genetic structure with three lineages defined as genotypes I (highly virulent), II, and III (both virulent in humans, genotype III unfrequent). Type I is generally associated to severe neurological dissemination, while type II is the cause of most of congenital toxoplasmosis (CT) in North America and Europe, Spain excluded, where the major cause of CT is type I. In Italy, the congenital toxoplasmosis seems due more frequently to the clonal, virulent genotype I, and it is genetically diverse and much more polymorphic than those isolated in France, Austria, England, and North America. The prevalence of the three archetypal genotypes of *Toxoplasma gondii* associated with congenital toxoplasmosis in Italy differs from previous reports showing type II strains to be mostly associated with human toxoplasmosis. The genotypic picture of human toxoplasmosis in Italy looks highly similar to the situation recently reported in Spain and in South America [40, 41]. In other areas such as South America, these types of *Toxoplasma gondii* show a greater genetic variability and atypical genotypes are also usually much more virulent. The clinical manifestations and severity of the disease, the possible reinfection, depend on several factors, some of which related to the parasite, such as the virulence of the toxoplasma genotype, the infective dose, the life stage, the way of infection and other related to guest, e.g. the efficiency of the immune response, age, gender, and genetic factors [42].

20.2.2 Risk Factors

Toxoplasmosis is a leading infectious cause of food borne death in United States, mainly in immune-suppressed individuals. The main routes of transmission are ingestion of raw or undercooked meats, vegetables, or contaminated water, exposure to oocyst-infected cat feces such as gardening without gloves or changing cat litter, and vertical transmission. Direct contact with cat does not increase the risk of infection. Transfusion or organ transplantation from an infected person can also transmit the organism.

Although uncooked meat products carry a risk of containing tissue cysts that are potentially infective, soil contact is a lesser-known risk factor. Soil contact through gardening allows contact with infective oocysts deposited by any recently infected cat. While oocysts take 1–5 days to become infective, they can remain infective in soil for up to 1 year. Since this method of transmission also requires fecal-oral transmission, wearing gloves and washing hands after gardening or soil contact should eliminate this risk factor.

Cat ownership and changing the cat litter are less likely to be risk factor for seroconversion for several reasons. First, only outdoor cats that hunt or indoor cats that are fed raw meat are at risk of primary infection; indoor cats that are fed canned and prepackaged food do not ingest tissue cysts and thus will never produce oocysts. Second, transmission of *T. gondii* through oocysts requires fecal-oral transmission. Most person who clean a cat's litter box are likely to practice good hygiene and wash their hands following handling cat litter regardless of their knowledge of toxoplasmosis. Finally, there is a narrow window when oocysts are produced and when they become infective. Oocysts are shed in a cat's feces for approximately 2 weeks after primary infection. Once a cat has been exposed to *T. gondii*, it develops immunity and is less likely to become reinfected. In addition, oocysts require at least 1 day to become infective after being deposited, allowing for safe removal of oocysts from a cat's litter through daily changing of the litter (Table 20.3).

Vertical transmission is the result of primary infection in pregnant woman or, unusually, it may occur from mothers who are already seropositive prior to the pregnancy, as a consequence of reinfection with a more virulent strain of the protozoan or reactivation of the latent chronic infection. Reactivation is more frequent in non-immunocompetent women.

A risk of transmission of this protozoan through placenta was estimated at ca 40 % during the whole pregnancy. The probability of transmission and severity of congenital toxoplasmosis are inversely related, according to the gestational age of primary infection. Percentage of transmission increases with the pregnancy week and amounts to 6–8 % and even 80 % in the week 10 and 38 of pregnancy, respectively. A risk of fetopathy is the highest if pregnant woman is infected prior to the week 24 of pregnancy, and it is higher as earlier the fetus is infected [38] (Fig. 20.7). Actually, congenital infections contracted early can cause serious damage to the fetus such as abortion, malformations, growth retardation, fetal

Table 20.3 Specific hygiene and dietary recommendations for pregnant women to avoid primary *T. gondii* infection

Wear gloves and thoroughly clean hands and nails when handling material potentially contaminated by cat feces (sand, soil gardening).
Reduce the exposure risk of pet cats by (1) keeping all cats indoors and (2) giving domestic cats only cooked, preserved, or dry food.
Change litter and get rid of cat feces (wearing gloves) on a regular basis (every 24 hours).
Disinfect emptied cat litter tray with near-boiling water for 5 minutes before refilling.
Eat only well-cooked meat (>67 °C).
Freezing meat to at least –20°C also kills *T. gondii* cysts.
Clean surfaces and utensilis that have been in contact with raw meat.
Do not consume raw eggs or raw milk.
Wash uncooked fruits and vegetables before consumption.
Prevent cross-contamination: thoroughly cleanhands and utensilis after touching raw meat or vegetables.
Do not drink water potentially contaminated with oocysts.
Be aware that:
The process of curing, smoking, or drying meat does not necessary result in a product free of parasite cysts
Refrigeration does not destroy the parasite (still liable after 68 days at +4 °C)
Microwave oven cooking does not destroy parasites.

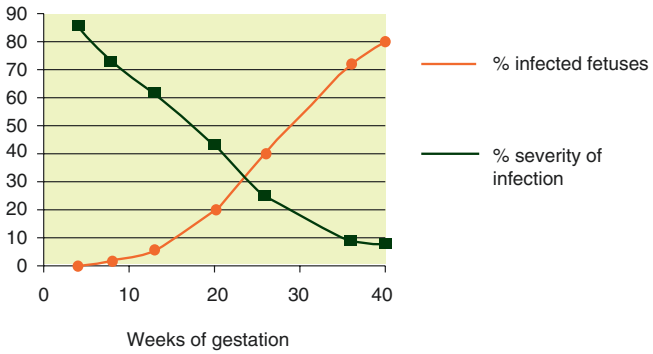

Fig. 20.7 Correlation between period of transmission and severity of congenital toxoplasmosis

death, or preterm birth. Conversely, congenital infections contracted during the third trimester are generally asymptomatic, with a frequency of subclinical infections of approximately 90 %. The diagnosis of acute infection in the mother should be made as early as possible. This would make it possible to promptly initiate therapy in order to try to reduce the frequency and severity of congenital toxoplasmosis [43, 44].

20.2.3 Epidemiology

Evidence of prior infection with *T. gondii* is common throughout the world.

Seroprevalence, however, varies considerably with high prevalence (>50 %) occurring in countries where raw meat is commonly eaten (France, 54 %) and in tropical regions of Latin America or sub-Saharan Africa where cats are numerous and the climate is favorable to oocysts' survival.

In the United States, the overall age-adjusted seroprevalence is 22.5 % and 15 % among women of childbearing age (15–44 years). There are approximately 255.000 cases of *T. gondii* infection per year, which result in 5,000 hospitalizations and 750 deaths, making *T. gondii* the third most common cause of fatal foodborne illness in the country. Although evidence of prior infection is common, congenital toxoplasmosis is relatively uncommon in the United States, with an estimated 400–4,000 cases per year [38]. In Canada, only a few serologic surveys or prospective studies of women have been carried out, and the seroprevalence was established between 20 % and 40 %. High seroprevalence (59,8 %) is documented in Inuit populations of Nunavik and other northern communities associated with drinking contaminated water and consuming raw or undercooked seal meat and wild fowl [39]. In Brazil, the prevalence of toxoplasmosis among pregnant women varies from 50 % to 80 % throughout the whole territory of this vast country [45].

Incidence and prevalence of the infection have markedly decreased during the last 30 years in Europe. This decrease may be explained by a lower exposure to the parasite by changes in food habits and by improved hygiene practices in meat production.

In Italy, despite a substantial decrease in *Toxoplasma gondii* seroprevalence (from 40 % to 20–30 % in the adult population in the last 20 years) and although no national registry of congenital infections is available, 1–2 congenital toxoplasma cases per 10.000 births are currently estimated; 1–4 % of them are at risk of death or serious neurological sequelae.

In France, the incidence decreased from 7.5/1,000 susceptible women in 1980 to 3.5/1,000 in 2000 and 2.4/1,000 in 2010. The predictive incidence and prevalence for 2020 were 1.6/1,000 and 27 %, respectively. The same trend was reported in the United Kingdom.

Despite the elevated frequency of toxoplasma infection, only four countries in Europe recommend the routinary

screening of congenital toxoplasmosis: Italy, Denmark, France, and Germany [46].

20.2.4 Clinical Manifestations

Toxoplasmosis infection has different manifestations depending on the immunity status of the patient. In immunocompetent persons (90 % of cases), it has an asymptomatic course or non-specific, mononucleosis-like symptoms. In ca 10 % cases, the infection causes enlargement of lymph nodes: most frequently occipital and cervical nodes which may even persist for a few months. After the acute status, there is a chronic stage with the parasite that remains latent in the cyst and reactivates in case of immune impairment in the host (eg. in case of AIDS): it can cause severe encephalitis, myocarditis, or hepatitis.

The infected person remains protected throughout the lifetime recurrence, because it responds to infection with production of specific antibodies and lymphocytes. The response of the subject to *Toxoplasma gondii* determines the transition to the second phase of the toxoplasmosis (post primary) characterized by the absence of clinical signs and acute infection laboratory, but with the persistence of the parasite in the body, "encysted" in muscles and the brain.

Most pregnant women (>90 %) with acquired *T. gondii* infection do not experience obvious signs and symptoms, and spontaneous recovery is the rule. Only a small proportion will develop clinical signs of the disease. The clinical presentation in pregnant women is not more severe than in nonpregnant women and most often occurs as a non specific, mononucleosis-like illness (low-grade fever, malaise, lymphadenopathy), with an incubation period of 5–18 days following exposure. Pregnant women will rarely show visual changes due to toxoplasmic chorioretinitis. In immunocompromised pregnant women, *T. gondii* can cause severe encephalitis, myocarditis, pneumonitis, or hepatitis via acute infection or reactivation of a latent infection [39].

Fetus may be infected most frequently due to primary infection acquired by pregnant woman, and unusually due to reactivation of the latent maternal infection or to reinfection with another strain of the protozoan. Primary *T. gondii* infection in pregnant women may result in spontaneous abortion, stillbirth, nonimmune hydrops fetalis, preterm labor, intrauterine growth restriction, or postpartum fetal death. Symptomatic congenital toxoplasmosis occurs in ca. 5–10 % of infected newborn in the following manifestations: triad of Sabin and Pinkerton with chorioretinitis, hydrocephalus or microcephaly, intracranial calcifications, sepsis, and organ manifestations (ocular disorders, myocarditis, hepatitis, enteritis).

Long-term complications in children include permanent impairment of visual and central nervous system. In a group of children who do not present clinical symptoms in postpartum period (90 %), long-term complications may appear months or years after birth with an estimated prevalence of 7–15 % [47].

20.2.5 Management in Pregnancy

20.2.5.1 Measures of Prevention

The prevention can be carried out at three levels:

- Primary prevention: It is aimed at preventing the infection in the mother through easy rules about food and risk factors during pregnancy. These measures should be brought to the attention of all women of childbearing age, preferably before pregnancy and as early as possible, after conception and should be followed up to childbirth [48, 49]. In the case of primary infection (positive IgM, low-avidity IgG) in a nonpregnant woman, she should wait at least 6 months before a possible pregnancy [50].
- Secondary prevention: It is based on serological screening of pregnant women in order to identify early and treat those who acquire the infection in pregnancy. The early maternal infection identification allows to schedule follow-up ultrasound and check with amniocentesis any maternal-fetal transmission of the infection, and to discuss with the woman all possible treatment options (treatment of maternal infection only, in order to contain the probability of infection transmission to foetus, treatment of fetal infection, therapeutic interruption of pregnancy).
- Tertiary prevention: It consists of the diagnosis, treatment, and clinical and serological follow-ups of newborns. Accurate and timely diagnosis in an infected newborn is crucial because even asymptomatic infants may develop over the years late, especially chorioretinal sequelae [51].

20.2.5.2 Diagnosis

Since more than 90 % of primary toxoplasmosis infections in immunocompetent persons are asymptomatic, the diagnosis of maternal infection is difficult. Provided the infection is suspected, it is required to confirm or exclude it based on the results of specific laboratory testing, including serologic and molecular methods. Results of such tests should allow for determining whether the person tested is infected, if it is acute stage of infection and when the person was infected.

Serologic testing is often the first step in diagnosis, using IgG and IgM specific antibodies. The diagnostic challenge is differentiating between a recent primary and a chronic infection. IgM antibody titles rise starting from 5 days to weeks following acute infection, reaching a maximum after 1–2 months and decline afterwards more rapidly than IgG. Although IgM antibodies can decrease to low or undetectable levels, in many cases they may persist for months or years following the acute infection. IgG antibodies appear

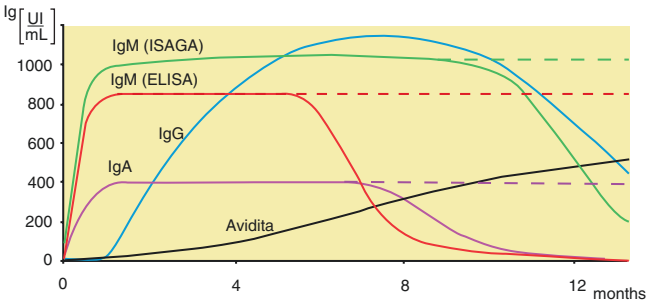

Fig. 20.8 Antibodies trend during primary *T. gondii* infection

later than IgM and are usually detectable within 1–2 weeks after the infection, with the peak reached within 12 weeks to 6 months after acute infection. They will be detectable for years after acquired infection and are usually present throughout life (Fig. 20.8). Only new seroconversions (IgM and IgG that become positive following a previous negative result) indicate a certain primary infection. If IgM and IgG are both negative, this indicates the absence of infection or extremely recent acute infection. If testing reveals a positive IgG and negative IgM, this indicates an old infection. If both IgG and IgM are positive in the absence of a previous determination, this indicates either a recent infection or a IgM false-positive result. In order to determine the timing of infection in IgG and IgM in positive pregnant women even with an unknown previous serostatus, it is recommended to determine the avidity (maturity) of specific IgG. The widescale diffusion of the IgG avidity assay is justified by its high positive predictive value for old infection (100 %) and by recent simplification of the original Hedman method, thanks to the introduction of cheaper standardized automated assays.

The IgG avidity test measures the strength of IgG binding to the organism. Avidity, in most cases but not all, shifts from low to high after about 4–5 months. If the avidity is high, this suggests infection occurred at least 4 months before testing [39, 47].

Amniocentesis is used as a confirmation test of fetal infection because it allows detection of genetic material of *T. gondii* in amniotic fluid by polymerase chain reaction (sensitivity 81–90 %, specificity 96–100 %) and should be offered to appropriate patients: when maternal primary infection is diagnosed, when serologic testing cannot confirm or exclude acute infection, and when there are abnormal ultrasound findings suggestive of toxoplasmosis infection. Amniocentesis seems advisable following primary infection because a negative result is associated with a low likelihood that infection has occurred. It should not be offered at less than 18 weeks' gestation because of the high rate of false-positive results, and it should be offered no less than 4 weeks after the time of suspected acute maternal infection [52–55] (Fig. 20.9).

The sensitivity of PCR on amniotic fluid is influenced by a number of parameters, such as the appropriateness of the levy (amniotic fluid should not be less than 10 ml), the conservation, any maternal therapy, and the technique employed. The real-time PCR is performed at least in duplicate on the sediment obtained by centrifugation of 10 ml of amniotic fluid. In the literature, PCR performed with the gene target B1 attributed a sensitivity of 64 % with a negative predictive value of 87.8 % and a specificity and a positive predictive value of 100 %. Sensitivity changes with gestational age, and it is significantly higher for infections occurring between 17 and 21 weeks of gestation [56]. Currently, the PCR system in real time and the use of the target gene region AF146527, which is repeated 300 times in the genome of *Toxoplasma gondii*, have definitely improved the performance of molecular diagnostic tests. Actually the test, correctly executed, has a specificity of 100 % and a sensitivity of 92 %, and these do not vary at different weeks of gestation when the mother became infected [57].

Fetal blood sampling (cordocentesis), which was previously the gold standard for diagnosing fetal infection, should no longer be offered as a diagnostic test because of reported high sensitivity and specificity of the amniotic fluid polymerase chain reaction test and because of the associated higher fetal risk with cordocentesis.

20.2.5.3 Ultrasound Screening

Toxoplasma gondii infection should be suspected, and screening should be offered to pregnant women with ultrasound findings including but not limited to intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction [39] (Fig. 20.10).

Ultrasound is an essential method in the clinical management of toxoplasmosis during pregnancy. It must be performed by experienced operators. The sensitivity of the method does not exceed 40 %. The detection of fetal abnormalities is usually due to infections contracted in the first half of pregnancy. The signs to look for are ventriculomegaly (early), intracranial calcifications, hepatosplenomegaly, liver calcifications, hydrocephalus, hydrothorax, ascites, hydrops, polyhydramnios, placental thickening with calcifications, intrauterine fetal growth restriction, and cataract [58]. In case of detection of ultrasound signs, follow-up must be made frequently because of the rapid evolutivity of these anomalies [59, 60]. The finding of normal fetal anatomy during ultrasounds is not enough to ensure a favorable neonatal outcome. Furthermore, some structural abnormality could not occur early, and, therefore, ultrasound evaluation should be performed frequently. The ultrasound should be performed every 4 weeks from the serological diagnosis, even in case of negative amniocentesis [61]. Finally, in case of suspected ultrasound abnormalities, women could decide to perform fetal magnetic resonance (FMR) after 23 weeks of gestation, but preferably at 32 weeks, in order to obtain further information for the diagnosis.

