The Placenta as the Mirror of the Foetus

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Leonardo Resta, Roberta 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 This conjecture means that placental pathology is in continuous evolution, ideas and theories becoming outdated in only a few years yet bringing to light other aspects previously ignored.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

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L. Resta (✉)
Department of Emergency and Organ Transplantation (DETO), Section of Pathological Anatomy, University of Bari, Bari, Italy

University of Bari, Bari, Italy
e-mail: leonardo.resta@uniba.it

R. Rossi
University of Bari, Bari, Italy

E. Fulcheri
University of Genova, Genova, Italy

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contrary, as he contributes to the genetic patrimony of the foetus, he can influence the placenta's metabolic 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).

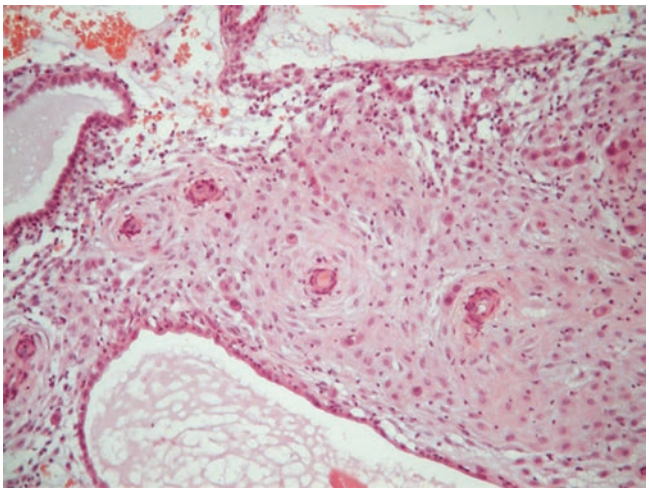

Fig. 1.1 Spiral arteries of the decidua capsularis. The arterial wall, without the action of the trophoblast, preserves the myometrial layer. The lumen is very narrow

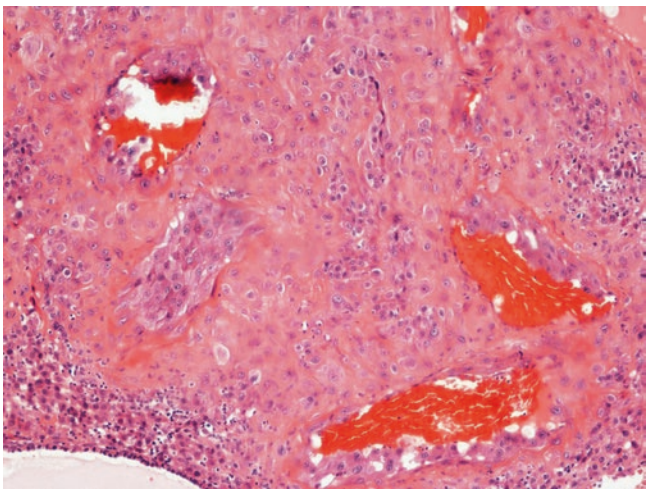

Fig. 1.2 Decidua in an 8-week pregnancy. The interstitium and the arterial wall are invaded by the trophoblast. Trophoblastic cells are present on arterial endothelium and in one artery occlude entirely the lumen

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,

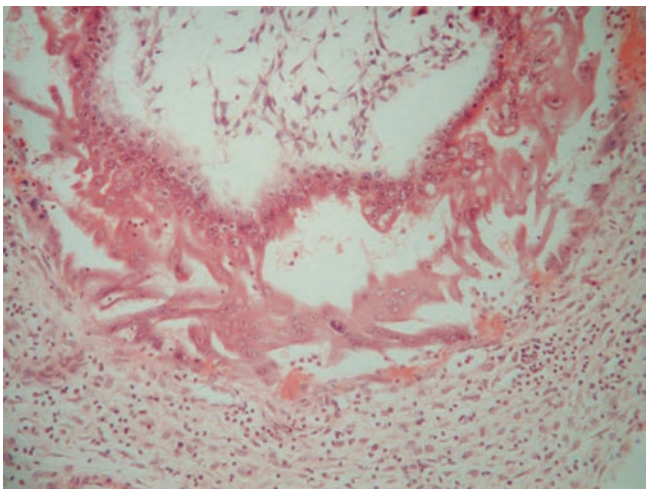

Fig. 1.3 Early stage of a blastocyst in endometrium. The wall of the blastocyst is composed of an internal layer of cytotrophoblast and a thick layer of syncytiotrophoblast in which a complex labyrinth of channel is promptly occupied by maternal blood

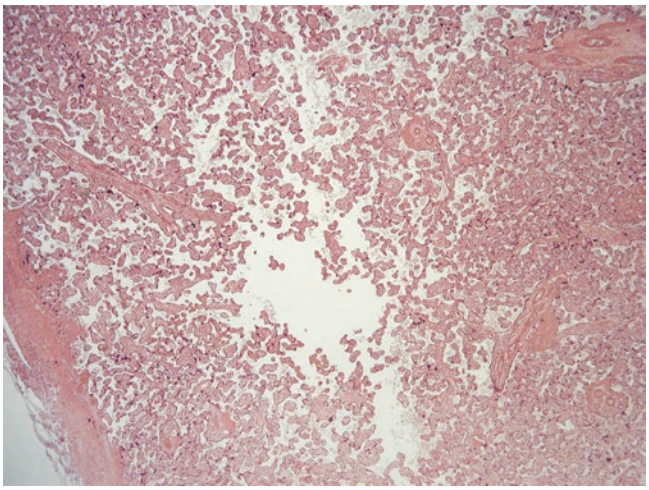

Fig. 1.4 Low magnification of a maternal cotyledon. The haematic lacuna is evident near the centre. Some immature intermediate villi are present around the lacuna

(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

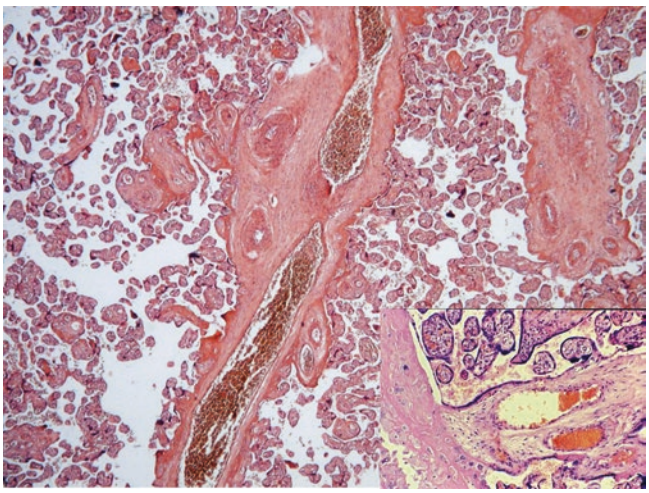

Fig. 1.5 Term placenta. In this picture many principal villi of different sizes are present. All villi are characterised by thick mesenchymal stroma in which two vessels (arteria and vein) are evident. The surface often lacks of the trophoblast, and a layer of fibrin separates the villus by the maternal 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

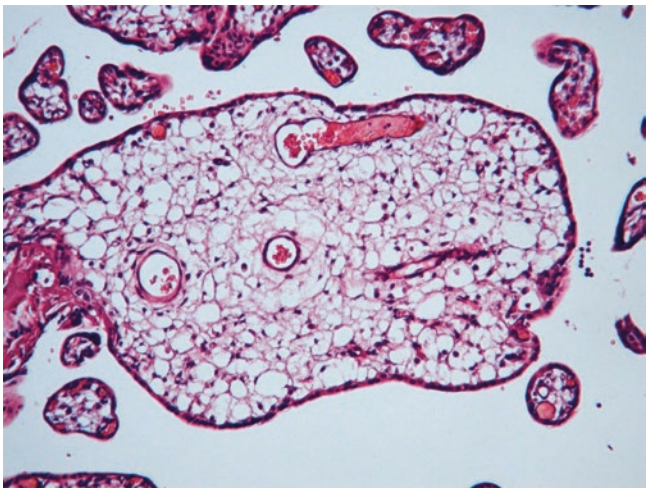

Fig. 1.6 The immature intermediate villus is large, and its stroma shows a reticular shape for the presence of a very complex network of channel. In each lacuna the Hofbauer cells show a dark nucleus anchored by thin cytoplasm projections to the channel wall. The capillary vessels are arranged at different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

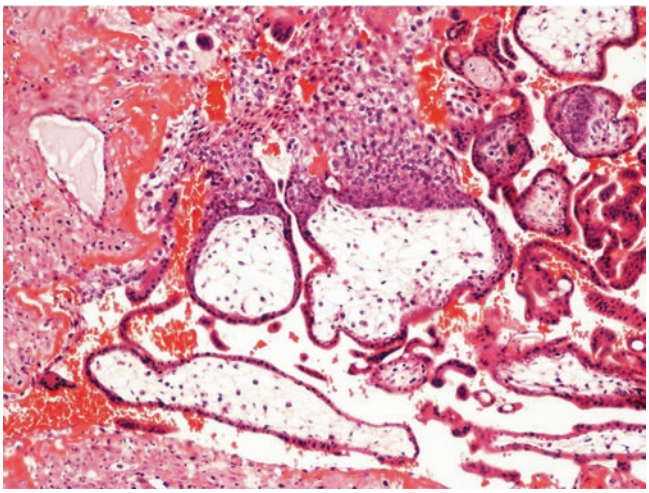

Fig. 1.7 Two mesenchymal villi characterised by a cap of proliferating cytotrophoblast cells, an edematous stroma and absence of vessels

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.

