Pathology of the Placenta

A Practical Guide

T. Yee Khong
Eoghan E. Mooney
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Preface

The placenta is one of the most misunderstood and neglected tissues in anatomical pathology. It is a transient organ lasting only for the duration of a pregnancy and yet is of immense value to clinicians in understanding the success or otherwise of the pregnancy. It is also a unique organ in that it is a composite of two genomic contributions and cells derived from the placenta invade maternal tissue during pregnancy; thus, it is of interest to basic scientists studying immunology and cancer biology.

This book describes the pathology of the human singleton third trimester placenta and builds on the initial effort of a group of pathologists, clinicians and scientists who met in Amsterdam in 2014. It aims to provide agreed nomenclature/nosology and definitions of lesions for pathologists; to define thresholds, where possible, for lesions to enable meaningful clinical correlations; to indicate how strong the evidence is for stated clinical correlations, and, hence, provide management guidance for clinicians; and to acknowledge areas of uncertainty to direct future research.

Internationally recognised experts contributed to this book, the contents and text of which were discussed and workshopped at a three-day meeting – the Dublin Consensus Meeting– to result in this collective text. Accordingly, we hope that this book is accurate and lacks bias and that it represents our best understanding of the pathology of the human placenta at this time.

The book is aimed at the practising pathologist in general and community hospitals as well as in teaching hospitals. It will also provide a source of reference for obstetricians, neonatologists, epidemiologists and researchers. Medico-legal practitioners may find the book useful.

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Part I

Background

Introduction: An Approach to Placental Pathology

1

T. Yee Khong, Eoghan E. Mooney, Sanne J. Gordijn, Terry K. Morgan, and Peter G. J. Nikkels

A historical account of the study of the placenta is provided elegantly in Boyd and Hamilton's monograph [1]. The placenta is named after its shape, resembling a flat cake, from the Greek word *plakoús*. Mossman described it anatomically as an apposition of fetal and maternal tissues for the purposes of physiological exchange. It has a limited lifespan lasting just the duration of each pregnancy.

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1.1 Reasons for Examining the Placenta

Placental pathology provides an autopsy of the pregnancy. There are many reasons for a pathological examination of the placenta, chief of which is to explain pregnancy outcomes. The information from such an examination may have important implications for management of subsequent pregnancies in addition to offering an understanding of the pathophysiology of any adverse outcome from the index pregnancy. It is not practical, however, to perform a pathological examination of every placenta, and, at most institutions, only complicated pregnancies lead to the submission of the placenta for pathology. In fact, a major gap in knowledge is the thorough characterization of "normal" placentas throughout gestation. The indications for pathological examination can broadly be divided into maternal, fetal/neonatal and placental and are discussed further in a later chapter (see Chap. 3).

There are also other reasons to study the placenta. Having paternal and maternal genomic contributions, it is a semi-allogeneic tissue that must partially evade the maternal immune system to support the pregnancy. Ovum donor pregnancies, thus being wholly allogeneic, that result in a healthy offspring point to studies that may have implications for solid organ transplants [2, 3]. The controlled proliferation, migration and infiltration of trophoblastic cells, which are derived

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from the trophoblastic shell and from the tips of anchoring villi, into the maternal decidua and superficial myometrium and especially in the arteries in these structures, are a necessary event for successful placentation; the placenta also spawns syncytiotrophoblast metastases to maternal lungs. These phenomena are akin to those seen in cancer [4, 5].

Placental influences are not restricted to the duration of the pregnancy. Increasingly, epidemiologists are keen to study the placenta and investigate how it affects the long-term well-being of both the mother and her child. The so-called "developmental programming" of fetal organogenesis and maternal cardiovascular function are now thought to lead to a range of adult diseases [6].

There is also a medical-legal imperative for examining the placenta. As the "diary of pregnancy", it may reveal answers that cannot be recovered otherwise. In cases of unknown cause of adverse outcomes, especially neurological, the placenta may help explain the status of the intrauterine environment and its consequences [7]. The increased prevalence of placental and cord abnormalities in children subsequently diagnosed with cerebral palsy underlines the importance of requesting placental histology in all cases where the baby is delivered in poor condition [8].

1.2 Diagnostic Challenge

Until recently, the placenta is one of the most misunderstood and neglected tissues in anatomical pathology. Since placental pathology provides insights into the pregnancy, it may not be a surprise that diagnoses often do not directly affect patient management, but we expect as gaps in knowledge are addressed, the overall significance of accurate and reproducible placental findings will modify our understanding of the underlying pathophysiology for many pregnancy complications, including the most common great obstetric syndromes (preterm labour, preeclampsia, fetal growth restriction and stillbirth). The diagnostic challenges appear to be that clinicians rarely employ the placental pathology report in patient management [9], and pathologists are often insufficiently prepared to recognize clinically significant patterns [10].

Table 1.1 Possible reasons for difficulty in the examination of the placenta

Reason	Example	Solution
Artefact hampers analysis	Ice crystal, poor fixation	Large fridge; adequate fixative
Insufficient or irrelevant clinical information	Gestational age and/or birth weight omitted Clinician unaware of significance of findings	Design of request/triage form Education of clinical and midwifery staff
Pathologist's lack of confidence in diagnosis	Insufficient numbers to maintain interest and expertise	Service planning

The reasons why the placenta is perceived as a difficult organ to examine and to provide a pathologic report are unclear. They may be related to the organ itself, to the clinical contexts and to the pathologist (Table 1.1).

The placenta is an organ that develops over the course of the pregnancy and its gross and microscopic features change over that time period. It is important to recognize these differences so as not to misinterpret findings. The clinical contexts are important also: pregnancies with an adverse outcome may have very normal placentas, and, conversely, abnormal placentas may not be associated with any antenatal or postnatal maternal or neonatal complications. Several features may be seen with one clinical condition, while the same feature may be seen in several clinical conditions or contexts. The clinical significance of identified lesions may depend also on the location of the lesions or their size relative to the size of the placenta.

Inter-observer reproducibility between perinatal/placental pathologists and between them and other anatomic pathologists can be poor. While lack of standardisation of diagnostic criteria has been a problem [10], recent developments [11] can be expected to improve the quality of diagnoses in this area.

1.3 An Approach to Examining the Placenta

No approach to a pathological examination of the placenta is any more or less valid than another, although results and comparability of studies rely on a standardised approach to sampling and examination. Unlike other tissues and organs where their examination will usually result in a single diagnosis, placental examination often does not result in a single diagnosis. More often, a synthesis of the various findings in the different parts of the placenta, namely, umbilical cord, membranes, chorionic plate, placental parenchyma and maternal surface/basal plate, is necessary to reach an opinion or diagnosis. Thus, the approach that is advocated in the layout of this book is to allow for a systematic examination of all the parts of the placenta (Figs. 1.1 and 1.2).

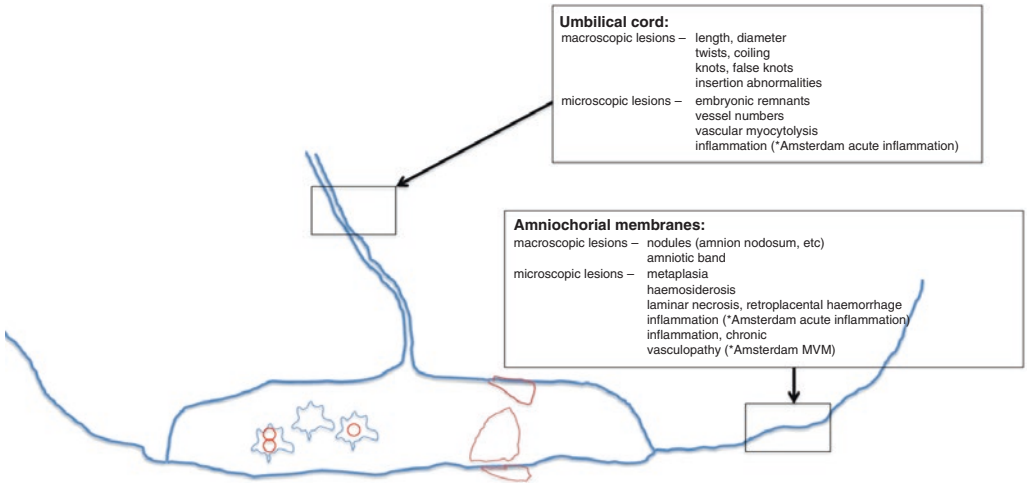

Fig. 1.1 Features or lesions in the extraplacental membranes and umbilical cord. *MVM* maternal vascular malperfusion; *Amsterdam [11]

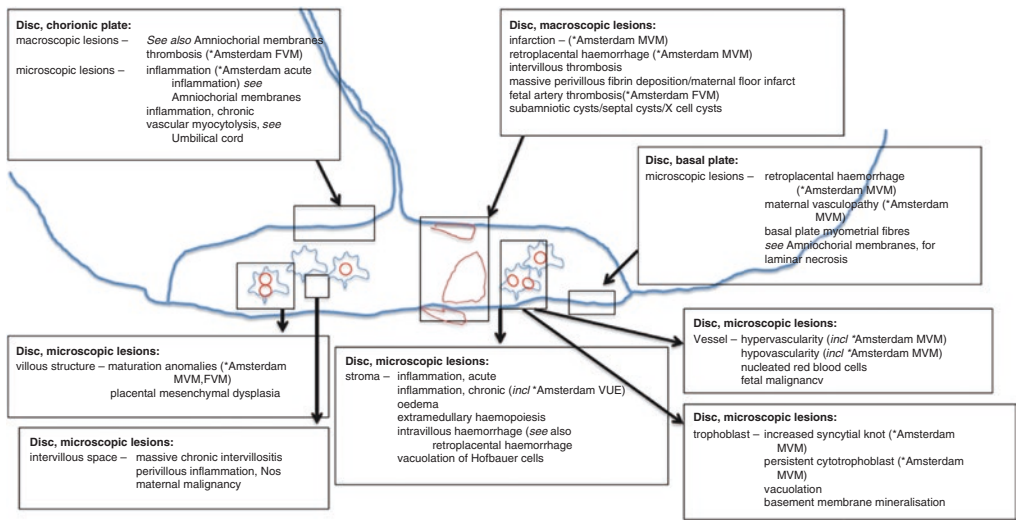

Fig. 1.2 Features or lesions in the placental disc. *FVM* fetal vascular malperfusion, *MVM* maternal vascular malperfusion, *NOS* not otherwise specified, *VUE* villitis of unknown aetiology; *Amsterdam [11]

This topographic approach is used for the gross and histological examination. Knowing what features or lesions should be sought in the different compartments of the placenta should reasonably eliminate omissions. Some pathognomonic lesions, such as perivillous fibrin deposition, may be seen in only one compartment. Others, such as amniotic fluid infection, may have one feature that may be distributed over different compartments, while other lesions, such as maternal vascular malperfusion, may have different features distributed over different compartments.

Clinical information is absolutely needed to interpret the abnormalities in the placenta. It may provide clues to look for lesions as lesions cluster with some clinical conditions [12], but such clinical information is often lacking in request forms that accompany the placenta for placental examination [13]. A thorough and methodical evaluation of the placenta would ensure that such clustered lesions are not missed but equally ensure that lesions unrelated to the clinical information provided are not missed either.

1.4 Clinical Pathological Significance

Merely cataloguing the various placental findings is not in itself helpful to clinicians. What is important to the clinician and to the patient is what do the lesions mean to them and what do they need to do about them [14]. It is essential that the placental findings be correlated with the clinical data.

Standardisation of diagnostic criteria of placental lesions is an important first step towards effective communication of the findings of placental examinations to clinicians. The lack of internationally accepted nomenclature has led to identical lesions being called differently, while variations or departures from the prototypical lesion features have led to the use of more descriptive labels. These diagnostic labels can be confusing for clinicians who find the placental reports unwieldy and difficult to comprehend. Even where the lesion is described clearly enough to be understood, the threshold where the lesion becomes critical is often unknown. It must be remembered though that clinico-pathological correlations are not static but are moveable, and clinical developments may change the threshold of diagnostic importance. As an example, chronic villitis was associated with basal ganglia and thalami injury in term infants with hypoxic-ischaemic neonatal encephalopathy but not following the introduction of therapeutic hypothermia (Table 1.2) [15, 16].

Table 1.2 Examples of clinico-pathological correlation

Period	Clinico-pathologic correlations
Antenatal	Ultrasound findings, e.g., lucency Biochemistry, e.g.. PAPP-A, AFP Hypertensive disease, e.g., haemorrhage
Natal and immediate postnatal	Obtunded infant—e.g., cord accidents Growth-restricted infant—extensive villous damage Stillborn—maternal vascular malperfusion
Future pregnancy	Basal plate myometrial fibres and possible placenta accreta Maternal uteroplacental vascular thrombosis Maternal vascular malperfusion and abruption

Evaluation of placental pathology is useful only if it can be communicated to the care providers in a form that is both comprehensible and easy to use for them. The quality of placental pathology reporting can be variable [17]. Synoptic reporting or structured reports may improve the quality of reports by ensuring that essential data are not omitted (explored further in Chap. 57). Obstetricians found reports that classified placental disease into broad pathological processes [18] would improve interpretation [19].

Clinical implications of placental examination findings are discussed in the individual chapters, but their synthesis into a clinical report is critical (discussed in Chap. 56). As alluded to earlier, gross and microscopic placental findings are contextual and need to be placed in the context of the pregnancy and of the placenta. Standardisation of nomenclature will be an invaluable contribution

in that respect. It will also allow prevalence studies to be compared between populations and the benchmarking of placental contribution to various pregnancy complications. Parenthetically, the significance of placental findings may be biased because almost all studies have been on convenience populations and not on large unselected populations [20], apart from the large Collaborative Perinatal Study which since when newer placental lesions have been described. There are no studies correlating placental disease with long-term follow-up and lack of cohort studies to truly determine likelihood of recurrence of lesions and their associations.

1.5 The Future

There have been no studies examining the positive or negative predictive values of individual placental histopathological entities. Much of the current literature in placental pathology is based on expert opinion and case or cohort studies [21]. The challenge now is using standardised nomenclature and whole-of-population studies to provide higher-level evidence to validate the predictive and prognostic value of placental examination.

It is essential to accept that there are significant gaps in knowledge between the snapshot in time examined at delivery and underlying pathophysiology. An explanted cirrhotic liver does not explain the cause of the cirrhosis any more than end-stage heart, or kidney pathology does not explain the lifelong effect of systemic risk factors. The same is true for the placenta and the maternal blood vessels that feed the placenta. Currently, most of what we know is from the end-stage disease process or early pregnancy termination samples that are not linked to pregnancy outcomes. What are needed are new approaches to monitor uteroplacental health throughout gestation and relate these metrics to pregnancy outcomes. Novel approaches using magnetic resonance imaging can provide insight into placental anatomy and function [22], while biochemistry profiles and calculated ratios act as surrogates for placental function [23, 24]. Shotgun next-generation sequencing has already challenged the concept of the microbiome of the placenta as being sterile [25], and, while it may be speculative at this stage, application of this technique may identify genomic, metabolic, transcription and protein profiles in different subsets of pregnancy complications. New technologies like quantitative uteroplacental blood flow assessment [26] and liquid biopsies of the placenta may also yield new insights. Moreover, despite differences between humans and animal models of pregnancy, these types of studies may be valuable to generate hypotheses that may then be turned back into human placental research.

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2 Placental Development with Expected Normal Gross and Microscopic Findings

Amy Heerema-McKenney

2.1 Introduction

The placenta originates with the outer cell layer of the blastocyst, the trophectoderm. The inner cell mass gives rise to the embryo. Differentiated subpopulations of trophoblast drive placentation and, together with the extra-embryonic mesenchyme, form most placental tissues [1]. The umbilical cord and amnion are derived from the inner cell mass (embryoblast). Fetal blood derives oxygen, nutrition, waste management and hormonal influence from the placenta. Fetal blood from the umbilical cord disperses into chorionic plate vessels, penetrates through the chorionic plate in artery-vein pairs into the proximal stem villi, travels further to branches of stem villi and, in the mature placenta, enters multiple series of coiled capillaries in the terminal villi via intermediate villi, eventually returning to the fetus along the same circuits via the umbilical vein (Fig. 2.1). Our understanding of how the placenta performs multiple functions is still evolving. The villous vasculosyncytial membranes of the mature placenta resemble the alveolo-capillary membranes of the lung and presumably optimise gas exchange. The histologic structure supporting many placental metabolic and endocrine functions remains undescribed. The pathologist usually handles tissues clinically characterized by the gestational age calculated since the date of last menses. Unless otherwise stated, all gestational ages described below are the menstrual age.

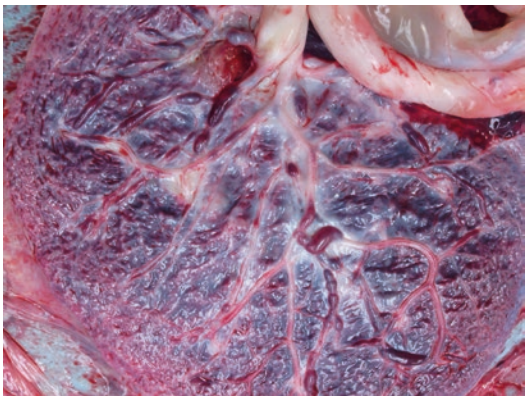

Fig. 2.1 Blood from the umbilical cord enters the chorionic plate vasculature and then travels on to the cotyledons

2.2 Umbilical Cord

2.2.1 Umbilical Cord Development

The umbilical cord develops from structures that exit the early embryo at the umbilical ring, the point where amnion meets the embryonic

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ectoderm. These early components are connected in a mesenchymal bridge to the implantation site termed the body stalk, containing paired allantoic arteries arising from the internal iliac arteries, the allantois connecting with the bladder and paired veins. A second mesenchymal bridge contains the vitelline duct connecting the primitive intestinal loop of the embryo to the yolk sac and accompanying paired vitelline vessels. As the amniotic cavity enlarges, it gathers these structures into one umbilical cord lined by amnion. The yolk sac remains separate and distal to the cord in the chorionic cavity between amnion and chorion. The right umbilical vein regresses in the second month of pregnancy. The vitelline (omphalomesenteric) duct, vitelline vessels and allantoic duct also usually regress but small remnants of one or more of these structures may persist. The normal mature cord has two arteries and one vein. Coiling of the umbilical cord is noted as early as 8-week gestation. It is unknown what exactly causes coiling but it appears related to fetal activity.

2.2.2 Gross Appearance of the Umbilical Cord

The normal cord is white, with increasing opacity as gestation progresses. The cord may be discoloured from prolonged meconium exposure, inflammation or maceration after fetal demise. The length and diameter of the cord increase with fetal growth, with increasing size of the umbilical vessels and increasing amounts of Wharton's jelly. Most cords have a left twist, with an average of 2 coils per 10 cm. The normal range of coiling is 1–3 twists per 10 cm [2]. In some cases a web of amnion tethers the cord to the surface of the disc. On cut section, three vessels (two arteries and one vein) are usually present (Fig. 2.2). A single umbilical artery is present in about 1% of cases. The umbilical arteries commonly anastomose and divide again near the insertion of the cord on the chorionic plate (Hyrtl anastomosis).

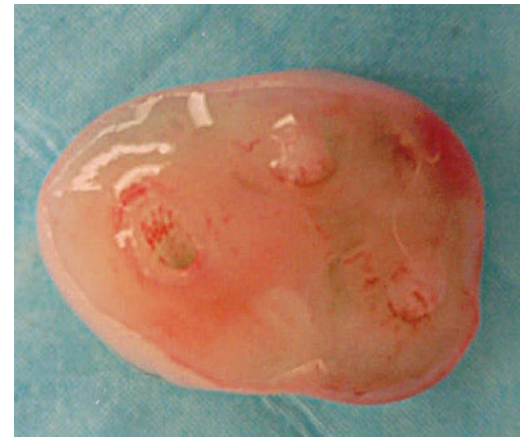

Fig. 2.2 On cut section three vessels are seen in the normal cord, surrounded by myxoid-appearing Wharton's jelly

2.2.3 Normal Histology of the Umbilical Cord

Microscopic examination shows a variable amount of gelatinous fluid-filled spaces rich in hyaluronic acids in the cord stroma, with scattered fibroblasts, myofibroblasts, rare mononuclear cells and mast cells. The umbilical vein may be larger in diameter than the paired umbilical arteries. The vein typically has a thinner muscular wall (Fig. 2.3). Allantoic or omphalomesenteric duct remnants are fairly common, as are remnants of the vitelline vessels which may show an accompanying small vessel proliferation.

2.3 Extraplacental Membranes

2.3.1 Development of the Extraplacental Membranes

2.3.1.1 Chorion and Decidua

The fetal membranes consist of three layers of diverse origin: amnion from the embryoblast bordering the trophoblast, amniotic and chorionic mesoderm from extraembryonic mesenchyme and chorionic extravillous cytotrophoblast cells from the trophoectoderm and decidua (endometrium

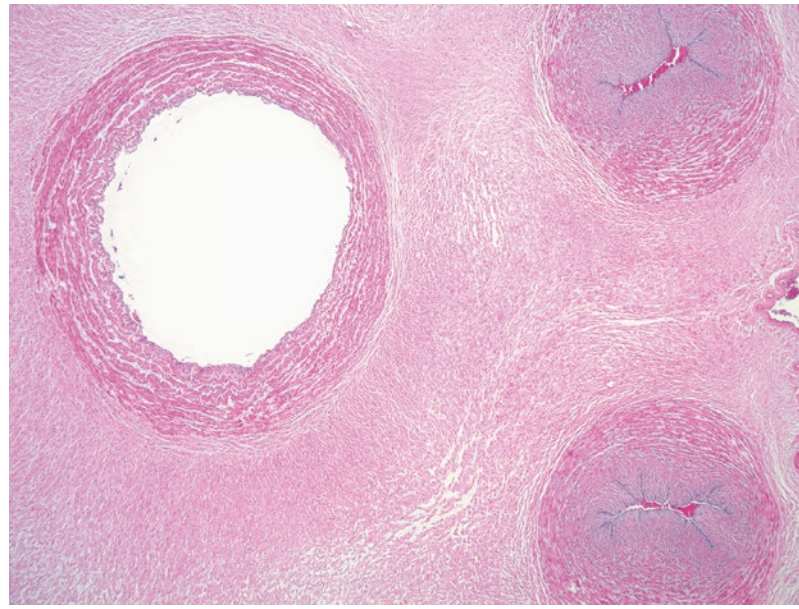

Fig. 2.3 The umbilical cord stroma contains tangled bundles of spiralled collagen fibres set in a gelatinous matrix rich in hyaluronic acid. The umbilical vein has a thin subintimal layer of elastin and layers of longitudinal and circular fibres. The arteries have less elastin and overlapping spirals of vascular smooth muscle

modified by pregnancy hormones). Shortly after implantation, decidua closes over the blastocyst. The decidua deep and lateral to the blastocyst (and eventually the placenta) is called the decidua basalis. The layer of decidua overlying the blastocyst is termed decidua capsularis. The rest of the decidua lining the uterus is termed decidua parietalis. The chorion is an expansion of the initial blastocyst lining. The cytotrophoblast layer is covered with chorionic mesoderm on the inner surface forming the primary chorionic plate. Projections of cytotrophoblast cells into surrounding lacunar spaces are invested by mesenchyme forming secondary villi. This layer of villi with the attached primary chorionic plate of the gestational sac is termed *chorion frondosum*. Around the fifth week gestation, the portion of sac farthest from the implantation pole becomes smooth as the villi degenerate (*chorion laeve*). This process spreads over the rest of the sac except for the approximately 30% of the sac closest to the implantation site pole. Further vasculogenesis in the chorion and villogenesis are concentrated in this region close to the connecting stalk (umbilical cord), giving rise to the placenta. As the chorionic sac enlarges, the decidua capsularis degenerates. The chorion laeve gradually approaches the decidua parietalis, and the chorionic extravillous cytotrophoblast cells interdigitate and appose decidual stromal cells. By 17–22-week gestation, the residual uterine cavity is obliterated. The regressed early villi of the chorion frondosum are still visible in the membranes near the disc margin at term.

2.3.1.2 Amnion

The amniotic epithelium is also invested by extraembryonic mesenchyme, the amniotic mesoderm, on the outer surface (away from embryo) (Fig. 2.4). The amniotic sac surrounds the embryo and cord. Further fetal growth and production of amniotic fluid cause the amniotic sac to enlarge. The amnion is first apposed to the connecting stalk and chorionic plate around week 8 (Fig. 2.5). By 14 weeks, the chorionic cavity between the chorionic mesoderm and amniotic mesoderm is mostly obliterated.

2.3.2 Gross Appearance of the Extraplacental Membranes

The membranes are usually slightly tan with a translucent amnion and thicker chorion. Velvety pink decidua may be present on the membranes of the delivered placenta. The amnion easily

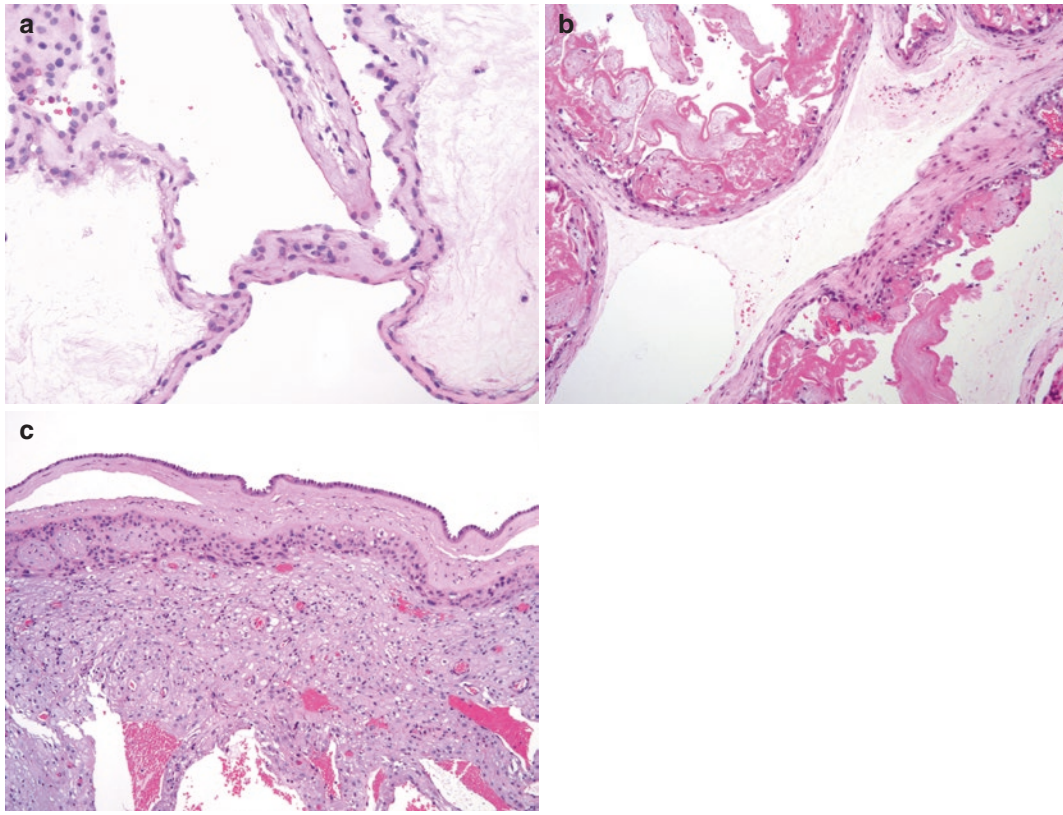

Fig. 2.4 (**a**) The amnion of the early embryo/fetus appears as a collapsed sac; a layer of mesenchymal cells forms a "mesothelial" layer on the mesodermal (outer) surface. (**b**) The secondary villi of the chorion frondosum degenerate becoming the smooth chorion. (**c**) All three layers are demonstrated in the mature membranes

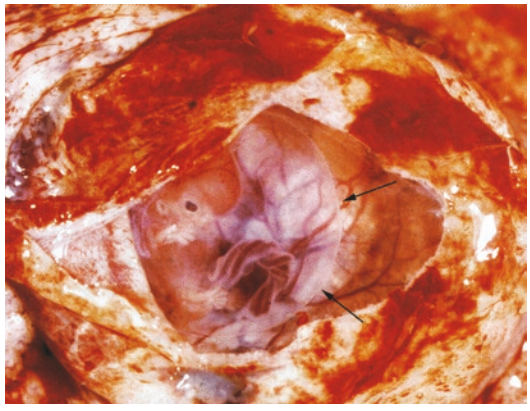

Fig. 2.5 The gestational sac of this 8-week pregnancy is shown in situ in the uterus. The chorion laeve bulges into the uterine cavity and is opened revealing the amniotic sac (arrows) surrounding the fetus; the amnion is apposed to the cord and chorionic plate; coiling is present in the umbilical cord. (Fig. 11.7 from Benirschke, Burton and Baergen, Pathology of the Human Placenta, 2012, with permission)

separates from the chorion and may seem almost gelatinous with its slippery consistency, especially with meconium exposure. Inflammation, infection, meconium and old haemorrhage may make the membranes opaque and discoloured.

2.3.3 Normal Histology of the Extraplacental Membranes

2.3.3.1 Amnion

The amnion is usually a cuboidal to low columnar epithelium. Reactive changes cause a vacuolated appearance and may cause pseudostratification. The amnion is closely related to the epidermis; rounded foci of squamous metaplasia are common in the mature placenta. The younger the gestational age, the more

notable the spindled to stellate mesenchymal cells of the mesoderm just below the epithelium basement membrane. The potential space between the amnionic mesoderm and chorionic mesoderm, once the site of the chorionic cavity, is usually visible as separation of the layers.

2.3.3.2 Chorion

The chorionic mesoderm also becomes less cellular appearing with increasing gestational age. One should not mistake the cellularity of first and second trimester chorionic mesoderm for inflammation. The extravillous cytotrophoblast cells of the cellular chorion are round to polygonal with round central nuclei. The cell borders are crisp and the cytoplasm typically eosinophilic on H&E stain, although clear-appearing cytoplasm is also common. Nuclear pleomorphism, evident as hyperchromatic, enlarged, irregularly shaped nuclei, is often seen. Cytotrophoblast cells are known to become aneuploid with numerous copies of the chromosomes from endoreduplication of the chromosomes without mitosis, likely manifest in these enlarged more bizarre-appearing nuclei [3]. The cellular chorion is typically 1–5 layers thick (Fig. 2.6). The cytotrophoblast cells may remain in layers or scatter amongst the decidual stromal cells. The term membranes may show few residual cytotrophoblast cells; other cases may show hyperplasia and microcyst formation [4]. Regressed villi of the chorion frondosum are nearly always seen, especially near the disc margin. Regressed villi may be surrounded by a variable amount of eosinophilic matrix-type fibrinoid.

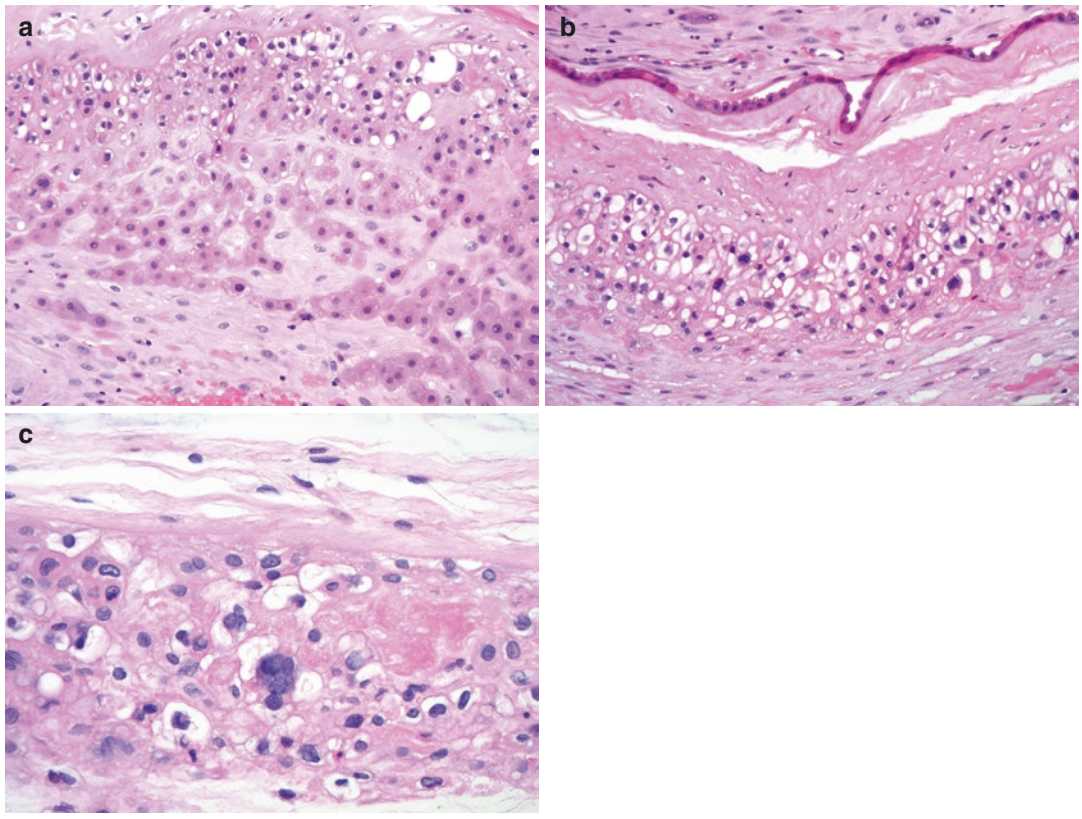

Fig. 2.6 (**a**) Hyperplasia of membranous chorion cytotrophoblast cells, with clusters of cells deeper in the decidua. (**b**) Clear-cell change of membranous chorion cytotrophoblast cells. (**c**) Nuclear pleomorphism of membranous chorion cytotrophoblast cells

2.3.3.3 Membranous Decidua

The membranous decidua contains mostly modified endometrial stromal cells, (the plump, spindled "decidual cell"), scattered lymphocytes and histiocytes, occasional decidual glands, frequent spiral arteries that have undergone thinning of the vascular smooth muscle with pregnancy and larger thin-walled decidual veins (Fig. 2.7). Frequently at term, the uppermost decidua under the cellular chorion becomes necrotic appearing, with loss of nuclear basophilia of the decidual cells and vessels, termed *laminar decidual necrosis* [5, 6]. In some foci, the genesis of the process may show apoptotic change of vessels, with a gradual spreading of cell death into the surrounding decidual stroma. Long considered a degenerative change, the process appears surprisingly orderly, confined to a laminar layer of tissue. While this change may be a part of the mechanism of decidual shedding at parturition, not all placentas from spontaneous vaginal delivery show laminar decidual necrosis (Fig. 2.8). In the majority of cases, the process is bland, whereas in a subset, foci or bands of leukocytoclastic necrosis are seen. Near regions of decidual necrosis, one may see clotting, often in residua of veins, and a variable amount of fibrinoid accumulation.

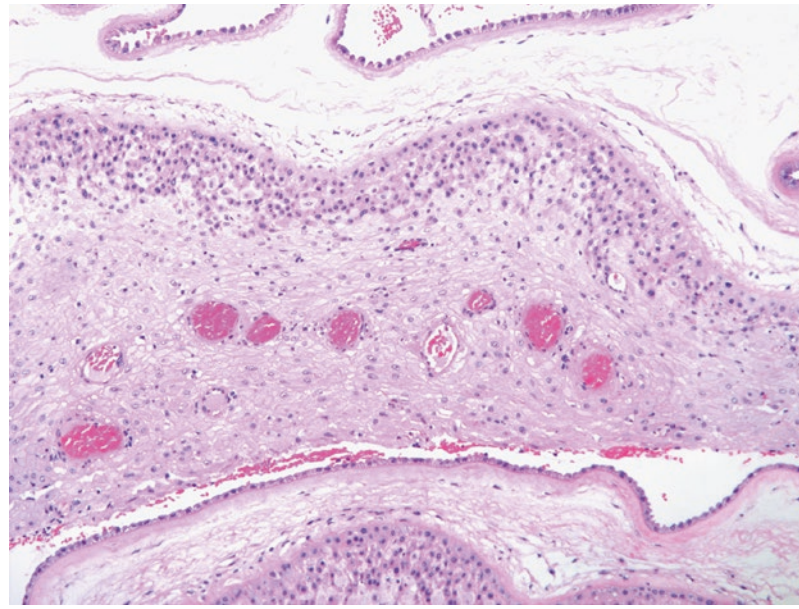

Fig. 2.7 Spiral arteries of the membranous decidua do not undergo remodelling by invasive extravillous cytotrophoblast cells; they do show thinning of the vascular smooth muscle

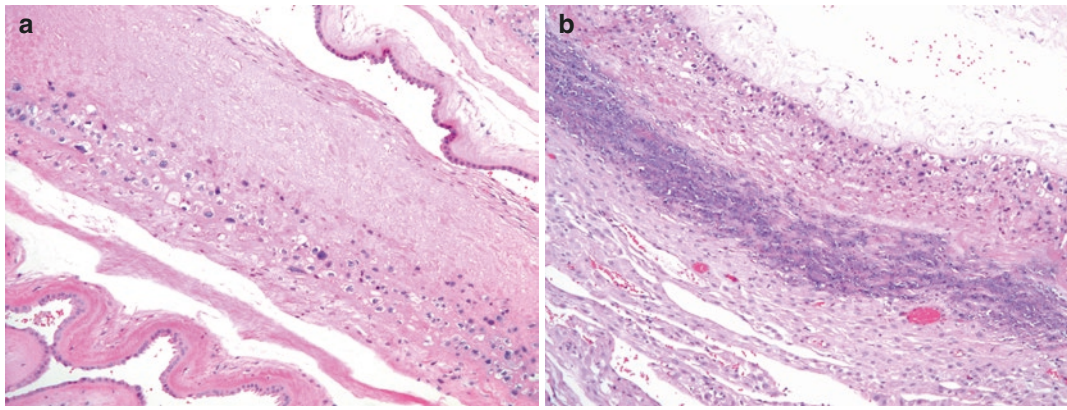

Fig. 2.8 (**a**) Laminar decidual necrosis in the mature membranes. (**b**) Leukocytoclastic decidual necrosis in the mature membranes

2.4 Chorionic Plate

2.4.1 Development of the Chorionic Plate

At the implantation site, trophoblast in contact with maternal tissues fuses forming syncytiotrophoblast. Closer to the lumen of the blastocyst, they remain cuboidal (cytotrophoblast). This inner layer closest to the embryoblast gives rise to the primary chorionic plate. During the second week post-conception, extraembryonic mesenchyme forms an inner layer over the trophoblast shell. Vasculogenesis begins in the mesenchyme, eventually giving rise to the chorionic plate vasculature [7]. By the fifth week post-conception, when the heart begins to beat, these vessels are connected to the embryonic heart via the connecting stalk. By the fourth month after menstruation, the primary chorionic plate in the region of the cord has formed the definitive chorionic plate of the mature placenta; the remainder of the primary chorionic plate from the gestational sac becomes the membranous chorion (chorion laeve).

2.4.2 Gross Appearance of the Chorionic Plate

2.4.2.1 Shape and Colour of the Chorionic Plate

The chorionic plate is usually oval and consists of tan-white tissue overlying the villous parenchyma on the fetal side of the placenta [2]. The shape of the plate and placental disc can vary (Fig. 2.9). The first and second trimester chorionic plate appears thin, white and transparent with barely discernable chorionic plate vessels. Inflammation causes opacity at this early age. The consistency becomes

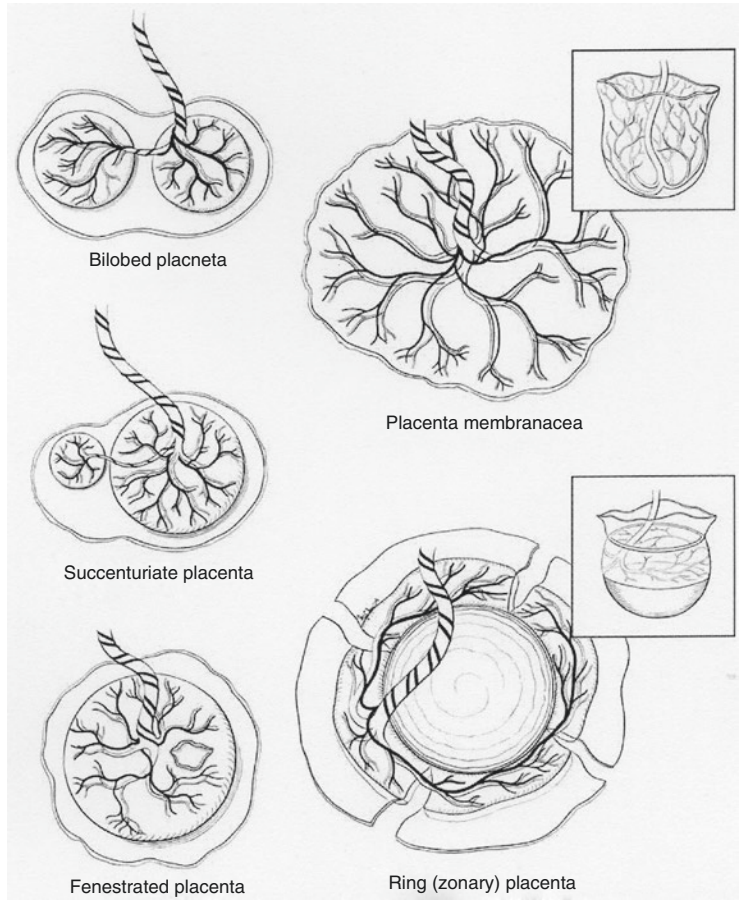

Fig. 2.9 Placental shape abnormalities. Multilobation (bilobed and succenturiate placenta) is relatively common, while the other abnormalities shown are rare. Placenta membranacea should be suspected when the disc is very broad and lacks significant associated extraplacental membranes. (Reproduced from Baergen, Manual of Benirschke and Kaufmann's Pathology of the Human Placenta, 2005—Fig. 13.1 p. 209—with permission)

firmer throughout gestation as the plate thickens with collagenous connective tissue, especially around the larger vessels near the cord insertion. The plate becomes more tan and opaque near term in the third trimester.

The overlying amnion is continuous with the membranous amnion and covering of the umbilical cord. The amnion is translucent but may become opaque and discoloured with inflammation or meconium exposure. These processes also may cause the amnion to slide away from the chorionic plate, though it remains firmly attached to the umbilical cord. Accumulation of fibrin beneath the chorionic plate is a common finding at term, visible as tan-white plaques. Thrombohaematomas beneath the chorionic plate may be visible on the surface. Cysts lined by extravillous trophoblast often form beneath the chorionic plate. They may extend into the plate and appear as protuberant thin-walled cysts on the fetal surface of the disc.

2.4.2.2 Umbilical Cord Insertion

The umbilical cord may connect with chorionic plate vasculature in the centre of the disc or at any site moving further out the radius to the extraplacental membranes. The cord most commonly has an eccentric insertion [2]. Insertion within 1 cm of the disc edge is termed *marginal* umbilical cord insertion. Insertion within the extraplacental membranes is termed *velamentous*. The umbilical vessels typically diverge from the cord within the chorionic plate or occasionally within the membranes. Rarely, the vessels separate before connection to the chorionic plate (*furcate* insertion) (Fig. 2.10). The chori-

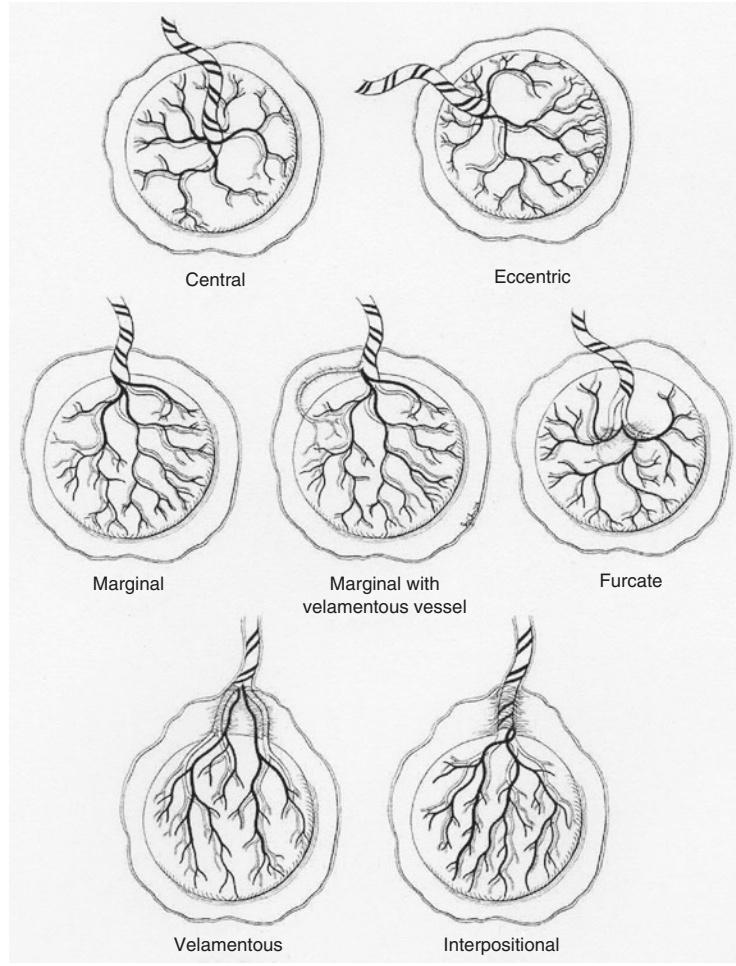

Fig. 2.10 Umbilical cord insertion patterns. Most cords insert eccentrically. Velamentous, furcate and marginal with velamentous vessel patterns leave fetal vessels unprotected by Wharton's jelly or the chorionic plate, where they may be subject to compression or injury. (Reproduced from Baergen, Manual of Benirschke and Kaufmann's Pathology of the Human Placenta, 2005—Fig. 15.17 p. 263—with permission)

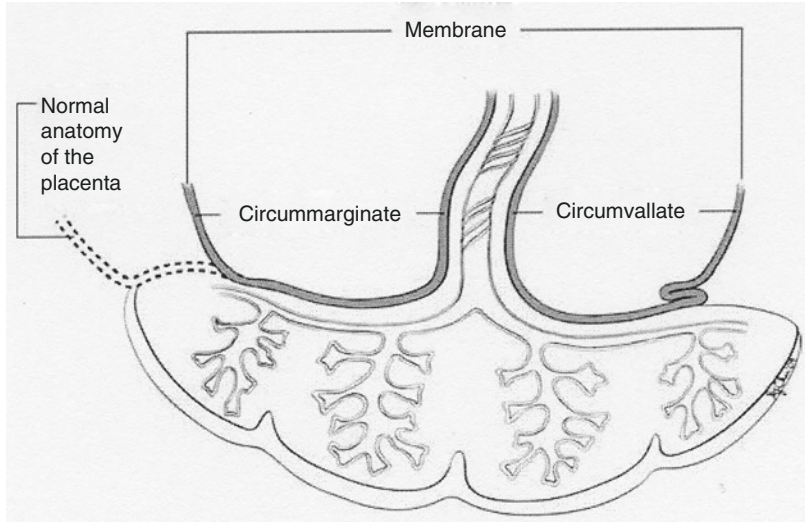

Fig. 2.11 Extrachorial placentation. The membranes usually insert at the margin of the disc. Insertion of the membranes inside the circumference of the placenta is termed extrachorial placentation. In circummarginate insertion, the junction between chorionic plate and membranes is flat. In circumvallate insertion, the membranes are folded inwards towards the centre of the disc and a fibrin ridge is palpable. The amnion does not usually accompany the chorion in the fold of circumvallate membrane insertion. (Reproduced from Baergen, Manual of Benirschke and Kaufmann's Pathology of the Human Placenta, 2005—Fig. 13.4 p. 212—with permission)

onic plate vessels branch away from a central or peripheral umbilical cord insertion site in a radial distribution. Chorionic plate arteries typically cross over chorionic plate veins. The vessels progressively decrease in diameter with each branching, with substantial cover of the chorionic plate by pairs of an artery and vein diving down to supply at the villous vasculature. With more peripheral umbilical cord insertions, especially marginal and velamentous insertions, the chorionic plate vessels maintain a more constant diameter as the vessels course across the placenta, with fewer apparent ramifications in the chorionic plate. This sparser appearing distribution with large calibre vessels is termed a *magistral* distribution. The vessels are often "empty" appearing in the first and early second trimester specimen. Progressing to term they become more and more engorged with fetal blood.

2.4.2.3 Insertion of the Extraplacental Membranes

The membranes usually connect with the chorionic plate at the margin of the disc, without extension of villous parenchyma outside the limits of the chorionic plate. Part, or all of the circumference, of the insertion may demonstrate *extrachorial placentation* with villous parenchyma extending beyond the point where chorionic plate and membranes meet. In these cases, the membranes leave the chorionic plate within the circumference of the disc. If the junction between membranes and disc is flat, this membrane insertion is termed *circummarginate*. If the junction between the membranes and disc shows a raised rim with membranes folded towards the interior of the disc, the insertion is termed *circumvallate* (Fig. 2.11). The cause of these variations is unknown. The significance of this change is in recognising chronic abruption, with circumvallate membrane insertion, and organising haemorrhage at the disc margin.

2.4.3 Normal Histology of the Chorionic Plate

The amnion overlying the chorionic plate is like that described above for the free membranes. A potential space lies between the amnion and the chorionic plate. The chorionic plate consists mostly of fibrous connective tissue supporting

the chorionic plate vasculature in its distribution to the cotyledons. The connective tissue contains fibroblasts, myofibroblasts and occasional macrophages (Hofbauer cells), including macrophages and occasional mast cells. The chorionic plate is lined by syncytiotrophoblast beneath the surface overlying the maternal blood space, with a variable number of underlying cytotophoblast (Fig. 2.12). Like the surface of proximal stem villi, this syncytiotrophoblast layer becomes progressively eroded approaching term and replaced by fibrin (Langhan's fibrinoid). Populations of extravillous cytotrophoblast cells may proliferate beneath the chorionic plate as dense cell clusters, lining of cysts or scattered extravillous cytotrophoblast embedded in fibrinoid. These cells are generally more numerous at the disc margin.

The chorionic plate vasculature appears as muscular vessels within the connective tissue (Fig. 2.13). No histologic features reliably distinguish chorionic plate arteries from veins, with exception of direct positioning of one vessel over another, suggesting an artery crossing over a vein. The amniotic side of the vessel is often thinned in comparison to chorionic side.

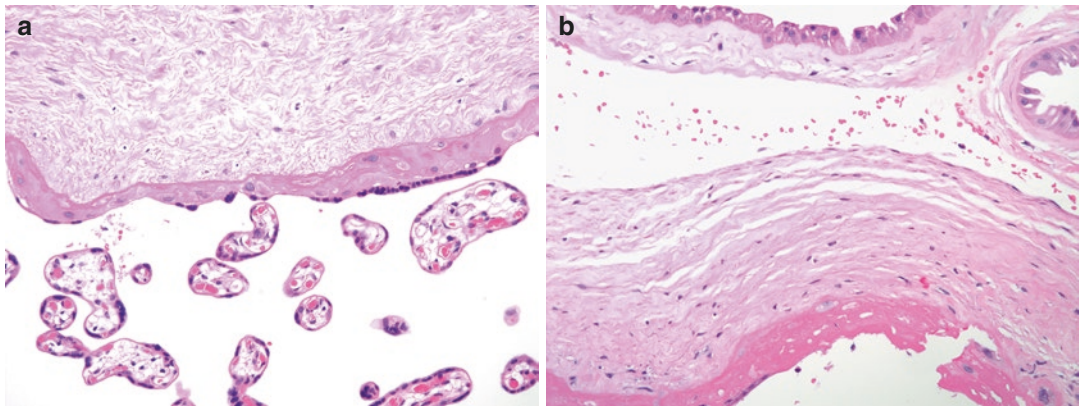

Fig. 2.12 (**a**) Chorionic plate. Syncytiotrophoblast lines the undersurface of the chorionic plate, facing the intervillous space; scattered cytotrophoblast cells are seen above the syncytiotrophoblast. (**b**) With advancing gestational age, fibrin deposition replaces most of the syncytiotrophoblast; occasional cytotrophoblast cells remain visible

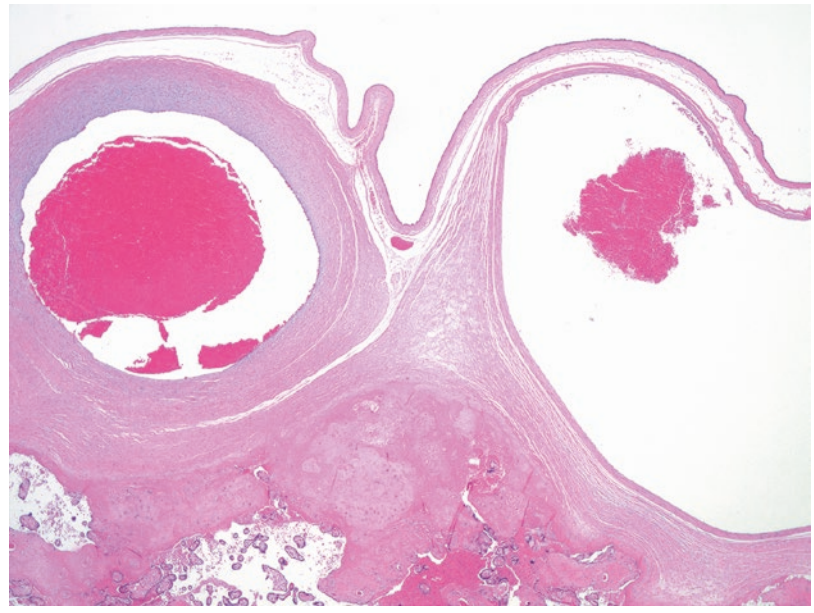

Fig. 2.13 The chorionic plate vasculature is supported by the dense collagenous connective tissue of the chorionic plate

The intima may appear focally prominent and bulge into the lumen. These changes have been termed *endothelial cushions*. Currently only those cushions associated with disruption of the endothelium and fibrin deposition are considered pathologic.

2.5 Stem Villi

2.5.1 Development of Stem Villi

Stem villi are recognised in the mature placenta as larger villi with muscular vessels and fibrous stroma. The proximal stem villi contain the first ramifications of chorionic plate vessels. They function as trunks of the villous tree and anchor to the basal plate and septa connecting the chorionic plate to the basal plate. In early pregnancy, the future stem villi are not readily distinguishable from other *mesenchymal villi* invested with extraembryonic mesenchyme and newly formed fetal vessels. Mesenchymal villi are seen with placental maturation wherever new villous growth occurs. The thick layers of cytotrophoblast and syncytiotrophoblast seen in the first trimester are not as prominent on mesenchymal villi of the more mature placenta (Fig. 2.14). The larger more proximal "stems" of these first trimester villi develop adventitia around the central vessels and are termed *immature intermediate villi*. Immature intermediate villi are recognisable around 8-week gestation. As the adventitia forms around central vessels, the Hofbauer cell-rich stroma forms rounded reticular spaces; a mesh-like capillary net is present beneath the trophoblast surface (Fig. 2.15). The rounded reticular spaces are lined by sail-like processes of stromal cells and appear to facilitate Hofbauer cell motility [8]. Trophoblast sprouting from the surface of these villi, together with branching angiogenesis, gives rise to more mesenchymal villi, which mature into more immature intermediate villi [9]. Throughout the second trimester, immature intermediate villi become more and more numerous. The earlier, more proximal generations of these villi become progressively larger with central muscular vessels and fibrous stroma. As immature intermediate villi mature into stem villi with progressive stromal development, the peripheral capillary net regresses, reticular spaces disappear and Hofbauer cells become inconspicuous. By the end of the second trimester, most immature intermediate villi have matured into stem villi and their mature intermediate villous ramifications. Throughout the third trimester, most remaining immature intermediate villi reside in the centre of cotyledons, where they may give rise to more generations of mature intermediate villi and terminal villi. At term, immature intermediate villi should

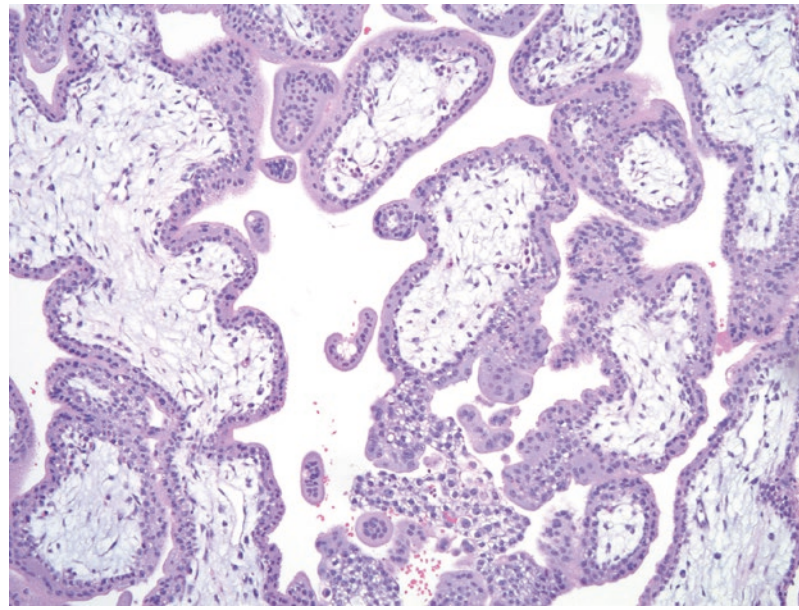

Fig. 2.14 Mesenchymal villi from the first trimester gestational sac with a continuous layer of villous cytotrophoblast, thick overlying syncytiotrophoblast, loose stroma of mesenchymal stromal cells, occasional Hofbauer cells and thin-walled blood vessels

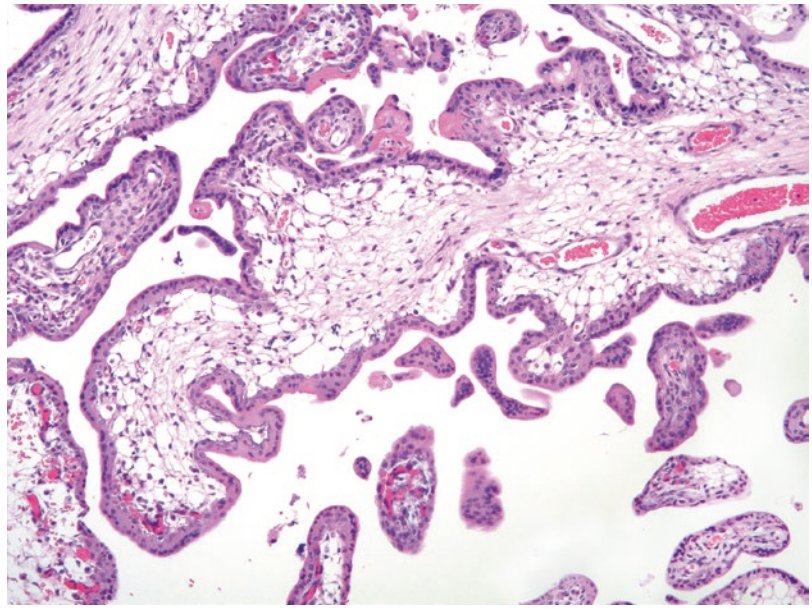

Fig. 2.15 Immature intermediate villi are most numerous in the second trimester, showing progressive development of adventitia around central vessels, rounded reticular stromal spaces containing Hofbauer cells and a peripheral capillary network

be present in focal groups, comprising no more than 10% of total villi.

2.5.2 Gross Appearance of Stem Villi

Larger proximal stem villi may be visible grossly as white thickenings around vessels in the upper third of the disc.

2.5.3 Normal Histology of Stem Villi

The mature stem villus ranges in thickness from 200 to 1500 μm in diameter, with more proximal stem villi being thicker, with greater amounts of supportive collagenous stroma. Secondary and tertiary branches of stem villi become progressively smaller with morphology transitioning to that of the mature intermediate villus. Muscular vessels run longitudinally through the core, supplying and returning blood from smaller branches. Vessels branch within the core of the proximal stem such that histologic section shows multiple vessels. Arteries are not reliably distinguished from veins (Fig. 2.16) although, in general, veins appear more thin-walled. The stem villous vessels may show significant variation in thickness. Proximal stem villi may show loosening of the stroma at the interface between the muscularis and fibrous connective tissue. Endothelial cells may appear vacuolated (Fig. 2.17). While striking at low power, these changes are of no known clinical significance. Secondary and tertiary stem villi may show stenotic appearing vessels with small lumens. These changes are exaggerated in distal villous hypoplasia and physiologically in tertiary stem villi beneath the chorionic plate (Fig. 2.18). The stroma also varies in appearance. Mature stem villi may show dense connective tissue nodules of unknown significance; sometimes they appear to surround small lumens as shown in Fig. 2.18. Alternatively, they may show foci of stromal thinning near the core, with scattered Hofbauer cells. Immature stem villi continue to show the perivascular capillary sheath, likely the precursor to chorangiomatous lesions often found in stem villi. Approaching term, the syncytiotrophoblast layer of proximal stem villi becomes replaced with Langhan's fibrinoid.

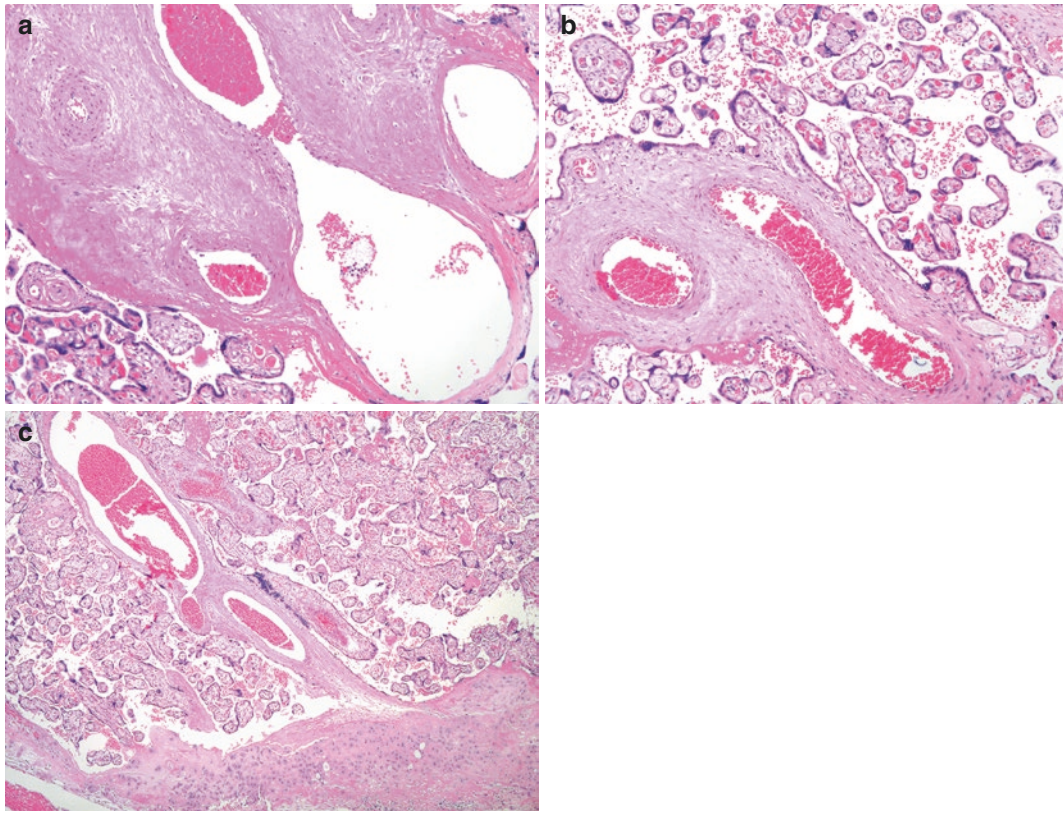

Fig. 2.16 (**a**) Collagen-rich proximal stem villus with multiple branchings of stem vessels. (**b**) Smaller stem villus showing projections of mature intermediate villi from the surface. (**c**) Anchoring stem villus connecting the basal plate

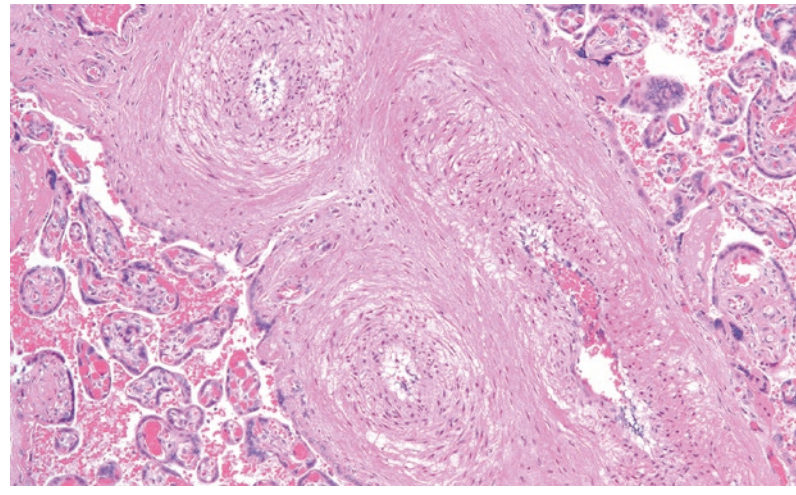

Fig. 2.17 Proximal stem villus showing thick-appearing vessels

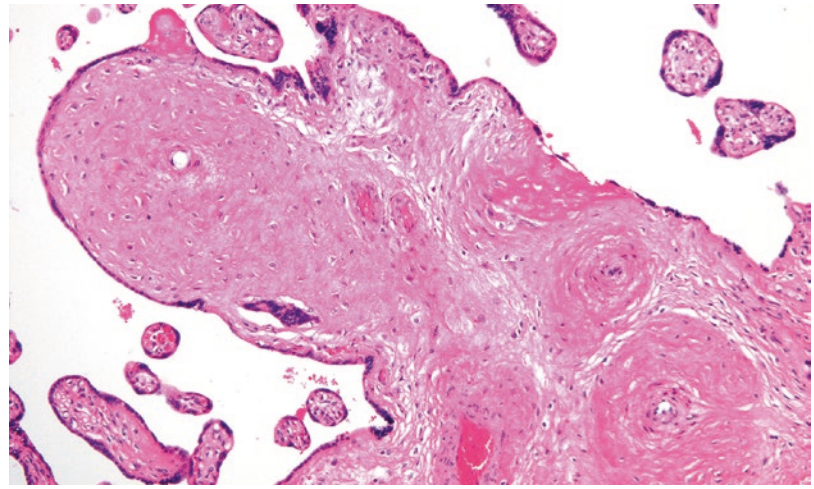

Fig. 2.18 More distal stem villus showing stenotic-appearing vessels with prominent collagenous stroma

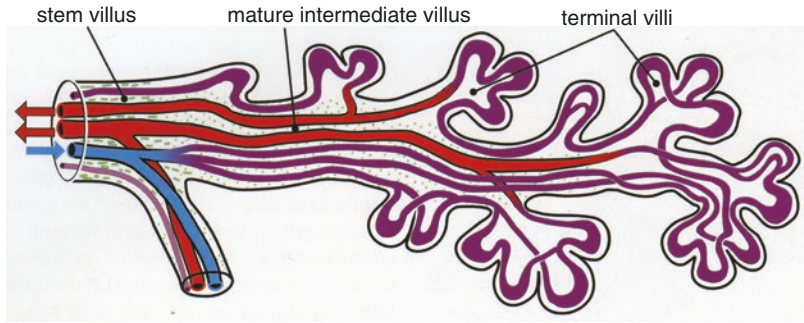

Fig. 2.19 Relationship of fetal vessels in mature distal villi. Terminal villi contain complex loops of capillaries that emerge and return to the intermediate villus in series. Capillaries frequently are rejoined after branching. Sinusoidal dilatation of terminal villous capillaries decreases resistance to flow. (Fig. 7.19 from Benirschke, Burton and Baergen, Pathology of the Human Placenta, 2012, with permission)

2.6 Distal Villi

2.6.1 Development of Distal Villi

Like stem villi and the chorionic plate, distal villi originate from layers of trophoectoderm and extra-embryonic mesenchyme [10]. Distal villi at term are comprised mostly of terminal villi with fewer numbers of mature intermediate villi. Both populations develop in the second trimester around 20-week gestation. Mature intermediate villi branch from stem villi. Terminal villi form as richly capillaried sprouts from the surface of intermediate villi through non-branching angiogenesis [11]. The course of a fetal erythrocyte enters the mature intermediate villus from the stem villus. Along the intermediate villus, it may enter and exit the coiled looped capillaries of multiple terminal villus clusters before returning to the fetal venous system via intermediate villi and subsequently stem villi (Fig. 2.19). Both populations are lined by syncytiotrophoblast, with progressively fewer numbers of villous cytotrophoblast (Langhan cells) visible as gestation proceeds towards term.

2.6.2 Gross Appearance of Distal Villi

Distal villi form the bulk of placental tissue seen on cut section of the disc. The tissue is normally soft, spongy and dark red appearing with a finely

granular appearance due to the underlying architecture. The degree of erythema is due to the fetal blood content of the villi.

2.6.3 Normal Histology of Distal Villi

Mature intermediate villi are 80–120 μm in size, with thin-walled central vessels embedded in a loose connective tissue showing little to no residual reticular stroma (Fig. 2.20). Terminal villi may be larger or smaller diameter depending upon the number of capillary loops in cross section and degree of sinusoidal dilatation. Terminal villi are comprised of at least 40% capillary space by volume, with thinning of the interface between fetal capillary and syncytiotrophoblast to form vasculosyncytial membranes (Fig. 2.21). This normal defining appearance is only visible in well-preserved villi that contain fetal blood. Syncytiotrophoblast nuclei are aggregated into knots, usually present on one-third of distal villi at term. Increasing amounts of fibrinoid both inside and outside the villous surface is evident approaching term. Incorporation of this fibrin within the villus appears to be associated with involution of the fetal vessels adjacent to the fibrinoid, termed *fibrinoid necrosis*. This process appears similar to the deposition of the fibrin known as Langhan's stria along mature stem villi and likely reflects fibrin deposition after syncytiotrophoblast damage. At term, fewer than 10% of villi show this change in the normal placenta (Fig. 2.22).

While this simplification describes the basic structure and appearance of distal villi, villous histology varies both within a single disc and from individual to individual. In general, maturity yields smaller calibre villi. In the central 40–60% of the parenchyma (from chorionic plate to basal plate), the classic villous morphology is predominant. Beneath the chorionic plate, distal villi of "normal" placentas frequently appear more sparse and smaller diameter, resembling the histology of *distal villous hypoplasia* (Chap. 15). Location beneath the chorionic plate suggests that these are the earliest terminal villi to develop. It is unknown if the histology is due to lower relative oxygen tension in this region, sluggish maternal flow or simply the age of the fetus at the time of terminal villous development. An immature placenta showing accelerated maturation tends to show expansion of this change in the subchorionic region and elsewhere. In contrast, the basal villi may appear larger with loose-appearing stroma. A mature placenta with delayed villous maturation often shows expansion of immature villi in the basal third. Small reserve populations of imma-

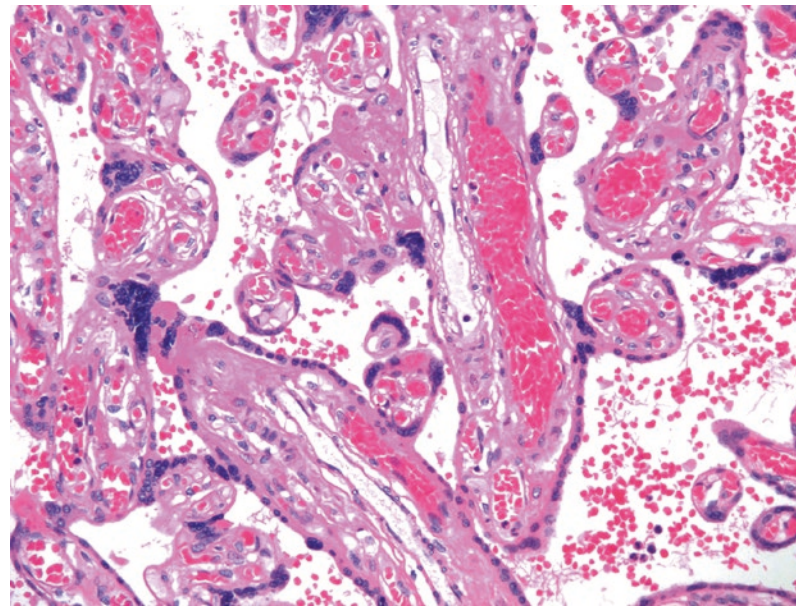

Fig. 2.20 Mature distal villi demonstrating longitudinal profiles of mature intermediate villi with projections of terminal villi

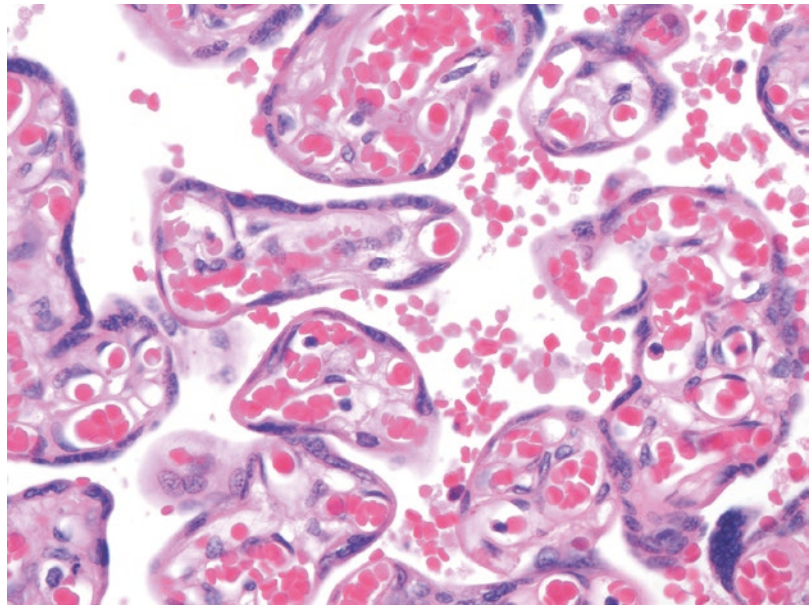

Fig. 2.21 Mature terminal villi show sinusoidal dilatation of the coiled capillaries with formation of vasculosyncytial membranes

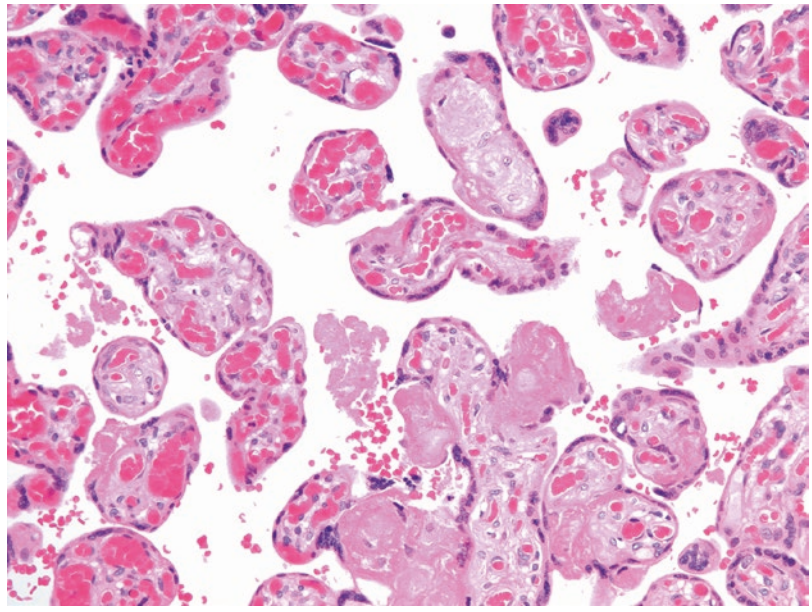

Fig. 2.22 Mature villi at term may show foci of fibrin deposition at areas of syncytiotrophoblast injury or degeneration; the fibrin is incorporated into the villus

ture intermediate villi and mesenchymal villi are normal in the term placenta, typically in the centre of cotyledons. These foci are termed "growth centres". Larger immature basal mesenchymal villi may appear to undergo stromal fibrosis without the usual capillarisation of mature intermediate or terminal villi. It is unclear whether or not this is the same process as fibrinoid necrosis of mature villi. Resulting histology shows clusters of *hypovascular villi* with cauliflower-shaped contours, few, mostly small, vessels, and poor vasculosyncytial membrane development. It is unclear what parameters of this change are acceptable as "normal", though application of the 10% standard

seems reasonable. Discerning normal villous maturation from dysmaturity is a skill that continuously evolves in the placental pathologist. It is refined from years of exposure to the range of morphologies seen across gestational ages. It has been said, "if you've seen one normal kidney, you've seen them all, but to see a normal placenta takes years of experience".

2.7 Intervillous Space and Nonvillous Parenchymal Elements

2.7.1 Development of the Intervillous Space

The intervillous space originates in vascular lacunae formed by lytic actions of syncytiotrophoblast upon endometrial tissues early in blastocyst implantation. Lumens formed in syncytiotrophoblast meet eroded endometrial capillaries to form blood-filled lacunae. Implantation site extravillous invasive cytotrophoblast eventually connects these spaces to spiral arteries and veins to create the maternal circulation of the early placenta. Maternal blood enters the intervillous space from transformed spiral arteries at the basal surface; it bathes villi and returns to the maternal circulation via veins in the septa and basalis. Septa and cell islands are nonvillous structures in the intervillous space. Cell islands are most numerous in the first and early second trimester placenta. They are formed by extravillous cytotrophoblast and associated matrix-type fibrinoid, similar to extensions from anchoring villi. Some authors equate cell islands in the early placenta with trophoblast cores destined to become invested with mesenchyme forming primary villi from the earliest stages of placentation [12]. Septa are folds of the basal plate within the parenchyma of the disc.

2.7.2 Gross Appearance of the Intervillous Space

The intervillous space only becomes notable when filled with elements such as fibrin. Gaping spaces known as "flow voids" may be visible on cut section. They are of no known clinical significance. Septa are visible as tan-white strands extending from the basal plate towards the chorionic plate. They outline the 15–20 cotyledons of the mature placenta.

2.7.3 Normal Histology of the Intervillous Space

The maternal blood space contains mostly red blood cells. If nucleated blood cells are frequent appearing at low power, high-power inspection is warranted to exclude pathology. In addition to maternal blood, other elements in the normal intervillous space include septa and cell islands. Septa are considered folds of the basal plate extending into the parenchyma, comprised predominantly of extravillous cytotrophoblast and fibrinoid (Fig. 2.23). A variable amount of decidua is present near the base of a septum. The extravillous cytotrophoblast of septa may form cohesive clusters, line cysts or be dispersed in strands and single cells within the mostly matrix-type fibrinoid. The surface facing the maternal blood space is typically layered in fibrin-type fibrinoid. Openings into maternal circulation, returning to veins, may be visible within the septum.

Cell islands are rare in the mature placenta, though frequent earlier in gestation and near the disc margin. They consist of proliferations of extravillous cytotrophoblast cells with a variable admixture of fibrinoid (Fig. 2.24). Limits for the amount of cell islands acceptable in a normal placenta have not been established. Perivillous proliferations of extravillous cytotrophoblast cells may also be seen. Extravillous cytotrophoblast cells of these foci often show nuclear and cytoplasmic enlargement sometimes striking nuclear pleomorphism (Fig. 2.25). Cell islands, foci of villous attachment to septa and foci of extravillous cytotrophoblast cells adjacent to villi, may all be related structures sectioned in different planes; this has not been definitively established.