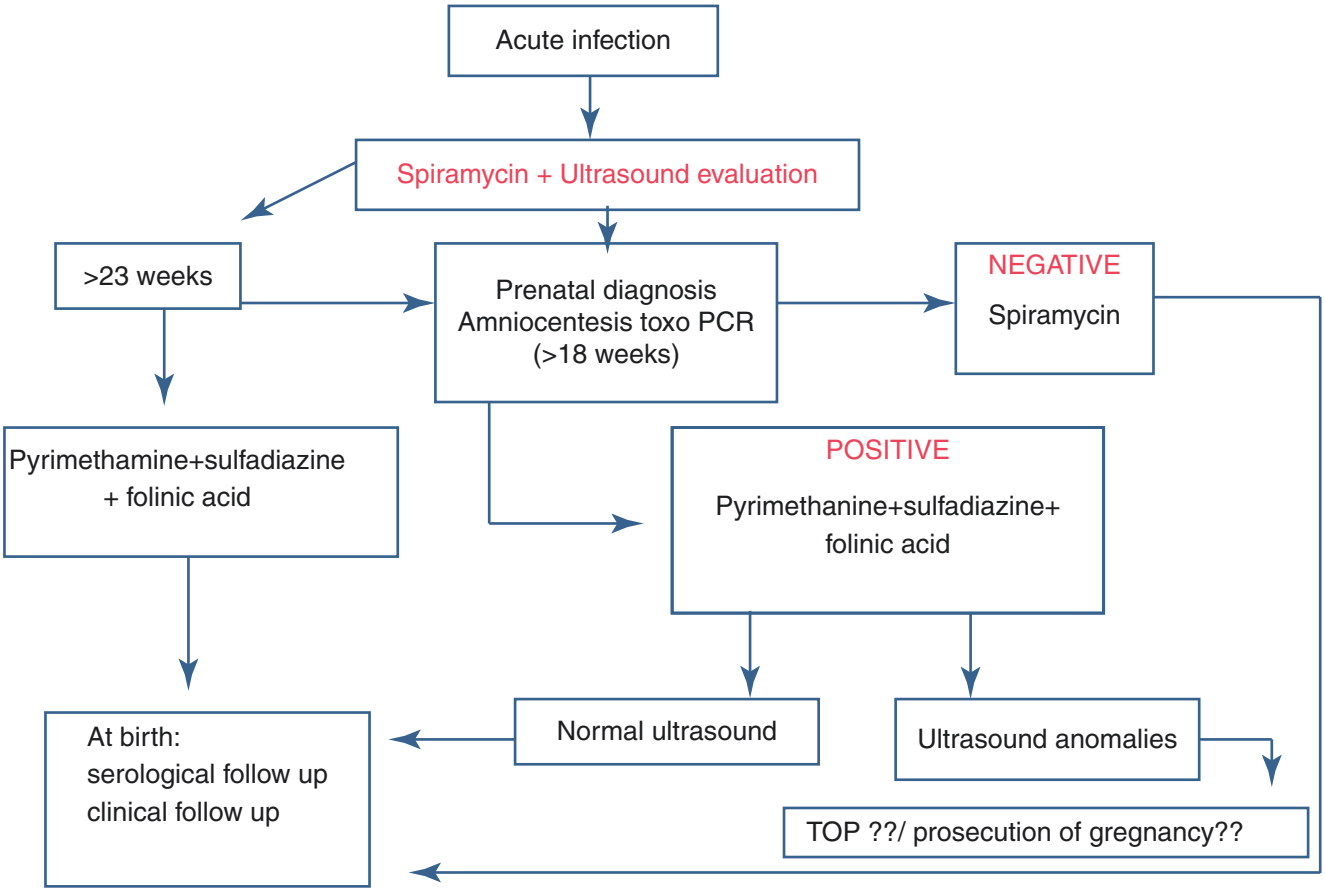

Fig. 20.9 Management of primary *T. gondii* infection in pregnancy

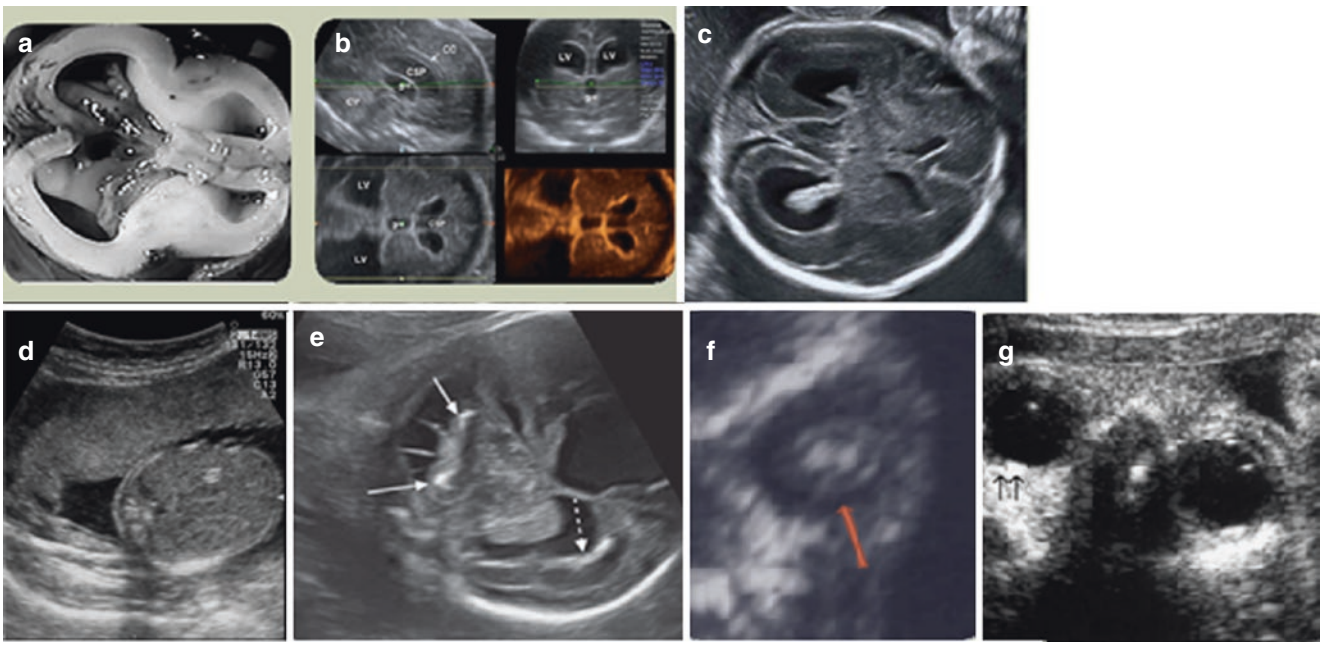

Fig. 20.10 (**a**–**g**) Ultrasound fetal anomalies of toxoplasmosis infection in pregnancy. (**a**–**c**) Histologic, 3D, and 2D ultrasound features of hydrocephaly in fetus at 21 weeks' gestation; (**d**, **e**) hepatic, periventricular, and cerebellum calcifications in patients with primary toxoplasmosis infection at 20 weeks' gestation; (**f**, **g**) ocular anomalies in *Toxoplasma gondii* infection: cataract and chorioretinitis

20.2.6 Treatment of Toxoplasmosis

Standardization of chemoprophylactic management in pregnancy is a very difficult task. Time of diagnosis of infection in pregnant woman and her child has an impact on the method of treatment [47].

There are two goals of drug therapy for toxoplasmosis, depending on whether or not fetal infection has occurred.

If maternal infection has occurred but the fetus is not infected, spiramycin is used in order to reduce the probability of the spread of toxoplasma, across the placenta from mother to fetus. Spiramycin is a macrolide antibiotic that is concentrated but does not readily cross the placenta and therefore is not reliable for treatment of fetal infection [62].

Its use during pregnancy has been recommended by many investigators in Europe and North America. It is given at a dose of 1 g (3 million UI) orally every 8 h. This therapy is based on the results of observational studies which have shown the role of spiramycin in preventing fetal infection. It is important that the patient receives spiramycin as early as possible after infection for a better effectiveness of the therapy. It is demonstrated that a treatment started within 3 weeks after seroconversion reduces the risk of transmission compared to a treatment started later [43, 51] (Table 20.4). It will be prescribed throughout the pregnancy if the amniotic fluid polymerase chain reaction is reported negative for *T. gondii*. The treatment with spiramycin is generally well tolerated. Collateral effects are rare: gastrointestinal symptoms (nausea, vomiting, diarrhea), skin hypersensitivity reactions, and occasionally transient paresthesia.

If fetal infection has been confirmed or it is discovered in the third trimester, pyrimethamine and sulfadiazine are used for treatment. Pyrimethamine is a folic acid antagonist that acts synergistically with sulfonamides. Unlike spiramycin, these drugs are able to cross significantly the placental barrier and can then treat already established fetal infection. This therapy should not be used in the first trimester because it is potentially teratogenic. It produces a reversible, dose-related depression of the bone marrow and therefore must be combined with folinic acid. The combination of pyrimethamine and sulfadiazine results in a significant decrease in disease severity [39, 63].

Pyrimethamine has to be given at the dose of 50 mg every 12 h for 2 days, 50 mg once a day since day 3 of treatment until the end of pregnancy; sulfadiazine is given at the dose of 3 g per day in two divided doses until the end of pregnancy. During treatment with pyrimethamine, it is required to perform complete blood count, hepatic and renal function panel, and urina analysis every 7–10 days, or less frequently, provided normal parameters were determined earlier [47]. Compared to spiramycin, pyrimethamine-sulfadiazine involves a higher risk for side effects (hematopoiesis, gastrointestinal disorders, neurological disorders, liver and kidney damage, hypersensitivity reactions), which often cause discontinuation of treatment. If tolerated, treatment with pyrimethamine-sulfadiazine should be assumed until the end of pregnancy. It is however considered appropriate to discontinue therapy with pyrimethamine-sulfadiazine about 2 weeks before the expected date of birth, continuing the treatment until the end with the spiramycin, to avoid any induced toxic effects in the newborn from sulfonamide. Therapy with pyrimethamine-sulfadiazine can be justified even without amniocentesis to confirm a fetal infection, when the mother acquires toxoplasmosis in the third trimester of pregnancy, due to the high rate of maternal-fetal transmission of infection at this gestational age [43, 51].

Unfortunately, there are no randomized controlled trials to assess the effect of prenatal antimicrobial therapy with either spiramycin or pyrimethamine-sulfadiazine. A large prospective cohort trial of 1,208 pregnant women in Europe

Table 20.4 Treatment of toxoplasmosis in pregnancy

Toxoplasmosis therapy during pregnancy
Spiramycin 9,000,000 IU/day orally divided into 3 doses (1 cp to 3,000,000 IU every 8 hours) until the end of pregnancy.
Treatment of toxoplasmosis during pregnancy in case of confirmed fetal infection
Pyrimethamine 50 mg/day orally in a single dose
Sulfadiazine 3 g/day orally in 2–3 divided doses
Folinic acid 10–15 mg day orally
The therapy should be carried out continuously until approximately 1 weeks after the end of the pregnancy, with resumption of spiramycin until delivery.
Treatment of toxoplasmosis during pregnancy in cases of maternal infection acquired after 24 weeks of gestation (not confirmed fetal infection)
Pirimetamina 50 mg/day orally in a single dose
Sulfadiazine 3 g/day orally in 2–3 divided doses
Folinic acid 10–15 mg day orally
Therapy to be carried out in alternating cycles of 3–4 weeks with 2 weeks spiramycin. It is necessary to program the cycles so that the last of pyrimethamine-sulfadiazine ends 2 weeks before the end of the pregnancy, with resumption of spiramycin until delivery.

with primary *Toxoplasma gondii* infection failed to reveal any difference in the risk of congenital infection with treatment (with spiramycin or pyrimethamine-sulfadiazine) or no treatment [64]. However, other uncontrolled studies have demonstrated the benefits of prenatal treatment with spiramycin or pyrimethamine-sulfadiazine. One study of 5,288 susceptible pregnancies showed the risk of congenital toxoplasmosis to be four times greater in neonates born to untreated mothers when compared with treated mothers [65]. Another study of 88 pregnant women with primary toxoplasmosis infection who were treated with spiramycin alone showed a 0 % rate of congenital toxoplasmosis at 2 years [66]. A systematic review of nonrandomized studies found therapy to be effective in five trials but ineffective in four studies [67]. Of the four trials without statistical benefit, two demonstrated a nonstatistically significant reduction in congenital toxoplasmosis with antiparasitic therapy. Thus, while there are no randomized studies yet, it is still recommended that all pregnant women who have been diagnosed with primary toxoplasmosis infection be treated with spiramycin with or without pyrimethamine-sulfadiazine [38]. Furthermore, interruption of treatment after a negative antenatal diagnosis is never considered.

20.2.7 Neonatal Management

Worldwide toxoplasmosis congenital incidence is 2–3 cases per 10,000 births. In Italy, a study in 2009 shows a congenital infection incidence of 2.4 % [67]. Infection with *Toxoplasma gondii* is transmitted from mother to fetus in approximately 30 % of cases. Eighty-five percent of congenital infections are asymptomatic at birth but if left untreated, they can lead to late sequelae (mainly chorioretinitis and psychomotor symptoms). The main symptoms are hydrocephaly, microcephaly, intracranial calcifications, chorioretinitis, strabismus, blindness, deafness, epilepsy, and psychomotor retardation. In severe cases, the signs and symptoms may be nonspecific and common to other congenital infections, such as CMV, herpes simplex, rubella, and syphilis. In all cases of infection, even asymptomatic, the therapy of choice is represented by pyrimethamine-sulfadiazine, which should be continued for at least a year and associated with the administration of folinic acid [51].

20.2.7.1 Diagnosis

The definitive diagnosis in the newborn in the absence of markers of infection as the positivity of PCR of amniotic fluid or the presence of specific antibodies IgA or IgM or IgG is based on positivity of toxoplasmosis antibodies at 1 year, while their negativity excludes infection (unless the child has not been treated during the first year of life). It is therefore recommended for all infants, in whom the diagnosis is not defined, a serologic follow-up monthly for the first 3 months and then every 2 months until the complete serologic negativity that must be confirmed the following month. Testing should be carried in the same laboratory and with the same method to verify the correct decrease of antibody titers. Among the tests for IgM, the best results are obtained with the IgM-ISAGA tests. It is absolutely useless the execution of the avidity test on the baby in the first months of life because of the transplacental passage of maternal IgG. The direct testing such as PCR of cord blood, peripheral blood, and placenta showed little sensitivity. Only infections acquired at the time of delivery can give a parasitemia detectable in the blood cord or in the peripheral blood of the newborn. The detection of the protozoan in the placenta may however not be indicative of a congenital infection as the placental colonization is not always followed by the transmission of the infection to the fetus. In literature, it is reported that at birth, with traditional tests, a diagnosis could be performed only in 85 % (95 % CI, 71–99 %) of infants whose mother hasn't been treated and in 73.5 % (95 % CI, 62–82 %) of infants whose mother had the therapy [51, 69]. In recent years, the effectiveness of the diagnosis is improved since the traditional serology tests are joined to immunoblot for IgG and IgM. The immunoblot tests, performed on paired serum samples from mother and newborn, can highlight in the antibody pool specific for toxoplasmosis of the newborn, which are produced after birth with a specificity different both from those maternal (at delivery) and, in the following months, from those present at birth. The test however is very sensitive and requires experienced staff and cannot be performed over the first 3 months of life, when its results are non-specific [70].

Immunological tests (dosages of lymphokines or evaluation of activation markers after stimulation with toxoplasma antigen), created recently, have the advantage of not being influenced by therapy but are still in the experimental stage [71, 72]. The congenital infection is diagnosed in the great majority of cases in the first 3 months of life and is confirmed by serological follow-up of IgG and IgM.

Serological evaluation must be joined by the clinical and instrumental assessment and other laboratory tests (blood tests, transfontanellar ultrasound, audiometric test, ocular test, EEG, CT) [73].

20.2.7.2 Clinical Manifestations

The classic symptoms described by Wolf in 1939 as a triad (hydrocephalus, intracranial calcification, and chorioretinitis) are very rare [51]. Overall 85 % of congenital infection is asymptomatic at birth. Mild cases are usually not easily recognized (except for cases of maternal history at risk for congenital toxoplasmosis). When neonatal infection is clinically apparent at birth, it is generally severe. In severe cases, the clinical manifestations may be those of a generalized

infection: anemia, thrombocytopenia, jaundice, hepatosplenomegaly, lymphadenopathy, eosinophilia, skin rash, prematurity, and small for gestational age. In other cases, the symptoms can be only neurological: nystagmus, seizures, abnormal increase in head circumference or microcephaly, and convulsions. Overall, the risk of clinical signs in infected infants is 19 %, 14 % with ocular lesions, and 8 % with intracranial problems. The involvement of the central nervous system (CNS) and the ocular system concerns over 60 % of symptomatic infected newborns [43, 51].

Ocular lesions are in the first place among the manifestations of congenital toxoplasmosis; chorioretinitis, active or quiescent, with single or multiple lesions, unilateral or bilateral, is an inflammatory process that begins in the deeper layers of the retina and secondarily affects choroid. The inflammation results in destruction and disorganization of retinal layers. The pathogenesis is the rupture of cysts in ocular tissues already infected with release of trophozoites that invade the adjacent cells. Other ocular manifestations that may be associated with chorioretinitis are strabismus, microphthalmia, cataracts, retinal detachment, and optic nerve atrophy. Among the intracranial lesions, some may have ventricular dilatation (3.8–2 %) and calcifications of the brain (11.4–9 %). Highly destructive forms could cause porencephalia [51].

20.2.7.3 Treatment and Evaluation of Child with Congenital Infection

Children who, according to prenatal or postnatal diagnosis, are infected begin the therapy with the combination of pyrimethamine and sulfonamide. The protocol that uses pyrimethamine and sulfadiazine is different, depending on whether the infection is subclinical or clinical. Some centers start pyrimethamine-sulfadiazine immediately after birth even in the absence of confirmed congenital infection when maternal toxoplasmosis was acquired late in pregnancy. This practice, however, interferes with the diagnostic procedure because it can lead to a confusing serological pattern with declining IgG titer and negativization even in infected children. No definitive international agreement exists on postnatal treatment [46]. Pyrimethamine in the subclinical form is administered every day for the first 2 months of treatment (dose, 2 mg/kg/day for the first 2 days and then 1 mg/kg/day as a single dose) and three times a week (Mondays, Wednesdays, Fridays) in the remaining 10 months, with the same dose. In clinically evident form, it is prescribed three times a week just after 6 months of continuous daily treatment. Sulfadiazine is administered for all 12 months of treatment (dosage: 100 mg/kg/day in two doses daily). A second therapeutic protocol uses the association of pyrimethamine with sulfadoxine with which shows a longer half-life as compared to sulfadiazine. This allows you to reduce the frequency of administration: pyrimethamine (1.25 mg/kg dose/every 10 days) and sulfadoxine (25 mg/kg/every 10 days). The total duration of treatment is 12 months and in both protocols is imperative supplementation with folinic acid (25 mg two times a week) for 12 months [74]. Among the side effects of therapy, most daunting is bone marrow toxicity with reversible neutropenia (30 %) and anemia (20 %) in addition to nausea and/or vomiting. Severe skin manifestations, such as rash, epidermolysis, and Lyell's syndrome, which impose the suspension of the therapy, are reported rarely. Before embarking on therapy which must always exclude a G6PD deficiency, following a regular monitoring of blood counts is essential, every 15 days in the first month and then a once a month. In case of neutropenia (<500 cells/mm^3), a temporary suspension of therapy is required. Folinic acid must instead continue to be administered, and hematological control must be repeated after about 15 days. In case of intolerance to treatment with pyrimethamine and sulfadiazine, the use of azithromycin is possible. In the presence of clinical or instrumental signs of inflammatory processes in the active phase such as encephalitis or chorioretinitis, it is useful to associate with the basic therapy a corticosteroid (prednisone: −1,5 mg/kg/day in 2 oral doses), which will gradually be suspended after the resolution of inflammatory signs [41, 42]. The spiramycin employed in the past in the therapy of congenital toxoplasmosis must not be used anymore, since no study has ever shown it to be effective, and it can cause an ECG QT interval prolongation syndrome that can cause malignant arrhythmias and death [43].