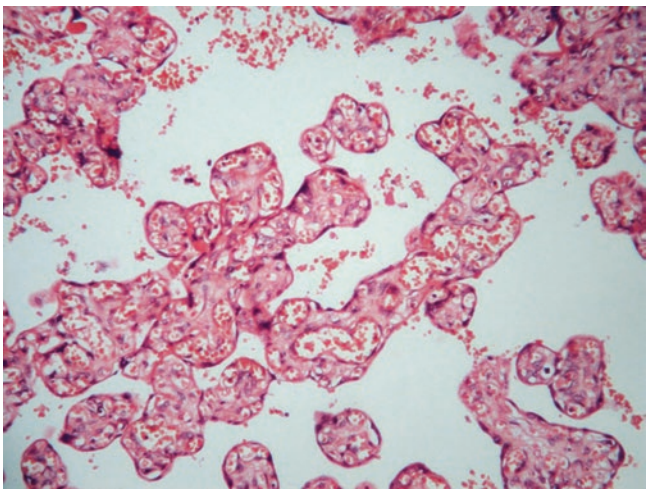

Fig. 1.8 The intermediate mature villi are smaller than the immature ones. Their axes contain expanded capillary vessels. Several term villi are exposed on their surface

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.

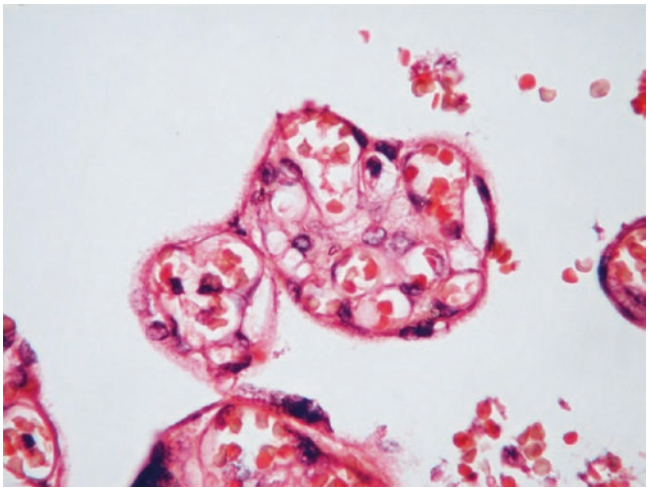

Fig. 1.9 Term villi are composed of some loops of capillary vessels, few interstitium and trophoblast. The dilated vessels are very close to the basal membrane in a region of the trophoblast without nuclei. The distance between foetal and maternal blood is minimal, and the maternofoetal changes reach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

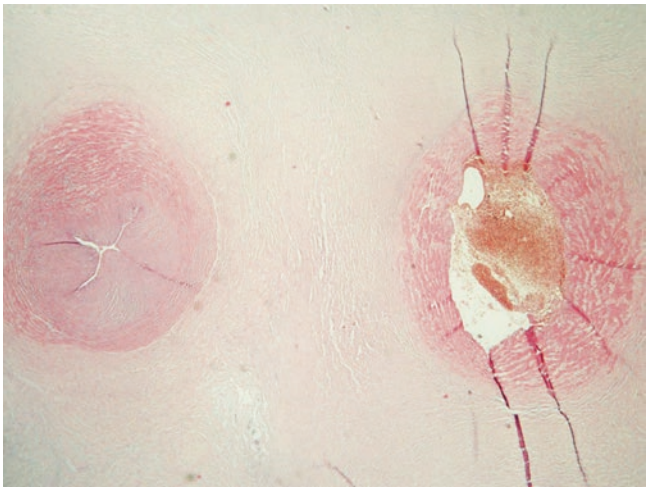

Fig. 1.10 Few hours after the foetal death, the arteries of the umbilical cord are contracted, the lumen is often virtual and the wall is apparently thickened

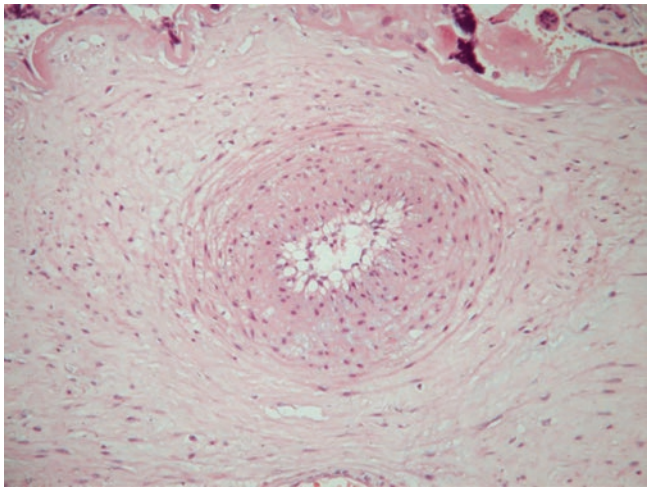

Fig. 1.11 In the stem villi the contracted arteries have an endothelial swelling. This picture was in the past confused with a glycogenic degeneration in diabetic placenta

(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.

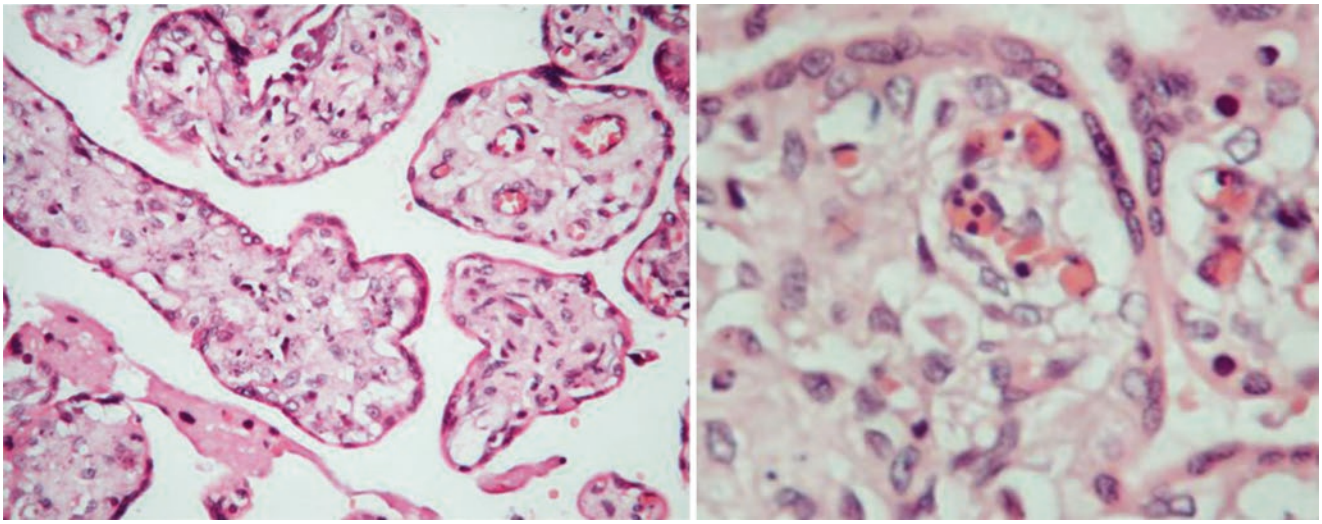

Fig. 1.12 Intravascular karyorrhexis. Nuclear fragments of the leukocytes are present in the lumina of the capillary vessels