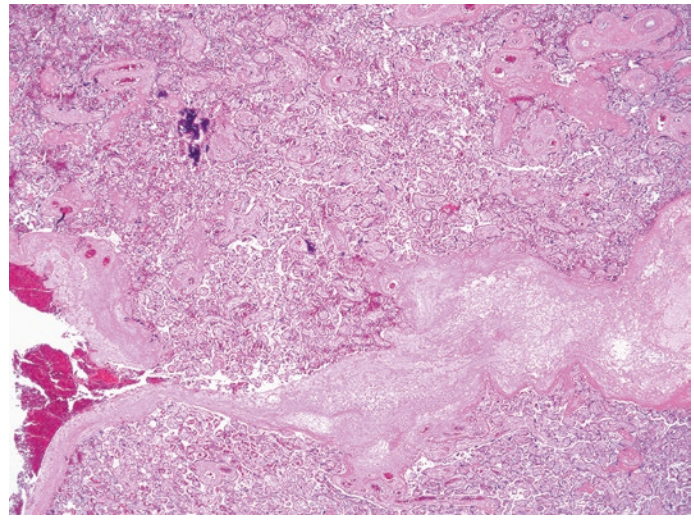

Fig. 2.23 Placental septa are infoldings continuous with the basal plate; in this image a septum connects with the basal plate on the left, with anchoring villi attaching to sides

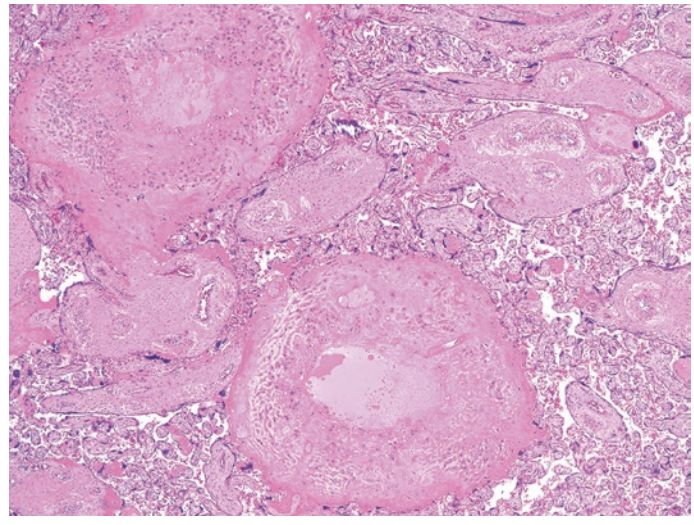

Fig. 2.24 Cell islands consist of extravillous cytotrophoblast cells and fibrinoid matrix, often with cyst formation

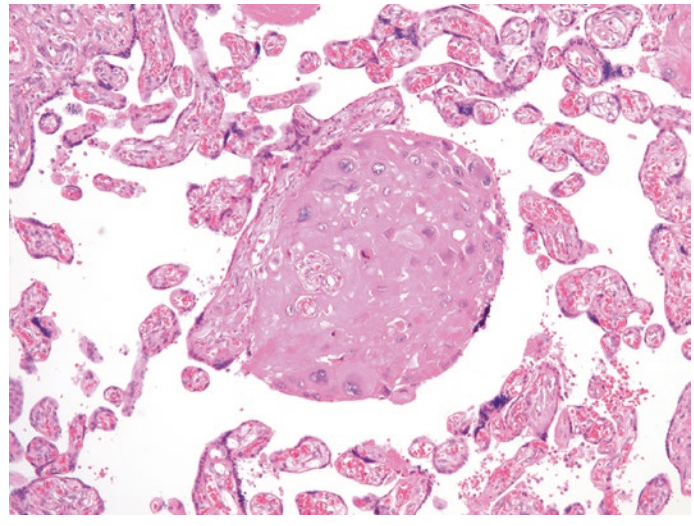

Fig. 2.25 Proliferation of extravillous cytotrophoblast cells with pleomorphism from the surface of a distal villus

2.8 Basal Plate

2.8.1 Development of the Basal Plate

The basal plate is roughly defined as the base of the intervillous space together with the placental and decidual tissues that adhere to it after delivery. It is only recognised on the delivered placenta. The precursor to the basal plate is the trophoblastic shell, separating the lacunae formed by trophoblast cells from the basal decidua. Initially formed by syncytiotrophoblast, the trophoblastic shell forms the leading edge of blastocyst implantation. Cytotrophoblast cells reach the shell through trabeculae and break up the interdigitations of syncytiotrophoblast and decidual stroma as invasive-type extravillous cytotrophoblast cells (Fig. 2.26). The invasive extravillous cytotrophoblast cells continue to locally remodel the decidua through interactions with the vasculature and deposition of matrix-type fibrinoid. Additional generations of invasive-type extravillous cytotrophoblast are supplied from cell columns, where anchoring villi contact the basal plate (Fig. 2.27).

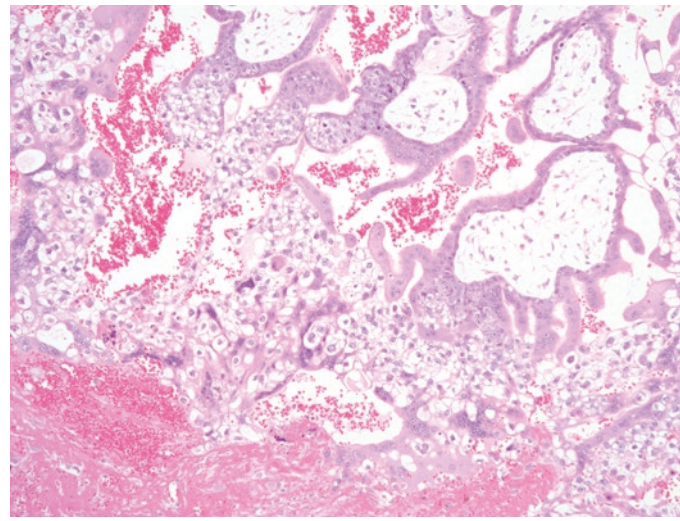

Fig. 2.26 Trophoblastic shell as seen in an ectopic pregnancy

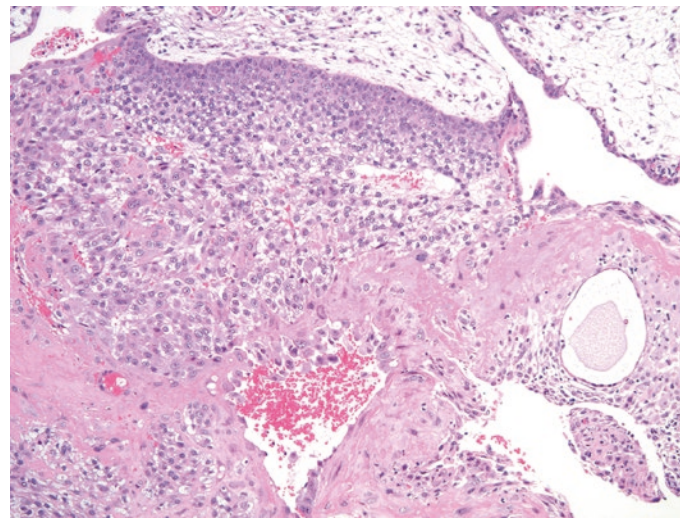

Fig. 2.27 Extravillous cytotrophoblast emerges from cell columns and build the interface between placenta and decidua; the most immature smaller cells are closest to the anchoring villus; more differentiated cytotrophoblast cells remodel the maternal vasculature (15-week gestation)

2.8.2 Gross Appearance of the Basal Plate

The placenta spontaneously delivered before 18 weeks may not show much of a basal plate, as there is generally less fibrinoid deposition to hold the tissues together. Later in the second and third trimester, the basal surface is more likely to show the rounded appearance of cotyledons with further development of the basal plate. The basal plate appears as a slight grey-tan sheen on the maternal surface of the more mature placenta (Fig. 2.28). Vascular openings through the basal plate may be visible as small erosions. Longitudinally arrayed vessels or coils of modified spiral arteries may also be visible. Smeared blood is usually present, especially in the marginal sinus.

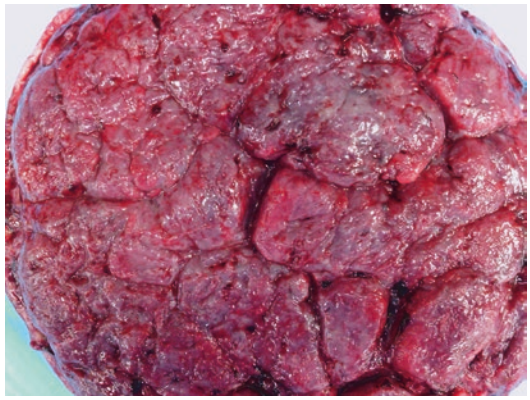

Fig. 2.28 Gross appearance of basal plate. Septa fold in between cotyledons. Openings of larger maternal vascular spaces are visible on the surface

2.8.3 Normal Histology of the Basal Plate

On the side of the basal plate facing the intervillous space, fibrin deposition (Rohr's fibrinoid) is common. The basal plate contains numerous foci of necrotic-appearing vessels, decidua and regressed villi enmeshed in fibrinoid (Nitabuch's fibrinoid) as well as remodelled vessels supplying and draining maternal blood to and from the intervillous space. It can be difficult to distinguish arteries from veins in the fibrinoid, unless the residual spiral architecture is evident to identify the remodelled arteries (Fig. 2.29). Deep to the layer of fibrinoid is the adherent decidual basalis. The central 2/3 of basal decidual spiral arteries are transformed into low-resistance vessels with dilation, dissolution of vascular smooth muscle and replacement of the vascular media by fibrin with extravillous cytotrophoblast remaining in the remodelled wall of the vessel. These

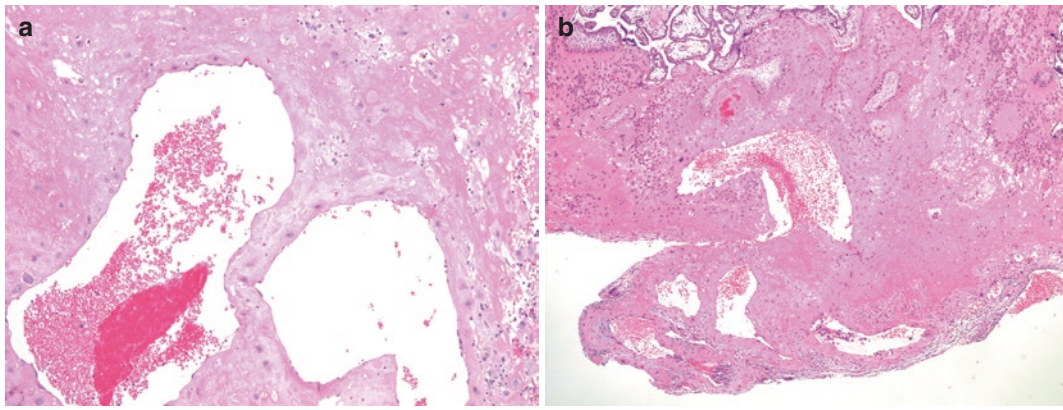

Fig. 2.29 (**a**) Maternal vessel in basal plate surrounded by Nitabuch's fibrinoid and occasional extravillous cytotrophoblast cells. (**b**). The configuration of these remodelled vessels in the basal plate and decidua is consistent with a spiral artery; extravillous cytotrophoblast cells are seen in the lumen

may be seen in regions of basal plate with more intact decidua basalis. Decidual veins along the basal plate and at the margin are greatly dilated. Villous parenchyma extends into decidual veins with progressive placental growth. Vascular smooth muscle remains to some degree in veins, forming a discontinuous muscular ring around the basalis and disc margin.

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3 Indications for Examining the Placenta

Beata Hargitai, Tamas Marton, and Amy Heerema-McKenney

3.1 Introduction

"So many countries, so many customs". The conventional wisdom faithfully reflects multiple varieties of triaging systems routinely used in obstetric and perinatal pathology practices. In general, a triage system is appropriate if it fulfils three criteria: indication of examination is based on medical evidence, practice is determined by (local) clinical demand, and it is reliant on resources (both financial and staffing). In case of unfavourable pregnancy outcome, there is also a legal aspect of the placental examination.

Placental examination by pathologists with training in perinatal pathology can explain aspects of the clinical presentation, maternal or neonatal condition and, in up to 65% of the cases, relevant information about the cause of intrauterine fetal demise [1]. Clinical indications for placental pathologic exam are important to appropriately triage cases. Triaging of the placentas needs to be done by consultants or appropriately trained staff, i.e., senior trainees. Pathologists have published recommendations for placenta triage, yet interestingly, there are no official guidelines from American College of Obstetricians and Gynaecologists or the Royal College of Obstetricians and Gynaecologists. The most recent guideline is from the Royal College of Pathologists *Tissue Pathway for Histopathological Examination of the Placenta*, published in July 2017 [2]; other guidelines include the *Journal of Clinical Pathology* Best Practice No. 178 article [3] and the *Practice Guideline for Examination of the Placenta* developed by the Placental Pathology Task Force of the College of American Pathologists [4]. The authors of this chapter reflected on the various existing recommendations, revisited guidelines and amalgamated experience of working at busy perinatal pathology departments to form practical advice we hope will be useful. The RCPath guideline indicates: "Histopathological examination of the placenta following a pregnancy affected by medical complications, pregnancy loss or neonatal death may provide an explanation of the pregnancy complications, pregnancy loss or neonatal death and may also provide information relevant to the management of the associated infant and/or subsequent pregnancies and be of use to serious incident reviews and other audits of patient care". It is also stated that the indications for referral of placentas for pathological examination need to be agreed locally [2]. Unfortunately, perinatal

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pathology suffers globally from lack of resources [5] and it is usually placental examination that is suspended when staff shortages or other limitations endanger the service in a pathology department. In the USA, placental examination is not necessarily limited by a larger system. However, subspecialty expertise in perinatal pathology is limited to a very small number of practitioners. In addition, universal coverage of healthcare costs is not guaranteed in the USA; prudence in examination potentially adding to cost is warranted given that some patients may be saddled with already overwhelming debt from medical care.

It must be emphasized that placental examination should be driven by clinical demand and in partnership with obstetricians and neonatologists. Triaging systems can give general directions but each case should be judged individually. A clinician may request placental examination with specific concerns not necessarily included in published guidelines. If such a request is reasonable, that specimen should be evaluated and, if the answer might influence patient care, urgently. Pathologists have the responsibility to produce reports which can be easily understood and utilised by clinicians. A survey of American obstetricians suggests that even among maternal fetal medicine specialists, our language can be obtuse [6]. While most (65%) obstetric providers reported understanding the placental pathology report nomenclature "most of the time", only 21% reported understanding reports "all of the time", and 14% of respondents reported only "sometimes" understanding the reports.

3.2 Classification of Placentas Based on the Clinical Indication for Referral

Both the RCPath guideline and the CAP guideline share categories of clinical indications for examination. In general, the RCPath approach is more conservative, with fewer broad recommendations for full exam. In the RCPath statement, the raised clinical question determines the type, depth and urgency of placental examination. Sixteen of the most frequently represented referral groups will be shortly discussed in this paragraph. These recommendations are made as an accommodation for evidence-based placental examination in the setting of limited resources. They should be considered the minimum basic requirements and be adjusted as needed. Ideally, the placenta should be retained in all births for 72 h to 1 week, to allow for examination in cases of neonatal illness that arise after initial triage.

"Full" placenta examination includes macroscopy and histology. In selected cases, for example, a baby requiring intensive care, "fast tracking" and urgent reporting may be helpful. In those cases when histological reporting is not indicated, "macroscopic examination" can provide sufficient information. In selected cases, during macroscopic examination blocks can be taken and stored if further examination would be necessary. "Storage" of the placenta for a period of time is recommended in several groups of patients when immediate examination is not necessary but can be performed in individual cases for further clinical request.

3.2.1 Stillbirth (Antepartum or Intrapartum)

In unexplained intrauterine death, the placenta ultimately needs to be examined, either in the context of a postmortem examination—as part of a "consent" postmortem or as a separate surgical pathology evaluation (i.e., a "no consent" placenta only exam); therefore after intrauterine death in the first, second or third trimester, the placenta must be examined. The same is true for intrapartum and neonatal death. The aim of the investigation is to determine the cause of intrauterine death, to identify relevant contributing factors or other pathologies in particular with known risk of recurrence.

3.2.2 Early or Late Miscarriages, Recurrent Miscarriages

Full examination is necessary to exclude a placental cause of miscarriage. In early pregnancy loss, haemorrhagic complications, molar changes

Box 3.1 List of Recognisable Placental Conditions that May Cause Recurrent Pregnancy Loss
Massive perivillous fibrin deposition.
Chronic histiocytic intervillositis.
Villitis of unknown aetiology (VUE).
Maternal vascular malperfusion.

or chronic histiocytic intervillositis can be identified. In the second trimester, ascending amniotic fluid infection, haematogenous infection, symptoms of chronic abruption-oligohydramnios sequence or excessively long, overcoiled umbilical cord can be revealed.

In recurrent miscarriages, or in conditions with risk of recurrence of placental pathology, the placenta should be referred and examined (see Box 3.1).

3.2.3 Termination of Pregnancy

Termination of undesired pregnancy does not require pathological examination. It should be noted that a very small number of cases of very early complete and partial mole may be missed with this approach [7]. Examination of the placenta following termination of pregnancy can add very little or nothing to the prenatal diagnosis in cases of known fetal abnormalities, inherited genetic conditions, chromosomal abnormalities, complex cardiac disease or, for example in diaphragmatic hernia, if there is no consent for a postmortem examination. Despite the recommendation for placental examination in the older CAP guideline, the rationale to do a full examination is questionable. This of course is dependent upon the local policy. A gross evaluation, macroscopic description and processing only can be a solution. In some cases, sampling of fetal and or placental tissues for ancillary tests (QF-PCR, CGH microarray, PCR, exome or genomic sequencing) may be indicated. Communication between the delivering physician and laboratory is required to insure specimens are not inadvertently placed in formalin. Such needs should be clearly indicated on the referral form and consent provided as appropriate.

3.2.4 Unexpected Need for Neonatal Resuscitation or Intensive Care

Synonyms used for this group of indication could be “baby born in poor condition”, “low Apgars”, “Floppy baby” and “abnormal cord gases”. **Full** placenta examination is necessary and can be helpful in identifying infection with fetal inflammatory response, placental compromise from inflammatory or fetal or uteroplacental malperfusion, villous maturation disorder or, rarely, metabolic storage disease.

3.2.5 Severe Fetal Distress

For this group of patients, the obstetric history can be longer than in the previous group and clinicians may refer to “fetal tachycardia”, “pathological CTG”, “lack of variability”, “suspicious CTG”, “category I/emergency caesarean section” and “meconium-stained liquor”. **Full** placenta examination is necessary to establish the causes which can range from undiagnosed fetal growth problem with uteroplacental malperfusion to cord accident, reduced placental reserve capacity with various potential pathology or, often, silent chorioamnionitis.

3.2.6 Prematurity (Under 30 Weeks of Gestation)

Causes of spontaneous extremely premature labour and delivery have to be sought on **full** placenta examination to exclude most frequent placental causes—infection, abrupt separation or chronic abruption-oligohydramnios sequence. Additional information on the referral form, such as “history of antepartum haemorrhage”, “premature rupture of membranes” or

history raising suspicion of infection, may help the pathologist. The CAP statement includes recommended full evaluation for all births under 34 weeks.

3.2.7 Fetal Growth Restriction

Synonyms and abbreviations used on referral forms may include FGR, IUGR, SGA and poor fetal growth. Also, abnormal Doppler findings can be listed, sometimes without mentioning fetal growth. If underlying maternal history—preeclampsia and hypertension—is known, it may be mentioned. **Full** examination is recommended in cases of severe fetal growth restriction when birth weight falls below the 10th centile (examination is desirable if birth weight falls below the 10th centile and essential if under the third centile). In less severe cases, storage of the triaged but non-examined placenta for a period can provide opportunity for examination in case of late-onset complications or if clinicians would still request full examination. Similarly, placentas referred with uncomplicated preeclampsia, known but uncomplicated maternal autoimmune condition or coagulopathy may not necessarily require full examination, providing the baby is well grown. Other practices may prefer to fully examine all placentas with "clinical concern for mother or infant such as severe diabetes, impaired glucose metabolism, hypertensive disorders, collagen vascular disease" as proscribed in the CAP guideline.

3.2.8 Fetal Hydrops

To find the cause of fetal hydrops can be challenging and often not possible based on placenta examination only. If the specimen is referred with this indication, **full** examination is recommended as only histology can reveal viral infection, in particular parvovirus, pathological storage, or may contribute to diagnosis of fetal anaemia.

3.2.9 Suspected Intrauterine Infection/Clinical Diagnosis of Amniotic Fluid Infection

Clinical referral can be made for maternal pyrexia in labour, increased maternal CRP and more severe complications with maternal sepsis but, in some cases, "offensive" liquor or placenta is the main indication. If indications of Groups 2, 4, 5 and 6 are mentioned in association, **full** examination should commence. Without obvious fetal-neonatal complications, histological confirmation of the clinical diagnosis may not be necessary and storage of the placenta or embedded blocks could be sufficient. Similarly, GBS positivity and premature rupture of membranes without associated clinical complications and symptoms of infection do not require full examination and storage of the placenta is sufficient.

3.2.10 Abruption

As synonyms, antepartum haemorrhage or retroplacental haematoma can be mentioned. Acute abruption is a clinical diagnosis and only subacute-chronic haematomas can be identified with certainty on pathological examination. The depth of the examination depends on the associated complications and **full** examination is necessary if symptoms overlap with Groups 1, 2, 4, 5, 6, and 7.

3.2.11 Morbidly Adherent Placenta

Macroscopic and histological (**full**) examination is necessary to exclude placenta accreta. On referral forms can be mentioned as "placenta creta", "manual removal" or "piecemeal placenta"—referring to the same situation.

3.2.12 Gestational Diabetes

Currently, **storage** of the placenta is recommended unless other complication-indication is mentioned in association. This differs from the CAP guideline and local practice may vary.

3.2.13 Various Maternal Comorbidities, Isoimmunisation and Maternal Substance Misuse

Similarly, as in gestational diabetes, **storage** of the placenta and full examination recommended only for individual clinical request.

3.2.14 Abnormal Placenta Shape or Macroscopically Abnormal Placenta

This group can include a huge variety of often impressive macroscopic lesions that are obvious at the delivery of the placenta for the examining midwife or doctor. Bilobed, membranous placenta, large chorangioma, infarct, subchorionic haematoma and excess of calcification are just a few of the endless causes of referral. A careful **macroscopic** examination usually answers the question. Based on the appearance of the lesion at grossing, the examination can be converted to full examination with histology.

3.2.15 "Two Vessels in the Cord" and Other Macroscopic Cord Pathologies

Histological confirmation of single umbilical artery is not generally necessary. However, of note, umbilical artery thrombosis with vessel wall necrosis can be interpreted as a two-vessel cord on prenatal ultrasound. Careful **macroscopic** examination with conversion to full examination may be required as many pathological lesions of the cord—tight knot, haematoma and thrombosis—are clinically significant.

3.2.16 Twin Placentas

Twin placentas are frequently referred to the pathology laboratory for examination. If the pregnancy and delivery have been uncomplicated, it may be appropriate to undertake macroscopic examination only, with the aim being to confirm chorionicity. The examination may be of limited value in this situation and may equally be undertaken in the delivery suite by an appropriately trained midwife or doctor. If this approach is taken, the clinician should refer the placenta to the pathology for assessment if he/she is uncertain of the chorionicity in the delivery suite. The CAP guideline calls for examination of any fused discs with same sex infants. If the pregnancy has been affected by one of complications noted above warranting exam, the approach to examination should be the same as for singleton placentas. If not, there is no need for further assessment. Monochorionic placentas are different from the dichorionic placentas and their examination is appropriate in specialist perinatal pathology departments. Disorders of growth discrepancy, twin-to-twin transfusion and other conditions are unique to these gestations. Rates of complications are also significantly higher and the pathologic evaluation may reveal changes from medical intervention during pregnancy to treat the complications.

3.3 Submission of Placentas to the Pathology Department

As demonstrated by this list, guidance for placentas of live born babies is complex. Local consensus between the clinicians and pathologists should be established for practice. With routine examinations, the capacity of the pathology department needs to be considered and, as mentioned before, placental examination should be driven by clinical demand and in partnership with the clinicians. Placental pathology is a unique field, with expertise limited worldwide. Severe limitation of the number of placentas examined will, unfortunately, limit our ability to discern what pathology is truly clinically relevant. If the only cases we see are severe fetal growth restriction and stillbirth, the significance of common changes such as chronic villitis may be

Table 3.1 Triage system for dealing with submitted placenta to the pathology department

Triage system for placental examination based on clinical situation (with agreement of local clinicians)
Full examination including histology
Stillbirth (antepartum or intrapartum)
Late miscarriage
Severe fetal distress requiring admission to NNU (pH <7.21, scalp lactate >4.8 mmol/l or Apgar <7 at 5 min)
Prematurity (less than 30^{+0}-week gestation)
Fetal hydrops
Morbidly adherent placenta
Fetal growth restriction (birth weight below first centile)
Full examination—histology taken but only examined if further clinical indication/on request of clinician
Fetal growth restriction (birth weight below third centile)
Maternal pyrexia
Placental abruption
Fetal abnormality
Rhesus (and other) isoimmunisation requiring in utero transfusion
Maternal coagulopathy
Maternal substance abuse
NB—All of these conditions, with exception of maternal substance abuse, are considered indications for full examination recommended by the CAP guideline
Macroscopic examination—no histology (placenta retained for 2 weeks after examination)
Twins or other multiple pregnancy (uncomplicated)*
Abnormal placental shape (if clinically relevant)
Two vessel cord, etc.*
*These conditions have full examination recommended by the CAP guideline
Storage for 2 weeks (no examination)
A report indicating that the placenta has been received and is being stored without examination may be sent to the referring clinician depending on local agreement/policy
Prolonged rupture of the membranes (more than 36 h)
Prematurity (30^{+0}–36^{+6} weeks)*
Gestational diabetes*
Rhesus-negative mother (no fetal anaemia)*
Maternal group B streptococcus
Uncomplicated preeclampsia/maternal hypertension*
*These conditions have full examination recommended by the CAP guideline, with prematurity <34 weeks

NNU neonatal intensive care unit

overestimated. Unfortunately, resource allocation may force such restrictions. An example of placenta triage protocol is shown in Table 3.1, designed for a busy department providing perinatal pathology and/or placenta pathology service for obstetric departments and neonatal units, based on recommendations from the Royal College of Pathologists [2].

There have been calls to examine all placentas in the past [8]. This approach would generate the kind of familiarity with what is normal or different but still clinically insignificant morphology. Many births complicated by neurologic injury may not be flagged by the clinical indications listed above. Less stringent triage would guarantee that more of such cases could be captured. While a more liberal approach to placental evaluation may be a valuable source of information to explain or exclude placental background of long-term or late-onset neurological sequels in the offspring, it is not feasible in most parts of the world due to capacity issues. However, if a clinician feels that a placenta has got to be examined because of potential litigation risk, that request should be acceded. Kraus states that more than 90% of neurological injuries occur before labour and hospital admission and, despite ever closer intrapartum monitoring and escalation of the number of caesarean sections, the number of children suffering from cerebral palsy has not decreased. The statements of that editorial and the responses to the editorial are still valid, such as the call for better placental pathology reports, better communication between health professionals, flagging cases with adverse outcome and better presentation of clinico-pathological correlation to the parents [9].

3.4 Information Submitted with the Placenta

This is an essential part of the diagnostic work. It is beyond the scope of this chapter to give a detailed description of what clinical information needs to be submitted with the placenta specimen; however, the pathologist can only put the case in the clinico-pathological context if appropriate clinical information is submitted. The more relevant details are submitted, the more nuanced answers can be given. Questions can only be answered if asked.

3.5 Conclusion

Placental pathology is a relatively young field with an evolving literature of clinical associations and few robust studies that link findings with positive or negative predictive values for clinical outcomes. It may be premature to demand that a triage system for placental pathology be evidence based. Still, across the globe, perinatal pathology is practised in a resource-limited environment. The system we describe in this chapter describes a practical example of how a placental pathology service can work in a routine histopathology laboratory based upon the RCPath guideline. Local practices will need to be created and adhered to, based on a locally adapted guideline which takes into account the department's capacity, to ensure that all those placentas that require examination are examined.

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Part II

Gross Examination

Gross Examination

4

Cynthia Kaplan

4.1 Introduction

A competent gross examination and careful reporting are the crucial first steps in evaluating a singleton placenta [1–3]. While much has changed in procedures used for many surgical specimens, the method of gross examination of the placenta has remained relatively unchanged for at least 50 years [4, 5]. During that time there has been greatly expanded interest in the role of the placenta in fetal, neonatal and even adult life [6].

As most placentas get only a cursory look in the delivery area, pathology laboratories will be the site of the significant gross examination. In various hospitals this is done by physicians, residents and/or pathology assistants. While the techniques of examination are not difficult, it is necessary to evaluate many placentas to appreciate the spectrum of normal and abnormal and to learn what to ignore. Close supervision of new grossers by an experienced pathologist is necessary until they are comfortable with the procedure and findings. Many placental lesions are clearly identifiable on gross examination, requiring limited histologic confirmation if one is confident of the observer's skills.

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Ideally one receives significant clinical history with the submitted placenta. This should include gestational age, birth weight, mode of delivery and significant problems arising prenatally, during birth or in the early postpartum/neonatal period. While ideally all placental pathologic lesions will be identified on gross, a history of "abruption" or "neonatal anaemia" may focus the examination on findings potentially thought to be artefact or insignificant.

4.1.1 Fixation

It is frequently asked whether to submit and/or examine placentas fresh or fixed. There is no "correct" answer, only individual preferences. Thorough examination can be done in both states. Adequate fixation requires a large container with at least several times the placental volume of formalin. Fixative can be added in the delivery suite or preferably in pathology, where the appropriate amount is more likely to be used.

The only fixative suitable for entire placentas is 10% neutral buffered formalin. Non-formalin fixatives do not fix large bloody specimens and result in poor quality microscopic sections. Hardening fixatives, such as Bouin's, are never suitable for an entire placenta but are sometimes used for small samples. When the placental tissue is fresh, membrane

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rolls are easily made, colour is not distorted, parenchymal lesions are more palpable and fresh tissue is available for special tests. If refrigerated, placentas can be held fresh for several days with little change in gross and microscopic findings. Tissue cultures are usually still successful. A major advantage of fixation is to eliminate the need for refrigeration. It will also reduce concerns about infection. Usually the relative processing time is not substantially shortened.

4.1.2 Techniques

Placentas are large, messy specimens. It is more efficient to gross several placentas sequentially in an easily cleaned area. Sometimes an autopsy table can be used. It is important to have a systematic approach to examination to insure completeness. While other pathologists can review microscopic slides, the gross findings only exist as originally observed and recorded. Documentation with photographs is useful with unusual or unknown processes but impractical for every case.

4.1.3 Methodology

The steps for examining a placenta are detailed below. They include measurements and observations of the cord, membranes and fetal and maternal surfaces along with cutting or appropriate weighing and sampling (Fig. 4.1). Sometimes the clinical information leads to slight variations in method. Concerns from delivery should be addressed thoroughly. Appropriate instruments simplify the process of grossly and include straight knives, thin tapered forceps and sharp scissors. "Routine" placentas should not take long to gross with experience.

1. The placental exam begins with observing and opening the container. A bulging lid and unpleasant odour may indicate infection or bacterial overgrowth. While some blood is often present in the container, large amounts of fresh clot are frequent with premature separation (abruption). Except in stillborns, haemolytic colouration indicates improper storage (Fig. 4.2). If fresh tissue is needed for special studies, it is taken before the placenta is significantly handled. It has been suggested

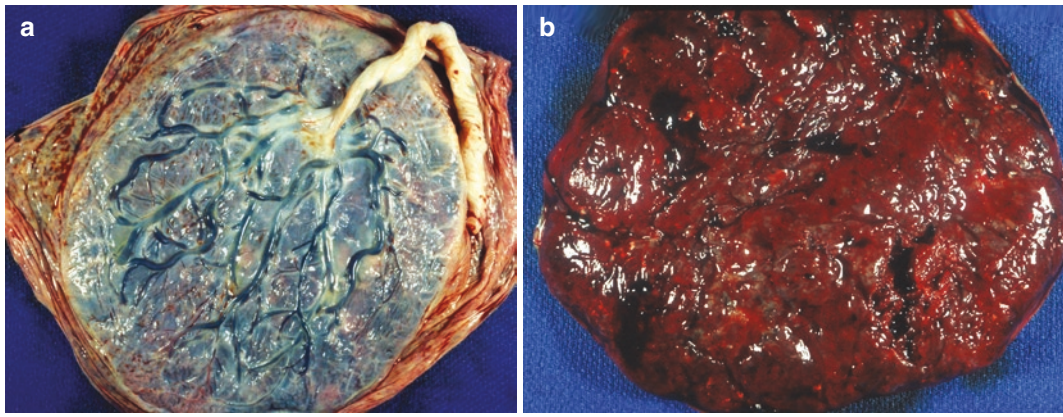

Fig. 4.1 (**a**) This intact fresh normal term placenta shows the fetal surface after refrigeration for 2 days. The surface is bluish with no opacity or unusual colouration. Subchorionic fibrin, usual in mature placentas, is the white localized areas. After longer storage there is often more opacification grossly, without histologic abnormalities. The cord is present inserting just off centre. Free peripheral membranes can be seen at the margin. (**b**). This view of the maternal surface in a term placenta shows the villous tissue to be complete, except for a small area of disruption at 5 o'clock. A small amount of loose, soft, postpartum clot is present which should be removed prior to weighing and further examination. There are large and small yellow flecks of calcium (Used with permission from Color Atlas of Gross Placental Pathology, 2ed, by CG Kaplan, Springer Nature 2006, Chapter 1 Figures 2 and 6)

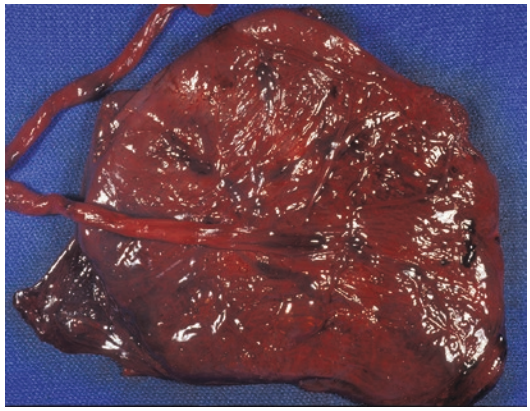

Fig. 4.2 The placenta shows severe haemolytic colouration of the cord, membranes and surface. This placenta was inadvertently placed in betadine scrub at delivery. A few bubbles are visible. Similar haemolysis will be seen if the placenta is frozen or left unrefrigerated (Used with permission from Color Atlas of Gross Placental Pathology, 2ed, by CG Kaplan, Springer Nature 2006, Chapter 1 Figure 3)

that fresh tissue from every submitted placenta be saved. This would be difficult in most busy laboratories.

2. Once the placenta is removed from its container, a quick overall evaluation is done before cutting. Abnormal findings may require alterations to usual procedure. The general shape is assessed and extra lobes noted. The fetal surface and membranes are examined for colour, surface changes, haemorrhage, subchorionic deposits, cysts, vascular pattern and thrombi. The maternal surface is inspected for colour, completeness and adherent blood clot. The villous tissue is palpated for lesions to help guide later cutting.
3. While we typically measure the length of the cord, it should be noted that true cord length is best evaluated in the delivery room. The number of pieces of cord should be noted. The site of insertion of the cord in the disk or membranes is important. Measuring the distance of insertion to the margin of the placenta is more precise than terms such as "paracentral". Particular attention should be given to the presence, length and intactness of vessels in the membranes (velamentous). This may be crucial in the setting of neonatal anaemia.
4. The cord is inspected for true knots, twist, tethering and discolourations. Some count the number of cord twists per centimetre. The cord is cut from the placenta several centimetres from its insertion to avoid Hyrtl anastomoses. The cut end is examined for the number of vessels, thrombi and discolorations. Maximal and minimal cross-sectional cord diameters are measured. Portions of cord from the proximal and distal portions are sampled. There are many delivery artefacts which alter the vessel integrity. Areas with clamp marks or substantial intra-parenchymal haemorrhage are avoided if possible.
5. The peripheral membranes are inspected for the type of insertion into the disk with marginal insertion normal. Circummargination and circumvallation can be quantitated as the percentage of the circumference and the width of the extrachorial portion. Recreating the relative anatomic positions of the membranes to the disc will help in assessing the completeness of the membranes. The opening in a complete sac is relatively small. When membranes appear complete, the distance from the point of rupture to the edge of the placenta can be measured. In vaginal deliveries, this gives a rough indication of the position of the placenta in the uterus. A short distance suggests a low-lying placenta. An extensive opening or fragmentation indicates the membranes are incomplete. At term the amnion separates readily from the chorion and will often be loose, attached only to the cord. Opacity, fresh and old haemorrhage and other lesions such as compressed twins are other membrane findings.
6. The "jellyroll" of membranes is done at this point. There are several methods for this and the "right" one is that preferred by the examiner. The roll is made preferably from a thicker portion with more decidua. A small piece of marginal placenta can be used as the centre of the roll. One can also cut a broad strip of membranes from the edge of the rupture site to the disc margin. The strip is rolled from the cut edge end toward the disc, putting the point of rupture at the centre. The weight

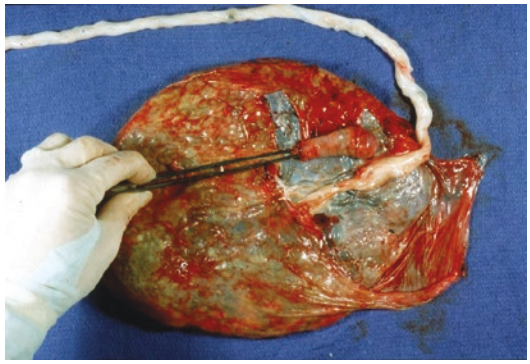

Fig. 4.3 The membranes of this normal, term placenta have been placed in their in situ uterine position. A membrane roll is being made from the rupture point to the margin of the placenta. It is then pinned, cut from the placenta and fixed (Used with permission from Color Atlas of Gross Placental Pathology, 2ed, by CG Kaplan, Springer Nature 2006, Chapter 1 Figure 7)

Fig. 4.4 This is a mature placenta after transverse cuts (1.5–2 cm) have been made on the maternal surface to examine the villous tissue. The knife has a tendency to skip over firmer areas and simultaneous palpation of the villous tissue is necessary. The fetal surface is not usually cut and keeps the placenta somewhat intact (Used with permission from Color Atlas of Gross Placental Pathology, 2ed, by CG Kaplan, Springer Nature 2006, Chapter 1 Figure 9)

of the still-attached placenta facilitates rolling (Fig. 4.3). Pinning the roll will keep it intact during fixation. Finally it is cut from the placenta. Pins are unnecessary if a roll is placed briefly in hardening fixative or liquid nitrogen. Rolls are difficult to make once the placenta is fixed or the membranes are severely disrupted and/or "slimy" from meconium.

7. Any remaining membranes are trimmed away and loose soft clot is removed from the maternal surface. The placenta is now weighed, without cord or membranes. Measurements are taken of the discs, diameters and thickness. Extra lobes, either partial or complete, are measured and described. When the placental shape is very unusual, diagrams or photographs may be useful.
8. Transverse cuts are made at approximately 1–2 cm intervals. Fresh placentas are cut from the maternal surface, leaving the chorionic plate intact (Fig. 4.4). A fixed placenta can be sliced through entirely. Palpation of the slices will reveal lesions the knife may have skipped over. Lesions are described/identified and measured. If involvement of the parenchyma is extensive or there are multiple lesions, an estimation of the percentage of villous involvement is made. Calcification and features such as overall villous colour and texture are noted. The colour should be relatively similar through the parenchyma, and small areas of pale or yellow villi usually indicate microscopic abnormality.
9. If the placenta is initially examined fresh, representative portions can be saved and fixed in relatively small amounts of formalin. The remainder of the placenta is usually discarded. Placentas with unusual or extensive findings should be entirely saved and fixed. If space allows, all placentas could be saved in formalin. Representative pieces of the villous tissue to fix include the margin, central villi from several cotyledons. A full-width slice including several centimetres of tissue on either side of the cord will accomplish this. Keeping the cord stump in the sample helps retain the amnion which is continuous with the cord surface. Significant gross lesions to be sampled such as haemorrhages, infarcts and thrombi are also saved.

4.1.4 Cutting Tissue Blocks

While it is possible to cut blocks from fresh placental tissue, it is far easier after fixation. Even a few hours in formalin helps with cutting when

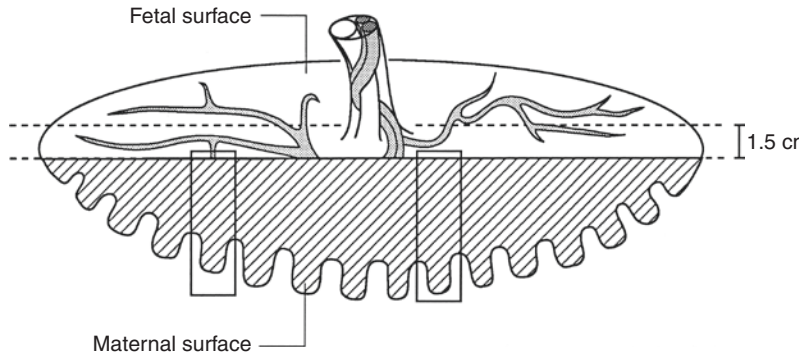

Fig. 4.5 A transverse strip of placental tissue from the central region including the cord is routinely saved. Histologic blocks of villi including small surface vessels are taken from at least two separate areas in the placental midzone (boxes). These should not be from areas with thick subchorionic fibrin or haemorrhage as these can mask inflammation. The placental margin has substantial artefact and is not ideal for assessing villous configuration. Placentas with significant pathologic processes require extra blocks (Used with permission from Color Atlas of Gross Placental Pathology, 2ed, by CG Kaplan, Springer Nature 2006, Chapter 1 Figure 10)

cases need to be expedited. It is difficult to keep the amnion on the surface in mature placentas. Sharp blades will help.

The number of blocks submitted on "routine" placentas varies widely among pathologists. Adequate sampling can usually be done in four blocks (Figs. 4.4 and 4.5) [2, 7, 8]. This includes cord (two pieces from sites approximately 5 cm from the insertion and one near the fetal end), slice of membrane roll and three full-thickness pieces of villous tissue including fetal and maternal surfaces. The pieces of villous tissue should be from different areas and **not** from the margin of the placenta, which frequently shows changes of diminished blood flow and excess fibrin deposition. They should include one close to the cord insertion and two more peripheral. Marginal sections may show inflammatory or decidual vascular changes and can be submitted in addition or as a part of the membrane roll. The fetal surface sections should include small blood vessels and be free of substantial subchorionic clot or fibrin which can mask early inflammation.

At times, more than four cassettes may be needed to adequately sample a placenta. When lesions or abnormally appearing areas are present, additional blocks of these areas should be submitted, including adjacent normal tissue. Placenta from stillborns and from severely growth-restricted infants may require more if initial ones are unrevealing. Representative examples of widespread lesions suffice. Generally two to four additional samples will be adequate. A competent observer can recognize grossly the nature of most lesions. Some full-thickness sections may be too large to fit in the cassette. Halving the pieces in two cassettes and using just the fetal and maternal thirds or long narrow section bisected are options for embedding such thick slices (Fig. 4.6) [8]. It is imperative to have at least two to three slides of uninvolved villous tissue to evaluate. These reflect the status of the functional tissue. Additional membrane roll slices or "en face" blocks of the basal plate may reveal more maternal decidual vessels [9].

4.1.5 Reports

Gross description may be done as a narrative or a check list. Examples of such forms are available in the references [1, 3]. Templates are often used for gross examination and may be helpful to be complete. There is a tendency to omit observations that are not part of the template rather than make the alterations necessary. Space to note such additional gross findings should be available. These can be incorporated into the final report.

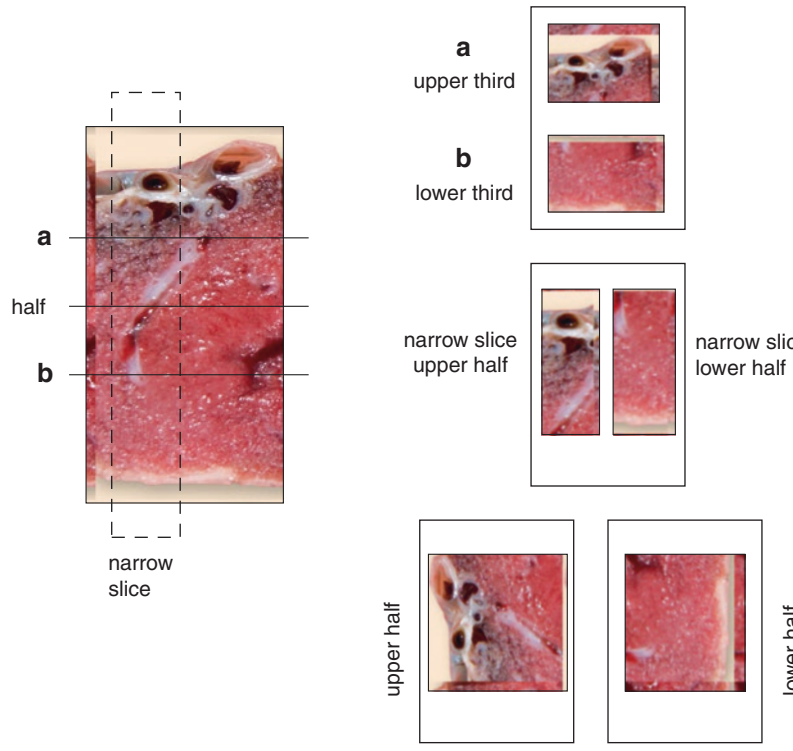

Fig. 4.6 Options for embedding a thick placental slice: preferred options are embedding the lower and upper thirds in one cassette or embedding the lower and upper halves in two separate cassettes (Used with permission from Khong et al., Arch Pathol Lab Med 2016; 140: 698–713 Fig. 4.4)

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Placental Weight, Shape and Gross Vascular Morphology

5

Carolyn Salafia and Drucilla J. Roberts

5.1 Placental Weight

It is uniformly recognized that the placenta is a major determiner of fetal growth, since appropriate fetal growth relies upon adequate placental nutrient transfer. By extension, one would expect proportionality between the size of the baby (birth weight, BW) and the size of his/her nutrient supply organ (placental weight, PW). This proportionality is expressed as the BW:PW ratio, or fetoplacental weight ratio (FPR). The placenta may be able to modify its function to produce an optimal BW [1]. Alternatively, patterns of placental structure/anatomy, specifically, the relationship of chorionic plate area and disk thickness as well as the packing density of the placental villi, are known to impact placental efficiency [2–4]. In a recent study, we found that mean FPRs differed significantly by PW group (Table 5.1) with smaller placentas having increased efficiency in terms of birth weight relative to placental weight, with the caveat that compensation is incomplete, and may leave newborns at increased risks with prenatal and neonatal stressors [5].

5.1.1 Definition

Placental weight is the weight of the placental disk rinsed clean of loose blood and trimmed at the margin to remove the extraplacental membranes and the umbilical cord at its insertion into the chorion.

5.1.2 Synonyms

Not applicable.

5.1.3 Epidemiology

Centiles of the mean and standard deviation of PW have been generated across gestational age, comparing singletons versus twin and male and female infants and considering variables such as race/ethnicity and parity. By convention, extremes of PW are marked by the 10th and 90th centiles. Small for gestational

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Table 5.1 Relationships of chorionic plate and disk thickness by quartile to FPR and ponderal index

			Chorionic plate area		
			Lower quartile mean ± SD	*Midquartile* mean ± SD	*Upper quartile* mean ± SD
Thickness	*Lower quartile*	FPR	8.8 ± 0.95	8.02 ± 1.13	6.70 ± 1.31
		PI	2.57 ± 0.01	2.69 ± 0.33	2.86 ± 0.35
	Midquartile	FPR	7.77 ± 1.52	6.85 ± 1.21	5.79 ± 0.80
		PI	2.69 ± 0.35	2.81 ± 0.35	2.94 ± 0.36
	Upperquartile	FPR	6.92 ± 1.20	5.91 ± 9.94	5.24 ± 0.71
		PI	2.76 ± 0.26	2.82 ± 0.34	2.99 ± 0.30

FPR fetoplacental ratio, *PI* ponderal index

age placental weights can be related to fetal growth restriction and/or intolerance of labour and genetic anomalies whereas large for gestational age placentas are related to maternal anaemia, diabetes, chorangioma, circumvallate membrane insertion and abnormal cord insertion [6].

5.1.4 Gross Findings

How the placenta is grossed should be recorded as fresh or fixed in formalin, since fixation can alter placental weight.

5.1.5 Histopathology

PW depends on villous histology, both villous structure and spatial distribution; both gestational age and concurrent medical disorders (e.g., diabetes, hypertension, lupus or kidney disease) should be considered when assessing implications of PW in any clinical case.

5.1.6 Immunohistochemistry

Not applicable.

5.1.7 Genetic Susceptibility

The National Collaborative Perinatal Project showed that placental weight and/or the fetoplacental weight ratio may vary by race and ethnicity [7].

5.1.8 Prognosis and Predictive Factors

Aspects of placental measurement in vivo may predict low BW [8]. Recently, the US National Institutes of Health has made a significant investment in the development of in vivo placental measures that predict maternal and/or fetal outcome, from preeclampsia and low birth weight to diabetes and fetal macrosomia [9]. Placental weight, or more specifically the ratio of the observed BW to the BW predicted by a regression of PW (and other gross placental measures), has been correlated with paediatric outcome metrics, including BMI and blood pressure.

5.2 Placental Shape

The average shape of the delivered human placenta is more or less round, it has a more or less centrally inserted umbilical cord and it has a relatively uniform thickness. When the placenta is irregularly shaped, there may be substantial inter-observer variability in choosing a major and minor axis to measure [10]. We recommend a simple surface photograph, from which precise measurements can be made, and measurement methods improve as technology advances. Empirical models have suggested specific shape variations to have their origins at distinct periods in gestation (Fig. 5.1).

5.2.1 Definitions

Placental shape is currently defined by the chorionic plate aspect ratio, but a 3D digital image may be more useful to understand the timing

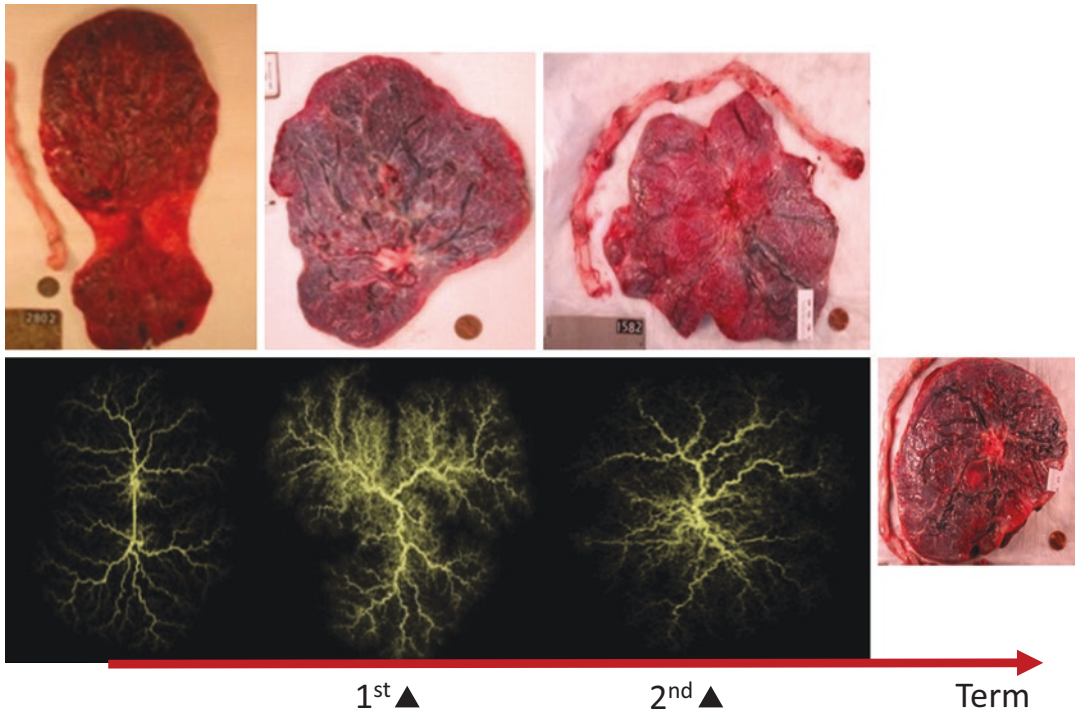

Fig. 5.1 Varieties of placental shape abnormalities and time of origin, based on empirical modelling of fractal growth

and cause of variations in placental shape (e.g., Fig. 5.2a, b).

Placental thickness reflects the achieved branching structure of the mature placental vascular trees. It can be measured at the umbilical cord insertion, at the "centroid" of the area of the chorionic surface shape or at random. It should be reported as an approximate mean with minimum and maximum thickness (Fig. 5.3a, b).

5.2.2 Synonyms

Not applicable.

5.2.3 Epidemiology

In the National Collaborative Perinatal Project, abnormalities of placental shape (described qualitatively as bipartite, tripartite, crescentic, etc.) were more common in women of higher parity, women with prenatal bleeding, placental praevia and morbidly adherent placenta. We have identified black race as a risk factor for reduced placental area and thickness; otherwise, there are little data with regard to thickness correlations. A case series of 16 placentas with disk thickness >95th centile as measured by Doppler ultrasound included 12 (75%) who delivered before 34 weeks of gestation; 8 of these cases ended in perinatal death [11]. In the National Collaborative Perinatal Project, a single measure of disk thickness was obtained at the base of the umbilical cord insertion. Increased placental disk thickness adjusted for placental weight was associated with decreased placental efficiency, as reflected in the fetoplacental weight ratio. Finally, in a study in which placental measures were obtained in vivo at 11–14 weeks of pregnancy, a flatter placenta was inversely correlated with both the placental weight and chorionic plate area, possibly indicating the importance of placental thickness even in the first trimester before villous arborization [12]. There was also a strong correlation between delivered placental thickness and first trimester cord marginality ($r = -0.368$, $p = 0.009$) [13].

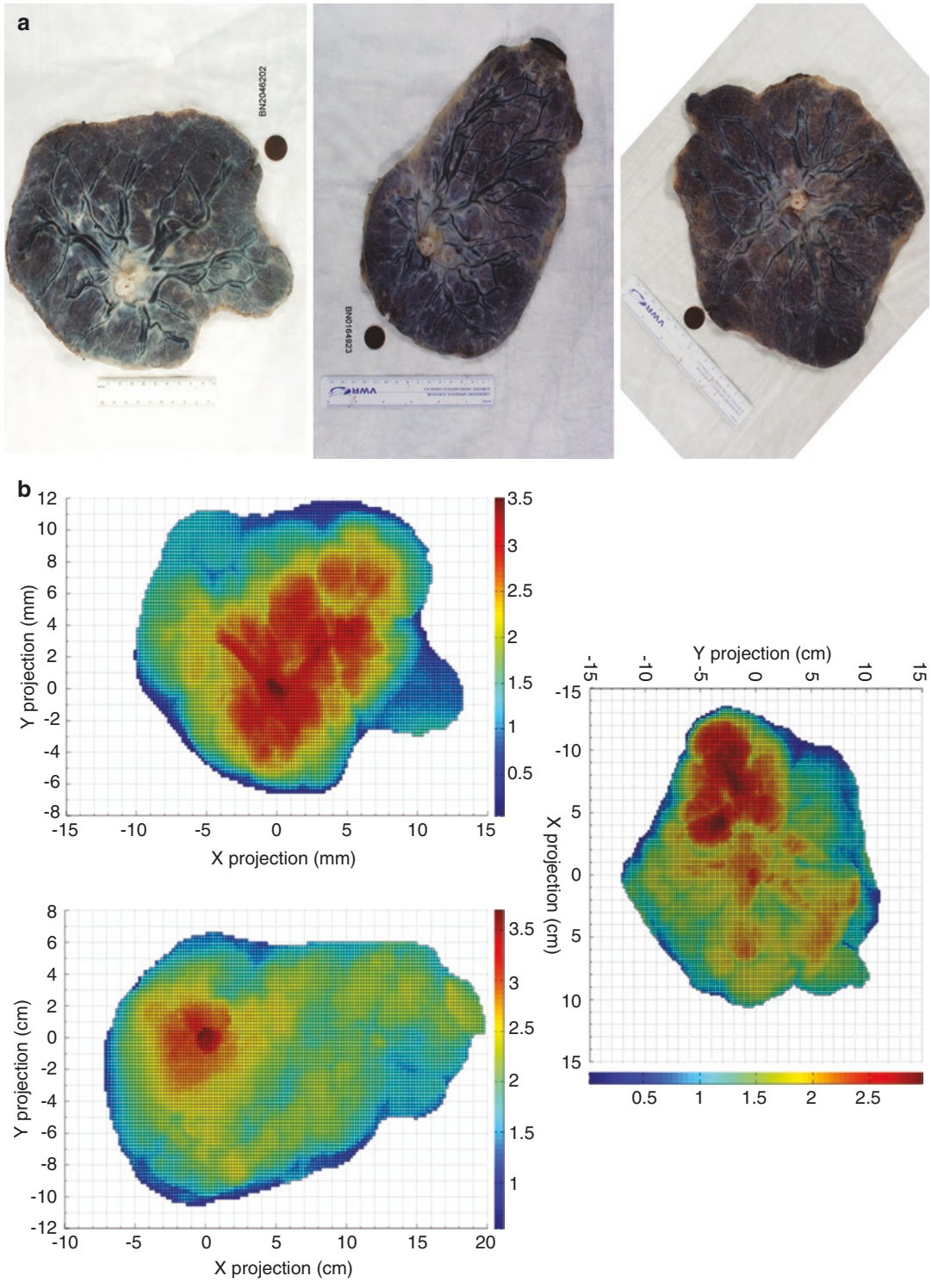

Fig. 5.2 (**a**) The chorionic surface photographs of three placentas. (**b**) Their corresponding 3D shapes as Cartesian topographical maps

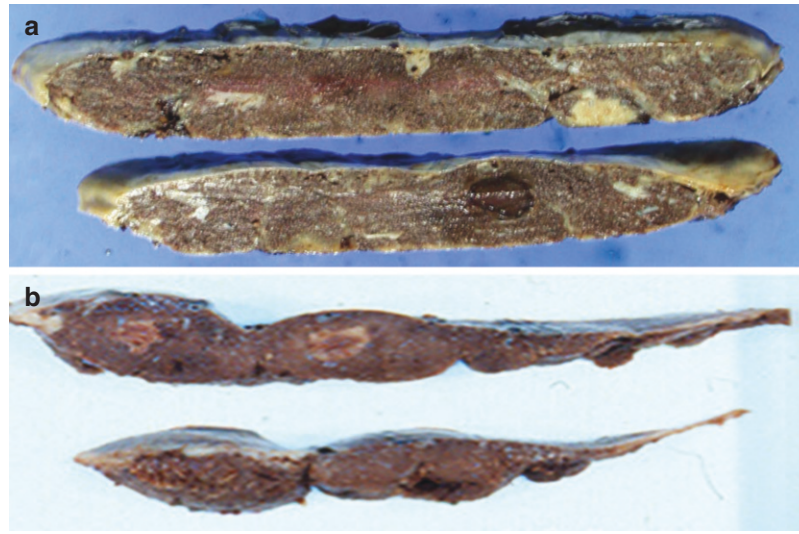

Fig. 5.3 (**a**) Uniform and (**b**) non-uniform disk thickness

5.2.4 Gross Findings

The chorionic surface shape is quantified by its area in cm^2 and by the ratio of its perimeter to its area. The rounder a placenta, the more is consistent the relationship between pi*r^2 (formula for area) and 2*pi*r (formula for perimeter). The chorionic plate shape perimeter marks the zone of transition from the chorion frondosum to the chorion laeve of the extraplacental membranes. The radial standard deviation, the variability in radii drawn from the placental centre to the disk edge, is also a useful marker of placental chorionic surface shape irregularity.

The chorionic surface shape perimeter may not delimit the full extent of the chorionic plate shape because of circummarginate or circumvallate insertions, which are associated with gestational and newborn complications [14].

5.2.5 Histopathology

Not applicable.

5.2.6 Immunohistochemistry

Not applicable.

5.2.7 Genetic Susceptibility

Not applicable.

5.2.8 Prognosis and Predictive Factors

The major and minor axes can be described as "length" and "breadth"; the cited authors claimed a specific biological role in nutrient transfer for "breadth" (minor axis) since it alone, independently of the "length", can predict BW. Both "length" and "breadth" are measures of placental size and would be expected to correlate with the BW. Furthermore, "breadth" is clearly not a measure of a single placental aspect. Rather, it combines a measure of placental size with a measure of irregularity; the greater the difference between length and breadth, the less round the placenta is. This discussion is detailed further [15].

5.3 Gross Vascular Morphology

This is a relatively new field with the exception of gross associations between marginal and velamentous cord insertions and outcomes. We have largely pioneered studies to test whether

more subtle variations in cord insertion and chorionic plate vessel branching is related to clinical outcomes, which will be the focus of this section [16].

5.3.1 Definitions

Umbilical cord insertion is the site where Wharton's jelly ceases and the umbilical vessels make a right angle turn onto the chorionic plate. Abnormal cord insertion can accompany abnormal placental shape (Fig. 5.4). A significant proportion of the variance in umbilical cord insertion relative to the disk edge is determined by 11–14 weeks [10, 12].

The chorionic plate network of arteries and veins on the chorionic plate connects to the umbilical arteries and vein (Fig. 5.5).

5.3.2 Synonyms

Not applicable.

5.3.3 Epidemiology

Not applicable.

5.3.4 Gross Findings

The umbilical cord is normally inserted close to the centre of the chorionic plate [10, 13]. The location of cord insertion may be independent of placental surface shape, but it is associated with reduced chorionic surface vascularity [10, 13]. Marginal and velamentous cord insertions reflect either a failure of early embryo orientation relative to the primitive placenta or such severe asymmetry of placental growth that the placenta effectively grows out from under the umbilical cord early in pregnancy [13]. Both marginal and velamentous cords reflect early impacts on placental growth trajectory and increased risk due to the mechanical instability of the umbilical cord and vessels located at the edge of the chorionic plate and the extraplacental membranes, which is to some degree stabilized by amniotic fluid pressure. Risk increases with increasing gestational age as amniotic fluid volume decreases and especially after membrane rupture.

The chorionic surface vascular network at term is, to a large degree, predicted by the mean placental diameter by ultrasound at age 11–14 weeks [12]. Little is known about the factors that influence this network development. Gordon et al. [17] described the branching archi-

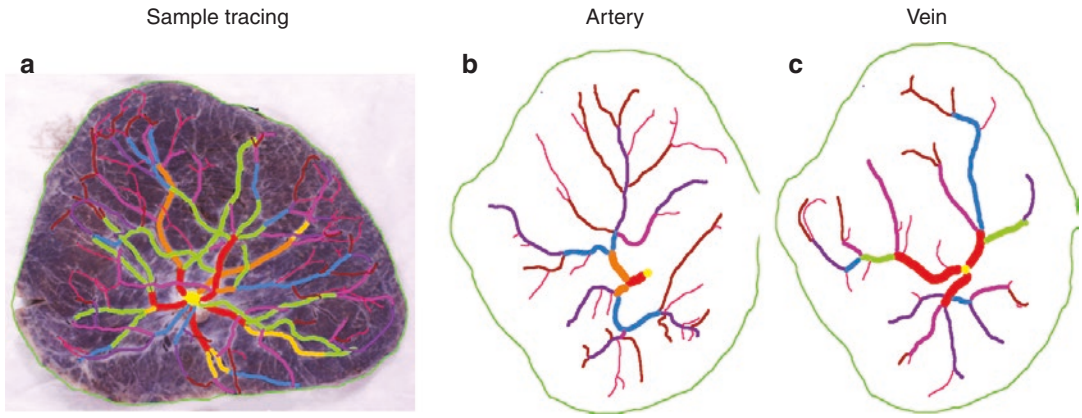

Fig. 5.4 (**a**) Completed tracing, decomposed into (**b**) Arterial network and (**c**) Venous network

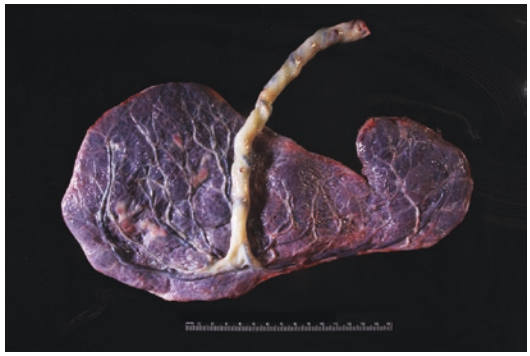

Fig. 5.5 Abnormal placental shape and abnormal cord insertion

tecture of the chorionic vessels as a combination of dichotomous and monopodial patterns, the latter a term reflecting when the terminal bud continues to grow as a central leader shoots and the lateral *branches* remain subordinate, where the first two to three generations are always dichotomous. Furthermore they observed that chorionic vessel networks are mostly monopodial when cord insertion is marginal and mostly dichotomous when cord insertion is more or less central. This is consistent with our observation of decreasing chorionic vascular density in the context of more eccentric cord insertion [14]. The variations in patterns of the chorionic plate vessels are local adaptations themselves to optimize distribution (via arteries) and drainage (via veins) of placental blood flow.

We have reported a protocol for manually tracing placental chorionic surface vessel networks from digital 2D images of post-delivery placentas and its validation by a shape matching method to compare the similarity between paint-injected and unmanipulated (uninjected and deflated vessels) tracings of placental chorionic surface vessel networks [18]. Using the National Children's Study, we have also compiled mean values for a wide range of chorionic vessel network features [19].

5.3.5 Histopathology

Not applicable.

5.3.6 Immunohistochemistry

Not applicable.

5.3.7 Genetic Susceptibility

Not applicable.

5.3.8 Prognosis and Predictive Factors

Non-central cord insertions are significantly more common in low birth weight infants although it may be a poor screening test with high rates of false-negative results. The combination of low birth weight and abnormal cord insertion has been found to predict a high risk of poor neurological outcomes [20, 21]. Abnormal cord insertions are well known to be more common in multiple gestation.

We have identified significantly altered chorionic vascular networks in placentas of children who received a diagnosis of autism (the Avon Longitudinal Study of Parents and Children, ALSPAC) and in the placentas of newborns with an older sibling with a diagnosis of autism spectrum disorder (Early Autism Risk Longitudinal Investigation, EARLI) [19].

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Part III

Placental Disc: Macroscopically Visible Lesions

Infarction

6

Brendan Fitzgerald

6.1 Introduction

Within the placental parenchyma, the maternal circulation courses through the intervillous space bringing oxygen and nutrients to the surface of the villi while removing waste products. Abnormal maternal circulation in an area of placental parenchyma can result in a variety of compensatory or deleterious effects but, as with all organs, near-complete or complete obstruction to circulation in a localised area of the placenta will result in an area of infarction, which in the placenta is characterised by an area of collapse of the intervillous space and villous ischaemic necrosis.

Infarction is one of a group of placental findings characteristic of maternal vascular malperfusion (MVM), which include distal villous hypoplasia, accelerated villous maturation, villous agglutination, certain patterns of perivillous fibrinoid deposition and decidual vasculopathy. When identified, it is not just important because of its locally destructive effect but as a marker of MVM with all the clinical consequences and associations that follow. In MVM, infarction is thought to occur because of restriction of flow by narrowing or thrombotic occlusion of maternal myometrial and decidual arterioles affected by vasculopathy [1]. Susceptibility to obstruction of these maternal vessels appears to relate back to defective physiological transformation of the maternal arterioles in the first trimester [1].

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6.2 Definition

A placental infarct is an area of ischaemic coagulative necrosis of the placental parenchyma.

6.3 Synonyms

Villous infarction.

6.4 Epidemiology

Placental infarction is one of the more commonly observed grossly visible placental lesions seen during pathological examination of the placenta. They are not infrequently seen in term placentas and in one recent study were reported in 10.9% of placentas of term pregnancies without fetal growth restriction or maternal hypertension [2]. The edge of the placenta is relatively ischaemic and, at term, small marginal infarcts are very common at this site and are often old [2]. In this context they are generally not considered to have major clinical significance. In the first or second trimester, however, all infarcts are regarded as abnormal.

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In term placentas, when infarcts are multiple and centrally located, the association with pregnancy complications such as maternal hypertensive disease and fetal growth restriction increases [2]. The increased frequency of infarction in hypertensive and growth-related pregnancy complications is reflected in the study of Mousa and Alfirevic, where infarcts were seen in 69% of their cases of preeclampsia/eclampsia, 47% of their cases of abruption and 59% of their cases of fetal growth restriction [3]. The frequency of infarction also increases in preeclampsia and growth restriction as the gestational age at delivery decreases [4–6], and it is argued that this is reflective of a different pathogenesis of early-onset and late-onset hypertensive disease in pregnancy [5].

The major maternal risk factors for placental infarction are prior preeclampsia, chronic hypertension, fetal growth restriction, pre-gestational and gestational diabetes, pre-pregnancy obesity (body mass index (BMI) >30) and assisted reproductive technology [7].

6.5 Gross Findings

The macroscopic appearance of a typical focus of placental infarction depends on its age and the state of fixation of the placenta and, in general, formalin fixation allows for easier visualisation (Fig. 6.1). Infarcts are identified as reasonably well-defined areas of discolouration of the parenchyma; initially an infarct may be congested or not very different in colour from the adjacent placenta but, with time, it becomes progressively paler due to the loss of villous vascularity, loss of red cells in the intervillous space and deposition of perivillous fibrinoid material. In areas of infarction, the collapse of the intervillous space means that the infarct will be less spongy and more firm than the surrounding uninvolved parenchyma; this helps with identification of recent examples which can be missed during examination of the cut surface of the fresh placenta. Because villi are contained within the lesion, they give the cut surface of infarcts a granular appearance; this contrasts with intervillous thrombi (where the villi are displaced to the lesion edge). The infarct may be located at any position in the placenta and infarcts may be single or multiple. Individual infarcts are usually 2–3 centimetres in size [2] but can be large and confluent (Fig. 6.2).

Some infarcts have central haemorrhage and have been termed rounded intraplacental haematomas (RIHs) [8, 9] or infarction haematomas [10] (Fig. 6.3). As they are also seen in the context of MVM, the clinical context is essentially the same but they may be a marker of a severe clinical phenotype [9]. It is possible that previous descriptions of infarcts as haemorrhagic or as having undergone haemorrhagic or cystic degeneration may be now be superseded by delineation of the various features of these RIHs. The distinctive appearance of these lesions is either proposed to be related to reperfusion of an infarcted area [10] or alternatively to result from an expanding haematoma that causes secondary infarction of the surrounding, compressed placental tissue [8, 9]. Lesions showing infarction with central haemorrhage progressively age, resulting in better definition of the infarct, while the central area of haemorrhage becomes smaller with breakdown of the haematoma component so that the contents look necrotic or even serous.

6.5.1 Gross Differential Diagnosis

On gross examination, the main differential diagnoses are intervillous thrombi and localised foci of perivillous fibrinoid deposition. In most instances centrally located intervillous thrombi may be distinguished from infarcts by the lack of granularity to their cut surface, their often laminated appearance and the frequently pointed or angular appearance to some aspect of their periphery. Subchorionic intervillous thrombi also have laminations that run parallel to the chorionic plate. Foci of fibrinoid deposition may be difficult to distinguish from infarcts but fibrinoid deposits tend to be less distinctly circumscribed and may be associated with other foci of lacy deposition of fibrinoid material. However, fibri-

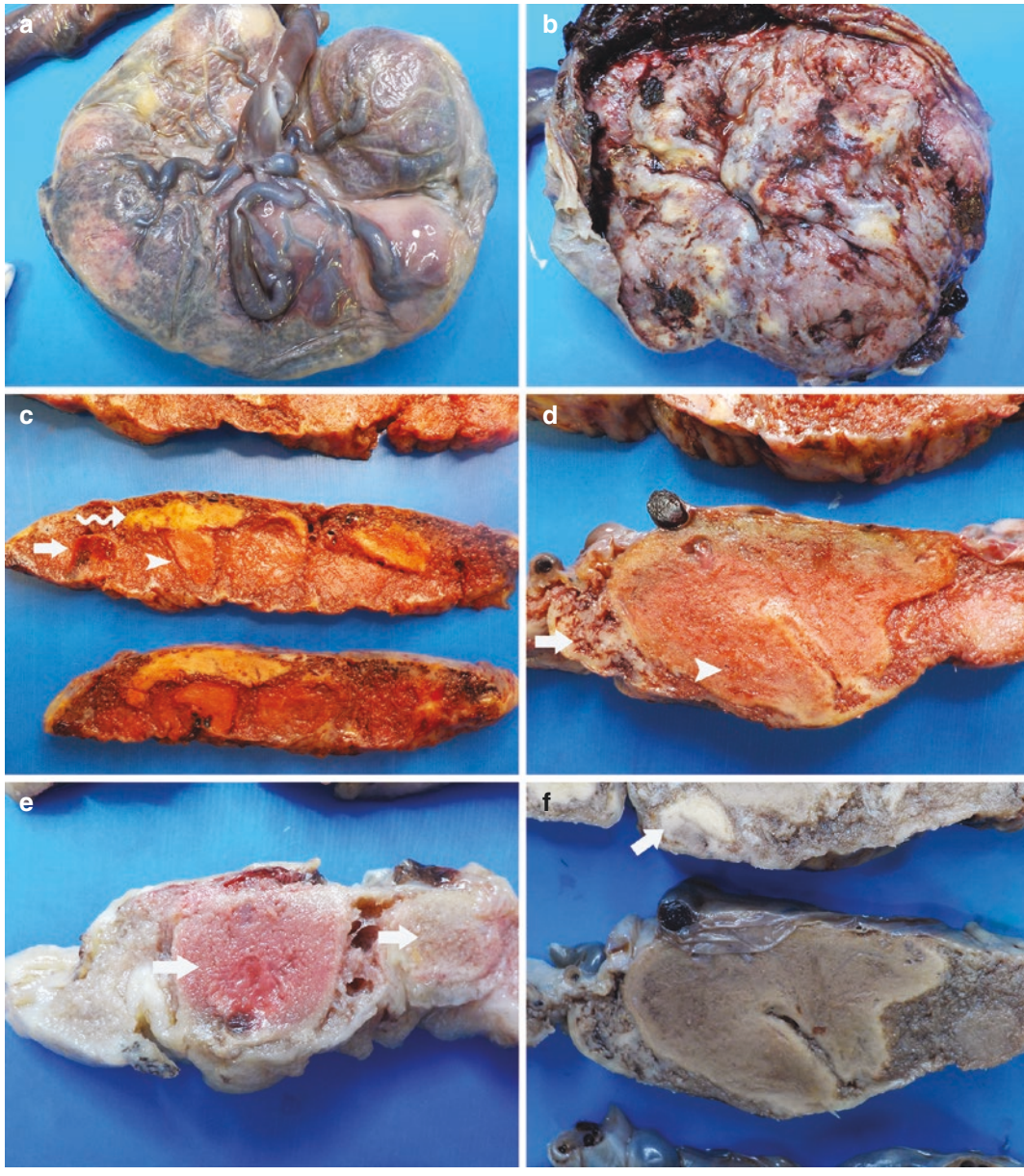

Fig. 6.1 Gross appearance by gestational age and fixation. In (**a**), the fetal surface of this 28-week placenta is discoloured due to underlying infarcts which in this case resulted in intrauterine fetal death; the maternal surface, seen in (**b**), is irregular with patchy pale plaques. The cut surface of this placenta is seen in (**c**) and shows infarcts of various ages, recent (arrow), intermediate (arrow head) and old (wavy arrow). In (**d**) the firm solid texture of an infarct (arrow head) contrasts with the adjacent, more lacy, fibrinoid (arrow). In (**e**) the granular texture of the cut surface of the infarcts is evident in this second trimester case. In (**f**) the effect of longer fixation is evident when contrasted with image (**d**); the firm white appearance of an old infarct is present at the arrow

noid deposition is also a marker of MVM, so infarcts and fibrinoid deposits may intermingle. A rare differential diagnostic possibility is intraplacental choriocarcinoma. As the gross appearance of choriocarcinoma has been described as infarct-like [11], sampling for microscopy is indicated if there is any doubt about the nature of a macroscopically visible placental lesion.

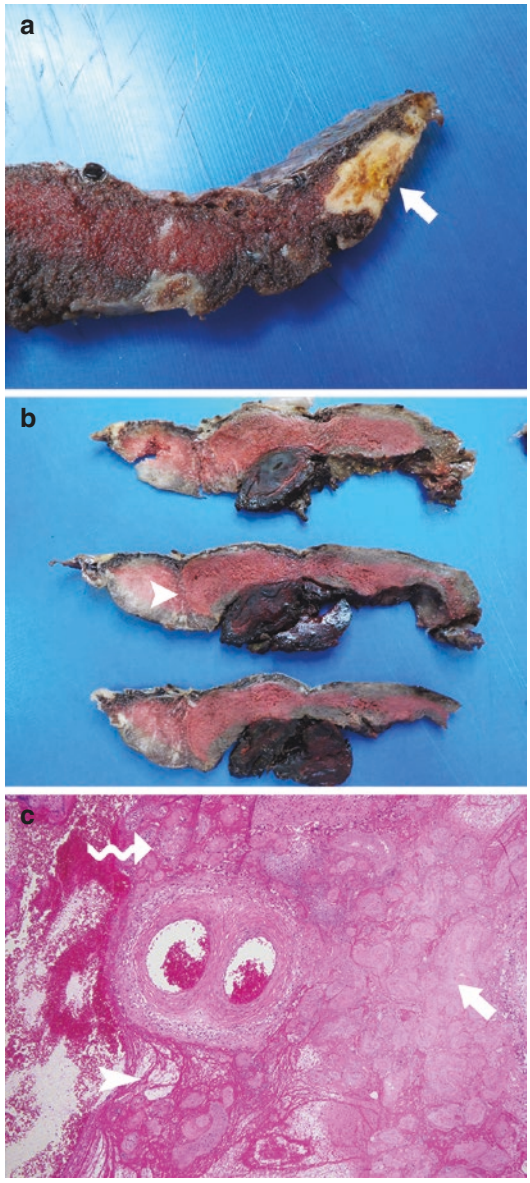

Fig. 6.2 Gross and microscopic appearance of remote infarction. (**a**) shows a typical peripheral infarct, generally not thought to be significant in term placentas. In (**b**) a large recent retroplacental haematoma is seen to compress the overlying placenta resulting in early infarction (the edge of which is at the arrow head). In (**c**), infarction (arrow) and intervillous thrombus (arrow head) formation are seen in a case of massive fibrinoid deposition due to severe chronic villitis of unknown aetiology (evident on high-power view of edge at wavy arrow)

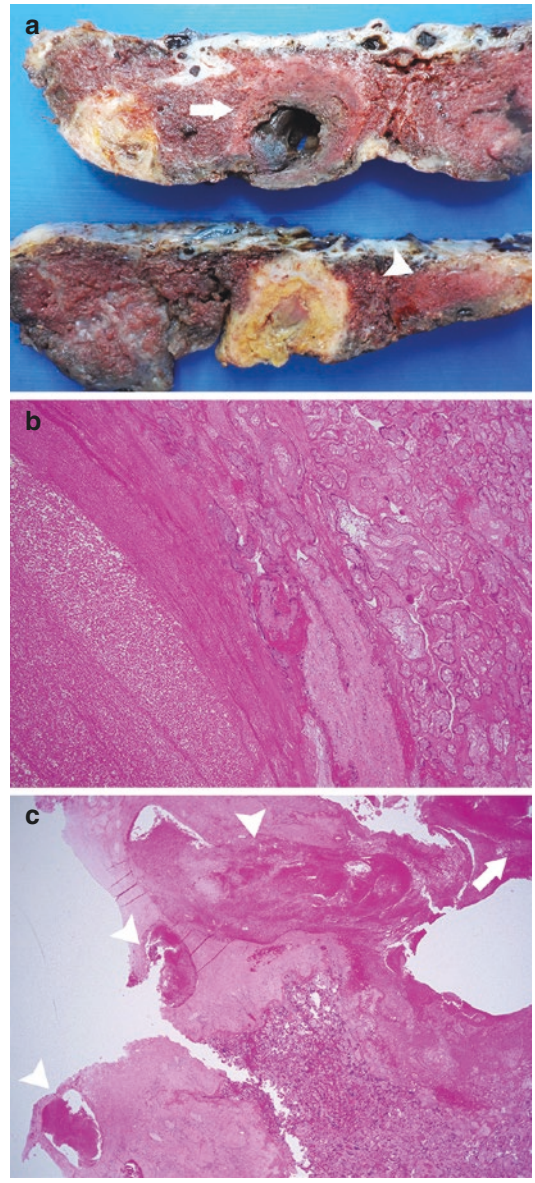

Fig. 6.3 Rounded intraplacental haematomas. In (**a**) a rounded intraplacental haematoma shows peripheral infarction around a central haematoma (arrow); as the lesion ages, the peripheral infarction becomes more defined with central liquefaction (evident in the lower slice). A subtle, recent infarct is present at the arrow head. (**b**) shows a low-power view of the haematoma with its compressed, infarcted surrounding border. In (**c**) abnormal "feeder vessels" (arrow heads) are present beneath a rounded intraplacental haematoma (in direction of arrow)

6.6 Histopathology

The most distinctive features of acute placental infarction are collapse of the intervillous space and early degenerative changes in the villous trophoblasts, the latter characterised by lessening of nuclear basophilic staining and loss of nuclear detail (Fig. 6.4a, b). As the infarct ages, the villous trophoblasts progressively lose nuclear detail and degenerative change in the

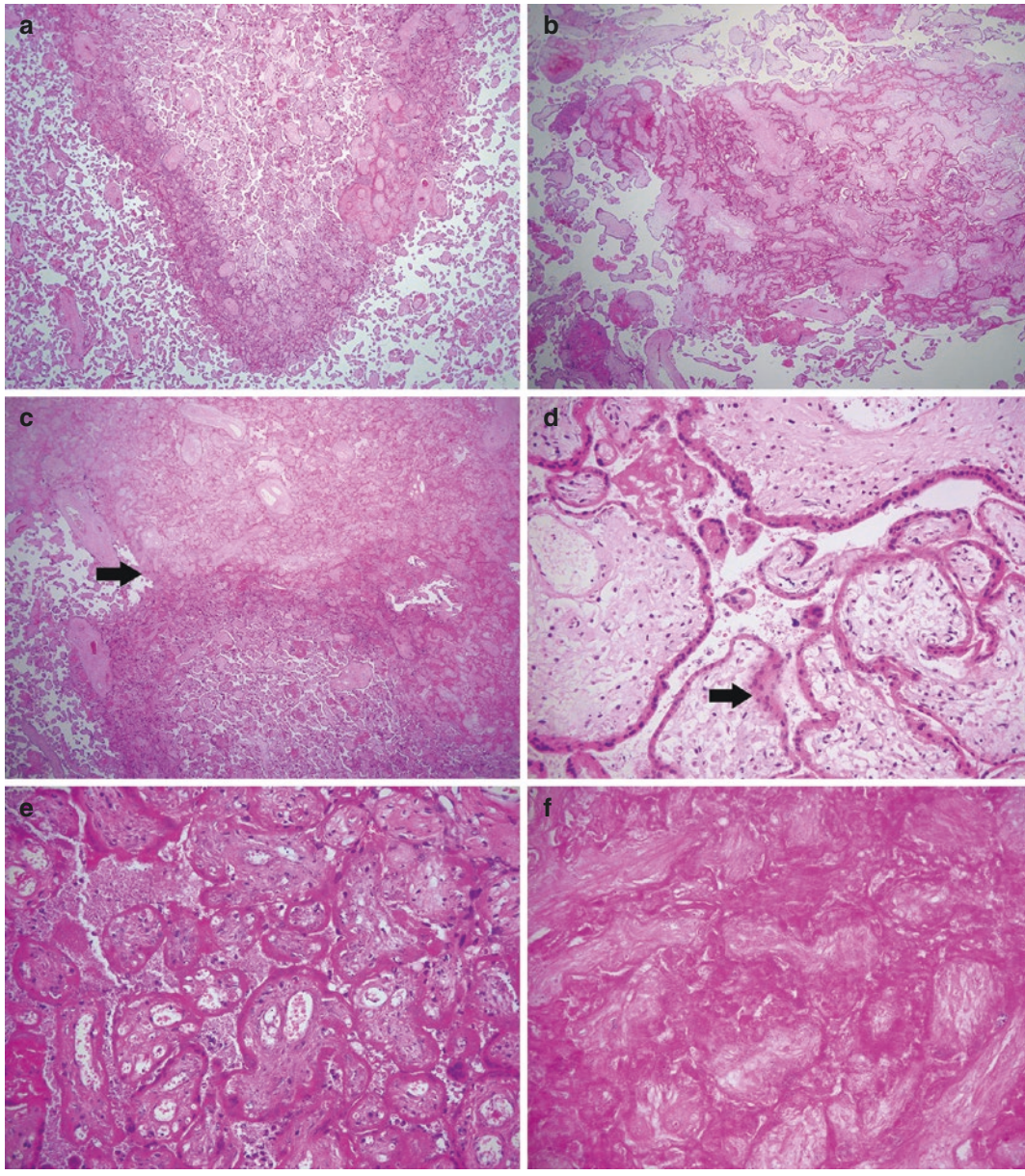

Fig. 6.4 Microscopic appearance of infarction time course. (**a**) and (**b**) show recent infarcts with obvious collapse of the intervillous space. In (**a**) the lesion edge is highlighted by a zone where there is karyorrhectic debris. In (**c**) two adjoining infarcts meet at the arrow with a paler more eosinophilic old infarct above and a more recent infarct below. (**d**, **e** and **f**) show the progressive degenerative changes in villi from infarcts. In (**d**) subtle smudging of trophoblast nuclei is evident in this second-trimester placenta (from the infarct seen in (**b**)). In (**e**) karyorrhectic debris is prominent and nuclei are losing their staining. (**f**) shows an old infarct with ghost villi embedded in fibrinoid

syncytioplasm leads to surface deposition of fibrin, occasional infiltration of the intervillous space by neutrophils, accumulation of karyorrhectic debris and villous agglutination (Fig. 6.4d, e). In parallel with this process, similar nuclear changes affect the villous stromal elements with stromal cells and vessels progressively losing their staining qualities, undergoing karyorrhexis and becoming progressively featureless.