Although the congenital infection is asymptomatic at birth in about 85 % of cases, new chorioretinal lesions may appear in long-term follow-up in children. It is therefore necessary to perform the control of the fundus oculi at least once a year throughout childhood [77, 78]. Latest bibliographic data shows that the association between congenital infection by *T. gondii* and subsequent risk of hearing loss is related to the precocity and adequacy of treatment; the follow-up therefore provides a check at birth and subsequent evaluations at 6 and 12 months [79]. The neurological follow-up is continuing in the first years of life until the achievement of the neurobehavioral development; if there were no neurological lesions detectable by ultrasound at birth, there will not be neurological sequelae [51]. In the course of therapy, there may occur transient negativity of serological specific antibodies titers, which do not, however, justify the interruption of treatment [80]. The antibody rebound, which occurs in 70–97 % of cases, several months after the completion of a year of therapy of an infected infant, usually has no clinical relevance. If the rebound antibody occurs late (after 2 years of life), it is recommended to examine the fundus to exclude the possibility of a parasite proliferation [75].

Conflict of Interest Authors certify that there is no actual or potential conflict of interest in relation to this article, and

they reveal any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated – including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

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Neonatal Encephalopathy

21

Giuseppe Loverro, Lucrezia De Cosmo, Matteo Loverro, and Salvatore Andrea Mastrolia

21.1 Introduction

Neonatal encephalopathy (NE) is a heterogeneous syndrome characterized by neurological disorders appearing in the first days of life in neonates delivered at 35 weeks or more of gestation. Principal signs are (1) reduced level of consciousness, (2) difficulty with beginning and maintenance of respiration, and (3) depression of tone, reflexes, and often seizures [1].

Birth asphyxia and acute hypoxic-ischemic encephalopathy (HIE) are responsible for some, but not all of the cases of NE.

NE occurs also as a consequence of intracranial hemorrhage, various metabolic disorders, neurodegenerative disorders, epileptic encephalopathies, intracranial infection, and other conditions often unexplained [2].

A distinctive feature of neonatal encephalopathy is cerebral palsy which is classified based on the type of neurological dysfunction (spastic, dyskinetic, or ataxic), as well as on the number and the distribution of the affected limbs (quadriplegia, diplegia, hemiplegia, or monoplegia).

Spastic quadriplegic and less commonly dyskinetic cerebral palsy can be the result of a peripartum acute ischemic event, while hemiplegic cerebral palsy, spastic diplegia, and ataxia are hardly the consequence of a pure intrapartum event. The ataxic or dyskinetic cerebral palsy, especially when accompanied by learning disability, usually have a genetic origin [3].

According to recent reports, the incidence of neonatal encephalopathy is 3 per 1,000 live births (95 % CI 2.7–3.3), increasing up to 9 per 1,000 live births in neonates born prematurely [4–7], while the incidence of hypoxic-ischemic encephalopathy is between 0.27 and 1.5 per 1,000 live births (95 % CI 1.3–1.7) [8, 9].

21.2 Etiology of Neonatal Encephalopathy

During almost a century, there was the erroneous belief that all neonatal encephalopathies were related to asphyxia occurring during childbirth [10].

Nowadays, the etiology of neonatal encephalopathy seems the result of a multifactorial combination of genetic (chromosomal abnormalities and gene mutations), environmental, underlying obstetrical pathologic processes, as well as malformations (including brain defects), while only a few cases of neonatal encephalopathy are certainly associated with the occurrence of peripartum events leading to asphyxia [11].

In addition, important causes of neonatal encephalopathy are suggested to be low birth weight (<2,000 g) and prenatal infections [11, 12].

Prematurity below 32 weeks remains today one of the main causes of neonatal encephalopathy despite the increasing attention on the identification of intrapartum fetal distress in these women [13]. Preterm delivery of 23–27 weeks, therefore, continues to be the single most important risk factor, with a risk ratio of 78.9 (95 % CI 56.5–110) [14, 15].

Although there are so many causes of neonatal encephalopathy and cerebral palsy, the attention of obstetricians has been focusing on the HIE that recognizes its origin in the intrapartum period and is characterized by clinical evidence of brain damage as well as laboratory alterations due to subacute or acute asphyxia associated with systemic hypoxemia and reduced blood flow to the fetal brain [16–18].

Hypoxia and acidosis just before or during labor may determine clinical signs of fetal impairment: pathological

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changes of fetal heart rate and meconium stained amniotic fluid. However, when sentinel events occur next to labor, an incidence of HIE of 10 % and a perinatal mortality of 6 % are described [19]. The sentinel events are acute events that can cause HIE in a previously healthy fetus such as (a) signs of uterine rupture, (b) severe placental abruptions, (c) cord prolapse, (d) amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia, (e) maternal cardiovascular collapse, and (f) fetal exsanguination from either vasa brevia or massive feto-maternal hemorrhage [20].

In neonates without a sentinel event, placental pathology can provide valuable information regarding the cause and timing of the adverse events in utero. For example, placentas with decreased maturation of the terminal villi are associated with injury to the white matter/watershed areas and basal ganglia. Immature placental villi increase the distance between the maternal and fetal blood with a net effect of reduced oxygen diffusion to the fetus or fetal hypoxia. Placentas with reduced weight can represent an adverse intrauterine environment owing to decreased uteroplacental perfusion [21].

21.3 Pathophysiology of Neonatal Hypoxic-Ischemic Encephalopathy

Most of the knowledge regarding neonatal encephalopathy has been developed studying the pathophysiology of hypoxic-ischemic encephalopathy. In the initial phase of the event, hypoxia and hypercapnia are compensated by an increase in cerebral blood flow, both as a result of the redistribution of the cardiac output to the essential organs (brain, heart, and adrenal glands) and an increase in blood pressure [22].

The persistence of hypoxia, especially in the fetus in which the threshold for the deterioration of the cerebral flow is lower (10–20 mmHg) compared to adults (40 mmHg), determines the loss of the compensatory mechanism of cerebral autoregulation and therefore a reduction of cerebral blood flow [23].

Cerebral ischemia and the subsequent cerebral hypoxia are accompanied by serious and persistent neuronal damage, to which damages from reperfusion after the recovery of the cerebral vascularization, characterized by inflammation and oxidative stress, are to be added (Fig. 21.1).

In this scenario, seizures and abnormal movements such as clonus or tremors are correlated to an impaired synaptic glutamate uptake in the brain. Since glutamate is an excitatory neurotransmitter, there is a subsequent overactivation of its excitatory postsynaptic receptors (AMPA, NMDA, and kainate) with intracellular accumulation of Na^+ and Ca^{++}.

There is a primary energy failure phase that occurs at the cellular level due to the loss of readily available oxygen to the brain. For this reason, cellular metabolism shifts to anaerobic, and this reliance upon anaerobic metabolism pathways leads to depletion of adenosine triphosphate (ATP) and a lack of energy from enzymes such as Na^+/K^+-ATPase, with a subsequent rapid cytotoxic edema and necrotic cell death (Fig. 21.2).

After an initial phase asphyxial damage, cerebral metabolism may reactivate, with the establishment of regular blood perfusion. This event leads to a secondary damage, called "delayed phase neuronal damage" that starts at about 6–24 h after the initial damage and is characterized by mitochondrial dysfunction and apoptotic damage. Neonatal seizures typically occur in this phase. The delayed phase damage duration is not precisely known in the fetus and in human

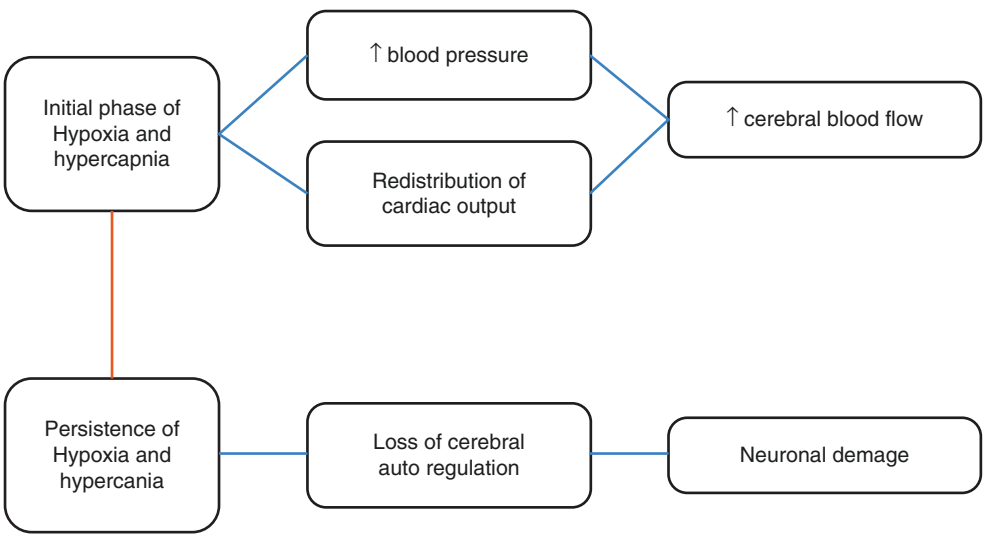

Fig. 21.1 Fetal adaptive response to hypoxia and hypercapnia. Compensative mechanisms work in the initial phase through an increase in cerebral blood flow. If the insult persists, neuronal damage is due to the loss of these mechanisms

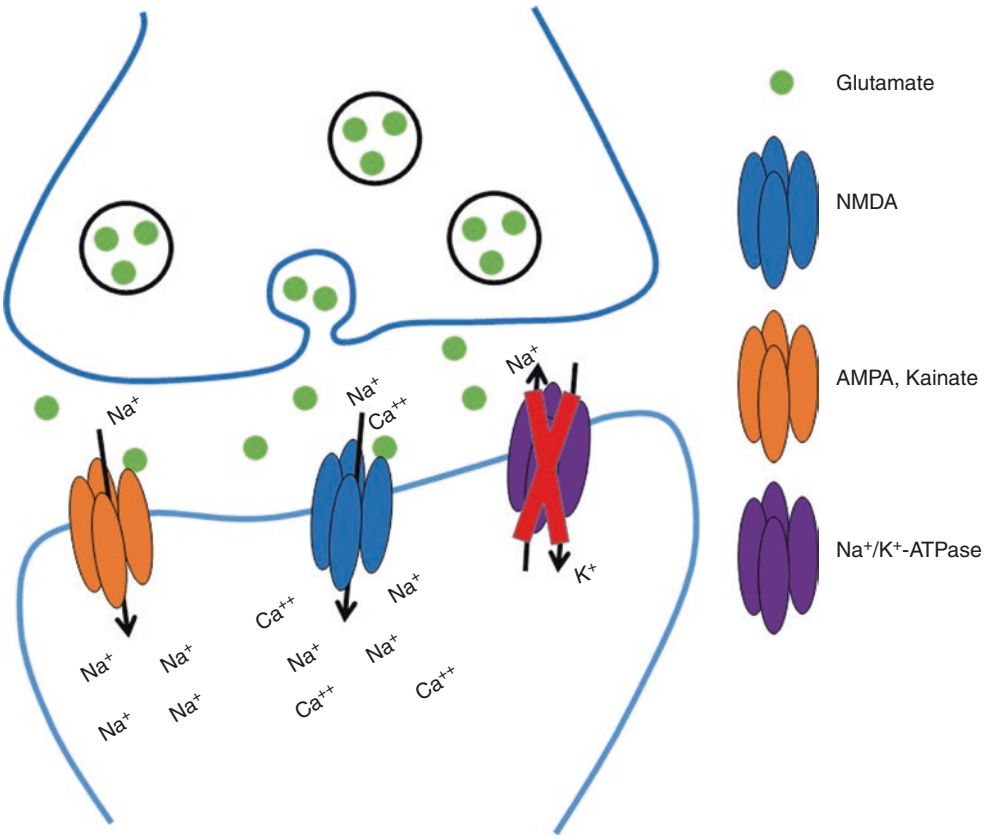

Fig. 21.2 Excitatory postsynaptic effect due to impairment of glutamate uptake, resulting in increased intracellular Na^+ and Ca^{++}, associated with a reduced function of the Na^+/K^+-ATPase and cellular damage

infants, but appears to increase in the first 24–48 h and is correlated with a poor prognosis of neurodevelopment at 1 and 4 years after the insult [24].

During the reperfusion period, enzymes such as cyclooxygenase, xanthine oxidase, and lipoxygenase increase the production of free radicals, resulting in damage to the brain of the newborn, damages that are amplified by the immaturity of his antioxidant defenses.

The increase of free radicals can lead to lipid peroxidation as well as to damage of DNA and proteins and can trigger apoptosis. Finally, free radicals can combine with nitric oxide (NO) which production has an early and transient increase. NO concentration observed in the initial phase of hypoxia is due to the activation of NMDA receptors and neuronal nitric oxide synthases (NOS). The excessive production of NO plays an important role in the pathophysiology of ischemic perinatal hypoxic hypoxia [25]. Its neurotoxicity depends in large part on the rapid reaction with superoxide to form peroxynitrite which is the cause of lipid peroxidation, nitration and protein oxidation, mitochondrial damage, and DNA damage [25] (Fig. 21.3).

In addition, the existence of a third phase where deleterious factors may cause further damage and potentiate neuronal injury worsening neonatal outcomes has been recently proposed. This third phase is thought to include mechanisms of inflammation and epigenetic changes that lead to an impairment or alteration of axonal growth, neurogenesis, and synaptogenesis [26].

21.4 Clinical Signs associated with Neonatal Hypoxic-Ischemic Encephalopathy

The clinical symptoms of HIE start early, at birth, or in the first hours of life. The newborn with HIE may show an abnormal state of consciousness (irritability, lethargy, stupor, coma), reduction in spontaneous movements, difficulties in breathing or nutrition, reduced tone, abnormal posture, lack of primitive reflexes, or seizures. HIE is the major underlying cause of seizures in term infants, with a large variety of clinical presentations from subtle, clonic, tonic, and myoclonic, potentially ranging from focal, multifocal, or generalized. Status epilepticus is common as well as an involvement of other organs (liver, kidney, heart).

In the delivery room, the Apgar score is generally low and crying is weak or absent. The severity of neonatal encephalopathy can be classified as mild, moderate, or severe, depending on the clinical symptoms and on the Sarnat three-stage grading system, as follows [16, 17, 27, 28]:

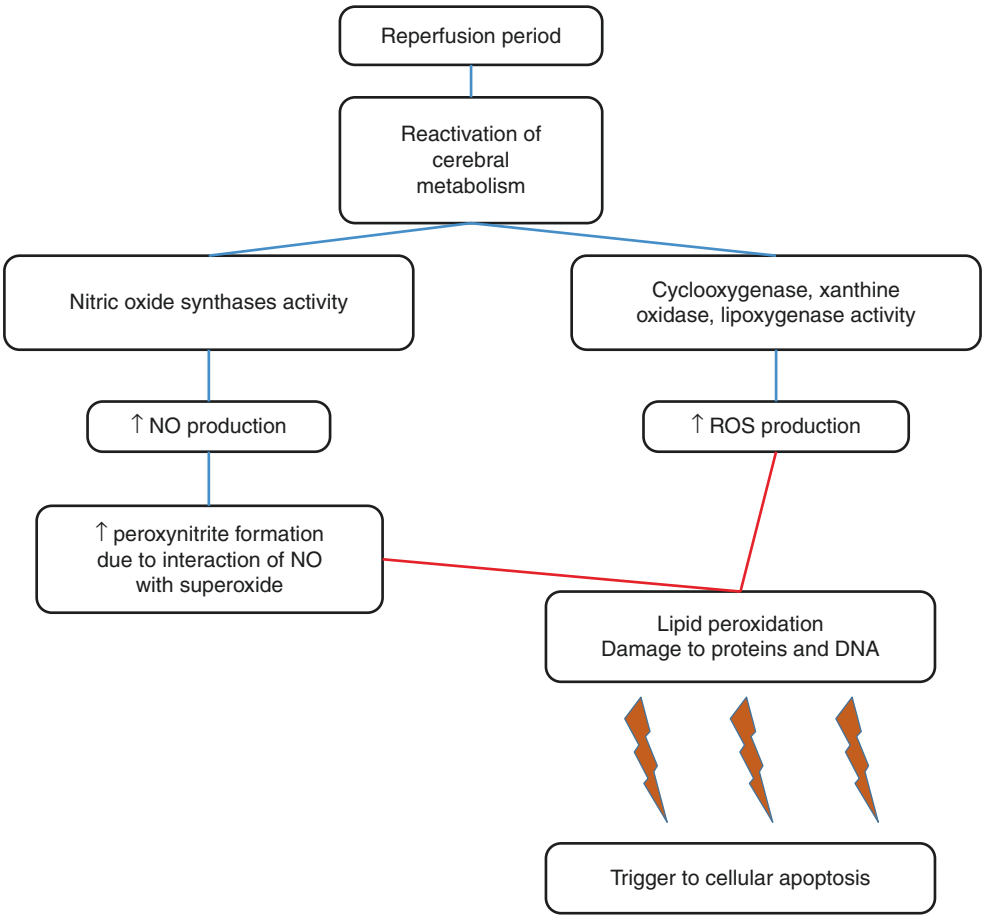

Fig. 21.3 Delayed phase neuronal damage after reperfusion period and restart of cerebral metabolism. The oxidative stress is not adequately opposed by an immature antioxidant system of the fetal brain. *ROS* reactive oxygen species, *NO* nitric oxide

(a) *Mild encephalopathy*: it is characterized by irritability, increased muscle tone, and accentuation of deep tendon reflexes during the first days of life. They may also present transitional behavioral abnormalities, such as poor nutrition, excessive weeping, or absence of sleep. These symptoms usually resolve within 24–48 hours after birth.