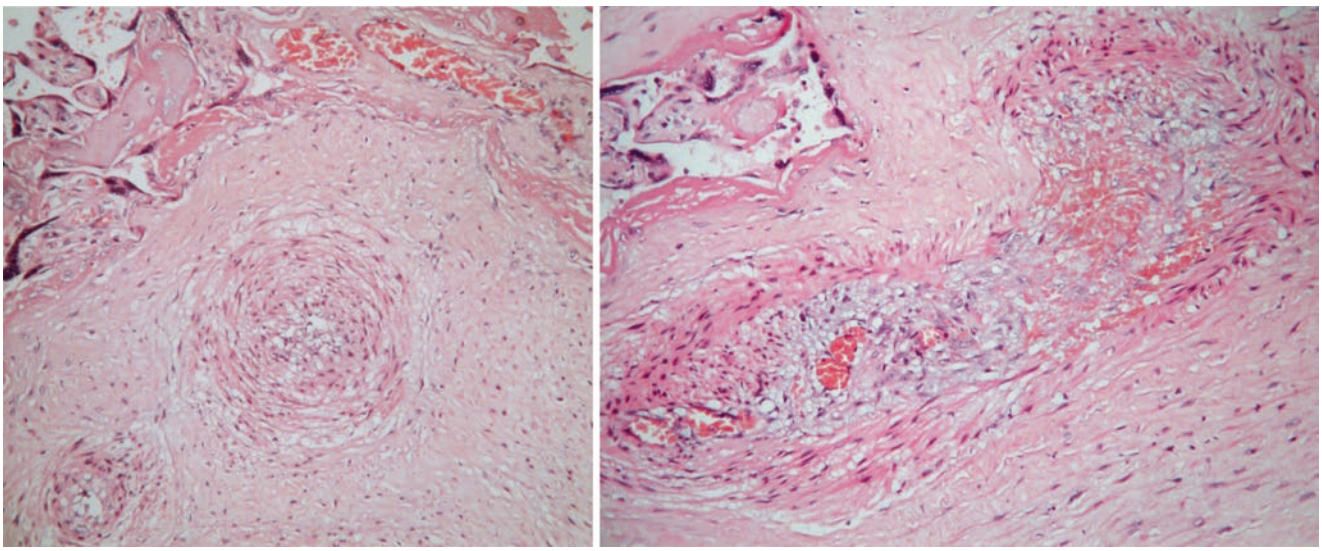

Fig. 1.13 Regressive aspects of the villar arteries, with intimal fibrosis, some days after the foetal death

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

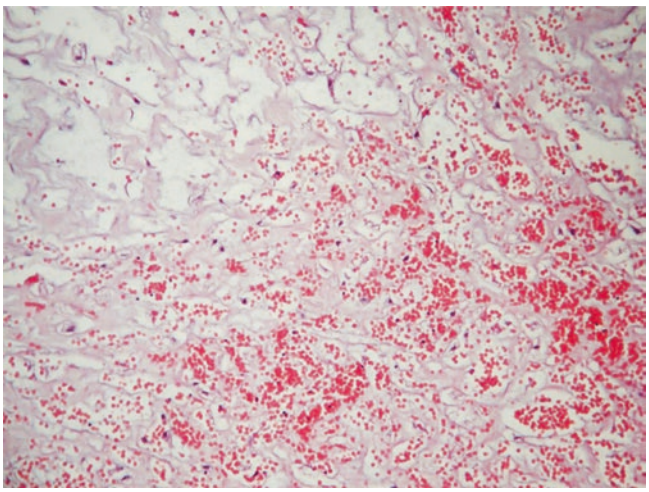

Fig. 1.14 Diffusion of the erythrocytes in the Wharton jelly of the umbilical cord. Macroscopically the cord appears red brown some days after the foetal death

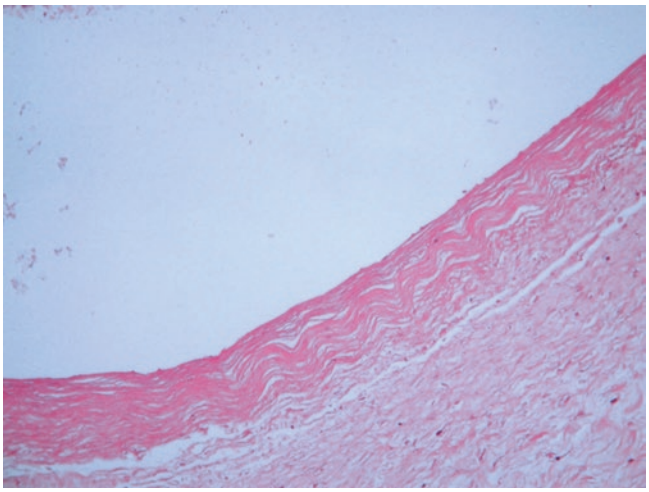

Fig. 1.15 Coagulative necrosis of the muscular cells of the cord vessels, with cytoplasm hypereosinophilia and absence of nuclei. The foetus is dead from 1 week

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.

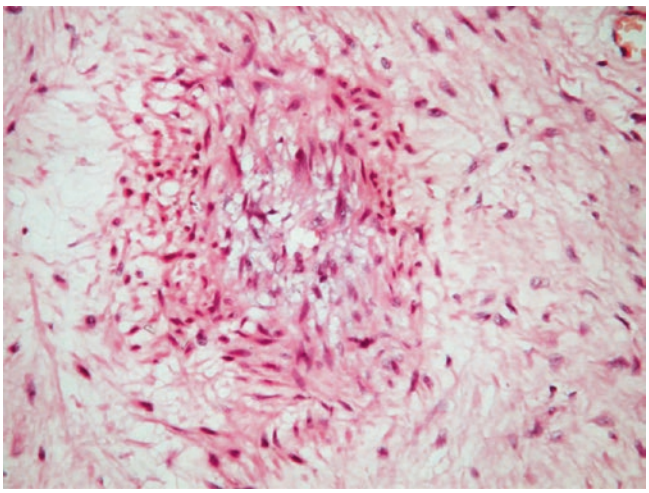

Fig. 1.16 Complete dissociation of the arterial wall after the disappearance of the lumen

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

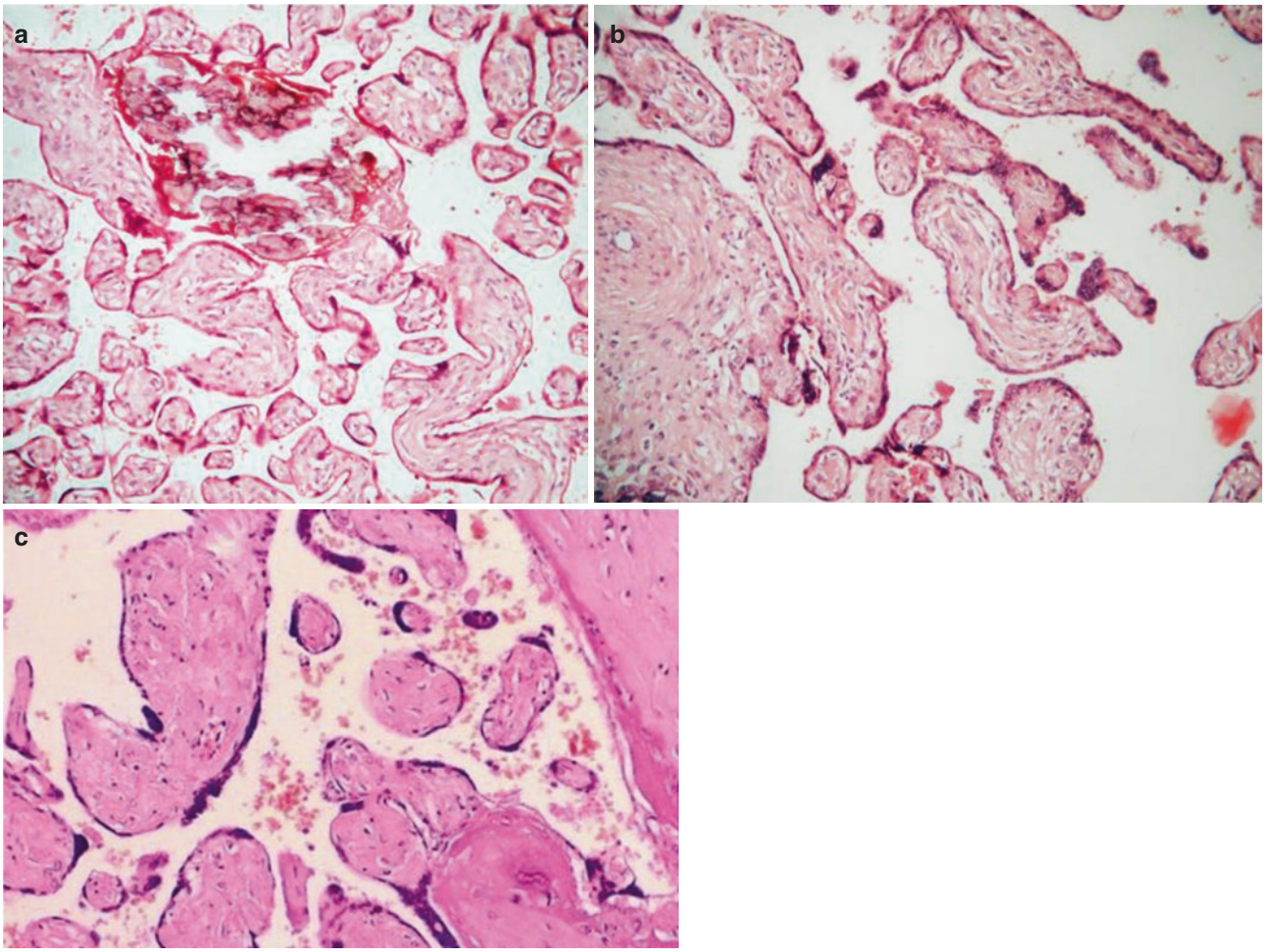

Fig. 1.17 (**a**–**c**) Disappearance of vessels, progressive fibrosis and reduction of cells in villi after a week of foetal death. The trophoblastic nuclei are amassed in large and dark nodules