In old infarcts, all nuclear staining is lost in the central areas of the infarct and the appearance becomes one of back-to-back "ghost villi" with hinted outlines of pre-existing structures (Fig. 6.4f). There is no ingrowth of fibroblasts in these areas and there is no "organisation" of the infarct.

At the edge of infarcts (Fig. 6.5), there is a gradient of ischaemic injury. The villi at the edge of the infarct retain viability but lose their vascularity and become fibrotic. Due to collapse of the intervillous space and villous trophoblast alterations, the villi in this area become adherent and encased in perivillous fibrinoid populated by extravillous trophoblasts. Outside of this transitional parenchymal zone, the parenchyma surrounding the infarct frequently shows other evidence of MVM such as increased syncytial knotting or accelerated maturation (Chap. 17). Fetal vessels overlying large infarcts may show secondary thrombotic changes.

In rounded intraplacental haematomas, the sequence of changes seen in the peripheral infarcted zone is the same. The base of the lesion, abutting the basal plate, may sometimes have abnormal vasculopathic "feeder vessels" that appear to lead into the area of haemorrhage (Fig. 6.3c). As the central area of haemorrhage ages, it loses its staining characteristics and shows progressive degenerative changes. As with the more typical infarcts described above, fibroblast ingrowth or organisation does not occur.

6.6.1 Microscopic Differential Diagnosis

These changes, resulting from disruption of the maternal circulation, are in contrast to interruption of the fetal circulation which will result in a sequence of changes eventually resulting in avascular villi with essentially unaltered villous trophoblast and intervillous space. The microscopic differential diagnosis is thus mainly related to lesions characterised by loss of the intervillous space and fibrinoid deposition; these include foci of villous agglutination and

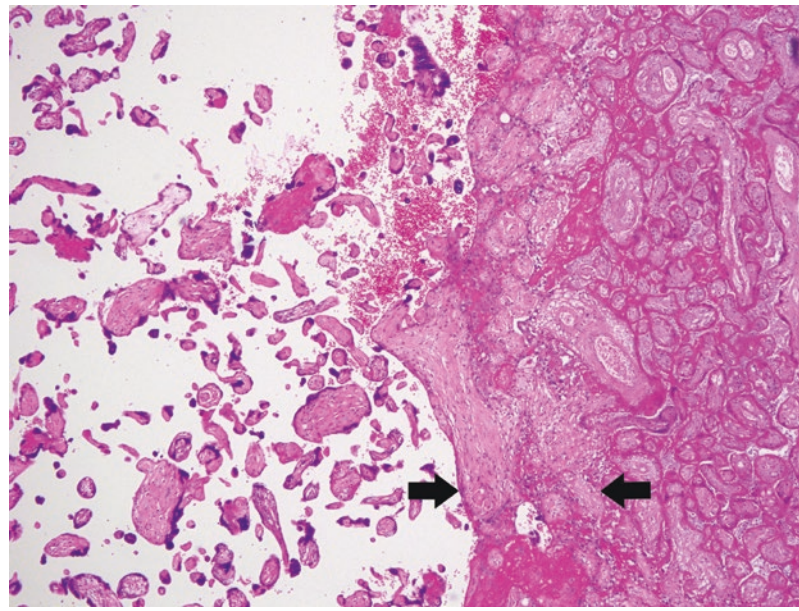

Fig. 6.5 Microscopic villous architecture at the edge of infarction. At the edge of the infarct, there is an area of intermediate viability (between the arrows) where fibrotic villi become encased in fibrinoid containing extravillous trophoblast. Distal villous hypoplasia with increased syncytial knots is evident in the adjacent parenchyma

large perivillous fibrinoid deposits (including those seen in a context of MVM, villitis of unknown aetiology, chronic histiocytic intervillositis, massive perivillous fibrinoid deposition and maternal floor infarction). Villous agglutination is a form of placental parenchymal injury seen in MVM and consists of small foci of villi that clump together in association with degenerative changes in the covering villous trophoblast; they are smaller than infarcts, and the affected villi maintain nuclear viability in their stromal elements. Larger fibrinoid deposits are similar in that the stroma of the villi within the deposits generally remains viable although usually the villi are fibrotic and avascular. There tends to be greater separation of villi within the lesion due to the deposition of the fibrinoid material, which will contain some extravillous trophoblast cells. In large fibrinoid deposits, the central portions may become infarcted, but the volume of this secondarily infarcted parenchyma tends to be minor in comparison to the size of the area affected by fibrinoid deposition. Depending on the aetiology of the fibrinoid deposits, evidence of villitis of unknown aetiology or chronic histiocytic intervillositis may be seen, and this inflammatory element is often best appreciated at the edge of the deposits. It should be noted that "maternal floor infarct" is not an infarct but refers to a particular gross and microscopic pattern of deposition of fibrinoid material in the placental parenchyma above the basal plate (Chap. 8).

Rounded intraplacental haematomas need to be distinguished from intervillous thrombi and occasionally septal cysts (extravillous trophoblast cysts), particularly if the latter have had haemorrhage into them. All rounded intraplacental haematomas will show a distinctly rounded area of haemorrhage that is different from the angular shape of intervillous thrombi; intervillous thrombi also do not usually significantly compress the surrounding villi or cause surrounding ischaemic change. Septal cysts can be identified because of their position within the septum and the lack of compression/infarction of the surrounding placental parenchyma.

6.7 Immunohistochemistry

There is generally no indication for immunohistochemistry in the diagnosis of infarction. In some instances where the differential diagnosis includes perivillous fibrinoid deposition, immunohistochemistry for CD68 or CD3 may assist in identifying histiocytic intervillositis or villitis of unknown aetiology but these are usually also identifiable in routinely stained sections.

6.8 Genetic Susceptibility

Since placental infarction may be related to occlusion of maternal decidual arterioles, genetic susceptibility to thrombosis, as seen in the inherited thrombophilias, has been investigated. The role of thrombophilias in MVM pregnancy complications (e.g., pregnancy loss, preeclampsia and growth restriction) is controversial and good evidence is currently lacking [12, 13]. In any case, it appears that in women with preeclampsia, fetal growth restriction and stillbirth, there are no specific lesions that distinguish women with positive or negative thrombophilia testing [3]. Any potential association between thrombophilia and infarction would be complex, as infarction is but one manifestation of the broader group of lesions that define MVM. As such, susceptibility to infarction is not simply one of a susceptibility to vascular thrombosis but ties into the incompletely understood mechanisms that underlie maternal vascular malperfusion syndromes. For example, preeclampsia has a genetic predisposition but the genetics are multifactorial without clear inheritance patterns [14, 15].

6.9 Prognosis and Predictive Factors

6.9.1 Maternal Implications

The maternal implications of placental infarction do not necessarily relate directly to the development of infarction itself but rather to its role as a marker of MVM and therefore maternal

hypertensive disease in pregnancy. Preeclampsia itself is also a significant risk factor for future maternal ischaemic heart disease, chronic hypertension, peripheral vascular disease and stroke [16].

6.9.2 Fetal Implications

Infarcts and the related lesions of MVM are some of the most important pathological lesions associated with fetal growth restriction [6, 17, 18], preterm birth [19, 20] and fetal death [21–24]. In surviving infants, placental infarction has been associated with cerebral palsy [25] and abnormal neurodevelopmental tests [26]. In addition, growth-restricted infants are increasingly being recognised as being at risk for developmental programming of many adult-onset diseases [27, 28].

It is reasonable to assume there may be a correlation between placental infarction percentage and pregnancy outcomes [24]. However, the placenta has reserve capacity and any attempt to set an absolute threshold for significance of a particular infarct volume will be problematic; this is because placentas with infarcts will vary in weight, the fetus will vary in size, the background placental morphology will differ and the mother's risk factors will vary. The same total volume of infarcts in two similar placentas may also have formed over different time periods allowing for potentially differing abilities to compensate. In individual cases it seems more logical to take into account the sum of the pathological and clinical features in individual cases in order to synthesise potential clinical significance. This type of multivariate analysis with adjusted odds ratios is unfortunately uncommon in most placental clinicopathologic studies.

New imaging modalities are now making it possible to evaluate placentas antenatally for the presence of textural and flow anomalies including infarction [29–31]. Pathological examination of subsequently delivered placentas will be important for improving the diagnostic accuracy of these imaging techniques.

Antenatal morphological assessment of the placenta using ultrasound may also be used in conjunction with clinical risk assessment and maternal biochemical markers to help identify women at increased risk of preeclampsia and fetal growth restriction in early pregnancy [32, 33]. Early identification of at-risk women allows for intervention, e.g., through prophylactic use of aspirin [34] and increased monitoring. The ability to accurately identify at-risk pregnancies will also facilitate the design of clinical trials to evaluate preventative treatments with thus far conflicting results, e.g., heparin [35], and in evaluation of more novel potential interventions, e.g., with sildenafil [36]. Pathological evaluation of delivered placentas should form part of the study design of these trials and its absence in prior studies has been cited as a potential reason for conflicting results [35]. Incorporating standardised placental pathological evaluation will both improve study design and add to our knowledge of placental clinicopathological correlations [37].

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Intervillous Thrombosis

7

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7.1 Introduction

Coagulation of blood within the intervillous space may result in a variety of pathologic lesions. Most of these have a laminated appearance and displace adjacent chorionic villi. They are commonly referred to as thrombi, haematomas or thrombohaematomas. The lesions discussed here are all intervillous (i.e., occurring within the intervillous space); however, the term "intervillous" may or may not be explicitly used in the lesion name, depending on convention for each lesion. Intervillous thrombi may be located adjacent to the chorionic plate ("subchorionic" or "subchorial"), in the middle of the parenchymal mass ("central") or adjacent to the basal plate ("basal"). These lesions have multiple potential aetiologies relating to the classical causes of coagulation articulated in Virchow's triad (stasis, endothelial injury, hypercoagulability) and include:

1. Haemorrhage from fetal capillaries (i.e., feto-maternal haemorrhage), where thrombosis may be related to blood group incompatibilities or the release of thrombogenic material from necrotic tissue, and fetal red blood cells may be identified within the thrombus by immunohistochemistry for fetal haemoglobin [1]. This is the proposed aetiology for most centrally located intervillous thrombi.
2. Stasis or abnormal flow of blood, manifesting in circumstances that include:
   (a) Severe villous oedema such as in erythroblastosis fetalis and hydatidiform mole, where it is thought that marked distortion of the villi causes local eddies and stasis, resulting in thrombi. This is one proposed aetiology for intervillous thrombi [2] as well as for massive subchorionic thrombohaematomas [3].
   (b) Labour, when fresh-appearing thrombi may be due to areas of abnormal flow due to direct compression or changes in uterine geometry resulting in localized stasis [2, 4]. This is a possible aetiology for relatively small thrombi that occur singly or in small numbers.
   (c) Special characteristics of the subchorionic region; this is where blood is farthest from maternal arteries in the basal plate and thus most likely to experience stasis, particularly near term as the placental thickness increases; this is also where maternal blood is redirected laterally from

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its initial upward trajectory upon entering the intervillous space and hence can be a region of turbulence; these are proposed aetiologies for subchorionic intervillous thrombi [4, 5].

3. Maternal hypercoagulability, which may be due to inherited thrombophilia or an acquired state (e.g., preeclampsia) and in which thrombi occur spontaneously, likely in areas of relatively low flow. This is one aetiology of intervillous thrombi ([2], p. 356).
4. Maternal preeclampsia and hypertension have been associated with basal intervillous thrombi [4, 5] and are quite strongly associated with rounded intraplacental haematomas [6]. The aetiology of the former is proposed to be thrombosed maternal veins while the aetiology of the latter is likely arterial rupture in decidual vasculopathy.
5. Associated with placenta increta and percreta and commonly found in gravid hysterectomies performed in this context [7], potentially due to altered flow in invasive placentation.

Intervillous thrombi are usually isolated lesions measuring up to 2 cm in greatest dimension (occasionally larger) but it is also common to see several such lesions in the same placenta. The total volume these lesions occupy is typically less than 5% of the parenchymal volume.

It is important to distinguish the various types of thrombi, which are the main topic of this chapter, from another set of lesions that result from deposition or coagulation of fibrinoid in the intervillous space—referred to as "perivillous fibrinoid deposition"—and which are grossly and histologically quite distinct. Perivillous fibrinoid deposition is not the focus of this chapter but is mentioned here for clarity. Fibrinoid deposition commonly occurs in areas of microscopic syncytiotrophoblast disruption, which is patched over by fibrinoid, and sometimes also in areas of sluggish maternal blood flow such as the subchorial and marginal zones ([4, 5], p. 227–32). Morphologically, these lesions lack gross and histologic lamination and do not displace villi, instead presenting as the solidification of eosinophilic material (typically hyaline or fibrillar in quality) around trophoblastic villi with neither relative expansion nor collapse of the affected intervillous space. A small amount of perivillous fibrinoid deposition may be seen in almost any placenta, is normally more abundant in third-trimester placentas and may be increased in regions with poor maternal perfusion, as well as where trophoblast integrity may be compromised, such as in chronic villitis. Note that fibrin-type and matrix-type fibrinoid are morphologically indistinguishable on haematoxylin-and-eosin-stained slides and typically co-occur; it is thought that a layer of fibrin-type fibrinoid (deposited from maternal blood) is generally interposed between maternal blood and matrix-type fibrinoid and that conversely a layer of matrix-type fibrinoid (secreted by extravillous trophoblast) is generally interposed between extravillous trophoblast and fibrin-type fibrinoid ([4], p. 227–32).

7.2 Definitions

An intervillous thrombus (IVT) is a localized area of thrombosis within the intervillous space that is generally polygonal in shape, displaces adjacent trophoblastic villi and contains straight parallel laminations (lines of Zahn). A subchorionic intervillous thrombus has a similar histologic composition to an IVT but borders the chorionic plate and is often much wider than tall, following the contour of the chorionic plate.

A massive subchorionic thrombohaematoma is a similar—but much larger—lesion that underlies a large portion of the chorionic plate and is associated with a high rate of fetal morbidity and mortality. It appears that massive subchorionic thrombohaematoma is composed of maternal blood (demonstrated by molecular techniques in one case) [3] but otherwise the pathogenesis remains poorly understood. While there is no consensus on exactly how large a massive subchorionic thrombohaematoma should be, some investigators have used the criteria that it should be ≥1 cm thick and underlie ≥50% of the chorionic plate [8].

A basal intervillous thrombus is an intervillous thrombus that abuts the basal plate at the maternal surface or a septum and has been traditionally associated with maternal vascular malperfusion and thought to arise due to thrombosed maternal decidual veins [5]. However, there has been considerable debate as to whether basal intervillous thrombus truly has a separate aetiology from central intervillous thrombus. Recent research now suggests that basal intervillous thrombus with classic intervillous thrombus morphology (polygonal shape, prominent parallel laminations) may have similar implications to central intervillous thrombus and it is those basal lesions with a distinct morphology (see rounded intraplacental haematoma below) that are strongly associated with maternal vascular malperfusion and decidual vasculopathy [6].

Where stasis-related thrombus or fibrinoid is in direct contact with the basal plate, it may demonstrate organization with age, showing spindled myofibroblasts oriented parallel to the basal plate. This spindled lesion has been called a basal plate plaque and most such lesions are small and clinically insignificant [9].

A rounded intraplacental haematoma (or infarction haematoma) has a similar location to a basal intervillous thrombus (adjacent to the basal plate) but has a rounded contour (instead of polygonal) and shows either no lamination or a small number of concentric/circular laminations, as well as marked compression of adjacent villi, often resulting in a rim of villous infarction [6]. The proposed aetiology is the rupture of a diseased maternal spiral arteriole in the context of decidual vasculopathy or, alternatively, reperfusion of an area of placental infarction [10].

7.2.1 Synonyms

An intervillous thrombus is also known as intervillous thrombohaematoma, intervillous haematoma and Kline's haemorrhage. Intervillous thrombus was the term preferred by the Dublin Consensus meeting because of its entrenched usage, although intervillous thrombohaematoma may be preferable to the synonyms "intervillous thrombus" or "intervillous haematoma," firstly, as the most inclusive term and, secondly, because the other terms may be misleading (since a haematoma is generally extravascular by definition and a thrombus typically causes tissue damage due to vascular obstruction, neither of which applies here); "Kline's haemorrhage" is an eponym that refers to the mechanism (fetal haemorrhage) underlying most intervillous thrombi rather than the lesion itself.

Subchorionic intervillous thrombus is also known as subchorionic haematoma and occasionally as subchorionic fibrin deposition. The term "subchorionic thrombus" is preferred to "subchorionic haematoma," which has a conflicting definition in the obstetric and radiologic literature, where it refers to a retroplacental or retromembranous haematoma in early pregnancy [11, 12]. Although massive subchorionic thrombohaematoma was first described by Breus, the eponymous term "Breus' mole" is not recommended due to the potential for confusion with hydatidiform mole.

7.3 Epidemiology

Intervillous thrombi are found in about one fifth of term placentas [2] and have been documented in as many as one in two placentas when are assiduously identified [13]. Subchorionic intervillous thrombi increase in frequency with increasing gestational age, are seen in 20% of mature placentas [5] and may show increased incidence in mothers with cardiac disease [4]. They are typically small and incidental. Massive subchorionic thrombohaematoma is an unusual lesion, with literature estimates of incidence ranging from 1 in 1887 to 3133 deliveries [14, 15], and shows an association with maternal hypertension, diabetes, circulatory disorders and thrombophilia [4, 16], as well as fetal monosomy X and partial mole [3, 17].

Basal intervillous thrombus and rounded intraplacental haematoma, both basally located lesions, have an uncertain incidence due to a paucity of studies addressing this question. In our practice, basal intervillous thrombus is a rela-

tively common finding in delivered placentas whereas rounded intraplacental haematoma is less common. Basal intervillous thrombus has been traditionally ascribed an association with maternal hypertension, preeclampsia and thrombophilia [4, 5] but it is possible that this is due to prior conflation of these two morphologically similar lesions. A recent study differentiating these two lesions showed a strong association of rounded intraplacental haematoma with maternal vascular malperfusion and decidual vasculopathy but did not show any association between basal intervillous thrombus and maternal clinical factors [6]. Rounded intraplacental haematoma has also been associated with maternal hypertension, preeclampsia and gestational diabetes, as well as fetal growth restriction, preterm delivery and fetal death [6, 18].

7.4 Gross Findings

All thrombi form as laminated lesions, usually showing alternating layers of red and tan. These laminations may be inconspicuous in very recent lesions, which have a more uniform dark red appearance, as well as in very old lesions, whose colour gradually fades to a uniform yellow tan. An intervillous thrombus or basal intervillous thrombus is polygonal in shape while a subchorionic intervillous thrombus is most commonly an elongated lesion paralleling the chorionic plate (Fig. 7.1).

Massive subchorionic thrombohaematoma is similar to a subchorionic intervillous thrombus but much larger in scale, forming a thick layer of laminated thrombus that lies immediately beneath the chorionic plate and separates it from the underlying villous parenchyma. In typical cases, this thrombus will occupy >50% of the placental thickness, chorionic plate surface area and disc volume. The overall thickness of the placental disc is often markedly thickened and may be discoloured (due to underlying blood and related haemosiderin deposition) with a nodular fetal surface due to tenting of the chorionic plate between stabilizing stem villi (Fig. 7.2).

A rounded intraplacental haematoma classically shows a basally located, round-contoured, red lesion with no laminations or else inconspicuous concentric laminations. This lesion will be surrounded by compressed villous parenchyma that often shows induration and colour change as infarction of this tissue develops [6]. These haematomas may be single or multiple in a placenta, and the regions of adjacent infarction may sometimes be quite extensive (Fig. 7.2).

7.5 Histopathology

The lamination of all thrombi is histologically composed of alternating layers of red blood cells and fibrin. Thrombi typically contain no chorionic villi, which are displaced as the lesions form, but may sometimes entrap a few villi, which are then often infarcted or avascular. At their edges, thrombi may cause secondary effects resulting in villous infarction, avascular villi, acute or chronic villitis and/or increased perivillous fibrinoid deposition. As thrombi age, the layers of red blood cells degenerate and acquire a uniform granular eosinophilic appearance with H&E staining that is similar to fibrin and may obscure the laminations. In the vicinity of aging thrombi, it is common to see haemosiderin-laden macrophages, particularly within the chorionic plate near subchorionic intervillous thrombi and within the decidua near basal intervillous thrombi. Massive subchorionic thrombohaematoma, more often than other lesions in this chapter, may show regions of differing ages, implying a gradual or stepwise formation of the lesion. Of note, thrombi (along with other lesions of the placenta) generally do not exhibit histologic organization over time as seen in other organs, i.e., with fibrous ingrowth, neovascularization, and scarring. One possible exception consists of lesions directly adjacent to the (partly maternal) basal plate, where the fibroblastic lesion termed a basal plate plaque may occur (Fig. 7.3) [4, 9].

The thrombi and thrombohaematomas described in this chapter all have a generally similar histologic composition although they differ in location and shape, as well as in pathogen-

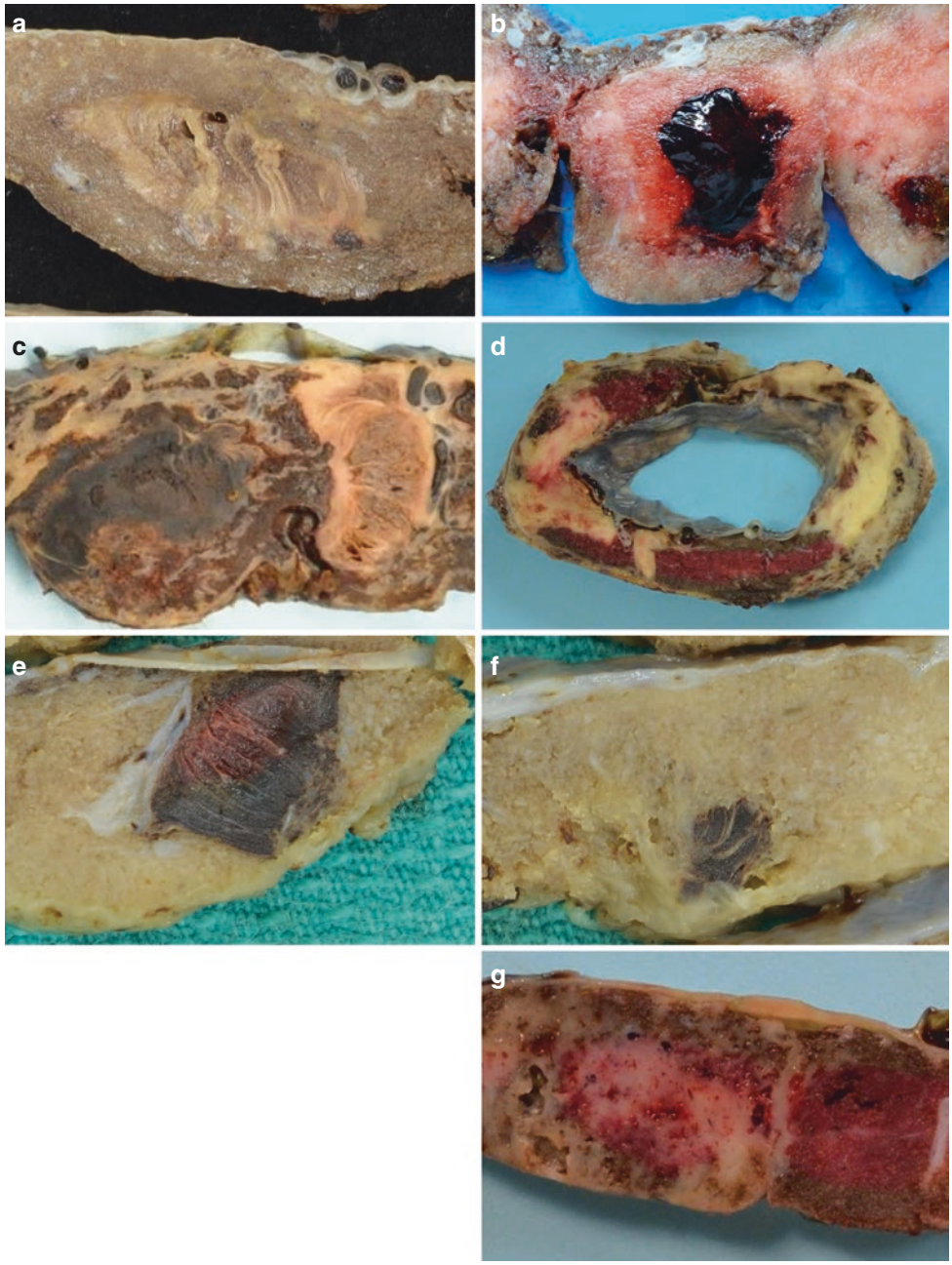

Fig. 7.1 Gross appearance of thrombi. (**a**–**b**) Intervillous thrombi; classical lesions are located within the centre of the parenchyma, are polygonal in shape and show well-developed laminations (**a**); very fresh lesions may show few laminations, as in this case from a fetal death due to fetal-maternal haemorrhage (suggested by the pale background parenchyma) (**b**). (**c**–**d**) Intervillous thrombi in a background of other severe pathology; **c** shows a recent (left) and older (right) lesion in a case of massive perivillous fibrinoid deposition (evidenced by the reticular tan material occupying the background parenchyma); **d** shows older transmural lesions (extending from the fetal to maternal surfaces) in a gravid hysterectomy for placenta increta. (**e**–**f**) Non-central intervillous thrombi; the lesion in **e** is adjacent to the chorionic plate but does not show the characteristic elongated shape of a true subchorionic thrombus; **f** shows a basal intervillous thrombus. (**g**) Perivillous fibrinoid plaque; in contrast to the thrombi above, this region of localized deposition of perivillous fibrinoid (left hand side) shows a pale reticular pattern without evident laminations

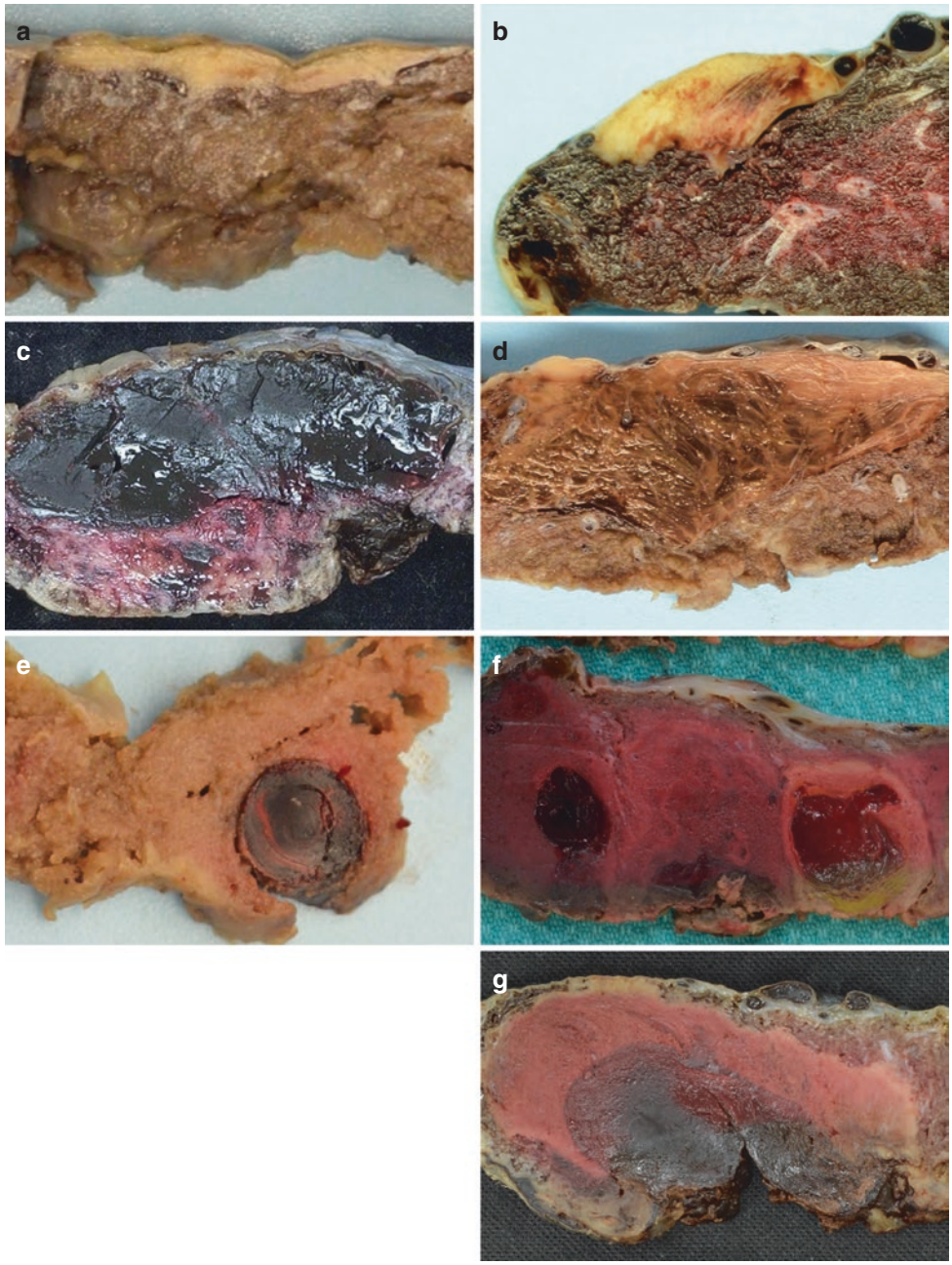

Fig. 7.2 Gross appearance of subchorionic thrombi and rounded intraplacental haematoma. (**a**–**b**) Subchorionic intervillous thrombi: these older lesions are yellow tan and wider than tall and follow the contour of the chorionic plate; their laminations have become less conspicuous with age. (**c**–**d**) Massive subchorionic thrombohaematomas (Breus' mole): **c** is recent and composed of freshly coagulated blood, while **d** is older with previously well-developed laminations that are now beginning to fade. Both cases show characteristic separation of the chorionic plate from the villous parenchyma by the thrombohaematoma; however, diagnosis must be based on the size and distribution of the lesion throughout all slices of the placenta. (**e**–**f**) Rounded intraplacental haematomas: these lesions are basally located and circular and show few laminations (which are curved when present) and compression/infarction of surrounding tissue; circumferential infarction is visible as a pale region around the lesions in **f**. (**g**) Retroplacental haematoma with surrounding infarction: note the similarity in appearance to the rounded intraplacental haematoma in **f**; these lesions likely have a closely related pathogenesis and are in some cases distinguishable only by their location relative to the basal plate

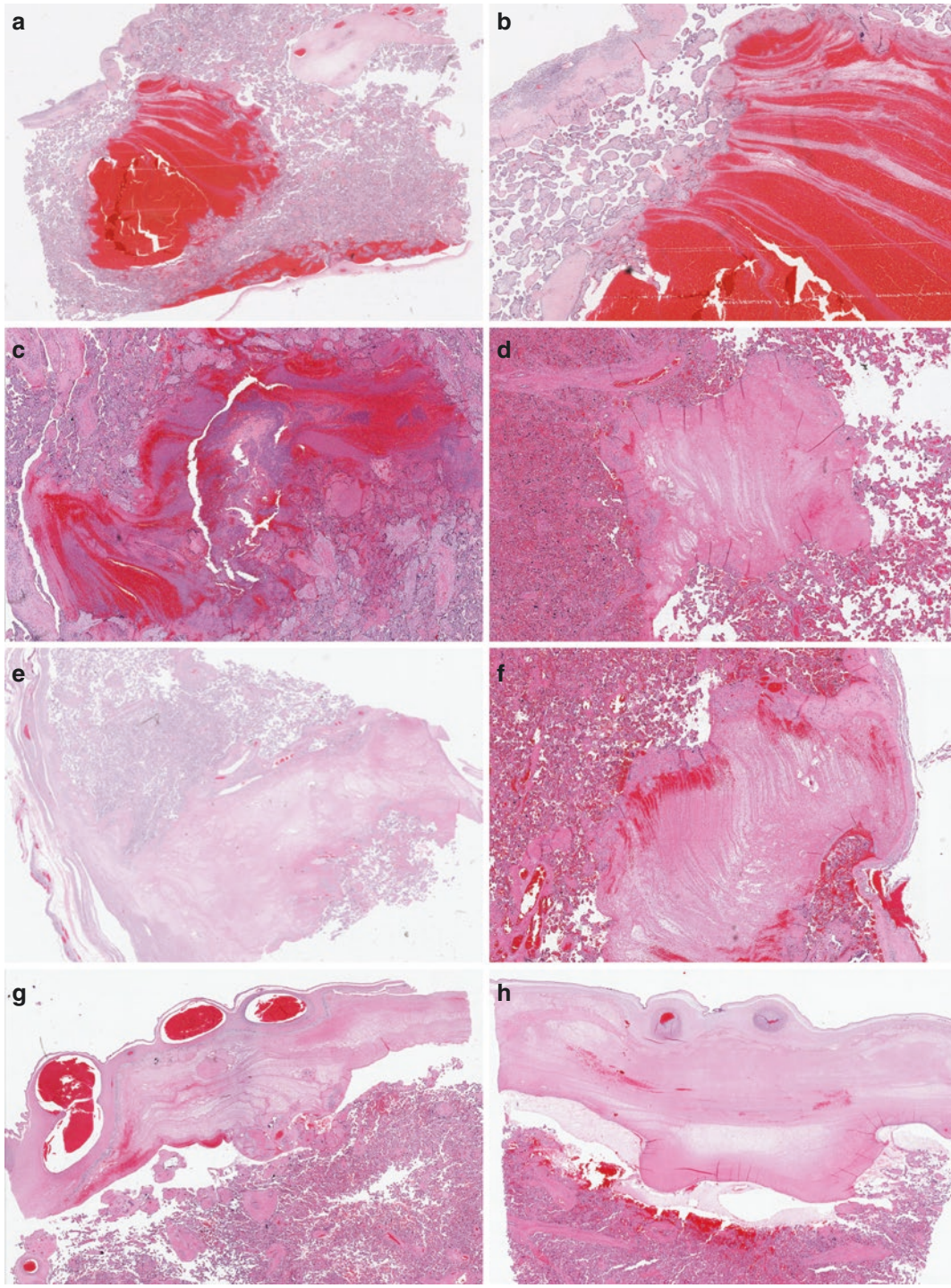

Fig. 7.3 Microscopic appearance of intervillous thrombi. (**a**–**e**) Intervillous thrombi: classic lesions (**a**–**b**) are polygonal in shape, show well-developed parallel laminations and may show some occasional areas of adjacent compressed villous parenchyma; abundant entrapped neutrophils may sometimes be present, as in **c**; lesions become paler with age and laminations less conspicuous (**d**); (**e**) shows a transmural lesion in a gravid hysterectomy for placenta percreta. (**f**) Basal intervillous thrombus. (**g**–**h**) Subchorionic intervillous thrombi, following the contour of the chorionic plate and showing laminations

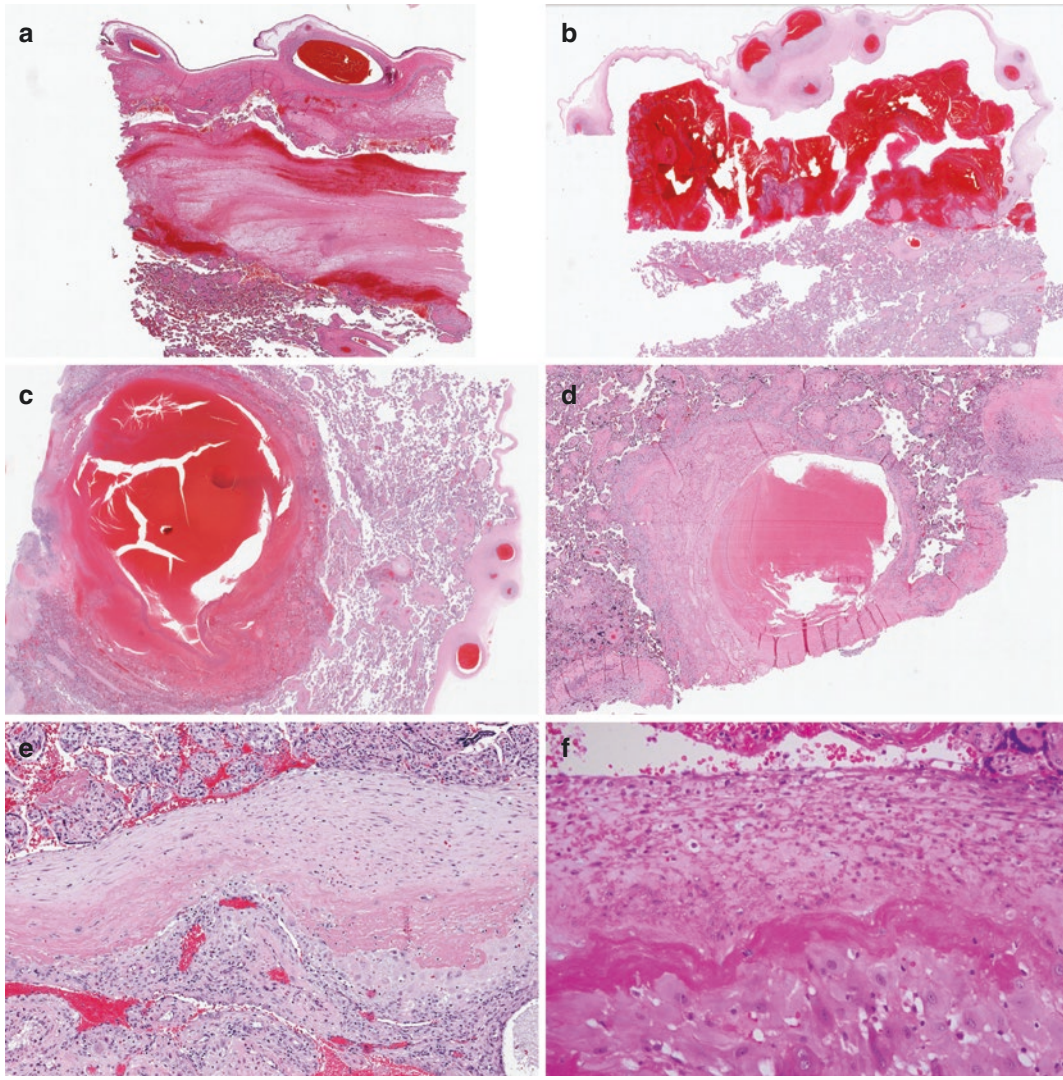

Fig. 7.4 Microscopic appearance of other thrombosis-related lesions. (**a**–**b**) Massive subchorionic thrombohaematoma: **a** is older showing abundant laminations, which are inconspicuous in the more recent lesion in **b**. (**c**–**d**) Rounded intraplacental haematomas: classic features demonstrated here include the basal location, rounded shape, paucity of laminations and peripheral rim of compressed and infarcted villous parenchyma. (**e**–**f**) Basal plate plaque: both lesions show a bland spindle-cell proliferation at the fetomaternal interface in the process of replacing an underlying region of eosinophilic coagulated blood

esis, epidemiologic associations and clinical implications. In contrast, rounded intraplacental haematomas are composed predominantly of red blood cells, with inconspicuous or absent fibrin laminations and a circular rim of infarcted villi secondary to compression [6]. This rim of infarction may be quite thin (one or two villi thick) or may occasionally involve substantial portions of villous parenchyma. Rounded intraplacental haematomas typically occur in a background of advanced villous maturation and/or distal villous hypoplasia, which may also be seen in massive subchorionic thrombohaematoma and basal intervillous thrombus (Fig. 7.4).

Subchorionic intervillous thrombus should be distinguished from the more typical deposition of subchorionic fibrinoid beneath the chorionic plate, which underlies most of the chorionic

plate, although its thickness is quite variable. However, subchorionic fibrinoid is uniformly eosinophilic and does not typically show laminations. As a parenthetical but practical point related to the diagnosis of acute chorioamnionitis, regions with thick fibrinoid or thrombus beneath the chorionic plate appear to act as barriers to either chemotactic factors or inflammatory cells in the context of amniotic fluid infection, and hence features of chorioamnionitis are usually muted or masked in these regions.

7.6 Prognosis and Predictive Factors

In many cases, intervillous thrombi are due to fetal haemorrhages from chorionic villi and there is a degree of correlation between the identification of intervillous thrombi in delivered placentas and the presence of fetal red blood cells in maternal circulation ([2], p. 355). However, it appears that the formation of an intervillous thrombus walls off the fetal haemorrhage, typically limiting fetal blood loss to tiny amounts that are not clinically significant. In cases where maternal and fetal blood are sufficiently compatible, no intervillous thrombus may form and there is a potential for large fetal blood losses. In addition, if intervillous thrombi are large or numerous, it is worth considering the possibility of a significant fetomaternal haemorrhage. However, in the vast majority of cases where intervillous thrombi are seen, there is no clinically significant impact [2, 5].

Subchorionic intervillous thrombi are generally incidentally discovered and without significant clinical implications [5]. They are also typically small and relatively few in number. In situations where there are numerous such lesions or they occupy a substantial portion of the placenta, the differential of massive subchorionic thrombohaematoma should be considered. In cases where there are numerous intervillous thrombi or subchorionic intervillous thrombi but the criteria are clearly not satisfied for massive subchorionic thrombohaematoma, consideration should still be given to other factors that may have promoted this unusual degree of intervillous thrombosis, including thrombophilias and factors causing abnormal blood flow in the intervillous space.

Massive subchorionic thrombohaematoma is associated with notable complications for the fetus and pregnancy, including oligohydramnios, pulmonary hypoplasia, antenatal haemorrhage, preterm delivery, growth restriction and intrauterine/neonatal death [8, 19, 20]. Antenatally diagnosed massive subchorionic thrombohaematoma is associated with a high rate of fetal growth restriction and fetal/neonatal death [8, 14, 15].

In the 39 cases reported so far, the finding of a rounded intraplacental haematoma was strongly associated with decidual vasculopathy, as well as a high frequency of severe growth restriction, stillbirth, premature delivery and maternal hypertensive disorders [6, 18]. In our clinical experience, the lesion appears to be reasonably specific for maternal vascular malperfusion, typically appearing with accelerated villous maturation or distal villous hypoplasia and accompanied by multiple infarcts and/or decidual vasculopathy. Traditionally, basal intervillous thrombus has been said to have similar associations to the above (see further discussion in the definitions section).

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8 Massive Perivillous Fibrinoid Deposition and Maternal Floor Infarct

Philip J. Katzman, Linda M. Ernst, and Irene B. Scheimberg

8.1 Introduction

Perivillous fibrinoid material has been shown to be a mixture of blood proteins, including fibrin, fibrinogen, fibronectin, basement membrane collagen, laminin and major basic protein [1, 2]. Because of this admixture, the word "fibrinoid" is used by many pathologists. Fibrinoid material occupies the perivillous space. An increased amount of perivillous fibrinoid material is designated as a pathologic process. The spectrum of this pathology ranges from patchy perivillous fibrinoid deposition (that may not be pathological) to increased larger areas of perivillous fibrinoid deposition to maternal floor infarct and to massive perivillous fibrinoid deposition. Although no studies have methodically evaluated the contents of any of these variations of increased perivillous fibrinoid deposition, it is likely that all variations are composed of some, if not all, of the proteins described above. Fibrinoid material in maternal floor infarction and massive perivillous fibrinoid deposition has been hypothesized to include deposits from the coagulation cascade products or extracellular material, including pregnancy-associated major basic protein, that is localized to extravillous intermediate trophoblasts, previously known as "X cells" [2]. Often maternal floor infarction and massive perivillous fibrinoid deposition are seen grossly when the placenta is sectioned.

8.2 Definition

Increased perivillous fibrinoid deposition is when 25–50% of parenchyma of a single slide is involved by fibrinoid material.

Massive perivillous fibrinoid deposition is when there is gross involvement of >50% parenchyma and/or microscopic involvement of >50% by fibrinoid material on a single slide, in which the fibrinoid material involves the intervillous space spanning from the fetal to the maternal surfaces.

Maternal floor infarct is when there is fibrinoid material involving at least 3 mm of parenchyma adjacent to the maternal floor on a single slide [3].

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8.3 Synonyms

When the fibrinoid deposition is based near the fetal surface, subchorionic perivillous fibrinoid deposition can be used. Some pathologists use the terms maternal floor infarction and massive perivillous fibrinoid deposition and the words "fibrin" and "fibrinoid" interchangeably, respectively. Note that maternal floor infarction is not a true vascular infarction and was a misnomer that originates from the German word "Gitterinfarct."

8.4 Epidemiology

The reported incidence ranges from 0.028% to 0.5% of pregnancies [3–8]. Patchy perivillous fibrinoid material (PFM) is common in placentas and is likely non-pathologic. Maternal floor infarction and massive perivillous fibrinoid deposition are less common lesions that may recur in subsequent pregnancies in up to 40% of patients [3, 4]. In case reports, these lesions have an association with infection [9, 10], autoimmune disease [11], elevated maternal serum alpha-fetoprotein [12–14], long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and gene mutations [15], maternal coagulopathies such as antiphospholipid antibody syndrome [16, 17], dysregulation of angiogenic/antiangiogenic factors [18], fetal renal dysgenesis [19] and a maternal antifetal rejection-like process similar to those proposed for chronic villitis of unknown aetiology and massive chronic intervillositis [20]. Massive perivillous fibrinoid deposition has also been reported in twins with discordant intrauterine growth and associated with Coxsackie virus placental infection [9]. Massive perivillous fibrinoid deposition may coexist with chronic intervillositis and cases of malaria [10].

8.5 Gross Findings

Massive perivillous fibrinoid deposition shows a marbled or "tigroid" cut surface on slicing the parenchyma (Fig. 1a), reflecting patchy parenchymal consolidation. Maternal floor infarction shows a thickened basal plate. The main gross differential diagnosis of intraparenchymal lesions is massive perivillous fibrinoid deposition or maternal floor infarction, intervillous thrombi and infarction. Intervillous thrombi often have lines of Zahn that may be seen grossly and histologically. Infarctions are often better delineated than maternal floor infarction or massive perivillous fibrinoid deposition, while maternal floor infarction and massive perivillous fibrinoid deposition often have a more serpiginous appearance.

8.6 Histopathology

Perivillous fibrinoid material is often seen in the normal placenta (Fig. 2a, b) but when large areas of parenchyma are involved by perivillous fibrinoid material, maternal floor infarction or massive perivillous fibrinoid deposition is diagnosed, as defined above. Whether occurring along the maternal floor or fetal surface, perivillous fibrinoid material fills the perivillous space without villous crowding or collapse of the intervillous space (Figs. 1b and 2c). The differential diagnosis of perivillous fibrinoid material, maternal floor infarction and massive perivillous fibrinoid deposition includes infarction, intervillous thrombus, old lesions of fetal vascular malperfusion and "burnt-out" chronic villitis. Unlike infarctions, which are usually well circumscribed (Fig. 1c), perivillous fibrinoid lesions tend to have a serpiginous appearance, involving groups of villi with spared villi within the lesion. The surrounded villi eventually become sclerotic, and often extravillous intermediate trophoblasts grow into the fibrinoid material. Older lesions can have central necrotic villi, while peripheral villi may appear more viable. An infarction often has reactive villi surrounding the main lesion which have increased syncytial knots (Fig. 2d). This pattern is generally not seen in lesions of perivillous fibrinoid material. Lesions of perivillous fibrinoid material often have adjacent or admixed areas of intervillous thrombus, often with lines

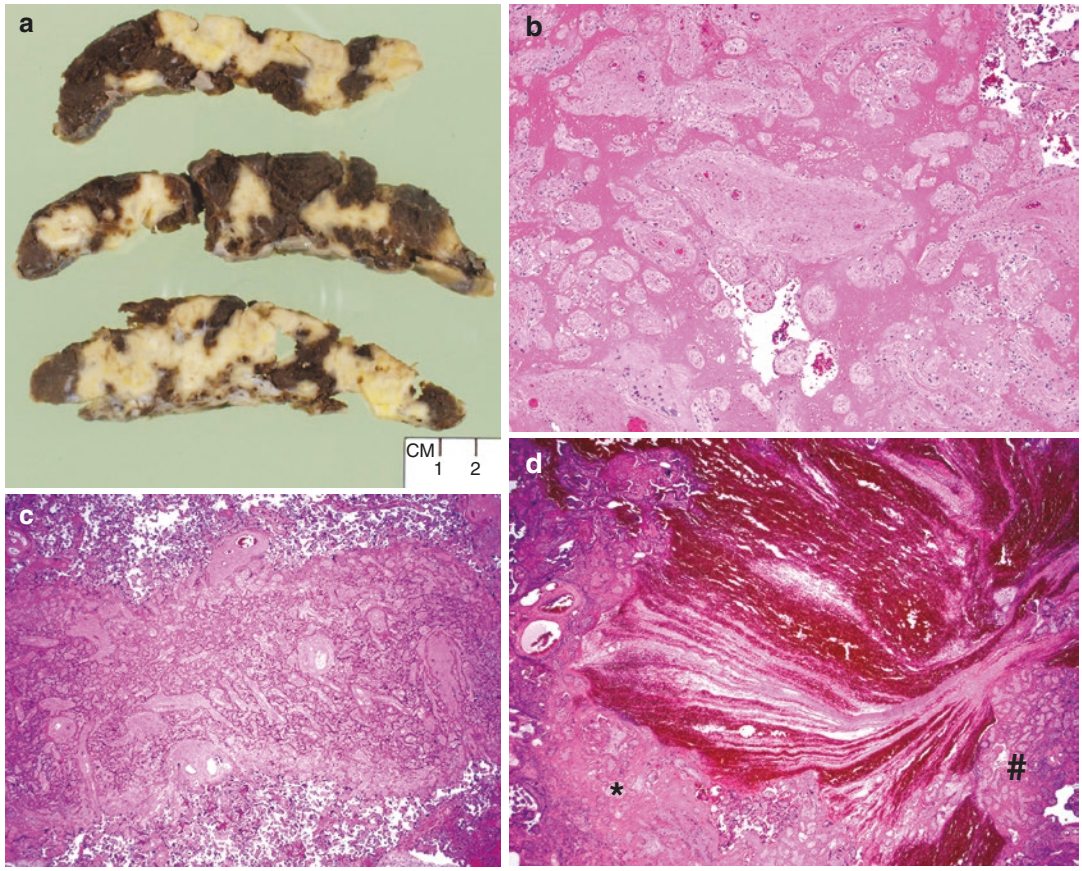

Fig. 8.1 (**a**) sectioned placenta contains massive perivillous fibrinoid deposition with the classic "tigroid" pattern. (**b**) The fibrinoid deposition in massive perivillous fibrinoid deposition causes aggregation of villi without villous crowding. Compared to infarctions (**c**), chorionic villi often appear viable. Infarctions tend to be more circumscribed and demonstrate villous crowding. (**d**). Intervillous thrombi often contain lines of Zahn; they may be isolated lesions or have adjacent areas of perivillous fibrinoid deposition (*) or infarction (#)

of Zahn (Fig. 1d). While intervillous thrombi cause expansion of the intervillous space with displacement of villi, the intervillous space is maintained in the lesions of perivillous fibrinoid material. The mixing of perivillous fibrinoid material and intervillous thrombus is especially common in the subchorionic space. It is not clear whether blood stasis in the subchorionic space plays a role for these lesions forming in this compartment of the placenta. Areas of villous sclerosis secondary to fetal vascular malperfusion can be confused with perivillous fibrinoid material. Similarly, because chronic villitis usually causes sclerosis and agglutination of involved villi, they can be mistaken for an area of perivillous fibrinoid material. Most cases of maternal floor infarction and massive perivillous fibrinoid deposition are diagnosed in the third trimester of pregnancy but the placental tissue from some first-trimester miscarriage specimens can have focal or multifocal areas with perivillous fibrinoid material. In cases of miscarriage, it is not clear whether the perivillous fibrinoid material plays a role in miscarriage or if perivillous fibrinoid material is laid down after demise of the pregnancy.

8.7 Immunohistochemistry

Not relevant to this lesion.

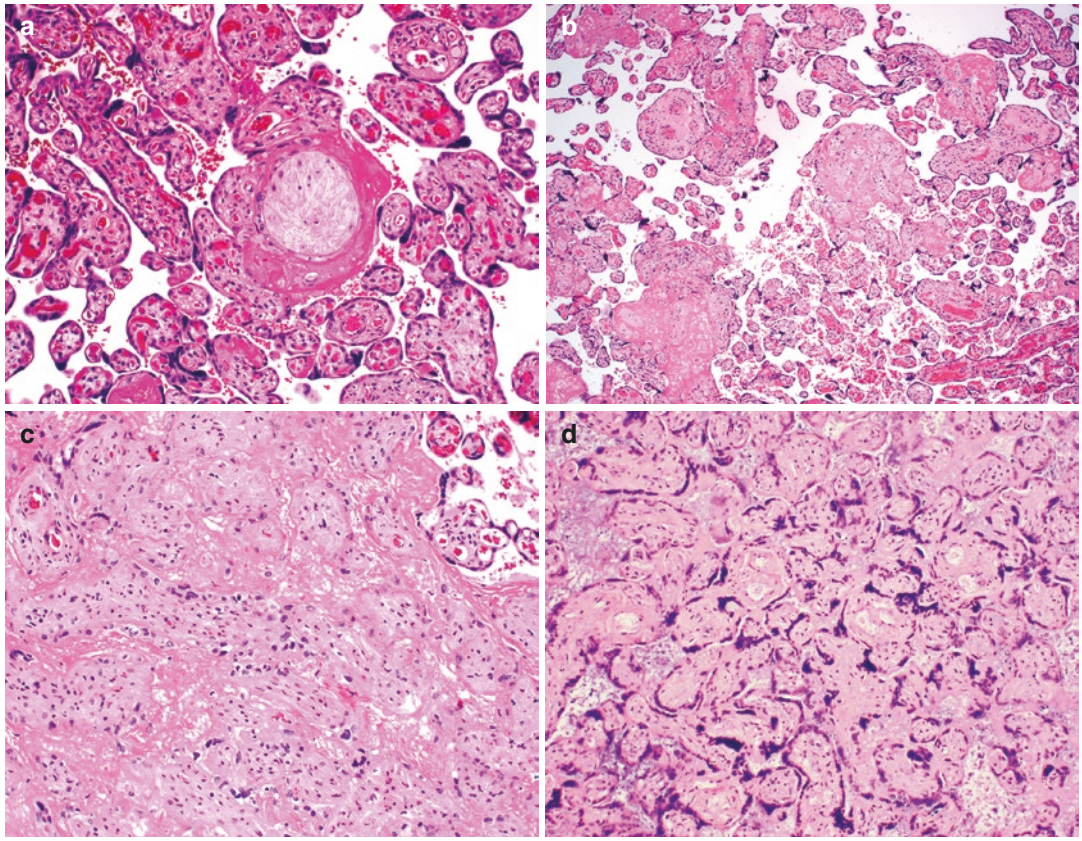

Fig. 8.2 (**a**) single villus is surrounded by fibrinoid material, and some adjacent villi are adherent to this material. (**b**) Perivillous fibrinoid material can be multifocal without being pathologic. (**c**) In a pathologic area of perivillous fibrinoid material, the fibrinoid material fills the intervillous space, but the villi still appear viable. (**d**) In contrast, in a focus within an early infarction, there is villous crowding, where the intervillous space is lost, and there are numerous syncytial knots surrounding most of the villi

8.8 Genetic Susceptibility

A small case series described heterozygous mutations in the *HADHA* gene that resulted in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency in three preterm pregnancies in which maternal floor infarction or massive perivillous fibrinoid deposition was identified in the placentas. The authors note that since the background incidence of heterozygosity for LCHAD mutations is approximately 1 in 220, these mutations may be causative of maternal floor infarction and massive perivillous fibrinoid deposition [15]. Another study found no association between genetic polymorphisms in genes of the fibrinolytic system with either massive perivillous fibrinoid deposition or maternal floor infarction [13].

8.9 Prognosis and Predictive Factors

Examination of the placenta is important in cases of fetal growth restriction and intrauterine fetal demise because these clinical outcomes are associated with massive perivillous fibrinoid deposition and maternal floor infarction [3, 14]. Adverse neurologic outcomes have also been cited in cases of maternal floor infarction [21]. In addition to the case reports of possible associations described in the Epidemiology section, some

authors feel that maternal floor infarction and massive perivillous fibrinoid deposition are final common pathways of different processes in the placenta. This speculative idea is suggested by the frequent finding of perivillous fibrinoid material adjacent to intervillous thrombi and the possibility that perivillous fibrinoid material is extending or leaking out of the thrombus to adjacent villi. Identification of massive perivillous fibrinoid deposition and maternal floor infarction is also important because these lesions can recur in subsequent pregnancies. One author identified the presence of chorionic septal cysts (also known as extravillous trophoblast cysts because they are lined by extravillous trophoblasts) as a significant indicator of recurrence [22], but that association did not have consensus support at the Dublin Placenta Consensus meeting.

No unique ultrasound findings are diagnostic of massive perivillous fibrinoid deposition; however, it has been suggested that the combination of fetal growth restriction, oligohydramnios and echogenic cystic lesions may allow the diagnosis of massive perivillous fibrinoid deposition, particularly in high-risk cases due to previous clinical history [13].

A recent paper suggests treatment with intravenous immunoglobulin, heparin and aspirin resulted in two healthy pregnancies after previous pregnancies showed massive perivillous fibrinoid deposition [23]. Also, the cholesterol-lowering agent, pravastatin, was used in a woman with recurrent miscarriages that resulted in a live-born preterm infant. Pravastatin, which has also been used to treat pregnancies with pre-eclampsia, is thought to ameliorate an abnormal balance of angiogenic/anti-angiogenic factors that may contribute to the pathogenesis of maternal floor infarction/massive perivillous fibrinoid deposition [24].

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9 Retroplacental Haemorrhage and Marginal Haemorrhage

Robert W. Bendon

9.1 Introduction

Premature (before the infant is born) separation of some portion of the placenta from the underlying uterus forces the tearing of decidual vessels that bleed and form a retroplacental haemorrhage (RPH). If the separation causes symptoms, such as vaginal haemorrhage, uterine pain and tenderness and/or fetal distress, the obstetrical diagnosis is placental abruption. Premature separation occurs in the same decidual plane as normal postpartum separation but, in normal separation, the emptying of the intrauterine cavity allows a persistent uterine contraction to compress the decidual vessels and stop the haemorrhage. Premature separation will continue to bleed because the uterus cannot contract sufficiently, being filled with the fetus and amniotic fluid. If the blood cannot escape from beneath the placenta through the vagina, it will form a retroplacental haematoma (blood clot). Different underlying causes and extent of an RPH will modify the clinical and pathological expression.

9.2 Definition

A retroplacental haemorrhage occurs in the decidua beneath the functional placenta or chorion frondosum. A haemorrhage/haematoma may also occur in the decidua at the placental margin or beneath the reflected membranes, designated, respectively, as a marginal or as a submembrane haemorrhage/haematoma. Premature separations beneath the membranes or placental margin do not infarct the overlying placenta. Acute RPHs can occur from a transient, incomplete separation of the placenta in the third stage of labour but these RPHs have no clinical consequence.

Retroplacental haematoma is not a synonym for placental abruption. There may be unequivocal pathological evidence of an RPH but no clinical symptoms. This generally occurs with smaller haematomas. In a clinical abruption, a sudden, complete separation may demonstrate a completely detached placenta at caesarean hysterotomy but no pathological evidence in the placenta of an RPH [1].

Below is a useful standardized classification of placental abruption [2]:

Grade 0. These are clinically unrecognized before delivery (diagnosis based upon examination of the placenta).

Grade 1. These show external bleeding only or mild uterine tetany but no evidence of maternal shock.

Grade 2. In this group there is uterine tetany, ordinarily with uterine tenderness, possibly

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external bleeding and fetal distress (or death) but no evidence of maternal shock.

Grade 3. Here there is evidence of maternal shock or coagulation defect, uterine tetany and intrauterine death of fetus.

The authors emphasize that *Grade 1* did not progress to *Grade 2* or *3* and fetal mortality was related to the tendency for this grade to occur in premature infants and not directly to abruption. *Grade 2* often progressed to *Grade 3* with time and complications were related directly to the abruption.

9.3 Synonyms

A separation of the placenta from the uterine wall prior to delivery of the infant is a premature separation of the placenta. The separation must disrupt blood vessels in the decidua which will haemorrhage and blood will frequently be trapped producing a retroplacental haematoma. This haemorrhage often produces vaginal haemorrhage. Edward Rigby, a British physician, published a monograph in 1776 in which he distinguished accidental haemorrhage (premature placental separation) from unavoidable haemorrhage (placenta praevia) and recommended that they be treated differently to prevent mortality [3].

Premature separation of the placenta may cause clinical symptoms, which include uterine tenderness, fetal distress and maternal coagulopathy. The term "abruptio placentae" (placental abruption) for the complex of clinical symptoms associated with premature placental separation first appeared in the influential textbook by Dr. DeLee. A retroplacental haematoma may not always result in clinical symptoms, and a retroplacental haematoma may not be identifiable with acute placental abruption.

9.4 Epidemiology

A study using ICD-9 codes from the National Hospital Discharge Survey (approximately 400 hospitals) from 1979 to 1987 found rates of reported abruption, based on 286,000 cases, to be 0.8 to 1.2% with higher numbers in the most recent data [4]. The associated obstetrical complications included chronic hypertension and preeclampsia. This study also showed that the prevalence of acute coagulopathy was 2.5% and of stillbirth 7.1% in patients with abruption compared to 0.05% and 1.2% in those without. At a community hospital, approximately 1% of unselected placentas demonstrated a RPH larger than 2 cm without clinical signs of abruption [5].

Most population surveys have found an association of abruption with maternal arterial disease including chronic hypertension, pregnancy-induced hypertension or the use of vasoactive drugs such as cocaine and cigarettes. A retrospective chart review of 265 pregnancies more than 20 weeks gestation with the clinical diagnosis of abruption (275 infants with twins) found a 24% (13/55) incidence of abruption in eclampsia, 10% (29/290) in chronic hypertension and 2% (54/2320) in preeclampsia from 24,258 deliveries [6]. A review of 415 cases of abruption from 36,875 unselected deliveries at one hospital found significant associations with fetal growth restriction, preeclampsia, chronic hypertension and cigarette smoking [7].

9.5 Gross Findings

A retroplacental haematoma usually remains adherent to the maternal surface and often sits in a pronounced depression on that surface (Fig. 9.1). Even if the haematoma has detached,

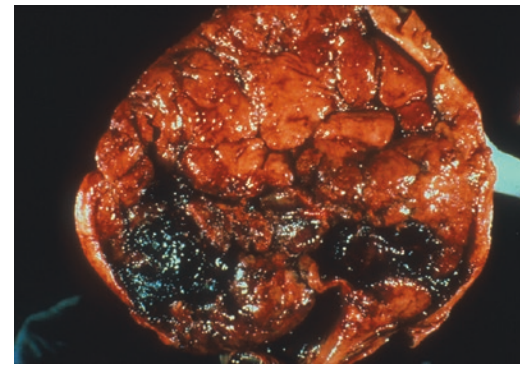

Fig. 9.1 This is the maternal surface of a placenta half-covered by a retroplacental haematoma following an automobile accident and a subsequent delayed fetal death

the depression is likely to remain (Fig. 9.2). The haematoma, if removed, often leaves a shaggy and usually discoloured maternal surface. The colour of the haematoma changes over the interval from its formation to the time of delivery. As with any haematoma over time, haemoglobin leaches out and breaks down. Phagocytosis leads to conversion of the haemoglobin iron to haemosiderin. The colour transforms from deep red to brown to tan to pale yellow (Fig. 9.3). The functional significance of the haematoma depends not only on its absolute area of the placental separation but also on the relative size compared to the placental area. This ratio of RPH to placental area can be estimated by calculating the areas of the haematoma and placenta using standard geometry formulas (πr^2 or $\pi(r_1 \times r_2)$) from the measured radii or diameter. Since the shapes are not true circles or ellipses, the values are best estimates based on the choice of radial measurement. The use of ratio eliminates pi and yields the proportion of the placental area overlying the haematoma. The location and shape of the haematoma may also have clinical significance. Haematomas may be confined to the periphery of the placenta, or they may be within the centre (Fig. 9.4).

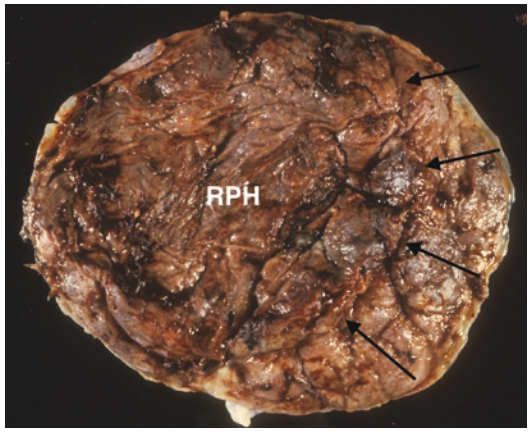

Fig. 9.2 This maternal surface demonstrates the crater produced by a retroplacental haematoma that was not adherent but did cause fetal death. The extent is difficult to see in the fresh specimen. After fixation, the margin of the crater is more distinct (arrows), and the extent of the placental separation was estimated to be 75%

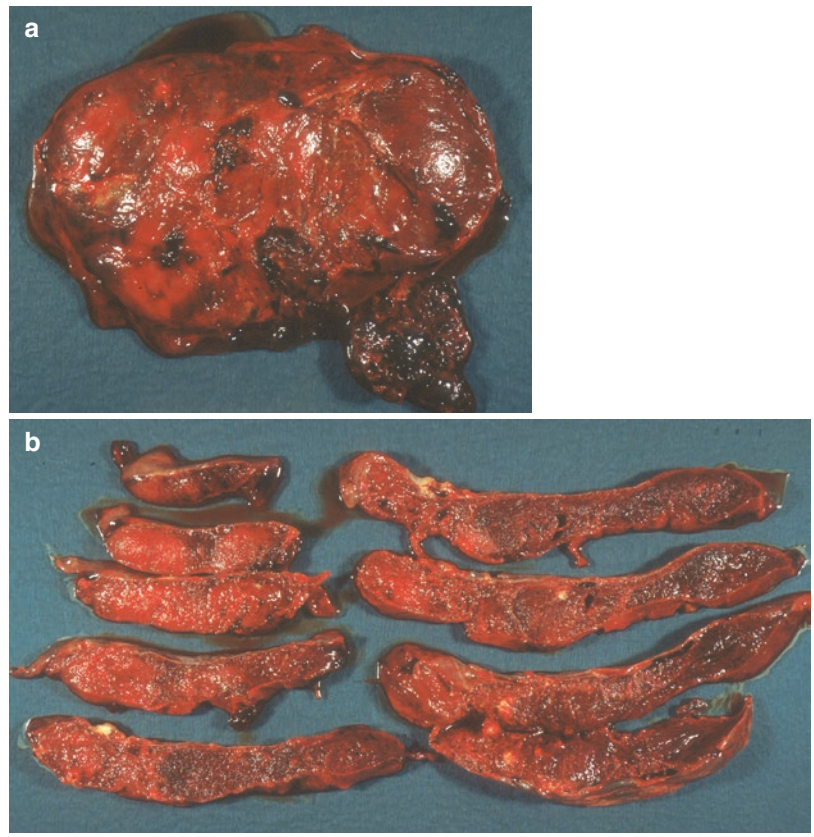

Fig. 9.3 (**a**) This is the maternal surface from a clinical abruption causing fetal death. There is haemorrhage over the surface but the extent of the separation is difficult to discern. (**b**) Slicing the placenta shows the darker acutely infarcted placenta contrasting with the pale viable placenta

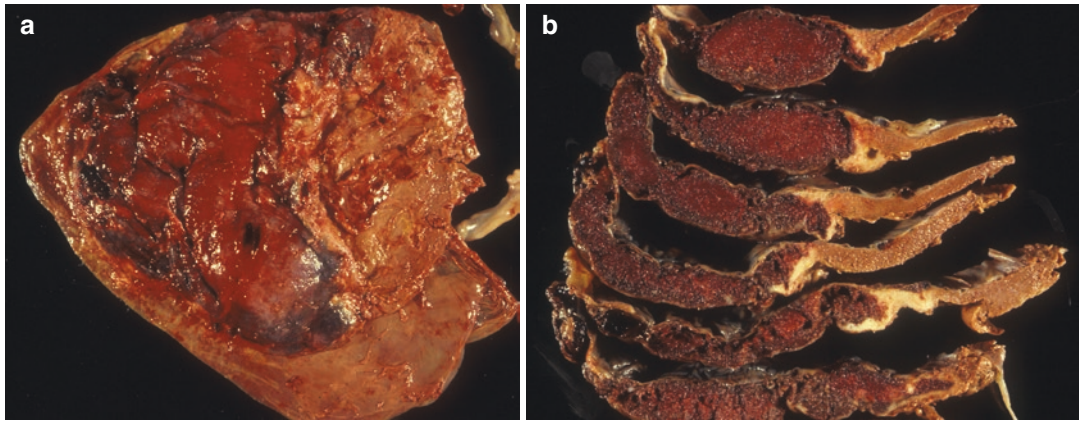

Fig. 9.4 (**a**) The maternal surface of this placenta demonstrates an old RPH that extends under the fetal membranes as well as under the placenta. There is also a paler crescent of haematoma along the inner placental margin that may be an older haematoma. (**b**) The cut sections demonstrate an extensive older infarction of the placenta 1/4 to 1/3 of the parenchyma. At the junction of the viable and infarcted pale placenta, there is a very pale small volume of placenta of an older RPH and overlying infarction that have been the nidus for the larger RPH

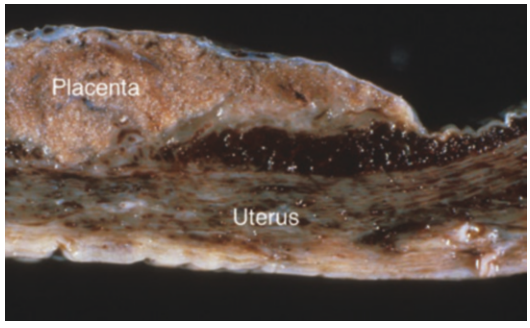

Fig. 9.5 This is a cross section of the placenta in situ in the uterus showing a marginal separation at the lower pole of the uterus that was unrelated to the fetal or maternal death

Separating the placenta from its spiral artery blood supply infarcts the overlying villi but does not directly affect the fetal circulation. The extent of this infarction is a measure of the functional size of the placental separation. The size can be estimated from 1-cm-thick placental slices (Fig. 9.5). The infarction has the same appearance as those produced by spiral artery occlusion. There is collapse of the intervillous space probably exacerbated by the compression of the haematoma. The villi are initially dark and engorged. This appearance could be due to vasodilation with a large vascular shunt through the low-resistance infarcted villi. However, the subsequent villous changes of occlusive vasculopathy suggest that there is cessation of fetal blood flow likely due to chorionic venous vasoconstriction that produces the dilated capillaries. The infarcted villi then progress through brown, tan and yellow to white over time. One rough estimate of the interval for these changes was made in stillborn infants by correlating the interval of postmortem retention using the histological criteria of Genest with the histologic progression of villous infarction [8].

In some placentas, there may be infarctions, additional retroplacental haematomas, villous changes of uteroplacental ischaemia, acute atherosis and/or rarely the appearance of a stepwise expansion of a haematoma. The cut sections may also demonstrate dissection of the haematoma into the intervillous parenchyma that can be difficult to distinguish from an infarction haematoma except for the contiguous RPH.

A very soft jellylike haematoma lightly adherent to the maternal surface may not be distinguishable that formed prior to delivery from a haematoma forming in the third stage of labour (after delivery of the infant). Such very recent, usually also small and peripheral, retroplacental

haematomas are common in very preterm labour particularly with premature rupture of membranes [9]. Uterine contraction-induced decidual shearing is the normal mechanism of placental separation after delivery of the infant. In early pregnancy there is a relatively large amount of amniotic fluid compared to the fetus. Logically, the rupture of membranes in early pregnancy could lead to a proportionately large loss of intrauterine volume and consequent myometrial contraction to accommodate the smaller fetal volume, which could shear a portion of the placenta from the uterus.

9.6 Genetic Susceptibility

Clinical studies suggest that genetic thrombophilia may increase susceptibility to clinical abruption and retroplacental haematoma. The association with thrombophilia and abruption was suggested by case reports [10–12] and by early studies showing an association of low folate levels with abruption [13, 14]. Studies of hyperhomocystinuria and those of polymorphisms of the methylene tetrahydrofolate reductase gene have demonstrated mixed results [15–17]. Studies of folate supplementation also have had mixed results [18, 19]. The studies have small patient numbers and use different outcome variables including placental infarction, vaginal bleeding or retroplacental haematoma. The association is biologically plausible in that placental infarctions or uterine venous thrombi are potential mechanisms for the pathogenesis of premature placental separation.

9.7 Prognosis and Predictive Factors

9.7.1 Recurrence Risk

Abruption regardless of cause has a significant risk of recurrence in subsequent pregnancy [20–22]. That risk is modified if a pathological cause is identified. Hypertension, coagulopathies, cocaine use and behaviours that could compress the vena cava can all be modified. Preeclampsia is less likely in subsequent pregnancies and recurrence from this cause is lessened.

9.7.2 Fetal Prognosis

The infant can suffer asphyxia from decreased gas exchange from premature placental separation. The incidence of large or lethal retroplacental haematomas ranges from 0.5 to 4/1000 deliveries. The rate of stillbirth from abruption also varies among studies but is usually less than 2/1000 [23, 24]. Given approximately 26,000 stillbirths in the USA annually, a very rough estimate is that 1300 stillbirths are due to abruption. A study based on obstetricians reported estimate of the abruption showed a correlation of percentage size of the separation and a logarithmic risk of stillbirth [25]. The curve begins to inflect upward after 40–50% separation. Infants with additional uteroplacental ischaemia such as that with preeclampsia would be more susceptible [26]. In my review, very large placental separations produced changes of sudden total asphyxia in the infant [8]. Smaller but still lethal separations produced changes of heart failure. The lethal abruptions compromised at least 50% of the placenta.

Nonlethal placental separation might cause hypoxic-ischaemic brain injury but one study failed to demonstrate such an association in 16 placentas with RPH larger than 2 cm diameter [5]. There is little information on how many infants that survive large RPH then suffer lasting neurologic injury.

9.7.3 Maternal Prognosis

It is an axiom of the management of abruption that defibrination or disseminated coagulation is always a potential complication and may even be lethal to the mother [27]. One study correlated peripheral blood coagulation parameters, especially fibrinolytic, with the severity of the abruption by clinical criteria, which also correlated with their estimate of the observable extent of placental separation [27].

9.8 Retroplacental Haematoma Is Caused by Different Pathogenic Mechanisms with Different Risk Predictors

9.8.1 Trauma

Placental separation from the motion of the placenta relative to the uterine wall occurs with motor vehicle accidents. Not surprisingly, the more severe the maternal trauma, the more likely abruption will occur [28, 29]. There have also been reports of delayed fetal death from abruption in less severe motor vehicle trauma [30–33].

9.8.2 Preeclampsia

A study following mothers with first-trimester retroplacental or subchorionic (beneath the membranes) haematomas found significant correlations with multiple obstetrical complications later in gestation [34]. The largest relative risks of the haematoma (retroplacental and subchorionic combined) were for abruption or preeclampsia. As demonstrated by the epidemiologic data, preeclampsia/eclampsia is a risk factor for abruption. The mechanism may be related to haemorrhage into a decidual infarction or due to abnormality in the remodelling of spiral arteries. Elevated systemic blood pressure may contribute to vascular rupture, especially in weakened vessels. However, measures of the severity of preeclampsia are poor predictors of developing placental abruption [35].

9.8.3 Cocaine and Cigarette Smoking

The risk of abruption is increased with cigarette smoking and cocaine usage [7, 36–40]. The abruption following cocaine use anecdotally has occurred minutes to hours following snorting the drug [41, 42]. Histological studies have not shown a consistent lesion associated with abruption and cigarette smoking. The suggested mechanism of haemorrhage is deep vasospasm causing necrosis of spiral arteries with reperfusion and rupture.

9.8.4 Venous Occlusion

Experimental studies in dogs and then humans at caesarean section demonstrated that direct compression of the vena cava and left ovarian vein caused premature placental separation [43–45]. Based on subsequent human cases, the mechanism was proposed that lifting the uterus to get to the vena cava may have directly obstructed uterine veins as the mechanism of abruption [44]. Logically, uterine venous obstruction by compression or thrombus could elevate the venous pressure and lead to haemorrhage in the fragile decidual vessels. This mechanism could apply to sleep position but there is no direct evidence.