(b) *Moderate encephalopathy*: it is associated with lethargy, significant hypotonia, and reduced deep tendon reflexes. The reflexes such as Moro and suction can be reduced or absent. There may be occasional periods of apnea and seizures within the first 24 hours after birth.

The recovery may occur within 1 to 2 weeks after birth.

(c) S*evere hypoxic-ischemic encephalopathy*: seizures are usually generalized with onset in the 24–48 hours after birth, correlating with the reperfusion phase. Generalized hypotonia is associated with depressed tendon reflexes and absent neonatal reflexes (suction, swallowing, grasping, Moro). A state of stupor or coma is typically present, so the child does not respond to the external stimuli except to the most harmful. Examination of the cranial nerves may reveal abnormalities such as altered eye motion (distorted deviation of the eyes, nystagmus, and loss of doll's eye movement, pupils may be dilated, fixed, or poorly reactive to light). In case of recurrent apnea, the infant often requires ventilatory support.

21.5 Diagnosis of Neonatal Encephalopathy

The American College of Obstetricians and Gynecologists (ACOG) recommends a comprehensive evaluation in all cases of neonatal encephalopathy [1]. This evaluation should include an assessment of neonatal clinical status and consideration of all factors potentially contributing to neonatal encephalopathy, including a thorough maternal and family history, focusing on thromboembolic disorders, maternal infection, maternal drug use, obstetric antecedents, and intrapartum factors (including fetal heart rate monitoring results and issues related to delivery).

Blood samples should be used to determine umbilical artery cord pH and base deficit. The presence of oliguria, cardiomyopathy, or abnormal liver function tests may suggest a global hypoxic-ischemic event. In addition, a gross

and histologic examination of the placenta and umbilical cord may provide evidence of a possible cause, such as a placental vascular lesion or infection, or an umbilical cord thrombosis [24]. The presence of neonatal dysmorphic features and congenital anomalies may suggest the presence of an inborn error of metabolism or genetic disorder.

21.5.1 Neuroimaging in the Workup for Neonatal Encephalopathy

Neuroimaging is a useful tool to provide information regarding the type and timing of brain injury, since there are certain distributional patterns of brain injury seen in term and late preterm infants that are considered to be typical of hypoxic-ischemic brain injury [29–31].

The findings on CT and MRI of the brain may provide clues regarding the time during which the injury occurred [32, 33].

Other modalities of neuroimaging have been used to evaluate brains of infants with neonatal encephalopathy, including cranial sonography, and MRI with magnetic resonance spectroscopy.

Among these techniques, MRI yielded the most useful information.

21.5.1.1 Neonatal MRI

Neonatal MRI is rapidly becoming a standard of care at tertiary care centers in the United States and some other developed countries. It is the most sensitive imaging tool for detecting cortical and white matter injury, deep gray matter lesions, arterial infarction, hemorrhage, developmental brain malformations, and other underlying causes of neonatal encephalopathy [29, 30, 34–37].

Injury to the deep gray nuclei (especially the lateral thalami and posterior putamina) [16, 34, 38, 39] corresponds to brain damage seen in animal models of acute total asphyxia [40] and has been found in 74 % of term neonates with hypoxic encephalopathy associated with a sentinel event [41].

Deep gray matter lesions involving the bilateral basal ganglia and thalami are particularly common findings on brain MRI in encephalopathic term infants with a recognized preceding sentinel hypoxic-ischemic event such as placental abruption, uterine rupture, or umbilical cord prolapse [41]. Brainstem injury may also be common in these circumstances [2, 42].

Parasagittal injury of the cerebral cortex and subcortical white matter in the arterial watershed distribution may occur in the setting of mild hypoxia or ischemia of prolonged or chronic duration.

Conventional MRI may be of limited value in the early phases, so the use of advanced techniques, such as magnetic resonance spectroscopy or diffusion-weighted imaging, has been utilized to detect early injury [37, 43].

Magnetic resonance spectroscopy allows in vivo quantitative analysis of brain metabolites and therefore may serve as an early biomarker for brain injury. Indeed, an elevated ratio of lactate to N-acetyl aspartate in the basal ganglia can predict long-term neurologic impairments and can be seen in the first 48 h of life [37].

Diffusion-weighted imaging measures the self-diffusion of water molecules detected as an apparent diffusion coefficient (ADC). Thus, the ADC decreases with acute injury and is reflective of reduced water diffusion in the tissue. However, during the first hours after the injury, this technique may underestimate the final extent of the injury [37].

Studies of adult arterial infarcts have shown that diffusion-weighted imaging signal changes occur within minutes from symptom onset and hours before changes become apparent on T1- or T2-weighted images. This earlier detection of injury may facilitate intervention prior to irreversible injury [43].

Alternatively, a brain imaging study may reveal a developmental malformation, focal arterial infarction, or intraparenchymal hemorrhage, indicating a different underlying pathogenesis for the neonatal encephalopathy, venous infarction, isolated intraparenchymal or intraventricular hemorrhage, and porencephaly.

21.5.1.2 Cranial Sonography

Cranial sonography ultrasound has the advantage of being noninvasive, easily repeatable and less expensive. It has a high sensitivity and specificity (91 % and 81 %, respectively) for detecting hemorrhages and ventricular size [44, 45]. It may also detect severe parasagittal white matter damage and obvious cystic lesions, but it does not adequately describe the outer limits of the cerebral cortex [46] as well as milder white matter abnormalities [47].

Cranial sonography can be used to detect severe cerebral edema, appearing as diffuse increased echogenicity that causes sulci and fissures to be obscured, blurring of other anatomical landmarks, decreased arterial pulsations, and compression of the cerebral ventricles [48, 49].

Although in early neonatal period, areas of increased echogenicity correspond to regions of necrosis, it is not always possible to establish an exact correlation between these images and infarction or hemorrhage in the term neonatal brain [50]. However, Doppler sonography, when used for assessment of neonatal hypoxia, may identify a decrease in refractive indexes in arteries due to a relative increase in diastolic flow velocities. A number of other limitations of sonography for the diagnosis of hypoxic-ischemic injury in the term neonate have been identified. These include a substantial percentage of false negative, a low sensitivity for detecting cortical lesions, and dependence on the skill of the operator performing the test [37].

21.5.1.3 Neonatal Brain Computed Tomography (CT)

Computed tomography is more sensitive than cranial sonography for diagnosing intracranial hemorrhage [30] but is also a valuable diagnostic tool in identification of cerebral edema, cerebral atrophy, abnormal ventricular size, and severe white matter lesions [51–54]. Since the white matter in a term newborn brain has a high water content, CT is less sensitive in the identification of milder degree edema and white matter injury.

Radiation exposure is a limiting factor in its use in small infants [30], although CT is more feasible than MRI for children who are acutely ill or medically unstable.

21.5.2 Electroencephalography (EEG)

EEG is a tool to evaluate the severity of brain damage in neonates with HIE. This technique supplies information on the functional aspects of the central nervous system.

An EEG can help to distinguish neonatal seizures from other phenomena and can also identify subclinical seizures. Due to difficulties in the provision of expert interpretation of conventional multichannel EEG in the neonatal intensive care units, amplitude-integrated EEG is more commonly used.

Amplitude-integrated EEG using a continuous, single- or dual-channel recording of background cerebral electrical activity is easy to use and interpret at the bedside and has been used to distinguish mild from severe neonatal encephalopathy in large clinical trials [55, 56].

An abnormal EEG is one of the necessary criteria to enroll infants with HIE in brain cooling treatment [57].

21.6 Definition of Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE, also called birth asphyxia) is a subset of neonatal encephalopathy, but determining whether an acute hypoxic-ischemic event contributed to neonatal encephalopathy is challenging, since there is no gold standard test for diagnosis. In order to consider a HIE as a possible cause of an acute perinatal asphyxial damage, the following symptoms and signs have been suggested by the American College of Obstetricians and Gynecologists (ACOG) and the American Pediatric Association (APA) [1]: pH <7, metabolic acidosis, Apgar score 0–3 for over 5-min period, neonatal neurological sequelae (convulsions, coma, hypotonia), and multisystem involvement.

A pH of the cord artery >7.2 is hardly associated with HIE, although the arterial blood gas of the cord alone is not sufficiently accurate in predicting long-term neurological sequelae [58, 59].

A pH <7.0 is the threshold for a clinically significant acidemia [60]. The incidence of adverse neurological outcomes is described as 0.36 % with a neonatal pH <7.1 and 3 % with a pH <7.0 [59], although many acidemic infants will be neurologically normal [61].

A base deficit ≥12 mmol/L increases the possibility that a neonatal encephalopathy is caused by HIE. In fact, the encephalopathy develops in 10 % of infants in which the base deficit of the umbilical artery is between 12 and 16 mmol/L, and 40 % of those whose deficit is >16 mmol/L [62].

In addition, lactate concentration in the umbilical cord may have a higher value compared to base deficit for the prognosis of neurological disorders [63].

A low (<5) Apgar score at 5 and 10 min is associated with increased risk of neurological damage, and this risk is higher if the Apgar scores at 5 min are 3 or less [58].

The persistence of an extremely low (0–3) Apgar score over 5 min after birth strongly correlates with increased risk of neurologic morbidity and death [64, 65].

Finally, an Apgar score of 0 at 10 min is correlated to a high mortality rate or serious long-term disability [66].

21.7 Treatment of Neonatal Encephalopathy

Therapeutic hypothermia is considered the standard of care for neonates with HIE.

This treatment employs mild hypothermia in the range of 33.5–35.0 °C, maintained for 72 hours and started within the first 6 hours after delivery, as the only effective neuroprotective therapy currently available for treatment of neonatal encephalopathy for term or late preterm infants.

Potential mechanisms of neuroprotection with hypothermia include (a) inhibition of glutamate release, (b) reduction of cerebral metabolism which in turn preserves high energy phosphates, (c) decrease in intracellular acidosis and lactic acid accumulation, (d) preservation of endogenous antioxidants, (e) reduction of nitric oxide production, (f) prevention of protein kinase inhibition, (g) improvement of protein synthesis, (h) reduction of leukotriene production, (i) prevention of blood-brain barrier disruption and brain edema, and (j) inhibition of apoptosis. Therapeutic hypothermia can reduce also seizures and epileptiform activity burden in term newborns with moderate HIE [67, 68].

Treatment with hypothermia improves survival and outcome at 18 months after neonatal asphyxia and/or neonatal encephalopathy. This conclusion is supported by a meta-analysis of seven randomized controlled trials of therapeutic

hypothermia involving 1,214 newborns with moderate to severe neonatal encephalopathy [69].

It should be associated with a supportive management of moderate and severe neonatal encephalopathy which should take place in a neonatal intensive care unit. Major goals include the maintenance of physiologic homeostasis and treatment of the manifestations of brain injury [2, 70]. Central aspects of supportive care include (1) maintenance of adequate ventilation (avoidance of hypoxemia or hyperoxia), (2) maintenance of sufficient brain and organ perfusion (avoidance of systemic hypotension or hypertension, avoidance of hyperviscosity), (3) maintenance of normal metabolic status (normoglycemia, nutritional status, pH), (4) control of seizures, and (5) brain edema, avoiding fluid overload.

Therapeutic hypothermia is easy to administer and appears to be safe. Although direct comparisons are lacking, selective head cooling and whole body cooling appear to have similar safety and effectiveness. Whole body cooling is preferred in most centers in the United States due to ease of administration. Whole body cooling also provides easier access to the scalp for electroencephalogram (EEG) monitoring.

In general, eligibility criteria include the following [71]:

(a) Gestational age ≥35 weeks and ≤6 hours of age
(b) One of the following:
    - A 10-min Apgar score of <5
    - Ongoing resuscitation (assisted ventilation, chest compressions, or cardiac medications) initiated at birth and continued for at least 10 min
    - pH of ≤7.0 or a base deficit of ≥16 mmol/L in a sample of umbilical cord blood or any blood obtained within the first hour after birth
(c) Moderate to severe encephalopathy on clinical examination (indicated by lethargy, stupor, or coma) and either hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), an absent or weak suction, or clinical seizures
(d) Abnormal background activity of at least 30-min duration or seizures on EEG or amplitude-integrated EEG

When therapeutic hypothermia is not used, a close monitoring of body temperature is suggested, and it is reasonable to avoid hyperthermia given currently available data. There is a consensus among experts that therapeutic hypothermia should be more widely available, based upon its benefit and safety and the lack of other effective treatments [72–74]. Thus, hypothermia has become the standard of care in most neonatal intensive care units in the United States, Europe, Australia, and Japan, and national guidelines support the use of therapeutic hypothermia for infants who meet the criteria used in the published trials [75–77].

21.8 Long-Term Outcomes of Affected Neonates and Follow-Up Strategies

Regardless of interventions, long-term complications and their degree depend, in affected neonates, on the degree of the injury, which is initially difficult to predict [78].

In previously studied children with HIE, those who were not cooled had the largest deficits in speech and hearing, which clearly amper all other aspects of learning [79]. In addition, subtle disabilities, not measurable at younger ages, will sometimes declare themselves at or near the school age [79].

Evaluations of infants with moderate HIE who were not cooled showed lower ability in language domains, narrative memory, and sentence repetition in the absence of overt sensorimotor impairment [80].

Of interest, advanced imaging provides information to correlate the location and extent of brain injuries to potential outcomes [81]. Indeed, infants with certain types of injuries (watershed pattern), which would be discernible on MRI, are often normal at 12–18-month neurodevelopmental evaluations but exhibit suboptimal head growth, behavioral problems, and abnormal with language acquisition [80].

The influence of the interventional therapy currently available (therapeutic hypothermia) on children's long-term outcome is supported by a paucity of data [82]. Later evaluations would include fine motor development, executive function and attention deficits and/or ability, as well as psychological outcomes [82].

Care providers should strive to identify infants at risk to maximize their potential for independent function [81]. Moderately affected children may have conditions resulting in delayed school entry and requiring additional educational support. Delays may include increased hyperactivity, visual-motor or visual-perceptive dysfunction, and memory impairment. Children with severe HIE have a greater risk of cerebral palsy and mental retardation [81].

The importance of environmental, socioeconomic conditions, access to follow-up, and interventional therapy on neurodevelopmental outcomes is crucial and needs to be taken into account [81]. Lastly, follow-up affords the clinician to reassure those parents of children with favorable outcomes that they are progressing normally and that special interventions are not indicated [79].

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Puerperal Complications

22

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22.1 Postpartum Complications

Postpartum (or puerperium) begins immediately after the delivery of the placenta and lasts 6–8 weeks, when maternal body usually returns to its prepregnancy state.

During this period several issues may arise: early complications usually develops in the first few days after delivery, while late complications can manifest after discharge, even weeks postpartum.

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22.2 Readmission

A review of a database including over 200,000 postpartum women observed from delivery until 180 postpartum days found that 1.2 % were readmitted within 6 weeks (0.83 % after vaginal delivery and 1.8 % after cesarean delivery) [1]. The most common reasons for readmission were hypertension, uterine, and wound complications like infection and hemorrhage, urinary tract infection, and mastitis.

22.3 Postpartum Hemorrhage

Postpartum hemorrhage (PPH) was usually defined as a maternal blood loss ≥500 mL after vaginal birth or ≥1,000 mL after cesarean delivery (Fig. 22.1); lately, after several studies showed the inadequacy of this definition, the Royal College of Obstetricians and Gynaecologists (RCOG) defined PPH as minor (blood loss between 500 and 1,000 mLs) or major (>1,000 mLs), with further subdivisions of major hemorrhage into moderate (1,000–2,000 mL) or severe (>2,000 mL) [2].

PPH can also be classified as primary or secondary: primary (or early) PPH occurs in the first 24 h after the delivery, while secondary (or delayed) PPH occurs between 24 h and 12 weeks after the delivery. Common causes of primary PPH are uterine atony, spontaneous or iatrogenic uterine lesions, cervical or vaginal lacerations, and coagulopathies.

Causes of secondary PPH are usually infections, retained products of conception (Fig. 22.2), and rarely a choriocarcinoma or a uterine vascular anomaly like pseudoaneurysms of a uterine artery or arteriovenous malformations.

Secondary PPH has its peak incidence 1–2 weeks postpartum and affects 0.2–2 % of women [3]. A personal history of PPH is a risk factor for developing primary or secondary PPH after a following pregnancy [4].

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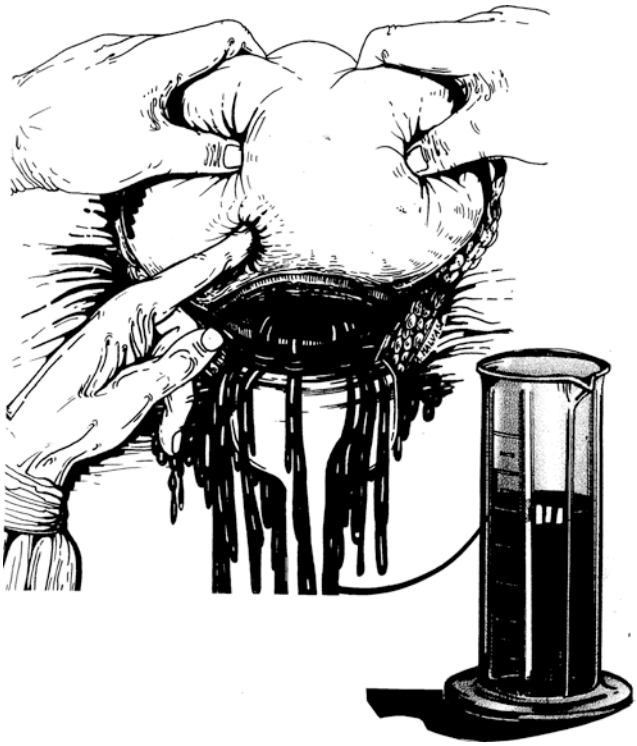

Fig. 22.1 Uterine atony during cesarean section: postpartum hemorrhage (PPH) was usually defined as a maternal blood loss ≥500 mL after vaginal birth or ≥1,000 mL after delivery

A reasonable diagnostic approach to a patient with secondary PPH must include:

- Basic laboratory screening for bleeding diathesis, with blood and platelet count, prothrombin time, and activated partial thromboplastin time (these tests can be normal even in women with bleeding diathesis, such as Von Willebrand disease). Also, we suggest to perform a quantitative pregnancy test, in order to exclude choriocarcinoma, retained products of conception, or a new pregnancy.
- Ultrasound examination: it's mandatory, because it can directly detect the cause of bleeding or exclude some potential bleeding sources in the differential diagnosis (Fig. 22.3). In fact the uterus may look empty or can contain gas, liquids, or echogenic material. Positivity of this material on color Doppler suggests retained products of conceptions, while lack of Doppler findings is related to blood clots, but cannot exclude the presence of necrotic placental tissue.