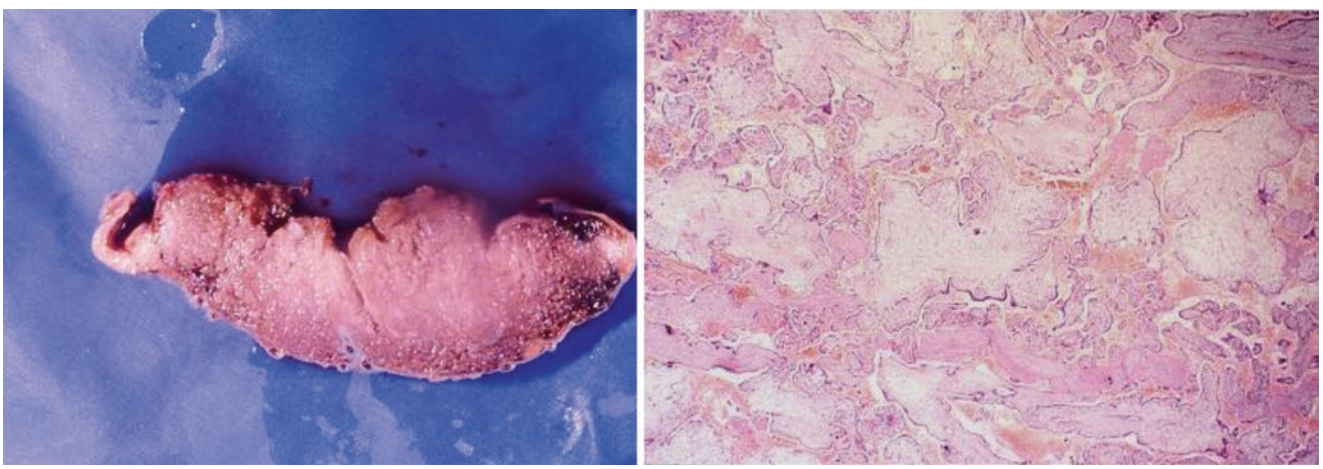

Fig. 1.18 Placenta in a case of foetal anaemia: large and pale aspect in the macroscopical section. At histology we can observe giant edematous villi with scanty vessels

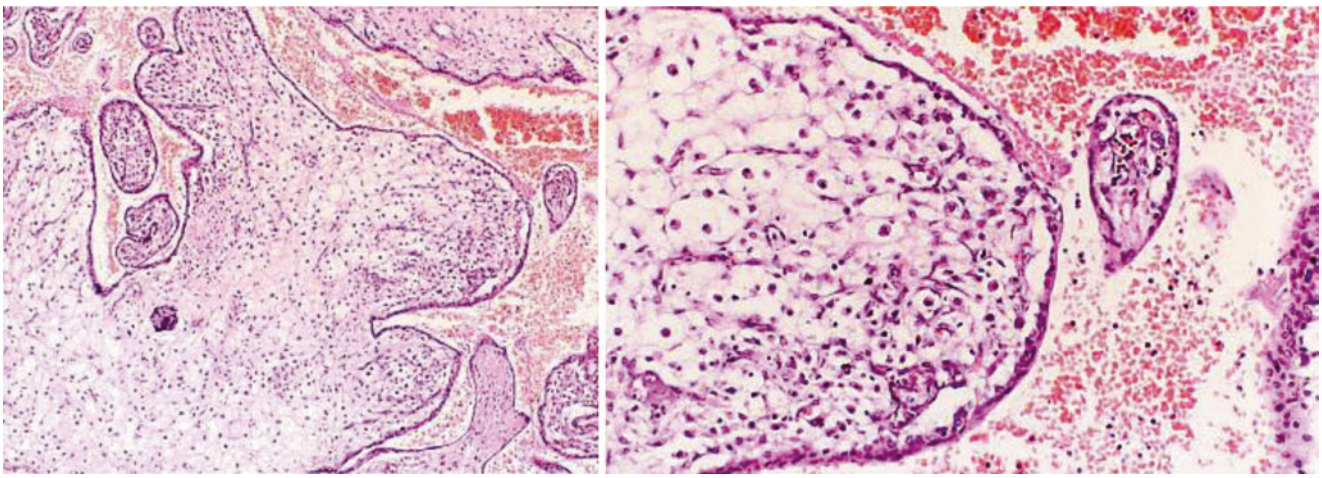

Fig. 1.19 Foetal anaemia. The large villi present a large amount of the Hofbauer cells and numerous erythroblasts in the vessels

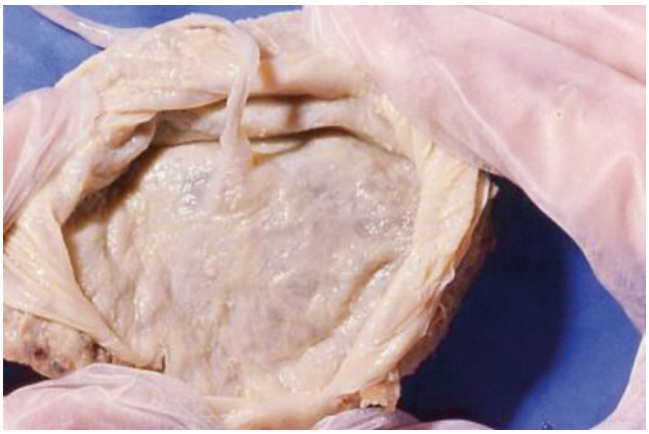

Fig. 1.20 Severe amnionitis. The membranes are opaque and covered by a fibrin exudate

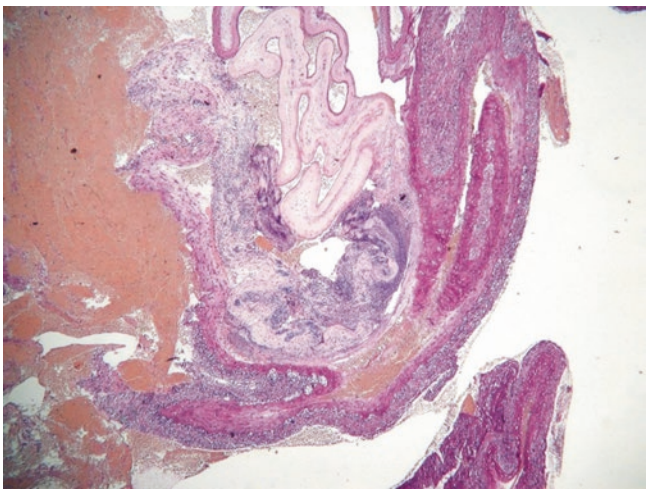

Fig. 1.22 In this case the neutrophil infiltration is more severe in the site of the membrane rupture. We can conclude that the premature rupture of membranes is the consequence of the chorioamnionitis

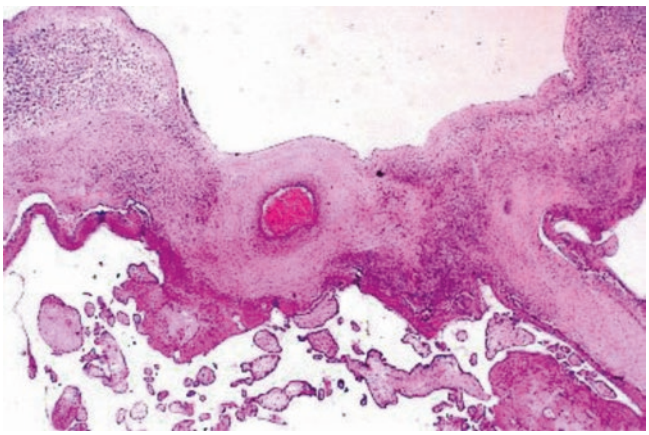

Fig. 1.21 Histologically, the severe chorioamnionitis is characterised by a diffuse and intense infiltration of neutrophils. Also the chorial vessels are included in the phlogosis