9.8.5 Haemorrhagic Diathesis

A mother with congenital hypofibrinogenaemia who had only easy bruisability between pregnancies had two fetal losses from abruption [46]. In another case report, a 32-week-gestation woman with disseminated intravascular coagulation and renal failure following a snake bite demonstrated a 75% placental separation seen at caesarean section [47]. Placental separation from hypocoagulation is a plausible risk factor for retroplacental haematoma that might apply to patients receiving anticoagulant therapy.

9.9 Conclusion

The placental examination often, but not always, provides evidence of an RPH underlying a placental abruption. The size of the RPH is a measure of the severity of the fetal compromise, with separations over 50% likely to be lethal. However, the placenta does not show intrinsic evidence as to the mechanism of the separation. Even in preeclampsia, there are no consistent features that explain why a particular placenta suddenly develops an RPH and pre-

mature placental separation. In many cases, it is unclear whether the RPH led to the separation or the placental separation led to the RPH. More research into the mechanism of RPH is still needed.

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Fetal Vascular Thrombosis

10

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10.1 Introduction

Vascular thrombi in the fetal circulation can be identified grossly and should always be part of a careful gross examination of the placenta. Documentation of vascular thrombi in the umbilical vessels or chorionic plate vessels can offer immediate information to the paediatrician about risk for presumptive thromboembolic disease to the infant that may have occurred in utero, like congenital ischaemic stroke. It can offer important information as to cause of death in cases of intrauterine fetal demise.

Macroscopically identified thromboses are not uncommon. It has been reported that the incidence of umbilical vessel thromboses ranges from 1 in 1300 deliveries to 1 in 250 high-risk gestations with venous thromboses more common than arterial [1].

Once identified grossly, careful sampling of the lesion and up- and downstream vessels is important. The differential diagnosis should be considered at the grossing bench to ensure that proper sampling and testing follows. For example, if the thrombus is identified in a large chorionic plate vein, then attention to the umbilical cord for pathology should be a focus (velamentous or marginal insertions, coiling index [2–6] and coiling pattern [7], kinking, true knot, discolouration suggestive of meconium or fetal inflammatory response should be commented on in the gross description). A photograph of the placenta is prudent. A good clinical history is essential as maternal coagulopathy [8] and glucose intolerance may be predisposing factors for in utero thromboses [9, 10].

As always, it is important to be thorough in the gross examination of the placenta and macroscopic vascular thrombi are just one of the many things that should be looked for. As all placental findings (or for that matter, lack of findings) are potentially litigious, language is important, and we prefer using analytic terminology to subjective adjectives and using measurements and numbers instead of words like "large" or "multiple."

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10.2 Definition

Thrombus formation: (1) within the umbilical cord, (2) within its tributaries on the chorionic plate, (3) within stem villi.

10.3 Synonyms

Fetal thrombotic vasculopathy; Fetal artery thrombosis; Endothelial cushion: Endothelial cushion with fibrin cap; Stem vessel endovasculopathy; Fibromuscular sclerosis; Haemorrhagic endovasculosis/endovasculitis; Fibrinous vasculosis; Thrombosclerosing placentitis; Endarteritis obliterans.

10.4 Epidemiology

Thrombosis of an umbilical vessel is a rare finding; umbilical artery thrombosis occurs in approximately 1 in 1500 placentas submitted for pathologic examination. Umbilical vein thromboses are reportedly more common [11, 12]. Thrombosis of chorionic plate vessel is the most common, occurring in approximately 4% of placentas submitted for pathologic evaluation [13]. Clinical presentations include fetal growth restriction (FGR), fetal demise, fetal distress and meconium exposure. Umbilical cord abnormalities are often present including excessive length, abnormal coiling, cord stricture and marginal or velamentous insertion [14]. Virchow's triad (blood stasis, endothelial injury, hypercoagulable state) summarises associations with these fetal thrombi, with cord complications and poor fetal cardiac output contributing to stasis, severe inflammation or toxic effects of meconium leading to vessel injury and maternal diabetes or rare presentations of a fetal inherited thrombotic disorder contributing to a hypercoagulable state.

10.5 Gross Findings

When a placenta is received at the grossing bench, it has often acquired artefacts. It may be formalin fixed or fresh and may have torn and detached membranes and adherent blood clot. It may be compressed and folded. After trimming, cleaning and recording basic measurements, it is inspected to identify often subtle abnormalities. Kinking, varix formation and coiling abnormality of the umbilical cord potentially predisposing to thrombosis should be noted. Segmental haemolysis, barber-pole appearance or increased firmness (other than column of fresh blood clot) of the umbilical cord should be noted and photographed and transverse sections taken.

A vessel may be seen to be very small or absent on section at one level and may be dilated with abnormal haemolysed or necrotic wall and containing macerated blood clot at another level. Suspicious lesions must be sampled for histology where complete occlusion, calcification and necrosis may be confirmed. Regular samples of cord from fetal and placental sides are placed with a membrane roll in the first cassette; suspicious cord lesions are sampled as extra.

On inspection of arteries and veins on the chorionic plate, peeling off the amnion where necessary, general features, such as whether dilated, constricted, varicosity or normal, should be noted. Thrombosis in a chorionic vein should be suspected when the vein appears thickened, is firmer or has a dull colour difference when compared to other normal thin-walled veins. Older lesions may have cream or white linear stripes of calcification in the vessel wall. The suspect lesions should be sectioned to improve and confirm identification on cross section by comparison with adjacent normal vessels. The thrombosed blood fills the vessel, is often grey, granular and powdery but sometimes laminated and, if non-occlusive at that level, may have a distinct border with adjacent fresh blood clot. On occasion, when opening into the vessel, lines of Zahn may be seen grossly but are best confirmed on histology of horizontal sections. Chorionic artery thrombi, which may be thromboemboli, are seen in constricted arteries as dense fibrin nodularity most often at a bifurcation; sometimes a deep bifurcating vessel is not identified. When the suspect lesion is sectioned, the thrombus appears to expand the vessel and it

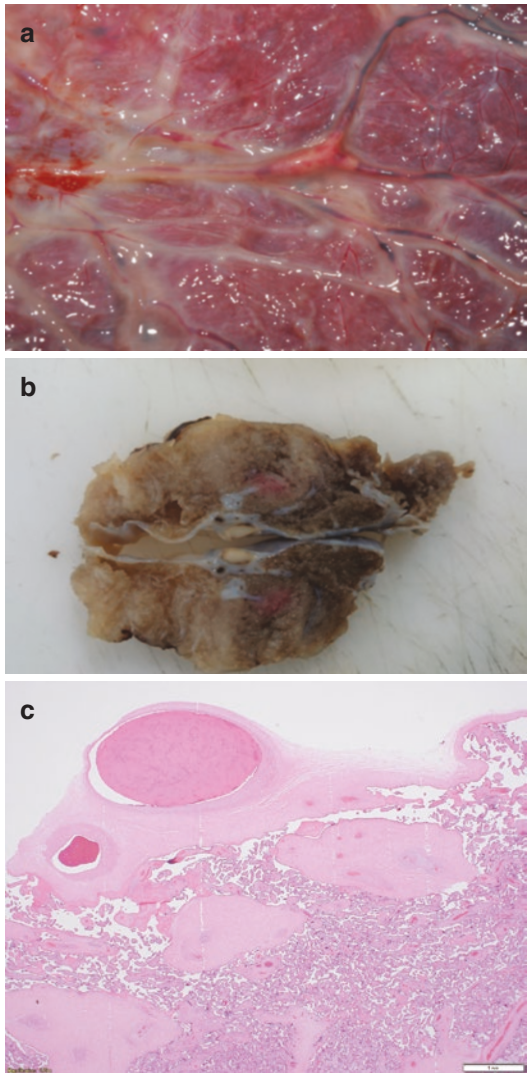

Fig. 10.1 (**a**) Chorionic plate with hard nodular lesion at the bifurcation of a chorionic artery, (**b**) same lesion bisected after fixation, (**c**) histological confirmation of a solid compacted fibrin thrombus (thromboembolus)

appears impacted and has a solid white cut surface, without appreciable lamination (like a phlebolith, it may be extruded from the vessel) (Fig. 10.1).

It is thought best to slice the placenta from the chorionic plate, taking 1.5 cm slices and removing a block of each suspect lesion for secondary fixation. This allows quality photographic record of parenchymal lesions on the cut surfaces and, because downstream stem villous lesions are not often in the same vertical plane, the fixed blocks

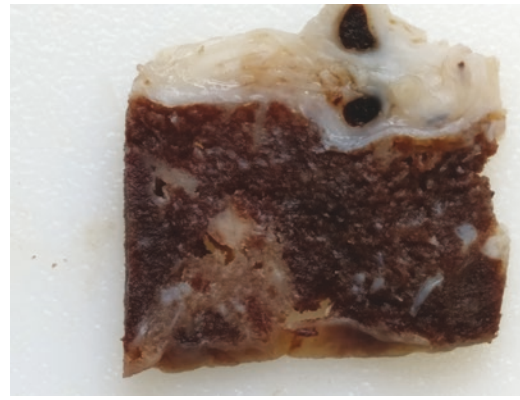

Fig. 10.2 Gross of a wedge-shaped lesion in the placenta due to avascular villi from a fetal arterial thrombus

may be thinly sliced to identify wedge-shaped foci of avascular villi (Fig. 10.2).

10.6 Histopathology

See Chap. 25.

10.7 Immunohistochemistry

See Chap. 25. Special stains such as Mallory's trichrome, Martius Scarlet Blue and diastase PAS have had a place in placental pathology illustrating and demonstrating extent of disease. Immunohistochemistry will undoubtedly contribute. CD61 may define and possibly age platelet web in fibrin clot.

10.8 Genetic Susceptibility

There are not much data on the genetic susceptibility for placental vascular thromboses. Heritable coagulopathies have been reported as enriched with fetal vascular malperfusion histopathologies in one study [8], but this finding was not validated in others [15, 16]. It is our opinion that inherited thrombophilias should remain as a possible aetiology for FVM until this controversy is settled with more data. We have seen dramatic cases of FVM that was the presenting finding for maternal and neonatal

Factor V Leiden mutation. See Chap. 25 for more discussion on this topic.

10.9 Prognosis and Predictive Factors

With respect to grossly identified umbilical artery thrombi, significant morbidity and mortality have been reported—stillbirth, FGR and various forms of neurologic developmental abnormality and damage [17, 18].

The prognosis and predictive features of macroscopic fetal vascular thrombosis within the chorionic plate and downstream tributaries, with respect to neonatal outcome, rely not only on grossly identified thrombi and/or downstream zones of avascular villi but rather on the overall extent of fetal vascular malperfusion identified both macro- and microscopically. Fetal vascular malperfusion—even high grade, which is most strongly associated with an increased risk of morbidity and mortality—is almost always diagnosed microscopically (see Chap. 25 for further discussion).

Fetal vascular thrombi, when multifocal and/or associated with high-grade microscopic fetal vascular malperfusion, portend a number of morbid consequences, renal vein thrombi, perinatal stroke, cerebral palsy, FGR and stillbirth to name a few [19–24]. Fetal vascular malperfusion is one of the most common placental pathologies in live births with unexpected untoward outcome that eventuate in medical malpractice litigation [20], and personal experience. It is important to underscore, however, that the presence of fetal vascular thrombi in circumstances of fetal/neurologic injury identifies neither the mechanism of damage nor its timing. Additional intrauterine processes, including those with placental footprints (e.g. amniotic fluid infection), and/or circumstances of the intrapartum may also play into pathophysiology that ultimately proves injurious to the fetus or neonate.

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Extravillous Trophoblast Cyst

11

T. Yee Khong

11.1 Introduction

Extravillous trophoblast cysts are grossly visible cysts usually located in the subchorionic region or within the septa. They are not an uncommon finding in cut slices of the mature placenta.

11.2 Definition

Cyst that is filled with eosinophilic proteinaceous fluid and lined by an irregular layer of extravillous trophoblastic cells.

11.3 Synonyms

The preferred term to use is extravillous cytotrophoblast cyst. 'X' cell cyst is a derivative term of extravillous cytotrophoblastic cell cyst, which is a fuller version of extravillous cytotrophoblast cyst. Different terms have been given to these cysts based on their location within the placenta: placental surface cyst, subchorionic placental cyst, septal cyst and microscopic chorionic cyst. It is a misnomer to label these cysts as chorionic cysts as they are neither part of a villus nor are they bound by a villous trophoblastic layer. They have also been called decidual septal cyst but the adjectival decidual is unnecessary since the septum is formed from a pulled-up portion of the basal plate, which includes the Rohr's stria, decidua and extravillous cytotrophoblast.

11.4 Epidemiology

Placental cysts are found in 10–20% of placentas examined at term [1]. It is uncommon before 38 weeks gestation [2] and said to be rare before 36 weeks gestation [3]. Depending on how many microscopic sections are examined, the incidence of extravillous trophoblast cysts rises correspondingly [4].

There are two theories for the pathogenesis of the extravillous cytotrophoblast cyst, in both of which hypoxia may play a part. Cytotrophoblast proliferates in response to hypoxia. One posits that the cyst results from degeneration due to the expanded extravillous trophoblastic population outstripping the nutritional support. The other is that cytotrophoblastic cells produce major basic protein that is toxic and causes degeneration and cyst formation and fills the cyst [3].

The clinical significance of the extravillous cytotrophoblast cyst is unclear. They are thought to be of no clinical significance [1, 5]. Early reports indicate that the incidence of septal cysts is considerably increased in maternal diabetes and preeclampsia [2]. The histomorphological

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similarity of the extravillous cytotrophoblast cysts in the placental disc to those seen in the chorion laeve of the amniochorial membranes (Chap. 42) has prompted a re-evaluation of the clinical associations and it has been suggested that the extravillous cytotrophoblast cysts in the placental disc is also associated with in utero hypoxia [6].

Rare cases of extravillous cytotrophoblast cysts that are large enough to reduce umbilical cord blood flow and cause fetal asphyxia and growth restriction have been described [7].

11.5 Gross Findings

Grossly visible cysts are usually small, less than 30 mm, and are usually spherical or ovoid. They are most commonly located under the chorionic plate where they are termed subchorionic cysts or within placental septa when they are termed septal cysts. They are filled with fluid that appears gelatinous grossly (Fig. 11.1). Grossly visible cysts are usually singular. Most extravillous trophoblast cysts are discovered microscopically.

11.6 Histopathology

The cyst wall is composed of an irregular layer of extravillous trophoblastic cells and is filled by an amorphous eosinophilic proteinaceous fluid. Occasionally, the cyst may be devoid of contents or only partially filled with fluid.

Cysts located in the subchorionic region (Fig. 11.2) can be found to be continuous with a placental septum which can be followed down to the basal plate. The septum is an invagination of the decidual basal plate that anchors the chorionic plate to the basal plate. Similar cystic spaces are found anywhere along the septa (Figs. 11.3 and 11.4), cell islands (Fig. 11.5) and also in the basal plate (Fig. 11.4). Thus, despite their different locations in the placental disc, they have similar histomorphologic features and likely have the same pathogenesis.

Cases labelled as subchorionic placental cysts that contain haemorrhage [8] and also called subchorionic haematoma or chorionic haematoma are likely to be a different type of cyst. They are likely to be subchorionic intervillous thrombi or haemorrhages that have undergone cystic degeneration.

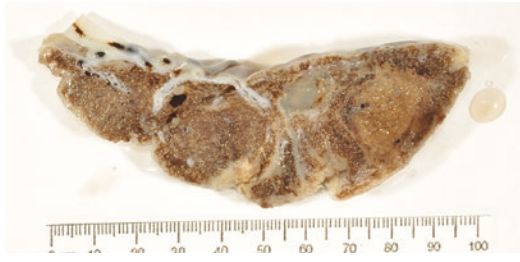

Fig. 11.1 An extravillous cytotrophoblast cyst located in the subchorionic zone and is within a septum that can be traced to its origin from the basal plate

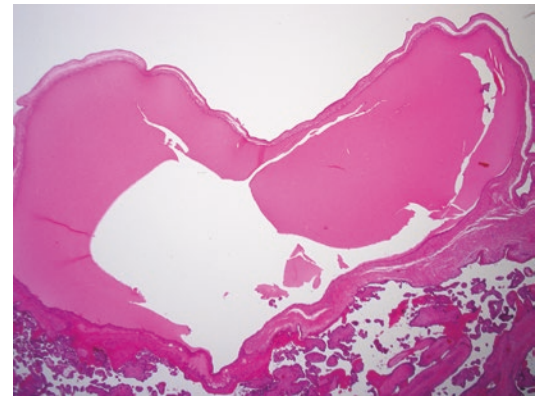

Fig. 11.2 An extravillous cytotrophoblast cyst located in the subchorionic zone and bulging into the amniotic cavity

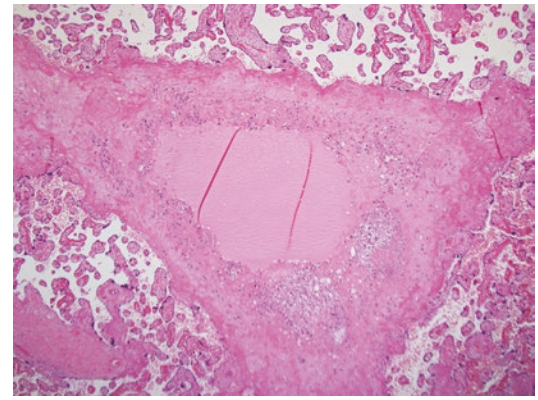

Fig. 11.3 An extravillous cytotrophoblast cyst located within a septum

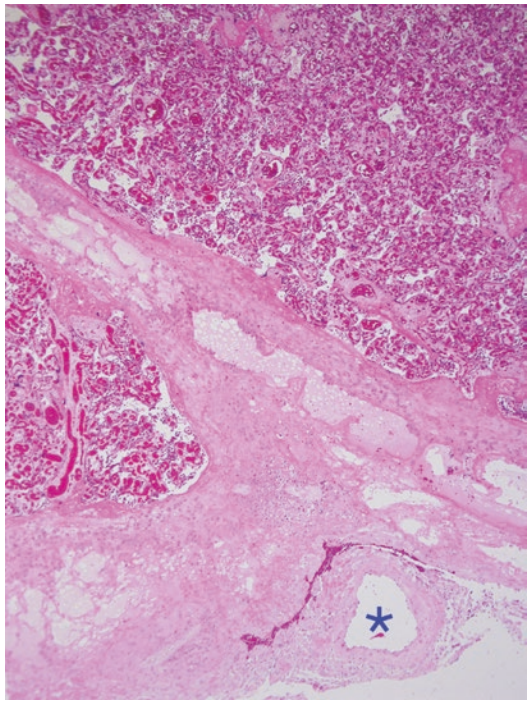

Fig. 11.4 Multiple extravillous cytotrophoblast cysts located within a septum (coursing from the base to upper left) in continuity with similar cysts in the basal plate (right side) and cystic degeneration around the extravillous cytotrophoblastic cells in the basal plate (left side). An uteroplacental artery is present at the base of the septum (starred)

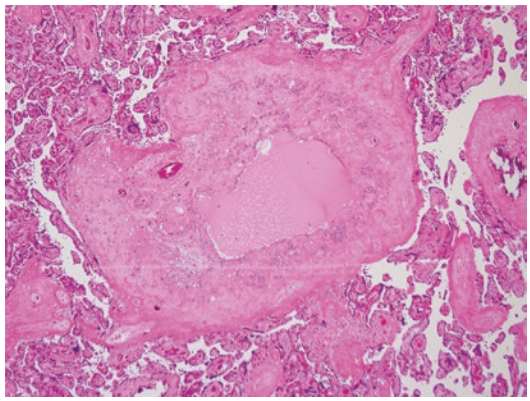

Fig. 11.5 An extravillous cytotrophoblast cyst located within a cell island

11.7 Prognosis and Predictive Factors

None known at this stage.

11.8 Future Research

There does not appear to be agreement about whether these grossly visible cysts should be sampled for histological examination. Some pathologists view these as lesions and sample them while others do not sample them on the heretofore premise that they have no clinical significance. A blinded study involving unselected placentas from non-complicated pregnancies without any clinical indication for placental pathology examination as well as from complicated pregnancies may be informative with regard to their clinical significance. Also noteworthy is that the incidence of the grossly non-apparent microscopic extravillous trophoblast cyst would depend on the number of microscopic sections examined, re-iterating a standardised approach to sampling of the placenta.

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Part IV

Placental Disc: Microscopic Lesions

Acute Chorioamnionitis

12

Phillip Cox, Marta C. Cohen,
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12.1 Introduction

Acute inflammation of the chorionic plate of the placenta is part of the spectrum of acute chorioamnionitis (intra-amniotic infection or amniotic fluid infection syndrome). Acute chorioamnionitis commonly results from ascending polymicrobial infection from the lower genital tract into the sterile amniotic cavity with subsequent invasion of the fetus [1, 2]. Clinically, infection of the amniotic cavity may result in a febrile illness and abdominal pain in the mother, tachycardia and fetal distress in the baby and the preterm onset of labour. Infection usually enters the amniotic cavity following rupture of the membranes but may also invade across closed membranes or gain access through small membranes breaches. Causative organisms include normal and abnormal endogenous vaginal flora and organisms colonizing the vagina from the gastrointestinal tract (group B β-haemolytic streptococci *(Streptococcus agalactiae), Listeria monocytogenes, Escherichia coli*, etc.) [3]. Occasionally infective organisms can also reach the uterus by contiguous spread (from infections in the peritoneum, fallopian tubes or bladder) or haematogenous dissemination (such as *T. pallidum*) [4].

12.2 Definition

Histological acute chorioamnionitis (ACA) is an inflammatory response in the chorionic plate of the placenta and amniochorial membranes usually in response to the presence of microorganisms in the amniotic fluid [3]. Acute inflammation involving the umbilical cord is dealt with in Chap. 5, whilst acute inflammation of the amniochorial membranes is discussed in Chap. 4.

12.3 Epidemiology

The incidence of histological ACA is inversely proportional to the gestational age, ranging from 67% in less than 24 weeks gestational age to 24% at term [3, 5, 6]. In placentas between 37 and 42 weeks, the incidence of inflammation in the chorionic plate has been shown to be 3.9% [5]. However, the use of molecular techniques has shown that in a subset of histological ACA cases, the culture does not demonstrate placental infection in term deliveries [7].

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Factors that are associated with ACA include prolonged rupture of membranes, prolonged labour, multiple digital examinations with rupture of membranes, nulliparity, group B streptococcus colonization, bacterial vaginosis, alcohol or tobacco use, meconium-stained amniotic fluid, internal monitoring and epidural anaesthesia [8–14].

Acute inflammation involving the chorionic fetal blood vessels is more likely to result in neonatal disease, and fetal white cell activation plays a prominent role in fetal/neonatal white matter damage (periventricular leukomalacia), [15] particularly in preterm babies. Chorioamnionitis and the fetal inflammatory response syndrome are strongly associated with the occurrence of necrotising enterocolitis, neonatal sepsis, intraventricular haemorrhage and chronic lung disease in premature babies [16, 17]. In very low birth weight infants, Redline showed that the incidence of cerebral palsy was increased when the placentas showed intense fetal chorionic vasculitis with intravascular thrombi [18]. In term infants severe chorionic vasculitis alone was a significant risk factor for cerebral palsy and the risk was even more elevated if the placenta showed other lesions such as meconium-associated vascular necrosis, increased circulating nucleated red blood cells, chorionic vessel thrombi and other patterns of placental injury.

12.4 Gross Findings

The normal chorionic plate is covered by a loosely attached, clear, shiny amniotic membrane. Beneath this the chorionic plate is a smooth fibrous layer, within which run the fetal chorionic arteries and veins; the veins usually run deep to the arteries. In the presence of acute chorioamnionitis, the amniotic membrane and chorionic plate are becoming progressively opacified and may appear cream coloured, yellowish or greenish. Greenish discolouration may indicate concomitant meconium exposure (Fig. 12.1a). Opacification may be more marked around blood vessels or at the margin of the placental disc (Fig. 12.1b). The surface is often dry and may be granular if there is amnion nodosum due to prolonged oligohydramnios. Spotty inflammation may indicate *Candida* infection.

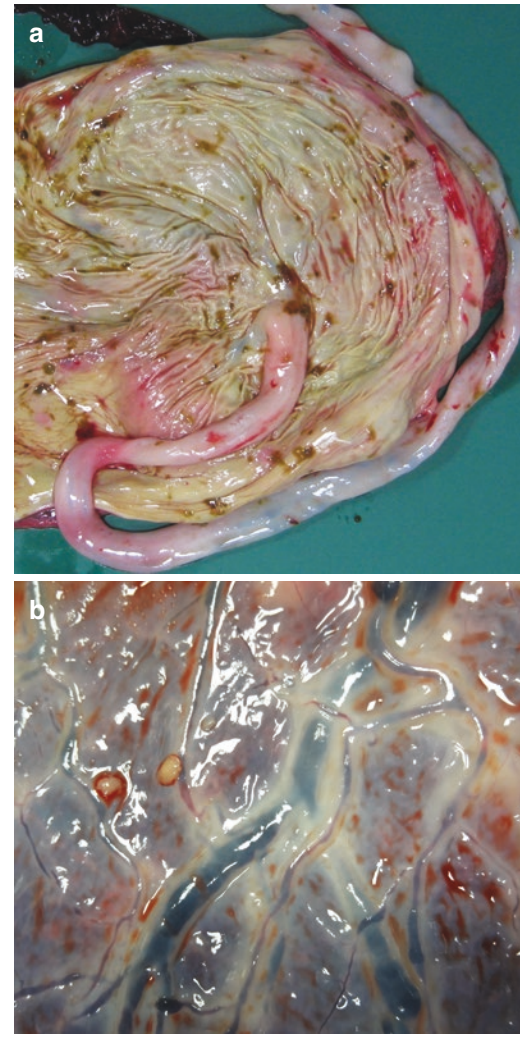

Fig. 12.1 Macroscopic appearances of acute chorioamnionitis of the chorionic plate. (**a**) Severe acute chorioamnionitis with diffusely opaque, cream-coloured, fetal surface of the placenta; (**b**) opacification of the fetal surface, accentuated alongside the fetal vessels in early chorioamnionitis

12.5 Histopathology

The inflammatory response in acute chorioamnionitis may arise from the maternal circulation, the fetal circulation or frequently both.

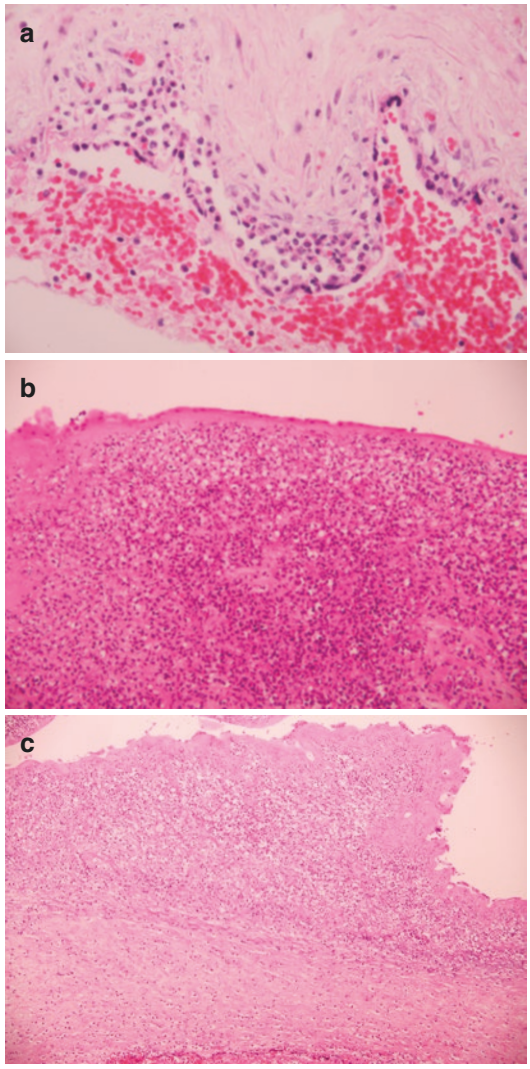

Fig. 12.2 Maternal inflammatory response. (**a**) Early acute inflammation concentrated along the maternal side of the chorionic plate; (**b**) severe acute inflammation with a dense inflammatory infiltrate involving the full thickness of the chorion and amnion; (**c**) severe acute inflammation with necrosis of the amniotic stroma and karyorrhexis of neutrophils

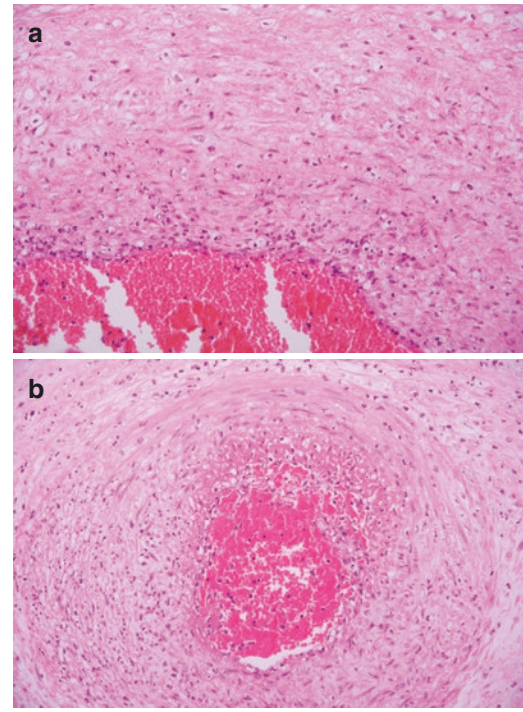

Fig. 12.3 Fetal inflammatory response. (**a**) Mild acute inflammation of a chorionic vessel with margination of neutrophils along the endothelium and emigration into and through the vessel wall; (**b**) inflammatory vasculitis of a chorionic plate vessel showing vessel wall necrosis and non-occlusive thrombosis

A maternal inflammatory response starts with aggregation of acute inflammatory cells in the subchorionic zone, immediately beneath the fibrous chorion (Fig. 12.2a). The inflammatory cells migrate through the fibrous chorion and into the overlying amnion, where they may concentrate. Inflammation may be focal, patchy or widespread/diffuse and may range in severity from a sparse infiltrate to dense, confluent inflammation (Fig. 12.2b) with associated necrosis of the chorionic stroma or amnion (Fig. 12.2c). The inflammatory infiltrate is usually predominantly neutrophil polymorphs but, in well-established, partly treated or low-grade infections, lymphocytes and macrophages may also be present. Following prolonged rupture of the membranes, amnion nodosum may be seen as small aggregates of fetal squamous cells embedded in the surface of the amnion.

The fetal inflammatory response arises from the arteries and veins in the chorionic plate. Inflammation commences in the vessels with margination of neutrophils, followed by emigration into and through the vessel walls into the surrounding stroma (Fig. 12.3a), towards the amniotic cavity. Severe inflammation may be associated with evidence of endothelial injury, with inflammatory thrombosis orientated towards

Table 12.1 Staging and grading of the maternal and fetal inflammatory responses in ascending intrauterine infection

Maternal inflammatory response	
Stage 1—acute subchorionitis or chorionitis Stage 2—acute chorioamnionitis: polymorphonuclear leukocytes extend into fibrous chorion and/or amnion Stage 3—necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis and/or amnion basement membrane hypereosinophilia	Grade 1—not severe as defined Grade 2—severe: confluent polymorphonuclear leukocytes or with subchorionic microabscesses
Fetal inflammatory response	
Stage 1—chorionic vasculitis or umbilical phlebitis Stage 2—involvement of the umbilical vein and one or more umbilical arteries Stage 3—necrotizing funisitis	Grade 1—not severe as defined Grade 2—severe: near-confluent intramural polymorphonuclear leukocytes with attenuation of vascular smooth muscle
Ref. [19] (reproduced with permission)	

the amniotic cavity (Fig. 12.3b). Occasionally, thrombosis may be occlusive and be associated with evidence in the placenta of fetal vascular malperfusion. Necrosis of the chorionic stroma overlying the vessels may be present, the equivalent of necrotising funisitis (see Chap. 55). Fetal inflammation may be absent in early infections and in mid-trimester spontaneous miscarriages and will be absent if the fetal demise has occurred prior to the onset of ACA. A fetal inflammatory response in the absence of maternal inflammation is unusual.

Both the fetal and maternal inflammatory components may be graded and staged, although this is not regarded as essential by the authors of the recent Amsterdam Consensus Statement [19]. One suggested grading and staging protocol is shown in Table 12.1. When reporting chorioamnionitis it is, however, important to comment on the extent and severity of the maternal and fetal inflammatory components, whether or not a grading/staging scheme is used.

It may be possible to demonstrate the causative organism. Particularly in severe infection, bacteria may be abundant and may be seen on the H&E stain but are better demonstrated by Gram-Twort staining. Small spots of necrotising inflammation in the amnion are characteristic of *Candida albicans* infection, which may be demonstrated by PAS or Grocott staining. Severe acute chorioamnionitis associated with intraplacental abscesses is characteristic of *Listeria monocytogenes* infection but may also be seen with other organisms such as *Staphylococcus aureus.* Rare causes of acute chorioamnionitis include herpes simplex and varicella zoster.

12.6 Immunohistochemistry

Immunohistochemistry is not necessary to diagnose acute chorioamnionitis. However, if herpes simplex or varicella infection is suspected, immunohistochemistry or molecular techniques may be employed to confirm the infection.

12.7 Prognosis and Predictive Factors

A history of ACA in one delivery carries a 3.43-fold increased risk of ACA in the next delivery, with the strongest association found in women who do not smoke during pregnancy. [8]

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13 Chorionic Plate Chronic Inflammatory Lesions Including Eosinophilic/T-Cell Chorionic Vasculitis

Philip J. Katzman

13.1 Introduction

The fetal surface consists of the chorion, amnion and chorionic vessels that emanate from the umbilical cord. It is contiguous with the free membranes that form the amnionic sac enveloping amnionic fluid and the fetus. The placental fetal surface interfaces between the amnionic sac and the intervillous space that contains maternal blood. In addition to providing a barrier between the fetal space and the maternal blood supply, it can also be a conduit for inflammatory cells that cross from the maternal and fetal circulation into the amnionic fluid.

The normal cellular population of the chorioamnion includes Hofbauer cells [1], which are histiocytes that also appear in the stroma of chorionic villi as well as mesenchymal stem cells, which are thought to have a fibroblast-like morphology but remain undifferentiated and act to inhibit the actions of T-cells [2, 3]. There may also be smooth muscle actin-positive myofibroblasts in the upper chorion [4].

Acute and chronic chorioamnionitis, eosinophilic T-cell/chorionic vasculitis, acute chorionic vasculitis and chorionic histiocytic hyperplasia are lesions that involve the fetal surface that can be diagnosed on routine placental pathologic examination. While acute chorioamnionitis and acute chorionic vasculitis are common lesions that are associated with ascending intrauterine infections, chronic chorioamnionitis, eosinophilic T-cell/chorionic vasculitis and chorionic histiocytic hyperplasia are less common lesions whose aetiologies are less clear.

13.2 Definition

Chronic chorioamnionitis is a collection of lymphocytes within the chorioamnion of the fetal surface and/or free membranes [5]. The infiltrate may be diffuse or focal in the chorioamnion. When involving the free membranes, Jacques and Qureshi used a grading scheme: 1+, few scattered foci; 2+, up to half of membrane roll involved; and 3+, more than half of membrane roll involved [6]. It is considered to be a chronic inflammatory lesion of the placenta and can be seen concurrently with villitis of unknown aetiology and chronic deciduitis.

Eosinophilic T-cell/chorionic vasculitis is a collection of lymphocytes, eosinophils, and histiocytes that is present often in the wall of a single chorionic vessel on the side facing the intervillous space [6–9], in contrast to acute chorionic vasculitis, which almost always involves neutrophils marginating from the chorionic vessel towards the amnionic space. The inflammation

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in eosinophilic T-cell/chorionic vasculitis is often in the side of the involved chorionic vessels and occasionally can involve a majority of the circumference of the chorionic vessel.

Chorionic histiocytic hyperplasia is a recently described lesion that has increased number of histiocytes at the base of the chorion, often in a linear or "lichenoid" distribution, hugging the interface with the intervillous space [4]. It can be seen diffusely or in a patchy distribution in all fetal surface sections. The lesion is often not present in the chorion underlying chorionic vessels ("skip areas") and it is generally not seen in the chorion of the free membranes.

13.3 Synonyms

None described.

13.4 Epidemiology

The prevalence of eosinophilic T-cell/chorionic vasculitis is estimated to be 0.37% in one population [9]. This is in contrast to villitis of unknown aetiology and chronic chorioamnionitis, which have reported prevalences that range from 5 to 17% and 0.8 to 3.5%, respectively. The prevalence of chorionic histiocytic hyperplasia in the study that first reported the lesion is 1.3% and it occurs frequently with other inflammatory lesions including villitis of unknown aetiology (68%), maternal acute inflammatory response (49%), chronic deciduitis (40%), chronic chorioamnionitis (31%) and fetal acute inflammatory response (11%) [4]. These associations suggest that chronic inflammatory lesions of the placenta have a varied histologic presentation between individual placentas but that there is a limited repertoire of inflammatory responses seen. The presence of histiocytes as native cells within the chorioamnion suggests that chorionic histiocytic hyperplasia is a hyperplastic lesion and not an infiltrative lesion, in which new cells would migrate into the chorionic plate. This idea is supported by the finding that the histiocytes in chorionic histiocytic hyperplasia are of fetal origin, as shown by sex chromosome-specific fluorescent in situ hybridization (FISH) [4]. The same type of FISH testing also identified fetal inflammatory cells as a part of eosinophilic T-cell/chorionic vasculitis [9]. Thus, the cells of eosinophilic T-cell/chorionic vasculitis are migrating out of chorionic vessels and not migrating from the intervillous space into the chorion and chorionic vessel wall. While villitis of unknown aetiology has been shown to be a recurrent lesion in subsequent pregnancies [10], this tendency to recur has not been shown in eosinophilic T-cell/chorionic vasculitis, chronic chorioamnionitis or chorionic histiocytic hyperplasia. All of the chronic inflammatory lesions of the chorionic plate, as well as villitis of unknown aetiology, are primarily lesions that occur in the third trimester. Because several of these chorionic plate lesions are associated with villitis of unknown aetiology, they are often seen concurrently with villitis of unknown aetiology in preterm pregnancies.

13.5 Gross Findings

The chronic inflammatory lesions of the chorionic plate are seen only microscopically.

13.6 Histopathology

The diagnosis of chorionic plate lesions requires adequate sampling of the fetal surface. Our laboratory generally submits two sections of the fetal surface in addition to sections of any lesions, such as subchorionic thrombi, that are seen grossly. The Amsterdam recommendation is to submit three full-thickness tissue sections [11]. It is important to sample fetal surface areas that have chorionic vessels as well as areas that have grossly thin chorioamnion. If the fetal surface has a thickened chorioamnion, if there are excessive chorionic vessels or chorionic stem villi, or if there is excessive subchorionic fibrinoid material or thrombus, then inflammation that would marginate from the intervillous space into the chorioamnion will not be seen because the distance is too large for chemotaxis to occur from an intrauterine bacterial infection.

Chronic chorioamnionitis is seen as a collection of lymphocytes in the chorion of the fetal surface and/or free membranes that are CD3-positive (Fig. 13.1a, b). The lymphocytic infiltrate can be focal or diffuse. Isolated cases of chronic chorioamnionitis are the exception rather than the rule; usually chronic chorioamnionitis is accompanied by any of the following other chronic inflammatory lesions of the placenta: villitis of unknown aetiology, chronic deciduitis, eosinophilic T-cell/chorionic vasculitis or chorionic histiocytic hyperplasia.

Chorionic histiocytic hyperplasia and the early form of acute chorioamnionitis, acute subchorionitis, have similar patterns of inflammation. In placentas with these lesions, along thin stretches of the chorionic plate, there are the linear array of histiocytes of chorionic histiocytic hyperplasia and the aggregating neutrophils of acute subchorionitis within the thin fibrinoid layer just below the chorion (Fig. 13.1c). In areas of the chorioamnion with large fetal chorionic vessels that widen the chorioamnion, these inflammatory cells are generally not seen. Chorionic histiocytic hyperplasia rarely occurs in the free membranes. Because maternal acute inflammatory responses can occur concurrently with chorionic histiocytic hyperplasia, it is important to distinguish chorionic histiocytic hyperplasia from the neutrophilic infiltrate of the lower chorion in early acute chorioamnionitis. Identifying a maternal acute inflammatory response indicates the presence of an ascending infection that can be treated with antibiotics

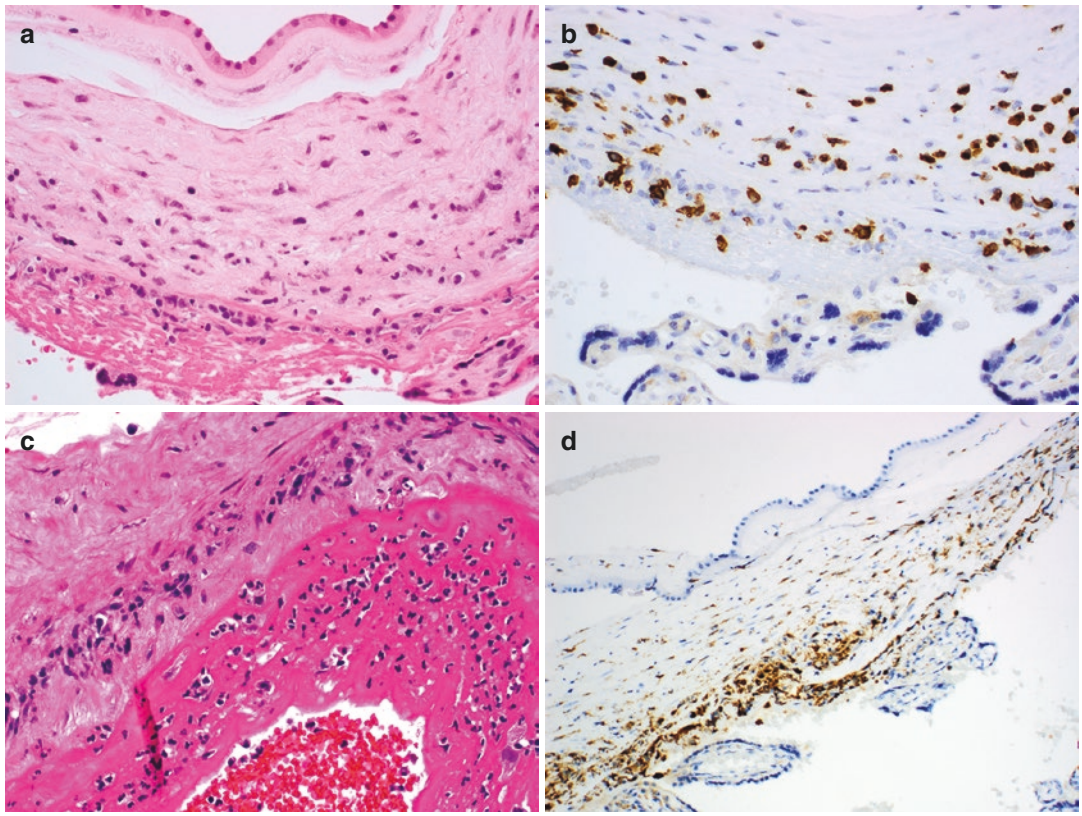

Fig. 13.1 (**a**) Chronic chorioamnionitis presents as a mononuclear infiltrate in the chorioamnion that includes CD3-positive lymphocytes (**b**). (**c**) In contrast, chorionic histiocytic hyperplasia has a tighter, linear (or "lichenoid") collection of histiocytes that are CD68-positive (**d**). In the case in **c**, there is an accompanying acute subchorionitis that includes neutrophils in the subchorionic fibrin layer (**a**, **c**, haematoxylin and eosin; **b**, CD3 immunostain; **d**, CD68 immunostain)

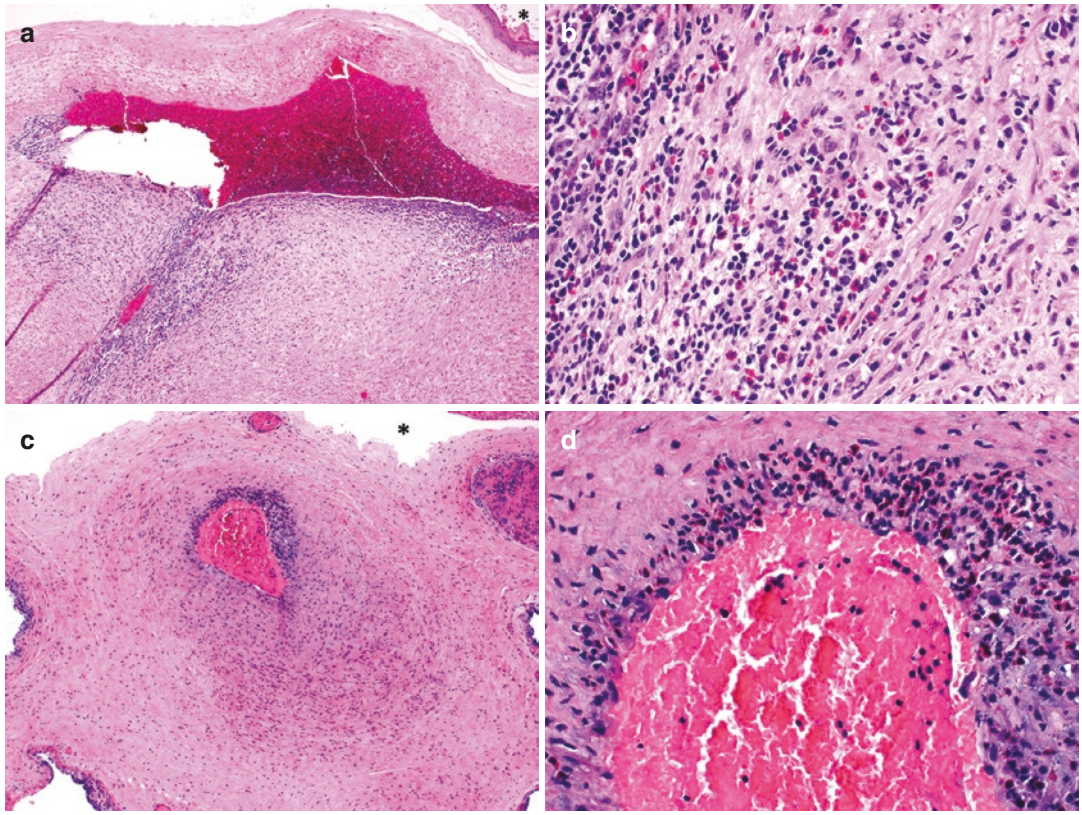

Fig. 13.2 (**a**, **b**) Eosinophilic T-cell/chorionic vasculitis has a mixed lymphocytic and eosinophilic inflammatory infiltrate migrating from the chorionic vessel in the fetal surface towards the intervillous space (marked in **a** and **c** with asterisks). (**c**, **d**) In contrast, in acute chorionic vasculitis, the inflammation is migrating towards the amnionic space. In this case of acute chorionic vasculitis, there are a large number of eosinophils

whereas the clinical significance of chorionic histiocytic hyperplasia is unknown. The histiocytic infiltrate of chorionic histiocytic hyperplasia can be confirmed using a CD68 immunostain (Fig. 13.1d).

One of the unusual features of eosinophilic T-cell/chorionic vasculitis is that it is typically a focal lesion. Usually only one chorionic vessel is affected within fetal surface sections sampled. When eosinophilic T-cell/chorionic vasculitis appears to involve two vessels, the possibility of a single involved vessel that is cut tangentially should be considered. The inflammatory cells of eosinophilic T-cell/chorionic vasculitis are primarily T-cells admixed with histiocytes. The number of eosinophils varies between cases (Fig. 13.2a, b). Some cases of eosinophilic T-cell/chorionic vasculitis have an associated vascular thrombus. However, eosinophils and vascular thrombi are not specific to eosinophilic T-cell/chorionic vasculitis; they can also be seen in some cases of acute chorionic vasculitis (Fig. 13.2c, d).

13.7 Immunohistochemistry

Although the orientation of the inflammatory infiltrate of eosinophilic T-cell/chorionic vasculitis should be useful in diagnosing this lesion and in distinguishing it from acute chorionic vasculitis, a CD3 immunostain can be used to confirm the presence of T-cells in the chorionic vessel infiltrate.

Chorionic histiocytic hyperplasia was identified initially in cases that were being evaluated for chronic chorioamnionitis. A CD3 immunos-

tain can be performed to confirm the presence of lymphocytes in the chorion. In those cases, it was observed that the linear population of cells of chorionic histiocytic hyperplasia were CD3-negative. Further immunostaining identified the cells of chorionic histiocytic hyperplasia as CD68-positive, vimentin-positive histiocytes (Fig. 13.1d) [4].

13.8 Genetic Susceptibility

There are no known genetic causes for chronic chorioamnionitis, eosinophilic T-cell/chorionic vasculitis or chorionic histiocytic hyperplasia. They are likely reactive lesions to unknown factors.

13.9 Prognosis and Predictive Factors

While villitis of unknown aetiology is known to be associated with fetal growth restriction and has a recurrence risk, chronic chorioamnionitis, eosinophilic T-cell/chorionic vasculitis and chorionic histiocytic hyperplasia appear to be sporadic lesions that may or may not be seen concurrently with villitis of unknown aetiology. When chronic chorioamnionitis occurs with villitis of unknown aetiology or chronic deciduitis, an alloimmune aetiology is more likely. The clinical significance of chronic chorioamnionitis as an isolated lesion is currently unknown.

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Maturity Anomalies

14

Gitta Turowski, Eoghan E. Mooney, and Irene B. Scheimberg

14.1 Introduction

The placenta is a dynamic organ that matures through the whole of pregnancy but starts functioning before maturation is completed. Normal maturation occurs when growth and differentiation proceed in tandem, giving a characteristic morphologic pattern at term. Disorders of maturation, teleologically described as either accelerated or delayed, result in morphologic patterns that are inappropriate for gestation. These patterns reflect both the response of the placenta to a suboptimal maternal environment or fetal abnormality but may themselves impair the core function of the placenta, namely, the effective passage of oxygen and nutrients to the fetus. Acceleration and delay may be useful to explain abnormalities of development to clinical colleagues but the terms are simplistic, as these placentas are poor phenotypic copies of premature and term placentas [1].

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14.1.1 Villous Development and Maturation

Villous development according to gestational age is described in detail in Chap. 2.

Placental development starts with the formation of primary villi between days 13 and 15 postconception (p.c.), when trophoblast columns develop in the basal plate, connect to the chorionic plate, and are infiltrated by cytotrophoblast. Primary villi are then transformed into secondary villi at day 15–16 p.c., characterized by mesenchyme infiltration (secondary villi). Secondary villi are transformed into tertiary villi by capillary proliferation into the villous stroma from day 17/18 p.c. Histologically, primitive walled vessels in the chorionic plate/umbilical cord and villous capillaries close to the chorionic plate can be seen at this stage [2]. Tertiary villi undergo a maturation process from first to third trimester.

Maturation by longitudinal growth and ramification includes the differentiation of the stroma, villous epithelium (trophoblast), and fetal vessels. The distribution of stem villi, intermediate villi, and terminal villi changes through gestational weeks. Terminal villi are first seen from 20 weeks of gestation, until they constitute 40 to 60% of villous cross sectional area at term [3, 4] (Table 14.1).

Stem villi are characterized by collagenous stroma with smooth muscle containing veins and

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Table 14.1 Distribution of villous types through gestational weeks in % (modified after Vogel/Turowski)

Gestational week	16	20	24	28	32	36	40
Villi, in %							
Stem villi	17	13	10	9	11	10	9
Intermediate villi, central immature type	54	51	32	16	10	5	1
Intermediate villi, peripheral mature type	29	35	50	56	52	47	32
Terminal villi	0	1	8	19	27	38	58

arteries. The shape of these villi follows its own pattern of maturation independent of delayed or accelerated maturation of the rest of the villi. Maturation of intermediate and terminal villi includes villous stroma reduction and capillary elongation. Development of vasculosyncytial membranes between syncytiotrophoblast and capillaries with lack of pericytes enlarges the fetal-maternal exchange surface and shortens the diffusion distance between maternal and fetal circulation. The decrease of distance increases oxygen transport with the third power. From gestational week 10 to 40, placental oxygen diffusion capacity increases 30-fold [5]. In normal terminal villi, more than 50% of the villous cross-sectional area should be occupied by capillaries, with mean number of 2 to 3 vasculosyncytial membranes per terminal villus [6–8].

The underlying trigger for this developmental switch is unknown but may involve intrinsic differentiation and extrinsic factors such as maternal oxygen tension, fetal flow-dependent remodelling, or the presence or absence of specific placental growth factors [1]. However, in term placentas, there are often still foci of persisting immature intermediate villi, especially in placentas with a high normal weight, also known as a growth centre.

14.1.2 Villous Maturation Disorders

Diagnosis of maturation disorders depends on the knowledge of clinically calculated and measured gestational age and an appreciation of normal villous maturation.

Maturation defects can be diagnosed by the distribution of several villous subtypes and villous architecture. Villous maturation disorders may be identified as focal or diffuse disorders of villous ramification and tissue development with qualitative and quantitative and/or chronological deviation from normal villous maturation.

Maturation may be accelerated or delayed for gestational age.

14.2 Accelerated Villous Maturation (AVM)

14.2.1 Definition

AVM is defined as the presence of small or short hypermature villi for gestational period, usually accompanied by an increase in syncytial knots (Fig. 14.1) [9].

14.2.2 Synonyms

Placental villous hypermaturation.

14.2.3 Epidemiology

AVM is a common pattern with mild, moderate, or severe forms and reflects maternal vascular malperfusion (MVM). It may also be seen in cases with increased fetal blood volume (e.g. in the recipient of twin-twin transfusion syndrome) [10].

14.2.4 Gross Findings

Placentas with AVM may be normal and small or may show gross evidence of MVM such as infarction.

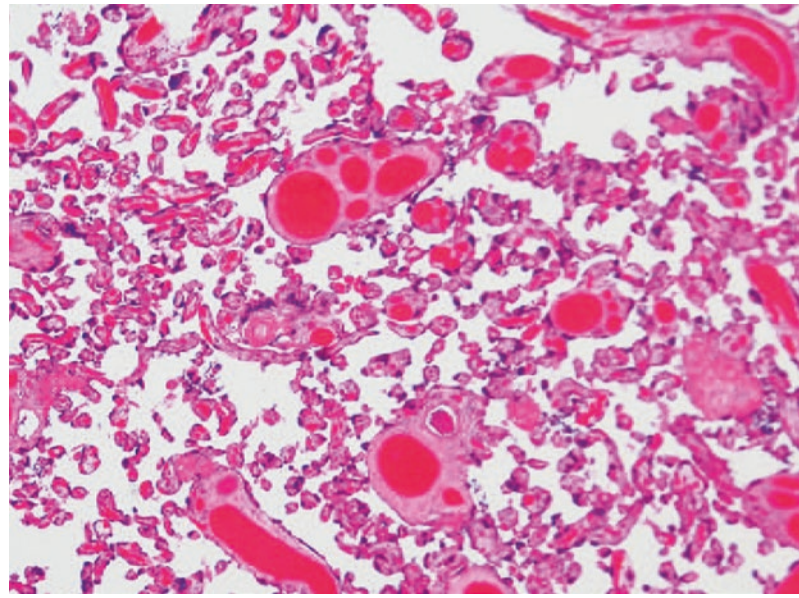

Fig. 14.1 Accelerated villous maturation: small villi with increased syncytial knots

14.2.5 Histopathology

AVM is often accompanied by increased syncytial knots and intervillous fibrin, which leads to its interpretation as compensatory increased villous ramification and fetal vessel proliferation, due to maternal vascular malperfusion. It should not be diagnosed in areas adjacent to infarcts (see Chaps. 24, 25, 34, and 35). The pattern of AVM can be focal, with alternating areas of appropriate maturation for the gestational age. AVM may be difficult to recognize in term placentas but is reproducible prior to term [9].

With earlier and more severe MVM, premature placentas show distal villous hypoplasia, characterized by missing branching of mature intermediate and terminal villi. They may show thin, unbranched and poorly vascularized villi at the periphery of the lobule and larger immature villi with a patchy increase in syncytial knots, intervillous fibrin deposition and villous agglutination at the centre.

14.2.6 Prognosis and Predictive Factors

MVM is the most common single pathology found in small for gestational age infants and the presence of AVM is part of the spectrum of that pathology.

14.3 Delayed Villous Maturation (DVM)

14.3.1 Introduction

DVM is essentially a diagnosis made in the latter third trimester. DVM can be characterized by an increased presence of immature villi, e.g. an abnormal high presence of immature or mature intermediate villi for the gestational age or a deficient development of terminal villi after 36 weeks of gestation and rarely before 34 weeks of gestation.

14.3.2 Definition

DVM is defined by a monotonous villous population (defined as at least 10 such villi) with centrally placed capillaries and decreased vasculosyncytial membranes. The diagnosis should be made when it is present in at least 30% of one full-thickness parenchymal slide.

14.3.3 Synonyms

Defective villous maturation; distal villous immaturity.

14.3.4 Epidemiology

The aetiology is varied, with biochemical abnormalities (e.g. maternal diabetes mellitus), circulatory abnormalities (fetal vascular malperfusion, fetal cardiac malformations, fetal low colloid osmotic pressure, or high placental weight) and chromosomal abnormalities accounting for varying proportions [1, 11]. An increase in the frequency of DVM has been reported in placentas from infants with trisomy 21. Fetal vascular malperfusion (FVM) is also over-represented in these placentas and, given the known hyperviscosity in patients with trisomy 21, it is possible that FVM may result in DVM in many of these cases [12]. Hypercoiling of the cord shows an association with DVM and is another possible form of FVM that may be aetiologically related [8]. Obesity is associated with DVM and also with fetal vascular supply abnormalities [13]. Other mechanisms include excessive placental growth factor expression, villous stromal-vascular remodelling and dysregulation of developmental placental gene expression [1]. Fetal hyperinsulinemia and Beckwith-Wiedemann syndrome (IGF-2) or excessive supply of nutrients may inhibit terminal differentiation. Insulin-dependent increase in VEGF expression may stimulate proliferation of immature capillaries and stromal expansion [14]. DVM was found more commonly in placentas of women exposed to opioid maintenance therapy [15].

14.3.5 Gross Findings

Placentas with DVM may be normal or may be pale and enlarged.

14.3.6 Histopathology

Three different patterns of DVM can be recognized.

One pattern shows a very monotonous aspect of most of the peripheral parenchyma. Almost all villi consist of mature intermediate villi with a continuous trophoblast lining with a severe decrease and, in some cases, almost complete absence of terminal villi with vasculosyncytial membranes (Figs. 14.2 and 14.3). This pattern has been described [6, 8] and has been observed with hypercoiled umbilical cords.

A second pattern is much more heterogeneous and shows an irregular increase in villi with an appearance that is immature for the gestational age. In term placentas with this type of DVM, a

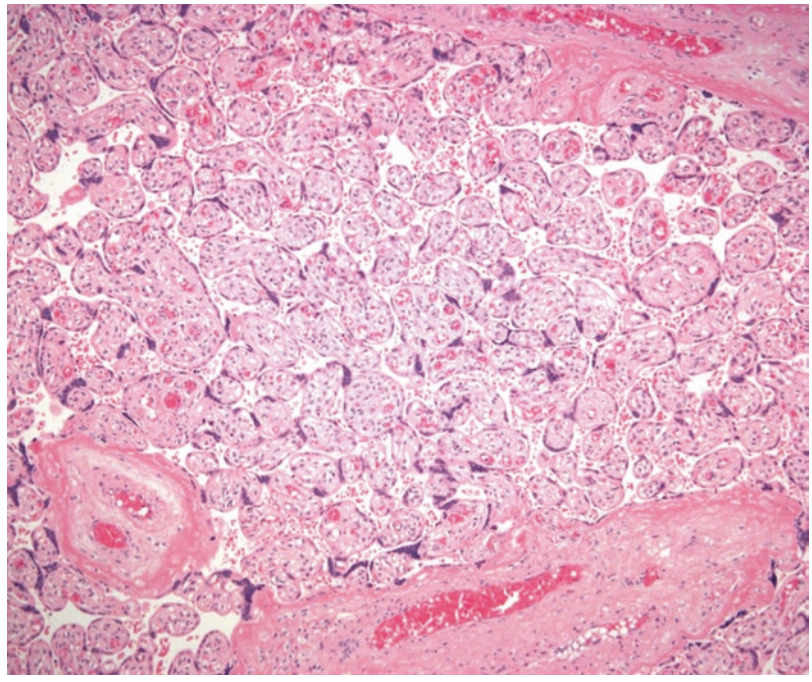

Fig. 14.2 Delayed villous maturation: villi with centrally located fetal capillaries and rare vasculosyncytial membranes. 41 weeks of gestation

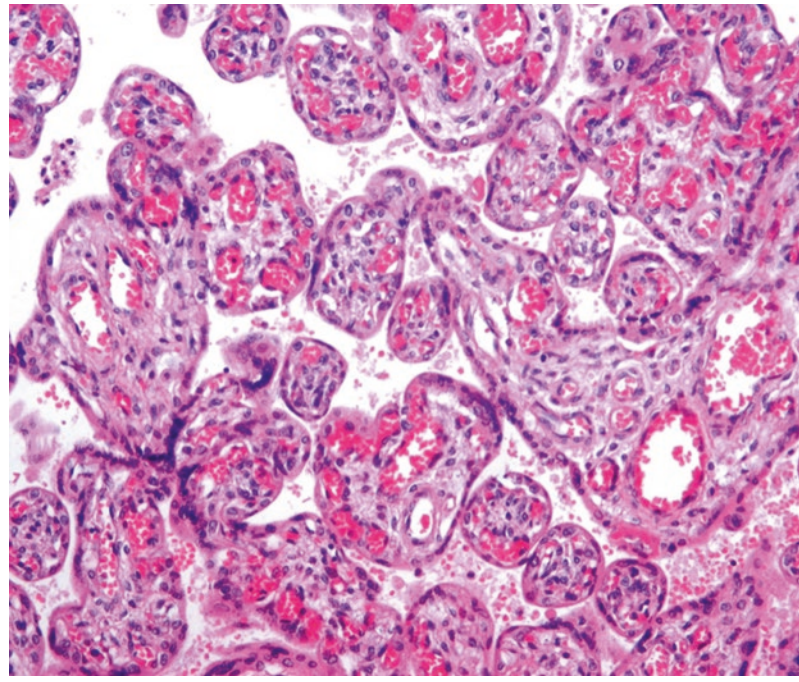

Fig. 14.3 Delayed villous maturation (high-power magnification): villi with cell-rich stroma and mainly centrally located fetal vessels and decreased vasculosyncytial membranes. 40-week placenta

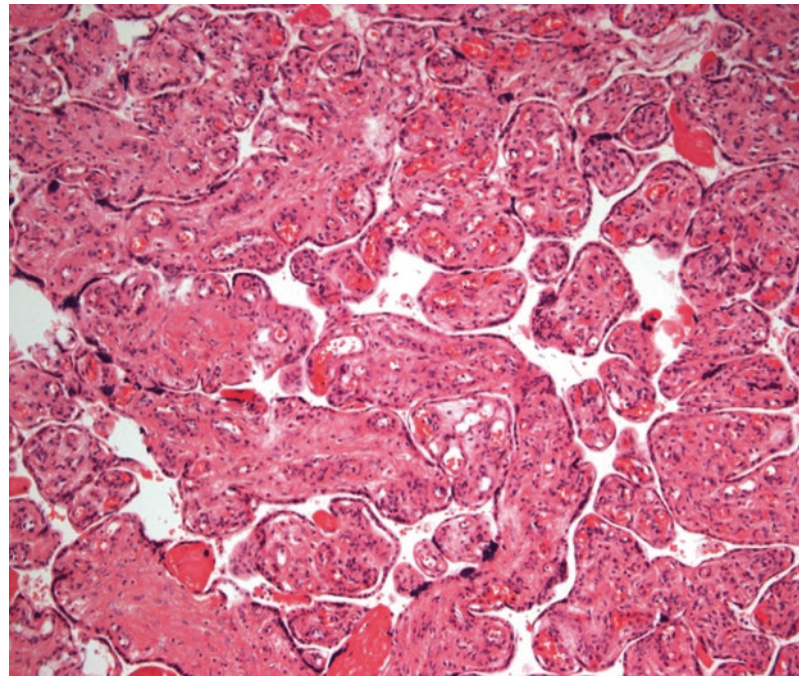

Fig. 14.4 DVM: placental villi of mature intermediate and terminal type, with few vasculosyncytial membranes. 38 weeks of gestation: mother with gestational diabetes

relative high number of mature intermediate villi can be seen in combination with immature intermediate villi. In these placentas there is also a low number of terminal villi with normally developed vasculosyncytial membranes. This pattern can be seen in placentas from mothers with diabetes or in placentas with a high weight (Fig. 14.4) [11].

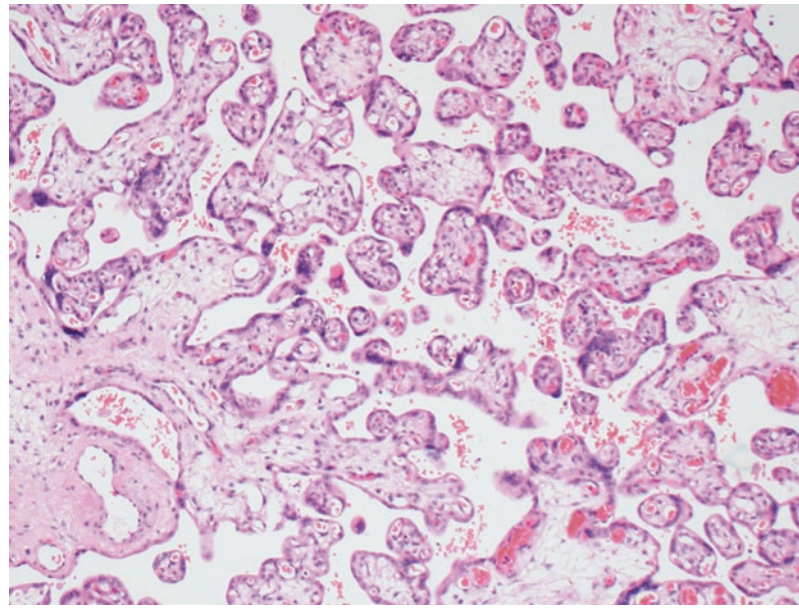

Fig. 14.5 DVM: abnormal villi with poor vasculosyncytial membrane formation

A third pattern of DVM can be observed in cases with congenital and/or chromosomal abnormalities or in cases with chronic villitis of unknown aetiology and is characterized by the presence of abnormal, relatively large villi that cannot be classified as typical immature or mature intermediate villi and usually have a more dense fibrotic stroma with centrally placed vessels. In these cases there are also a low number of terminal villi with normally developed vasculosyncytial membranes (Fig. 14.5).

DVM can be classified according to the presence of immature intermediate villi that are abundantly present in placentas from 20 to 28 weeks of gestational age or mature intermediate villi that are prominently present from 28 to 34 weeks. It can occur in combination and it can be combined with villi that are not really classifiable. The presence of the very immature mesenchymal villi, normally present before 20 weeks of gestation, in term placentas is extremely rare.

Mixed patterns of AVM and DVM may occasionally be seen. Villitis (VUE) may be associated with a delay in maturation and insufficient formation of terminal villi. Interobserver variability in the diagnosis of DVM has been highlighted [16].

14.3.7 Immunohistochemistry

Expression of CD15 in the endothelium of large fetoplacental vessels was found in severe DVM [17].

14.3.8 Differential Diagnosis

Hydrops fetalis, metabolic storage diseases, chorangiosis, vascular-stromal karyorrhexis and increased Hofbauer cells may mimic DVM. Differentiation of DVM from a truly premature placenta may be noted by the presence of stem villi with an immature aspect appropriate for the gestational age, increased stromal cellularity and extracellular matrix deposition, higher ratio of distal to proximal villi, homogeneity of the abnormal villous trophoblast and absence of vasculosyncytial membranes.

14.3.9 Prognosis and Predictive Factors

DVM is associated with an increased risk of adverse perinatal outcome due to the diminished

capacity of the placenta to deliver enough oxygen to the fetus, including intrauterine fetal death, fetal growth restriction (FGR), neonatal hypoxic-ischemic encephalopathy and poor neurological outcome [18]. Stillbirths and neonatal deaths showed a quantitative reduction in vasculosyncytial membranes that was less than controls but also less than live-born infants with DVM [7]. Clinical outcome associated with delayed villous maturation includes increased risk of stillbirths, chromosomal abnormalities and gestational and pre-gestational diabetes compared to non-diabetic controls [19, 20].

The risk of recurrence of DVM is not quantified.

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Distal Villous Hypoplasia

15

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15.1 Introduction

From the second month of gestation, a range of villous types are formed, all with a different structure and function: stem villi, mesenchymal villi, immature intermediate villi, mature intermediate villi, and terminal villi [1]. These different villous types all originate from tertiary villi undergoing a complex process of villous differentiation that is substantially controlled by vascular development [2, 3]. In cases of severe early-onset maternal vascular malperfusion, a specific pattern of villous development called distal villous hypoplasia (DVH) may occur. This pattern is associated with low placental weight and severe early-onset intrauterine fetal growth restriction (FGR) with absent or reversed end-diastolic flow of the umbilical artery [4–8]. Specifically, DVH is defined as the paucity of terminal villi in relation to the surrounding stem villi.

15.2 Definition

Distal villous hypoplasia is the paucity of terminal villi with an apparent increase in intervillous space. The total number of villi is decreased in the centre of the placenta, and the terminal villi are smaller, elongated, and slender compared with normal terminal villi (Fig. 15.1). The diagnosis should be made when the features are seen in the lower two-thirds (not subchorionic plate) and involve at least 30% of a full-thickness slide (chorionic plate to the decidua basalis). It may be further graded as focal finding of the lesion in one full-thickness slide only or diffuse if present in two or more full-thickness slides. Distal villous hypoplasia can be seen with increased syncytial knotting, but this is not necessary for the diagnosis of DVH (Fig. 15.2). Using this definition there is fair to substantial interobserver agreement among expert perinatal pathologists [9, 10]. A similar pattern of DVH can focally be observed in otherwise normal placentas in a small area below the chorionic plate and close to infarcts but, as mentioned above, does not qualify for the diagnosis of DVH.

15.3 Synonyms

Distal villous hypoplasia is sometimes referred to as terminal villous deficiency but the latter term is preferably not used because terminal villi are

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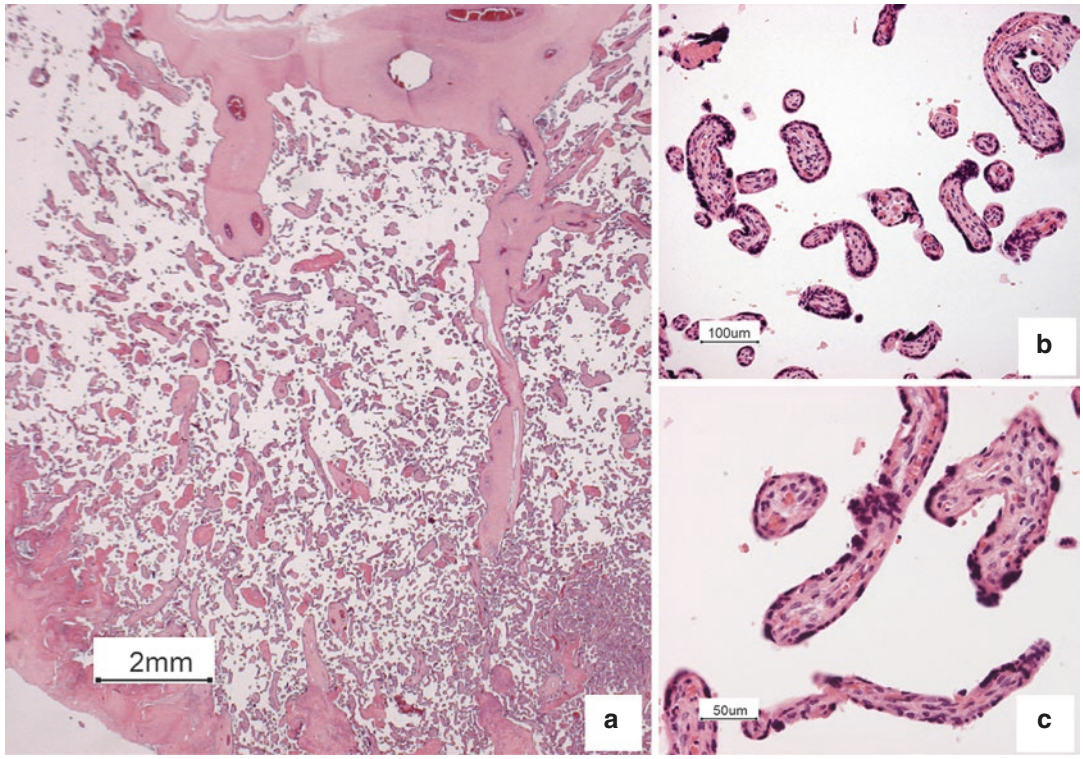

Fig. 15.1 (**a**) Overview; (**b** and **c**) high-power detail of villi with ischaemic changes of trophoblast lining): mother G3P1, ultrasound at 20 weeks showed normal growth and from 28 weeks FGR was demonstrated with an estimated birth weight below third percentile. At 32 weeks GA, an abnormal umbilical artery Doppler was found, and a caesarean section was done at 32^{+3} weeks because of a suboptimal CTG and severe FGR, birthweight 1370 g, AS 9/10. The placenta had a trimmed weight of 170 g (far below tenth percentile), and on cut surface, a few infarcts were seen far less than 5% of the placental volume

present and, although the total number could be decreased, they are abnormally formed with a widening of the intervillous space.

15.4 Epidemiology

DVH is associated with severe early-onset fetal growth restriction with absent or reversed end-diastolic flow of the umbilical artery, which is a sign of high-risk pregnancy [11]. In a retrospective cohort of severe fetal growth restriction with a weight below the tenth percentile and born before 34 weeks of gestational age, the incidence of DVH was 35%–36% in women with either a normotensive or hypertensive pregnancy [6]. Distal villous hypoplasia was seen in 44% of cases with absent or reversed end-diastolic flow [6]. Distal villous hypoplasia can also be seen in placentas from mothers treated with chemotherapy [12].

15.5 Pathophysiology

The pathophysiology of DVH is unknown. However, since placental villous development is largely dependent on vascular development [2], the working hypothesis is the process may be driven by an imbalance in angiogenic factors in response to changes in oxygen tension and/or shear stress [3, 13, 14]. The angiogenic factors involved are influenced by the oxygenic state, which in turn is influenced by the degree of spiral artery remodelling/maternal malperfusion and pre-existing maternal risk factors [15–19].

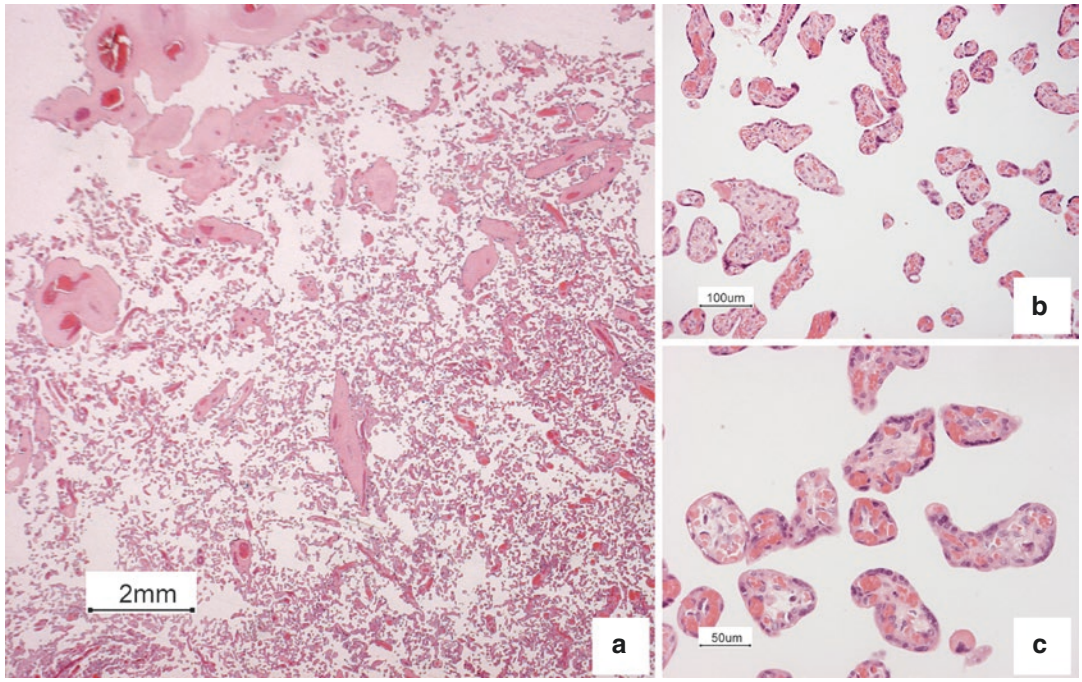

Fig. 15.2 (**a**) Overview; (**b** and **c**) high-power detail of villi without ischaemic changes of trophoblast lining): first pregnancy of this mother with preeclampsia and severe FGR. A caesarean section was performed at 30 weeks GA because of the maternal condition. Birth weight, 965 g. Placenta trimmed weight, 178 g (far below tenth percentile) without gross lesions on cut surface

However, the precise mechanisms leading to maternal malperfusion syndromes and DVH are unknown. Hypoxia might be an important factor and is well known to influence placental angiogenesis [15]. Placentas with DVH show a major loss of surface area, and this will hamper maternofetal exchange which may explain the often observed severe FGR.

15.6 Future Research

The intriguing feature of fetal vascular development in the villi needs further research to better understand normal and abnormal growth of the villous architecture since villous development is largely dependent on vascular development [2]. The relation of villous vascular and structural development with Doppler flow characteristics such as absent or reversed end-diastolic flow of the umbilical artery merits investigation: one theory posits that placental stem villus vessels play an important role in placental haemodynamics, minimizing ventilation-perfusion mismatch [20]. This pattern is compatible with the perfusion distribution in the lung [21]. In the lung, alveolar hypoxia causes vasoconstriction, reducing perfusion of poorly oxygenated alveoli and, thus, diverting blood flow towards better-ventilated areas [21]. Whether this pattern is functional in the placenta with different oxygen tensions is not known nor is the role of different factors that may have an effect on this process such as VEGF, VEGF receptors, and PIGF.

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Placental Mesenchymal Dysplasia

16

Debra S. Heller

16.1 Introduction

Placental mesenchymal dysplasia (PMD) is a rare placental lesion that can be mistaken for a molar gestation. This is due to the cystic structures seen on the fetal surface, which can be misinterpreted as molar villi both grossly and on ultrasonography (Fig. 16.1) [1, 2]. Placental mesenchymal dysplasia is characterized by cystic dilatation and oedema of stem villi and vascular abnormalities including tortuosity, aneurysmal dilatation and thrombosis of vessels on the fetal surface and in stem villi.

PMD was first described in 1991 [3] and had been previously termed "placentomegaly with massive hydrops of placental stem villi and pseudo-partial mole" [1]. The exact incidence of the lesion is not known, but it is estimated at 0.02% [4], with a marked female/male predominance. The lesion is highly associated with Beckwith-Wiedemann syndrome [5], as well as with placentomegaly, growth restriction, stillbirth and neonatal death.

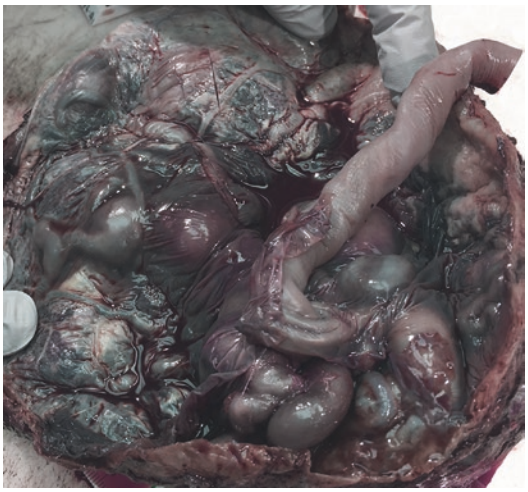

Fig. 16.1 Fetal surface in placental mesenchymal dysplasia shows tortuous surface vessels and cysts. Courtesy Randal Juengel, MD

16.2 Definition

Cystic dilation and oedema of stem villi and vascular abnormalities including tortuosity, aneurysmal dilatation and thrombosis of vessels of the chorionic plate and stem villi, with absence of trophoblastic proliferation.