Ultrasonographic evidences of intrauterine accumulations of clots and fluids are common findings in an involving uterus, so ultrasound may not be exhausting in order to understand if surgical or medical is indicated [5, 6]. Moreover, there are no randomized controlled trials regarding the optimal management of a secondary PPH [7].

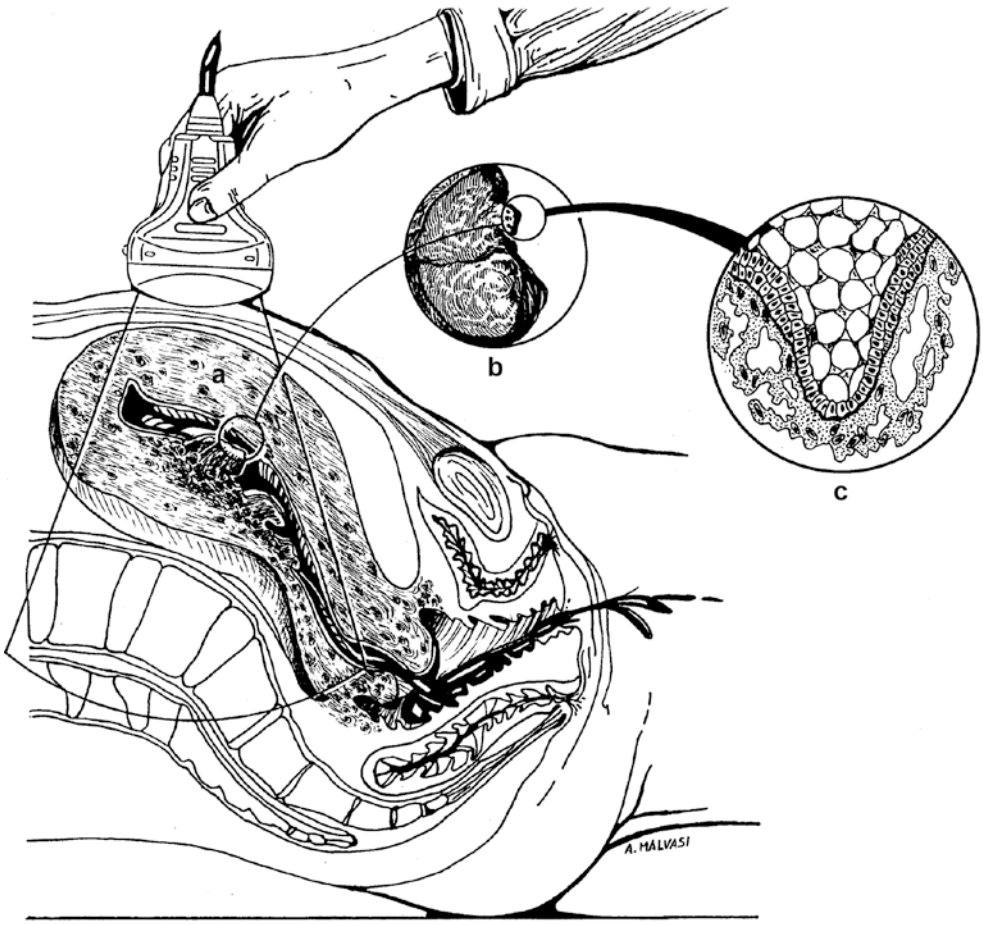

Fig. 22.2 Among the secondary causes of postpartum hemorrhage is the retention of the uterine cotyledon uterus after afterbirth: (**a**) placental residues, (**b**) fragment of cotyledon removed, and (**c**) chorionic villi, which confirm the diagnosis. Modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012

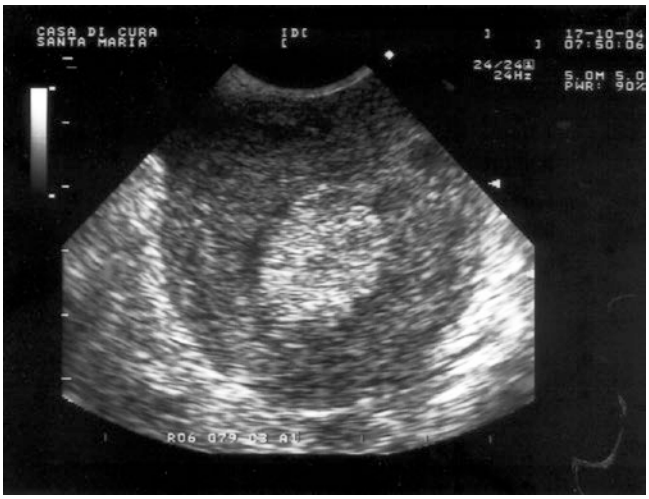

Fig. 22.3 Transvaginal ultrasonographic scan showing placental residues

Endometritis should always be suspected if bleeding is not excessive, and uterine tenderness, fever, and/or malodorous discharge are present. These patients should be treated with broad-spectrum antibiotic therapy, even to prevent potentially lethal causes like *Clostridium* infections and streptococcal or staphylococcal toxic shock syndrome [8, 9]. If uterine atony is suspected, uterotonic agents should be administered, like oxytocin or methylergonovine (oxytocin can be prescribed in breastfeeding mothers). Women with bleeding diathesis should be treated as appropriate for the underlying disorder, and hematologic consultation should be offered. Surgical procedures (like dilatation and curettage) are often effective in case of unsuccessful medical therapy and can be the first choices when retained products of conception must be evacuated from uterine cavity. Curettage should be performed under sonographic guidance, in order to minimize the rate of uterine perforation and to confirm the complete evacuation of retained products of conception [10].

22.4 Uterine Inversion

Uterine inversion or prolapse is a rare puerperal complication and an obstetrical emergency which can lead to severe hemorrhage and shock. It occurs when the uterine fundus collapses into the cavity, turning the organ partially or entirely inside out, and is a complication of both cesarean and vaginal delivery. The classification of uterine inversion is based on the extension [11]: it can be divided into 4° (Figs. 22.4 and 22.5):

- First degree or incomplete inversion: the uterine fundus is within the endometrial cavity.
- Second degree or complete: the fundus protrudes through the cervical os.
- Third degree or uterine prolapse: the fundus protrudes beyond the introitus.
- Fourth degree or total uterine and vaginal: both the uterus and vagina are turned inside out.

Moreover, we can also divide the types of uterine inversion by the time of occurrence: acute (within 24 h of delivery), subacute (between 24 h and 4 weeks postpartum), and chronic (1 month or more postpartum) [12].

The incidence is between 1 in 1,200 and 57,000 deliveries; risk factors are fetal macrosomia, retained placenta, short umbilical cord, fast labor and delivery, use of uterine relaxants, leiomyomas, and other uterine anomalies.

Uterine inversion is also supposed to be related to incorrect obstetric maneuvers during of third stage of labor, in particular an excessive fundal pressure (Kristeller maneuver) and excessive cord traction [13]; this relationship has never been proved [14], and the pathogenesis of uterine inversion is not yet completely understood.

Presentation of uterine inversion varies by the extension of the pathology: the most common is the complete variant, with the fundus absent on transabdominal palpation, but present on transvaginal examination (Fig. 22.6), lower

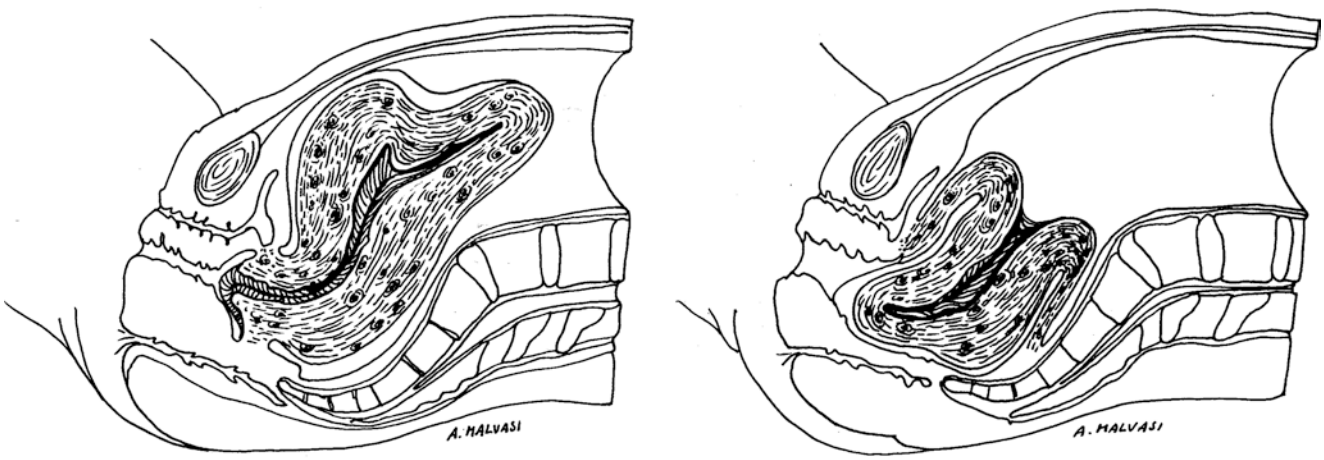

Fig. 22.4 On the left, a first degree or incomplete inversion; on the right, second degree or complete uterine inversion

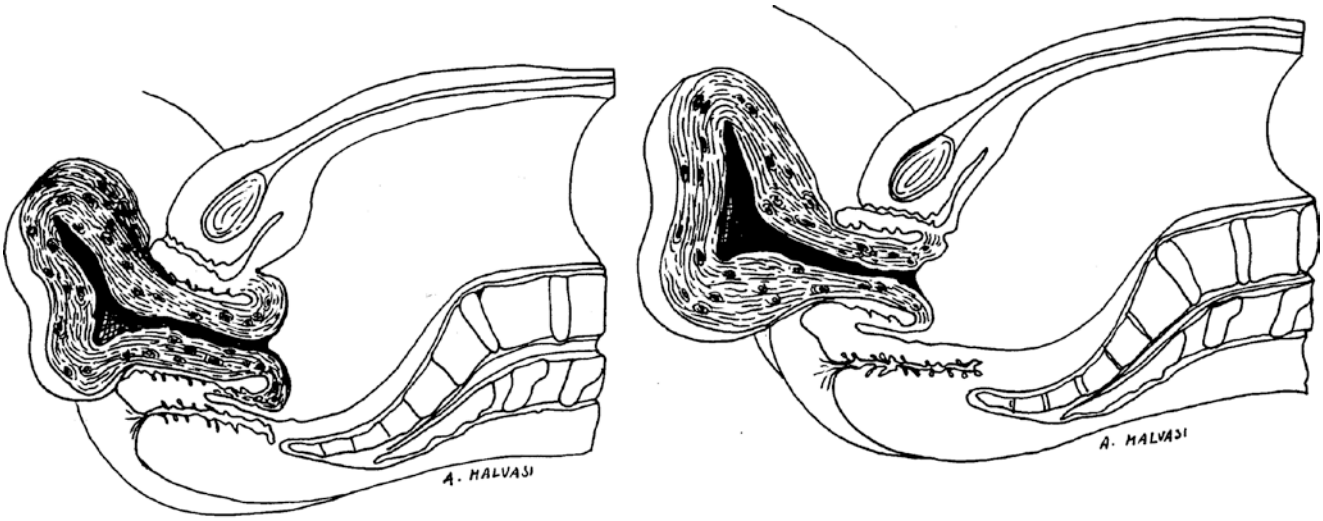

Fig. 22.5 On the left, third degree or uterine prolapse; on the right, fourth degree or total uterine and vaginal prolapse

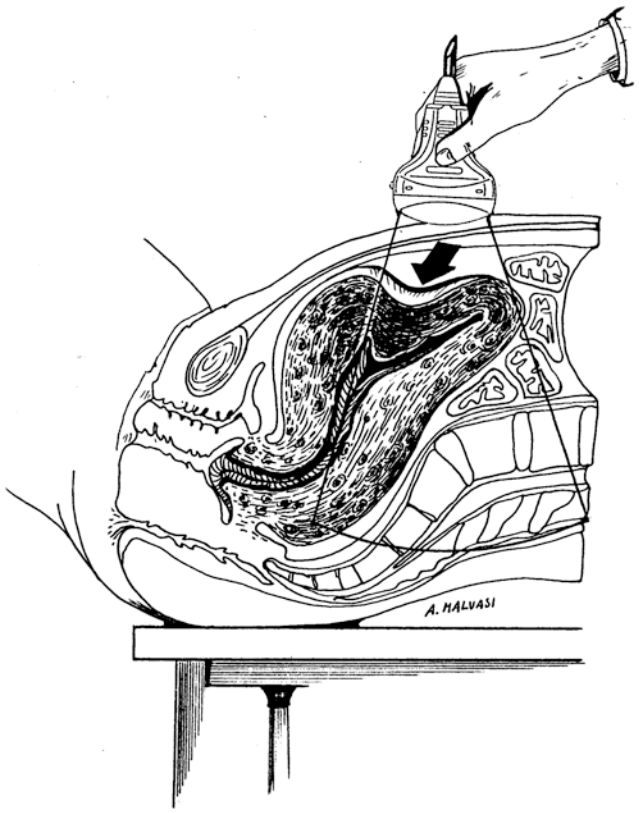

Fig. 22.6 Initial uterine inversion detected by transabdominal ultrasound

abdominal pain, and severe hemorrhage often leading to hypovolemic shock.

An incomplete inversion occurs in 10 % of cases, and its presentation is more devious than the complete one: blood loss can be minimal, and just a little fundus defect can be noticed on transabdominal palpation.

When not promptly recognized, uterine inversion usually requires a surgical intervention.

The diagnosis is usually based upon the clinical findings listed above, and radiographic imaging is usually used to confirm the diagnosis when the patient is stable, but because uterine inversion is an obstetrical emergency, radiologic exams are not mandatory.

The management of uterine inversion consists in replacing the uterus in its correct position and correct postpartum hemorrhage and shock (if present) and prevents recurrency. These objectives can be achieved using the following passages:

- Discontinue uterotonic drugs.
- Call for assistance.
- Establish intravenous access and fluid resuscitation.
- The placenta must not be removed, because its removal before the correction of the uterine inversion is related to a more severe blood loss [15, 16]. Removal of placenta must be attempted only after the uterus has been replaced and after its spontaneous detachment. Alternatively, manual removal should be attempted in the operating room, with a hemodynamically stable patient under anesthesia. If the detachment of placenta doesn't happen, a placenta accreta must be suspected.
- Immediately attempt to manually replace the inverted uterus by placing a hand in the vagina and pushing the fundus along the vaginal axis toward the umbilicus (Johnson maneuver). Prompt replacement is critical since the lower uterine segment and the cervix will contract, making this maneuver more difficult as time passes by.
- When uterine replacement is unsuccessful, an alternative option can be to give uterine relaxants, like nitroglycerin, terbutaline, or magnesium sulfate, and then reattempt to replace manually the uterus.

In case of failing of the above procedure, the patient should be promptly taken to the operating room, and a surgical correction of the inversion must be attempted, using Huntington procedure (simultaneous gentle traction with

two Allis or Babcock clamps of the two round ligaments, which are usually involved into the inversion) or the Haultain procedure (incision of the posterior uterine surface and manual reduction with Huntington procedure).

Uterine atony is a common complication after repositioning of the uterus. For that reason uterotonic agents are administered to induce uterine contraction, avoid reinversion, and reduce hemorrhage.

Main uterotonic agents are oxytocin (20–40 units in 1 L of crystalloid infused at 150–200 mL per hour), misoprostol (800 μg intravaginally or rectally), dinoprostone (20 mg rectally), and methylergonovine (200 mcg intramuscularly up to four doses per day).

Also, administration of a single dose of first-generation cephalosporin (cefazolin) is recommended for endometritis prophylaxis.

22.5 Postpartum Preeclampsia and Eclampsia

Preeclampsia and eclampsia can manifest clinically in the antepartum or postpartum period. Most of these cases occur within 48 h of the delivery. Read Chap. 7 for informations about incidence, diagnosis, and management of these complications.

22.6 Postpartum Fever

Postpartum fever is defined as an oral temperature ≥38.0 °C (≥100.4 °F) on any two of the first 10 days postpartum, exclusive of the first 24 h. The first 24 h is excluded because low-grade fever during this period is common and often resolves spontaneously, especially after vaginal birth.

If fever is present, a physical examination should be performed to identify the source of infection and direct optimal therapy (Fig. 22.7). Surgical site infections may occur at sites of episiotomy, lacerations, or cesarean delivery. Typical physical examination findings include cellulitis with redness and induration at the surgical site, which may or be accompanied by tenderness or not. Purulent incisional drainage can also be present.