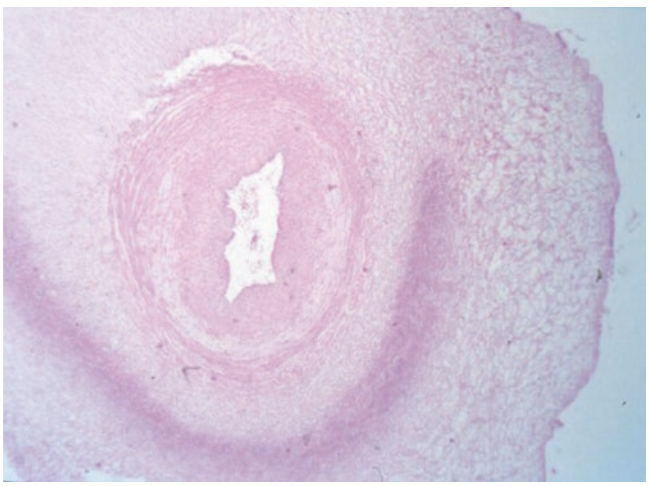

Fig. 1.23 A case of congenital syphilis with a dissecting infiltration of the umbilical cord near an arteria

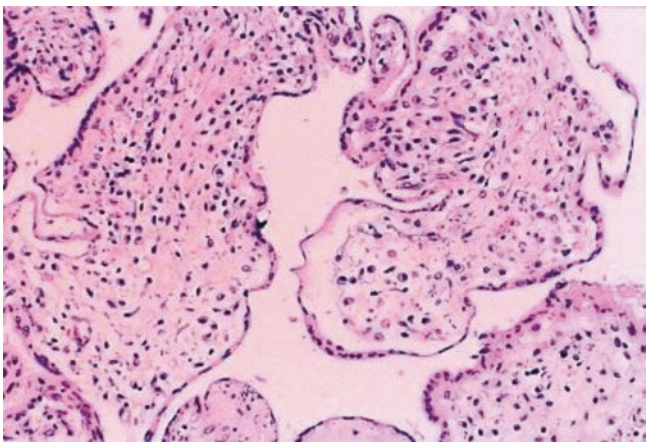

Fig. 1.24 Chronic viral villitis characterised by an infiltration of lymphocytes and plasma cells

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

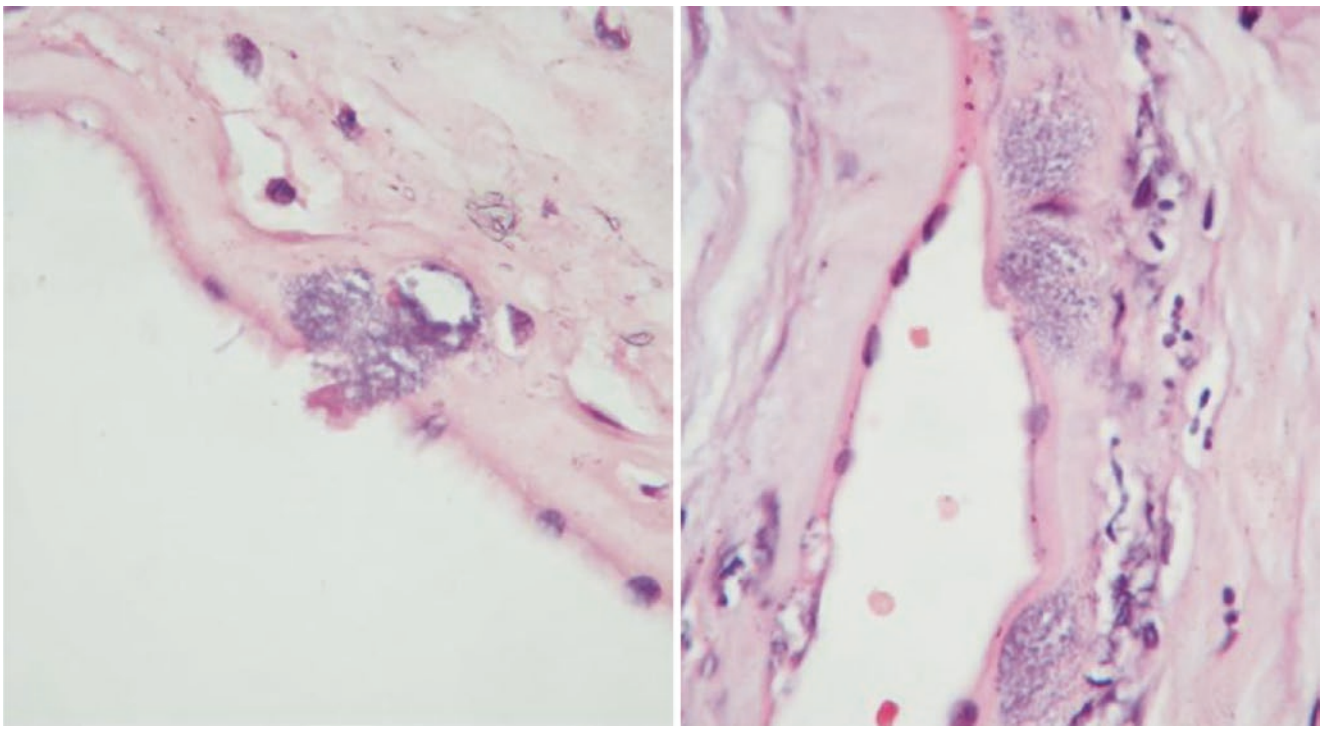

Fig. 1.25 Proliferation of *Listeria* colonies in the amniotic membrane

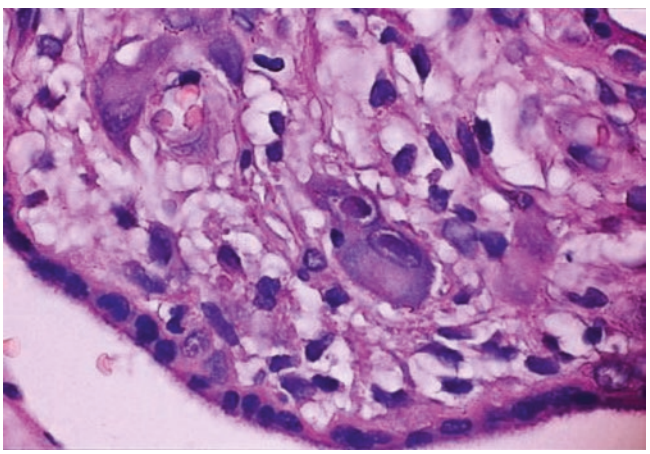

Fig. 1.26 Cytomegalovirus infection. Presence of large cells with eosinophilic cytoplasm, giant nuclei and evident nuclear inclusion. In this condition the viral cytopathy may be present in all kinds of placental cells

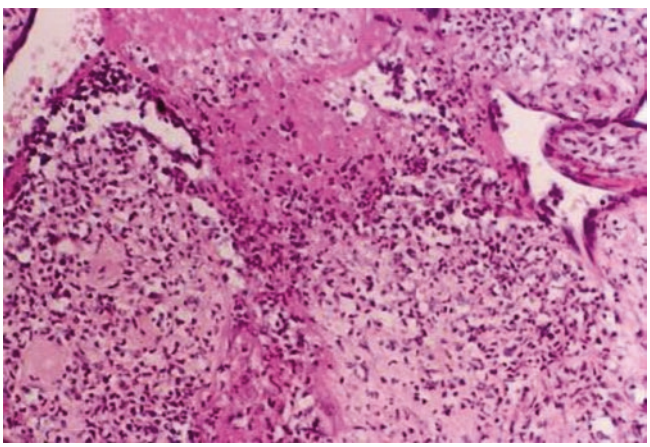

Fig. 1.27 Infection of *Listeria*. Infiltration of granulocytes in the villi and in the perivillar space with abscessual evolution