16.3 Clinical Features

PMD can be mistaken for a partial mole on both ultrasonography and placental gross evaluation. There are no specific early presenting symptoms

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and the condition is usually detected on ultrasound performed either routinely or for an abnormal laboratory result such as elevated alpha-fetoprotein [6]. Ultrasound shows an enlarged thickened placenta with cystic anechoic or hyperechoic regions, which can be confused with a partial mole, chorangioma or subchorionic haematoma, although these last two findings would be less diffuse than PMD, particularly later in pregnancy. Earlier in pregnancy, the ultrasound appearance of the cysts of PMD may be more diffuse but, as pregnancy progresses, the location of the cystic structures migrates towards the chorionic plate. This, as well as the ultrasound presence of a structurally normal fetus, should raise the consideration of PMD [6]. PMD is most often detected in the second or third trimester [7]. Later in pregnancy, growth restriction or stillbirth evaluation may lead to the diagnosis of PMD. Beckwith-Wiedemann fetuses may have swallowing issues, with resultant polyhydramnios [6]. Placental changes become more pronounced as the pregnancy progresses. Genetic abnormalities include Beckwith-Wiedemann syndrome in about 25% of cases [5] and occasional cases of trisomy 13 and Klinefelter's syndrome, although many fetuses are normal. Alpha-fetoprotein is often elevated, although beta-hCG is normal for gestational age or only mildly elevated [1, 8]. PMD is associated with preterm delivery, gestational hypertension and preeclampsia, eclampsia, and HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome [4, 5, 9].

16.4 Genetics

Placentas with PMD have a diploid complement, and the fetus is typically normal structurally, although often growth restricted if not affected by Beckwith-Wiedemann syndrome [2]. PMD is associated with genetic abnormalities including androgenetic/biparental mosaicism or allelic imbalance of imprinted genes [2]. One theory [10] is that the androgenetic biparental mosaicism represents a mid-spectrum level of androgenetic expression, with normal pregnancies being entirely biparental and complete moles being entirely androgenetic. These authors suggested that their case of a dichorionic twin gestation with one side showing PMD without a fetus, umbilical cord or fetal surface may represent a step further on the spectrum of androgenetic expression than the usual PMD [10].

16.5 Gross Findings

The placenta with PMD is markedly enlarged and thickened, with weights of more than the 90th percentile [6]. There are cystic structures seen on the fetal surface and within the parenchyma, representing dilated stem villi. The parenchymal dilated stem villi are concentrated at the fetal surface and intermixed with normal calibre villi, which may be why PMD is misinterpreted as a partial mole. Fetal surface vessels are enlarged, aneurysmally dilated and tortuous and may be thrombosed (Fig. 16.1). The vascular and cystic abnormalities develop over time, progressively worsening, and placentas less than 20 weeks do not show such obvious features [6]. Increased cord length with hypercoiling and varices may be seen, particularly in association with Beckwith-Wiedemann syndrome [2].

16.6 Histopathology

Histologically, stem villi show cystic dilatation and enlargement, with enlarged vessels, which may be thrombosed, and may show fibrinoid necrosis. Large cisterns may be present, and cellularity of the stroma is variable. Myxomatous change of stem villi is common. The vessels are thick-walled, with fibromuscular hyperplasia (Figs. 16.2, 16.3, and 16.4). Trophoblast proliferation is not a feature, distinguishing PMD from hydatidiform mole. Vessels in distal villi may also be abnormal in PMD, with dilatation and thromboses, and foci of chorangiosis, chorangioma, chorangiomatosis, and increased nucleated red blood cells may be seen in fetal vessels [2]. The

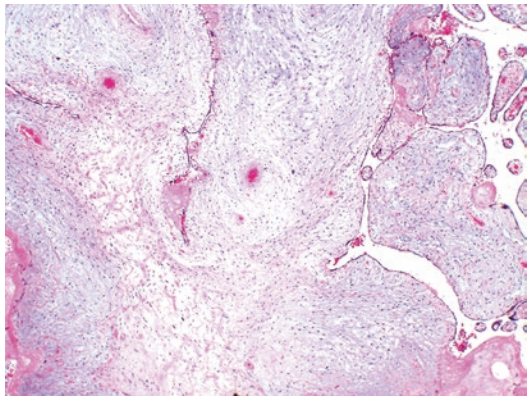

Fig. 16.2 Oedematous stem villi with myxoid change admixed with normal-sized distal villi

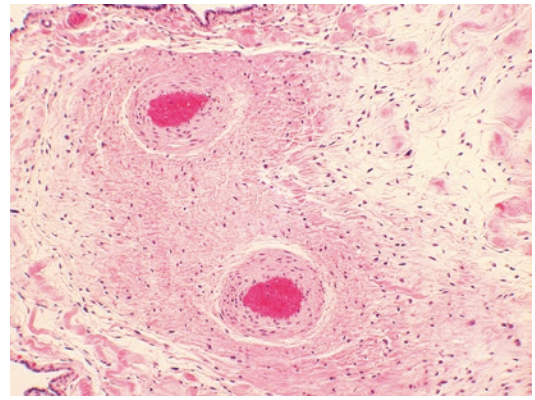

Fig. 16.4 Vessels show fibromuscular hypertrophy

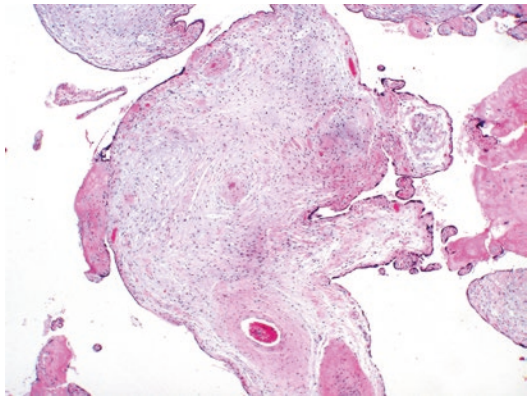

Fig. 16.3 Thick-walled vessels are seen. There is no trophoblast proliferation

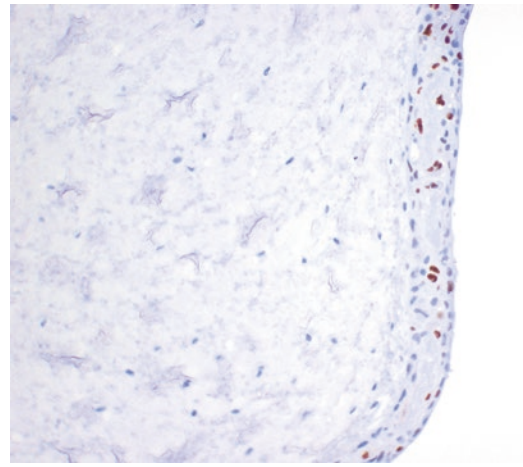

Fig. 16.5 p57 immunostain shows nuclear staining of surrounding trophoblast, but not of stem villous stroma

villous stroma of the abnormal stem villi is negative for smooth muscle actin although positive for vimentin and desmin like normal stem villi, which also stain for smooth muscle actin. This may reflect arrest at an earlier stage of differentiation [6, 11]. P57 immunostaining is usually negative in stem villous stroma but positive in the overlying maternally derived trophoblast, while adjacent normal villi show normal staining in stroma and trophoblast (Fig. 16.5) [2]. The lack of androgenetic material in the villous trophoblast may explain the lack of trophoblast proliferation seen in PMD [6], as well as the positive p57 staining in these cells. Because the androgenetic cell distribution may not be uniform, immunohistochemistry may not give uniform results [2].

16.7 Differential Diagnoses

PMD should not be mistaken for hydatidiform mole. A full discussion of the features of molar gestations is beyond the scope of this chapter; however, a few features will be mentioned. Both partial and complete moles involve distal villi rather than stem villi, with diffuse involvement of distal villi, as opposed to the more proximal stem villous involvement in PMD. Trophoblast proliferation is a feature of both complete moles and partial moles. The scalloped villi with trophoblast inclusions seen in partial moles are not seen

in PMD. Complete moles rarely have a fetus, and partial moles have structurally abnormal triploid fetuses, while PMD fetuses are usually structurally normal. Diffuse multifocal chorangiomatosis may also be confused with PMD; however, diffuse multifocal chorangiomatosis does not have the large tortuous chorionic plate vessels, large dilated stem villous vessels, or umbilical cord involvement (see Chap. 24) [2].

16.8 Prognosis

PMD is associated with Beckwith-Wiedemann syndrome, growth restriction, and a significant risk of stillbirth, in the region of 40% [12]. Fetal mortality may be related to cord abnormalities, fetomaternal haemorrhage, or coagulopathy [2, 12]. Hypoxia due to thromboses, decreased normal villi for gas exchange, and shunting in chorangiomas and dysplastic villi have also been postulated as mechanisms of growth restriction and demise [7]. Fetal and neonatal visceral hamartomas, such as mesenchymal hamartoma of the liver [13], as well as visceral and cutaneous haemangiomas are also associated [2].

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17 Increased Syncytial Knot Formation

W. Tony Parks

17.1 Introduction

Syncytium formation at the maternofetal interface is a common adaptation found in haemochorial placentas. Microinjection studies using fluorescent probes have demonstrated the free flow of tracer material throughout the confluent syncytiotrophoblast layer [1]. The syncytiotrophoblast forms one of the two layers of villous trophoblast in the placenta. The cells of the inner cytotrophoblast layer function as the proliferating precursors for the overlying syncytiotrophoblast layer, while the syncytiotrophoblast functions as the endothelium for the placenta, physically separating maternal blood from the fetal blood and other fetal tissues. Early in gestation, these cell layers surround the entirety of each floating villus and all intraplacental segments of the anchoring villi. The syncytiotrophoblast layer additionally lines the entire underside of the chorionic plate and the surface of the basal plate, covering all tissue with the potential to contact maternal blood. The syncytiotrophoblast layer degenerates in areas (particularly beneath the chorionic plate) where it is replaced by fibrin clot. The uninvolved portions of this layer continue as an intact syncytium.

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The syncytiotrophoblast is a highly metabolically active tissue containing large numbers of mitochondria and with multiple functions including nutrient transport [2, 3], metabolic regulation [4] and hormone production. Despite the high metabolic activity of the syncytiotrophoblast and the rapid growth of the placenta during pregnancy, the syncytiotrophoblast is entirely post-mitotic—all trophoblast proliferation occurs in the cytotrophoblast layer. This continued proliferation keeps the ratio of syncytiotrophoblast nuclei to cytoplasmic volume steady throughout gestation [5], and it maintains a constant percentage of transcriptionally active nuclei [6].

The ongoing injection of newly generated nuclei into the syncytiotrophoblast layer leads to nuclei of varying ages within this tissue and the function and morphology of these nuclei appear to change over time. Transcriptional activity is lost [6–8], the chromatin becomes heavily condensed, and some of the nuclei are collected into small clumps termed syncytial knots or syncytial nuclear aggregates. Syncytial knots are scarce in the early placenta but they increase with gestational age. By term, up to one-third of villi may harbour a syncytial knot [9, 10]. Importantly, the formation of syncytial knots appears to accelerate in the presence of hypoxia or hypoxia-reperfusion injury, as is seen with alterations in maternal blood flow to the placenta. An increased percentage of villi containing a syncytial knot,

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denoted as increased syncytial knots, is one of the canonical findings that defines maternal vascular malperfusion in the placenta.

17.2 Definitions

Syncytial sprouts are racquet-shaped protrusions from villi that are most apparent in the first trimester. They actually leave the placenta and enter the maternal blood stream, lodging in maternal lungs and surviving for years after delivery.

True syncytial knots are small aggregates of syncytiotrophoblast nuclei that bulge slightly above the villous surface. Their nuclei typically contain highly condensed chromatin and are thought to be aged and minimally functional [7]. Increased syncytial knots are present when the percentage of terminal villi containing a syncytial knot is increased above the baseline percentage for that gestational age. At term, the upper limit of normal has traditionally been set at 30% of villi. A recent study of normal placentas has corroborated this figure, finding that an average of 28% of villi at term have a syncytial knot on their surface [9]. Syncytial knots are less common in preterm placentas, with the percentage of villi harbouring a syncytial knot increasing throughout gestation [9]. Increased syncytial knots should also be widespread to be diagnostic (and to exclude normal regional variability). Specifically, increased syncytial knots should involve more than 30% of the bottom two-thirds of the central parenchymal sections.

False syncytial knots are plane of section artefacts that give the appearance of a syncytial knot but that in fact are not actually a true syncytial knot [11, 12]. The complexity of the villous architecture fosters tangential sections, and sites of villous branches are especially likely to generate false knots. For typical light microscopic histology, serial sections are required to distinguish between true and false knots.

Syncytial bridges are aggregates of syncytiotrophoblast that connect adjacent villi [11, 12].

Wave-like syncytial knots represent an unusual distribution of syncytial knots that is found primarily in second or early third trimester placentas. The knots have the same individual appearance as typical true syncytial knots but they take on a linear arrangement of nearly uniformly spaced tight clusters [13, 14]. Wave-like syncytial knots are found almost exclusively on stem or intermediate villi.

17.3 Synonyms

Syncytial nuclear aggregate is a term that applies globally to all types of syncytiotrophoblast groups. While the term syncytial knots can also be utilised as an overarching term for all of these same histologic features, syncytial nuclear aggregates are useful when segregating true and false syncytial knots from syncytial sprouts, for instance. This term appears largely in the research literature and is rarely used by clinicians. *Tenney-Parker change* is an eponymous term derived from the last names of the two authors who performed a major early study on the placental findings in preeclampsia [15]. It can be used synonymously with increased syncytial knots.

17.4 Epidemiology

The incidence of increased syncytial knotting is not known with certainty. Few large databases of placental pathology from unselected populations exist, making the problem difficult to study. The Collaborative Perinatal Project [16], likely the largest such database, reported increased syncytial knots in only 2.27% of 41,925 placentas. Unfortunately, this low percentage does not accord well with other Collaborative Perinatal Project data. Advanced villous maturation for gestational age was identified in 10.41% of their cases, for instance; yet in other studies, these two parameters have tended to show similar rates. Moreover, virtually all of the studies in the literature involve selected populations, making the true incidence difficult to determine.

Studies of syncytial knots also suffer from a reproducibility problem. While the dogma has long existed that up to one-third of villi at term can have a syncytial knot, careful quantitation

has not always been employed. Moreover, although a precise definition for a syncytial knot was recently proposed [9], the application of this definition is not always straightforward. These complications have often resulted in relatively high interobserver variability. Kappa statistics span from a low of 0.25 (not reproducible) in the absence of concordance training [17] to 0.50 (moderately reproducible) in areas with significantly increased knots with sufficient training [18]. Even with extensive pre-study efforts to synchronise definitions and diagnoses, combined with an optimal technique for counting, kappa is no better than 0.60 [19]. Concordance was best in the areas with most knots and worse in relatively normal sections of placenta [18, 19]. Developments such as automated image analysis may improve the accuracy and reproducibility of this lesion [20].

A finding of increased syncytial knots has been strongly associated with other lesions of maternal vascular malperfusion, such as villous infarction and decidual vasculopathy [21]. However, as the use of composite variables and the generation of latent constructs has increased, it has become more difficult to test these associations. An increase in syncytial knots may not be segregated as a discrete variable but may instead be incorporated as a component of a larger composite variable such as accelerated villous maturation or maternal vascular malperfusion. This problem is compounded by the use of increased syncytial knots as one of the criteria for accelerated villous maturation. The assessment and publication in future studies of both explicit individual lesions and composite variables will help advance this field.

Taking all of the above caveats into account, there are still clear associations between increased syncytial knots and several major clinical obstetrical disorders. The first definitive association was noted with preeclampsia [15, 22, 23]. Increased syncytial knots have also been associated with fetal growth restriction [24–26]. Interestingly, in cases of fetal growth restriction, increased syncytial knots were associated with reversed umbilical artery end-diastolic flow specifically in the women with preeclampsia [27]. A subset of preterm births also shows increased syncytial knots [28–31].

For each of the above entities, the heterogeneity of the clinical disorders likely confounds the association with this lesion. Typically, only a subset of the placentas from a given clinical disorder manifests this pathology. Even for a disorder such as preeclampsia that has long been associated with maternal vascular malperfusion, these lesions are only found in a modest percentage of the cases. Major efforts are currently underway to attempt to distinguish subtypes of disorders such as preeclampsia and preterm birth [32–34]. The preliminary findings from these studies suggest that subclasses may specifically be associated with placental pathologies such as increased syncytial knots.

17.5 Gross Findings

Syncytial knots themselves are purely microscopic features that do not generate any macroscopic pathology. That said, they are often accompanied by other findings of maternal vascular malperfusion, such as small placental size, low placental weight, or villous infarctions. While these macroscopic findings may suggest the presence of increased syncytial knots, they are not specific for this entity.

17.6 Histopathology

Syncytial sprouts are most easily identified in early pregnancy. They appear as extensions of syncytiotrophoblastic tissue from the underlying villi (Fig. 17.1a). One common morphology is that of a broad-based, slightly bulbous expansion of the syncytiotrophoblast away from the supporting villus. These structures, often termed trophoblastic sprouts, represent the first step in the development of a new villus. After the trophoblastic sprout has formed, mesenchymal stroma from the underlying villus moves into the sprout. Capillaries then migrate in, transforming the sprout into a new villus. Another characteristic appearance of syncytial sprouts is that of an ovoid

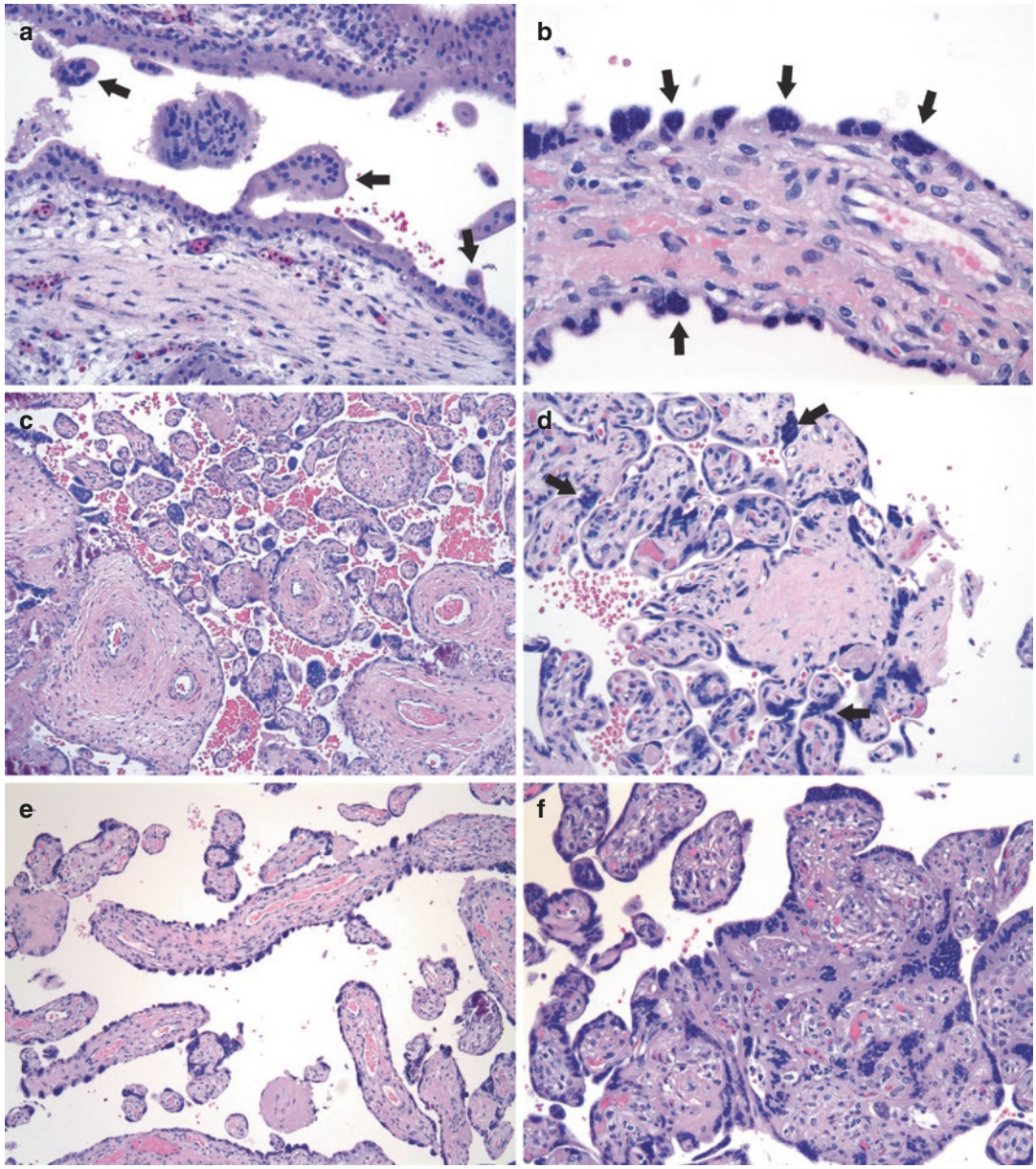

Fig. 17.1 Syncytial knots. (**a**) Syncytial sprouts. This image shows parts of two first trimester villi. Numerous syncytial sprouts emerge from each villus (black arrows). Several free-floating sprouts are also apparent between the villi. These latter sprouts may represent either sectioning artefacts of sprouts that remain connected to the villi or sprouts that have broken off the villi and are being deported into the maternal circulation. (**b**) Syncytial knots. This image shows one villus that harbours several individual syncytial knots (black arrows). Their nuclei are small, dark and tightly clustered. (**c**) Increased syncytial knots. This image shows a mix of stem villi with numerous small terminal villi. Syncytial knots are present on most of the smaller villi. (**d**) Syncytial bridges. This image shows a central hyalinised villus with increased branching. Numerous smaller villi surround the central villus. Syncytial bridges (black arrows) are readily identified between the villi. (**e**) Wave-like syncytial knots. Two of the central villi in this image of a late second trimester placenta are lined by regularly spaced hyperchromatic syncytial knots. This linear clustering is characteristic of wave-like syncytial knots. (**f**) Villous agglutination. Most of this image is occupied by a cluster of adherent villi. Large syncytial aggregates are common within the cluster

protrusion extending from the villus by a thin neck. These structures may break off from the villus and be deported into the maternal circulation. Histologically, sprouts have euchromatic nuclei with moderate to abundant surrounding syncytiotrophoblast cytoplasm. The nuclei generally do not appear crowded and heterochromatin formation is limited.

True syncytial knots represent the subtype of syncytial knot of most interest to pathologists and other clinicians. This type of knot is thought to develop most robustly in response to hypoxic damage or hypoxia-reperfusion injury. True syncytial knots consist of clusters of at least five syncytiotrophoblast nuclei [9] that bulge above the normal villous surface (Fig. 17.1b). These nuclei are generally small and dark, containing highly condensed chromatin. As expected, they do not show evidence of transcriptional activity. Surprisingly, they also do not contain the histone modifications typically associated with heterochromatin (H3K9me3 and H3K27me3) although they do have the H4K20me3 histone modification [35]. Instead, the DNA in these nuclei shows evidence of significant oxidative damage [7].

False syncytial knots are, by routine light microscopy, nearly indistinguishable from true syncytial knots. They also contain clumps of small, dark syncytiotrophoblast nuclei. Since these structures derive from sectioning artefacts, they may contain nuclei of younger ages than typically found in true knots and these younger nuclei may also have less dense chromatin.

Syncytial bridges are syncytiotrophoblastic structures that at least appear to connect adjacent villi (Fig. 17.1d). They are thought to arise from the fusion of syncytiotrophoblast structures such as true syncytial knots or syncytial sprouts. Increased villous branching promotes the formation of syncytial bridges. As with syncytial knots in general, both true and false forms of syncytial bridges exist with the majority of observed bridges actually representing artefacts of tangential sectioning [11, 12].

While it is possible to distinguish these individual subtypes of syncytial knots, doing so requires a combination of immunostains and serial sections, along with substantial time for counting sufficient numbers of nuclei. This much effort is not realistic for clinical practice. Instead, it is assumed that each placenta contains a background level of sprouts, false knots and bridges that is comparable to other placentas of the same gestational age. Since hypoxia preferentially increases the numbers of true knots, any significant increase in the number of counted syncytial knots above background likely represents an increase in true knots and therefore evidence of hypoxic damage.

It is also of critical importance that syncytial knotting only be assessed on sections of central placenta showing no macroscopically identifiable lesions. Syncytial knotting should not be evaluated in the parenchyma surrounding lesions (especially villous infarctions) since any lesion that results from or leads to localised hypoxia can induce increased numbers of syncytial knots in the immediate vicinity. The corollary to this concern is that the three suggested central sections of placental parenchyma must not contain lesions. The temptation to use one of these normal sections to also assess a small contiguous lesion should be strenuously resisted.

Two other structures involving syncytiotrophoblast may be identified on placental examination-wave-like syncytial knots and villous agglutination. Both are distinctive and unlikely to be confused with other trophoblastic structures.

Wave-like syncytial knots consist of typical true knots in orderly linear arrangements along villi (Fig. 17.1e). While no experimental evidence provides an explanation for this unusual patterning, it has been suggested that these arrangements represent pre-existing lines of syncytial nuclear organisation [14]. Unlike other types of syncytial knots, wave-like syncytial knots are found earlier in gestation (in the second and early third trimesters). Similarly, they do not appear on terminal villi but rather they are found only on stem or intermediate villi. They are inevitably accompanied by other features of maternal vascular malperfusion, such as accelerated villous maturation and distal villous hypoplasia.

Villous agglutination is thought to occur when localised hypoxia leads to focal trophoblast degeneration and loss. Fibrin adheres to the

affected villi, effectively gluing them together. Only a relatively small number of villi (ranging from 2 to 20) typically become agglutinated (18). Not uncommonly, these structures also contain large numbers of syncytial knots (Fig. 17.1f). Other features of maternal vascular malperfusion often accompany villous agglutination.

17.7 Immunohistochemistry

Immunohistochemistry is of limited clinical utility when assessing syncytial knots. Immunostains for transcriptional activity or oxidative damage have been used in research studies to distinguish true knots from false knots [7] but the quality of these immunostains is limited and they have not been validated for clinical use.

17.8 Genetic Susceptibility

Increased syncytial knots have been associated with maternal heterozygosity for the factor V Leiden mutation [36] but otherwise little is known about the genetic susceptibility of any lesions of maternal vascular malperfusion. These lesions, including increased syncytial knots, all appear to be associated with subsets of major pregnancy complications, including preeclampsia, fetal growth restriction and preterm birth. It seems likely that, as these clinical disorders become separated into distinct entities with different underlying aetiologies, malperfusion lesions will segregate with a limited number of these subtypes, allowing for more efficient and definitive genetic analysis.

17.9 Prognosis and Predictive Factors

The prognosis associated with lesions such as increased syncytial knots has not been studied extensively. It is clear that the combination of lesions that comprise maternal vascular malperfusion (including increased syncytial knots) can have a profound effect on the health of the fetus in utero. Such fetuses are significantly smaller than their peers not affected by maternal vascular malperfusion [30] and more susceptible to in utero fetal demise. Studies attempting to disentangle the effects on the fetus of the placental pathology from the effects of the clinical disorders are ongoing.

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Persistence of Cytotrophoblast

18

T. Yee Khong

18.1 Introduction

Throughout pregnancy, the villi are covered by a continuous uninterrupted outer layer of multinucleated syncytiotrophoblast. Subjacent to this is a layer of mononuclear cytotrophoblastic cells, which are considered to be stem cells for syncytiotrophoblast. Villous cytotrophoblastic cells form a complete layer in early pregnancy, but as pregnancy progresses, they become dispersed and do not form a complete mantle around each villus. Several factors regulate their proliferation and differentiation [1]. The hypoxic environment in the early embryonic period induces cytotrophoblast proliferation [1]. Culture of human villous cytotrophoblast cells under hypoxic conditions prevents syncytiotrophoblast formation [2].

18.2 Definition

There is currently no universally accepted definition of an excessive number of villous cytotrophoblastic cells.

18.3 Synonyms

Previous studies have referred to "undue prominence", "proliferation" or hyperplasia. Here we refer to them as "persistence of cytotrophoblast cells".

18.4 Epidemiology

In the majority of placentas from normal uncomplicated mature pregnancies from a hospital series, and acknowledged by the author as being "unduly weighted by high-risk cases", cytotrophoblast cells were identified in less than 20% of villi [3]. Therefore, a normal count was arbitrarily defined as the presence of villous cytotrophoblastic cells in less than 20% of villi, a high villous cytotrophoblastic cell count when seen in 20–40% of villi and a very high count when over 40% of the villi contain cytotrophoblastic cells [3]. Arguing that it is unusual to find one clearly identifiable cytotrophoblastic cell per cross section of a peripheral villus, increased numbers of villous cytotrophoblastic cells were termed when more than two were seen per peripheral villous cross section [4].

Given that hypoxia induces cytotrophoblast proliferation, it is not surprising that an excessive number of villous cytotrophoblastic cells, however described, has been described in placentas from pregnancies complicated by maternal

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diabetes, maternofetal rhesus incompatibility, preeclampsia, fetal growth restriction and gestations from high altitude [4–6].

18.5 Gross Findings

There is no grossly visible pathology associated with this finding.

18.6 Histopathology

Villous cytotrophoblastic cells can be observed on haematoxylin and eosin-stained sections (Fig. 18.1). The cytotrophoblastic cell may be flattened in shape and occupy a basal position but, more often, it is rounded and may indent beneath or apparently be embedded within the syncytial layer [7]. They can be highlighted by periodic acid-Schiff stain, which stains the syncytiotrophoblast and trophoblastic basement membrane but not the cytotrophoblast (Fig. 18.2). Rarely, a complete mantle of cytotrophoblast is present (Fig. 18.3); this is the pattern described in delayed villous maturation [8] (Chap. 14) and is seen with poor vasculosyncytial membrane formation.

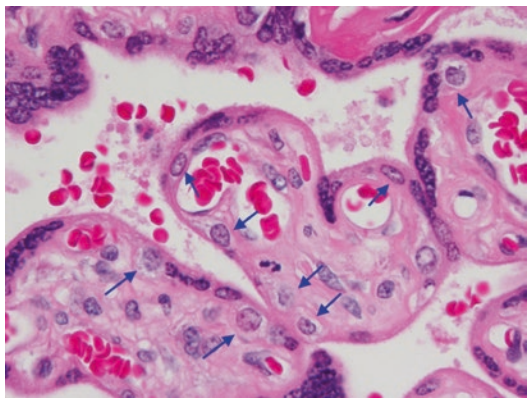

Fig. 18.1 Cytotrophoblastic cells (arrowed) seen beneath the syncytiotrophoblastic layer in villi from a 37-week pregnancy (haematoxylin and eosin staining)

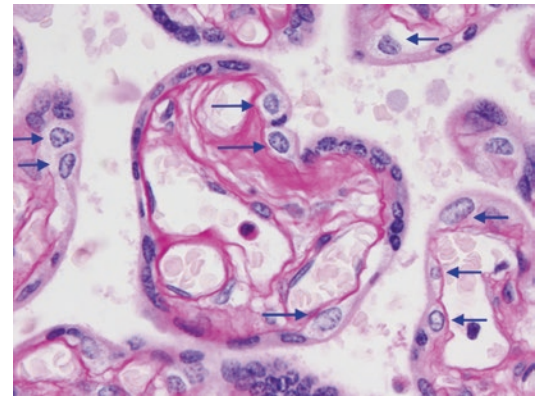

Fig. 18.2 Cytotrophoblastic cells (arrowed) highlighted by their absence of staining to PAS contrasted with the cytoplasm of the syncytiotrophoblastic layer and the basement membranes of the capillaries and trophoblast (periodic acid-Schiff staining)

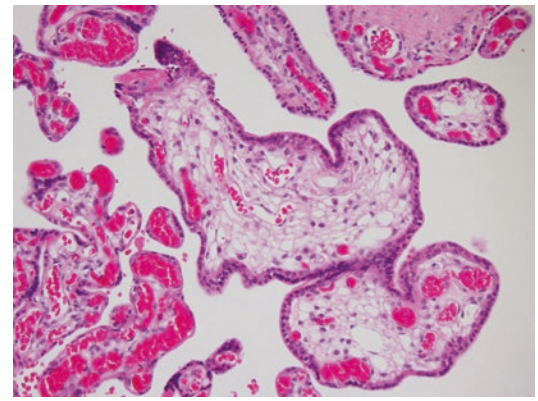

Fig. 18.3 A cluster of villi showing a circumferential layer of cytotrophoblast; the villi show poor vasculosyncytial membrane formation in comparison to surrounding villi

18.7 Immunohistochemistry

Keratin immunolabels both syncytiotrophoblast and cytotrophoblast [9].

18.8 Prognosis and Predictive Factors

None is currently known.

18.9 Recommendation/Future Studies

Further work is urgently needed to define and clarify the clinical significance of this morphologic feature. In the meantime, it is proposed that excessive number of villous cytotrophoblastic cells be separated into two types. The pattern of a complete mantle of cytotrophoblast is infrequent and the clinical associations and implications of their finding may differ from the commoner pattern of interposed cytotrophoblastic cells beneath the syncytial layer. It can be tedious to examine every terminal villus over three placental sections. A proposed workable definition of the pattern of interposed cytotrophoblastic cells could be the presence of two or more cytotrophoblastic cells per villus in ten villi over ten fields, following the enumeration of vascular channels for establishing the diagnosis of chorangiosis (Chap. 24). For the pattern of complete mantle of cytotrophoblast, thresholds could be a binary grading: isolated/singular villus per placental section or two or more villi per placental section. Since intrauterine hypoxia is suggested as a cause of cytotrophoblast proliferation, regional variation due to proximity to the uteroplacental artery should be explored. The use of iummunohistochemistry may not be practicable in routine practice but may facilitate research.

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Mineralization of Trophoblast Basement Membrane

19

Ilana Ariel and Karen Meir

19.1 Introduction

Minerals are essential chemicals transferred from the mother to the developing conceptus. These include the major minerals (calcium, phosphorus, potassium, sodium and magnesium) and trace elements, including iron, zinc and other weak metals each of which has a specific function in the body. The term "mineralization" regarding the trophoblast basement membrane (TBM) implies a more limited connotation and denotes sedimentation of calcium as phosphate salts (hydroxyapatite) and iron as haemosiderin.

The serum calcium level in fetal blood is higher than that in maternal blood implying an active transport mechanism. Adequate transport of calcium across the placental basement membrane is needed throughout pregnancy, especially so in the third trimester, due to its important role in growth and development. Diverse calcium channels are present in the TBM [1]. It is possible that there is a link between placental calcification and nanobacteria [2].

Iron supply through the placenta is facilitated by the primary iron uptake protein, TfR, located on the trophoblast apical membrane. The ferric iron taken up from the maternal circulation by placental TfR1 is transported across the placenta with the help of a series of iron transporter proteins before being incorporated onto fetal transferrin [3]. Iron sedimentation in tissues is mostly as haemosiderin, i.e. a complex of apoferritin and ferric iron.

19.2 Definition

Blue-purple discolouration of the TBM formed by sedimentation of minerals, specifically calcium phosphate and iron as haemosiderin along the basement membrane of the chorionic villus. This phenomenon is accompanied many times by stippled mineralization of the trophoblast, stroma and stromal cells.

19.3 Synonyms

Terms used in the literature included TBM calcification or TBM haemosiderosis, but the preferred term should be TBM mineralization.

19.4 Epidemiology

TBM mineralization is noted in most cases in fibrotic avascular villi from fetal vascular malperfusion in livebirths and is especially prominent in stillbirths [4]. It may also be seen in villi with

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normal-looking vasculature, especially in aneuploidy. This may implicate impaired placental or circulatory function as a mechanism for death in aneuploid fetuses [5]. Increased TBM mineralization has also been reported in polyhydamnios [6], fetal vascular malperfusion [7] and more, many times associated with degenerative changes and fibrosis. It also often observed in cases with right ventricular failure and placental and/or fetal hydrops.

Mutations of the calcium ion channels causing decreased renal tubular calcium reabsorption result in TBM mineralization (see below Bartter syndrome in "Genetic susceptibility"). TBM has also been documented in thalassaemia (see below in "Genetic susceptibility").

19.5 Gross Findings

There are no distinctive macroscopic features in placentas with villous basement membrane mineralization.

19.6 Histopathology

Light microscopic examination reveals fine linear or stippled basophilic discolouration along the TBM. Stippled mineralization is often also seen in adjacent trophoblast and stromal cells, along with perivillous fibrin. It should be noted that haemosiderin by itself is deposited as a granular golden yellow or yellow-brown pigment, whereas calcium salts assume a dark blue colour. When deposited together, the blue colour dominates (Fig. 19.1).

19.7 Histochemistry

Calcium deposits as phosphate are stained black by the von Kossa method. It should be noted that the von Kossa stain, in fact, identifies phosphate and carbonate salts, rather than calcium. The murexide method, which is considered specific for calcium, is not routinely used [6]. Perls' Prussian blue stain is used to identify ferric iron.

It is of note that calcium and iron may be deposited together in tissue disrupted by fibrosis (such as in splenic "Gamna-Gandy" bodies) [4].

19.8 Immunohistochemistry

Immunohistochemistry with antibody against ferritin was used for research purposes [8].

19.9 Genetic Susceptibility

Widespread mineralization of the basement membrane is observed in Bartter syndrome, an inherited renal tubular disorder associated with hypokalaemic alkalosis [5, 9–11]. Mutations in ion transport channels in this syndrome lead to decreased calcium reabsorption and hence to hypercalciuria. The mechanism is not entirely understood. It has been suggested that increased renal excretion of calcium by the fetus could lead to dystrophic calcification with trophoblast basement membrane involvement [9]. Another possible mechanism could be increased maternal transport of calcium to the hypocalcaemic fetus overloading the placental transport system and resulting in deposition along the basement membrane [10]. The possible mechanisms do not explain, however, the sedimentation of haemosiderin along with calcium.

Haemosiderin deposits in the trophoblast basement membrane may be seen in placentas of thalassaemic patients [12].

Aneuploidy and other malformation syndromes, especially congenital heart defects with venous congestion and right ventricular failure, are associated with increased trophoblast basement membrane calcification [5].

19.10 Prognosis and Predictive Factors

Prognosis depends on the underlying cause of mineralization.

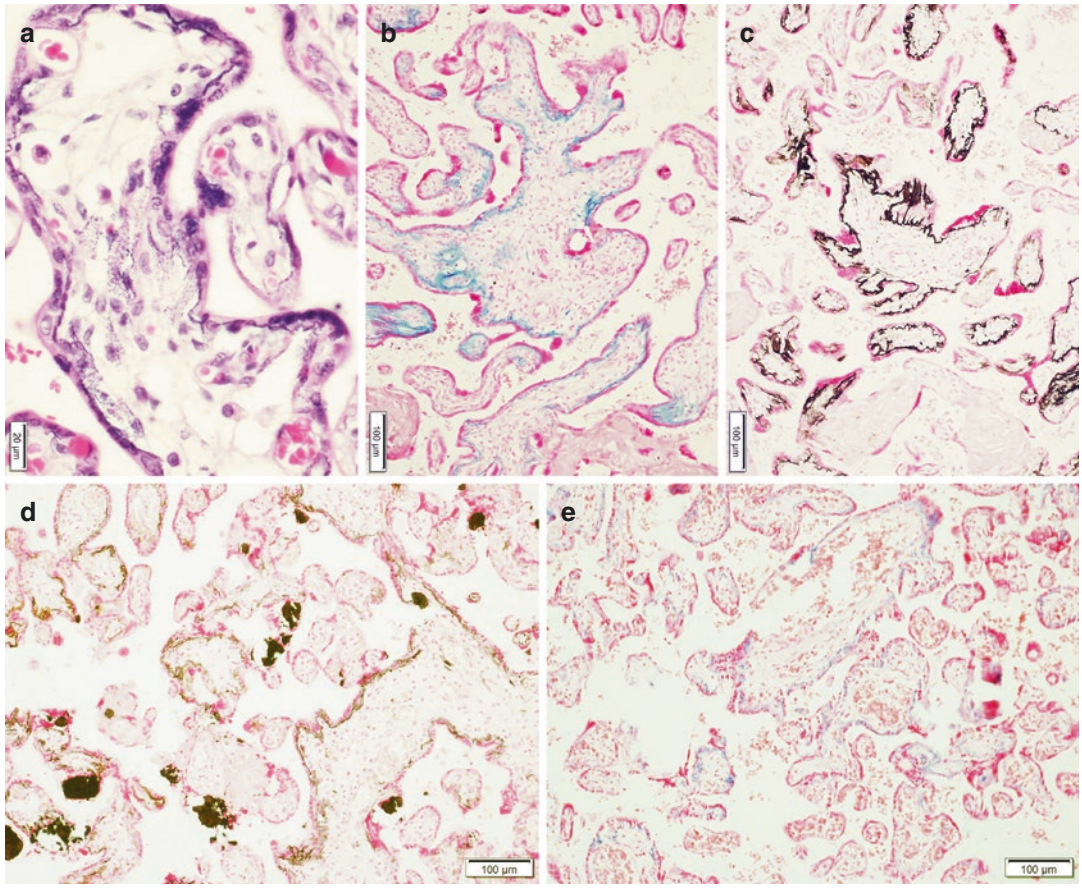

Fig. 19.1 (**a**-**c**) Trophoblast basement membrane mineralization (TBM) in induced abortion for multiple malformation syndrome, including phocomelia and narrow chest, hypoplastic left heart and hypertelorism. No further genetic investigation performed. (A) Bluish-purple discolouration of the TBM is noted along with stippled discolouration of adjacent stromal cells and trophoblast cells. (**b**) Perls' Prussian blue stain. (**c**) von Kossa stain. (**d**-**e**) TBM in placenta from induced abortion for Bartter syndrome. (**d**) Note linear calcium deposition in the TBM along with numerous coarse calcium deposits. (**e**) Perls' Prussian blue stain is also noted in this calcium metabolic disorder

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20 Trophoblast and Stroma: Vacuolation—Inherited Disorder of Metabolism

Margaret J. Evans, Glenn Anderson, and Neil J. Sebire

20.1 Introduction

Inherited metabolic disorders, also referred to as inborn errors of metabolism, are a group of congenital disorders caused by mutation in genomic or mitochondrial DNA. In the past few years more advanced genomic testing has enabled diagnosis. Not all disorders present in utero, and there is a wide spectrum of disease presentation; this chapter lists those which present specific changes in the placenta which may be seen on routine sections and which may lead to improved and early diagnosis of these conditions. There are many thousands of diseases, but broadly they may be divided into errors of:

- Carbohydrate metabolism.
- Protein metabolism.
- Fatty acid oxidation.
- Glycogen storage.

Each group may present a specific pattern of placental changes affecting the trophoblast. It is mainly the disorders of storage metabolism which are amenable to diagnosis as these produce inclusions or vacuoles in the tissue of affected individuals. The placenta may also be involved and chorionic villus sampling is often employed to make a prenatal diagnosis in families with known disorders [1].

20.2 Definition

Cytoplasmic vacuolation due to accumulation of storage material/metabolites within the trophoblastic cell, Hofbauer cell or other cell types such as villous stromal fibroblast and villous capillary endothelial cells.

20.3 Synonyms

None.

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20.4 Epidemiology

The incidence of inherited errors of metabolism ranges from 1 in 50,000 to 1 in 150,000. Although any given inborn error of metabolism is very rare, taken as a group, inborn errors occur in 1 in 2500 births.

20.5 Gross Findings

Most cases present with either fetal hydrops or fetal growth restriction. The placenta may be pale and bulky in hydropic cases.

20.6 Histopathology

Diagnosis of fetal metabolic storage disease by routine placental examination should be suspected by presence of diffuse cytoplasmic trophoblast and stromal Hofbauer cell vacuolation, often in association with fetal growth restriction or fetal hydrops [2, 3]. Detailed morphological descriptions are available of placental histological appearances with a range of specific metabolic diseases such as I-cell disease and sialic acid storage disease, with extensive syncytiotrophoblast vacuolation (Figs. 20.1 and 20.2) [4, 5]. Others, such as GM1 gangliosidosis and glycogen storage disease type II, may be associated with diffuse trophoblast, stromal cell and amniotic vacuolation (Fig. 20.3) [6, 7].

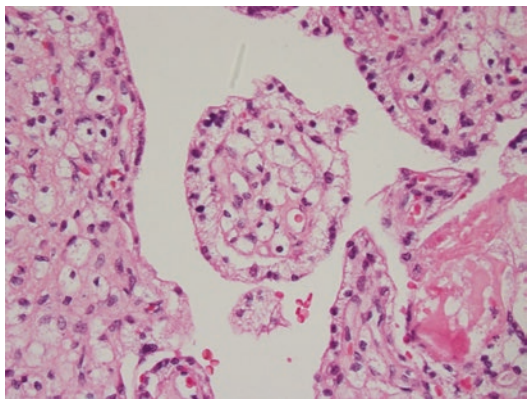

Fig. 20.1 Photomicrograph of a placenta affected by sialic acid storage disease with marked trophoblast and stromal vacuolation (H&E < original magnification ×400; Courtesy of Prof. Y. Khong)

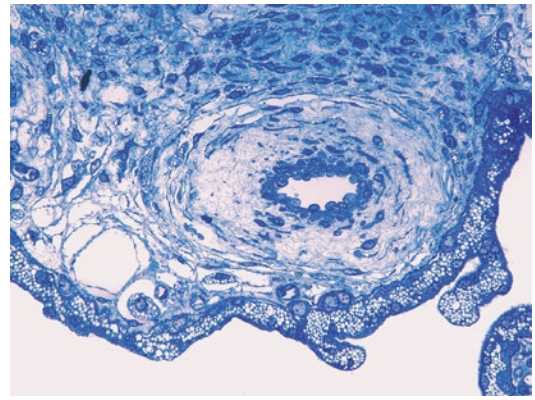

Fig. 20.2 Photomicrograph of a semithin section from a case of sialic acid storage disease, with prominent vacuolation of trophoblast and fibroblasts (Semithin resin section, Toluidine Blue, original magnification ×400)

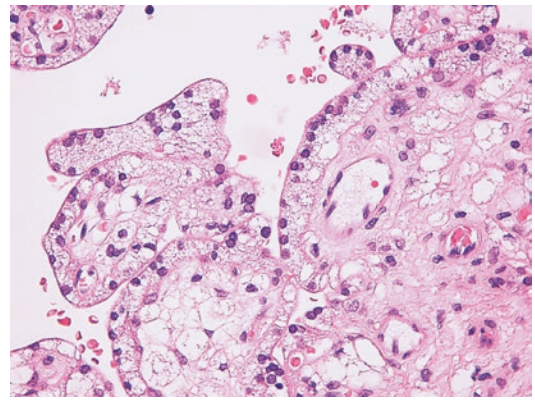

Fig. 20.3 Photomicrograph of chorionic villi affected by GM1 gangliosidosis showing florid cytoplasmic vacuolation (H&E, original magnification ×400)

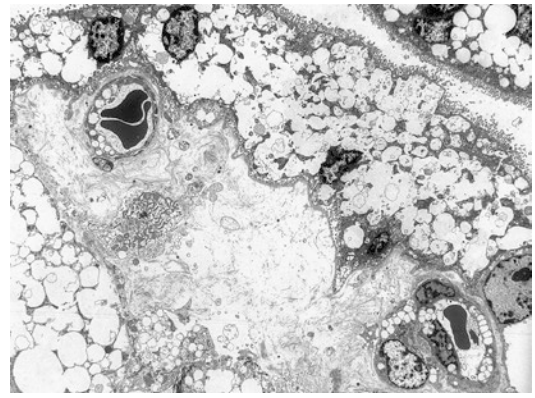

Fig. 20.4 Ultramicrograph of a case of GM1 gangliosidosis showing enlarged lysosomes in trophoblast layer and blood vessel endothelial cells (Electron microscopy original magnification ×500)

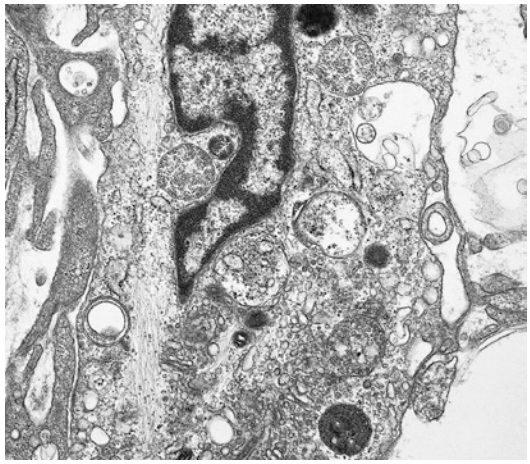

Fig. 20.5 Placental tissue from a case of glycogen storage disease type 2, Pompe disease, with membrane bound glycogen in endothelial cells. (Electron microscopy, original magnification ×15,000)

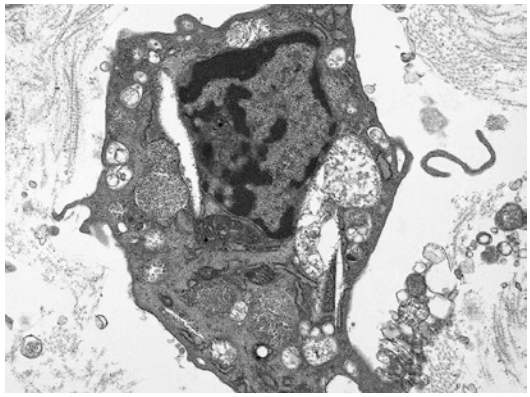

Fig. 20.6 Placental sample from a case of glycogen storage disease type 2, Pompe disease, showing a fibroblast with lysosomal glycogen (Electron microscopy, original magnification ×10,000)

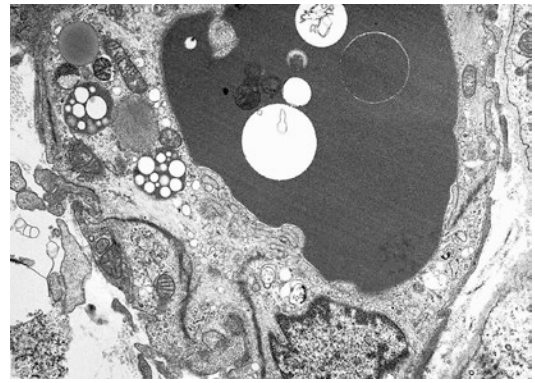

Fig. 20.7 Placental sample from a case of Wolman disease showing multiple, membrane bound lipid droplets in an endothelial cell (Electron microscopy, original magnification ×5000)

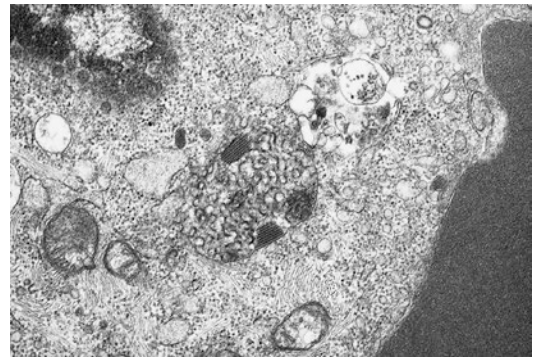

Fig. 20.8 Placental sample from a case of late infantile Batten's disease, NCL2, showing curvilinear inclusions in an endothelial cell (Electron microscopy, original magnification ×15,000)

Specific diagnoses are confirmed with biochemical and/or molecular genetic testing as required [6] and/or by use of electron microscopy, which can demonstrate characteristic membrane-bound vacuole appearances (Figs. 20.4, 20.5, 20.6, 20.7, and 20.8) [7].

Note that not all inclusions will be visible in paraffin-embedded sections and appearances may differ from vacuolation to granular eosinophilic material within cells. Furthermore, the extent of storage material may change with gestational age. Gaucher's disease and mucolipidosis type II or I-cell disease may show inclusion-bearing cells with the syncytiotrophoblast, Hofbauer cells and extravillous trophoblast cells within cell columns. In some disorders, the vacuoles are formed of mucolipid and may not therefore be seen in routine paraffin sections.

In cases of suspicion, it may therefore be wise to consider electron microscopy since ultrastructural placental features in metabolic storage disease have been described across all trimesters, including trophoblast and stromal cell vacuolation [8]. In a review of experience with ultrastructural examination of >100 cases of chorionic villus samples for diagnosis of metabolic storage disease, >30 diagnoses were made including glycogen storage disease type II, gangliosidosis

Table 20.1 Patterns of vacuolation

Disease	Fetal hydrops ± ascites	Trophoblast vacuolation	Höfbauer cells	Electron microscopy
GM1 gangliosidosis	+	+	?	
GM2 gangliosidosis type I (Tay-Sachs disease)	–	+		
GM2 gangliosidosis type II (Sandhoffs disease)—myelin bodies in trophoblast and endothelium	–	–	–	Myelin bodies in trophoblast and endothelium
Mucolipidosis II (I-cell disease)	+	+	+	+
Mucopolysaccharidosis I	±	–	+	
Mucopolysaccharidosis IV	–	–	+	
Mucopolysaccharidosis VII	+	–	+	+
Sialidosis	+	+	+	+
Salla disease	+	+	+	+
Gaucher disease	+	–	–	–
Niemann-Pick Type A	–	+	+	+
Cholesterol ester storage disease	+	+	+	+

type I, mucopolysaccharidosis type I, mucopolysaccharidosis not specified, Niemann-Pick type A, sialidosis/mucolipidosis type I, neuronal ceroid lipofuscinoses, Wolman disease, sialic acid storage disease and storage disease not specified [9].

The table below outlines the main sites of vacuolation in the different metabolic disease (Table 20.1).

20.7 Immunohistochemistry

Periodic acid-Schiff (PAS) and/or silver staining may be useful in defining the inclusions present within cells.

20.8 Genetic Inheritance

Examination of the placenta and identification of specific diagnostic factors have a role to play in identifying underlying metabolic disorders at an early stage and directing further molecular genetic analysis. The identification of the gene defect is required not only for genetic counselling but for appropriate early treatment of the patient, and treatment options are constantly evolving with the advent of enzyme replacement therapy, specific cell or organ transplantation and gene therapy both in vivo and ex vivo.

20.9 Prognosis and Predictive Factors

Recognising vacuolation within the trophoblast of the placenta may prompt focused investigation for specific gene mutations involved in specific inborn errors of metabolism. This will allow earlier diagnosis and the possibility for novel gene treatment. As most of the clinical manifestations are secondary to the build-up of "toxic" metabolites, early diagnosis may significantly alter the cause of the disease. It is important, however, to view the placental changes within the context of wider clinical picture and family history. It is also important to recognise that some diseases will not present with vacuolation but with inclusions, some of which will be better described on electron microscopy.

20.10 Non-storage Disease Placental Cell Vacuolation

It should be noted that extravillous chorion laeve trophoblast may be normally vacuolated, with large, clear cytoplasmic areas, corresponding to lipid droplets and pinocytotic vesicles, unlikely to be confused with abnormal vacuolisation secondary to storage disease [10]. Whilst not affecting the villous placental tissue, marked cytoplasmic

vacuolation of amniotic epithelial cells is well-recognised in association with gastroschisis [11].

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Villous Oedema

21

Peter Kelehan and Paul Downey

21.1 Introduction

Unlike other microscopic lesions, villous oedema is often a descriptive, not a diagnostic, term.

Diffuse villous stromal oedema may indicate fetal hydrops (immune/non-immune), but histologic assessment is often unable to establish an underlying diagnosis. Patchy or focal villous oedema may be insignificant or may be seen in association with established regional flow changes in the fetal circulation.

21.2 Definition

Villous oedema is characterised by an accumulation of fluid in the villous stroma and between capillaries and the trophoblast layer [1].

21.3 Synonyms

21.3.1 Epidemiology

Some degree of villous oedema is seen in about 11% of term placentas [2]. The incidence of diffuse villous oedema (hydrops) depends on the population being studied, e.g. thalassemia. Lesser degrees of oedema can be seen in a variety of other conditions, e.g. infection and conditions affecting fetal blood flow.

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21.4 Gross Findings

Gross findings are proportional to the extent and severity of oedema but do not help establish an underlying diagnosis. Diffusely oedematous (hydropic) placentas are heavy, large and pale with spongy villi; lesser (and localised/focal/patchy) forms of placental oedema may give no appreciable gross changes.

Pallor should be differentiated from oedema as pallor may reflect fetal anaemia (e.g. fetal-maternal haemorrhage) or an absent fetal circulation (e.g. villous involution in a macerated stillbirth).

21.5 Histopathology

Microscopically, villous oedema at term can be divided into two patterns:

1. Diffuse oedema (hydrops) is characterised by diffuse enlargement and pallor of terminal and stem villi. The extent of villous involvement required for diffuse oedema is not standardised but should involve the majority of villi in most parenchymal sections (Fig. 21.1), although it may be less prominent with retained stillbirth.

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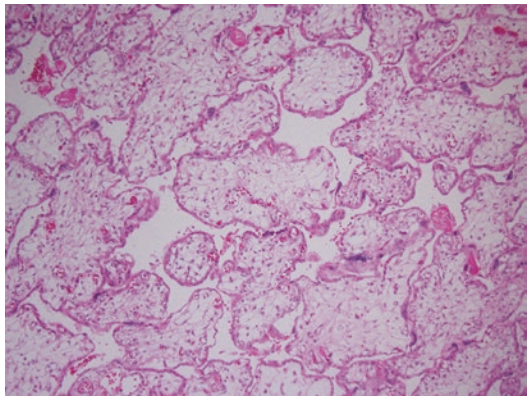

Fig. 21.1 Oedema in a bulky placenta at 35 w gestation that weighed 831 g trimmed after fixation. There is extensive villous oedema (courtesy Dr. Yee Khong)

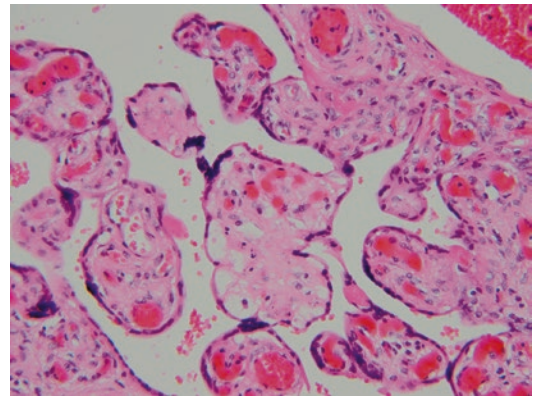

Fig. 21.2 Oedema in association with fetal vascular malperfusion

On low power microscopy, placental villi appear pale as the white space, accounted for by villous stroma, is diffusely increased. Villous stromal channels and Hofbauer cells become more prominent with preservation of the villous trophoblast layer. This pattern is typically seen with fetal hydrops (immune or non-immune). Fetal nucleated red blood cells may be increased with fetal anaemia; alloimmunisation to Rhesus, Kell and Duffy antigens and ABO incompatibility should be considered.

2. Patchy or focal oedema (non hydropic oedema) may be subtle and missed on low power. Oedematous terminal villi are interspersed between unaffected villi. Affected villi have an irregular, non-circumferential increase in villous stroma. As this pattern can be seen with fetal vascular malperfusion, additional evidence of aberrant fetal flow should be sought, e.g. karyorrhectic stromal debris (Fig. 21.2).

21.6 Differential Diagnosis

Villi in placentas from mothers with delayed maturation and/or diabetes may show some features suggesting villous oedema, but villous maturation defects are primarily characterised by a delay in normal villous maturation (Chap. 14)—not stromal oedema [3].

Metabolic disorders may mimic oedema. Intracellular vesicles in trophoblast and/or Hofbauer cells suggest intracellular storage inclusions occurring as a result of an underlying inherited metabolic disorder (Chap. 20). Beckwith-Wiedemann syndrome/mesenchymal dysplasia may give placentomegaly with variable oedema.

21.7 Immunohistochemistry

Immunohistochemistry is rarely used. Conspicuous fetal nucleated red blood cells (and precursors) may prompt parvovirus immunohistochemistry.

21.8 Genetic Susceptibility

21.8.1 Prognosis and Predictive Factors

In term deliveries, the prognosis (and recurrence potential) depends on identifying an underlying cause and ancillary placental pathology. Occasionally, fetal-placental hydrops may result in gestational proteinuric hypertension and give a maternal "Mirror syndrome" (Ballantyne syndrome).

Diffuse oedema (hydrops) is associated with high rates of fetal loss [2, 4], and, where non

hydropic oedema affects immature intermediate villi, it is a strong risk factor for the development of cerebral palsy and abnormal neurocognitive development in infants born prematurely [5]; villous oedema has recently been associated with a lower risk of autistic spectrum disorder [6].

21.9 Future Research

It is unclear how villous oedema should be graded and quantified. One system evaluated the percentage of villi affected (extent) and the percentage of the villous cross-sectional area affected by oedema (severity) and derived a score by multiplying the extent with the severity of oedema [1, 2]. These authors used different severity scores and graded villous oedema differently; one graded the oedema as being mild, moderate or severe [1], while the other had a binary score of either mild or moderate to severe [2]. Redline et al. graded diffuse villous oedema, defined by large vacuoles in the villous stroma, as 1, 2 or 3 based on involvement of 1–5%, 6–19% or ≥19% of all terminal villi, respectively [7]. Research into the pathophysiology underlying villous oedema may inform whether a grading system incorporating extent or severity or both will have the highest diagnostic value. For example, the pathologists present at the Dublin Workshop were divided as to whether villous oedema compresses the fetal vasculature, also discussed previously [8], a mechanism that could contribute to fetal hypoxia.

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Extramedullary Haemopoiesis

22

Luiz Cesar Peres

22.1 Introduction

Blood cells first appear during the third week of embryonic development within the mesoblastic tissue of the yolk sac. The peripheral cells of the blood islands then differentiate into blood vessels, and the centrally located ones differentiate into primitive blood cells [1, 2]. Haematopoietic stem cells (HSC) then colonise the umbilical cord and the aorta-gonad-mesonephros region. The liver is populated by cells from the latter [3, 4] and becomes the main haematopoietic site during the third to fifth month. In humans, the spleen latter becomes part of the haematopoietic sites, and the bone marrow progressively integrates this system, becoming the most important organ at term. Significant post-embryonic extramedullary haemopoiesis is abnormal in full-term fetuses, but it can reappear in the liver, spleen, lymph nodes and also in the placental villous stroma in face of hypoxia, provided the stem cells and macrophage microenvironment are available. The latter includes extramedullary matrix, stromal cells and local and systemic chemokine production.

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It has already been demonstrated that the placenta is an important source of multipotential haematopoietic progenitors before they colonise the liver [4] and provides a niche for HSC in the mouse [5]. The umbilical cord is also a source of stem cells [6].

22.2 Definition

Extramedullary haemopoiesis is defined as the formation and maturation of blood cells outside the medullary spaces in the bone marrow. In the placenta, they are found within the villous stroma.

22.3 Synonyms

Extramedullary haematopoiesis, Erythroblast precursors, Placental extramedullary haemopoiesis.

22.4 Epidemiology

The true incidence of EMH in the placenta is not known since it is seen as part of other conditions and not a specific pathological process on its own. It appears when there is increased demand for blood cells and thus can happen due to conditions leading to fetal anaemia or hypoxia. Fetal anaemia is typically the result of haemolysis such

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as in rhesus disease, fetal blood loss such as in fetomaternal haemorrhage and impaired erythrocyte production such as in parvovirus infection or haemoglobinopathy, e.g. haemoglobin Bart's disease [7]. Many of these conditions present as hydrops fetalis. However, not all cases of hydrops fetalis, for example, fetal congenital heart defects and storage disorders among others, induce placental EMH.

22.5 Gross Findings

Typically, placentas where EMH is present show generalised paleness, which is also noted in the fetus, due to anaemia. Bulky, oedematous placentas can be seen when there is also fetal hydrops. However, as noted above, the presence of the latter does not imply finding EMH. Placental weight may be within the expected range for gestational age in EMH without hydrops and, of course, is massively increased when it is present.

22.6 Histopathology

The sine qua non requirement for placental EMH is the finding of foci of haemopoiesis within the villous stroma (Fig. 22.1). The complex biochemical and cellular interactions involved in EMH are beyond the scope of this book and can be found elsewhere [8, 9]. In general terms, it happens in erythroblastic islands where a central macrophage physically and chemically provides a microenvironment for the development and maturation of the erythroblast. Integral to this is the erythroblast-macrophage protein, which inhibits apoptosis and promotes terminal maturation of erythroid precursors. This well-orchestrated sequence of events typically happens within the villous stroma.

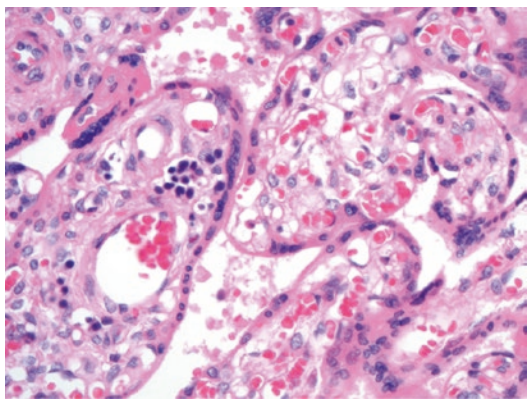

Fig. 22.1 Foci of extramedullary haemopoiesis within villous stroma. Note a central large macrophage and adjacent maturing erythroblasts. A nearby villous capillary can be seen next to it highlighting the stromal nature of extramedullary haemopoiesis (Courtesy of Dr. Amy Heerema-McKenney)

The pathological conditions associated with EMH within the villous stroma are classically seen in both immune and non-immune hydrops. Immune hydrops (erythroblastosis fetalis, haemolytic disease of the newborn) is mostly due to anti-D rhesus incompatibility [10]. Maternal antibodies against rhesus D antigen cross the placenta and induce fetal haemolytic anaemia, which in turn stimulate the release of normoblasts and erythrocyte precursors into fetal circulation and also induce EMH within the villous stroma. Although less common, immune hydrops can develop due to maternal-fetal incompatibility with ABO [11], Kell and other minor blood groups [12]. The degree of fetal hydrops in these cases is usually less severe than with rhesus anti-D as is the finding of placental EMH.

Non-immune fetal hydrops is nowadays more common than immune hydrops, but they do not necessarily cause placental EMH, as in congenital heart defect and storage disorder, for example. Of the causes of non-immune hydrops that induce placental EMH, infectious causes are more prevalent in western countries, especially parvovirus, which represents 0.7% of all fetal autopsies [13] and from 16% to 18% of non-immune hydrops [14]. Haemoglobin Bart disease is the most prevalent form of non-immune hydrops fetalis in South Asia [7].

Placental EMH can appear in chronic fetomaternal haemorrhage associated with intervillous or subchorionic thrombosis or without any recognisable source due to its insidious nature, leading to fetal anaemia with subsequent hypoxia, heart failure and hydrops. Such cases can be confirmed by Kleihauer-Betke test [15] or by flow cytometry

[16]. Acute fetomaternal haemorrhage, such as following blunt abdominal trauma, however, is not associated with placental EMH if delivery happens shortly after as the processes involved in EMH take time to develop.

22.7 Immunohistochemistry

Immunostaining may be useful in confirming parvovirus infection as a cause of placental EMH. Other placental infections, such as cytomegalovirus, herpes virus and toxoplasmosis, can also benefit from specific immunostains. The stromal nature of EMH in the chorionic villi can be highlighted by immunostaining of the endothelium (CD31, CD34, Factor VIII and GLUT-1) or vascular wall (smooth muscle actin (SMA)).

22.8 Prognosis and Predictive Factors

Prognosis and recurrence are dependent on the primary cause of fetal anaemia or hypoxia. This is particularly important for haemoglobinopathies, especially alpha-thalassaemia. Rhesus D antigen incompatibility may recur with increased severity if the appropriate anti-D immunoglobulin is not administered timely.

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Intravillous Haemorrhage

23

Karen Meir and Ilana Ariel

23.1 Introduction

Intravillous haemorrhage is a manifestation of an acute hypoxic event of the placenta and occurs as an early stage of placental parenchymal infarction [1]. Congestion along with hypoxic damage to the villous capillaries causes haemorrhage from fetal capillaries into the villous stroma and is most often seen in immature and mature intermediate villi. Intravillous haemorrhage is observed in most cases of, but not exclusively in association with, placental abruption [2].

23.2 Definition

Haemorrhage within the villous stroma, in any villus.

23.3 Synonyms

Villous stromal haemorrhage.

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23.4 Epidemiology

Since the majority of cases are observed in association with recent infarcts or placental abruption, it is seen more often in disorders associated with maternal vascular malperfusion. Because placental abruption may occur in other situations as well, e.g. in severe ascending intrauterine infection, and in cases with termination of pregnancy using misoprostol, intravillous haemorrhage is not necessarily linked to these disorders. Intravillous haemorrhage is also seen following manual removal of the placenta.

23.5 Gross Findings

Intravillous haemorrhage is essentially a microscopic diagnosis. On macroscopic examination, features of retroplacental haematoma may be seen causing indentation of the underlying placental parenchyma which looks haemorrhagic ("red infarct").

23.6 Histopathology

Intravillous haemorrhage is often one of the microscopic features associated with retroplacental haemorrhage, and features of the latter have been described previously [3]. Briefly,

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blood dissects the decidua from the placenta causing indentation of the parenchyma. Due to the severe acute hypoxia, the first adaptation of the placental vessels is dilatation; this causes severe congestion in the fetal capillaries, a comparable reaction as is observed in pulmonary ventilation-perfusion mismatch [4, 5]. In combination with endothelial damage, stromal haemorrhage may occur. The villi show haemorrhage within the villous stroma (Fig. 23.1) and various stages of infarction, depending on the age of the lesion. Immature and mature intermediate villi are more susceptible for this lesion as compared with terminal villi. It should not be confused with congestion of fetal vessels where there is no haemorrhage within the stroma (Fig. 23.2).

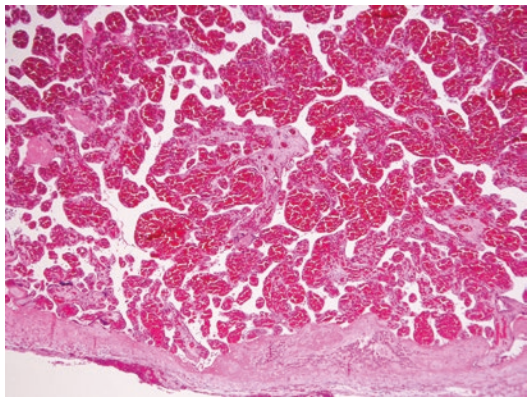

Fig. 23.1 Haemorrhage in the villous stroma obscures the villous architecture in this case of acute abruption (Courtesy of Dr. Yee Khong)

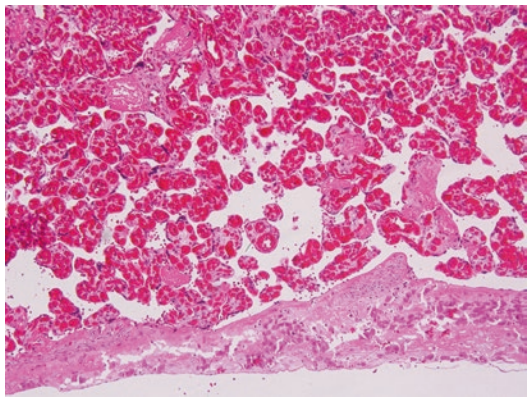

Fig. 23.2 Congestion of fetal vessels without interstitial haemorrhage in the stroma (Courtesy of Dr. Yee Khong)

23.7 Immunohistochemistry

None relevant.

23.8 Genetic Susceptibility

Dependent on aetiology.

23.9 Prognosis and Predictive Factors

Dependent on aetiology.

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Hypervascularity

24

Raymond W. Redline, Christina Bagby, and Sanjita Ravishankar

24.1 Introduction

Diagnostic entities characterized by villous hypervascularity (so-called villous capillary lesions) fall into three categories: chorangiosis, multifocal chorangiomatosis, and chorangioma (Table 24.1). One rare variant of the latter, the multiple chorangioma syndrome, can recur in subsequent pregnancies. The underlying causes of villous capillary lesions are incompletely understood but are believed to involve excessive angiogenesis [1–3].

Formation of mature terminal villi is driven by the "herniation" of elongating capillary loops as a consequence of accelerated nonbranching angiogenesis beginning at 24–32 weeks of gestation [4]. Continuing villous capillary growth normally parallels stromal growth resulting in an average of approximately 6–8 capillary cross sections per terminal villus. When capillary growth exceeds stromal growth, terminal villi can become hypervascularized and reach the diagnostic threshold for villous chorangiosis [5].

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Immature intermediate and stem villi have large central vessels, a loose reticular stroma, and variable amounts of a second, peripheral collateral circulation known as the paravascular capillary net which is connected to the larger vessels by anastomosing arterioles and venules [4]. Patchy-diffuse expansion of the paravascular capillary net by nonbranching angiogenesis results in multifocal chorangiomatosis. A more circumscribed nodular proliferation within this zone leads to a chorangioma [6].

24.2 Villous Chorangiosis

24.2.1 Definition

Patchy-diffuse increases in the number of capillary cross sections per villus, usually measured in terminal villi, but can extend into intermediate villi. Defined by the "rule of tens": 10 or more villi containing 10 or more capillary cross sections in several different regions of the placenta [5].

24.2.2 Synonyms

Chorioangiosis, increased villous vascularity, hypercapillarization, hypervascularization.

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Table 24.1 Selected characteristics of different villous capillary lesions

	Villous chorangiosis	Multifocal chorangiomatosis	Chorangioma/localized chorangiomatosis	Multiple chorangioma syndrome
Type of villi affected	Terminal	IIV and small stem	Large stem (subchorionic)	Small and large stem
Type of angiogenesis	Nonbranching	Branching	Branching	Branching
Presence of pericytes	No	Yes	Yes	Yes
Complete basement membrane	Yes	No	No	No
Nodular character	No	No	Yes	Yes
Pathogenesis/ associations	Preplacental hypoxia, Insulin, IGF-2	Malformations, FVM	Preeclampsia, twins	IUFD, neonatal distress
Recurrence risk	No	No	No	Yes

IIV immature intermediate villi, *FVM* fetal vascular malperfusion, *IGF-2* insulin-like growth factor 2, *IUFD* intrauterine fetal death

24.2.3 Epidemiology

Villous chorangiosis (VC) is seen in 5–10% of term placentas [6, 7] and is associated with two clinical scenarios: (1) decreased maternal oxygen tension despite normal perfusion of the intervillous space (so-called preplacental hypoxia) [8, 9]. Conditions in this category include maternal anaemia, smoking, pregnancy at high altitudes, and pregnancy in areas of high air pollution [10–13]. Increased vascularization with maternal anaemia and smoking begins in the first trimester [10, 14]. (2) Increased fetal growth factor expression, specifically hyperglycaemia in maternal diabetes, leads to fetal hyperinsulinaemia [15], and Beckwith-Wiedemann syndrome is associated with overexpression of insulin-like growth factor 2 (IGF-2) [16]. Of note, insulin receptors, which bind both insulin and IGF-2, are highly expressed at branch points in the terminal villous vasculature and may promote excessive angiogenesis in VC [17]. Additional conditions associated with VC in some studies are chronic umbilical cord obstruction, maternal alcohol abuse, intrahepatic cholestasis, and multiple pregnancies [18–21].

24.2.4 Gross Findings

Chorangiosis is most frequent in term placentas, especially those above normal weight for gestational age [5, 22]. One abstract described an increase in "less round" placentas (length greater than width) [23].

24.2.5 Histopathology

The diagnosis of VC has traditionally relied on the "rule of tens", as described above. To prevent overdiagnosis, at least 15–20 capillary cross sections should be seen in some villi (Fig. 24.1) [6]. Capillaries in VC are lined by a single layer of flattened endothelium, a continuous linear basement membrane, and lack surrounding pericytes. Unless accompanied by delayed villous maturation, peripheral capillaries in VC form normal vasculosyncytial membranes. VC may involve the entire placenta but, more commonly, has a patchy distribution in the lower two thirds of the placental parenchyma. VC is especially prominent at the periphery of parenchymal sections where capillaries are often dilated, but it is important to look for affected villi in other areas to avoid over diagnosis.

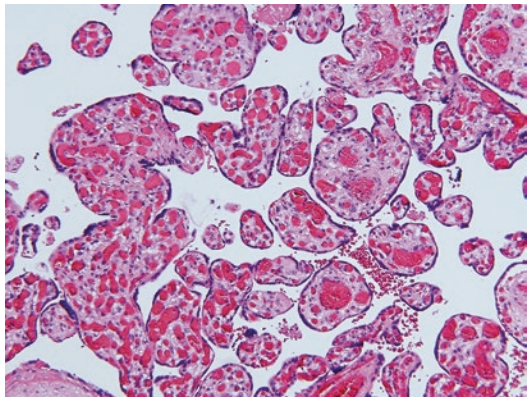

Fig. 24.1 Villous chorangiosis. Terminal villi are expanded by an excessive number of normal capillaries forming vasculosyncytial membranes at areas of juxtaposition with villous trophoblast

VC may coexist with delayed villous maturation, especially with maternal diabetes. Placentas from infants with adverse outcomes often show VC in combination with other lesions. While some cases of multifocal chorangiomatosis (see below) also show VC, the combination of VC and chorangioma in the same placenta is unusual. Focally increased capillaries may be seen in villi adjacent to foci of chronic villitis or fetal vascular malperfusion, but involvement of areas away from the abnormal villi is required for a diagnosis of VC. Mesenchymal dysplasia (seen with androgenetic biparental chimaerism mosaicism (ABMC) and some subtypes of Beckwith-Wiedemann syndrome) is distinguished from VC by abnormal fetal vessels at all levels of the villous tree and chorionic plate, strictly segmental distribution, cystic villi, and villous stromal overgrowth.

24.2.6 Immunohistochemistry and Special Stains

Special stains do not play a major role in the diagnosis of VC. Endothelial cell markers such as CD31 or CD34 are not recommended as they overestimate capillaries relative to the established diagnostic criteria [24]. Smooth muscle actin is negative for pericytes, and reticulin stain shows a continuous basement membrane [6]. Stromal-vascular p57 expression distinguishes VC from ABMC [25].

24.2.7 Genetic Susceptibility

VC is not associated with vascular lesions in the infant or recurrence in subsequent pregnancies. Some molecular subtypes of Beckwith-Wiedemann syndrome that include VC can recur [26].

24.2.8 Prognostic/Predictive Factors

The presence of VC in the placentas of Caucasian (but not African American) women with gestational diabetes is associated with later maternal type 2 diabetes [27]. Some authors have reported a correlation between increased severity of VC and adverse outcomes, but there is at present no grading system [5]. Finally, while more of a structural adaptation than a placental lesion, VC is a useful biomarker for an adverse intrauterine environment that increases the risk of outcomes such as CNS injury [28].

24.3 Multifocal Chorangiomatosis

Note: The term "chorangiomatosis" has been loosely defined in the past and used to describe several unrelated lesions. Examples include "localized or segmental chorangiomatosis" (see next section) and "multiple chorangioma syndrome" (sometimes called "diffuse chorioangiomatosis"), discussed in the final section.

24.3.1 Definition

Patchy to diffuse network of small anastomosing capillaries surrounded by prominent pericytes and stromal cells primarily affecting immature intermediate and small stem villi.

24.3.2 Synonyms

Multifocal chorioangiomatosis, diffuse multifocal chorangiomatosis.

24.3.3 Epidemiology

Multifocal chorangiomatosis (MC) has an incidence of 0.2–0.9% [6, 29, 30]. While most frequent in early preterm pregnancies, it can be seen at any gestational age. Maternal risk factors include advanced maternal age (>35 years), non-African-American ancestry, preeclampsia, and grand multiparity [29]. MC is associated with fetal malformations which may reflect either coexisting placental maldevelopment or a secondary change related to abnormal fetal blood flow, particularly in cases with cardiac anomalies. An anecdotal association with intravenous and/or multiple drug abuse has been noted [6]. MC is associated with preterm delivery, low 5-min APGAR scores, and NICU admission [29, 30]. Infants whose placentas show patchy MC are often small for gestational age, while those with extensive MC are more commonly large for gestational age [29]. Extensive MC is associated with congenital malformations, stillbirth, and neonatal death [29, 30]. In one case report, MC was associated with maternal obesity, luteinized cystic ovarian hyperplasia, and placentomegaly [31].

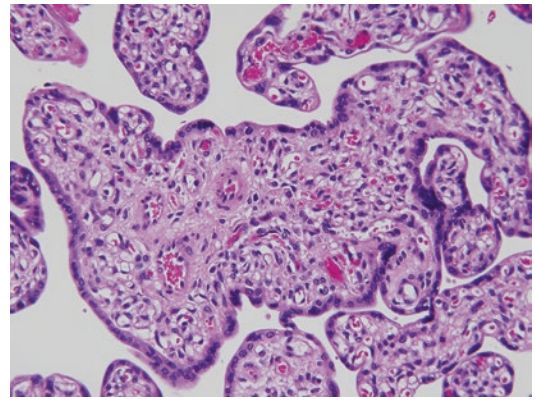

Fig. 24.2 Multifocal chorangiomatosis. Immature intermediate villus with small central muscular vessels surrounded by an excessive number of anastomosing capillaries with associated pericytes in the peripheral paravascular capillary net

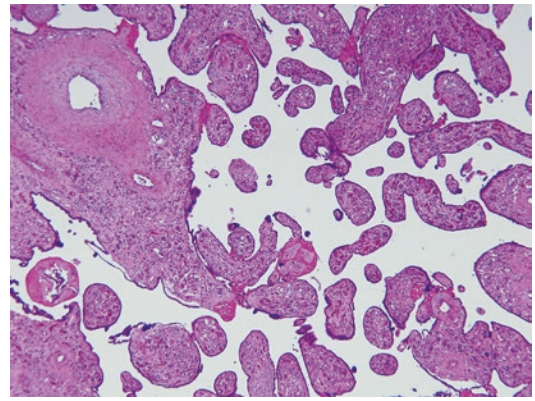

Fig. 24.3 Extensive multifocal chorangiomatosis in a preterm placenta. Stem and immature intermediate villi contain an extensive network of anastomosing capillaries entirely replacing the normal villous stroma surrounding large central vessels

24.3.4 Gross Findings

Placentas in MC are often large for gestational age [6, 29, 31].