In case of postpartum fever, the following conditions should be investigated: urinary tract infections, wound infection (episiotomy or other surgical site infections), mastitis or breast abscess, endometritis or deep surgical

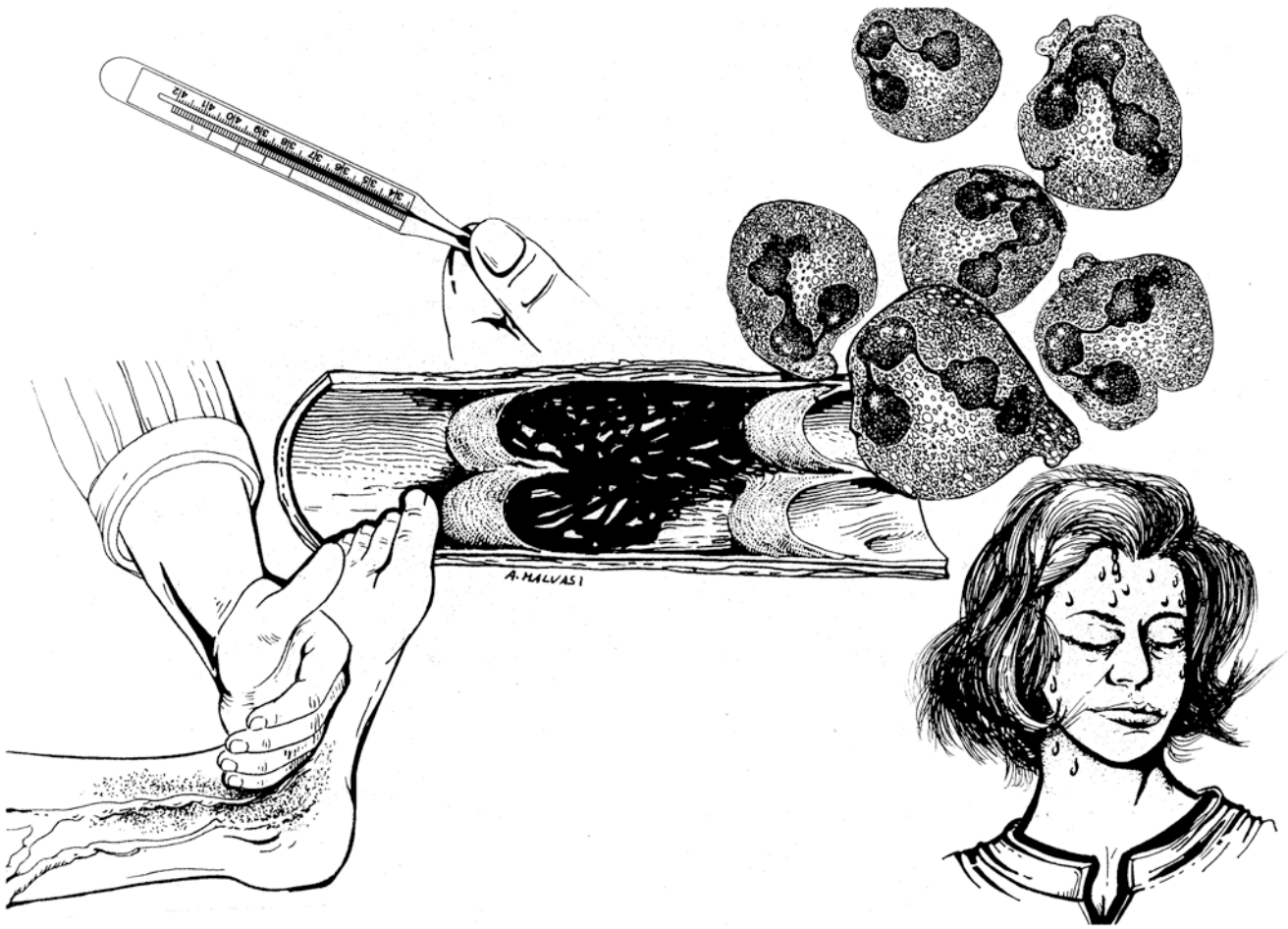

Fig. 22.7 Postpartum fever due to a thrombophlebitis

infection, septic pelvic thrombophlebitis, drug reaction, clostridium difficile-associated diarrhea, and complications related to anesthesia.

22.7 Dehiscence of Vaginal Lacerations or Episiotomies

Perineal infections, and subsequent breakdown of previously repaired lacerations or episiotomies, are a particularly onerous complication of episiotomy. The incidence is between 0.1 % and 0.2 % of all postpartum sutures [17], and common causes are all the ones who slow wounds healing, e.g., diabetes, obesity, infections, and local ischemia. Diagnosis is made when, on examination, the previously sutured area appears swollen and erythematous with a purulent exudate. Breakdown of perineal laceration repair has been associated with longer second stage of labor, operative vaginal delivery, mediolateral episiotomy, third- and fourth-degree lacerations, and presence of meconium-stained amniotic fluid. In the past, these defects used to be closed after 2 or 3 months after delivery, even if they could also lead to a perineal fistula (Fig. 22.8); nowadays early repair (within 2 weeks) seems to be more effective [18, 19, 20]. Many surgeons suggest to clean the area of necrotic tissue and sutures first than prescribe daily irrigation and antibiotic therapy if necessary; after some days, when the wound is granulating and free to exudate, it is sutured with the same technique of primary repair.

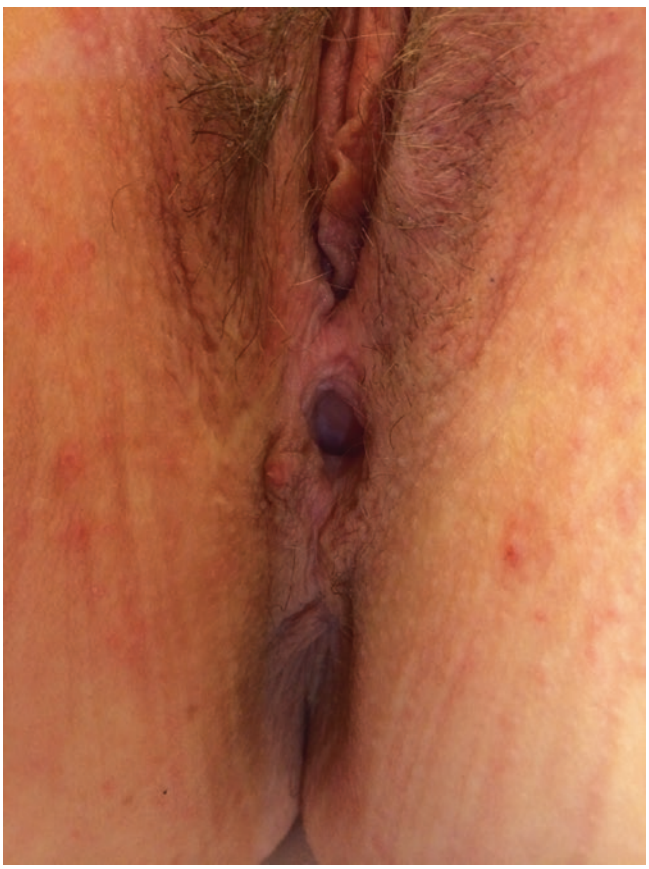

Fig. 22.8 A central perineal fistula, between the vagina and anus, after 12 months from the episiotomy dehiscence

22.8 Vulvar Edema

Vulvar edema has been associated with the use of tocolytics for preterm labor [21], prolonged second stage of labor, and preeclampsia; it is common after delivery and can usually be managed with ice packs in order to relief symptoms.

Rarely a unilateral or bilateral vulvar edema has been associated with maternal mortality [22], and usually these cases are related to obstetric procedures like forceps application, median episiotomy, and perineal injuries [23].

In these cases, especially if necrotizing fasciitis is suspected, clinician must closely monitor the patients, investigating if worsening of the edema, induration, pain, and leukocytosis (>20,000/mm2) are present; fever can be absent. A broad-spectrum empiric antibiotic therapy must be started, and a surgical debridement must be quickly executed in order to ensure correct blood perfusion of the necrotic tissue. In general, empiric treatment of necrotizing infection should consist of broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms; special consideration for group A *Streptococcus* and *Clostridium* species should be taken [24]. For these reasons, an acceptable empiric antibiotic regime should include carbapenem or beta-lactamase inhibitor, clindamycin, and vancomycin.

22.9 Surgical Wound Complications

Wound complications generally develop 4–7 days after cesarean section and are diagnosed in 2.5–16 % of patients [25]: the most common complications are infection, hematoma, and dehiscence. Therapy can vary from ice packing, antibiotic treatment to surgical debridement if necrotizing fasciitis (which is a surgical emergency that affects 0.18 % of cesarean deliveries [26]) is suspected.

Moreover, gynecologic sequelae due to deficient uterine scar healing after cesarean section (which prevalence ranges from 19.4 % to 88 %) [27] are only recently being identified and described: these conditions include infertility, cesarean scar ectopic pregnancy (Fig. 22.9), pelvic pain, and abnormal bleeding.

An abnormal uterine cesarean scar healing is often related to the development of isthmocele (Fig. 22.10), which is the result of incomplete healing of isthmic myometrium after a low transverse uterine incision performed for cesarean section (Fig. 22.11). Although mostly asymptomatic, it may

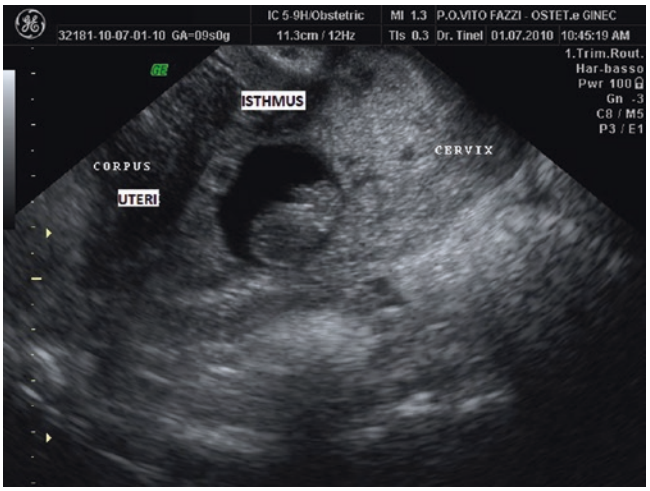

Fig. 22.9 Transvaginal ultrasonographic scan showing a cesarean scar ectopic pregnancy

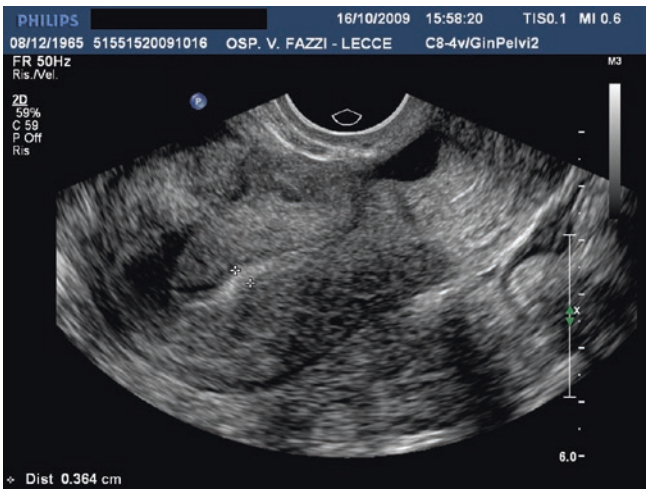

Fig. 22.10 Transvaginal ultrasonographic scan showing an isthmocele

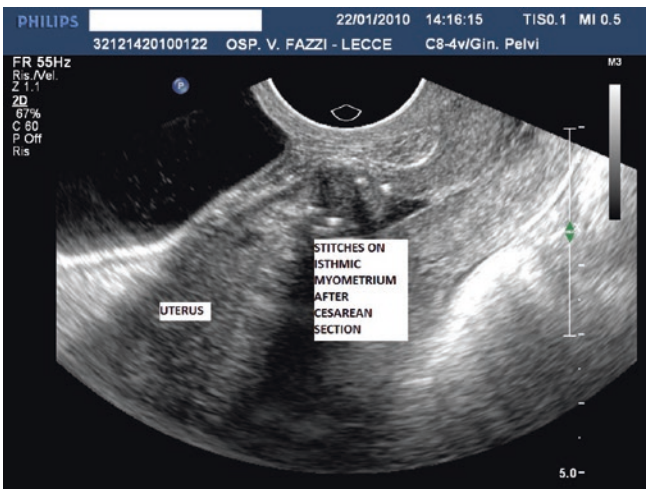

Fig. 22.11 Transvaginal ultrasonographic scan on the uterus on the 30th after a cesarean section; the images show the presence of stitches on isthmic myometrium

cause menstrual abnormalities (typically postmenstrual spotting), chronic pelvic pain, secondary infertility, and tissue necrosis.

Scar tissue dehiscence, scar pregnancy, and abnormally adherent placenta are some of the obstetric complications associated with isthmocele.

No standardized treatment has yet been accepted: currently, hysteroscopic resection and laparoscopic correction or hysterectomy are the minimally invasive approaches used to repair the defect.

22.10 Postpartum Endometritis

Postpartum endometritis (Fig. 22.12) is characterized by an oral temperature ≥38.0 °C (≥100.4 °F) between the second and tenth day postpartum [28]; in fact, during the first 24 h after delivery, low-grade fever is a common finding that often resolves spontaneously, especially after vaginal birth [29]. Other clinical findings in postpartum endometritis are uterine tenderness, midline lower abdominal pain, purulent lochia (in some women), and leukocytosis.

Retained products of conception after delivery can cause acute or chronic endometritis because microbes can infect the necrotic tissues retained inside the uterine cavity (e.g., membranes, placental fragments).

It is caused by polymicrobial infection involving various aerobes and anaerobes from the genital tract, which colonize the decidua (the pregnancy endometrium) even extending to myometrium (endomyometritis) or the parametrium (parametritis), and is a common cause of febrile morbidity after delivery.

The main risk factor for postpartum endometritis is cesarean delivery especially if performed after the onset of labor [30]: in fact, before routine antibiotic prophylaxis, the rate of infection was 28 % for cesareans performed after the onset of labor and 3.5 % for those performed electively (now is 11 % and 1.7 %, respectively) [31]. The frequency of postpartum endometritis after vaginal birth is less than 3 % [32].

Other risk factors are prolonged labor, multiple manual examinations, internal uterine fetal monitoring, chorioamnionitis, low socioeconomic status, HIV infection, postterm pregnancy, operative vaginal delivery, manual removal of placenta (Fig. 22.13), and colonization with group B *Streptococcus*, *Streptococcus agalactiae* or *Escherichia coli* [33].

In women with postpartum fever and mild uterine tenderness and no purulent loch, other causes than infections should be considered, like a surgical site infection (cesarean incision, episiotomy incision, or perineal lacerations) or a mastitis.

The value of laboratory studies is limited: leukocytosis is a common finding in postpartum period, but a rising of

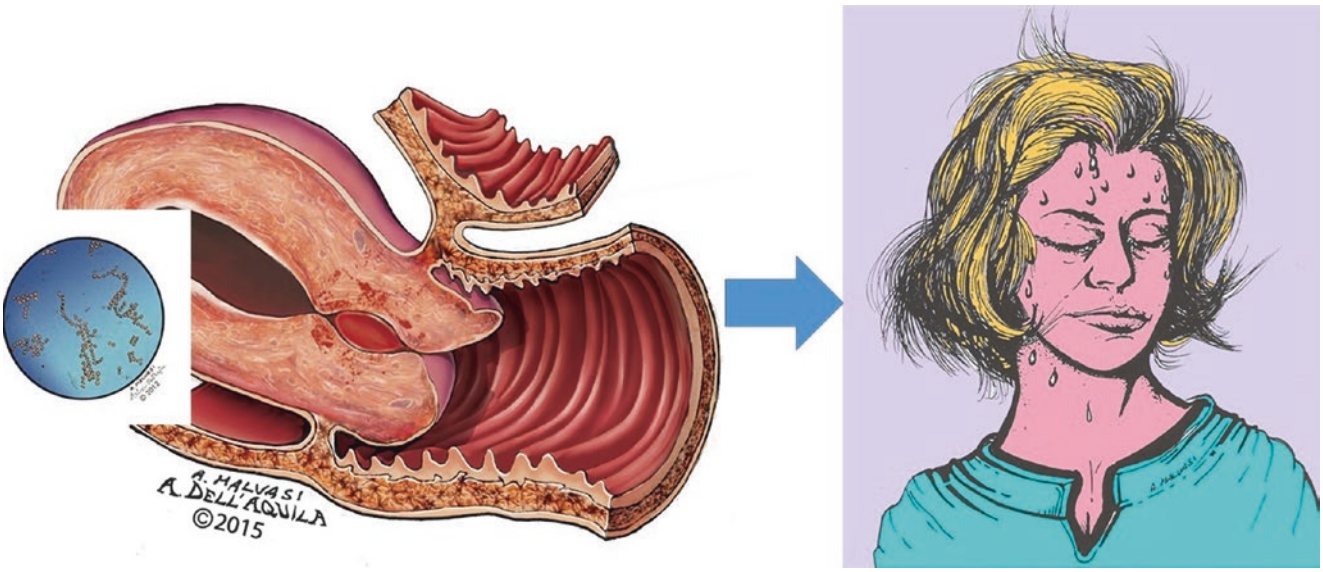

Fig. 22.12 A scheme depicting a postpartum endometritis: on the left, a uterine cavity rich of bacteria leading to a postpartum fever with patient sweating

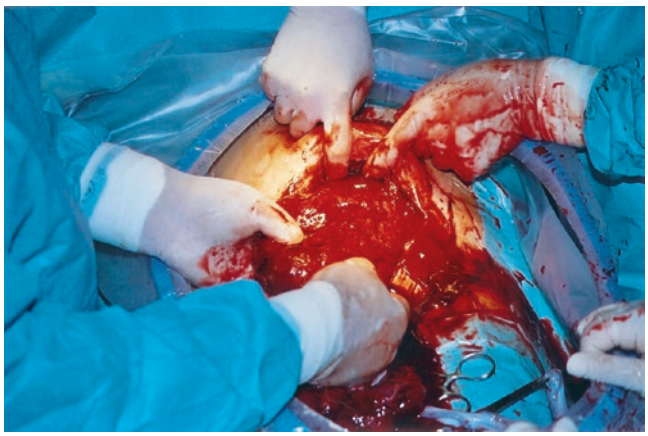

Fig. 22.13 Manual placental removal during cesarean section

neutrophil count associated with elevated numbers of bands is suggestive of infection.

Endometrial cultures are not routinely performed due to the difficulty to obtain a correct specimen through the cervix. Moreover, blood culture is not routinely performed because usually an antibiotic therapy must be started before the results are effectively available, and usually these results do not lead to a change of the initial empiric treatment [34].

The initial empiric treatment must include intravenous broad-spectrum antibiotics covering beta-lactamase-producing anaerobes: clindamycin 900 mg every 8 h plus gentamicin is a common effective option, with a cure rate between 90 % and 97 % [35]. The treatment should last until the patient is afebrile and clinically improved for at least 24 h. Alternative options reported to be equivalent include cefotetan, cefoxitin, ampicillin and sulbactam, and piperacillin.

Oral antibiotics after parenteral therapy are not indicated, unless a positive blood culture is obtained; in this case, antibiotic therapy can be prolonged orally for 7 more days [36].

Usually a good response to the therapy is obtained within the first 48–72 h.