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

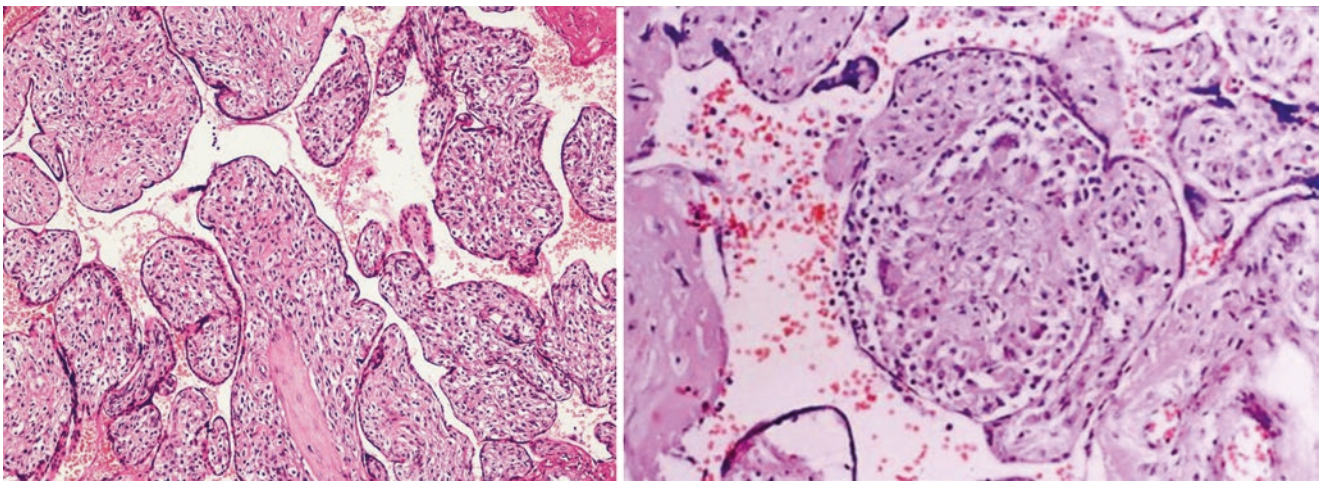

Fig. 1.28 Villitis of unknown etiology (VUE). This condition is not correlated with a known microbial inflammation. The villi are heavily infiltrated by leukocytes, and some giant multinucleated cells may be present. This picture may be associated with different foetal diseases, as a consequence of a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

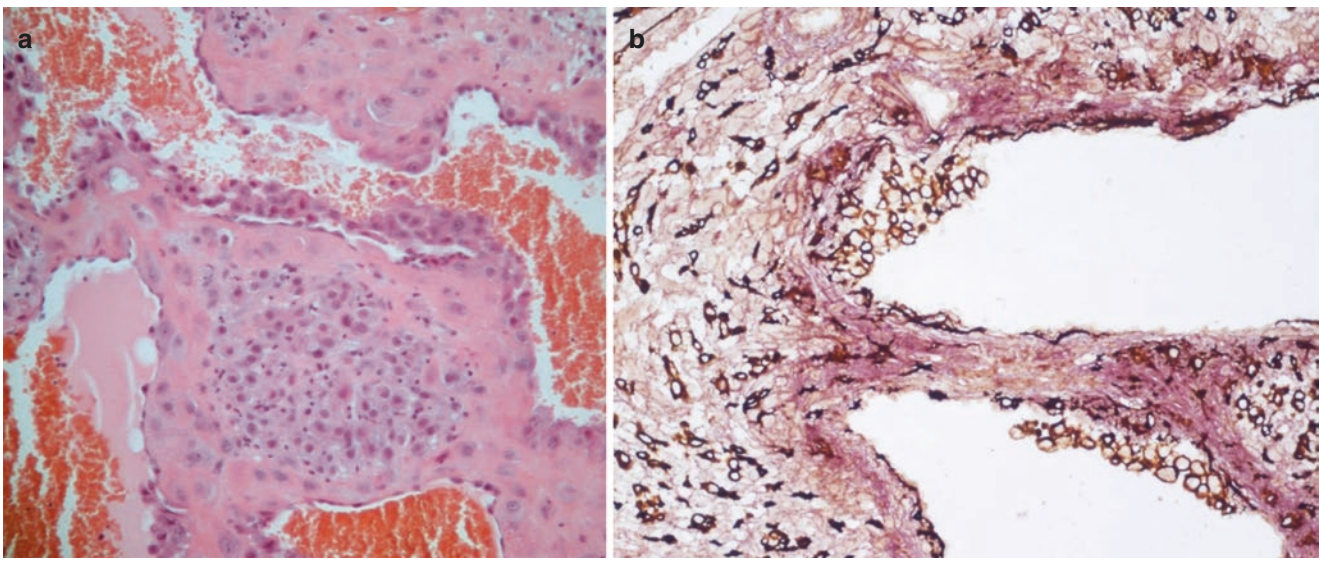

Fig. 1.29 (**a**) A physiological transformation of the utero-placental arteries. In (**b**) an original stain shows in *violet* (orcein) the scanty elastic fibres and in *black* (immunohistochemical reaction with anti-keratin antibodies) the cytoplasm of the trophoblastic cells. The latter are abundant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

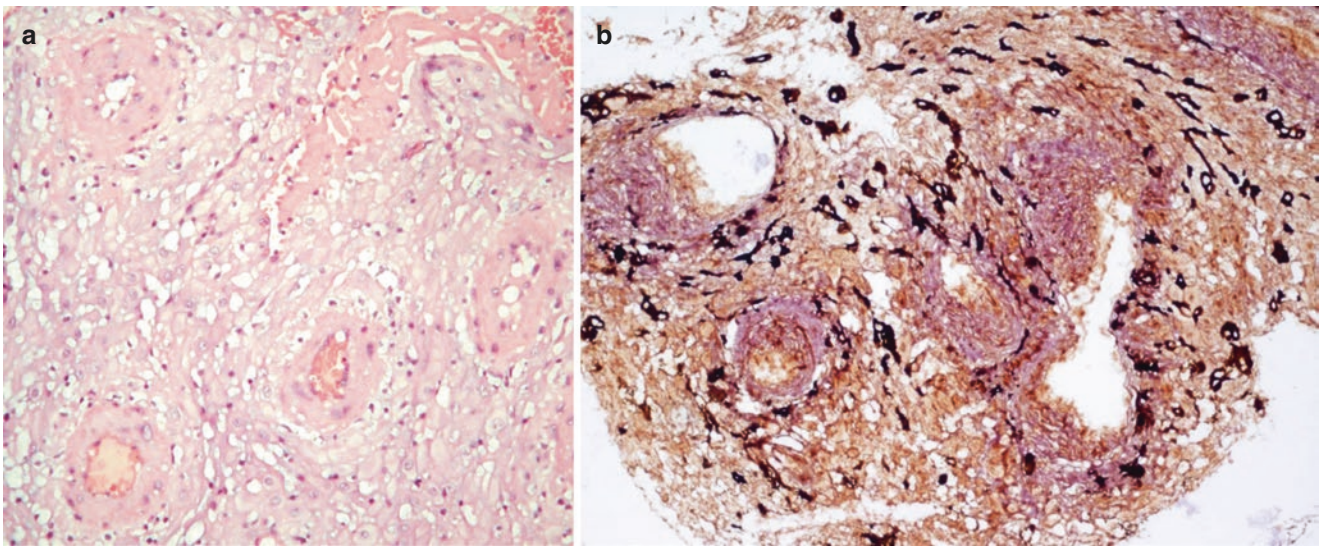

Fig. 1.30 (**a**) In this preeclamptic placenta, the utero-placental arteries lack the physiological transformation, and they show a thick muscular wall and a small lumen. The special stain (**b**) shows a large amount of elastic fibres (*violet*) in the arterial wall and the absence of cytotrophoblastic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

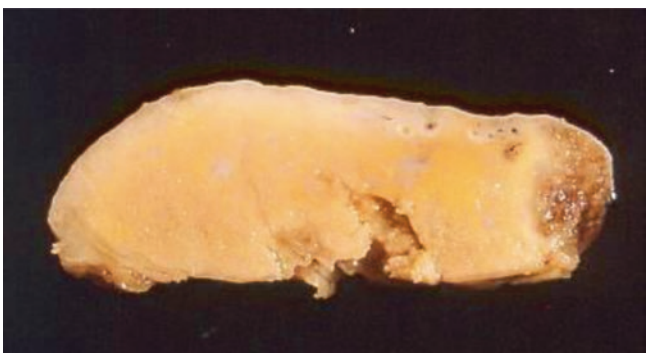

Fig. 1.31 A large infarction in a preeclamptic placenta, involving almost all the frontal section

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).