24.3.5 Histopathology

MC is characterized by small anastomosing capillaries at the margins of, and in extreme cases throughout, placental stem and immature intermediate villi (Figs. 24.2, 24.3, 24.4). Terminal villi are relatively spared. Often, a large muscularized vessel can be identified within the centre of the peripheral capillary network. At high magnification, MC shares some features with chorangioma including pericytes and discontinuous reticulin fibres but does not form a nodular expansile mass. Unlike villous chorangiosis, capillaries in MC lack a continuous basement membrane [6]. MC has been subcategorized based on the size of the largest focus of involved villi, patchy MC representing cases where all foci are smaller than a 4× microscopic field and extensive MC when some foci occupy more than a 4× field [29].

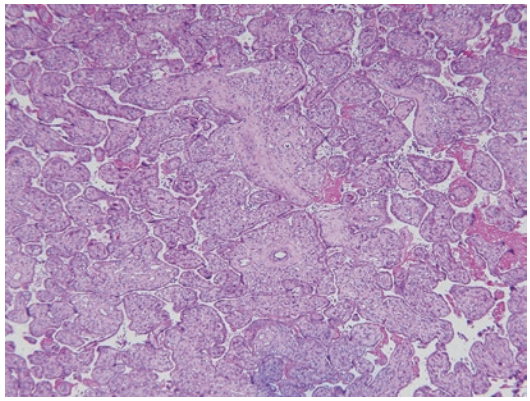

Fig. 24.4 Patchy multifocal chorangiomatosis in a term placenta. The periphery of immature intermediate and small stem villi shows a variably sized network of anastomosing capillaries

Placentas with MC may coexist with VC [6], particularly in term placentas. Other associated findings include fetal vascular malperfusion, delayed villous maturation, fetal arteriolar hypertrophy, villous edema, and dysmorphic villi [29]. One study reported excessive intraplacental extravillous trophoblast (so-called X cell hyperplasia) and stem vessel vasculitis [30].

24.3.6 Immunohistochemistry and Special Stains

While not routinely needed, MC shows smooth muscle actin-positive pericytes and a loose network of reticulin fibres surrounding the anastomosing capillaries [6].

24.3.7 Genetic Susceptibility

None reported.

24.4 Chorangioma (Sporadic)

24.4.1 Definition

It is a benign well-circumscribed nodular lesion composed of fetal capillary vascular channels and supporting stroma, surrounded by trophoblast.

24.4.2 Synonyms

Chorioangioma, placental haemangioma.

24.4.3 Epidemiology

The incidence of chorangioma (CM) is 0.5–1.0% [6, 32, 33]. Small CMs are clinically insignificant. CMs are most common in term or late preterm placentas and are believed to form in response to reduced oxygen tension [34]. Incidence is increased in association with preeclampsia, multiple gestation, and pregnancy at high altitude [6, 35, 36]. Placentas with CM also show a significantly increased incidence of changes related to maternal vascular malperfusion [37]. Increased cellularity, cytologic atypia, and mitotic figures may be seen, but are not considered evidence of malignancy [38]. The term "chorangiocarcinoma" appears in the literature [39–41], but reported cases have not demonstrated malignant behaviour and are probably best described as "chorangioma with trophoblast proliferation" [6, 42]. CM has been associated with an increased incidence of infantile haemangioma in the neonate, raising the possibility of a common underlying genetic abnormality [43]. Large- or intermediate-sized CM (>3–4 cm) can be associated with fetal growth restriction, preterm delivery, and stillbirth [44, 45]. Rare complications of CM include polyhydramnios and fetal hydrops due to high-output heart failure related to arteriovenous shunting [32, 45] and disseminated intravascular coagulation due to platelet sequestration within the CM (Kasabach-Merritt syndrome) [46]. CMs may spontaneously involute in these conditions leading to regression of symptoms [32].

24.4.4 Gross Findings

Most CMs are less than 0.5 cm in greatest dimension and are incidental findings on microscopic examination. Larger lesions can be identified grossly as well-circumscribed, solid, firm nodular lesions most often found just below the

chorionic plate or at the placental margin. Depending on the ratio of the vascular and stromal components, the colour varies from red-brown to tan-white. Degenerative changes, including mineralization and necrosis, may be seen, particularly in larger lesions.

24.4.5 Histopathology

CMs are nodular expansile lesions arising in and protruding from large stem villi. They are composed of an anastomosing network of fetal capillaries, surrounded by pericytes and connective tissue with variable collagenization and cellularity (Fig. 24.5). Infarction, calcification, and haemosiderin deposition can predominate in some CM. CMs are usually surrounded by a single layer of trophoblast. In up to 50% of cases mild, or less commonly moderate, trophoblast hyperplasia may be seen (Fig. 24.6).

Localized (or segmental) chorangiomatosis (so-called "wandering" chorangioma") is clinicopathologically similar to CM, in that it occurs at a similar gestational age, is associated with preeclampsia and multiple gestation, and arises in large stem villi near the chorionic plate or placental margin (Fig. 24.7). This lesion is distinguished from typical CM by extension of the nodular chorangiomatous proliferation into one or more contiguous stem villi [6].

24.4.6 Immunohistochemistry and Special Stains

While not generally required for diagnosis, CD31 or CD34 will stain endothelial cells, smooth muscle actin demonstrates pericytes surrounding vessels, and reticulin stain shows absence of capillary basement membranes [6, 24]. Ki-67 proliferation index is low in the stromal component but may be elevated within areas of trophoblast proliferation.

24.5 Multiple Chorangioma Syndrome

24.5.1 Definition

Multiple chorangiomas (CM) are usually too numerous to count, ranging from early precursor lesions (0.1–0.2 cm) to typical macroscopic CM and occupying up to 80% of the total placental parenchymal volume.

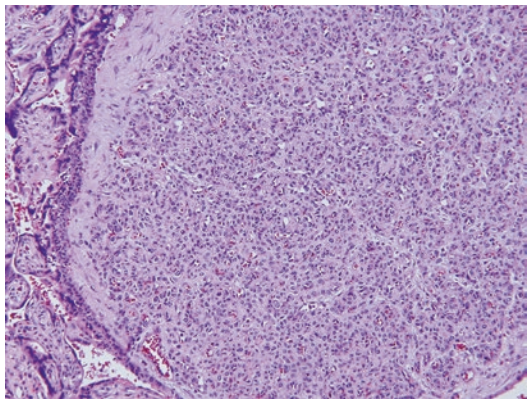

Fig. 24.5 Chorangioma. A nodular tumour-like lesion composed of anastomosing capillaries surrounded by pericytes and fibrous stroma. Surrounding villous trophoblast (left) shows mild nonspecific trophoblast hyperplasia. Adjacent villi are normal

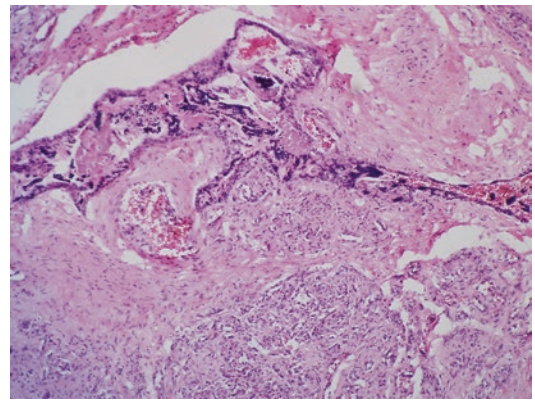

Fig. 24.6 Chorangioma with nonspecific trophoblast hyperplasia. Multinodular chorangioma (bottom) is surrounded by an arcade of hyperplastic villous trophoblast, predominantly syncytial, with focal degenerative changes

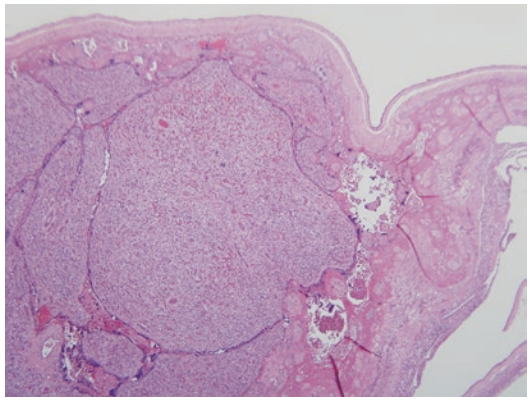

Fig. 24.7 Localized (segmental) chorangiomatosis ("wandering chorangioma"). Multinodular tumour-like lesion located under the chorionic plate at the placental margin with extension into adjacent large stem villi. Histologic features are identical to those seen in typical chorangioma

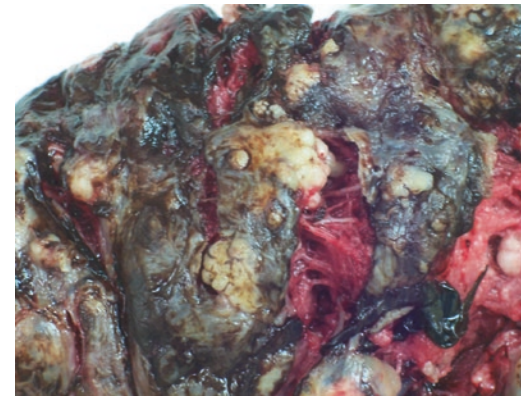

Fig. 24.8 Multiple chorangioma syndrome (macroscopic). Multiple discrete nodular lesions are seen on the basal plate in addition to a less well-defined "cauliflower-like" expansion of some cotyledons (centre)

24.5.2 Synonyms

Placental chorioangiomatosis, diffuse placental chorioangiomatosis.

24.5.3 Epidemiology

First described in 1966 [47], we are aware of a total of 13 cases of multiple CM syndrome, three personally observed in consultation [35, 48–52]. Five of the published cases recurred in subsequent pregnancies. No histologically documented case presented at less than 24 weeks gestation, but at least three additional cases were associated with prior early pregnancy losses.

24.5.4 Gross Findings

Placentas are often enlarged, sometimes exceeding 1000 g. In addition to the numerous typical CM, early lesions may manifest as "cauliflower-like cotyledons" (Fig. 24.8) [51]. Placental parenchyma can be pale and friable when associated with nonimmune hydrops [48].

24.5.5 Histopathology

Individual CM ranges from typical CM (as described in the previous section) to extremely small nodular foci of capillary proliferation with surrounding pericytes (Fig. 24.9). The CM in this syndrome differs from localized chorangiomatosis by virtue of their diffuse distribution, from multifocal chorangiomatosis by their discrete nodular character, and from mesenchymal dysplasia by the lack of associated mesenchymal overgrowth, cystic dilatation, and segmental localization.

24.5.6 Immunohistochemistry and Special Stains

As described above, CD31, CD34, SMA, and reticulin stains can document the chorangiomatous nature of the lesions, but are not necessary for diagnosis.

24.5.7 Genetic Susceptibility

Five cases have been documented pathologically to recur in subsequent pregnancies [35, 52]. One

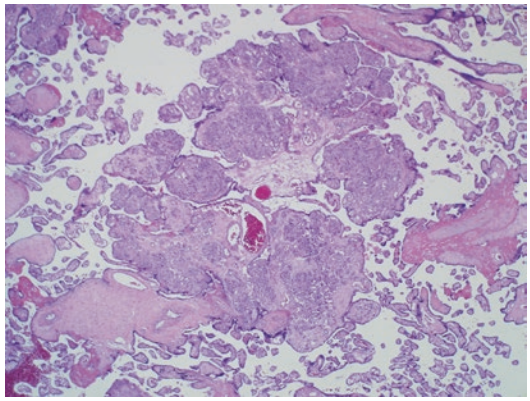

Fig. 24.9 Multiple chorangioma syndrome (microscopic): Numerous small foci of nodular chorangioma-like tissue protrude from a central intermediate-large stem villus. Adjacent villi are normal

study investigating gene expression in a typical case by cDNA array analysis showed increases in several angiogenic growth factors and decreases in several anti-angiogenic factors [52]. No single candidate gene was identified.

24.5.8 Prognostic/Predictive Factors

Multiple CM syndrome is associated with recurrent miscarriage and fetal coagulopathies including cerebral thromboemboli and disseminated intravascular coagulation [35, 48–51]. Cases with adverse outcomes have a higher percentage of placental parenchymal involvement (up to 80%) than those without complications [51].

24.5.9 Future Directions

Outstanding questions regarding the lesions described in this chapter include the following: (1) maternal glucose intolerance, altered IGF expression, and maternal hypoxaemia are all associated with chorangiosis. Whether they all act via a common final pathway is unknown. (2) Chorangioma can be accompanied by fetal vascular lesions and occasionally presents as a lethal recurrent condition. Environmental, genetic, and epigenetic factors explaining these associations are obscure. (3) Multifocal chorangiomatosis has poorly defined relationship with hypoxia, fetal perfusion, and developmental abnormalities. Future efforts should concentrate on better understanding the underlying pathophysiology and separating this entity into more distinct subgroups.

Finally, the lesions described in this chapter represent distinct clinicopathologic phenotypes. However, villous vascularity is a continuous variable, and many authors have observed a subjective increase in capillaries in other conditions that do not meet the diagnostic criteria for the entities described here. Improved quantitative analysis of the vascular architecture in different areas of the placenta with specific disease states may expand the list of definable phenotypes in the future.

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Fetal Vascular Malperfusion

25

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25.1 Introduction and Aetiology

Fetal vascular malperfusion, as outlined in its definition below, encompasses all potential mechanisms of restricted blood flow, and occurring in either direction, along the placental-umbilical-fetal circuit. Although this general concept was touched upon sporadically in the literature in decades long past [1, 2], the momentum for its current state of recognition began more recently [3, 4] with an increasing interest in high-grade fetal malperfusion lesions leading to an increased risk of untoward fetal/neonatal outcome [5–8].

Conceptually, the aetiology of fetal vascular malperfusion can be subdivided into "site of origin" (fetus, umbilical cord, placenta) and the further divided into pathophysiologic mechanisms (see below and Table 25.1).

25.2 Definition

Fetal vascular malperfusion (FVM) is defined as any pathology that is evidence of abnormal perfusion of the placenta from the fetus, and vice versa, in utero. Typically these are due to obstructed blood flow due to a variety of possible aetiologies, for example, anatomic causes (cord accidents, true knots of the umbilical cord, hypercoiled/kinked umbilical cords), thromboembolic causes (e.g. umbilical artery thromboses), vascular damage (e.g. meconium-associated myonecrosis), and inflammatory pathology (fetal inflammatory vasculitides as associated with acute chorioamnionitis or villitis), but it can also be due to slow flow from the fetus, for example, secondary to heart failure or long umbilical cords, or rarely due to a coagulopathy (inherited or acquired). FVM can be identified as a thrombus/embolus, either occlusive or non-occlusive, typically in a large muscularized vessel of the "downstream" effect of obstruction or impaired flow with vascular necrosis or totally avascular villi (see histopathology below). Very acute obstruction of impaired flow from the fetal side may not

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Table 25.1 Aetiology of fetal vascular malperfusion

Fetal
• Congenital cardiac disease [11], e.g.: Ebstein's anomaly[TKB, personal experience]
• Intrinsic fetal hypercoagulability, e.g.: Fetal hyperglycaemia in poorly controlled gestational diabetes mellitus [14, 36] Transient myeloproliferative disorder in trisomy 21 [12] Heritable hypercoagulability [TKB, personal experience]
Umbilical mechanical flow restriction [11, 22, 28, 37, 38], *e.g.:*
• Hypercoiling • Long cord • Abnormal cord insertion • Nuchal/body cord • True knot
Placenta, e.g.:
• Mechanical: Increased placental resistance (e.g., distal villous hypoplasia) [10] • Endothelial damage: Chorionic vasculitis [11, 32] • Altered fetal vascular tone: Meconium myonecrosis [33]
Intrauterine constraints, e.g.:
• Oligohydramnios [10] • Abnormal uterine anatomy[TKB, personal experience]

show any histopathologic footprint but can still be devastating and result in significant fetal morbidity or mortality. The absence of pathological findings does not exclude the possibility of a significant interference of fetal blood flow.

25.3 Synonyms

FVM has previously been termed fetal thrombotic vasculopathy. FVM is the new preferred term as many of the microscopic patterns are not thrombotic in origin. Other terms that fall under FVM are more specific and replace haemorrhagic endovasculitis, endovasculopathy, and fibromuscular sclerosis. *Stem villous obliteration* is applied to proximal muscular (stem, occasionally chorionic) lesions; *villous stromal-vascular karyorrhexis* (VSK) is used for villous capillary involvement. The end-stage pattern of VSK results in *avascular villi*. *Intramural fibrin deposition* has replaced endothelial cushion and intimal fibrin cushion.

25.4 Epidemiology

Categories of fetuses at risk for FVM include fetuses with higher likelihoods of abnormal cord insertion (e.g. multifetal gestations, placenta praevia), [9] fetuses in the setting of maternal vascular malperfusion (e.g., due to oligohydramnios, narrow umbilical cord, abnormal cord insertion), [10] fetuses with cardiac malformations resulting in diminished cardiac output, [11] trisomy 21 fetuses with transient myeloproliferative disorder, [12] and fetuses of diabetic mothers due to a panoply of associated factors such as fetal hyperglycaemia and upregulation of procoagulant molecules [13, 14].

25.5 Gross Findings

Please refer to Chap. 10, Macroscopic Lesions: Fetal Vascular Thrombi.

25.6 Histopathology

In general, FVM is a pathology of the fetal vasculature; therefore the lesion occurs within the fetal vessels anywhere along the fetal vascular territory: umbilical cord, chorionic plate, stem villi, or distal villi. The geography of FVM can be segmental (focal or regional, Fig. 25.1a) or global (Fig. 25.1b). There is also a temporal quality to FVM, as lesions evolve through early-, intermediate-, and end-stage phases. These patterns are useful in determining relevance, especially when FVM is present associated with stillbirth, in so far as FVM can be an antemortem cause or postmortem sequela of fetal demise. The pattern of involvement in favouring one or the other is helpful as temporal and/or spatial heterogeneity would support antemortem pathology, whereas one would expect a global pattern of uniformly timed lesions as a sequela of prolonged in utero retention following stillbirth. In live births, the significance of FVM is related to its extent, which is reflected by lesion grade (Table 25.2).

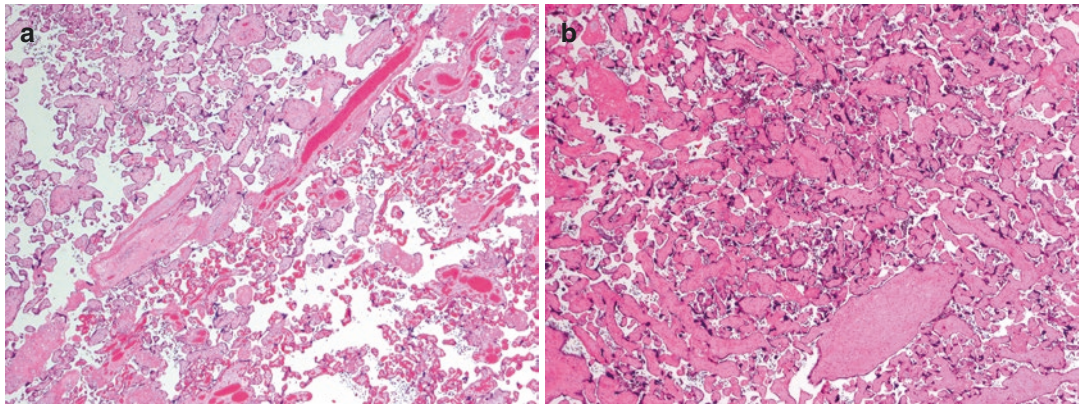

Fig. 25.1 (**a**) Regional avascular villi (left). (**b**) Global avascular villi

Table 25.2 Grading fetal vascular malperfusion

Grade	Definition
Low grade	
Muscular vessel thrombi	1 large vessel thrombus (mural or occlusive)
Capillary level changes	≥5 villi involved in <3 foci
High grade	
Muscular vessel thrombi	≥2 large vessels thrombi (mural or occlusive)
Capillary level changes	>1 focus cumulatively ≥45 involved villi

FVM presents in two major patterns: muscular vessel thrombi and capillary level changes.

1. Muscular vessel thrombi:
   FVM may be manifest as true intravascular thrombi/emboli as one would diagnose in any other organ. These generally are evidenced as occlusive or non-occlusive thrombi in one or more of the larger muscularized vessels in the placenta (umbilical vessels, chorionic plate or stem villous vessels). Non-occlusive thrombi are by far more common than those that fully obliterate the vessel lumen. These thrombi can be subdivided into temporal evolution phases.
   (a) Recent
   Confident identification of recent muscular thrombi requires intravascular fibrin that has adhered, at least focally, to the vessel wall, with resulting loss of endothelial integrity and with red cell extravasation into the subendothelial wall (Fig. 25.2).
   (b) Organizing
   Organizing mural thrombi exhibit fibroblast ingrowth into the adherent fibrin clot, resulting in development of a myofibroblastic "neointima" (Fig. 25.3).
   (c) Organized
   Fully organized thrombi are comprised of a neointima that fully envelops residual incorporated fibrin (Fig. 25.4).
   The microscopic patterns of organizing and organized chorionic or stem vessel thrombi generically fall under the rubric of intramural fibrin deposition. It is worth noting that intramural fibrin deposition is not necessarily a consequence of in situ thrombosis, as there is experimental evidence, and some authors believe this microscopic phenotype can result from any form of repaired endothelial damage—not strictly secondary to thrombosis – in which fibrin insudation is incorporated into the vessel wall. See further discussion below (under "3. Other forms of FVM").
   (d) Remote
   Remote thrombi are those that, in addition to organization, exhibit mural dystrophic calcification. These thrombi, the least common of the temporal patterns, likely occurred at least weeks prior to delivery (Fig. 25.5).

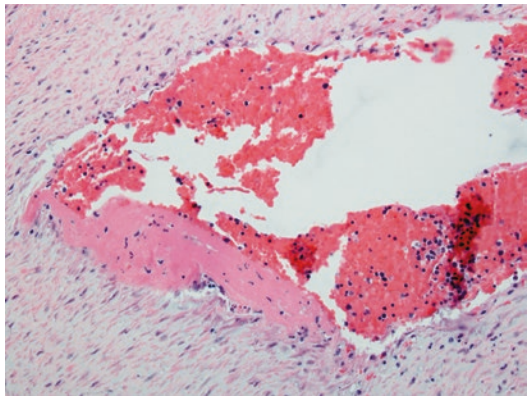

Fig. 25.2 Stem villus thrombus, recent, with adherent fibrin and erythrocyte extravasation into the subendothelial vascular wall

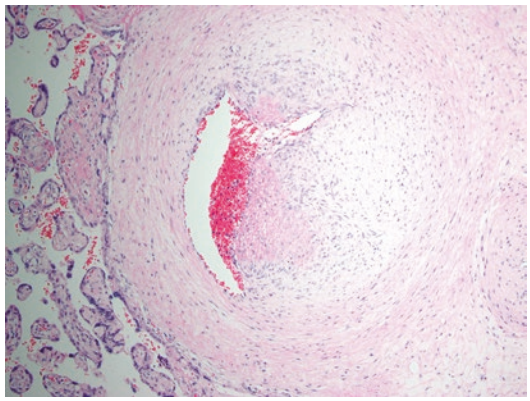

Fig. 25.3 Stem villus thrombus, organizing, with fibrin incorporation into the neointima; there were multifocal FVM features elsewhere

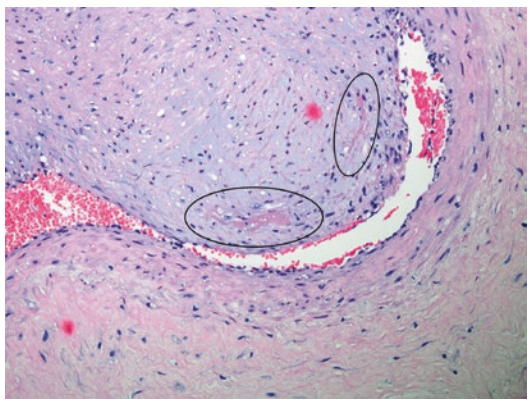

Fig. 25.4 Chorionic plate thrombus, organized, with residual fibrin fully incorporated within the neointima; there were multifocal FVM features elsewhere

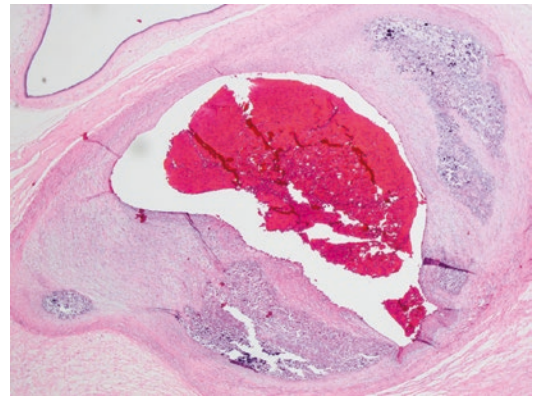

Fig. 25.5 Chorionic plate thrombus, remote, with extensive mural dystrophic calcification

2. Capillary level changes:
   (a) FVM is typically evident only in the distal villi, without finding the "upstream" obstructive event. These changes also have a temporal evolution pattern, with more recent FVM showing a different histopathology than remote FVM. It is generally believed that with obstruction of fetal blood flow to the distal villi, there are ischaemic changes that occur from the "inside out," meaning starting at the vascular endothelium and then progressing to the villous stroma. As maternal perfusion is unaffected, villous trophoblast remains viable, impervious to intravillous changes. With early capillary flow cessation and resulting ischaemia, the endothelium sloughs into the vessel lumen with loss of vascular integrity and with extravasation and fragmentation of fetal red blood cells into the villous stroma (Fig. 25.6). Both endothelial and stromal karyorrhexis ensue. An earlier widely used term for this microscopic pattern was haemorrhagic endovasculitis; however, in current nomenclature the preferred term is villous stromal-vascular karyorrhexis. As the time between fetal flow cessation and placental delivery lengthens, there is progressive stromal collagen deposition (fibrosis), eventuating in vessel obliteration. The end-stage pattern of this process is termed avascular villi (Fig. 25.7).

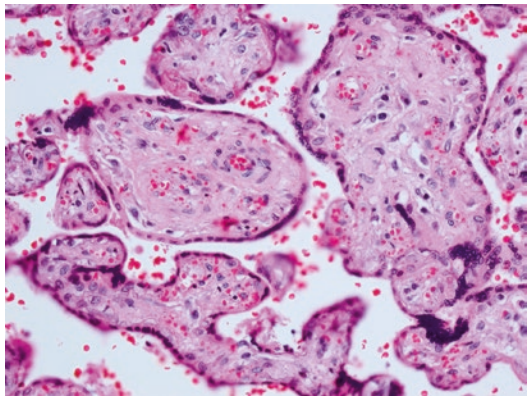

Fig. 25.6 Villous stromal-vascular karyorrhexis, intermediate stage, with capillary dissolution and erythrocyte extravasation and fragmentation

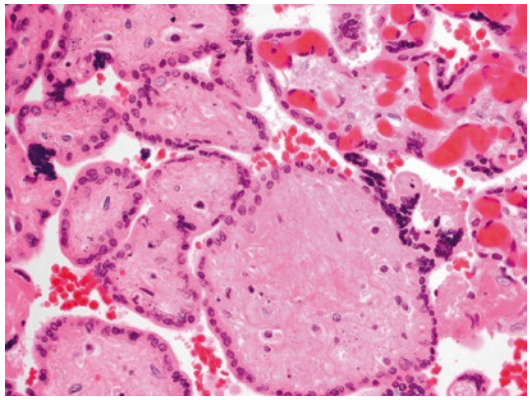

Fig. 25.7 Avascular villi with stromal collagenization and residual karyorrhectic debris

(b) A second capillary process is one termed delayed villous maturation, formerly called placental maturation defect and distal villous immaturity. The microscopic phenotype is of relatively immature villi for gestational age that are rounded, with reduced syncytial knots and most importantly with centrally placed capillaries that fail to abut the trophoblast basement membrane (so-called reduced vasculosyncytial membranes). Often the capillaries appear "hypoplastic" (i.e. of diminished luminal calibre) and reduced in number, and the villous stroma may contain nuclear debris, reflecting piecemeal dissolution of capillary integrity (Fig. 25.8a, b). Individual avascular villi may be admixed, in which all capillaries within a villus eventually involute (Fig. 25.9a, b). This pattern has been associated with maternal diabetes, umbilical hypercoiling and late intrauterine demise [15–17]. In the setting of fetal vascular malperfusion, this phenotype reflects fetal blood flow into the distal villi but at a reduced flow velocity. In the context of FVM, the specific aetiologies of delayed villous maturation can include all of those that predispose to fetal vascular malperfusion. It is important to underscore that, to date, published literature in support of delayed villous maturation as a phenotypic pattern of fetal vascular malperfusion is scant.

3. Other forms of FVM:
   Other lesions in the category of FVM do not neatly fit into these two broad classifications.

(a) Stem vessel obliteration (also known as fibromuscular sclerosis, stem vessel endovasculopathy).
   This is a lesion of the larger stem and occasionally chorionic villous vessels in which there is progressive luminal obliteration by fibroblastic ingrowth (Fig. 25.10). Early and intermediate changes can include fetal red blood cell extravasation and fragmentation into the vessel wall (Fig. 25.11); luminal septation, giving the appearance of "recanalization" (Fig. 25.12); and apparent mural hypertrophy. This pattern is the result of fetal blood flow cessation into or out of the affected vessel. In turn, this can result in cessation of blood flow distally and thus lead to the above-described capillary level villous changes.

(b) Intramural fibrin deposition (also known as intimal fibrin cushion).
   In this lesion, there is myofibroblast proliferation resulting in a bulbous protrusion of myxomatous stroma into the lumen of the affected vessel. This is usually seen in stem villous vessels but can be seen in any large fetal muscular vessel in the placenta. To make the diagnosis, one must also see either subendothelial or intramuscular fibrin deposition (Fig. 25.13). By definition, this lesion is non-occlusive. If global this

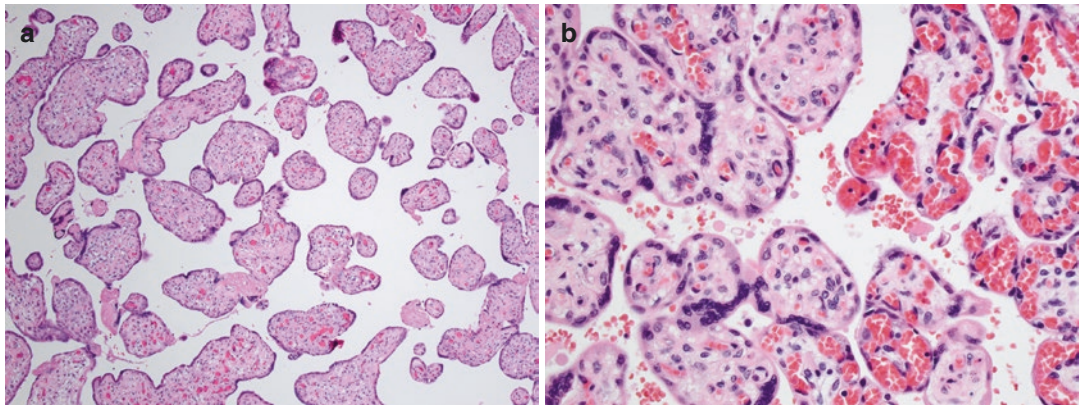

Fig. 25.8 Delayed villous maturation, with relatively immature chorionic villi and centrally placed "hypoplastic" capillaries (i.e. of diminutive luminal calibre); (a) medium- and (b) high-power fields

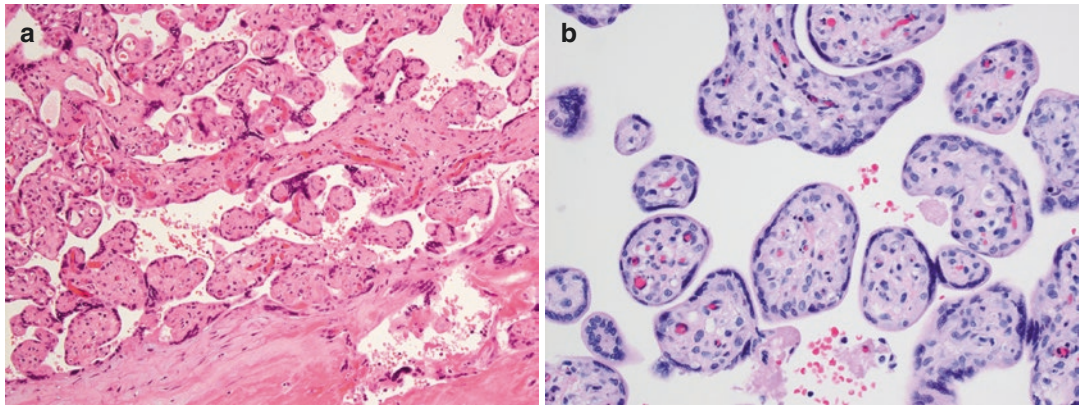

Fig. 25.9 Delayed villous maturation with scattered avascular villi; (a) medium- and (b) high-power fields

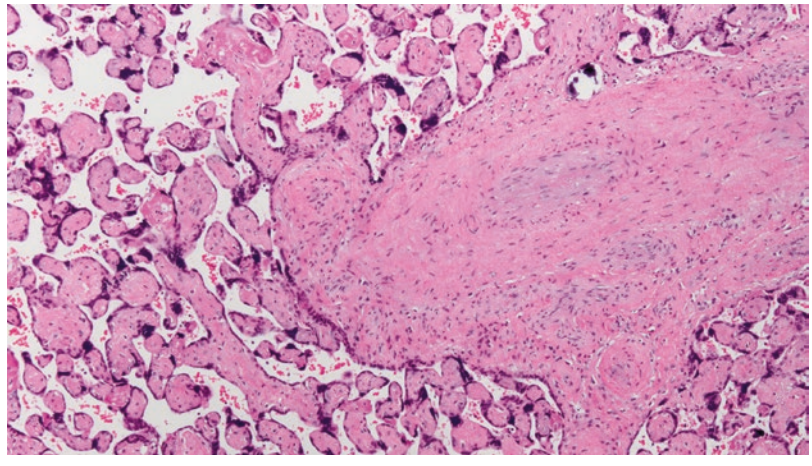

Fig. 25.10 Stem villous obliteration, fully developed, with complete luminal replacement; note associated avascular villi

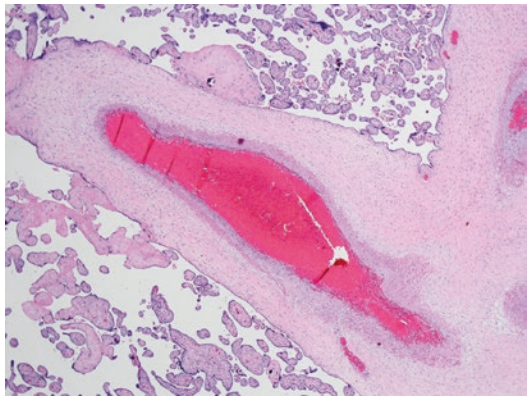

Fig. 25.11 Stem villous obliteration, recent, with loss of endothelial integrity and subendothelial erythrocyte extravasation

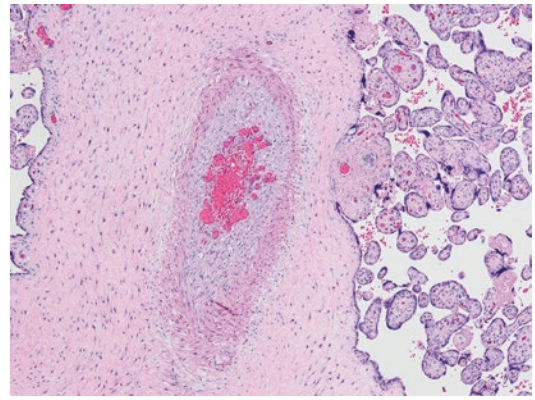

Fig. 25.12 Stem villous obliteration, intermediate, with intraluminal bland fibroblast ingrowth imparting septation that appears as "recanalization"

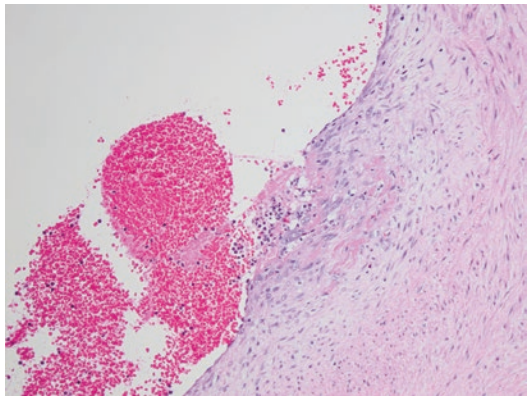

Fig. 25.13 Intimal fibrin deposition, organizing, with active fibrin incorporation into the neointima

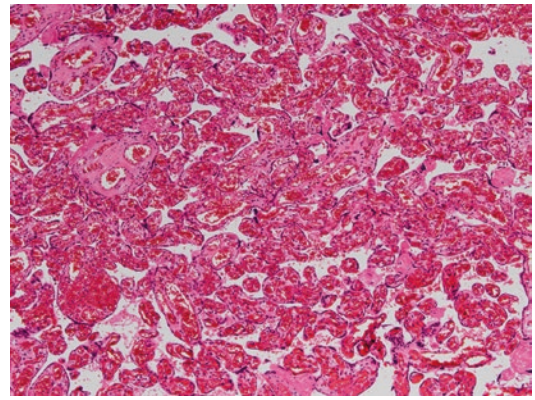

Fig. 25.14 Acute intravillous haemorrhage, a consequence of abrupt extravasation of largely intact erythrocytes into the villous stroma

is likely a result of upstream occlusion, as in umbilical vascular FVM. If isolated (one or two lesions) the significance of the finding is unclear.

(c) Intravillous haemorrhage

With sudden complete large vessel venous occlusion, the back pressure may result in rupture of the small capillaries in the distal villi, resulting in acute stromal haemorrhage termed intravillous haemorrhage (Fig. 25.14). This is not a specific finding as it can be seen due to other causes, e.g. acute placental abruption, vacuum dilatation and evacuation, difficult manual extraction of the placenta, and caesarean section. Intravillous haemorrhage is usually patchy, and, in circumstances of mechanical separation of the placenta from the uterine wall (i.e. above-noted placental abruption, etc.), this pattern is usually basally or parabasally located. When secondary to acute upstream venous (e.g. umbilical cord) obstruction, the pattern is more widespread and oriented toward the chorionic rather than the basal plate.

(d) Additional supportive histology

There are other features that support FVM, although are not diagnostic of such, and include marked vascular ectasia. This is a finding usually restricted to the large muscularized vessels and is characterized as marked dilatation of the vessel compared to the surrounding similar sized vessels. The

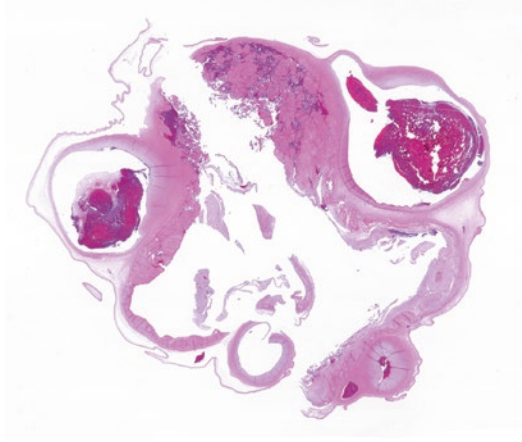

Fig. 25.15 Chorionic vascular ectasia; distended vessels are >4× the luminal calibre of adjacent unaffected ones

diagnosis can be made when the vascular ectasia is at least four times the luminal diameter of corresponding vessels (Fig. 25.15).

25.7 Microscopic Differential Diagnosis

1. Fetal demise
   The changes of fetal vascular malperfusion develop when fetal blood flow to the placenta significantly diminishes or ceases. After fetal death, fetal perfusion of the placenta ceases, and the changes of fetal vascular malperfusion develop throughout the placental parenchyma. Genest and colleagues described the sequence and extent of stem villous and distal villous changes that correlate with the in utero demise to delivery interval. In assessing cause of fetal demise, correlation with evidence of acute or chronic obstruction of fetal blood flow before death is essential. True thrombi do not form in the fetal vasculature after death. Global changes of FVM must be interpreted with caution in fetal demise >48 hours.
2. Fibrinoid necrosis of individual villi
   Replacement of the syncytiotrophoblast by fibrinoid is seen underneath the chorionic plate and along proximal stem villi with full placental maturation (Langhan's stria). A similar change affects small populations (<10%) of distal villi termed fibrinoid necrosis of individual villi with fibrinoid deposition both outside and inside the villus. Small groups of adjacent terminal villi with fibrinoid necrosis can be hard to distinguish from small foci of avascular villi due to FVM. Villi affected by fibrinoid necrosis may be only partially avascular, with the portion beneath the fibrinoid deposition affected first. Evidence of fibrinoid deposition should be present at least focally to distinguish this change from FVM. Unlike FVM, this process does not affect larger groups of villi [18].
3. Villous stromal-vascular karyorrhexis and avascular villi secondary to chronic villitis
   Chronic villitis may be associated with inflammation and involution of vessels in affected villi, impairing blood flow to more distal villi. The more proximal the chronic villitis, the more extensive the associated changes of FVM. While the pathophysiology is the same at the level of the cotyledon, these changes are not termed FVM [19].
4. Villous stromal-vascular karyorrhexis and avascular villi adjacent to intervillous thrombi or infarcts
   Foci of VSVK and/or AV may be seen adjacent to recent and remote intervillous thrombi, possibly related to effects of fibrin/fibrinoid deposition [20]. These changes are not termed FVM. Similarly, villi adjacent to infarcts may be seen and are considered collateral damage associated with the infarct, possibly from infarction of proximal villi.
5. Villous stromal karyorrhexis in foci of villous agglutination
   Acutely ischaemic villi in foci of villous agglutination frequently show VSK. This change is not considered FVM.
6. Stem villous vascular changes of uncertain significance
   Stem villous vessels may show significant variation between placentas. The vessels may appear thickened or stenotic, as described in chap. 2. These changes can be striking at low power, but in isolation they are not part of the constellation of changes attributed to fetal

vascular malperfusion at this time. Stenotic lumens may be seen in regions of accelerated maturation or distal villous hyperplasia. When extensive, these changes may be associated with fetal growth restriction and reduced or absent end-diastolic volume on umbilical cord Doppler studies [21, 22]. True thrombi may be seen in this setting, diagnostic of fetal vascular malperfusion, likely secondary to increased resistance to fetal perfusion.

25.8 Genetic Susceptibility

Genetic susceptibility to fetal vascular malperfusion due to hereditary hypercoagulability is uncommon, without a body of literature for support, but rather is restricted to isolated cases based on personal experience.[TKB, personal experience] In these rare circumstances, affected fetuses are either homozygous or compound heterozygotes.

Cases of subsequent pregnancies with recurrent fetal demise due to recurrent long and hypercoiled umbilical cords [23, 24] and due to recurrent nuchal cords[TKB, personal experience] have been reported. These cases beg the question of whether there is an underlying genetic or intrauterine environmental predisposition to excessive intrauterine fetal activity, which has long been asserted as a necessary mechanism in the evolution of long, hypercoiled, and nuchal/body cords.

25.9 Prognosis and Predictive Factors

Fetal vascular malperfusion is associated with a wide variety of untoward fetal/neonatal outcomes: stillbirth, various forms of neurodisability including cerebral palsy and perinatal stroke, fetal growth restriction, intestinal atresia, and perinatal liver disease [4, 6, 7, 11, 25–33].

Recent publications regarding the various histologic features of fetal vascular malperfusion have strived to stratify lesions with respect to high- vs. low-grade categories [5] with particular emphasis on lesions we now classify as high grade that bear an increased risk of untoward fetal/neonatal outcome [4, 6–8, 23, 34].

Potential recurrence risks are uncommon and as explained elsewhere include persistent/recurrent parental, maternal, and intrauterine conditions: hereditary hypercoagulability, poorly controlled maternal diabetes, chronic maternal vascular disorders associated with maternal malperfusion, anatomic uterine abnormalities, and recurrent umbilical hypercoiling or nuchal/body cords.

Recognition of fetal vascular malperfusion, particularly when high grade, has important medicolegal implications in pregnancies with unexpected untoward fetal/neonatal outcome [35]. Absent circumstances of acute catastrophic disorders (e.g. complete placental abruption following a motor vehicle accident), most pathologic placental processes present in medical malpractice cases are those of more prolonged evolution, with fetal vascular malperfusion chief among them. This is not to say that in any given case of live birth fetal malperfusion is *causative* of the outcome, which must be determined clinically, but rather that at a minimum its effect reduces the fetal threshold for tolerating additional intrauterine/intrapartum stressors.

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Presence of Nucleated Red Blood Cells

26

Marta C. Cohen and Theonia K. Boyd

26.1 Introduction

Nucleated red blood cells (nRBCs) first develop in blood islands of the yolk sac at 16–20 days of gestation [1]. Recent research has demonstrated that the first embryonic area to contain haematopoietic stem cells is the aorta-gonad-mesonephros region [2]. Embryonic bipotential stem cells are a common haemangioblast progenitor to vascular and hematopoietic elements [2–4]. A second wave of haematopoiesis originates from definitive progenitors in the yolk sac, which undergo differentiation in the liver [2]. Cell production then takes place in the liver and spleen and eventually in the bone marrow [1]. In the fetus, nRBCs contain haemoglobin tetramers (HbF) which allow the developing fetus to extract oxygen with greatest efficiency from the maternal blood.

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26.2 Definition

nRBCs are normal erythrocyte precursors. Once the nucleus has been extruded off the nRBC, the cell enters the peripheral blood as a reticulocyte.

26.3 Synonyms

Erythroblasts, normoblasts, or normocytes [5].

26.4 Epidemiology

According to multiple studies, the relative and absolute values of nRBCs at birth in healthy term newborns vary within certain ranges, given a number of parameters (mean, median, and average values; umbilical vs. first neonatal blood draws; etc.). Under normal neonatal circumstances, their numbers rapidly decrease and disappear by several days of postnatal life [5].

With respect to normative relative nucleated red blood cells counts, reported mean, median, and average values range from 0.3 to 8.6 nRBCs/100 WBCs, with a range of 0–89 nRBCs/100 WBCs. With respect to absolute nucleated red blood counts, the mean value of nRBCs at birth in healthy term newborns is equally varied, from 0.4 to 1.0 nRBCs/10^9 WBCs, with a range of 0–8.5 nRBCs/10^9 WBCs [5–10].

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In fetuses and newborns, increased nRBCs in the peripheral blood, and therefore the fetal vessels of the placenta, can be seen in abnormal clinical situations related to:

- Acute stress release: namely, acute hypoxia, mediated via fetal hormonal stimulation [11]. This can occur within an hour after the hypoxic event, through release of pre-existing fetal hepatic and marrow) stores.
- Subacute stress release: e.g. subacute hypoxia and chorioamnionitis, mediated via fetal hormones, interleukins and erythropoietin-mediated fast-track signaling [12–16].
- Increased erythropoiesis: through increased production of erythropoietin and release of immature erythropoietic elements, culminating in erythroblastosis. Circumstances are those of chronic stimuli in which fetuses adapt to ongoing and progressive stress: anaemia (blood loss, haemolysis, Rh isoimmunization), maternal diabetes, TORCH infections and, rarely in developed economies, conditions of severe maternal vascular malperfusion (hypertensive maternal vascular diseases, some forms of maternal autoimmunity). As an aside, in maternal diabetes, the increased nRBCs probably also involves a direct haemopoietic effect of hyperinsulinemia. Interestingly, large for gestational age infants have higher nRBC counts than those of appropriate size for gestational age [17].
- Post-natal hypoxia.
- Others: transient myeloproliferative disorder in trisomy 21, idiopathic.

With respect to nucleated red blood cell counts in circumstances of abnormal fetal/neonatal presentations at term, reported mean, median, and average relative values range from 1 to 86 nRBCs/100 WBCs, with a range of 0–732 nRBCs/100 WBCs [12, 18–27]. With respect to absolute nucleated red blood counts in term neonates with abnormal ante- and/or neonatal presentations, the mean, median, and average values are equally varied, from 0.2 to 25.7 nRBCs/10^9 WBCs, with a range of 0–43 nRBCs/10^9 WBCs [19, 22, 23, 25, 26].

26.5 Histopathology

When nucleated red blood cells (nRBCs) are released into the fetal circulation, the most mature lineage is released first followed, should the inciting stimulus continue, by progressively more immature forms. If the stimulus persists for a prolonged period (weeks), erythroblasts will enter the circulation, resulting in erythroblastosis fetalis.

The histology of nRBCs at various stages of maturation is standard to fundamental haematopathology. Generally speaking, the more mature the precursor, the denser the chromatin and the less basophilic the cytoplasm (see Fig. 26.1).

For reference:

- Orthochromatic erythroblast (late normoblast; 7–10 μm) (by contrast, a mature erythrocyte is 7–8 μm).
- Polychromatophilic erythroblast (intermediate normoblast; 10–15 μm).
- Basophilic erythroblast (early normoblast; 14–17 μm).
- (Pro)erythroblast (15–20 μm).

nRBCs are present in the placental vessels through the first half of pregnancy but are not readily visible later in pregnancy [5]. There is good correlation between the number of nRBCs

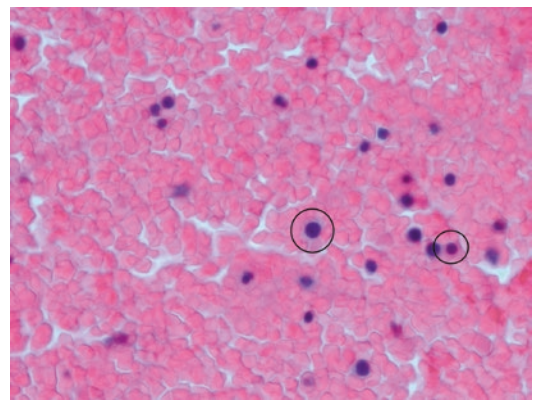

Fig. 26.1 Circulating nucleated erythroid precursors, umbilical vessel. Polychromatophilic erythroblast (left circle; slightly less mature nRBC) and orthochromatic erythroblast (right circle; most mature nRBC)

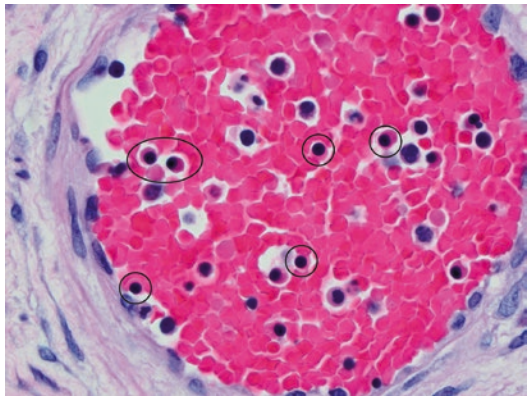

Fig. 26.2 Circulating nucleated erythroid precursors, stem villus vessel. Multiple orthochromatic erythroblasts (several circled)

in the placental fetal vessels within the chorionic villi and in the umbilical cord blood; therefore umbilical nRBCs can be used as a proxy for nRBCs elsewhere in the fetal circulation of the placenta [28, 29]. According to a few studies, at term 10 or more nRBCs per 10 high-power fields in chorionic villi correlate with increased umbilical cord and neonatal blood counts, fetal hypoxia and an increased risk of cerebral palsy and other forms of neurologic injury (see Fig. 26.2) [28, 29]. nRBCs were seen in all placentas of acidotic infants (cord pH < 7.0), but the usefulness of this finding as an indicator of acidosis is diminished by the presence in placental sections from infants with cord pH > 7 [30]. It is important to underscore the variability in normative term neonatal nRBC levels among a variety of studies using various terminologies.

26.6 Prognosis and Predictive Factors

A multitude of manuscripts have been published regarding the presence of nRBCs in the neonatal and/or fetoplacental circulation in relation to various parameters of outcome, particularly with respect to neurologic impairment. The literature is complicated by many factors: relative vs. absolute nRBC values, term vs. preterm infants, growth-restricted vs. non-growth-restricted infants, varying postnatal treatment methodologies (e.g. selective hypothermia), short- vs. long-term neurologic assessments, and utilizing various measures of neurologic injury (e.g., clinically diagnosed hypoxic ischaemic encephalopathy, neuroradiologic imaging at differential postnatal ages, types of somatic palsies and developmental delays). Limited studies involve placental pathology; most do not.

As a general statement, at term the majority of placentas associated with neurodisability in live births demonstrate in utero pathologic processes that antedate the intrapartum period. These processes usually incite elevated circulating nRBCs, with the notable exception being those processes of acute catastrophic origin. Higher nRBC values, and prolonged clearance times, are also associated with an increased risk of longstanding neurologic sequelae [27]. Having stated these generalities, the timing of intrauterine process that manifests in placental pathology, and the extent of nucleated red blood cells, does not time nor equate with the onset of neurologic injury. Neurologic injury must be timed clinically, a pivotal concept in the realm of medical malpractice [23, 25, 31–33].

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Fetal Vessels: Malignancy

27

Marie-Anne Bründler and Adrian K. Charles

27.1 Introduction

Placental involvement by fetal malignancies is extremely rare. Haematogenous spread of a fetal malignancy (neuroblastoma) to the placenta was first documented by Strauss and Driscoll in 1964 [1]. To date fewer than 50 cases have been reported in the literature [2–6]. About half are neuroblastoma and one third leukaemia or transient myeloproliferative disorder. The remainder include hepatoblastoma, malignant rhabdoid tumour, primitive neuroectodermal tumour and congenital malignant melanoma.

27.2 Definition

Placental dissemination of a congenital malignant fetal solid tumour, transient myeloproliferative disorder or leukaemia with tumour cells identifiable in chorionic vessels. In addition, stromal invasion and extension of neoplastic cells into the intervillous space may be seen.

27.3 Synonyms

None applicable.

27.4 Epidemiology

Placental involvement by fetal malignancies is extremely rare.

27.5 Gross Findings

Tumour nodules and other focal lesions, including infarcts and chorionic vascular thrombosis, are only sporadically identified in fetal malignancies spreading to the placenta [6–8]. Placentomegaly, villous hydrops and concomitant fetal hydrops are observed in >50% of cases but may also develop without placental tumour involvement [9].

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27.6 Histopathology

Involvement of fetal vascular spaces by neoplastic cells is a consistent finding. Villous stromal invasion and extension into the perivillous space, on the other hand, are uncommon particularly in neuroblastoma. Of the 33 cases reviewed by Dai et al. [2], 8 cases (25%) showed tumour cells invading the villous stroma including 1 case of neuroblastoma. Extension to the perivillous space was seen in only three cases (9%), not including neuroblastoma. Neuropil and rosette formation may be seen in neuroblastoma (Fig. 27.1). An epithelial morphology and large atypical cells with a rhabdoid morphology may be appreciated in hepatoblastoma and rhabdoid tumours, respectively. Increased numbers of circulating nucleated red cells are common in neuroblastoma and variably present in other solid tumours, transient myeloproliferative disorder and congenital leukaemia. In the latter two, circulating myeloblasts (Fig. 27.2) or lymphoblasts typically are present. The blasts in transient myeloproliferative disorder characteristically exhibit megakaryoblastic differentiation. In rare instances, choriovascular involvement by a myeloproliferative disorder may mimic a benign choriovascular inflammatory disorder, such as chorioamnionitis [5]. Deposits of melanocytic cells in chorionic vessels and the villous stroma were documented in a rare case of metastatic congenital malignant melanoma and several cases of congenital giant melanocytic naevi [10–13]. The latter are thought to derive from abnormal neural crest migration. Contrary to metastatic maternal malignant melanoma, the intervillous space is not involved.

Other benign heterotopic tissues occasionally identified in placental villi include nodules of adrenal cortical and liver cell nodules (Chap. 37) [14, 15]. Fetal erythroblastic reactions from infection or stress reaction moreover can mimic fetal leukaemias.

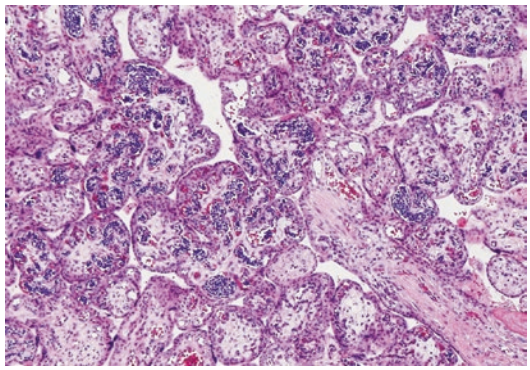

Fig. 27.1 Fetal neuroblastoma: Chorionic villi showing cohesive clusters of small round blue tumour cells in villous capillaries (Courtesy of Dr. Rebecca Baergen, New York, USA)

27.7 Immunohistochemistry

Immunohistochemistry is used to confirm the respective tumour cell lineage.

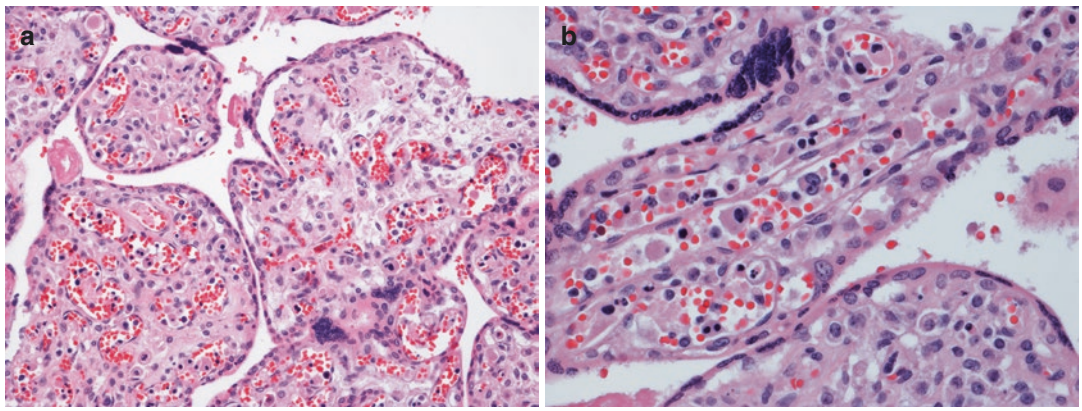

Fig. 27.2 Transient myeloproliferative disorder: Atypical myeloid cells showing megakaryocytic differentiation are identified in chorionic villi which are enlarged and hypervascular

27.8 Genetic Susceptibility

Trisomy 21 for transient clonal myeloproliferative disorder and congenital leukaemia [16].

27.9 Prognosis and Predictive Factors

Placental dissemination of neuroblastoma in most reported cases is associated with fetal hydrops and stage IV disease [1–4]. Hepatic involvement is a consistent finding due to the venous return of blood from the placenta to the liver. Placental involvement in neuroblastoma and other solid tumours, including hepatoblastoma and malignant rhabdoid tumour, is associated with a high rate of stillbirth, in the late second and third trimester, and early post-partum death. Only three patients with neuroblastoma are reported to have survived beyond early infancy [4, 17]. Maternal complications of disseminated neuroblastoma include mirror syndrome and catecholamine induced hypertension [18, 19]. Spontaneous remission and survival beyond infancy are more likely in cases with myeloproliferative disorders [2, 14].

Besides choriocarcinoma, there are very rare reports of fetal malignancies, including leukaemia, entering the maternal circulation (intervillous space), though these appear not to engraft or result in clinically manifest disease in the mother [2, 7, 20]. The case reported by Nath et al. likely represents direct uterine spread of a congenital primitive neuroectodermal tumour from the fetus after vaginal delivery [21].

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Acute Villitis

28

Adrian K. Charles

28.1 Introduction

Isolated acute villitis is uncommon and much less frequently seen than chronic villitis. It may be seen as part of haematogenously spread pathogen with maternal sepsis, most commonly seen in listeriosis, but also may be seen with other blood borne pathogens (usually bacterial). An acute inflammatory response may be seen as part of a severe villitis with necrosis due to a maternal reaction (villitis of unknown aetiology, VUE) or a viral aetiology, and placental infarcts may be associated with a significant inflammatory reaction involving the villi. It may be seen in severe bacterial intra-amniotic infection where the sepsis secondarily involves the maternal space, as well as the chorionic plate or the extraplacental membranes possibly by extension of the maternal inflammatory reaction seen on the chorionic plate down the roots of the stem villi. It may reflect fetal sepsis with bacterial spread to the villi by the fetal vasculature without maternal bacteraemia [1]. It may be seen in the haemorrhagic area seen as part of placental marginal separation changes with fibrin and an acute inflammatory reaction and in septic abortions. It has been associated with a poor fetal outcome due to bacterial infections, including Group B streptococci, *Klebsiella* [2], *E. coli*, *Campylobacter*, and *Haemophilus*, and has been described in tuberculosis and syphilis. Some viral infections such as vaccinia and herpes simplex may be associated with a necrotising villitis with neutrophils. *Coxiella* may show a necrotising villitis, and malaria also shows a villitis with intervillositis with neutrophils (more in P. vivax) but also histiocytes and pigment [3].

Acute villitis is briefly discussed in major textbooks of placental pathology. It is best regarded as a morphological pattern usually seen in association with other pathology (unlike chronic villitis where the villitis is the key feature and the differential usually due to maternal immune reaction—VUE or viral infection).

Ideally, microbiological investigations may have been taken from the placenta in cases with maternal symptoms or prematurity. If acute villitis is seen, organism stains for bacteria, acid-fast bacilli, and spirochaetes are worth considering, with review of the chart and other microbiological investigations on the mother and infant/fetus. Molecular techniques may also be used. Timely placental pathology results can be very useful for both maternal and neonatal care if the offspring is alive.

In many jurisdictions identifying listeria and syphilis are notifiable diseases and may initiate public health review.

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28.2 Definition

Infiltration of the chorionic villi with acute inflammatory (neutrophils) cells deep to the trophoblast and villous basement membrane and not in continuity with the chorionic plate with chorioamnionitis nor adjacent to infarcts or severe villitis lesions. The neutrophils may be of maternal or fetal origin.

28.3 Gross Findings

Usually no change, possibly congestion or haemorrhagic appearance of the placenta. Marginal haemorrhage may be seen in cases associated with chorioamnionitis. The placenta may be malodorous and have opaque or greenish membranes. Listeria may show as small pale areas in the parenchyma.

28.4 Histopathology

The pattern varies according to the aetiology. With ascending infections there is chorioamnionitis, usually with a fetal reaction, and evidence of involvement of the maternal blood space with neutrophils often in collections and often aggregates of fibrin. The maternal blood may show increased neutrophils as part of the septic reaction. There is often some degenerative change of the villous trophoblast, with neutrophil invasion through the trophoblast layer and the basement membrane (Fig. 28.1). The neutrophil reaction may be more central suggesting a fetal response to fetal septicaemia [4]. Acute villitis is currently neither graded nor staged.

With listeria there are small abscesses scattered through the placenta in the intervillous space involving the villi. This may be associated with villous necrosis and, often, chorioamnionitis. In listeria or tuberculosis, there may be patchy inflammation with macrophages and a granulomatous appearance (Fig. 28.2). Tuberculosis in the early stages may have acute non-granulomatous villitis [5], with histiocytes, and there may be a chorioamnionitis [6].

Syphilis may show small abscess with acute villitis as well as part of the triad with chronic villitis and chorioamnionitis. The complete triad is only seen in some cases [7, 8]. An enlarged placenta, immature appearing villi and plasma cell deciduitis may also be seen.

28.5 Immunohistochemistry

Immunohistochemistry or other techniques may be used to identify specific pathogens.

28.6 Genetic Susceptibility

Not applicable.

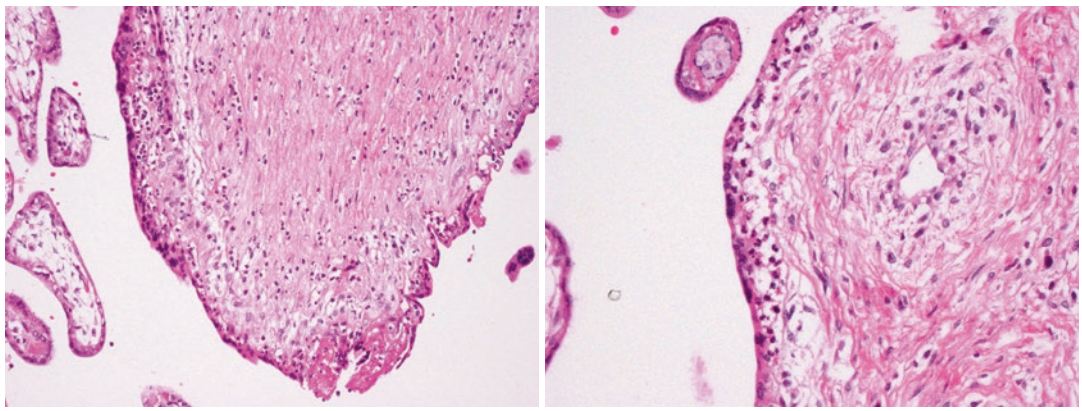

Fig. 28.1 Mid-second trimester severe villitis, showing neutrophil infiltration of the villi. No bacteria were cultured

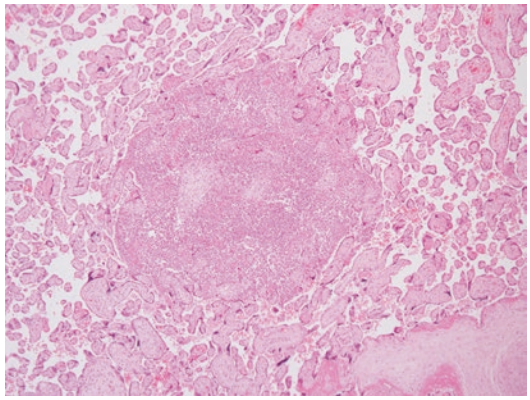

Fig. 28.2 Listeria intervillous focal inflammation with secondary involvement of the villi (courtesy Dr. Yee Khong)

28.7 Prognosis and Predictive Factors

None is known.

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Chronic Villitis

29

Chong Jai Kim and Jung-Sun Kim

29.1 Infectious Chronic Villitis

29.1.1 Introduction

In addition to TORCH, various organisms such as *Plasmodium falciparum* and *Treponema pallidum* can induce congenital fetoplacental infection largely by transplacental haematogenous spread from the mother. Placental villous lesions following infection by these organisms share certain histologic features of chronic villitis and at the same time display unique cytopathic effects according to the specific types of pathogens. While lymphocytic infiltration and certain degrees of villous destruction are common features of infectious chronic villitis, a recent report of Zika virus placental infection showed that Hofbauer cell proliferation, in the absence of lymphoplasmacytic infiltration and villous destruction, was the primary pathology [1]. The most common pathogen encountered in association with chronic villitis is cytomegalovirus (CMV) [2].

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29.1.2 Syphilis

29.1.2.1 Epidemiology

The incidence of congenital syphilis has been fluctuating (8.4–11.6/100,000 births) in the USA, and the disease remains as one of the major causes of miscarriage and stillbirth [3]. Syphilitic infection of the fetus and the placenta can occur at any time during pregnancy. Spread of *Treponema pallidum* to the fetus commonly occurs during the first and second stages of maternal infection, although it may occur in all stages of infection [4].

29.1.2.2 Gross Findings

Placentas infected by *Treponema pallidum* can become massively enlarged and pale [5, 6].

29.1.2.3 Histopathology

The histological triad of congenital syphilis encountered in the placenta is enlarged hypercellular villi, proliferative fetal vascular changes, and acute or chronic villitis [7]. The chorionic villi are enlarged and hypercellular due to infiltration of mononuclear cells. Predominant histiocytic infiltration is a typical histopathological pattern [8, 9], and lymphoplasmacytic cells may infiltrate the chorionic villi as well as the decidua (Fig. 29.1a–c) [9–12]. The inflammatory cells infiltrating the chorionic villi are reported to be mostly of maternal origin as in villitis of unknown aetiology (VUE); CD3+CD8+ lymphocytes and

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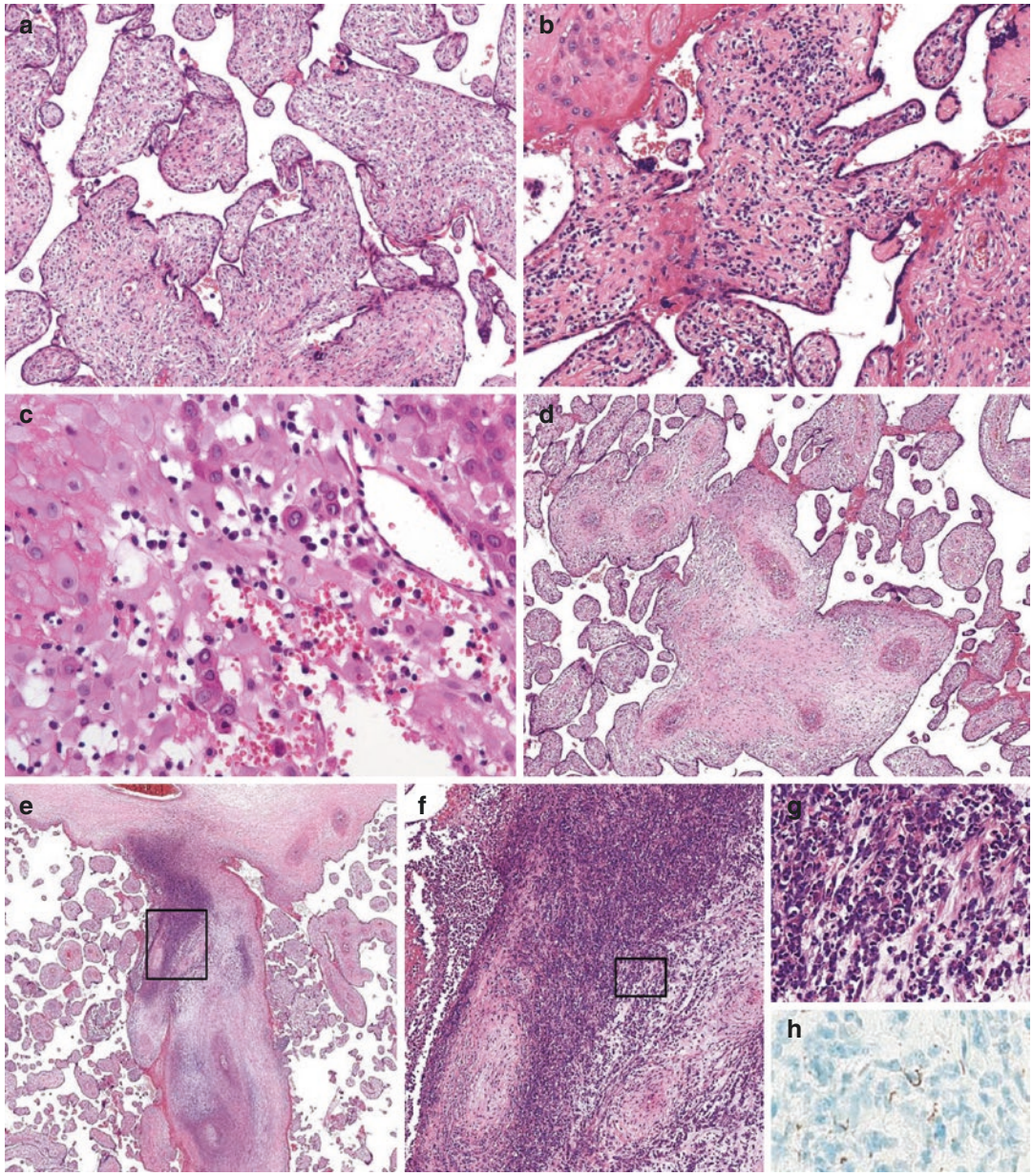

Fig. 29.1 Syphilitic infection in placenta. (**a**) Chorionic villi are infiltrated mostly by histiocytes. (**b**, **c**) Lymphoplasmacytic infiltration is occasionally identified in chorionic villi as shown in (**b**) and in decidua as shown in (**c**). (**d**) Proliferative endovasculitis in stem villi is characterized by concentric sclerosis, thrombotic occlusion, and luminal recanalization. (**e**–**g**) Marked inflammatory exudates with necrosis are deposited around the chorionic vessels. The boxed areas in (**e**) and (**f**) are magnified in (**f**) and (**g**), respectively. (**h**) *Treponema pallidum* organisms are identified in inflammatory exudates by immunohistochemical staining using a monoclonal antibody

CD68+ macrophages are the main inflammatory cells that participate in syphilitic villitis, while CD20+ B lymphocytes are rare [13]. This is also the case in villitis of unknown aetiology. In severe cases, abscess formation or villous necrosis is present, but granulomas are rarely found [9, 11]. Perivascular inflammation with concentric sclerosis can be found in the stem villi (so-called

proliferative endovasculitis) as in other tissues infected by syphilis (Fig. 29.1d) [8, 9, 11]. The inflammation is accompanied by narrowing, occlusion, or recanalization of the vascular lumen. The decidua also shows perivascular proliferation of fibroblasts with necrosis in addition to plasma cell infiltration. Necrotising inflammation in the umbilical cord or around the chorionic vessels is frequently seen in syphilitic placentas (Fig. 29.1e–g) [10, 14, 15]. Perivascular deposition of inflammatory exudate with necrosis is also found in the villi, which may be replaced with calcification. Necrotising funisitis and vasculitis are considered to be characteristic findings in syphilitic placentas, but they may also be present in other infections [16].

29.1.2.4 Ancillary Tests

Although certain histologic features described above are helpful in the diagnosis of syphilitic villitis, there is no pathognomonic histological finding for syphilis. Therefore, the demonstration of spirochetes is important for the confirmation of syphilitic infection. Silver nitrate-based Warthin-Starry stain has been widely used for the detection of spirochetes in tissue samples [17], and it also helps to visualize other microorganisms such as *Helicobacter pylori* and *Legionella* species. Immunostaining (immunofluorescence and immunohistochemistry) using anti-*Treponema pallidum* antibody seems to be superior to Warthin-Starry stain in the demonstration of *Treponema pallidum*, but there is a chance of cross-reactivity with other non-*Treponema* spirochetes (Fig. 29.1h) [18, 19]. Demonstration of the presence of *Treponema pallidum* by polymerase chain reaction (PCR) is also of diagnostic value [7]. The umbilical cord is most helpful for the identification of spirochetes by these ancillary tests.

29.1.3 Cytomegalovirus

29.1.3.1 Epidemiology

About 1% to 4% of women acquire CMV infection during pregnancy, and subsequent CMV infection of the fetus occurs in 20% to 50% of the cases [20]. The most serious cytomegaloviral fetal infections are detected during the second trimester of pregnancy, and they result from primary rather than recurrent maternal infections. Long-term morbidities of congenital CMV infection include sensorineural hearing loss, vision impairment, and major neurodevelopmental disability. CMV in maternal blood infects and destroys the trophoblast in the placenta to eventually infect the fetus [21]. Although there is no animal model of congenital CMV infection available, many studies have provided clues for understanding the mechanisms leading to cellular injuries by gene products encoded by CMV such as induction of apoptosis, chromosomal breakage, and modification of cell metabolism [22]. The incidence of congenital CMV infection is higher in HIV-infected neonates than in HIV-uninfected neonates. Greater immunosuppression in CMV- and HIV-coinfected neonates than in CMV-negative neonates suggests that fetal immunosuppression due to CMV infection is responsible for the more rapid progression of HIV [23]. It is also noteworthy that CMV DNA and proteins are detected in the placental and decidual tissue samples in more than half of uneventful term births, and CMV infection per se is ubiquitous in nature and asymptomatic in immunocompetent individuals [24].

29.1.3.2 Gross Findings

CMV-infected placentas show no specific gross features. Thrombosis of chorionic vessels may be detected with dystrophic calcification [25].

29.1.3.3 Histopathology

CMV-infected placentas show typical lymphoplasmacytic infiltration in the chorionic villi along with viral inclusions (Fig. 29.2a–c). The inclusions are identified in the nuclei (owl-eye cells), the cytoplasm of villous endothelial cells and stromal cells, and occasionally the amnion and the decidua [26–29]. The owl-eye inclusions have pathognomonic value in the diagnosis of CMV infection. Vasculitis of chorionic vessels may be accompanied by thrombosis, calcification, and haemosiderin deposits in the surrounding stroma. Villous necrosis and fibrosis may be present, followed by calcification (Fig. 29.2d).

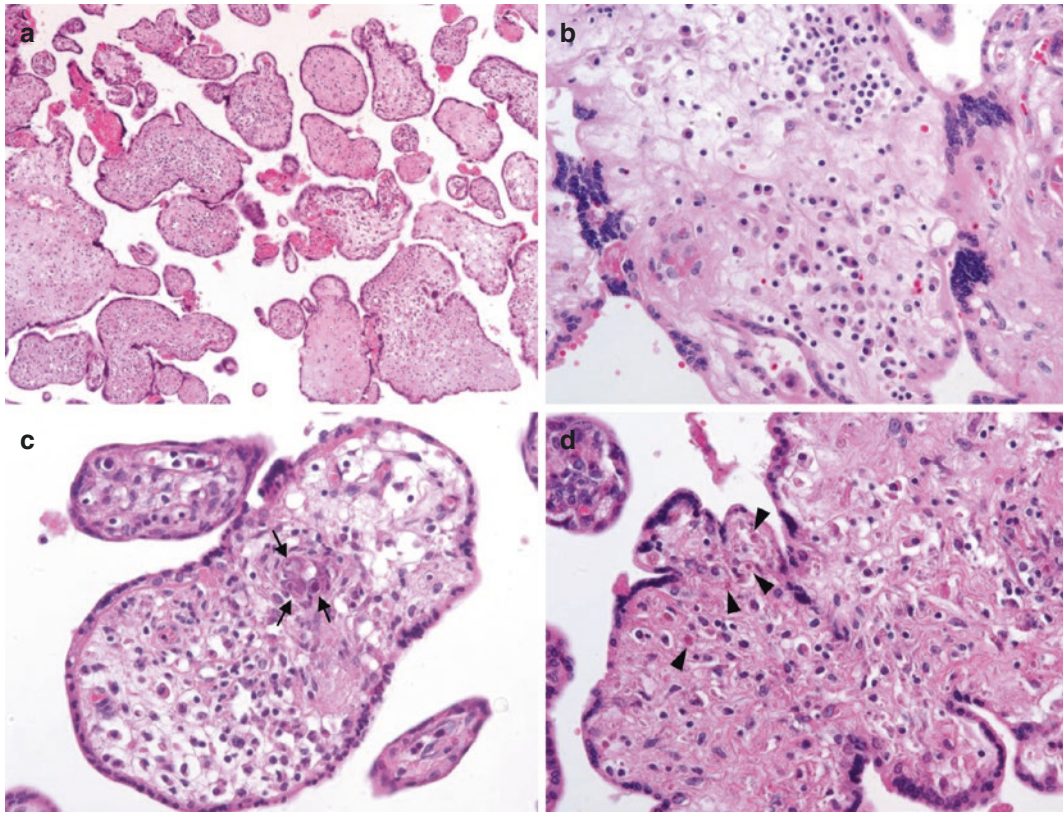

Fig. 29.2 Cytomegalovirus infection in placenta. (**a**) Chorionic villi are infiltrated by mononuclear cells and some are fibrotic. (**b**) Plasma cell-predominant infiltration is characteristic. (**c**) Endothelial and stromal cells are enlarged with intranuclear viral inclusions (arrows). (**d**) Villous stroma is fibrotic with haemosiderin deposition, with some viral inclusions (arrowheads)

The presence of plasma cells and haemosiderin deposits is a strong histological indicator of CMV infection, even in cases in which typical inclusion bodies are not found. Regarding the origin of plasma cells, it has not been clearly documented whether they are maternal cells or fetal cells, but fetal plasma cells can appear after 13 weeks of gestation [25]. The histological patterns are known to change according to the gestational age. The preterm placenta in the second trimester shows delayed villous maturation, abundant viral inclusions, with necrosis and calcification. In the third trimester, vascular involvement is prominent, but viral inclusions are scarce [26].