In case of retained product of conceptions, ultrasound may detect the retained tissues, and these should be removed in order to resolve the infection with dilatation and curettage procedures [37].

As we previously reported, usually postpartum endometritis develop within the first 7 days after delivery, but 15 % of cases have a late onset between 1 and 6 weeks after delivery.

These women have mild clinical signs and can be treated with oral antibiotic therapy: in order to give protection over facultative and anaerobic bacteria, a therapy with amoxicillin-clavulanate by mouth twice a day for 7 days can be prescribed [38].

22.11 Voiding Difficulty and Urinary Retention

Postpartum urinary retention (PUR) presenting in the puerperium has been explained with several definitions and widely reported rates.

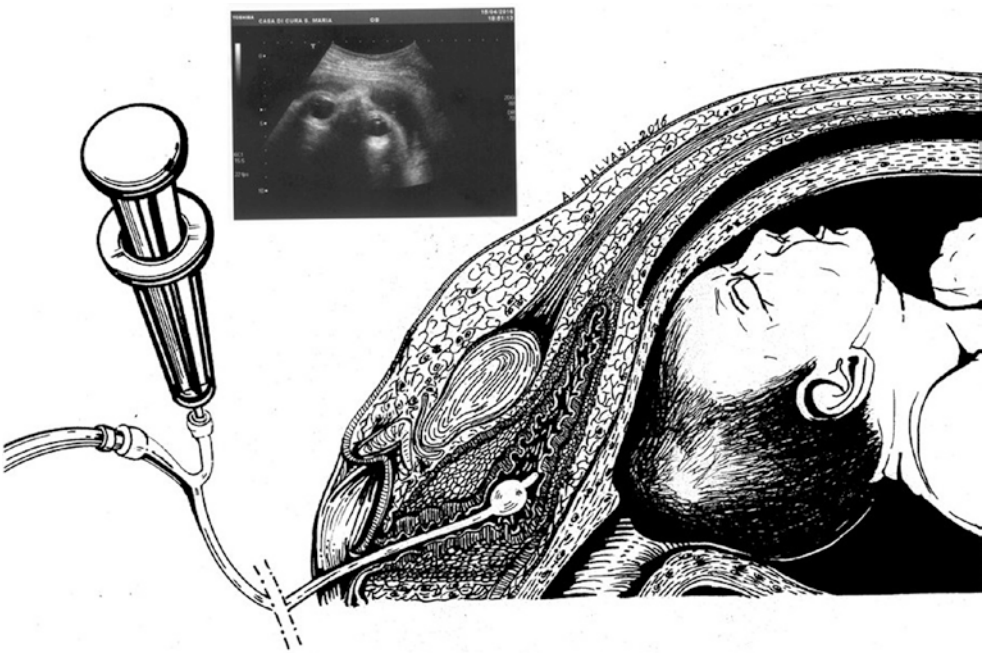

Fig. 22.14 A prolonged second stage of labor for a persistent occiput posterior position; on the top, the ultrasonographic image showing the fetal eyes under pubis; in the image below, the bladder catheterization to difficulty emptying the bladder

Actually two variants of PUR are considered: overt PUR as the absence of spontaneous micturition after 6 h from vaginal delivery and covert PUR as a post-void residual bladder volume of at least 150 mL after spontaneous micturition, after ultrasonographic diagnosis of bladder distension or catheterization [39]. Its incidence seems to be related to prolonged second stage of labor [40] (Fig. 22.14) and pudendal nerve injury after delivery [41], as well as epidural anesthesia, operative delivery, episiotomy, and primiparity.

Usually more than 90 % of PUR resolve spontaneously in 1 week.

Patients may be asymptomatic or refer voiding difficulty with small and frequent amounts of urine, slow or intermittent streams, bladder pain, urinary incontinence, and send of incomplete voiding [42].

Treatment of overt PUR is intermittent catheterization; routine antibiotic therapy is unnecessary, and treatment of overt PUR is intermittent catheterization, every 4–6 h or when the patient has void urgency.

In clinical practice, when the residual urine volume is <150 mL and the patient no longer has significant symptoms of voiding difficulty bladder catheters should be discontinued.

22.12 Hemorrhoids

Hemorrhoids are normal vascular structures in the anal canal (Fig. 22.15) that often produce variety of problems like anal pruritus, prolapse, bleeding, and pain due to thrombosis. Their incidence is higher after delivery than in the late pregnancy and postpartum period: in fact, of those women 91 % referred hemorrhoid complications in the first day after delivery, 30 % at 8 weeks postpartum, and 13–25 % in the first 6 months [43]. Moreover, it has been estimated that 35 % of pregnant women experienced anal lesions after delivery, 20 % external hemorrhoids, 15 % anal fissures, and 7.8 % thrombosed external hemorrhoids during late pregnancy [44]. Risk factors seem to be fetal macrosomia, prolonged second stage of labor, and operative and/or traumatic delivery.

Symptomatic hemorrhoids should be managed with conservative (fiber, analgesics, venoactive agents, or sitz baths) or surgical treatment.

22.13 Malodorous Lochia

Usually this kind of complication is due to a retained gauze sponge inadvertently left in situ after episiorrhaphy or perineal laceration repair. Removal of the foreign body will lead to resolution.

22.14 Varicose Veins

Pregnancy is a risk factor for varicose veins (Fig. 22.16), which may become symptomatic anytime during the antepartum or postpartum period. The incidence of varicose vein is estimated to be between 22 % and 50 %, but further research studies are needed [45]. The risk increases with older age and

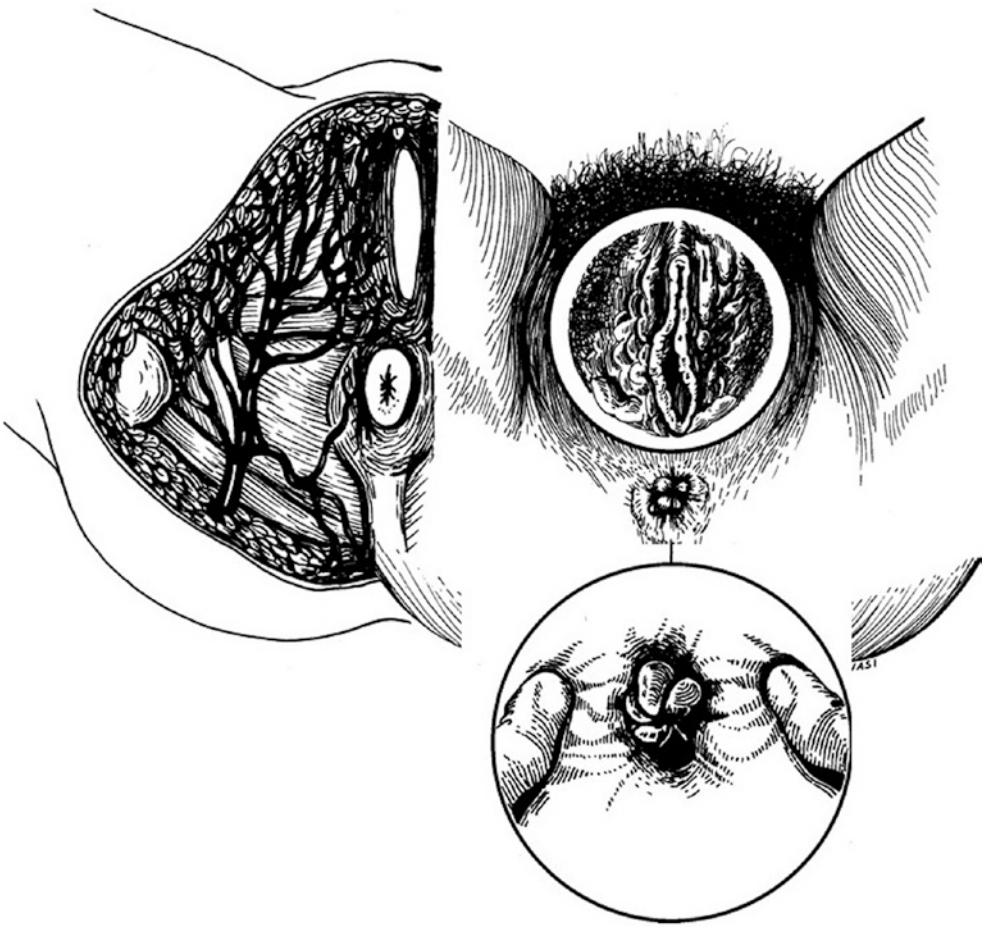

Fig. 22.15 A perineal frontal vision in gynecological position of the patient in the puerperal period: on the left, it shows the vascularization of the perineum; above, it is evident edema and vulvar varicose veins and hemorrhoids below

multiparty and family history and with increasing age and parity and family history.

Although compression stockings do not prevent varicose veins, they can improve symptoms and result to be useful for patient comfort.

22.15 Mastitis or Breast Abscess

Lactational mastitis (Fig. 22.17) is a localized, painful inflammation of the breast that occurs in breastfeeding women, usually in the first 6 weeks postpartum, associated with fever, myalgias, redness, and malaise.

It occurs in 2–10 % of breastfeeding women, usually after prolonged engorgement or poor drainage like in case of blocked milk duct, oversupply of milk, infrequent feedings, nipple excoriation, maternal or neonatal illness, maternal stress or malnutrition, and excessive pressure on the breast [46].

Frequent and complete emptying of the breast can reduce mastitis' development [47].

If not correctly treated, mastitis can evolve into a breast infection or abscess, which is a more uncommon localization of pus into the breast tissue. Differential diagnosis is with severe engorgement (which is bilateral and not associated with fever and myalgias), galactocele (a milk retention cyst caused by an obstructed min duct), and inflammatory breast cancer, which is usually diagnosed if mastitis doesn't resolve after treatment and skin thickening due to the presence of edema and erythema, together with axillary lymphadenopathy.

Mastitis is usually caused by organisms that through the nipple access to the stagnant milk, most episodes are caused by methicillin-resistant *Staphylococcus aureus* [48], but other pathogens can be *Escherichia coli*, *Streptococcus pyogenes*, *Corynebacterium* species, and coagulase-negative staphylococci.

For that reason, antibiotic therapy is important in the correct treatment of mastitis, possibly after culture of breast milk [49, 50, 51]. An empiric treatment should include agents against *S. aureus*, like dicloxacillin (500 mg orally four times per day for 10–14 days). Alternative regimens

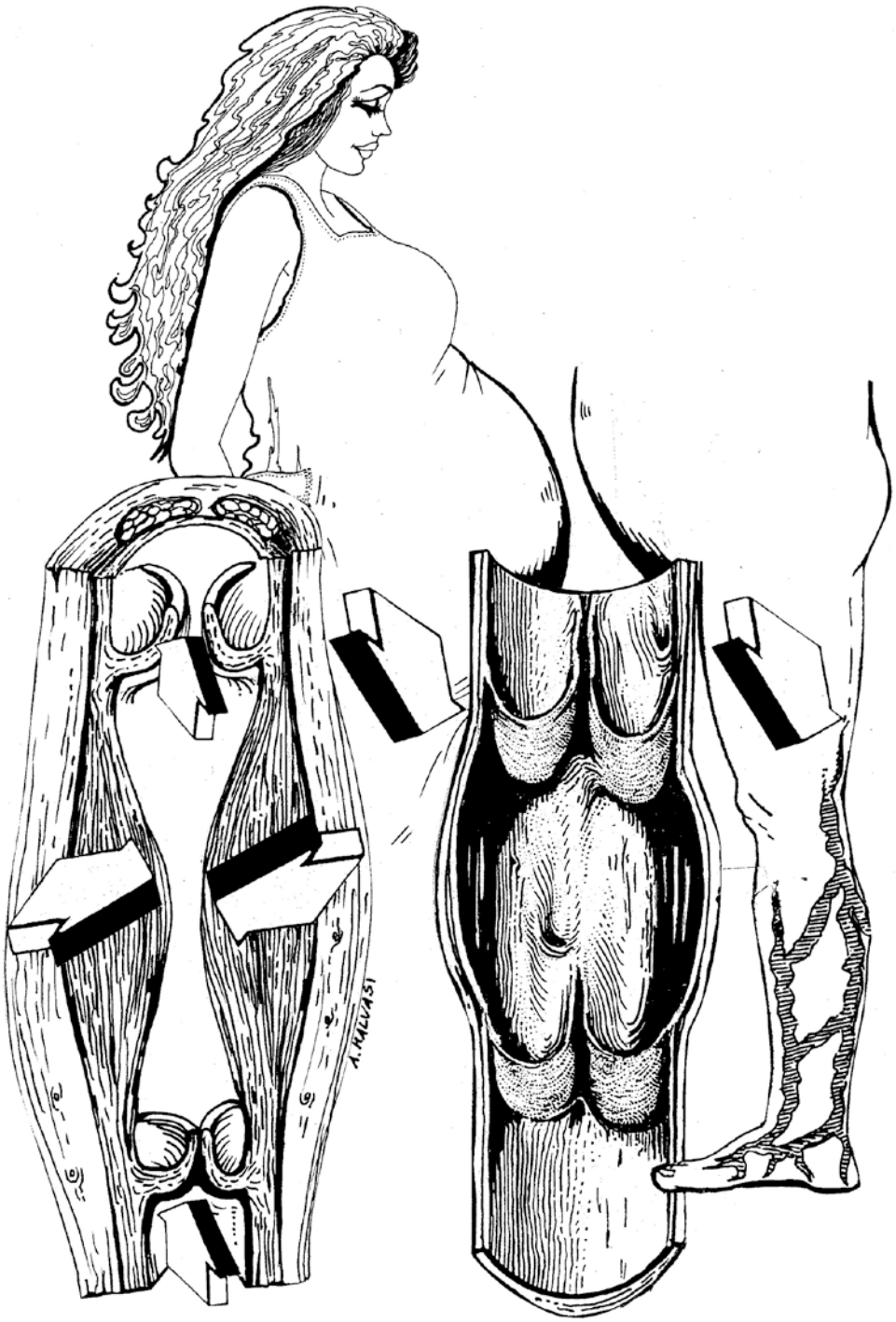

Fig. 22.16 Purpura with varicose vein problems in the lower limbs; in the bottom left, there is the venous valve incontinent system, in the center of the incontinent venous system, and on the right, the superficial varicose veins

include clindamycin (300 mg orally three times daily) or trimethoprim-sulfamethoxazole (one tablet orally twice per day, but it should not be used in case of compromised infants because it increases the risk of kernicterus).

Along with antibiotic therapy, it is important to provide symptomatic relief with nonsteroidal anti-inflammatory agents [52], ice packs, and cold compresses and also with complete emptying of the breast with breastfeeding and/or pumping.

Mastitis' treatment does not require cessation of lactation [53, 54].

If there's no clinical improvement within 48–72 h, ultrasound must be performed in order to exclude an underlying primary breast abscess, which develops as a complication of

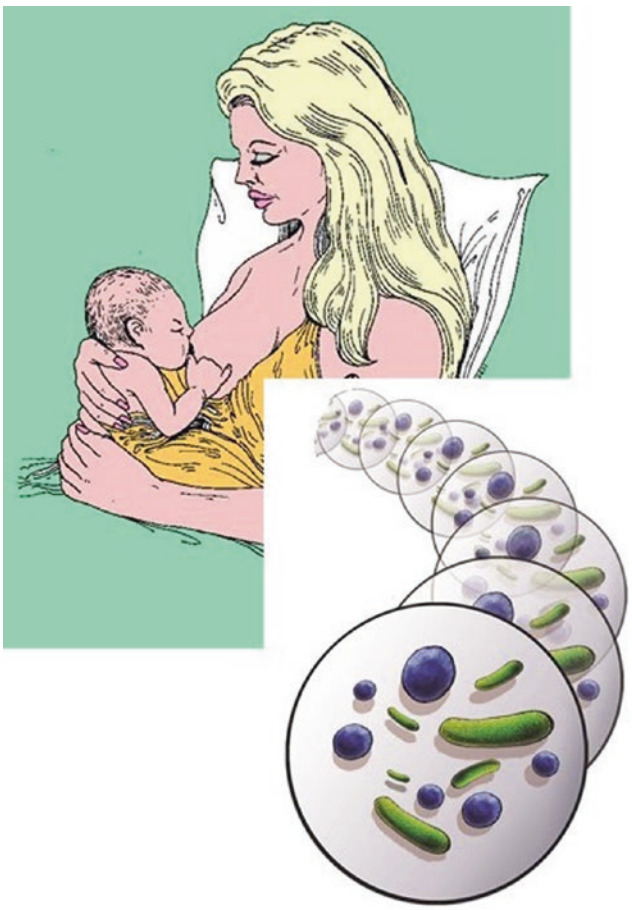

Fig. 22.17 Purpura with a lactational mastitis during breastfeeding

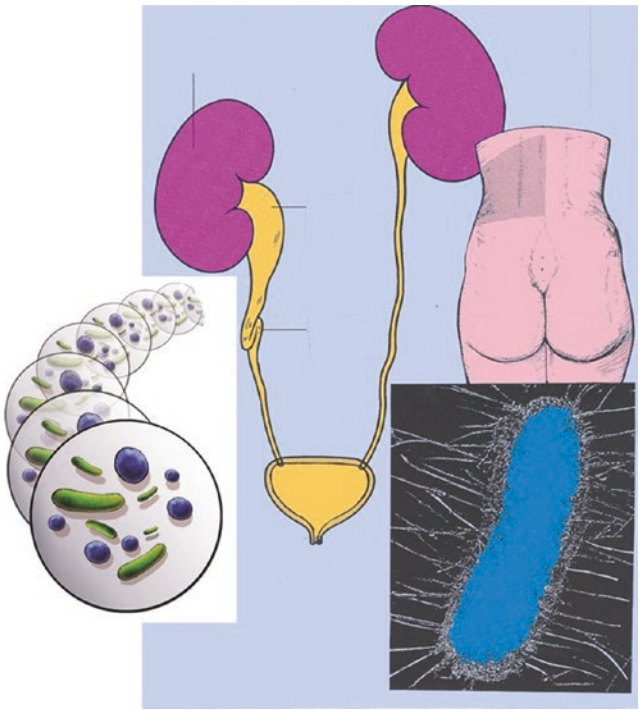

Fig. 22.18 Urinary tract infection in the postnatal period: at the center, ureter kinking and renal ptosis, and in the right lower box, the *Escherichia coli* (most frequent infectious agent). Modified from: Antonio Malvasi Gian Carlo Di Renzo, Semeiotica Ostetrica. C.I.C. International Publisher, Rome, Italy, 2012

mastitis [55] and requires a more complex treatment with needle aspiration or surgical drainage [56]. Primary breast abscess can also evolve into recurrent infection, poor cosmetic outcome, mammary duct fistula, milk fistula, and antibioma.