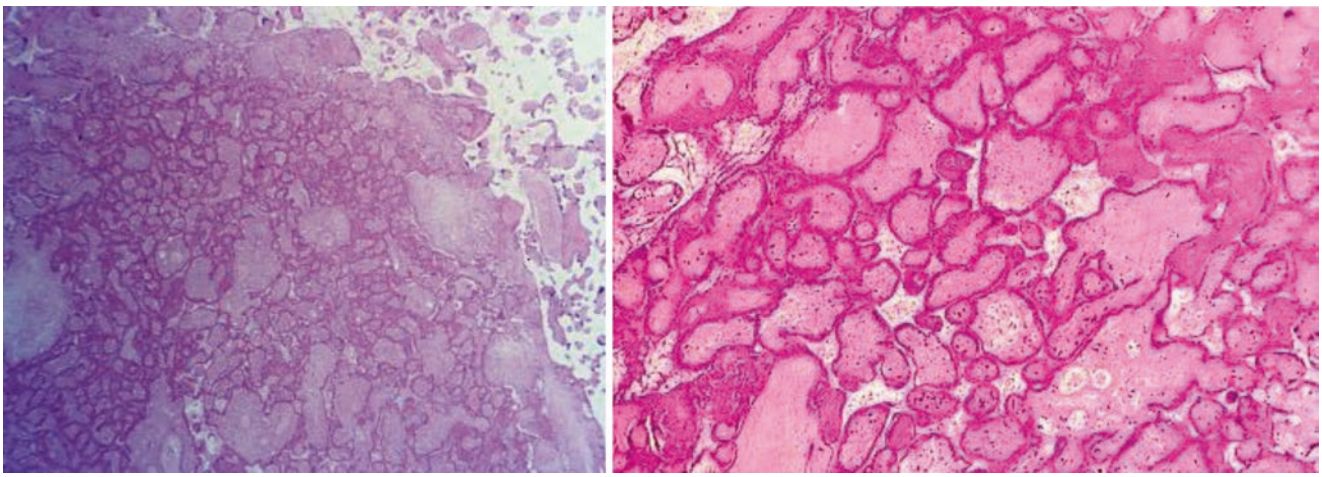

Fig. 1.32 Histological aspect of an infarct dated from several days. The intervillar space is collapsed. A diffuse coagulative necrosis makes the villi hyper-eosinophilic and acellular (ghost villi)

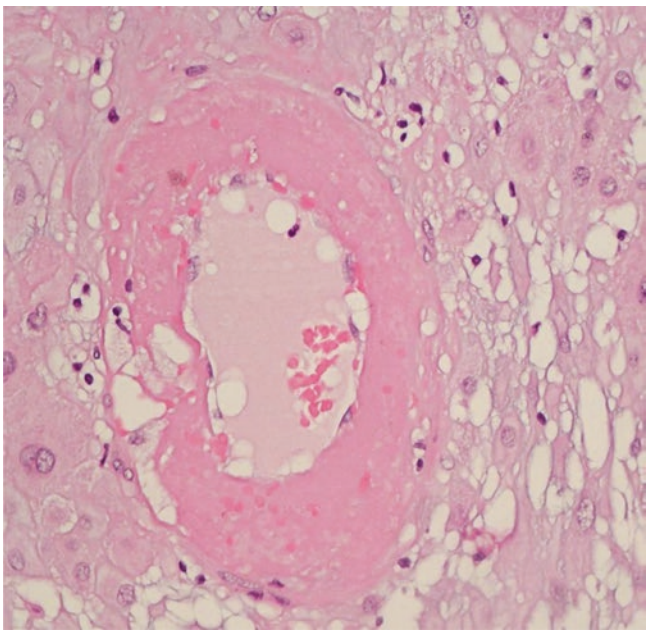

Fig. 1.33 Atherosis of a decidual utero-placental arteria. The arterial wall presents fibrinoid necrosis and infiltration of macrophagic foam cells. The lumen is narrow. This lesion predisposes to vascular thrombosis and rupture

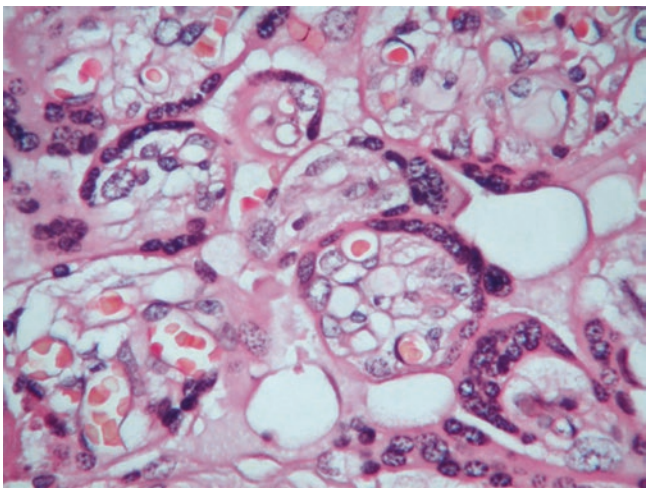

Fig. 1.34 Tenney-Parker changes: term villi present several hypertrophic cytotrophoblast cells, a sign of an anoxic damage of the trophoblast and an accelerated turnover of the trophoblast. Apoptotic nuclei are recovered in a region of the trophoblast (syncytial knots) and then expelled in the maternal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

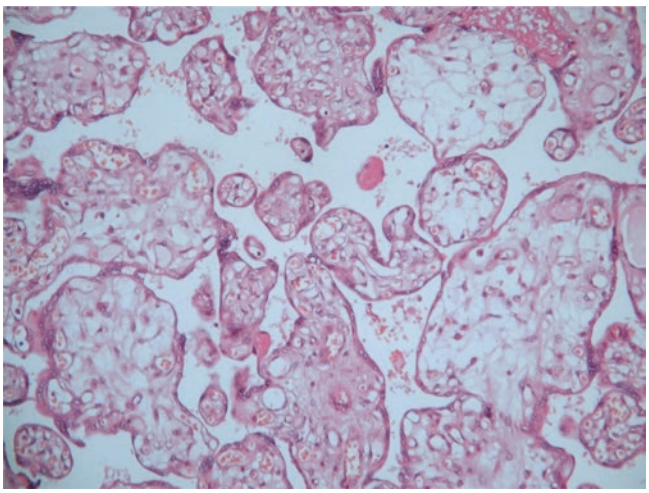

Fig. 1.35 Diabetic placenta with "dysmature" villi: large ("monster villi"), with pale stroma and several capillaries disposed at different distances from the basal membrane

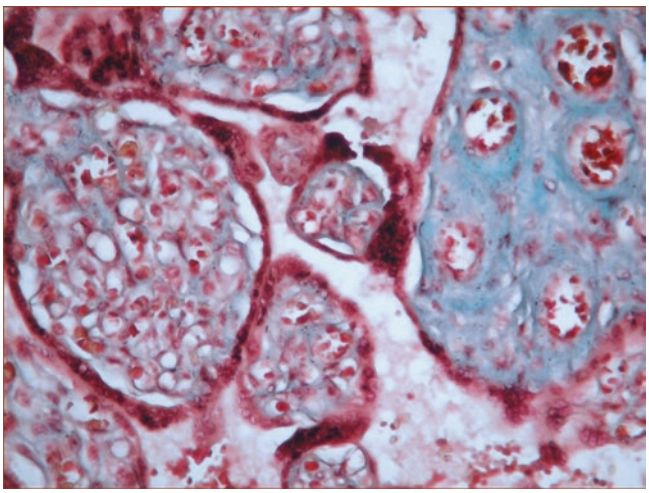

Fig. 1.36 The trichromic stain shows the very numerous capillaries present in a large intermediate villus in diabetic placenta

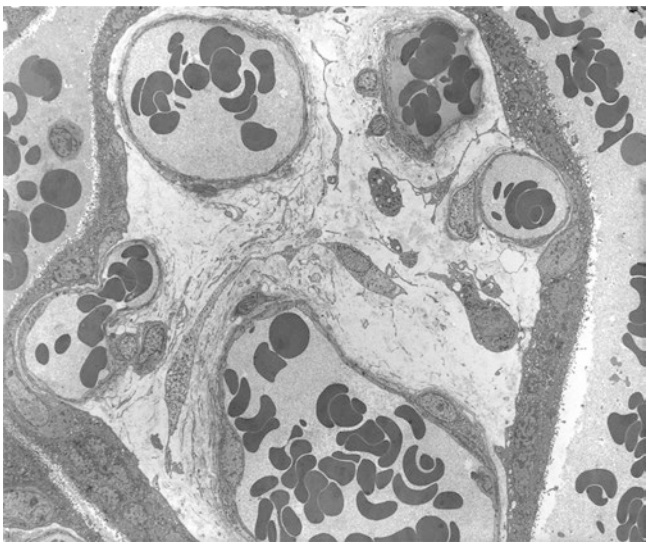

Fig. 1.37 Ultrathin section of a diabetic villus. The numerous vessels are arranged in different sizes. Note the unusual form of the fibroblasts which have very long and ramified cytoplasm connecting the different cells of the villus