29.1.3.4 Ancillary Tests

In addition to distinct histologic changes, confirmative diagnosis of CMV infection is made by immunohistochemistry [28], in situ hybridization [30, 31], and PCR [2, 32] when typical nuclear inclusions are not detected. Serological tests and virus isolation by culture are also clinically useful.

29.1.4 Parvovirus B19

29.1.4.1 Epidemiology

Infection with *parvovirus B19* is one of the most significant causes of second-trimester miscarriage and fetal hydrops associated with fetal anaemia. First-trimester fetal loss and third-trimester fetal death are also reported in association with *parvovirus B19* [33, 34]. Fetal infection occurs in 25% to 33% of pregnant women who acquire acute infection during pregnancy [35], and even embryonic malformations have been reported in a case of intrauterine infection during

early pregnancy (9 weeks of development) [36]. Fetal hydrops and anaemia are two main characteristics of congenital *parvovirus B19* infection because of the propensity of viral infection for erythroid precursor cells.

29.1.4.2 Gross Findings

The placentas with *parvovirus B19* infection are enlarged, pale, and oedematous, which are general characteristics of hydrops fetalis.

29.1.4.3 Histopathology

Although the chorionic villi may become enlarged by chronic inflammatory infiltration, extensive chronic villitis is not usually expected in association with *parvovirus B19* infection. Endothelial damage, villous necrosis, and haemosiderin-laden macrophages may be seen. The primary finding of placental parvoviral infection is the presence of ground-glass eosinophilic nuclear inclusions in the nucleated red blood cells, which are also called lantern cells (Fig. 29.3a) [37]. Therefore, lantern cells are in the fetal villous capillaries, yet these inclusions can also be found in other parenchymal cells [38, 39]. Basophilic blebbing projecting from the nuclear membrane surface can be seen as well, and this feature has been described as a popcorn profile [40].

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29.1.4.4 Ancillary Tests

Parvovirus B19 infection can be easily identified by immunohistochemistry (Fig. 29.3b) and in situ hybridization [41, 42]. Electron microscopic examination of the nuclear inclusions typically reveals crystals of 20 nm viral particles [43]. PCR is another helpful diagnostic adjunct [44, 45].

29.2 Villitis of Unknown Aetiology

29.2.1 Introduction

As the placenta and fetus are semiallografts to the mother, human pregnancy shares similar features with transplantation of an allograft. In fact, there are known neonatal disorders that result due to

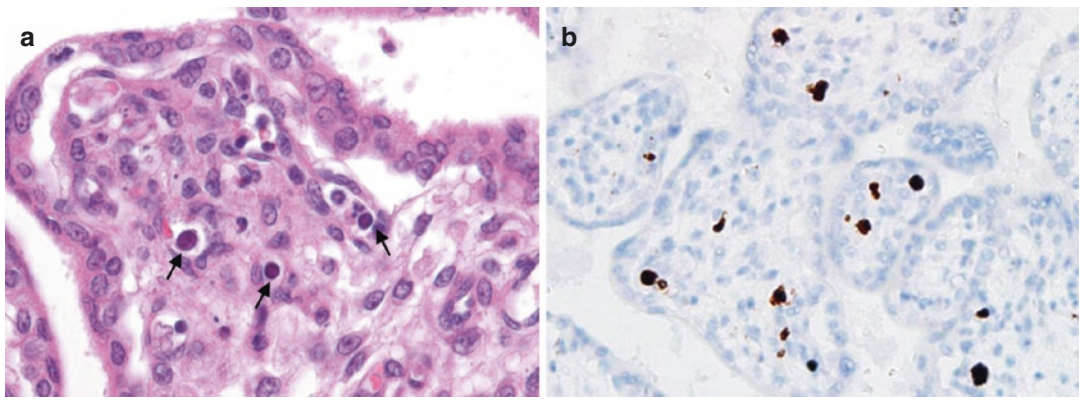

Fig. 29.3 *Parvovirus B19* infection. (**a**) Ground-glass eosinophilic intranuclear inclusions (arrows) are detected in the nucleated red blood cells. (**b**) The nuclei of infected cells are positive for anti-parvovirus B19 immunohistochemistry

maternal alloimmune responses against fetal antigens, such as alloimmune haemolytic disease of the newborn, neonatal alloimmune thrombocytopenia, and neonatal alloimmune hepatitis [46, 47]. Meticulous studies have demonstrated that the most common form of chronic villitis is not related to certain types of infection and more importantly that CD8+ cytotoxic T cells infiltrating into the fetal chorionic villi are of maternal origin. This enigmatic form of chronic villitis has been called villitis of unknown aetiology, and in situ hybridization of male baby placentas affected by VUE using X and Y chromosome-specific probes revealed that infiltrating T cells are of female (mother) origin and lacking the Y chromosome [48]. As maternal T cell infiltration into the fetal chorionic villi also seems to be a feature of chronic villitis of infectious origin [13], chronic villitis, regardless of aetiologies, is an intriguing inflammatory process that occurs at the fetomaternal interface.

At the tissue level, the expression of T cell chemokines CXCL9, CXCL10, and CXCL11 in the chorionic villi is increased, thereby recruiting CXCR3-positive T cells [49]. In the mother, therefore, this feature is basically analogous to cellular allograft rejection in which the placenta (fetal tissue) is the allograft to the mother. The changes in T cell chemokines are not restricted to the placenta. In the presence of VUE, the median maternal and fetal plasma concentrations of T cell chemokines CXCL9, CXCL10, and CXCL11 are higher than in normal placentas [49]. The view that VUE is a consequence of alloimmune response is further supported by robust relationship between VUE and the presence of fetal HLA-specific alloantibodies in the maternal circulation [50]. These HLA antibodies cross the placenta and are detected in the fetal blood. C4d deposition is also commonly found in the syncytiotrophoblast of the regions affected by VUE [51, 52]. Other closely related chronic inflammatory reactions can involve different compartments of the placenta. The one involving the chorioamniotic membranes is chronic chorioamnionitis, and the other involving the basal plate is chronic deciduitis with plasma cells [53–55]. Abnormal maternal autoimmunity is also likely to be associated with VUE because the fetus shares maternal antigens as is the case with paternal antigens. Therefore, it is possible that a small fraction of VUE is associated with maternal autoimmune reaction, because the incidence of VUE is increased when mothers have autoimmune diseases such as systemic lupus erythematosus and autoimmune thyroid disease [56]. In such cases, maternal antigens will take the role of paternal antigens in alloimmune reactions.

As the placenta is an interface organ between the mother and the fetus, inflammation of the placenta is inevitably associated with inflammatory responses of the mother, the fetus, or both. Of particular importance in terms of fetal and neonatal morbidities are systemic fetal inflammatory responses. The fetal inflammatory response associated with intra-amniotic infection and acute chorioamnionitis is characterized by elevation of fetal plasma IL-6 [57, 58]. On the other hand, the presence of chronic placental inflammation (VUE, chronic chorioamnionitis, and chronic deciduitis with plasma cells) and maternal HLA panel-reactive antibody seropositivity is associated with the elevation of fetal plasma antiangiogenic T cell chemokine CXCL10 [59]. The clinicopathological consequences of systemic fetal inflammation have been described as different types of fetal inflammatory response syndrome [59]. It is very likely that fetal inflammatory response associated with VUE accounts for the development of morbidities such as fetal growth restriction.

29.2.1.1 Definition

VUE is the infiltration of maternal T cells (CD8+ cytotoxic phenotype) into the fetal chorionic villi in the context of destructive villous inflammation. Prerequisite for the diagnosis of VUE is the exclusion of infectious aetiologies although there are no standard protocols for specific workups for common infectious causes and workups are not being done in routine clinical practice due to relatively distinct clinicopathological features.

29.2.1.2 Synonyms

There are terms synonymously used for VUE in the literature such as noninfectious chronic villitis, idiopathic chronic villitis, chronic nonspecific villitis, and chronic villitis of unknown aetiology.

29.2.1.3 Epidemiology

The frequency of VUE varies among studies, and the prevalence of the disease ranges from 2% to 33.8% [60–64]. This wide variation in the frequency of VUE is most probably due to differences in the study population and diagnostic criteria. The number of placental tissue samples also affects the chance of detecting VUE, and four blocks of placental disc sampling can maximize the chance [61]. Of interest, in in vitro fertilization setting, VUE is more common in pregnancies with donor oocytes than in those with nondonor oocytes [65, 66], which supports the relationship between VUE and maternal immune response to foreign antigens. VUE is also prone to recur in following pregnancies in more than one third of cases, and recurrent VUE is associated with poorer clinical outcomes such as fetal growth restriction and mortality [62, 67]. VUE is more frequent in the placenta of the smaller twin than in that of the larger twin in dichorionic pregnancies [68]. The relationship between VUE and chronic histiocytic intervillositis (massive chronic intervillositis) is discussed in Chap. 30 [69, 70].

29.2.1.4 Gross Findings

There is no known gross characteristic of VUE, although mottling of the parenchyma has been reported as a subtle change. The diagnosis of VUE is essentially being made based on microscopic findings.

29.2.1.5 Histopathology

VUE can be rather easily detected because affected chorionic villi are readily recognized due to destructive changes and typically increased stromal cellularity due to inflammatory cells. While it is evident that infiltrating T cells are maternally derived, the majority of histiocytes involved are activated placental macrophages (Hofbauer cells) of fetal origin [48, 71]. In terms of origin, VUE therefore features T cells and macrophages originating from the mother and the fetus, respectively. VUE is essentially fetal tissue damage by maternal T cells based on alloimmune response.

Histopathological features of VUE are variable and can show proliferative, necrotizing, or granulomatous inflammation. According to the type of chorionic villi involved, VUE pattern can be categorized as distal, proximal, or basal type [63]. Either terminal or mature intermediate villi are affected in distal type, while stem villi are affected in proximal type. The basal type involving anchoring villi commonly accompanies chronic deciduitis with plasma cells (Fig. 29.4a–d). There does not seem to be any predominant pattern among the three, and mixed patterns of VUE are common.

In terms of severity and extent of VUE, some grading systems have been proposed [61, 72]. A representative example proposed by Redline is based on the number of affected chorionic villi and the distribution of inflammation, and the distinction between low-grade and high-grade lesions is whether fewer or more than ten villi are affected per focus (Fig. 29.5a, b) [63]. Although it is a general understanding that higher-grade inflammation is likely to have poorer pregnancy outcomes due to villous destruction, histological severity does not necessarily indicate the severity of fetal growth restriction [64].

VUE can also feature fetal vascular obliteration or thrombotic occlusions due to vasculitis or perivasculitis, and this is called villitis with stem vessel obliteration [63, 73]. Hyalinized avascular distal villi are often found in the affected regions. This pattern is histologically indistinguishable from that found in association with fetal vascular malperfusion [73]. As the pathophysiology and clinicopathological characteristics of typical fetal vascular malperfusion are different from those of VUE, diagnostic distinction between these histologically similar categories needs to be made. The presence of villous inflammation should be a key in the differential diagnosis between the two.

Differential diagnosis with chronic villitis of infectious origin is also important. Generally,

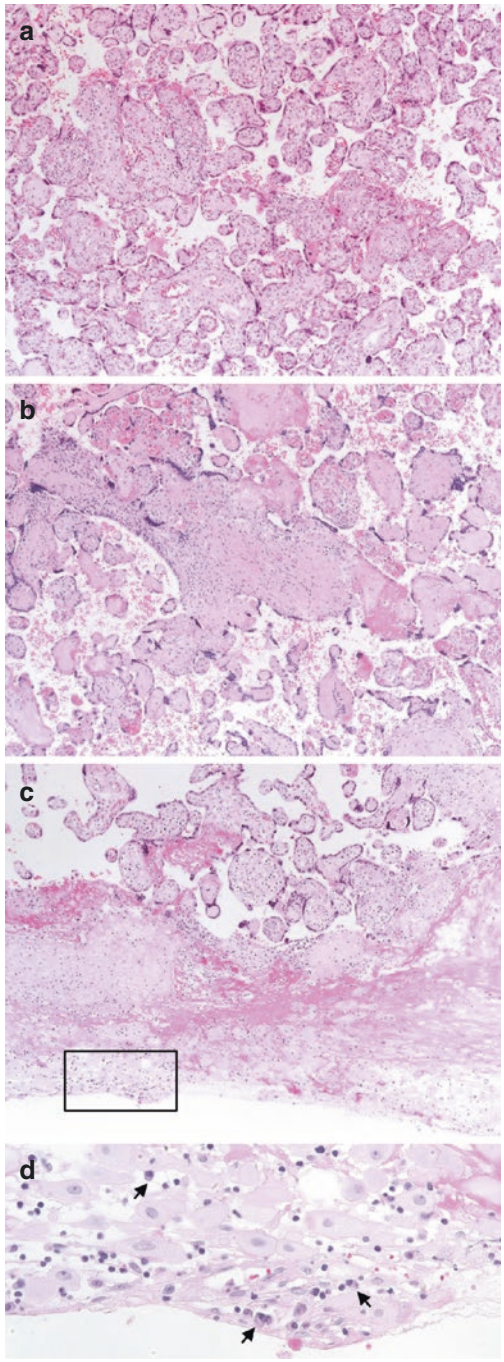

Fig. 29.4 Subtypes of villitis of unknown aetiology (VUE). (**a**) Distal type of VUE involves terminal or mature intermediate villi. (**b**) Proximal type of VUE affects stem villi and is associated with stem vessel obliteration, thereby leading to the hyalinization of avascular villi. (**c**) Basal type of VUE is characterized by the involvement of anchoring villi. The boxed area in the decidua of the basal plate is magnified in (**d**). (**d**) Basal type of VUE accompanies chronic deciduitis with plasma cells (arrows)

infectious villitis is much rarer than VUE, is found earlier during pregnancy, and shows diffuse involvement compared to VUE. The chance of recurrence in the following pregnancy is also far less in infectious villitis than inVUE [63]. In addition to distinct cytopathic changes, immunostaining for more common infectious organisms such as syphilis, cytomegalovirus, and *parvovirus B19* is helpful and of great diagnostic value. While rubella chronic villitis has been described as a histological mimicker of VUE, rubella chronic villitis has almost disappeared as a consequence of vaccination programs.

29.2.1.6 Immunohistochemistry

Although meticulous routine histological examination is enough for the detection of VUE, additional immunohistochemical stainings are helpful diagnostic adjuncts. T lymphocytes infiltrating chorionic villi are easily detected by CD3 or CD8 immunostaining [71]. CD4 expression is not limited to T cells, and Hofbauer cells are CD4-positive as are other macrophages. Of interest, it was reported that there is a paradoxical increase in the numbers of regulatory T cells (CD4+, CD25+, and FoxP3+) in VUE [74]. Hofbauer cells show increased expression of CD14 and high Ki-67 labelling, which indicates that these cells have a pro-inflammatory, activated phenotype [71]. As another distinctive feature, linear C4d immunoreactivity along the syncytiotrophoblast has been consistently detected in VUE, which indicates that complement activation is one of the mechanisms of villous injury in VUE [51, 52]. However, syncytiotrophoblast C4d immunoreactivity can be detected in different types of placental lesions induced by infection or ischaemia [75, 76].

29.2.2 Prognosis and Predictive Factors

VUE in a limited extent encountered in term deliveries does not seem to have any significant clinical implications so far. However, severe forms of VUE are associated with an increased risk of fetal growth restriction, preterm birth, and even fetal death [64, 77, 78]. This is relevant

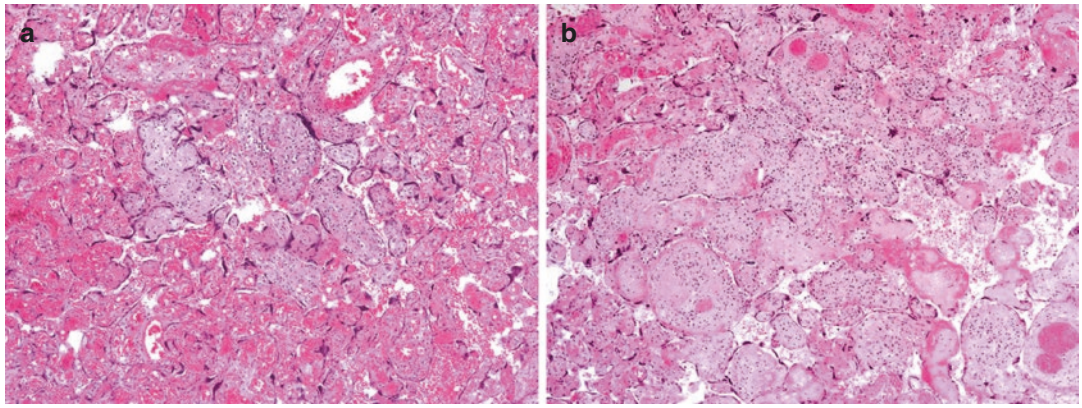

Fig. 29.5 Grading of VUE. (**a**) Low-grade VUE shows inflammation in less than ten villi per focus. (**b**) High-grade VUE is defined by the . involvement of more than ten villi per focus

because villous damage will result in compromised maternofetal transfer of biological substances such as nutrients and oxygen. There are sporadic reports of neonatal alloimmune thrombocytopenia associated with VUE [79, 80], and recurrent VUE cases had higher frequency of reproductive loss (up to 60%) in contrast to non-recurrent VUE cases [62].

There are also reports of increased perinatal and infant morbidities and mortalities. VUE with stem vessel obliteration is associated with neurologic impairment in term infants [81]. Presence of VUE had a predictive value for necrotizing enterocolitis and neurologic impairment at the age of 2 years in preterm growth-restricted fetuses with abnormal umbilical artery Doppler findings [82].

29.2.3 Future Research

VUE and the other synonyms fail to provide pathobiological implications of the condition, and it is evident that the vast majority of VUE is a feature of maternal antifetal cellular rejection. However, using the term rejection as in allograft rejection does not seem to be relevant, considering the relationship between the mother and the fetus. Therefore, it is necessary to find ideal nomenclature for this unique pathological condition. As VUE is of alloimmune origin, alloimmune villitis can be one option.

VUE has been shown to be associated with severe alterations of umbilical artery Doppler in nearly one third of cases [60]. Because of the high rate of recurrence after an index case of VUE, consideration could be given to therapy with aspirin, corticosteroids, statins, and maternal intravenous immunoglobulins in future pregnancies [70]; these therapies, however, have not been subject to randomized control trials.

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Chronic Histiocytic Intervillositis

30

Eoghan E. Mooney

30.1 Introduction

Chronic histiocytic intervillositis (CHIV) was described in 1987 [1] using the term "massive chronic intervillositis". It is a recurrent lesion associated with poor reproductive outcomes, including recurrent pregnancy losses and fetal growth restriction [2]. Unusual presentations include severe fetal growth restriction mimicking osteogenesis imperfecta [3].

30.2 Definition

CHIV is an infiltrate of maternal mononuclear cells in the intervillous space, usually accompanied by an increase in perivillous fibrin.

30.3 Synonyms

Massive chronic intervillositis; chronic intervillositis; Chronic histiocytic intervillositis of unknown (a)etiology; Chronic intervillositis of unknown (a)etiology.

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30.4 Epidemiology

CHIV is a rare condition that may occur in any trimester: the incidence is unknown, and it is found in <0.5% of placentas. It is associated with maternal immunologic conditions, found in up to 29% of cases. These include SLE, lupus anticoagulant, and antiphospholipid and other antibodies. Fetal/neonatal alloimmune thrombocytopenia (FNAIT) shows a significant association with chronic inflammatory lesions of the placenta, including CHIV [4]. Allergic conditions such as asthma are also more frequent [2, 5, 6]. An association with assisted reproduction has been reported in some cases [7]. Clinically, abnormal umbilical artery (31%) and uterine artery (40%) Dopplers have been reported, and elevated alkaline phosphatase levels are seen in over half of cases [8]. In a cohort of cases of FGR with abnormal umbilical artery Dopplers, those with intervillositis were more likely to have a normal uterine artery Doppler, and to deliver later, compared with those with maternal vascular malperfusion [9]. Between 32% and 38% of pregnancies with CHIV reach term [10].

30.5 Gross Findings

The gross appearance of the placenta in CHIV is rarely commented on. It may be normal or, if there is an increase in perivillous fibrin, a pale,

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firm placenta could be expected. In rare cases where CHIV co-exists with the entity of massive perivillous fibrin deposition, the placenta was reported as variegated and red/grey [11].

30.6 Histopathology

Perivillous fibrin may dominate the picture, and this should prompt careful evaluation for the presence of histiocytes. These may show the classic reniform nuclear outline. In many cases, they are diffuse and recognisable at low power (Fig. 30.1), but they may be focal and confined to areas with fibrin. Most (>80%) of the cellular infiltrate should be histiocytes (Fig. 30.2), with T cells accounting for the remainder. B cells and plasma cells are rarely seen [12].

Features of maternal vascular malperfusion are more frequently seen in CHIV compared with villitis or controls [13]. The original description noted that atherosis was present in three of six cases [1]. However, patients with preeclampsia were excluded from some studies [14].

No generally agreed grading system is in place. However, histologic severity seems to be associated with worse clinical outcomes. Cases grouped as villitis with intervillous monocytes, few intervillous monocytes, or massive chronic intervillositis showed a tendency for cases with fewer monocytes to have fewer complications than those with more monocytes [15]. Parant [14] assessed monocytes and fibrinoid as focal (<10% of the intervillous space involved), moderate (10–50%) or massive (>50%). They identified two clinical patterns: massive CHIV with diffuse fibrinoid characterised by a poor pregnancy outcome and moderate CHIV with focal fibrinoid, which showed a more favourable outcome following obstetric management. An increased intensity of fibrin was associated with early spontaneous abortions and FGR [8].

Chronic villitis is seen in 30% [14] to 47% [13] of cases of CHIV. In the original study of six cases, four of six had VUE, and five of six had anchoring villitis. However, some authors have specifically excluded cases with villitis from their study population [6, 12]. As inflammatory lesions such as CHIV, villitis and deciduitis may represent part of an immune response that is predominantly localised at the maternal-fetal interface [4], it is logical to permit an overlap of morphologic patterns, with reference made to the predominant location of inflammation [15] and to the extent of fibrinoid deposition.

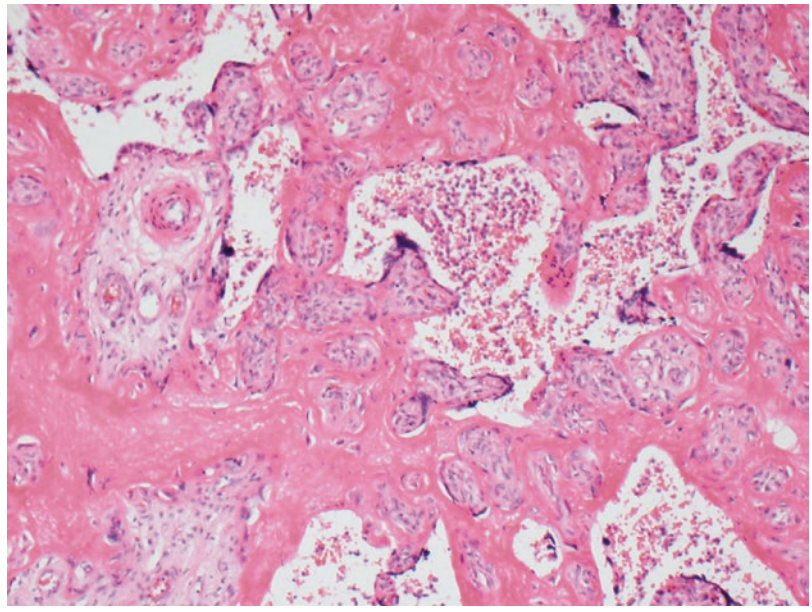

Fig. 30.1 Mononuclear cells are present in the intervillous space. Perivillous fibrin can be seen around adjacent villi

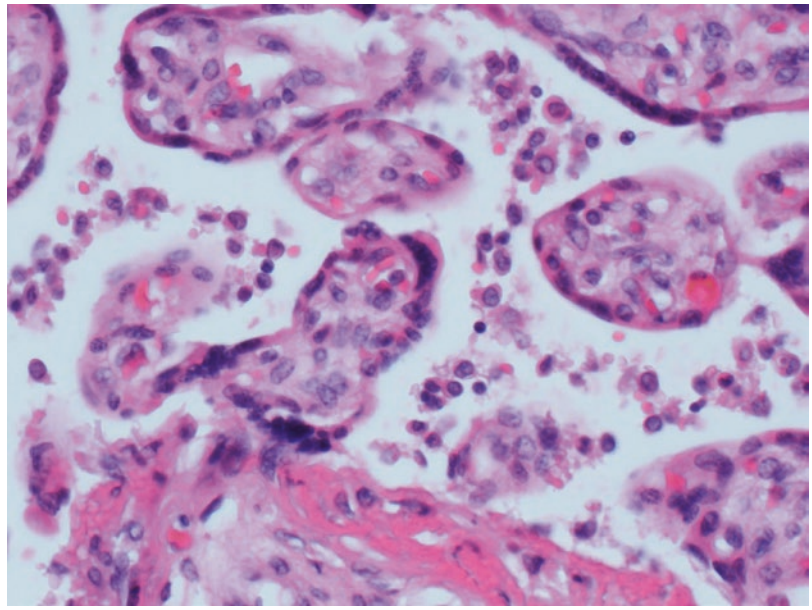

Fig. 30.2 The histiocytic nature of the infiltrate is appreciated at higher power

In a systematic review, Bos et al. [10] suggested three inclusion criteria for the diagnosis, with preferred terminology of "chronic intervillositis of unknown aetiology": the presence of an infiltrate in the intervillous space, approximately 80% of the mononuclear cells in the intervillous space being CD 68-positive cells and the infiltrate should occupy 5% or more of the intervillous space. The single exclusion criterion proposed was clinical or histopathological signs of infection.

The differential diagnosis on microscopy includes infectious causes. The histologic pattern of CHIV, i.e. of perivillous fibrin and an intervillous monocyte infiltrate, was seen in 17% of placentas with malarial parasites [16]. The presence of malarial parasites or pigment enables distinction to be made. Other organisms may cause intervillous inflammation, but this is predominantly neutrophilic—these include *Listeria*, *Campylobacter*, *Francisella* and *Coccidioides* spp. No organism has been consistently associated with CHIV. Intervillous inflammation by mononuclear cells may accompany CMV villitis [15, 17].

Acute inflammatory cells are commonly seen in the intervillous space where there is a maternal inflammatory response to amniotic fluid infection, and they may be admixed with fibrin. High-power examination will confirm that they are neutrophils rather than mononuclear histiocytes. The use of the term intervillositis to describe this finding is discouraged, and it should be reserved for the entity of CHIV.

30.7 Immunohistochemistry

CD68 highlights histiocytes (Fig. 30.3), with a mean of 88 ± 23/HPF in cases of CHIV versus 8 ± 5/HPF in normal pregnancies [18]. The level of C4d staining of trophoblast showed a direct relationship with monocyte numbers and was associated with CHIV rather than VUE [15]. Increased recruitment of FOXP3 regulatory T cells has been reported compared with normal pregnancies, and these cells were present in the decidua and in the intervillous space [12]. The composition of T cell subsets in CHIV was reported as having a CD4:CD8 ratio of approximately 0.85 [12], in contrast with the predominance of CD8 cells in infectious villitis and VUE [19]. Other studies show that CHIV and VUE have similar immune cell composition [13].

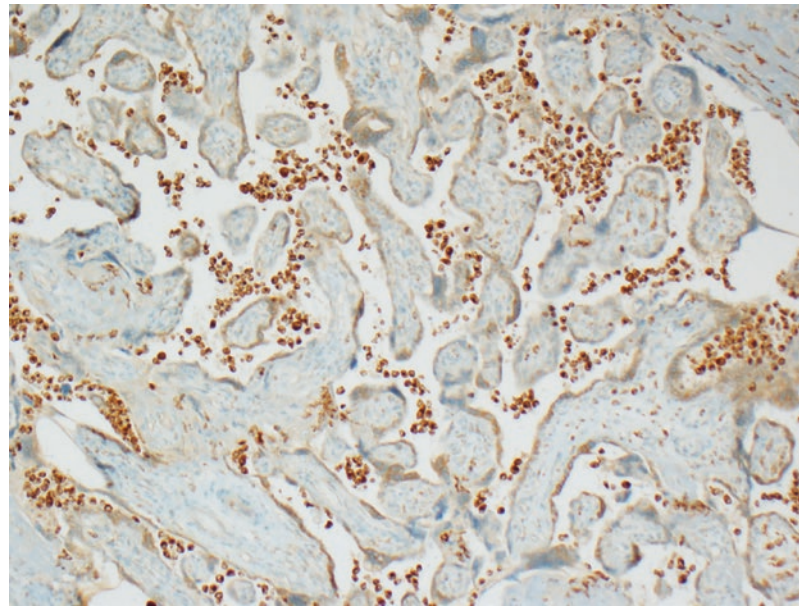

Fig. 30.3 Immunostain for CD 68 confirms the histiocytic nature of the infiltrate

30.8 Genetic Susceptibility

CHIV may represent a Th1-like immune response to the fetus, in contrast to the Th-2 response that is the usual pattern in pregnancy. ICAM-1 is expressed on syncytiotrophoblasts [13], with a high antipaternal cellular and humoral response and identification of anti-HLA antibodies [20]. The high recurrence rate is also consistent with an immune aetiology. C4d staining reflects complement injury following humoral rejection of a trophoblastic antigen, triggering local cytokine upregulation of monocyte cell adhesion [15]. An association between FNAIT and chronic chorioamnionitis, basal villitis and CHIV has been reported [4].

30.9 Prognosis and Predictive Factors

CHIV recurs in 67%–100% of cases and in 25% of 199 women in a systematic review of 18 studies [10]. High scores are associated with a worse outcome (see under grading above). Co-existent villitis, when adjusted for gestation, did not show an increased percentage of fetal loss. After 37 weeks, in a cohort of 23 cases, cases with CHIV alone had an 18% fetal loss, and those with CHIV and villitis had a 17% loss [21].

Over half of cases in one series (10/18) showed an elevation in maternal alkaline phosphatase (ALP), released from damaged syncytiotrophoblast and correlated with intensity of fibrin deposition [8]. This provides a potential method of monitoring future pregnancies in women with a diagnosis of CHIV. As ALP shows a physiologic increase in pregnancy, a level of 2.5 times the non-pregnant state has been used.

No single treatment regime has been defined, and aspirin, heparin, prednisolone and hydroxychloroquine, either alone or in combination, have been tried. Treatment reduces adverse outcome in the subsequent pregnancies from 67% to 30%. Even though the absence of CHIV correlated with live births in subsequent pregnancies, its persistence was not always associated with an adverse outcome [2]. Recently, combination therapy including immunoglobulin was reported to result in a successful pregnancy [22].

30.10 Future Research

The interaction between mother and fetus is reflected by inflammation at different interfaces. Placentas from infants with fetal/neonatal alloimmune thrombocytopenia showed significant increases in chronic chorioamnionitis and basal villitis in addition to CHIV. The role of the immune system in permitting successful implantation is recognised, and the frequency of findings of maternal vascular malperfusion in cases of CHIV is noteworthy. Recognising and documenting these findings in a systematic way will assist research into this uncommon condition.

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Intervillous Space: Infiltrates

31

Adrian K. Charles and Marie-Anne Bründler

31.1 Introduction

This chapter focusses on the histological lesions affecting primarily the intervillous space excluding inflammatory and infectious diseases and perivillous fibrin that are covered elsewhere. The main lesions include maternal malignancies, maternal haematological disease with morphological changes such as sickle cell disease and trophoblastic proliferations including choriocarcinoma.

The placenta, and especially the basement membrane around the villi, appears to act as a barrier for maternal cells. Usually widely metastatic maternal malignancies may involve the placenta but relatively few show chorionic villus invasion and fewer still affect the fetus or the neonate. Tumours that have crossed to involve the neonate, including melanoma and some leukaemias, often regress suggesting an immune response [1]. Failure of engraftment of maternal leukaemic cells present in the cord blood of an infant has been shown [2]. There is growing interest of the role of microchimerism with the transfer of long-lasting pluripotent cells between the mother and the fetus having a variety of beneficial and non-beneficial effects ranging from future pregnancies, autoimmune disease, biliary atresia and maternal malignancies [3–5].

There are three major pathophysiological steps in the development of metastases from the mother to the conceptus.

1. Involvement of the maternal blood space, or the perivillous fibrin, by malignant infiltrate. The infiltrate is confined to the maternal space external to the basement membrane of the villi.
2. Infiltration of the fetal placental tissues (e.g. the chorionic villous stroma) suggests an additional invasive property of the tumour. This may be implied where the fetus or neonate contains maternal malignant cells but the placental focus of invasion is not identified.
3. A further stage is the very rare case where the tumour establishes a metastatic focus in the fetus or infant. This may regress.

A possible further stage is where the tumour avoids immune surveillance from the infant, but this process may also be involved in preventing fetal tumour establishment. In the series reviewed

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by Al-Adnani et al. [1] chorionic villous invasion was documented in 18 of the 76 cases with placental examination. Chorionic involvement occurred at a rate of 50% in malignant melanoma but was infrequent in other tumour types, including lung cancer, leukaemia and breast cancer. Metastasis to the baby occurred in four cases, and three of these were malignant melanomas. An earlier review of cases of malignant melanoma metastatic to the placenta documented villous and/or fetal vascular invasion in 9 of 19 cases, 5 with fetal metastases [6]. Two of five cases with histologically confirmed fetal vascular invasion developed metastatic disease [7]. In another series, the risk of fetal metastasis in cases with placental involvement was estimated at 22% for malignant melanoma [8].

31.2 Definition

Intervillous space is the space usually occupied by the maternal blood between the villi beyond the syncytiotrophoblast layer, with the chorionic plate and the decidual surfaces forming the other borders.

31.3 Synonyms

Not applicable.

31.4 Epidemiology

Metastatic maternal malignancy is not very uncommon (~ 1;1000 pregnancies), though involvement of the conceptus is a relatively uncommon condition and probably underreported. Most papers reporting maternal malignancies affecting the conceptus are individual case reports. Breast cancer appears the commonest malignancy seen in pregnancy, with melanoma also seen depending on the population, as well as a range of other cancers [9, 10]. Melanoma and lung cancer may have a proportionally high risk of chorionic invasion and fetal/infant metastases (Table 31.1).

Some papers quote a cancer incidence of up to 1:1000–1500 pregnancies. Only a few tumours affect the placenta or infant, and different tumours show different tendencies to involve the placenta.

Table 31.1 Tumours reported with placental, fetal or infant metastases

Tumour	Reference	Comment
Melanoma	[7, 11–13]	~25% of infants/fetuses get metastases Some infant metastases regress, others progress
Breast carcinoma	[14]	Does not appear to metastasise to the fetus
Lung Small cell adenocarcinoma	[15–19]	26% of tumours in pregnancy. More SCLC spread to conceptus including fetus, but infants usually do well and may respond to therapy
Leukaemia	[2, 20]	AML and ALL described may be identified in fetal/infant blood but did not engraft
Lymphoma	[21–25]	Various types, including mature B cell, T cell, HIV-associated and anaplastic large cell. Usually only placental involvement; occasional fatal infant involvement
Others Cervical cancer Unknown primary Squamous cell carcinoma of maxilla Medulloblastoma Gastric cancer Pancreatic adenocarcinoma Uterine stromal cell tumour Primitive neuroectodermal tumour	 [9, 26] [27–29] [30] [13] [31] [1, 32] [33] [34]	Mostly isolated reports but some metastasise to the infant, with fetal death (cervical cancer) Other cancer types: fetuses may be stillborn, but usually not as a result of direct metastases

AML acute myeloid leukaemia, *ALL* acute lymphoblastic leukaemia, *SCLC* small cell lung cancer

Most tumours spread to the placenta by the haematogenous route, but direct involvement from uterine tumours and via lymphatics to the placental bed has been reported. Metastases of maternal malignancy to placenta or fetus are most frequently observed in tumours with a significant disseminated tumour load, such as melanoma (30%), leukaemias and lymphomas (17%), breast cancer (14%), lung cancer (13%) and cancer of unknown primary (2%) [9].

Choriocarcinoma involving a normal placenta is rare. Sickle cell disease is common in African populations.

31.5 Gross Findings

The main indicators for a close review of the placenta are a history of a maternal malignancy or an unusual appearance to the placenta. On gross examination, there may be no obvious abnormality even when there is extensive metastatic disease on microscopic examination. Some tumours may provoke perivillous fibrin or infarcts.

Focal choriocarcinoma may not be evident grossly with the focus only evident microscopically as a small infarct or fibrin.

31.6 Histopathology

Metastatic maternal malignancies characteristically involve the intervillous space in the form of localised tumour deposits or diffuse intervillous infiltrates. Metastatic malignant melanoma or carcinomas mostly present as loose clusters or small solid nodules of malignant cells with variable nuclear atypia, and cytoplasmic pigmentation may be appreciated in malignant melanoma. The tumour deposits lack vascularisation and can be confused with (intermediate) trophoblast (Fig. 31.1). Maternal leukaemia more typically affects the intervillous space diffusely. The malignant infiltrate in these cases can mimic intervillositis (see Fig. 31.2). Through the disturbance of local control of thrombosis, infarcts or perivillous fibrinoid deposition may be seen. Chorionic villous and/or fetal vascular invasion is observed in only a small proportion of cases (discussed above). Another issue raised in the literature is the distinction of metastatic melanoma to the fetus, from benign melanocytic naevus cells in the placenta.

Choriocarcinoma is a malignancy arising from the conceptus. There are some well-documented cases where the mother and the baby are affected

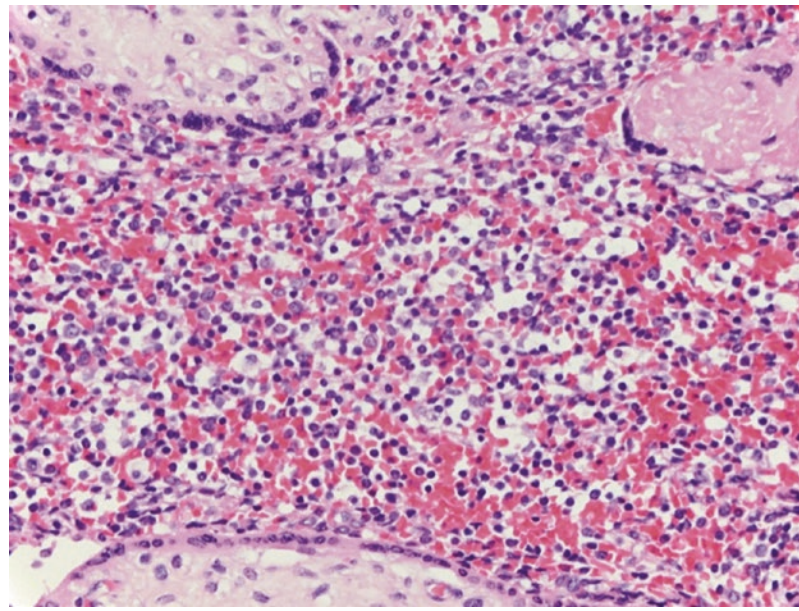

Fig. 31.1 Maternal acute myeloid leukaemia in mid-second trimester

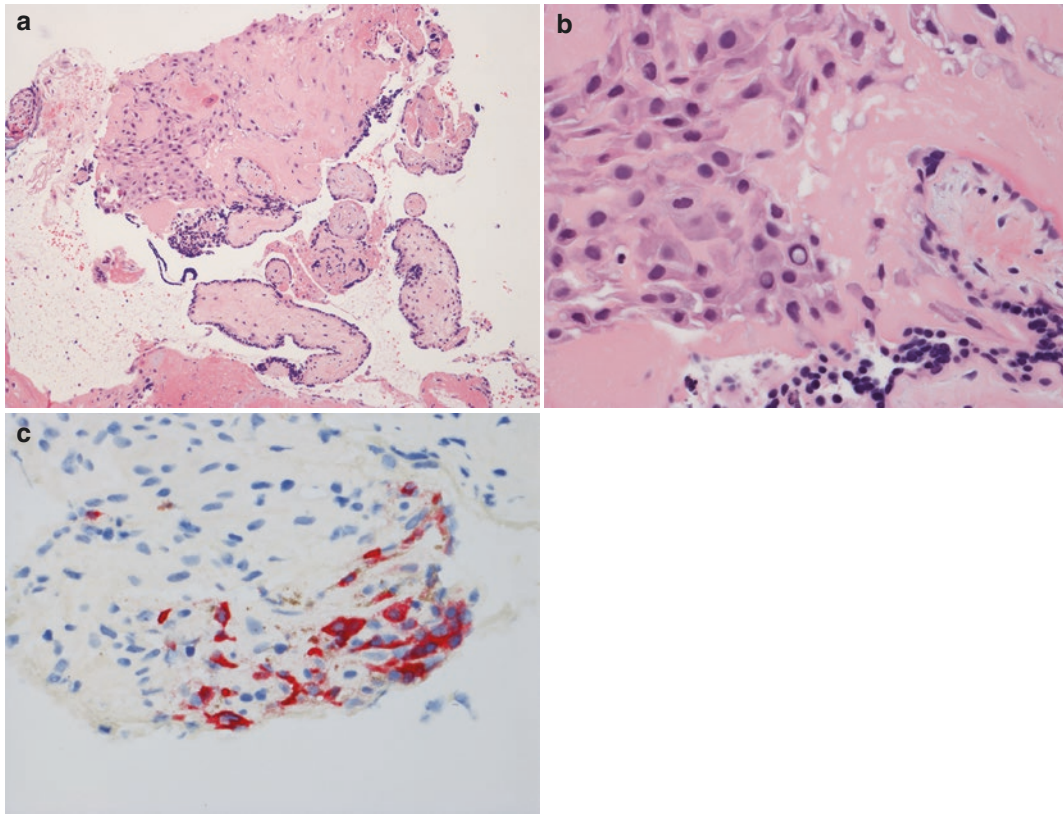

Fig. 31.2 Metastatic maternal malignant melanoma. (**a**) At low magnification the metastatic cells mimic extravillous trophoblast. (**b**) Higher magnification shows nuclear atypia and occasional nuclear pseudoinclusions. (**c**) Immunohistochemical staining with Melan A

by metastatic disease [35, 36]. In these cases the focus may be small, with a grossly unremarkable placenta. Microscopically there is often perivillous fibrin with cytologically atypical trophoblast arising from around villi (see Fig. 31.3). This should be considered with mothers with apparently metastatic disease after delivery or a baby with haemorrhagic lesions with no obvious cause. If treated, the disease can have a good response to therapy.

Sickle cell disease is included in this chapter as a maternal haematological disease affecting the placenta. Pregnancy in sickle cell trait is usually well tolerated, but the mothers with sickle cell disease are prone to veno-occlusive disease and crisis. The babies are often growth restricted and preeclampsia and placenta previa more common. The placenta is a hypoxic environment, and hence sickling is common (see Fig. 31.4). The histological changes of sickling can be seen, and this was suggested to be used diagnostically [37]. The sickling affects maternal blood flow and is associated with ischaemic changes in the placenta [38] and also ultrastructural changes in the umbilical cord. However, there are relatively few systematic studies of the morphological changes in the placentas of women with sickle cell disease.

31.7 Immunohistochemistry

Generally only relevant for confirming the presence of tumour cells and distinguishing from extravillous trophoblast. However, a low threshold for immunohistochemistry is prudent as the metastases may not be evident on haematoxylin and eosin staining.

31.8 Genetic Susceptibility

Not applicable

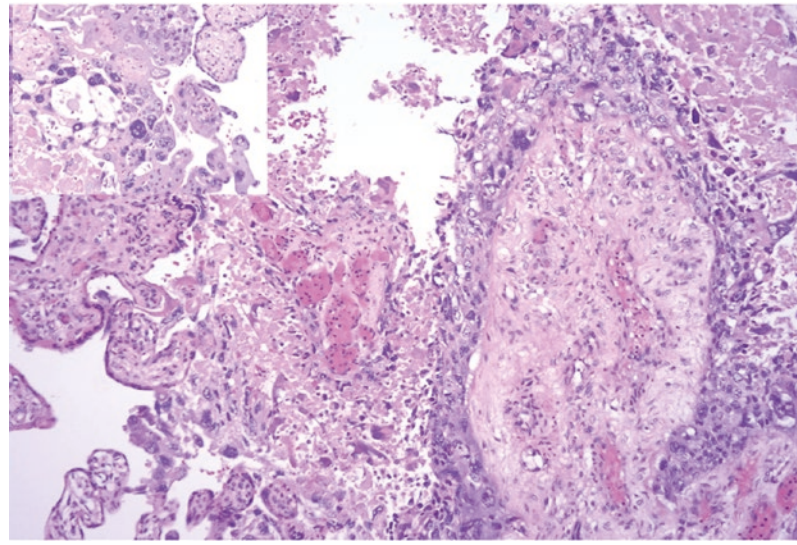

Fig. 31.3 Choriocarcinoma in situ. Baby born near term following abruption with a bleeding diathesis. Subsequently the baby died and the mother presented with metastatic disease a month or so later

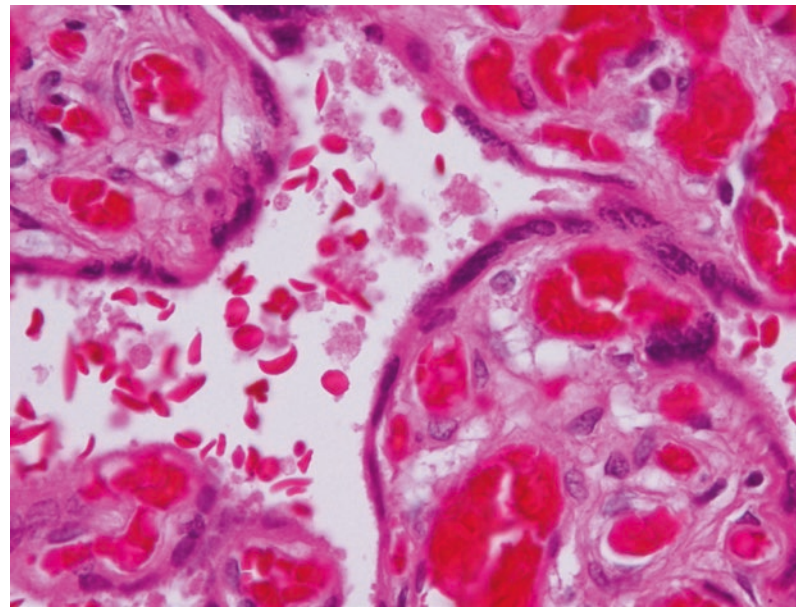

Fig. 31.4 Sickle cell crisis. Sickled red cells (drepanocytes) in maternal space

31.9 Prognosis and Predictive Factors of Maternal Metastatic Disease to the Placenta

The likelihood of placental metastasis appears greatest in patients with advanced disease and a high disease burden. The risk of fetal metastasis and subsequent death appears greatest in malignant melanoma and lung cancer [8, 15]. Tumour regression has been documented in rare cases both after and without chemotherapy. Some studies have looked at the issue of whether pregnancy is associated with relapse such as Hodgkin's disease and found no evidence [39] though other studies have shown a higher incidence of non-Hodgkin lymphoma in pregnancy [21].

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32 Pregnancy-Induced Uterine Vascular Remodelling and the Pathophysiology of Decidual Vasculopathy

Terry K. Morgan and W. Tony Parks

32.1 Introduction

Pregnancy-induced uterine vascular remodelling involves all levels of the uterine vasculature, and changes in vessels of all sizes are likely important for maintaining a healthy pregnancy (Fig. 32.1). However, the larger vessels, the myometrial radial and arcuate arteries, are only available to the pathologist in the very rare cases of hysterectomy around the time of delivery, and the histopathologic changes that develop in these vessels during pregnancy have not been well described [1–3]. At delivery, the pathologist receives the placenta and extraplacental membranes and cord. Usually, only a thin layer of decidua basalis from the placental bed remains attached to the maternal side of the placenta. The upstream myometrial arteries are retained in the uterus. Segments of the decidual spiral arteries can usually be identified within the narrow layer of basalis attached to the placenta. Consequently, it has been the decidual spiral arteries, not myometrial segments that have been most extensively studied and will be the subject of this chapter.

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Decidual vasculopathy is significant because it is associated with several major clinical obstetrical disorders, including preeclampsia, fetal growth restriction, preterm birth, and stillbirth [4–7]. A subject of intense research, it remains uncertain whether decidual vasculopathy is a cause of pregnancy complications, a consequence, or both. Recent work in animal models and human studies suggests that the answers to this causality problem may be on the horizon. It has long been thought that disorders such as preeclampsia and preterm birth represent final common pathways for disorder clusters of differing aetiologies, and indeed decidual vasculopathy may be associated with some phenotype subclassifications but not others [8–10].

32.2 Definitions

A plethora of terms has been proposed in the literature for the relatively small number of lesions detailed in this chapter. While most are reasonably precise and descriptive, those referring to abnormalities in the spiral artery muscular wall require modification to eliminate ambiguity. In general, the terminology employed in this chapter will follow those in our Amsterdam consensus paper as crafted by scores of placental pathologists [11].

Acute atherosis or *atherosis* is defined by the presence of foamy macrophages within the wall of a uterine vessel.

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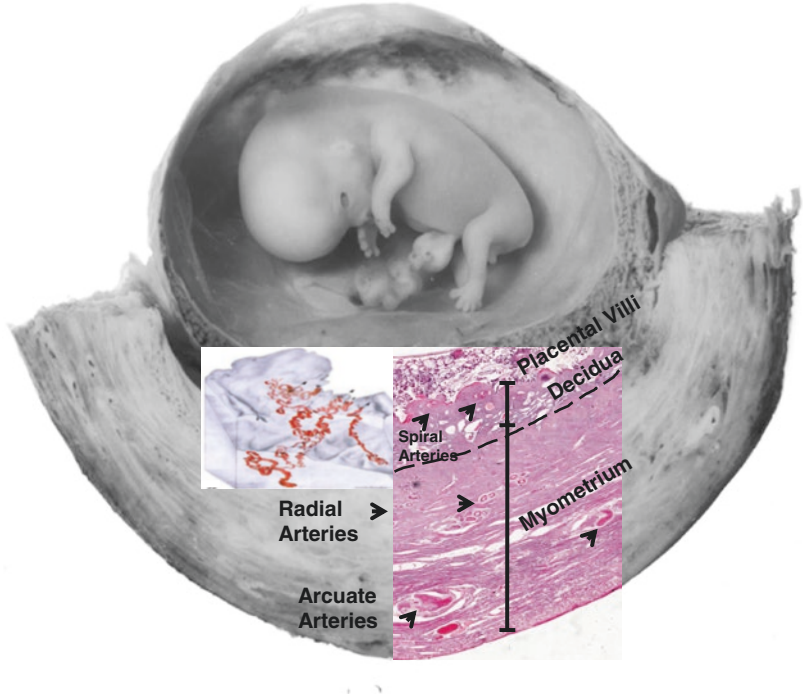


Fig. 32.1 *Pregnancy-induced uterine vascular remodelling*. Decidual spiral artery remodelling involves only the most distal aspect of a relatively much larger upstream vascular network that includes myometrial radial arteries and arcuate arteries. Recent studies suggest the radial arteries may be more important in the regulation of uteroplacental blood flow volume, while distal decidual spiral artery dilation may be more important for flux rate (speed of blood flow) to the placenta. This is important because rate of flow is related to shear stress damage, especially early in pregnancy when loose spiral artery plugs are impeding arterial flow to delicate chorionic villi. Elements of this figure used with the permission of the *Centre for Trophoblast Research* (https://www.trophoblast.cam.ac.uk/Resources/boyd-collection) derived from the Boyd collection [42] and 3D vascular reconstruction made by Harris and Ramsey [43]

Fibrinoid necrosis is an alteration of the uterine vascular wall characterized by a waxy or glassy, brightly eosinophilic degeneration in the absence of extravillous trophoblast (EVT) invasion.

Fibrinoid has two meanings in the pathology literature. In the general pathology literature, this term (as part of the two word phrase "fibrinoid necrosis") refers to a degenerative change of the arteriolar smooth muscle wall that may be seen in diseases such as lupus erythematosus, with immune complex deposition and fibrin leakage into the vessel wall. In the context of decidual vasculopathy, the term is used in two different circumstances. First, as a part of the process of spiral artery remodelling, EVTs and degenerating medial smooth muscle cells produce fibrinoid. This is part of normal EVT-induced physiologic change. Alternatively, the term fibrinoid necrosis is employed in placental pathology to refer to abnormal fibrinoid changes in the absence of EVT invasion.

Physiologic change is a specific term referring to the alterations in decidual spiral arteries and the distal aspect of myometrial radial/spiral arteries that develop following invasion of the vessels by placental extravillous trophoblasts (EVTs).

Vascular remodelling is a general term that encompasses the many changes that develop in the uterine vessels with pregnancy. Vascular remodelling is a structural change that involves cellular proliferation, growth, migration, changes in the extracellular matrix, and cell death. It is dependent on the dynamic interactions of local growth factors and haemodynamic changes. It is measured in vessel length changes, diameter

changes, and relationship between vessel wall area and luminal diameter [12].

Maternal vasculopathy (or *arteriopathy* [11]) refers to the group of related abnormalities in uterine vascular remodelling that occurs during pregnancy.

Incomplete physiologic transformation of the spiral arteries refers to a truncation of the EVT-mediated process of physiologic change in a spiral artery. In its most extreme form, the complete absence of trophoblast invasion along a spiral artery segment results in preservation of the smooth muscle wall. More commonly (particularly in the decidual segments), partial physiologic transformation takes place, with retention of some but not all of the smooth muscle wall, even in the presence of EVT invasion. Incomplete vascular remodelling is an acceptable synonym for this finding.

Mural hypertrophy is a secondary change that develops in spiral artery segments that did not completely undergo physiologic change. The alteration is similar to that seen in chronic hypertension, with hyperplasia and hypertrophy of the vascular smooth muscle wall.

Persistence of intramural endovascular trophoblast in the third trimester occurs when the extravillous trophoblast that migrate into the maternal vessels to form endovascular trophoblastic plugs fail to disintegrate during the second trimester of pregnancy [13, 14].

32.3 Synonyms

Maternal vasculopathy (or arteriopathy) is often referred to as decidual vasculopathy. This term is somewhat of a misnomer, since these abnormalities also occur in myometrial vessels in addition to decidual vessels. However, in the context of placental pathology, the term is acceptable. Decidua is the only maternal tissue that remains with the placenta after delivery, so the diagnoses that the pathologist makes will nearly always be based on findings from decidual vessels. In the research setting, or those rare instances where a uterus accompanies the placenta after delivery, lesions identified in myometrial vessels should be denoted by their specific diagnoses (e.g. acute atherosis) while reserving the overarching term "decidual vasculopathy" only for those lesions found in decidual vessels.

Absence of spiral artery remodelling has been used to describe some lesions of maternal vasculopathy, but this term imprecisely identifies the problem. These vessels have likely undergone a degree of vascular remodelling (changes in vessel length, size, etc.), but they have experienced only incomplete EVT-mediated physiologic change. Failed physiologic change is more accurate, although it may be misinterpreted as complete failure of physiologic change (absence of invasion by EVTs, with a resulting absence of physiologic change), even when that extreme form of decidual vasculopathy is not present. Persistence of muscularized basal plate arteries similarly implies a complete absence of physiologic change. Note, these alterations must be distinguished from normal decidual basal arteries, which also branch off of the radial arteries and do not undergo physiologic change.

32.4 Epidemiology

The incidence of decidual vasculopathy is difficult to determine with certainty. The largest comprehensive database of placental pathology from an essentially unselected population, the *Collaborative Perinatal Project* [15], only assessed fibrinoid necrosis and acute atherosis. They found fibrinoid necrosis in 1.74% of 41,142 placentas and acute atherosis in 0.42% of 41,696 cases. Overall, 2.00% of cases had fibrinoid necrosis, acute atherosis, or both. Kim et al. similarly reported acute atherosis in 2.2% of 14,786 placentas [16]. Incomplete physiologic transformation has been less well studied, but more than 10% of basal plate spiral arteries may show evidence of incomplete physiologic change [17, 18].

Importantly, decidual vasculopathy has two sets of strong associations. The first association is with other lesions of maternal malperfusion, such as accelerated villous maturation, increased syncytial knots, and villous infarctions [16]. The second association is with specific obstetrical

disorders, such as preeclampsia, fetal growth restriction, preterm birth (both spontaneous and medically indicated), and stillbirth [4–7, 17, 18].

Throughout the literature, there are surprisingly large variations in the reported prevalence rates for all types of decidual vasculopathy. This high degree of variability likely results from differences in the inclusion criteria for the placentas selected in the study (e.g. preeclamptic mothers, preterm births, etc.), the techniques employed for macroscopic examination and sampling of the placenta (particularly the number of sections taken and their locations in the placental bed), and the specific histologic criteria.

32.5 Gross Findings

The specific lesions encompassed within decidual vasculopathy are all microscopic and therefore not detectable macroscopically. Possible later effects of these lesions, such as a small placenta or multiple villous infarctions, can be identified by gross examination.

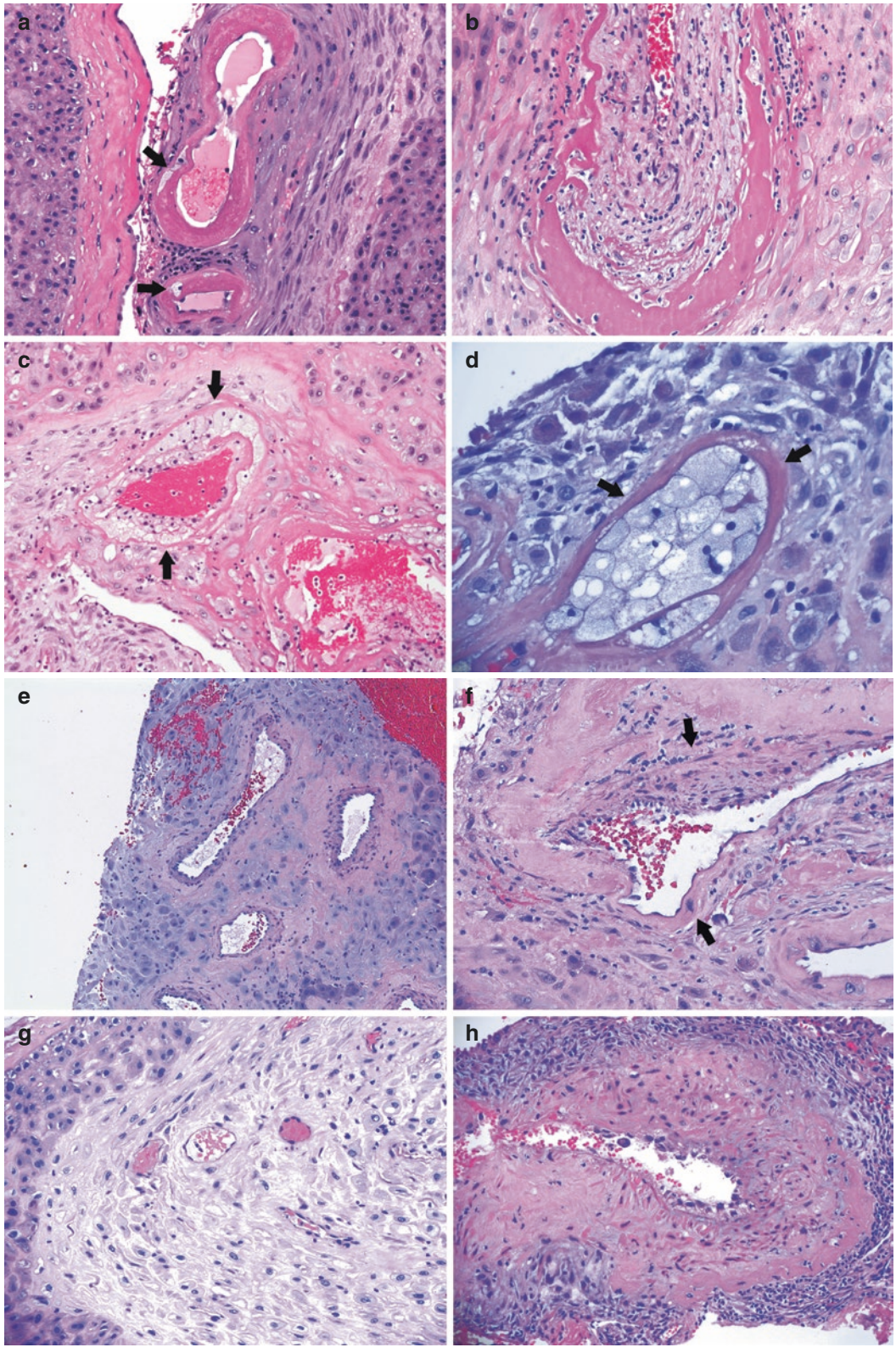
32.6 Histopathology

Decidual vasculopathy can have a range of appearances, including incomplete loss of the muscular wall, acute atherosis, and fibrinoid necrosis. In the myometrial segments, there may be completely intact muscular walls related to the so-called shallow placental invasion [19]. Interestingly, EVTs will generally be present (at least in the vicinity). In the decidual segments, EVTs are also generally present, but usually at least part of the vascular wall will be involved and show loss of smooth muscle with deposition of fibrinoid (Fig. 32.2).

The diagnosis of incomplete transformation of the spiral arteries is problematic. Not all basal plate spiral arteries remodel, even in an entirely normal pregnancy. In fact, more than 10% of spiral arteries in the placental bed may not remodel [17, 18]. In addition, basal arteries that do not undergo physiologic change may be mistaken for unremodelled spiral arteries. The basal arteries are small branches of the myometrial radial arteries that supply blood to the maternal decidua, but do not empty into the intervillous space—unlike spiral arteries. They do not undergo canonical physiologic conversion, their walls are not invaded by EVTs, and their smooth muscle walls are not lost [19].

While it is not incorrect to diagnose decidual vasculopathy in the presence of unremodelled basal plate spiral arteries, caution must certainly be used in the interpretation of this finding. The best remedy is thorough sampling of the decidua basalis attached to the placenta. Since physiologic change is more thorough in the central portion of

Fig. 32.2 *Decidual vasculopathy*. (**a**) Fibrinoid necrosis. This image from the extraplacental membranes shows two sections of vessel with fibrinoid necrosis of the wall. The arrows point to two lipid-laden macrophages within the fibrinoid material. A mild lymphocytic infiltrate is also present. (**b**) Fibrinoid necrosis. This image from the basal plate also shows fibrinoid necrosis of this vessel wall. The fibrinoid necrosis does not completely replace the smooth muscle wall. The inner aspect of the vessel wall shows retention of some smooth muscle. A mild lymphocytic infiltrate is scattered around the vessel. (**c**) Atherosis. In the centre of this image (between the black arrows) is a spiral artery segment showing extensive replacement of the smooth muscle wall by foamy macrophages. Only a thin rim of fibrinoid outlines the periphery of the vessel wall. (**d**) Atherosis. This image shows a small spiral artery segment occluded by foamy macrophages. Again, only a thin rim of fibrinoid outlines the periphery of the vessel wall. (**e**) Incomplete vascular remodelling. This spiral artery segment shows complete retention of the smooth muscle walls, with no appreciable EVT invasion or fibrinoid deposition. (**f**) Incomplete vascular remodelling. These spiral artery cross sections show focal retention of the smooth muscle wall (upper arrow), while the remainder of the wall has undergone physiologic transformation. The bottom arrow points to an EVT embedded within a thin layer of fibrinoid. (**g**) Normal decidual remodelling. This section from the extraplacental membranes shows several adjacent cross sections of spiral artery. The vascular smooth muscle wall is no longer present, but EVT has not invaded, and fibrinoid deposition has not occurred. A layer of EVT from the extraplacental membranes arcs across the left side of the image. (**h**) Mural hypertrophy. This spiral artery segment shows retention of the smooth muscle with prominent thickening. A significant chronic inflammatory infiltrate is also present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the placental bed, confining one's analysis to these sections can help to minimize the likelihood of misinterpreting an unremodelled vessel as decidual vasculopathy [20]. Similarly, since physiologic change is not necessary contiguous from distal to proximal, one should obtain deep levelled sections to confirm this diagnosis.

Spiral artery mural hypertrophy presents as a thickening of the normally thin and attenuated vascular smooth muscle wall (Fig. 32.2). Mural hypertrophy is primarily a finding of the extraplacental membrane roll. It can involve the arteries in the basal plate, but, since these vessels usually undergo physiologic change at least partially, mural hypertrophy is not commonly seen in the spiral arteries of the decidua basalis. Retention of vascular smooth muscle in the vessels of the extraplacental membranes is not sufficient for a diagnosis of decidual vasculopathy, because these vessels are not invaded by EVTs and are not expected to lose their medial layer; although, it is interesting that these arteries often undergo the early stages of pregnancy-induced vascular remodelling (Table 32.1). Finally, mural hypertrophy can be seen in the myometrial radial arteries in rare cases.

Fibrinoid necrosis of the spiral artery wall is an intensely orange-red, amorphous, waxy alteration (Fig. 32.2) [5]. A tight cuff of lymphocytes may surround the vessel wall, and EVTs are typically not present within the region of fibrinoid necrosis. While circumferential fibrinoid necrosis may be seen, incomplete forms, with only partial involvement of the vessel wall, may also be found (Fig. 32.2). While fibrinoid necrosis superficially resembles normal "physiologic change", the differences generally make the distinction easily determined. The fibrinoid found in normal remodelling is usually a lighter orange-red, and EVTs are frequently present within the fibrinoid of normal physiologic change.

Acute atherosis is a more definitive vascular pathology that may be present in areas of fibrinoid necrosis. Acute atherosis can also be found independent of fibrinoid necrosis, but this is less common. Acute atherosis is characterized by foamy macrophages present within the vessel wall (Fig. 32.2). Most often, these lipophages are embedded within fibrinoid necrosis, but, when abundant, they can extend into and even occlude the vascular lumen. Acute atherosis is reported to occur more commonly in the distal tips of decidual spiral arteries, and it is found less frequently in the myometrial segments [17].

Mural hypertrophy, fibrinoid necrosis, and acute atherosis can occur in the arteries of either the extraplacental membranes (see Chap. 43) or the basal plate (see Chap. 32). Incomplete physiologic transformation of spiral arteries can only occur in the vessels of the placental bed.

Table 32.1 Maternal and placental contributions to pregnancy-induced uterine vascular remodeling

Stage	Histologic observation	Contribution	Prime mediator(s)
1.	Angiogenesis, endothelial activation	MATERNAL*	Oestrogen, VEGF, uNK cells, changes in hemodynamics
2.	Spiral artery plugging and unplugging	COMBINATION	EVTs, marked changes in maternal hemodynamics
3.	Perivascular invasion by dendritic-like EVTs	COMBINATION	EVTs, interactions with maternal uNKs
4.	Medial invasion and increased PAS+ fibrinoid	COMBINATION	EVTs, fibroblasts, loss of smooth muscle cells
5.	Maternal vascular repair	MATERNAL	Re-endothelialization and intimal changes

*Stages of decidual spiral artery and distal myometrial radial/spiral artery response adapted from Pijnenborg 2006 [19]. They may be separated in terms of "maternal-related" and "placental-related" contributions. Since myometrial arterial segments are also involved, we prefer the term "maternal-related" rather than *decidualization* in stage 1. *VEGF* vascular endothelial growth factor; *uNKs* uterine natural killer cells; *EVTs* extravillous trophoblasts; *PAS* Periodic acid -Schiff stain

32.7 Immunohistochemistry

Immunohistochemistry has a limited role in the diagnosis of decidual vasculopathy. Diagnostic criteria are based on routine H&E histopathologic analysis, but smooth muscle markers such as desmin and/or h-caldesmon may be of utility in identifying and characterizing vascular smooth muscle. Alpha smooth muscle actin stains reactive myofibroblasts (present in vessels undergoing physiologic change) and should not be employed to stain for the absence of smooth muscle cells. EVTs are positive for pancytokeratin, human placental lactogen (hPL), HLA-C, and HLA-G. EVTs plugging the spiral arteries in the first trimester stain for NCAM (CD56), similar to uterine natural killer cells (uNKs).

32.8 Genetic Susceptibility

Most pregnancy-related genetic studies test for associations with pregnancy outcome [21, 22]. Genetic susceptibility for decidual vasculopathy is largely unexplored [23–26]. However, genetic anomalies in the placenta do seem to affect spiral artery remodelling. For example, shallow invasion and less remodelling are observed in cases of fetal aneuploidy [27]. Complete hydatidiform molar placentas seem to invade the decidua properly, but at least one study suggests they do not plug the spiral arteries properly [28].

It is exceptionally challenging to test for a relationship between maternal genetic susceptibility and decidual vasculopathy in humans. This is because cause and effect are difficult to prove. First trimester decidual tissue samples from miscarriage cases or elective terminations [23] are not linked to pregnancy outcomes at the time of delivery. They are a snap shot in time—an important time in spiral artery remodelling, but a tissue sample without an outcome. Conversely tissues obtained at the time of delivery may be linked to clinical outcomes, but they are confounded by systemic effects like hypertension and hyperlipidaemia associated with the pregnancy syndromes defined as the clinical outcome to be examined (e.g. medial hyperplasia and foamy macrophages may be the consequence of severe preeclampsia and not the cause).

To study maternal genetic susceptibility for decidual vasculopathy, we need better in vivo imaging methods to monitor uteroplacental blood flow throughout gestation [2, 29, 30]. Until then, animal models will be the subject of this type of study. At least in mice, differences in maternal gene regulation do seem to affect spiral artery angiogenesis [26]. However, mice are different from women. Unlike women, mice do not have spiral arteries until they get pregnant. Interestingly, spiral artery angiogenesis and dilation is complete by mid-gestation in mice, despite the absence of placental invasion until after this period [31], suggesting the early stages of spiral artery remodelling may be sufficient in mice during their brief gestational period (Table 32.1).

32.9 Pathophysiology

Decidual vasculopathy is a multifactorial syndrome that may be caused by maternal-related factors and/or placental-related factors. Maternal systemic disease like chronic hypertension, antiphospholipid syndrome, diabetes, gestational diabetes, and hyperlipidemia likely all contribute to the risk for decidual vasculopathy. However, most of the research to date has focused on abnormal decidualization and/or abnormal placental invasion as part of the underlying pathogenesis of decidual vasculopathy [19].

In brief, observations suggest that the pathophysiology of decidual vasculopathy may begin in the first trimester with perturbation of any of the five stages of vascular remodelling (Table 32.1). Stage 1 is a continuation of angiogenesis stimulated during proliferative and secretory phase of the menstrual cycle and progresses to endothelial activation (vacuolization and VCAM expression) and medial disorganization with increased fibrin deposition, which is also observed in ectopic pregnancies [32, 33]. It is currently uncertain whether placental factors contribute in a paracrine fashion to this stage. Stage 2 only occurs in the placental bed and requires plugging of the distal spiral artery interacting with the trophoblastic shell (Fig. 32.3). The plugs are composed of CD56+ EVTs and are

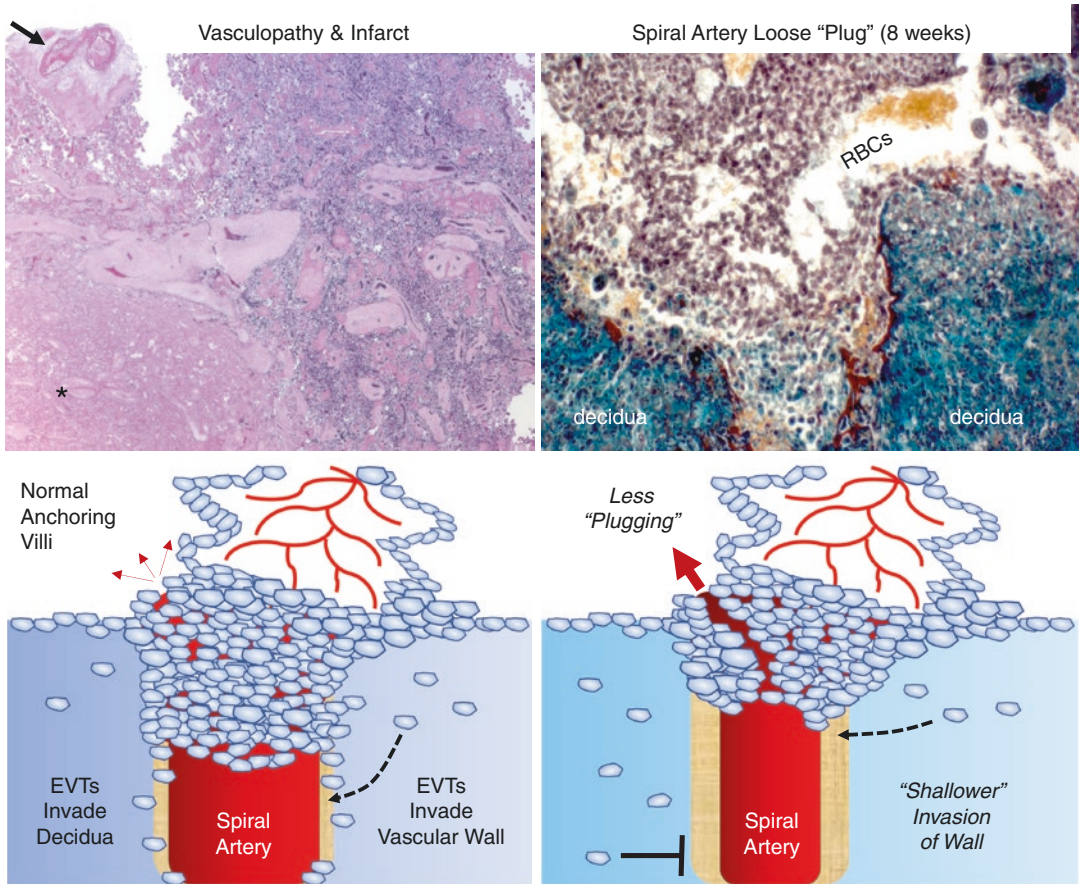

Fig. 32.3 *Abnormal placental invasion and decidual vasculopathy*. Decidual *vasculopathy (top left arrow) may be associated with features of placental malperfusion,* including placental infarctions (asterisk). Does that mean vasculopathy is the cause? The current dogma claims that spiral artery invasion by the placenta (top right) during the first trimester of pregnancy mediates normal remodelling (bottom left). This involves both transient "plugs" and progressive invasion of the vascular media. The so-called "shallow" invasion, or "abnormal *decidualization*," of these vessels could impair normal remodelling (bottom right), leading to abnormal intervillous blood flow, placental damage, and increased risk of pregnancy complications

only loosely held together with desmosomes [2], but they impede arterial blood flow until progressive disintegration after 7 weeks [1, 2]. Arterial blood flow obstruction would be expected to increase upstream pressure and stimulate relative medial hyperplasia/hypertrophy. Subsequent dissolution of the plug would decrease resistance and increase blood flow into the intervillous space and would be expected to stimulate dilation and attenuation of the artery. [12] Stage 3 requires the interaction of invading EVTs with their HLA-C genetic polymorphisms and the maternal immune response, including uterine natural killer cells with their variable KIR receptors for HLA-C [34]. Stage 4 is the classic "physiologic change", [35] which requires placental EVTs embedded in the wall of dilated arteries with increased fibrinoid deposition. This type of change only happens in the placental bed, and by definition the term physiologic change may only be used to describe this stage of remodeling [19, 33]. Stage 5 is the maternal response to vascular injury during placentation and is especially critical to the myometrial segments involved since they also undergo physiologic change, but are not shed like decidua at the time of delivery (Fig. 32.4).

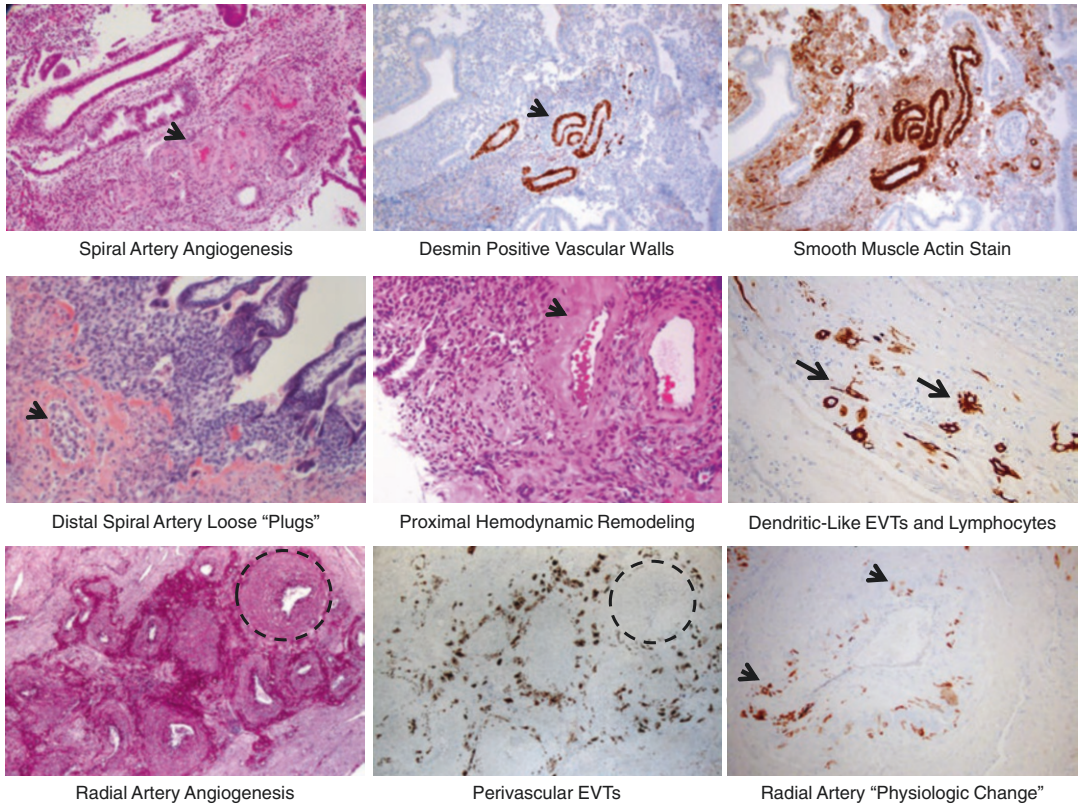

Fig. 32.4 *Representative histology of uterine vascular remodelling stages*. There is a growing consensus that pregnancy-induced vascular remodelling occurs in stages. The first stage is maternally-mediated angiogenesis leading to longer decidual spiral arteries, radial arteries, and likely arcuate arteries that coil in their adventitia. Medial smooth muscle is maintained and is best highlighted by desmin or h-caldesmon (not smooth muscle actin, which is not specific). The second stage is distal spiral artery "plugging" by extravillous trophoblasts (EVTs) that invade the vascular lumen—plugs are present at 6 weeks and progressively disintegrate beginning at 7 weeks; the obstructive plugs and subsequent opening into the intervillous space affect haemodynamic driven changes in vascular remodelling that occur more proximally and are independent of direct invasion of the vessel wall by EVTs. The third stage involves placental EVTs with dendritic-like processes invading the decidua, interacting with the maternal immune system, and eventually invading into "primed" arteries to complete "physiologic change" (strictly defined as presence of EVTs in the wall). The same process occurs in the myometrial radial/spiral arteries in the early second trimester. This is completed by 18 weeks gestation

32.10 Early Diagnosis

Currently, decidual vasculopathy can only be diagnosed on placental pathologic examination. Abnormal pregnancy-induced uterine vascular remodelling cannot be diagnosed prior to delivery. New imaging approaches to measure uteroplacental blood flow early in pregnancy like 3D power Doppler [36], MRI [30], and contrast-enhanced ultrasound [2] are increasingly employed for research purposes, but they have not been validated for clinical testing. Monitoring placental invasion in vivo may require liquid-based biomarkers in maternal blood [37] that could be followed throughout pregnancy, correlated with pregnancy outcomes, and validated using first trimester elective termination decidual specimens.

32.11 Potential Therapies

There are currently no clinically accepted interventions targeting the treatment or prevention of decidual vasculopathy. There have been a number of trials designed to treat oxidative stress in pregnant women using vitamin C, vitamin E, or aspirin [38–40], but they have been largely disappointing. As of this writing, there is a planned clinical trial to test the impact of VEGF delivery to the uterine vasculature using an approach "validated" in pregnant guinea pigs. [41] The hypothesis is that VEGF delivery to the uterine artery will improve downstream angiogenesis and ameliorate potential decidual vasculopathy in women with a history of severe early onset pregnancy complications.

Unfortunately, the overarching problem is that decidual vasculopathy is multifactorial, and until we better understand the pathophysiology, have means for early diagnosis, and a more rational approach to personalized intervention, it is unlikely that generalized population-based therapies will reduce the prevalence of this pathology.