22.16 Urinary Tract Infection

Postpartum women have an increased risk of urinary tract infection (Fig. 22.18); these complications may be related to several factors like catheterization, epidural anesthesia, and operative delivery, and the prevalence is 2.8 % after cesarean and 1.5 % after vaginal birth [57].

For that reason, urinary catheters should be removed as soon as they are no longer needed.

22.17 Complications of Anesthesia

Epidural and spinal analgesic techniques provide pain relief for women undergoing both cesarean section and vaginal delivery, but it is associated with uncommon side effects.

Postdural puncture headache (also called postspinal headache) after neuraxial analgesia can be due to leakage of cerebrospinal fluid through a dural rent, traction on cranial structures, or cerebral vasodilation (Fig. 22.19).

The quality of this headache is its positional nature, worsened by sitting or standing and relieved by lying down. The incidence can depend by the size and the shape of the needle used for analgesia induction [58], and it is estimated to be around 1 %.

Most of the headaches will resolve in 7–10 days and symptomatic therapy with analgesic or caffeine can be established.

Spinal hematoma is a rare complication and is more likely in patients receiving anticoagulants. Epidural abscess and/or meningitis are uncommon but are serious complications of neuraxial block. Other untoward effects are caused by known pharmacological effects of the analgesic medications, such as hypotension, pruritus, nausea and vomiting, and respiratory depression.

22.18 Peripartum Cardiomyopathy

Peripartum cardiomyopathy (Fig. 22.20) is a rare, potentially lethal disorder of unknown etiology, with reported incidences of 1:2,200–1:4,000 live births in the United States [59].

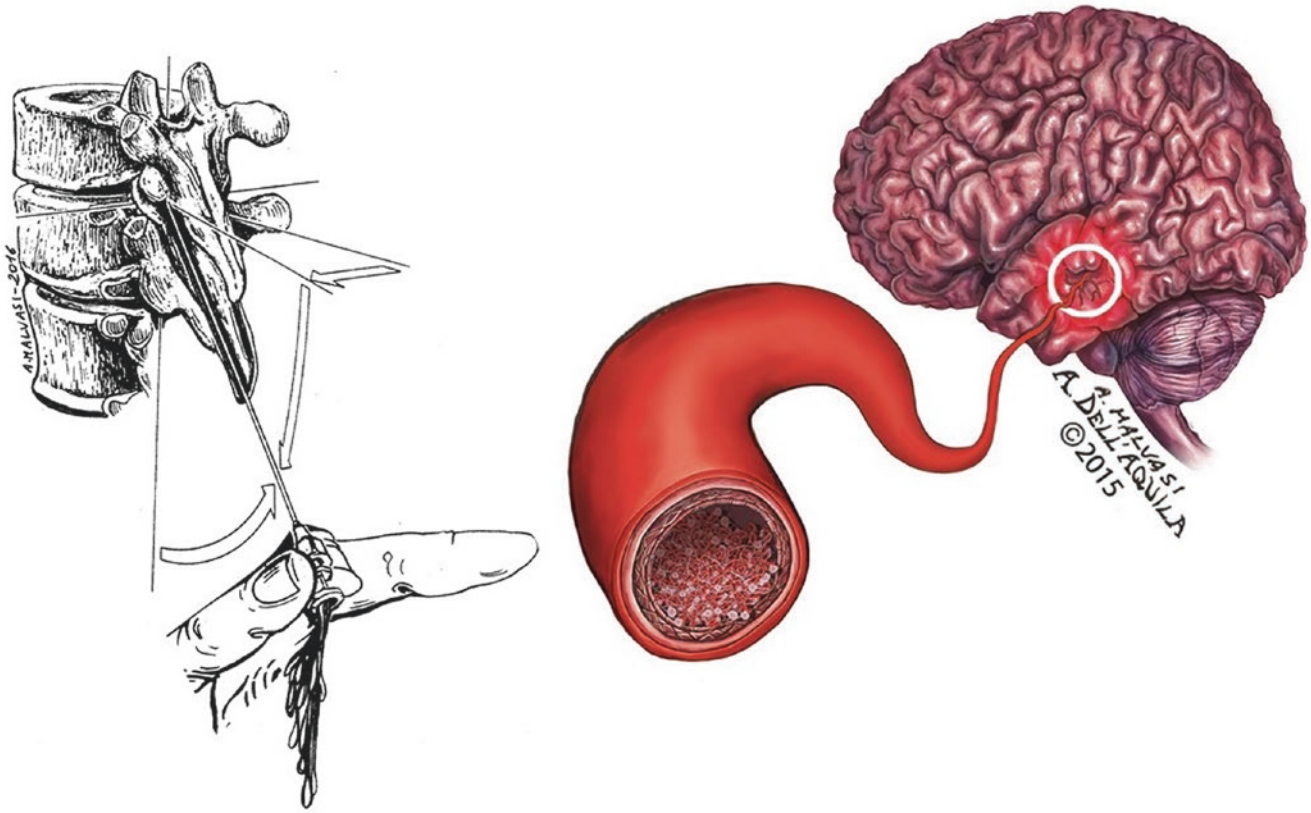

Fig. 22.19 To the left, accidental puncture of the dura mater during epidural anesthesia, right next to the puncture headache

In these women the following characteristics are present: development of heart failure between the last month of pregnancy and 5 months after delivery, absence of other identifiable sources of heart failure, and left ventricular systolic dysfunction with an ejection fraction less than 45 %. Inflammatory and autoimmune factors may be involved. Risk factors include older age, multiparity, and African descent.

22.19 Postpartum Neuropathy and Musculoskeletal Pain Postpartum

The incidence of postpartum neuropathy is approximately 1 % of deliveries. Postpartum nerve deficits result usually from compression, stretch, transection, or vascular injury, one of the nerves involved during labor and delivery. In fact, the most commonly injured nerves are the lateral femoral cutaneous nerve, the femoral nerve, peroneal nerve, lumbosacral plexus, sciatic nerve, and obturator nerve. These nerves can be seriously damaged by fetal passage through the birth canal in case of macrosomia or malpresentation, operative delivery, prolonged lithotomy position, prolonged second stage of labor, obesity, and improper use of leg stirrups or retractors [60]. Rarely, mononeuropathies are related to complications of neuraxial anesthesia, such as epidural hematoma and epidural abscess [61].

Symptoms of postpartum neuropathies are pain, weakness, and/or sensory abnormalities in the lower extremities. The precise presentation depends on the nerve affected.

Pain in the pelvic area and the lower extremities after delivery can also be due to increased mobility of pubic symphysis (or even a pubic diastasis), a higher pressure on the coccyx during childbirth (also called postpartum coccydynia), as well as from pelvic girdle syndrome or unilateral/bilateral sacroiliac joint trauma.

For a correct evaluation of the vascular, neurologic, and musculoskeletal function, a detailed exam of lower extremities should be executed.

Treatment depends on the woman's symptoms and can include anti-inflammatory drugs, topical patches, physiotherapy, or peripheral nerve block. Most women will have spontaneous resolution of their symptoms over days to weeks (median is 8 weeks) [62].

22.20 Urinary and Anal Incontinence

Postpartum incontinence of urine, flatus, or feces is common in the first year after childbirth. The real incidence of these complications is still unknown, but it seems to be a common complication especially in women who had vaginal delivery;

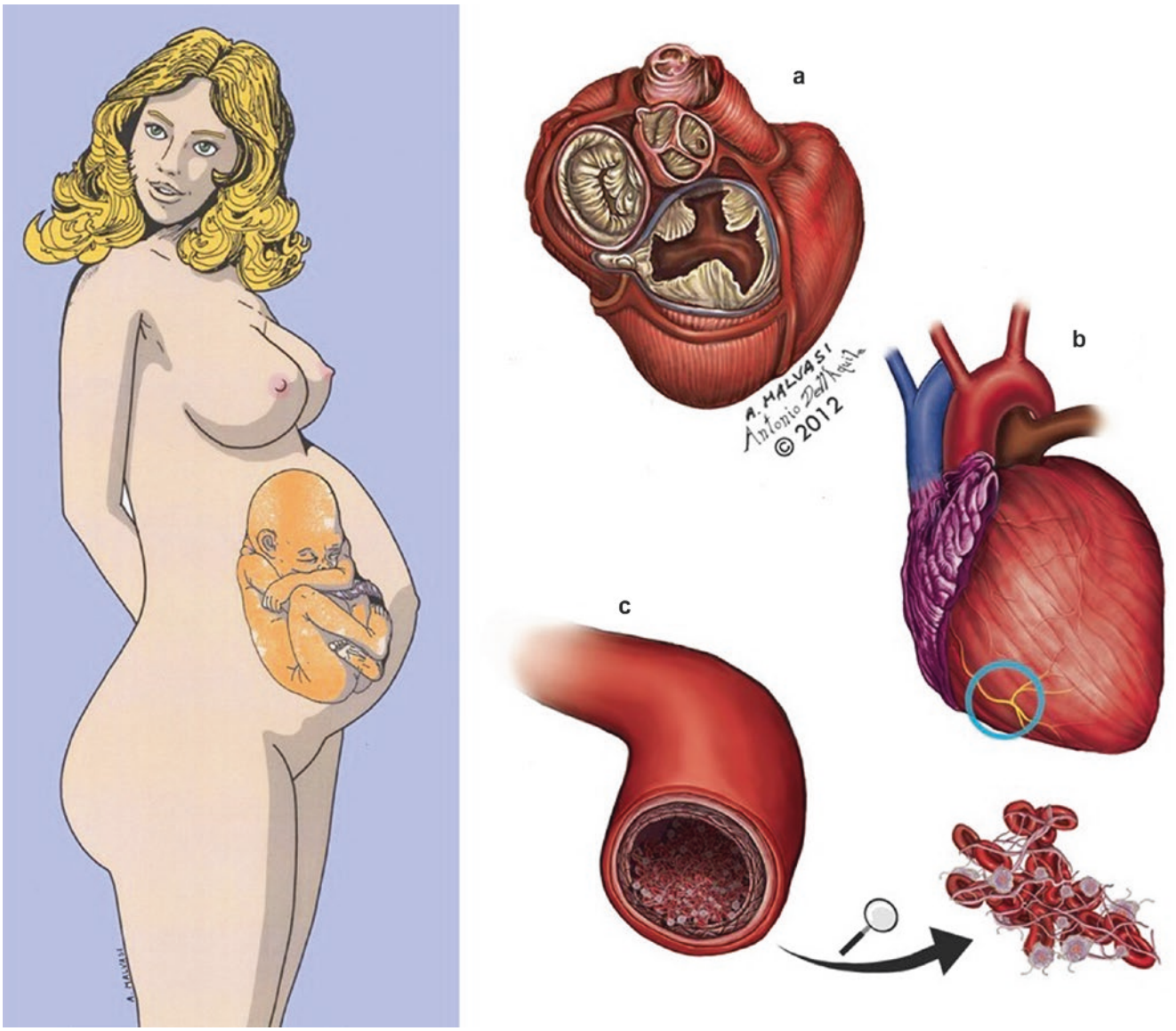

Fig. 22.20 Pregnant women are predisposed to cardiac valvular disease (**a**), coronary heart disease (**b**), and coronary thrombosis (**c**)

other risk factors are older age at first birth, overweight/obesity, and greater parity.

Symptoms appear to be persistent in time, beginning in the first months postpartum and lasting for more than 10 years [63].

22.21 Sexual Dysfunction

Sexual dysfunction after delivery is common. Some studies report that 89 % of women refer sexual health issues after vaginal delivery in the first 3 months postpartum. Factors beyond delivery that can contribute to postpartum sexual dysfunction include perineal trauma, emergency cesarean delivery or vacuum-assisted vaginal delivery, and low estrogen and lubrication levels especially in breastfeeding women [64, 65]. Low libido is a common finding, and for that reason clinician must ask women about their sexual function at postpartum visits.

22.22 Postpartum Blues, Depression, and Psychosis

After childbirth women can experience psychosis more than any other time in their lives: in the first weeks postpartum, symptoms like delusions or even hallucinations can emerge, but usually symptoms appear several weeks after delivery, usually with depression. A milder form of psychosis (postpartum blues) can appear 3 to 5 days after delivery. Women

with postpartum psychosis are more likely to commit suicide or infanticide than general population.

Postpartum blues (or baby blues) is a transient condition characterized by mild symptoms like sadness, tearfulness, irritability, anxiety, insomnia, and decreased concentration [66]; these symptoms appear within 2 or 3 days after delivery and typically resolve within 2 weeks [67].

Its incidence is estimated to be between 40 % and 80 %, and risk factors are psychosocial impairment, family history of depression, and antepartum depressive symptoms. The transitory nature of this condition doesn't require a specific therapy, but just psychological support and education.

The difference between depression that occurs after childbirth and the one that already begins in the prenatal period is not clear. In fact, the National Institute of Clinical Excellence of the British Health Service, in its guideline on mental disorders during pregnancy and postpartum, prefers definitions of schizophrenia or bipolar disorder rather than terms like "puerperal psychosis" and "postpartum depression" rather than schizophrenia or bipolar disorder due to the lack of evidence identifying them as separate diagnostic entities [68]. The term should not be used generically to identify any maternal mental disorder after childbirth (e.g., panic attacks, acute stress disorder and post-traumatic stress, obsessive compulsive disorder, etc.) and should not be confused with baby blues, disorder short afflicting at least 50 % of women after childbirth, characterized by tearfulness, sadness, and emotional lability, as we previously defined [69].

The prevalence of postnatal depression varies between 4.5 % and 28 % depending on the method and timing for assessing [70]. A health report of Agency for Healthcare Research and Quality shows a prevalence of depression in the period between pregnancy and the first year of the child's life, comparable to the general population of women of the same age, but with a three times higher chance of developing a new episode of major depression within 5 weeks postpartum.

There are not enough data to support a different prevalence of this disease in different cultures and different ethnic groups.

According to the American Psychiatric Association, postnatal depression is characterized by the presence of five or more of the following symptoms, persisting for at least 2 weeks: low mood tone, lack of interest, increased or decreased appetite, insomnia or hypersomnia, psychomotor slowing or agitation, fatigue or feeling of loss of strength, sense of guilt or unworthiness, decrease in concentration, and recurrent suicide thoughts.

Women can be reluctant to "confess" these symptoms, for shame, sense of failure, or fear of being judged inadequate to their child's care. Sometimes women attribute their mood swings and attitude to fatigue and difficulties in relationship, rather than admitting to be depressed.

Sometimes mild or moderate cases are recognized by the woman, partner, family, or even by health professionals, raising the morbidity of this disorder that usually depends by the time of diagnosis and treatment: in UK psychiatric disorders contribute to 12 % of maternal deaths, and untreated maternal depression can also interfere with cognitive, emotional, and behavioral development of infants.

Risk factors for postpartum depression include history of depression, history of sexual abuse, young age, unplanned pregnancy, lack of social and financial support, not breastfeeding, family psychiatric history, diabetes, unemployment, immigrant status, congenital malformations of the infant, and stressful life events in the months before delivery [71].

Very little is known on accuracy of screening tests: The Edinburg Postnatal Depression Scale (EPDS) or Edinburgh Scala is a screening tool used to identify women at risk of postnatal depression. Its administration to women, by specifically trained professionals, has been used in most of the screening programs.

Subsequent studies following the introduction of the EPDS realized that this is not a diagnostic tool, because postnatal depression diagnosis is possible only after a clinical evaluation; EPDS should just be only a part of a larger screening program.

Postpartum psychosis is a less frequent disturbance than postnatal depression: in fact its incidence is 1–2 women in 1,000, but its symptoms are certainly more serious. The most common symptoms are confusion, severe mood swings, eccentric behavior, delirium, and hallucinations.

Risk factors include personal or family history of schizophrenia or manic depression. Even women with previous puerperal psychosis are at high risk of recurrence in subsequent pregnancies (25–57 % of women).

The onset can be dramatic, beginning immediately after birth or within 48–72 h. In most cases the symptoms develop within 2 weeks after birth.

Management of postpartum mental disorders must be started as soon as possible and may include mother's hospitalization, pharmacologic treatment, and psychotherapy.

22.23 Postpartum Thyroiditis

Postpartum thyroiditis (PT) is a condition induced by autoimmune events which can occur within 1 year after delivery. The prevalence of postpartum thyroid dysfunction was 7–8 % for the general population. This risk is reported to be doubled in women with type 1 diabetes and more than fivefold higher in women with antithyroid peroxidase antibodies [72, 73]. Usually 20–30 % of PT have signs and symptoms of hyperthyroidism, 1 to 4 months after delivery, and last for 2 months; then 8 weeks of hypothyroidism is followed and then recovery. Another 20–40 % of patients with PT have

only hyperthyroidism, and the remaining 40–50 % have only hypothyroidism, which begins 2–6 months after delivery.

PT can be considered as a variant of autoimmune thyroiditis, because these two disorders have similar pathologic findings and both are associated with peculiar HLA haplotypes. Moreover, women with PT thyroiditis have a subclinical disease, usually revealed by high levels of serum antithyroid peroxidase antibody concentrations early in pregnancy, which decline later (because immunologic tolerance increases during pregnancy), and rise again after delivery [74]. The consequent thyroid inflammation leads to a state of high release of thyroxine (T4) and triiodothyronine (T3) due to thyroid follicles damage. As this status ends and the stores of thyroglobulin are exhausted, the thyroid follicles regenerate, and synthesis and secretion of thyroid hormones resume.

When present, main symptoms of hyperthyroidism are weight loss, palpitations, anxiety, fatigue, tachycardia, and tremor. Hypothyroidism is also usually mild, presenting with lack of energy, dry skin, constipation, and cold intolerance.

22.24 Postpartum Weight Retention

Weight retained after pregnancy is defined as the difference between postpartum and prepregnancy weight. Even if 50 % of gestational weight gain is lost in the first 6 weeks after delivery, it has been estimated that mean postpartum weight retention was 5.4 kg [75].

Main risk factors are excessive weight gain during pregnancy, black race, obesity, and quitting cigarette smoking.

Recommended strategies to achieve postpartum weight reduction are diet and exercise, which can also improve maternal cardiorespiratory fitness and preservation of fat-free mass [76].

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