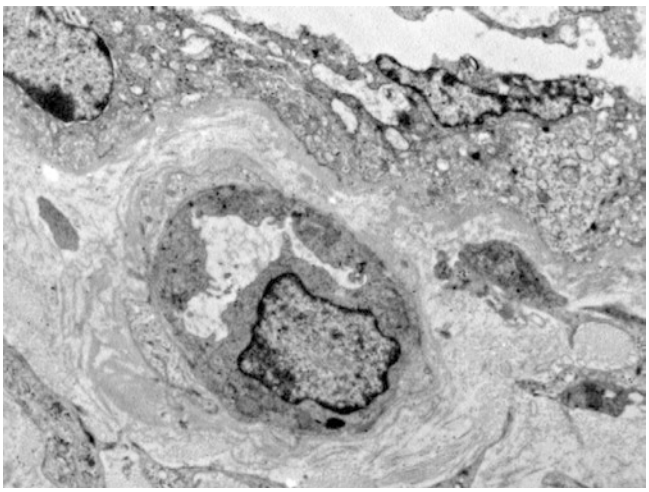

Fig. 1.38 Villus of a diabetic placenta. This vessel is distant from the membrane and shows a swollen nucleus and a consequent restricted lumen

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

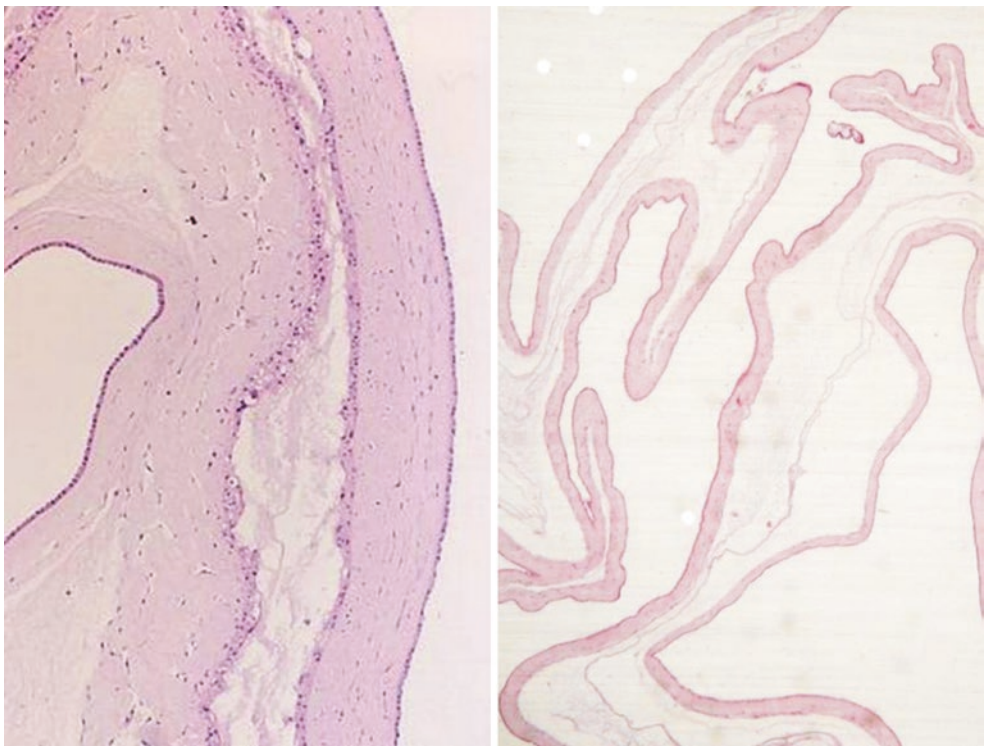

Fig. 1.40 On the *left*, the interamniotic septum in a dichorionic diamniotic placenta is composed of two distinct layers of amnions/chorion. On the *right* the septum of a monochorionic diamniotic placenta shows only two amniotic membranes without interposed chorion layers

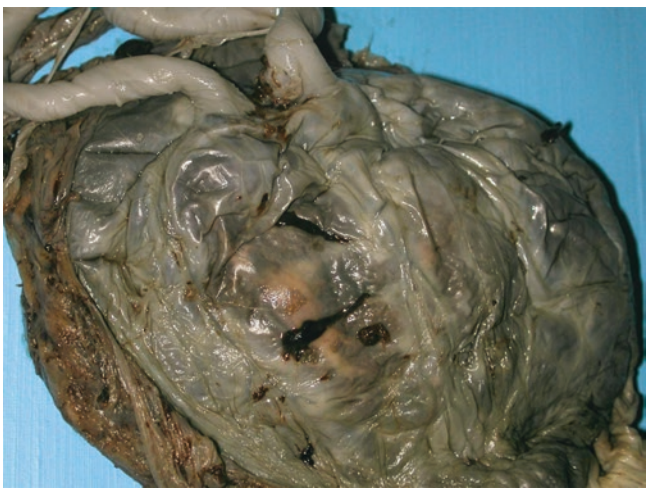

Fig. 1.41 A monochorionic monoamniotic placenta: a single amnion cavity presents two umbilical cords

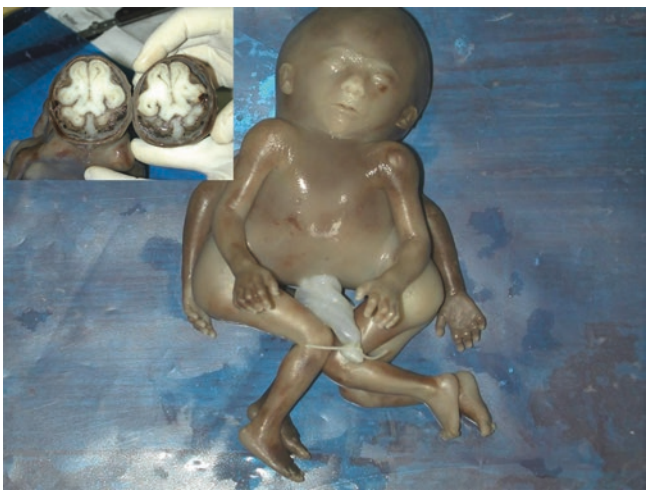

Fig. 1.42 An example of conjoined twins (cranio-thoracopages), with a single umbilical cord. In the insert, the encephalon shows one cerebrum and two distinct posterior fossa and cerebellum

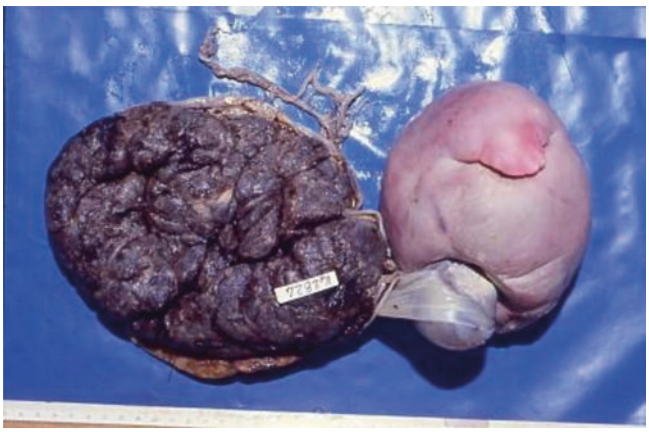

Fig. 1.43 An acardiac twin. The placenta permits the full development of the foetus which was circulatory connected with an amorphous embryo without a heart

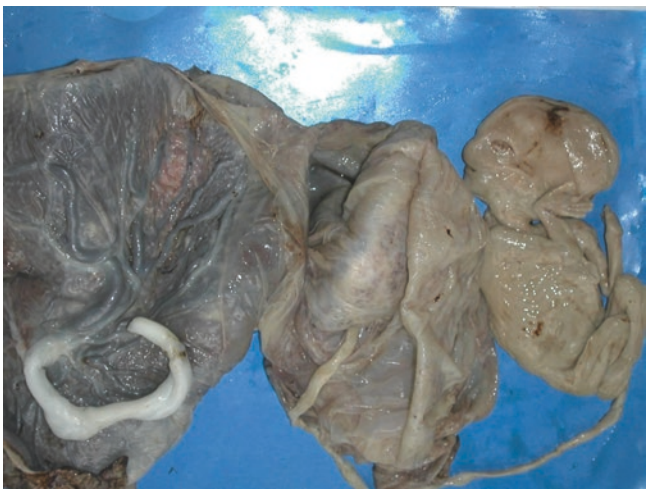

Fig. 1.44 In this tween pregnancy, an embryo dead precociously and remained in his amniotic sac till the birth of the healthy foetus. Dehydration and mummification produced a particular aspect defined as papyraceus foetus.

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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