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Chronic Deciduitis

33

Suzanne M. Jacques, Faisal Qureshi, and Linda M. Ernst

33.1 Introduction

Chronic deciduitis is one of the chronic inflammatory lesions of the placenta, the involved placental compartment being the decidua [1]. It is diagnosed in the presence of plasma cells and lymphocytes, or in the absence of plasma cells, diffuse and intense non-perivascular lymphocytes [1]. Chronic deciduitis is frequently seen in association with chronic chorioamnionitis and VUE [2]. The association of chronic deciduitis with other placental chronic inflammatory lesions supports it being a histologic manifestation of maternal anti-fetal rejection; however, the possibility of microbial infection of the endometrium must also be considered as a cause [3]. The association of chronic deciduitis with higher rates of IgG class I and IgG class II HLA panel antibodies [4] and placental C4d deposition [5] when compared to controls supports the association of chronic deciduitis with maternal immune response to fetal antigens, rather than to infection. Chronic deciduitis is more frequent in placentas resulting from egg donor pregnancies (immunogenetically unrelated to the mother) when compared to non-egg donor pregnancies (semi-allografts) [6, 7] also supporting an immune mechanism. Chronic deciduitis is an association with preterm labour [8].

33.2 Definition

Chronic deciduitis is diagnosed in the presence of lymphoplasmacytic inflammation in the decidua or, in the absence of plasma cells, the presence of diffuse and intense (>50/HPF) non-perivascular lymphocytic inflammation.

33.3 Synonyms

Lymphoplasmacytic deciduitis, Chronic lymphoplasmacytic deciduitis, Chronic deciduitis with plasma cells, Chronic plasma cell deciduitis, Chronic lymphocytic deciduitis.

33.4 Epidemiology

Chronic deciduitis is a commonly diagnosed lesion. It is more frequent in preterm compared to term placentas, having been reported in 8–25% of preterm compared to 2–13% of term placentas [2, 9].

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Chronic deciduitis is frequently seen with chronic chorioamnionitis [2] and VUE, particularly basal chronic villitis [2, 10]; however, it is not uncommon to see chronic deciduitis in isolation [2]. Chronic deciduitis is also frequently seen in decidualized endometrium from first trimester spontaneous miscarriage, having been reported in 9–20% of chromosomally normal and 4–30% of chromosomally abnormal spontaneous miscarriage [5, 11]. It is particularly common in recurrent chromosomally normal spontaneous miscarriage [11]. In comparison, it has been reported in 0% of elective abortions [5].

33.5 Gross Findings

Chronic deciduitis is not associated with any gross morphologic changes in the basal plate or the placental disc.

33.6 Histopathology

Chronic deciduitis is diagnosed when plasma cells and lymphocytes are identified in the decidua (Figs. 33.1 and 33.2) or there is diffuse and intense lymphocytic infiltration (>50/HPF) [1]. Plasma cells are frequently present in small scattered clusters admixed with the lymphocytes, although they can be sparse. There are no current data to correlate the numbers of lymphocytes or plasma cells with clinical outcomes; however, this quantification of lymphocytes represents an agreed-upon definition by the authors allowing for reproducibility and future research. The lymphocytes should be non-perivascular, as lymphocytes in a perivascular location may be seen with maternal vasculopathy, and therefore may have a different connotation. As chronic deciduitis is associated with other chronic inflammatory lesions, especially basal chronic villitis [2, 10], the presence of basal chronic villitis should prompt a search for chronic deciduitis.

33.7 Immunohistochemistry

Immunohistochemical stains for CD138 will highlight plasma cells but are not necessary to confirm the diagnosis (Fig. 33.3).

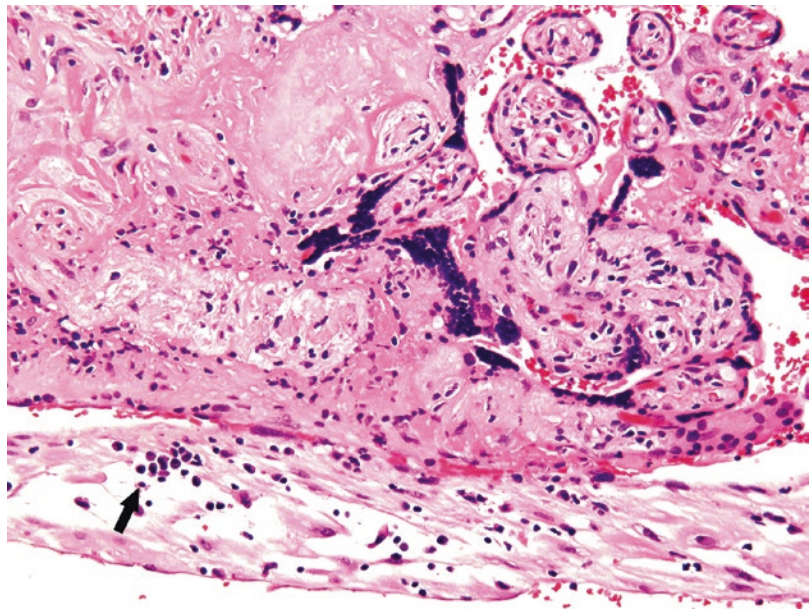

Fig. 33.1 Chronic deciduitis: the basal decidua is infiltrated by plasma cells (arrows) and lymphocytes. Basal chronic villitis is also present in the adjacent anchoring villi

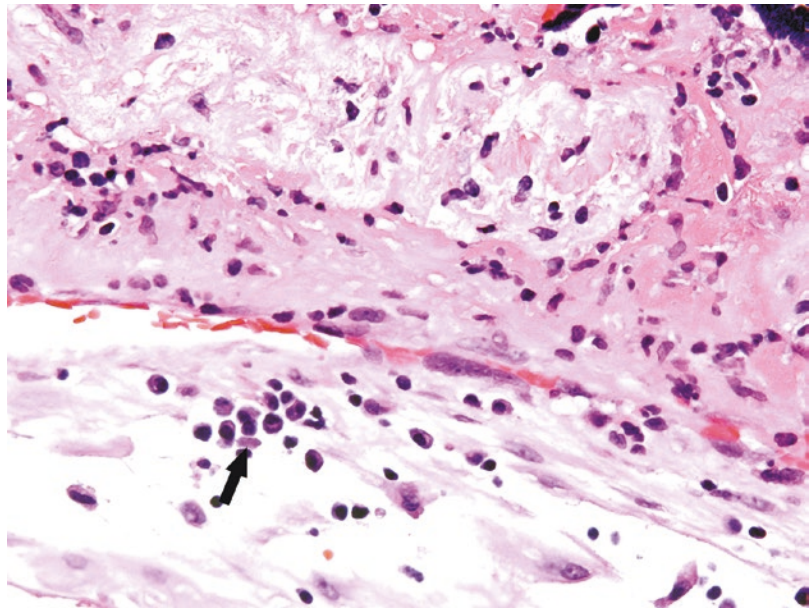

Fig. 33.2 Chronic deciduitis: plasma cells are seen in the inflammatory infiltrate in the basal decidua (arrows)

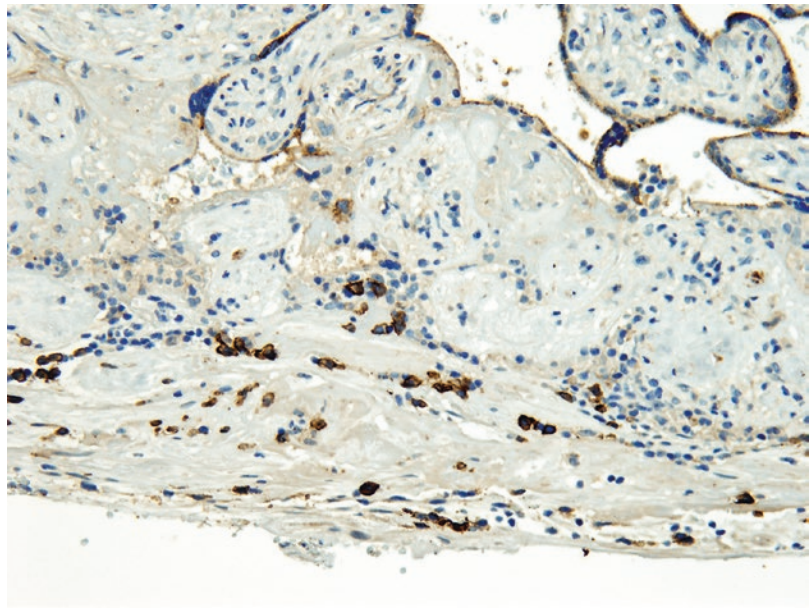

Fig. 33.3 Chronic deciduitis: immunohistochemical staining for CD138 highlights the plasma cells

33.8 Genetic Susceptibility

Currently, there is no known genetic susceptibility to develop chronic deciduitis.

33.9 Prognosis and Predictive Factors

Chronic deciduitis is an association with preterm labour [2, 8]. It is also an association with

chromosomally normal and abnormal spontaneous miscarriage [5, 11], being particularly frequent in recurrent spontaneous miscarriage [11], supporting a role for maternal anti-fetal rejection in early fetal loss. Chronic deciduitis is frequently associated with C4d deposition in the placenta in spontaneous miscarriage, a feature of classical complement pathway activation, and it has been proposed that this might be a mechanism of placental and fetal injury [5]. A recent study has shown an association of basal chronic deciduitis with morbidly adherent placenta; however, the role of chronic inflammation in the pathogenesis of abnormal placental adherence is unclear [12]. As with other chronic inflammatory lesions of the placenta, the antigenic stimulation eliciting the inflammation is not known. The association of chronic deciduitis with preterm labour and spontaneous miscarriage requires further investigation. Most studies have required the presence of plasma cells for the diagnosis of chronic deciduitis, and the significance of chronic deciduitis with plasma cells may be different from that without plasma cells.

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Basal Plate Myometrial Fibres

34

Linda M. Ernst, Suzanne M. Jacques, and Faisal Qureshi

34.1 Introduction

The basal plate has a complex architecture characterized by multiple layers of maternal and fetal tissue [1], including a layer known as the separation zone at which the placenta separates from the uterus during labour and delivery. Abnormalities of implantation and/or separation of the placenta can lead to myometrial fibres attached to the basal plate. While on occasion grossly recognizable fragments of myometrium might be seen attached to the basal plate, the presence of basal plate myometrial fibres (BPMF) is predominantly a histologic finding.

More generally, BPMF can be used to represent a spectrum of changes seen in the delivered placenta that culminate with diagnostic findings of placenta accreta. In hysterectomy specimens, placenta accreta is defined as implantation of chorionic villi upon myometrium without intervening decidua [1]. Most placentas with BPMF show the presence of basal decidua of variable thickness, ranging from normal to absence. Therefore, the spectrum of BPMF is defined by the amount of decidua between the myometrium and chorionic villi and surrounding basal fibrin (Rohr's fibrin).

34.2 Definition

BPMF is the presence of myometrial fibres adherent to the basal plate/maternal surface of the placenta (Fig. 35.1).

34.3 Synonyms

Occult placenta accreta, Basal plate with adherent myometrial fibres, Mild placenta accreta, Histologic placenta accreta

34.4 Epidemiology

Large multi-institutional studies examining the incidence of BPMF have not been performed; however, the reported incidence of BPMF ranges from as low as 0.9% to up to 40% [2–5]. Location and extent of sampling can certainly affect the incidence of BPMF [3]. BPMF have been reported more commonly in preterm placentas

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than term placentas [5]. Diagnostic placenta accreta is a rare finding in delivered placentas of patients with no significant risk factors for accreta [4, 6]; however, the incidence of BPMF has been shown to be higher in patients who develop placenta accreta in a subsequent pregnancy [4, 7].

The clinical term "morbidly adherent placenta" (MAP) encompasses the continuum of placenta accreta, increta and percreta, and the incidence of MAP has been increasing in parallel with the increasing caesarean section rate and occurs in up to 3 per 1000 pregnancies [8–11]. MAP is an important cause of massive obstetrical haemorrhage, maternal death, and is the most common indication for caesarean hysterectomy [8]. Risk factors include prior caesarean section(s), placenta praevia, uterine instrumentation, endometrial ablation, submucosal leiomyoma, Asherman syndrome, and advanced maternal age [12, 13]. Defective decidualization is a leading theory explaining the pathogenesis of placenta accreta. Because decidual cells play a role in regulation of trophoblast invasiveness, control of the maternal immune response, and protection from oxidative stress, proper decidualization of the endometrial stroma is required for normal implantation and separation of the placenta [14].

34.5 Gross Findings

BPMF is a histologic diagnosis, but on rare occasions large portions of myometrium may be attached to the maternal surface of the placenta. A careful histologic search for diagnostic findings of accreta should be sought when grossly visible myometrial fragments are present on the delivered placenta. The junction between the smooth surface of intact and ragged disrupted basal plate is often the site of BPMF [3].

34.6 Histopathology

Adherent myometrial fibres are easily recognized on haematoxylin- and eosin-stained sections of the basal plate oriented on edge because they demonstrate a more eosinophilic cytoplasm than the adjacent decidual or extravillous trophoblast cells at scanning power. At higher power, the myometrial fibres may be seen as small clusters of smooth muscle cells oriented longitudinally or on cross section with boxy to cigar-shaped nuclei [2–7]. In the most superficial cases of BPMF, myometrial fibres are attached at the separation zone of the basal plate, and numerous layers of basal decidua are present (Fig. 34.1). Less

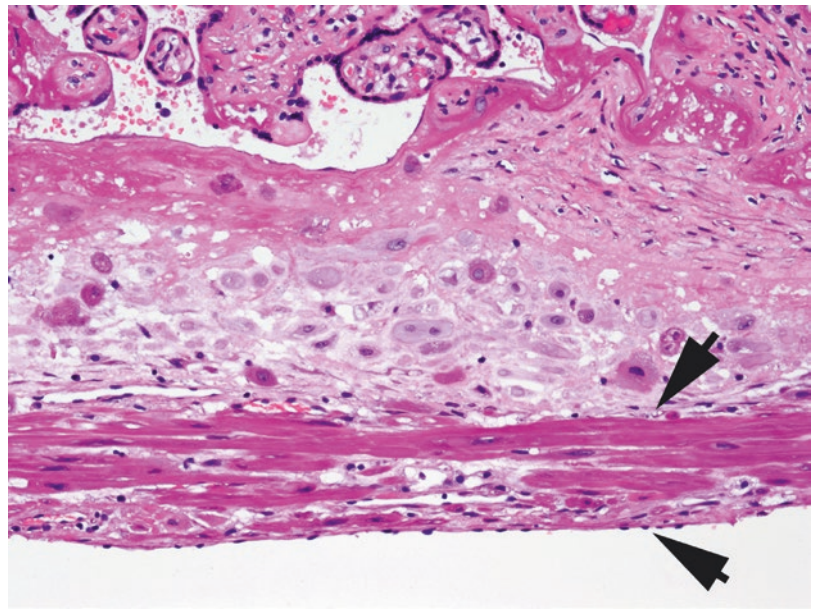

Fig. 34.1 BPMF: basal plate showing longitudinally arranged myometrial fibres (between arrows) at the separation zone. Note the relatively thick decidual layer with a few extravillous trophoblast cells between the intervillous space and the myometrial fibres

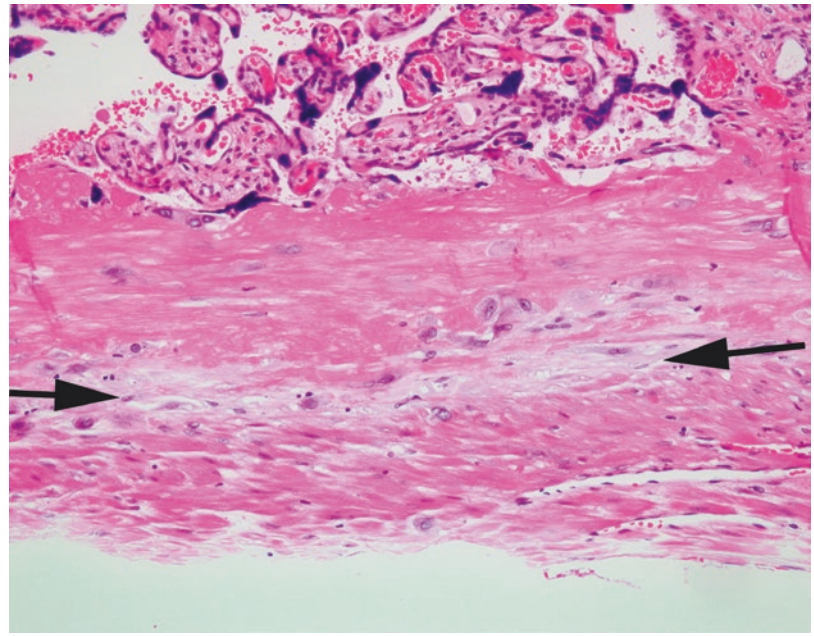

Fig. 34.2 BPMF with changes suggestive of accreta: basal plate showing longitudinally arranged myometrial fibres at the lower aspect of the image. Note the relatively thin decidual layer (between arrows) separating the myometrial fibres from Rohr's fibrin layer

frequently, the decidual layer between chorionic villi and myometrium is reduced into two cell layers or less, and this has been called "BPMF with changes suggestive of focal accreta" (Fig. 34.2) [4]. When the myometrial fibres are in contact with basal chorionic villi and/or Rohr's fibrin, a diagnosis of "histologic accreta" can be made (Fig. 34.3).

Associated placental pathologic findings include decreased placental weight, evidence of intrauterine bleeding, separate retroplacental blood clot, findings of maternal vascular malperfusion, chronic basal villitis, and plasma cell deciduitis [5, 15, 16].

34.7 Immunohistochemistry

BPMF are generally fairly easily recognized by careful review of routine haematoxylin and eosin sections of the maternal surface. Smooth muscle actin immunohistochemistry can be used to highlight the myometrial fibres, but is generally not needed or recommended in routine practice.

34.8 Genetic Susceptibility

There is no known genetic susceptibility for BPMF; however, there may be genetic contributions affecting decidualization or trophoblast invasiveness, as up to 18% of MAP occurs in nulliparous women without significant risk factors for accreta [10].

34.9 Prognosis and Predictive Factors

More research is needed to determine the prognostic significance of BPMF. While most agree not all forms of BPMF represent diagnostic placenta accreta, BPMF may be an indication of abnormal placentation with abnormally deep trophoblastic invasion [5]. BPMF may also be an indication of focal accreta elsewhere along the basal plate or alternatively be a risk factor for inadequate decidualization in the next pregnancy. Case-control studies have demonstrated that the presence of BPMF increases the risk of developing morbidly adherent placenta in a

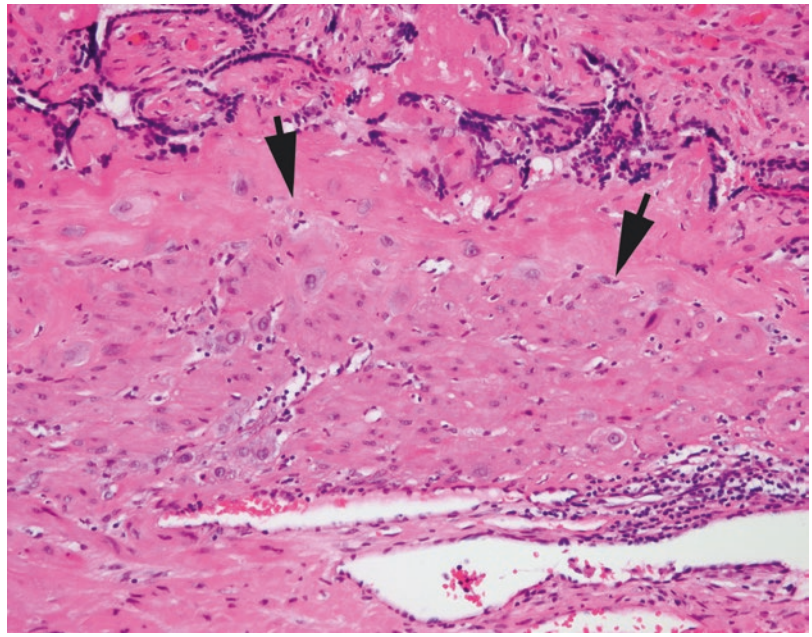

Fig. 34.3 BPMF with changes consistent with histologic accreta: basal plate showing myometrial fibres occupying the majority of the basal plate and adjacent to Rohr's fibrin layer (arrows). No intervening decidual is apparent

subsequent pregnancy [4, 7]. The risk is greater when the decidua separating the myometrial fibres from chorionic villi or Rohr's fibrin is ≤2 layers thick or when there is a large quantity of attached myometrium [4]. Furthermore, it has been shown that adding BPMF to a clinical algorithm along with other risk factors for accreta such as placenta praevia and previous caesarean section can help to predict the risk of subsequent MAP [7]. Additional clinical studies utilizing prenatal imaging and testing with imaging pathological correlation are needed to further refine the clinical significance of BPMF.

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Basal Plate Laminar Necrosis

35

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35.1 Introduction

Basal plate laminar necrosis or diffuse decidual leukocytoclastic necrosis (DDLN) is a diffuse band of coagulative necrosis at the chorio-decidual interface, admixed with karyorrhectic debris [1]. Little is known in the literature about the clinicopathologic correlations of DDNL. Decreased uteroplacental perfusion is suggested as a cause of DDLN [1] although this is not yet established.

35.2 Definition

A band of coagulative necrosis variably admixed with a deeper region containing karyorrhectic debris at the maternal surface of the placenta in at least one of the slides examined [1].

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35.3 Synonyms

Diffuse decidual leukocytoclastic necrosis of the decidua basalis; Laminar necrosis; Bland necrosis; Leukocytoclastic necrosis; Linear necrosis.

35.4 Epidemiology

DDLN is found in 27% of the placentas of infants born at 23 to 32 weeks of gestation and only in 2.2% of term pregnancies [1].

DDLN is significantly correlated with preterm delivery in women with preeclampsia (57.6%) and is also encountered more frequently in women with an indicated preterm birth (61.9%) and in women with a history of indicated preterm birth (12.7%). DDLN is more strongly associated with preeclampsia than decidual necrosis of the placental membranes [1]. DDLN is also associated with fetal growth restriction. An association with diabetes, smoking, chorioamnionitis with/without fetal response and/or a positive placental culture and a diagnosis of placental abruption could not be found. There was a negative association with neonatal systemic inflammatory response syndrome [1].

A similar lesion is seen at the chorio-decidual interface in the extraplacental membranes (Chap. 42) [2].

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35.5 Gross Findings

It is essentially a microscopic diagnosis.

35.6 Histopathology

There is band-like distribution of coagulative necrosis with loss of basophilia of the decidual cells in the basal plate of the placenta (Fig. 35.1). This may be admixed with karyorrhectic debris (Fig. 35.2) [1]. It is often associated with an overlying infarct.

It should be distinguished from Nitabuch's membrane, which is the fibrinoid material at the trophoblastic-decidual interface, a normal finding of the basal plate [1]. The presence or absence of trophoblastic and/or decidual ghost cells could be helpful to distinguish between the two.

So far, no grading for DDLN has been proposed although a cut off value of 30% or more of the maternal surface in at least one of the slides examined is given [1].

35.7 Prognosis and Predictive Factors

The recurrence risk and associations with recurrence are not presently known.

35.8 Recommendation and Future Research

Thus far, diffuse decidual leukocytoclastic necrosis (DDLN) has been described in one publication only. More research is needed to ascertain the incidence in normal pregnancies, in complicated pregnancies and in preterm versus term pregnancies. Whereas the amount of necrosis is said to be 30% in one slide for basal

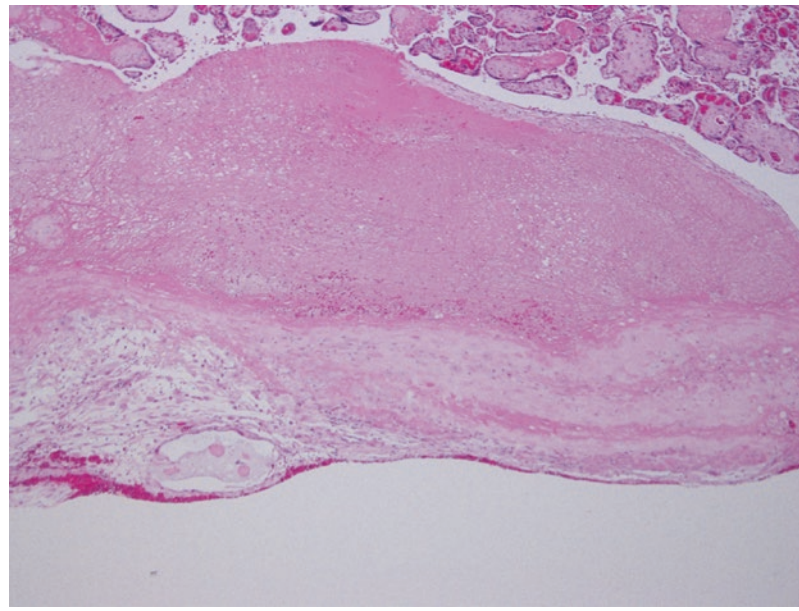

Fig. 35.1 Bland necrosis in the basal plate

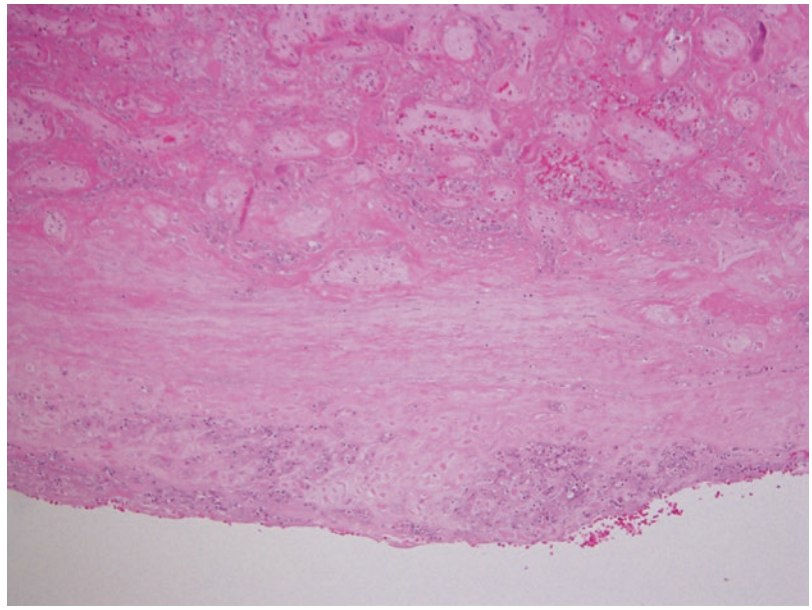

Fig. 35.2 Band-like necrosis with karyorrhectic debris in the basal plate, associated with an overlying infarct

laminar necrosis [1], it varies between 10% and 30% for the similar lesion in the extraplacental membranes [1, 2]. The percentage of basal plate will vary depending on how much is sampled, if it is placed on long axis or short axis of the slide and also if the full-thickness block is split in two when it is a thick block. Because of this being an arbitrary lesion, we recommend to state if it is present or not instead of using a cut off value.

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36 Retroplacental Haematoma/ Haemorrhage

Robert W. Bendon

36.1 Introduction

The microscopic lesions of retroplacental haemorrhage (RPH) include the changes in the basal decidua, the changes in the overlying villi and the correlated findings in decidual arteries (see Chap. 9 for description of gross findings).

36.2 Synonyms

The pathologic finding is retroplacental haemorrhage or haematoma. The clinical diagnosis is placental abruption. The correlation between the pathological and the clinical diagnosis of abruption is poor (see below).

36.3 Histopathology

36.3.1 The Basal Decidua

Microscopically a portion of the RPH may be seen attached to the basal decidua. Red blood cells, often distorted and elongated, may be found within the decidua. In stillborn infants with an interval from death to delivery determined by histologic organ criteria, the earliest histological response to a placental separation is the migration of neutrophils into the basal plate of the placenta (Fig. 36.1) [1]. In extensive haematomas, neutrophils are often most identifiable at the margin of the haematoma. Over time, the basal plate will show progressive coagulation necrosis.

36.3.2 Overlying Villous Infarction

The immediate effect of RPH and placental separation on the overlying placenta is the loss of maternal blood circulation. The villous changes are the same as those with infarction due to the occlusion of a spiral artery but extend over the entire area of the RPH. The progression of the infarction can estimate the duration of the RPH from occurrence to delivery. The earliest change of infarction is marked vasodilation and collapse of the intervillous space. The villi may also show acute intravillous haemorrhage, often adjacent to the RPH and more frequent in younger gestation (Fig. 36.2) (Chap. 23) [2]. However, intravillous haemorrhage is not pathognomonic for RPH.

36.3.3 Vascular Lesions

One postulated aetiology of retroplacental haemorrhage is the rupture of a vessel in the basal decidua with an expanding haematoma. Most spiral arteries beneath the placenta undergo a complex trophoblastic remodelling that results in

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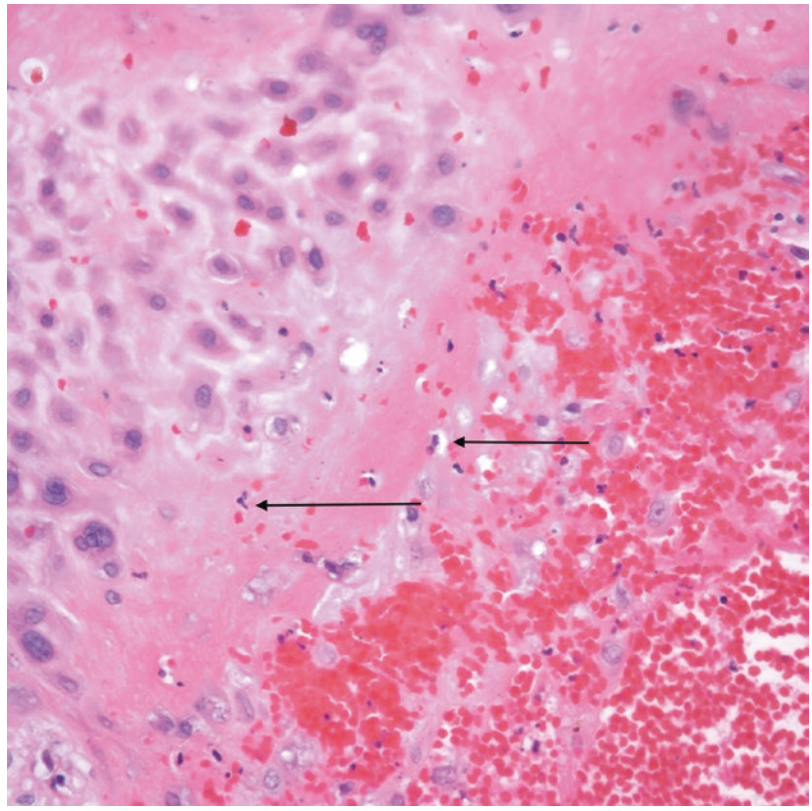

Fig. 36.1 This photomicrograph of a placenta with a very acute RPH demonstrates sparse neutrophils entering the basal plate of the placenta (arrows). The upper left corner is composed of the cytotrophoblast of the plate and, below, there is acute haemorrhage disrupting the decidua

loss of medial muscle and replacement of some endothelium with cytotrophoblast. In preeclampsia, this process is hypothesized to be abnormal and the abnormal remodelling could underlie the risk of RPH. To test this hypothesis, direct observation of a ruptured artery in abruption has been attempted with placental bed biopsies. A ruptured decidual artery in continuity with a small basal decidual haemorrhage was identified using serial sections in a placenta with a larger 25% placental separation from a woman with eclampsia [3]. Another study of placental bed biopsies beneath abruption demonstrated myometrial haemorrhage and abnormal vessels in 12 of 18 patients but no direct evidence of a ruptured vessel [4].

The hormonally sensitive basal spiral arteries in decidua that have not been remodelled by trophoblast can demonstrate acute atherosis in preeclampsia as demonstrated by placental bed biopsies [5]. In one study of fetal membranes, acute atherosis was found only seven times in 174 cases of RPH associated with toxaemia [6]. As indirect evidence of arterial bleeding, a study found that decidual haemosiderin beneath the placenta correlated with preterm pregnancy-induced hypertension and non-hypertensive abruption [7]. The basal arteries attached to the decidua above RPH may demonstrate haemorrhage (Fig. 36.3). Elevated systemic blood pressure in the mother could also contribute to vascular rupture, especially in weakened vessels. Specific pathologic or even clinical risk factors for RPH in patients with preeclampsia remain unknown.

36.4 Clinical Correlations and Risks

36.4.1 The Timing of an RPH

The histologic estimate of duration of the RPH based on the overlying infarction can be correlated with the time of death in stillborn infants [1].

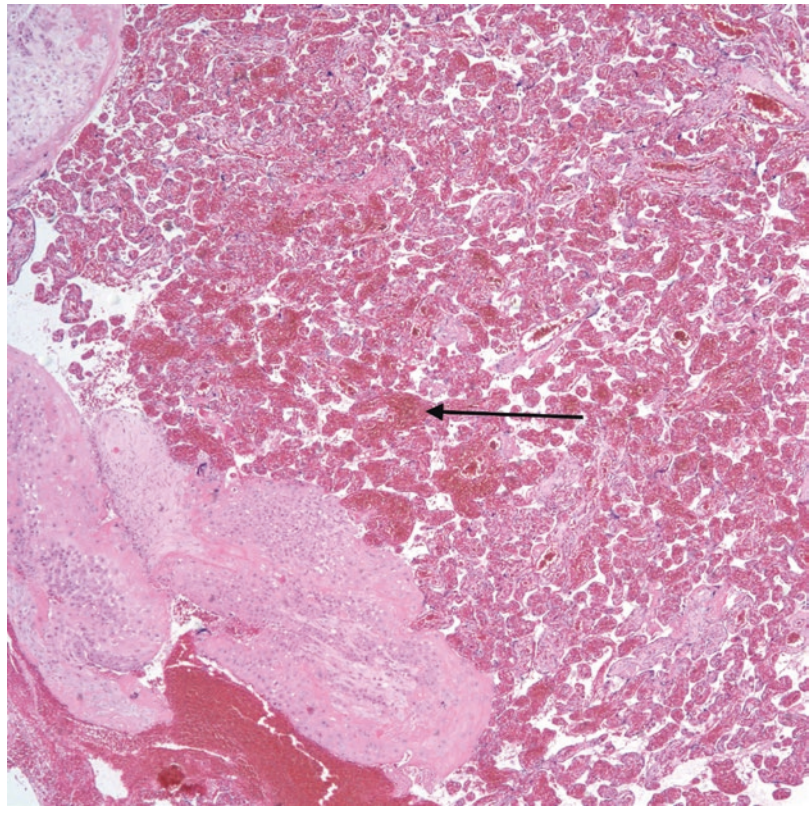

Fig. 36.2 This is a photomicrograph of the villi over an acute RPH (lower right corner) with multiple villi demonstrating distention by haemorrhage (arrow pointing to one example)

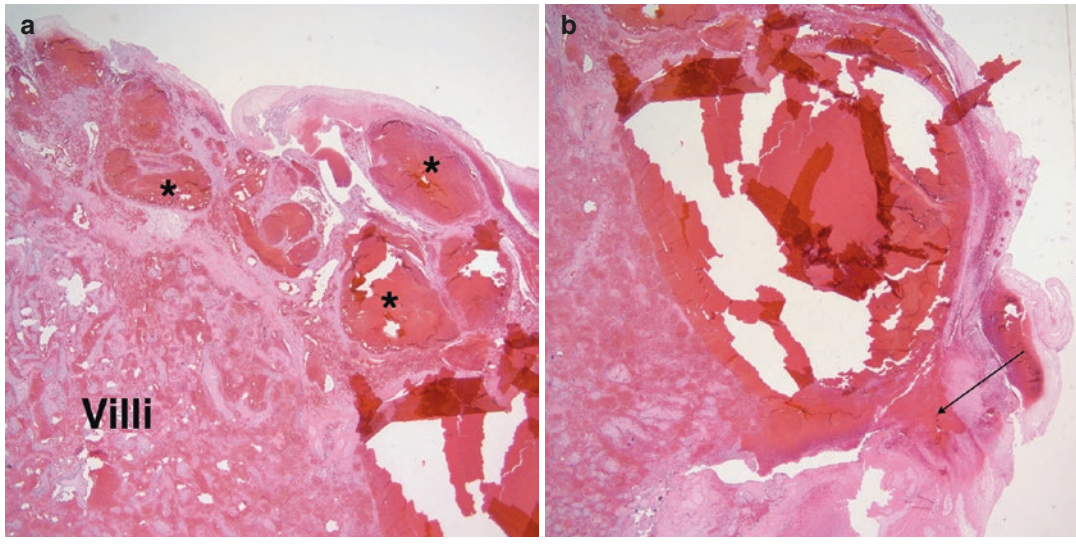

Fig. 36.3 (**a**) This photomicrograph demonstrates dilated vascular lumens (*), most likely profiles of a spiral artery beneath an RPH. The villi show acute changes of compression of the intervillous space and dilated fetal capillaries. (**b**) This photomicrograph is a continuation of the previous starting in the lower right corner of (**a**). The arrow points to the area of apparent rupture of a vessel in continuity with the underlying RPH

In placentas with RPH from living infants without a history of abruption, the estimate of duration could potentially correlate with the timing of clinical events.

When an abruption has a rapid and witnessed clinical onset, an emergency caesarean section will usually deliver a living infant. Typically, the placenta will show a retroplacental haematoma in situ at caesarean section. The pathologist often cannot identify that retroplacental haematoma from the examination of the placenta. Gruenwald and colleagues emphasized the existence of clinical abruption without pathological retroplacental haematoma and retroplacental haematomas without clinical abruption [8]. They reviewed the clinical chart and the pathology of 612 cases with either a clinical abruption or a pathological diagnosis of placental separation. The two designations overlapped in less than half of either category alone. A more recent paper by the New Jersey Placental Abruption Study also noted the poor correlation between the pathological and the clinical diagnosis of abruption with only 49 of 162 clinical abruptions confirmed pathologically [9].

If a placenta is delivered vaginally with an adherent jelly-like blood clot, this is not necessarily evidence that the placental separation occurred prior to delivery of the infant and it may have occurred with incomplete separation of the placenta in the third stage of labour. However, if neutrophils are present in the basal plate, this is evidence that the placental separation occurred likely hours prior to delivery based on the findings in stillborn infants [1]. If there is no positive histologic evidence of RPH, then the pathologist can only describe the gross lesion and correlate it with the clinical history.

36.4.2 Acute Marginal RPH in Preterm Delivery

A vexing problem for the pathologist is the interpretation of relatively recent marginal RPH adherent to the placentas of infants with preterm labour and preterm premature rupture of membranes. A pathological study of 90 preterm placentas compared to 45 term placenta found more marginal haematomas, as well as marginal necrosis and fibrin, in the premature placentas [10]. The description of these marginal haematomas is typical: “At the placental margin, an adherent clot is present. This clot is readily differentiable from the clot often seen after normal postpartum separation in that the antepartum clot is adherent to the placenta and membranes and is removed only with difficulty. It is dark in colour, frequently contains fibrin, and may be laminated. Polymorphonuclear infiltration is often noted.” The histological evidence of duration of the RPH can be timed and correlated with the clinical history. These placental cases almost invariably, in my experience, also demonstrate chorioamnionitis, which does not have inherent histological criteria to determine an absolute duration. Inferences about relative timing of infection, RPH, and causes of preterm labour and rupture of membranes cannot be made and hence inferences of causation should be made with caution.

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37 Miscellaneous Lesions of the Villous Parenchyma

M. Halit Pinar and Salwa Khedr

37.1 Placental Calcifications

37.1.1 Introduction

Calcification in the placenta is a relatively frequent finding that has attracted the attention of placental pathologists and radiologists. The presence of calcification during placental imaging has prompted radiologists to investigate whether the calcification could be a useful marker for placental pathology and clinical outcome [1]. Although the human placenta calcifies with advancing gestational age, the clinical relevance of identifying calcifications in preterm placentas is unknown [2].

Mineralizations are located in various parts of the placental parenchyma and show changes in intensity and location [3]. The three processes that may lead to tissue calcification are physiological, dystrophic and metastatic. In physiological calcification, osteoblasts produce osteoid matrix, which permits hydroxyapatite formation in and on collagen fibres. Dystrophic calcification occurs in tissue necrosis. Metastatic calcification develops in an environment that is supersaturated with calcium and phosphate or oxalate. The mechanism of placental calcification appears to be dystrophic and metastatic in nature [4].

37.1.2 Definition

Deposition of calcification as coarse structureless deposits in the placenta or as stippled linear and particulate deposits in villi usually extending for a variable distance from the trophoblastic basement membrane to the villous stroma. The latter is discussed further in Chap. 19.

37.1.3 Synonyms

Calcification, mineralization.

37.1.4 Epidemiology

The calcium content of placentas normally increases with gestational age. This process may be accelerated by some disorders of pregnancy [5]. The incidence of macroscopic placental calcification detectable by the pathologist has varied from 14% to 37% [6]. Data about the association between placental calcifications and adverse pregnancy outcome are controversial [1]. Although this type of calcification is considered abnormal in preterm placentas, their significance is undetermined when present in term placentas. One recent study demonstrated these lesions to

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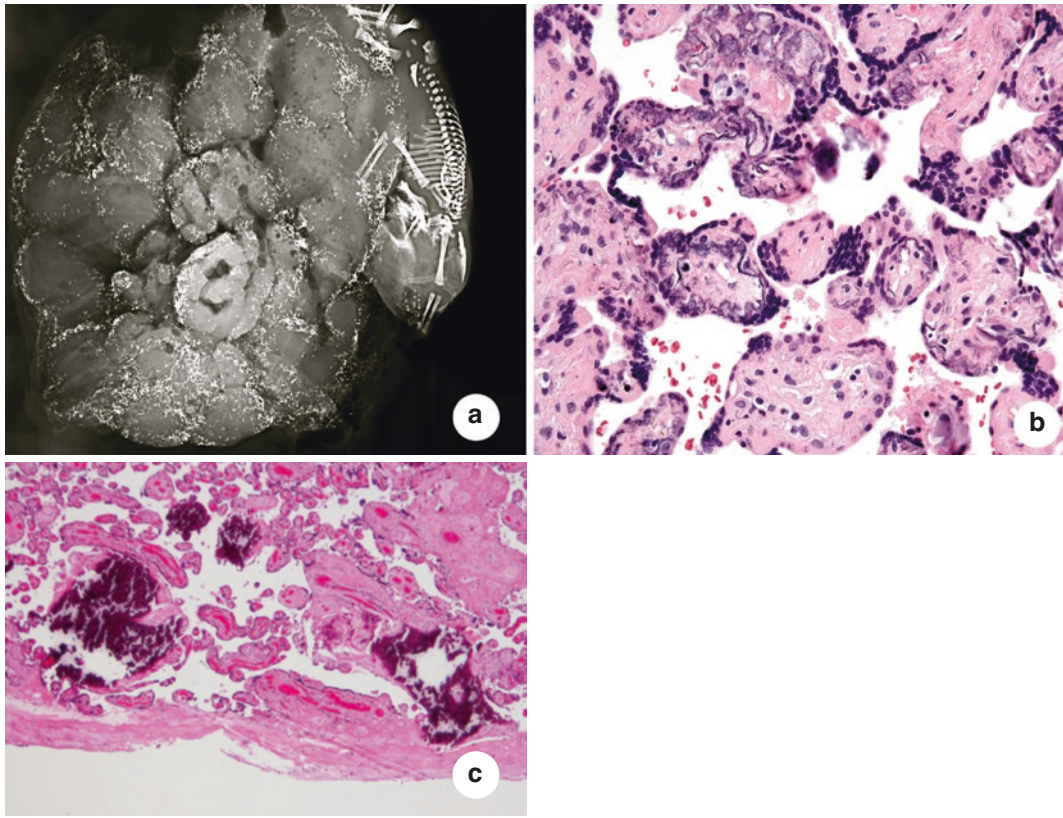

Fig. 37.1 (**a**) Radiograph of a term placenta with a fetus papyraceous. In addition to the skeletal remains of the fetus papyraceous, diffuse scattered calcifications are present. (**b**) Placenta from a term stillborn with placental calcifications. The cause of death was total umbilical cord obstruction. The linear and particulate calcifications in mostly avascular villi are seen. (**c**) Coarse structureless calcification near the placental basal plate from a term uncomplicated pregnancy

be more frequently seen in areas associated with decreased placental perfusion such as infarcts and stillbirth [7]. When calcifications are present in viral infections, they may provide a useful clue in the differential diagnosis. When they are seen in the walls of fetal blood vessels with thrombi, it provides pertinent information about the duration of those lesions (see Chap. 25).

37.1.5 Gross Findings

Calcification is seen on the maternal surface as small, hard, scattered tan-to-white flecks. In some instances, when the flecks are encountered in the villous parenchyma, a gritty sensation is felt when the specimen is sliced. Radiographs reveal the degree of calcification and in instances with fetal papyraceous, the fetal remnants (Fig. 37.1a).

37.1.6 Histopathology

Calcification can occur in any part of the chorionic villi, perivillous fibrin and foci of parenchymal infarction or thrombi, in the fetal vessel walls or old thrombi and in areas of intense inflammation that are associated with necrosis [8–10]. In

Table 37.1 Maternal conditions associated with placental calcification

Pregnancy-induced hypertension, preeclampsia
Abruptio placenta
Postpartum haemorrhage
Cigarette smoking [11, 12]
Infections
Viral infections from rubella, cytomegalovirus, herpes simplex and varicella zoster [13]
Nanobacteria infections [14]
Connective tissue diseases
Bartter syndrome [15]
Pseudoxanthoma elasticum [16]
Scleroderma [17]

haematoxylin and eosin stained sections, they appear to be dark blue (Fig. 37.1b, c). Von Kossa stain can highlight the areas of calcification.

37.1.7 Aetiology and Pathogenesis

Various patterns of calcification in the placenta have been associated with different factors. These are summarized in Table 37.1.

37.1.8 Prognosis and Predictive Factors

None known.

37.2 Heterotopia

37.2.1 Introduction

Heterotopia is very rare in the placenta. Only hepatic, adrenal cortical and intestinal heterotopic tissues have been described in .the literature. Frequently, they are incidental findings in well-sampled placental specimens and identified during histological examination.

37.2.2 Definition

The presence of hepatic, adrenal cortical or intestinal tissues in the placental parenchyma.

37.2.3 Synonyms

Ectopia, benign hepatocellular tumour of placenta, hepatocellular adenoma of the placenta, placental teratoma.

37.2.4 Epidemiology

These are very rare.

37.2.5 Gross Findings

Heterotopic tissues usually appear grossly as a single, well-defined, smooth nodule that ranges in size from 0.1 cm to less than 0.5 cm in greatest diameter [18]. Owing to the small size of the nodules, most of them are not grossly visible and are only seen microscopically [19–21].

37.2.6 Histopathology

Histologically, they are similar to their normal counterparts. They are located within the villi [18–21], chorionic plate [22] or subchorionic space [21]. Adrenocortical nodules appear as nodules of large oval or polyhedral cells with granular to clear eosinophilic cytoplasm, similar to the cells of the normal adrenal cortex [18–20, 23]. Hepatic nodules resemble fetal liver and are composed of cords of polygonal cells with eosinophilic cytoplasm, with rare haematopoietic cells and no pigment or bile ducts (Fig. 37.2a, b) [20, 21, 23, 24]. Heterotopic intestinal segment(s) are described to be fully developed intestinal seg-

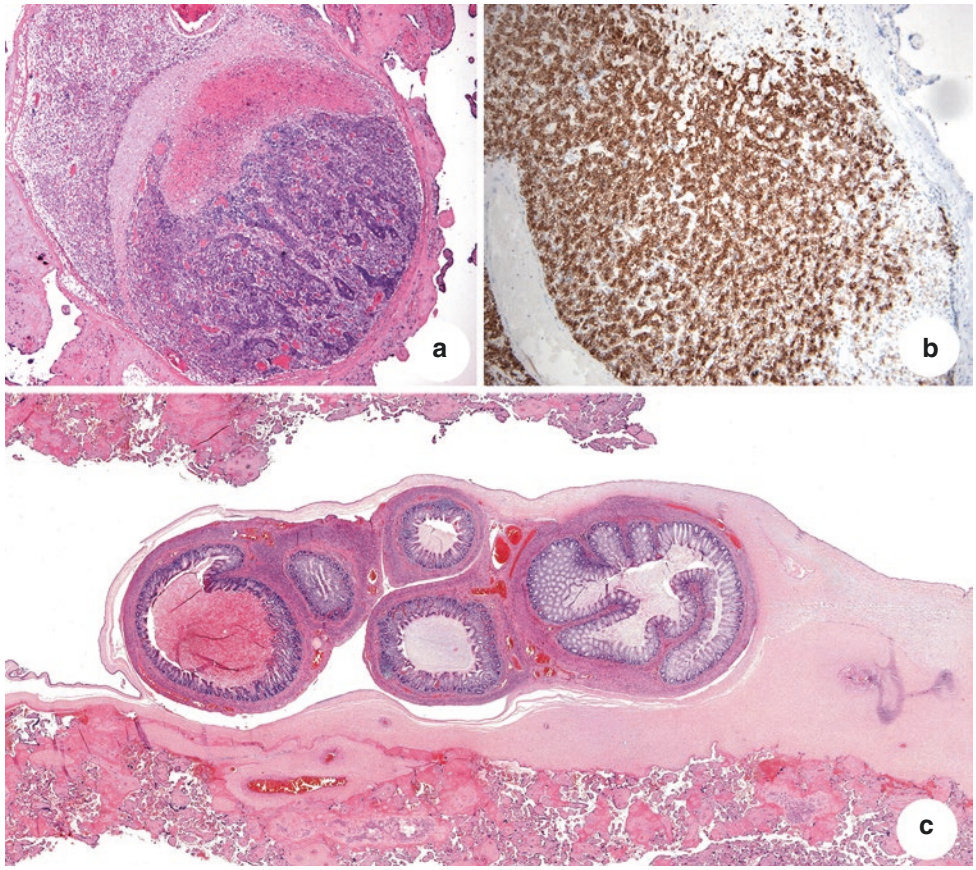

Fig. 37.2 (**a**) Placental hepatic heterotopia in the chorionic villi. (**b**) Immunohistochemical staining with the anti-hepatocyte antibody (Genpath®, clone OCH1E5) illustrates diffuse positivity. Adrenal vs hepatic rests may be difficult to differentiate in H&E-stained sections. (**c**) A rare example of a well-differentiated intestinal heterotopia identified under the amnion of a term placenta

ments with mucosa, submucosa, muscularis propria and serosa (Fig. 37.2c) [22].

37.2.7 Genetic Susceptibility

None has been described.

37.2.8 Aetiology and Pathogenesis

Currently it is not known how these heterotopic tissues end up in the placenta. Several theories have been suggested to explain this phenomenon. One theory is aberrant migration of primordial cells [18, 20, 23], and another theory is organoid differentiation of pluripotential stem cells [22].

37.2.9 Prognosis and Predictive Factors

Heterotopic tissue in the placenta is not known to cause identifiable fetal or maternal adverse events [20–24].

37.3 Villous Fibrinoid Necrosis

37.3.1 Definition

A condition where there is deposition of fibrinoid under the syncytiotrophoblast but external to the trophoblastic basement membrane [25].

37.3.2 Synonyms

Not applicable.

37.3.3 Epidemiology

Fibrinoid deposition is seen more often in pre-eclampsia, diabetic pregnancies, maternal-fetal Rh incompatibility and premature onset of labour [26].

37.3.4 Gross Findings

The lesion is frequently not identified grossly, but when it is abundant, it appears as firm, yellow-tan areas with irregular borders.

37.3.5 Histopathology

The accumulation starts between the syncytiotrophoblast and basement membrane. Over time the accumulations push into the stroma but never rupture the basement membrane. Eventually the entire villus is converted into a fibrinoid nodule (Fig. 37.3) [27].

37.3.6 Aetiology and Pathogenesis

Several theories have been suggested for how fibrinoid deposition develops. It may result from degeneration of the villous cytotrophoblast [28], or as a consequence of aging [29], or to immunologic process within the villous stroma [28].

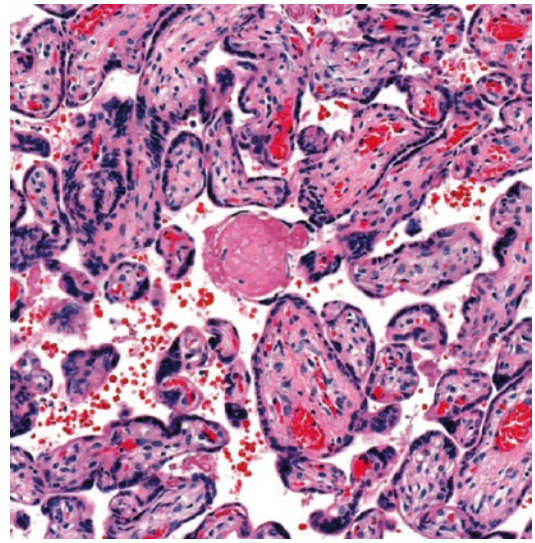

Fig. 37.3 A term placenta illustrating an advanced stage of fibrinoid necrosis in a villus

37.3.7 Prognosis and Predictive Factors

In cases of rhesus incompatibility, the incidence of villous fibrinoid necrosis is directly related to degree of haemolysis and to the titre of anti-D antibody in maternal serum [28]. Fibrinoid deposition may also affect oxygen exchange [30]. This entity has been described in recurrent spontaneous miscarriages and in the placentas of the stillbirth.

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Part V

Amniochorial Membranes: Macroscopically Visible Lesions

Amniochorial Membrane Nodules

38

Jerzy Stanek

38.1 Amnion Nodosum

38.1.1 Introduction

Amnion nodosum is commonly regarded as a placental hallmark of severe and prolonged oligohydramnios [1–3].

38.1.2 Definition

Deposits of cellular elements from the fetal skin on the surface of the amniotic epithelium.

38.1.3 Synonyms

None.

38.1.4 Epidemiology

Amnion nodosum can be observed in the membranes as early as at 9–16 weeks of pregnancy and was observed in 4% of our population of high-risk pregnancies, half of those in the second trimester of pregnancy [4, 5], mostly in conditions associated with prolonged oligohydramnios [6–8]. Amnion nodosum was more than three times more frequent in fetal growth restriction [9, 10].

38.1.5 Gross Findings

1–5 mm in diameter, multiple, firm, circumscribed, round to ovoid, raised, shiny, yellowish nodules are present on the surface of the amnion of the chorionic disc, placental membranes or umbilical cord, sometimes coalescing into larger plaques (Fig. 38.1) [2, 3]. The nodules can usually be easily wiped out, as opposed to the squamous metaplasia.

38.1.6 Histopathology

Varying proportions of squamous cells (occasionally keratinized) are embedded among degenerative amorphous acidophilic debris, sometimes with hair or sebaceous material [3] on the amniotic surface or embedded in amniotic mesoderm or projecting through the amnion into the spongy layer cleft between the amnion and the chorion. The amniotic epithelium may be present either as a complete or as an incomplete cell layer between the basal side of the nodule and the basement membrane, but it eventually grows over the nodules (Fig. 38.2).

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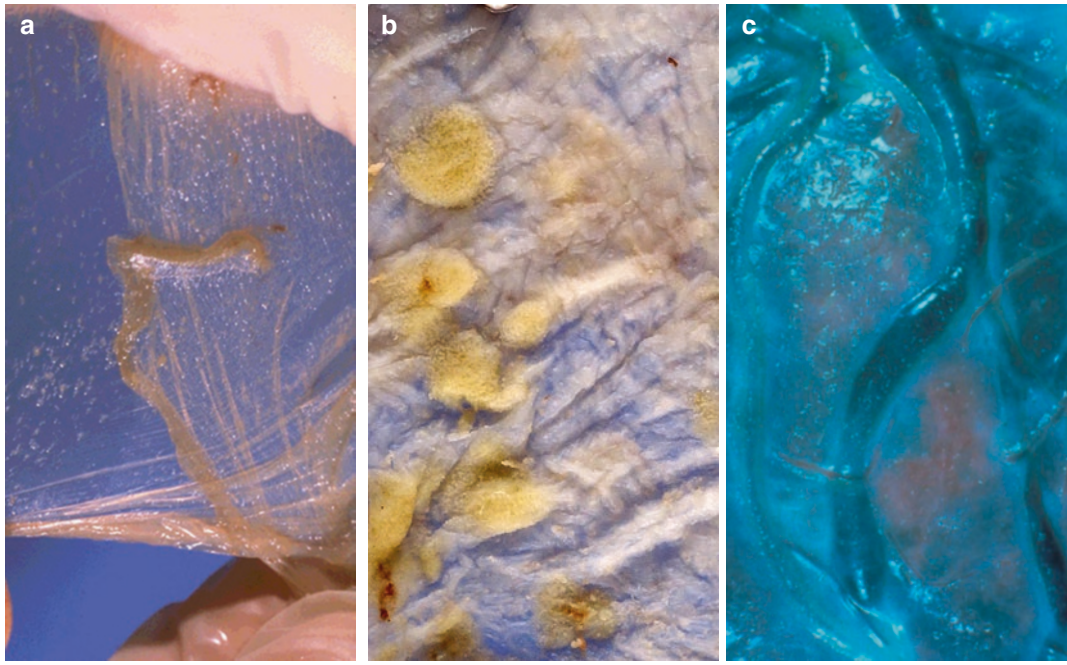

Fig. 38.1 Gross appearance of amnion nodosum. (**a**) Delicate ("dew-like") nodules on placental membranes. (**b**) More advanced lesions in placental membranes. (**c**) Amnion nodosum on the chorionic plate

The differential diagnosis includes squamous metaplasia, subchorionic fibrin deposits and chorion nodosum, all three lesions more commonly present on the surface of the chorionic disc but encountered also on the placental membranes (except for subchorionic fibrin deposition in which the amnion can be made to slide over the lesion).

38.1.7 Immunohistochemistry

Immunohistochemistry is not needed for the diagnosis.

38.1.8 Genetic Susceptibility

Related to congenital malformations, if present.

38.1.9 Prognosis and Predictive Factors

Although amnion nodosum is regarded an excellent hallmark of oligohydramnios [2], the oligohydramnios may be not diagnosed antenatally in such cases [5].

Amnion nodosum is associated with a very high probability of perinatal mortality and morbidity (35%), lethal congenital malformations and/or oligohydramnios-induced pulmonary hypoplasia, the latter being the main cause of postnatal deaths [5]. There were more intrauterine deaths than live infants with good outcomes in cases with AN [11].

38.2 Squamous Metaplasia

38.2.1 Introduction

The term "squamous metaplasia" is a misnomer because the amniotic epithelium is squamous although immature [1]. Although the term "squamous hyperplasia" would be more appropriate [2], the term "squamous metaplasia" is entrenched in medical literature.

38.2.2 Definition

Patches of keratinizing squamous epithelium firmly attached to the amniotic surface.

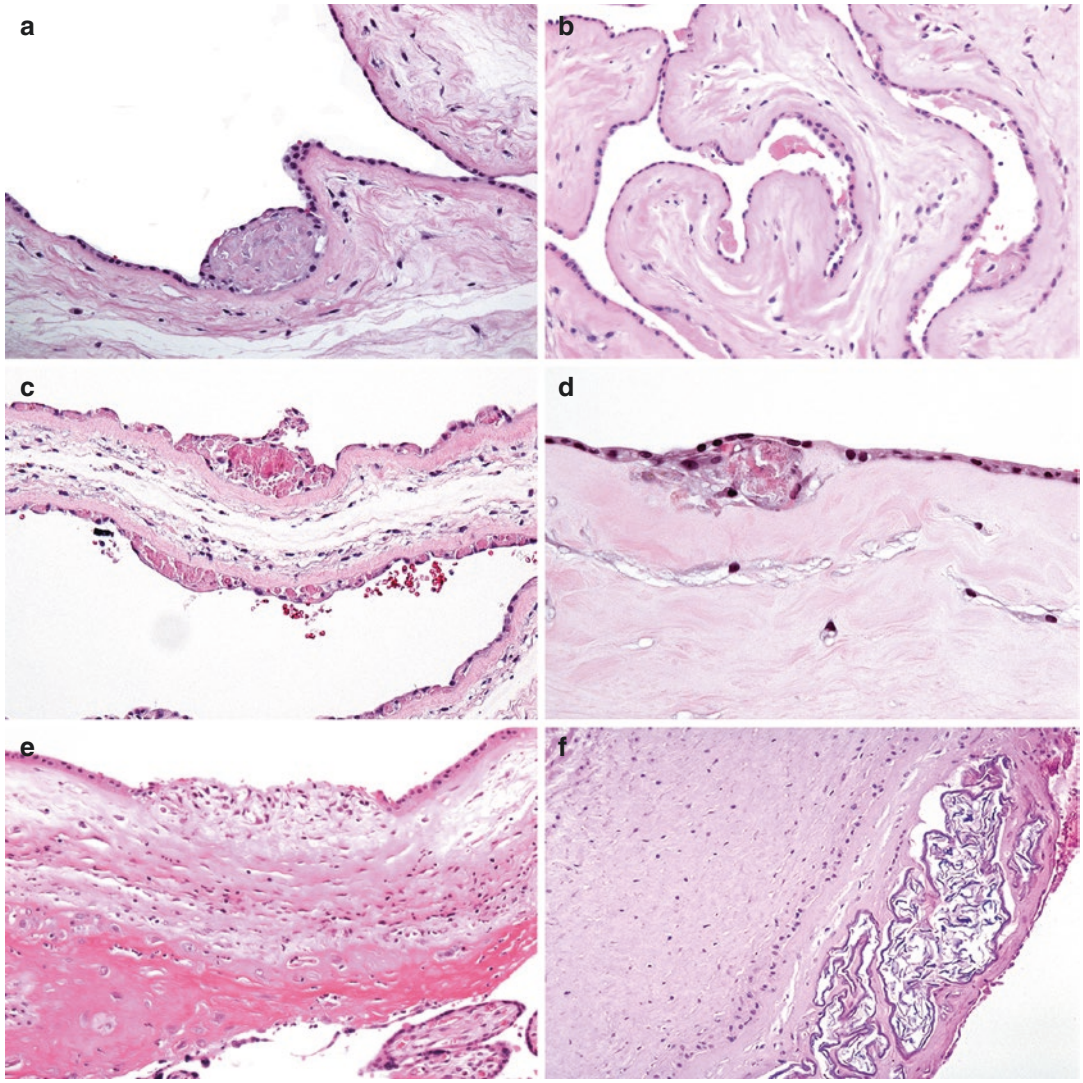

Fig. 38.2 Microscopic appearance of amnion nodosum. (**a**) Amnion nodosum epithelialized by amniotic epithelium. (**b**) Early amnion nodosum on one side of dividing membranes of monochromic pregnancy (donor's side). (**c**) Amnion nodosum on an amniotic fold. (**d**) Amnion nodosum within a pericardial amniotic collar of extra-amniotic pregnancy. (**e**) Amnion nodosum on the chorionic plate. (**f**) Amnion nodosum on the umbilical cord

38.2.3 Synonyms

Squamous hyperplasia.

38.2.4 Epidemiology

Present from 4% to up to 60% of term placentas [2, 12].

38.2.5 Gross Findings

Irregular, dull, grey or white hydrophobic plaques, up to few millimetres in diameter, slightly elevated, rough to granular to touch [2] (Fig. 38.3a) of diffuse thickening of the amnion, and the plaques cannot be easily separated from the amnion [11]. They sometimes coalesce and can measure a few centimetres in diameter.

Squamous metaplasia is usually seen near the umbilical cord insertion site [12].

38.2.6 Histopathology

Keratinizing stratified squamous epithelium on the chorionic plate measuring several layers in thickness, with keratohyalin granules and, possibly, melanin (Fig. 38.3b). There is a sharp transition between the lesion and the adjacent amniotic epithelium.

38.2.7 Immunohistochemistry

Not relevant.

38.2.8 Genetic Susceptibility

Not known.

38.2.9 Prognosis and Predictive Factors

Squamous metaplasia has no prognostic clinical or pathologic significance [1].

38.3 Vanishing Twin

38.3.1 Introduction

Vanishing twin (VT) occurs when the embryo dies in the first trimester and may be observed within the placental membranes and, less commonly, on the chorionic disc. Death of the fetus later in pregnancy with survival the other twin results in the fetus papyraceous, which usually is discussed with multiple gestation.

38.3.2 Definition

VT is a nodular structure present in the membranes or less commonly on the placental disc or at its margin, recapitulating the shape of the embryo. The presence of a pigmented eye spot usually betrays the diagnosis.

38.3.3 Synonyms

The nodular embryo dies earlier and does not recapitulate the gross shape and an organized histological structure of an embryo [13].

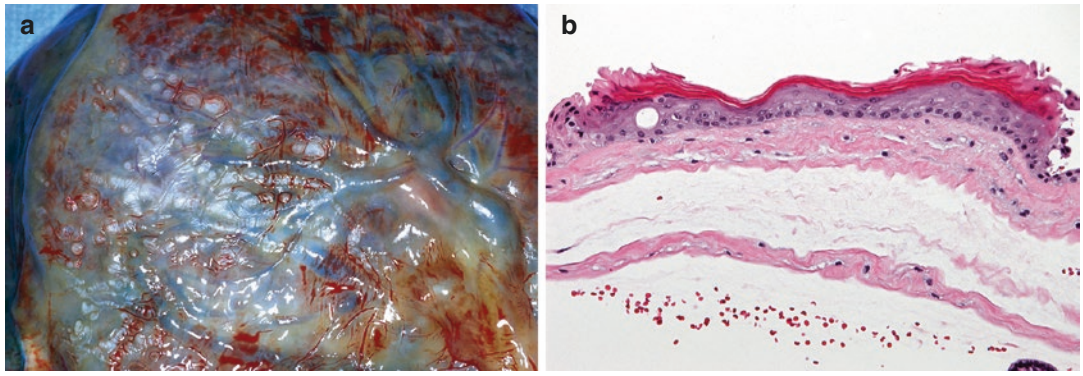

Fig. 38.3 Squamous metaplasia of amnion. (**a**) Gross appearance. (**b**) Microscopy

38.3.4 Epidemiology

The incidence of dizygotic (or polyzygotic) pregnancy is related to the treatment of infertility. The rates of multiple conceptions may constitute more than 12% of natural conceptions (70% of them are dizygotic), but only 2% of them survive to term [13]. The failures of multiple pregnancy range from nodular embryo (NE), through vanishing twin, fetus papyraceous and stillbirth.

38.3.5 Gross Findings

VT is a flattened grey longitudinal structure recapitulating the shape of an embryo (Fig. 38.4a, b). Occasionally, a cyst seen on the chorionic plate is usually extravillous trophoblast cyst, and only sectioning and microscopy may establish the lesion to be a VT (Fig. 38.4c–e). A vessel transversing a cyst is usually an extravillous trophoblast cyst and not VT.

38.3.6 Histopathology

Usually a well-seen embryonal spine is seen (Fig. 38.4f). A nodule without the grossly appreciated shape of an embryo and featuring a disorganized embryonal tissues is called the NE [13]. Both VT and NE have their own totally sclerotic (not infarcted) placentas. Examination of the dividing membrane may differentiate between a monochorionic and dichorionic pregnancy. A nodule composed of disorganized embryonal/fetal tissues without a placenta is a teratoma. VT and NE may rarely be associated with a partial hydatidiform mole [14].

38.3.7 Immunohistochemistry

Immunohistochemistry for VT is not usually performed with possibly rare exception of a suspicion of an associated complete hydatidiform molar pregnancy (p57), and FISH can also be helpful to confirm a triploidy [15]. Karyotyping of VT may reveal chromosomal abnormalities [12].

38.3.8 Genetic Susceptibility

VT frequency is proportional to the frequency of multiple gestation in the general population.

38.3.9 Prognosis and Predictive Factors

The prognosis is good, and the pathological diagnosis is usually needed to confirm the early sonographic findings in pregnancy.

38.4 Yolk Sac Remnant

38.4.1 Introduction

An embryonic remnant of the yolk sac which functions as the primary embryonal haematopoietic organ, surrounded by the extraembryonic mesoderm and adjacent to the ectoderm amniotic vesicle, and undergoes atrophy with regression of the omphalomesenteric duct (Fig. 38.5a, b) [1]. The fetal liver then takes over as the main fetal haematopoietic organ.

38.4.2 Definition

An oval, white sharply demarcated subamniotic disc.

38.4.3 Synonyms

None.

38.4.4 Epidemiology

A minority of placentas shows a calcified yolk sac remnant.

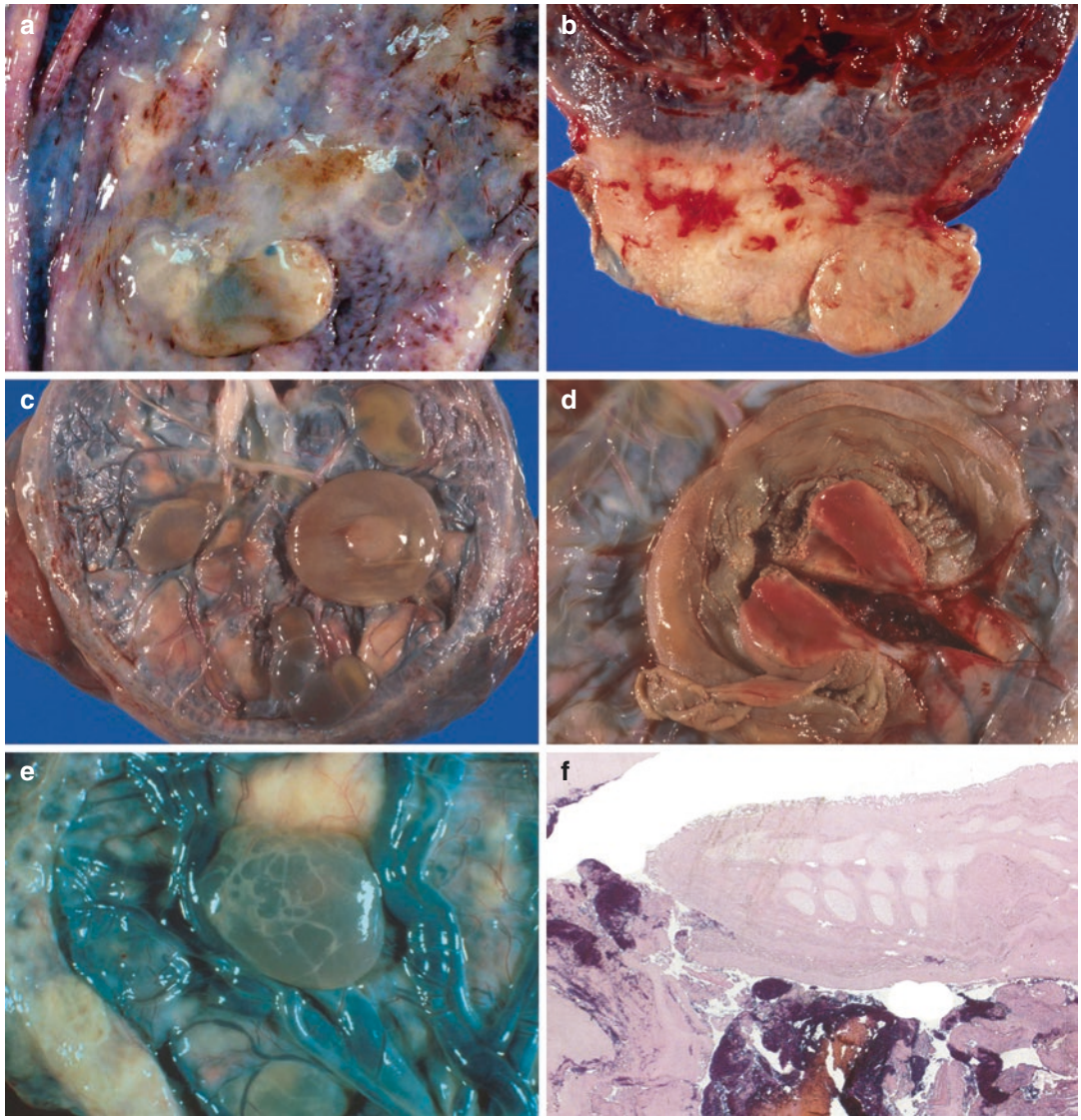

Fig. 38.4 Vanishing twin. (**a**) Vanishing twin in placental membranes. (**b**) Vanishing twin at the edge of the chorionic disc. (**c**) Vanishing twin, resembling a chorionic cyst, on the chorionic disc. (**d**) Same, after opening the sac and transecting the embryo. (**e**) Extravillous trophoblast cyst. (**f**) Vertebral spine is histologically seen in vanishing twins

38.4.5 Gross Findings

A sharply demarcated few mm white, chalky flat disc on the chorionic disc, usually its margin (Fig. 38.5c), or within the placental membranes.

38.4.6 Histopathology

Oval deposit of a basophilic calcified material in the amniotic mesenchyme between the amnion and chorion (Fig. 38.5d) [16].

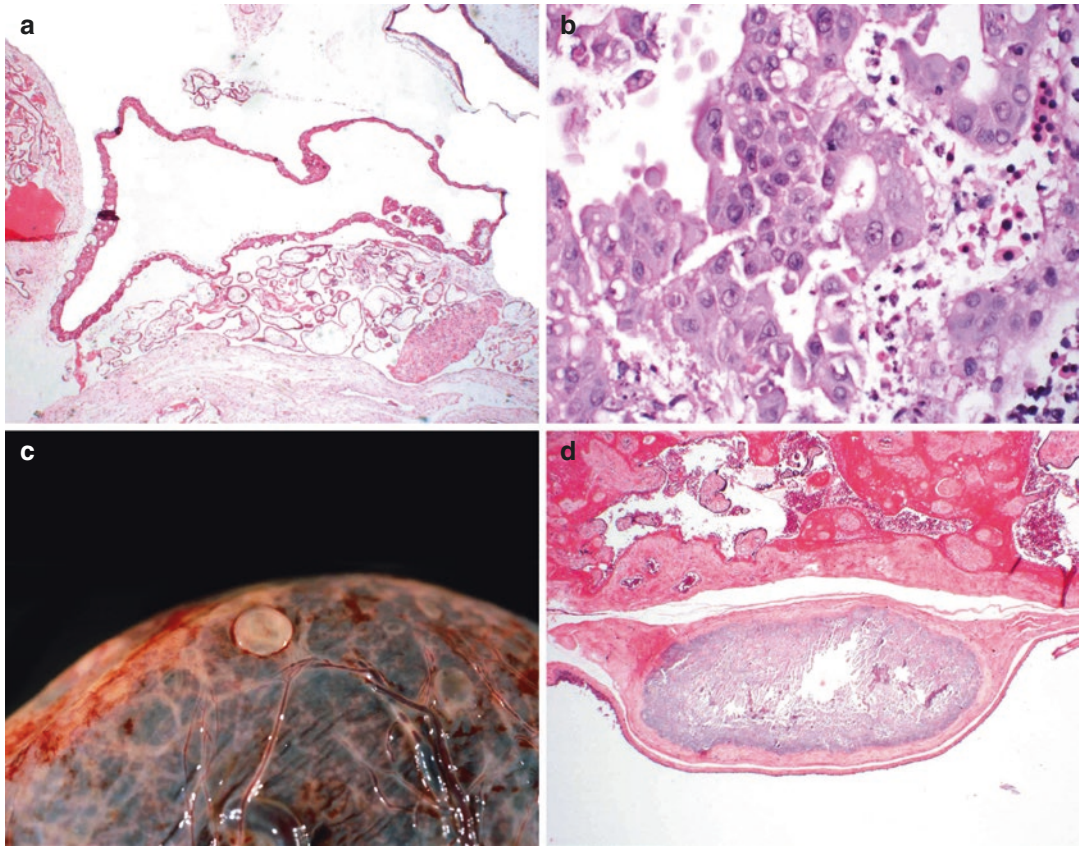

Fig. 38.5 Yolk sac remnant. (**a**) Yolk sac in an abortion specimen. (**b**) Yolk sac-derived erythroblasts are seen. (**c**) Calcified yolk sac on the chorionic disc. (**d**) Microscopic appearance of a calcified yolk sac remnant

38.4.7 Immunohistochemistry

Not applicable as the haematoxylin and eosin-stained slide is diagnostic.

38.4.8 Prognosis and Predictive Factors

None.

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39 Placental Changes in Amniotic Band Sequence, Extra-Amniotic and Extramembranous Pregnancy

Eumenia Castro and Eileen McKay

39.1 Amniotic Band Sequence

39.1.1 Introduction

Amniotic band sequence (ABS), which is also known by various other terms, is a group of congenital abnormalities most commonly involving fetal limb and digital amputation. The most severe forms show formation of fibrous bands or sheets from the placenta attaching to the fetal abdominal wall or cranial structures leading to severe malformations. Three main theories have been proposed to explain the constellation of findings in ABS. The first advocates for an intrinsic defect in the germinal disc occurring prior to 26 days postconception which would lead to abnormal morphogenesis [1]. According to this theory, the amniotic bands would represent macerated sheets of epidermis or scar tissue secondary to the defective histogenesis. The intravascular theory implies thrombosis of fetal vessels resulting in disruption and necrosis with subsequent scarring of the extremity; the amniotic bands would become attached to the fetal organs and limbs secondary to the tissue scarring [1]. The last theory purports early rupture of the amnion in an intact chorionic sac yielding strands of amnion bands which would entrap and disrupt the formation of the fetal extremities [1].

39.1.2 Definition

Amniotic band is a disruption of the amnion from the chorion and can result in the amniotic band sequence, which includes a spectrum of fetal congenital malformations, affecting mainly the limbs and craniofacial region that may be associated, or not, with visceral anomalies and abdominal wall defects.

39.1.3 Synonyms

Amniotic band disruption complex or sequence; Amniotic Constriction Band Syndrome/Constriction Band Syndrome; Amniotic Deformity, Adhesions and Mutilations (ADAM) complex or sequence; Amniotic adhesion malformation syndrome; Early Amnion Rupture Spectrum (EARS); Streeter anomaly/Streeter('s) dysplasia/Streeter bands.

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39.1.4 Epidemiology

One epidemiologic study evaluating birth prevalence identified evidence of early amnion rupture sequence in approximately 1 in 10,000 births [2]. Variable risk factors, including living in high altitude, primiparity, febrile illness in the antenatal period and history of vaginal bleeding in the first trimester, are contentious [2]. Limb deformities are one of the described complications of amniocentesis and chorionic villus sampling when performed in the first trimester [3]. There is a higher prevalence of thrombophilia in women whose pregnancies were complicated by fetal congenital limb defects [4]. ABS may occur after selective fetoscopic laser photocoagulation for twin-twin transfusion syndrome [5].

39.1.5 Gross Findings

The spectrum of abnormalities in the amniotic band sequence is variable. It may be limited to a single extremity or digit amputation with fibrous bands noted around the amputated parts. In such cases, the membranous placental surface should be carefully examined for small strands of residual amnion, which can be facilitated by immersing the fresh placenta in water. The placenta often shows an intact, yet thickened chorion and a globular portion of disrupted amnion at the base of the umbilical cord with small tethers to the cord (Fig. 39.1) and an intact chorion appearing more opaque due to thickening (Fig. 39.2). The exposed chorionic surface is dull and rough compared to the smooth, reflective surface of an intact amnion. Such findings seem to support the extrinsic theory of early rupture of the amnion in an intact chorionic sac yielding strands of amnion bands which entrap and disrupt the formation of fetal structures [1]. The bands may be identified encircling the umbilical cord leading to strictures which are more commonly identified at the fetal end of the umbilical cord (Fig. 39.2). Fetal malformations may be restricted to a single extremity amputation (Fig. 39.3) or major malformations of the face and abdomen with defects involving the internal organs (Fig. 39.4). Occasionally,

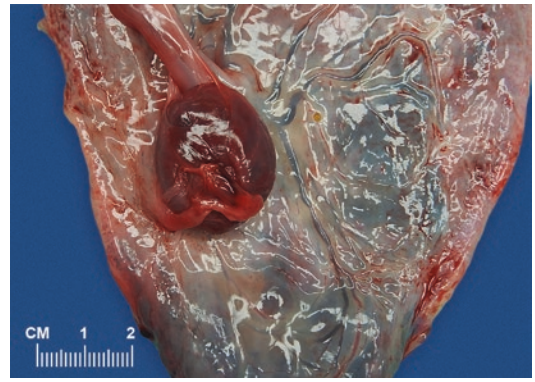

Fig. 39.1 Placenta showing chorionic plate devoid of amnion epithelium. The disrupted amnion is noted as a globular structure at the base of the cord

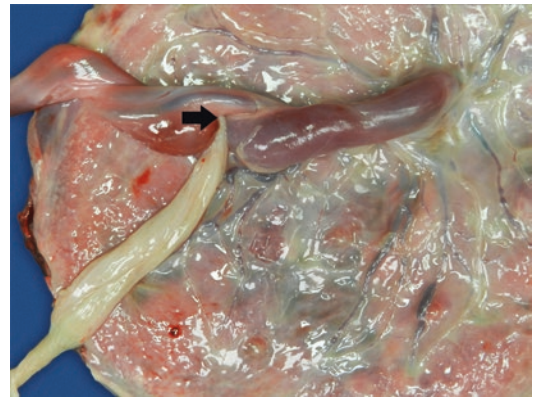

Fig. 39.2 Placenta fetal surface showing opacification of the chorion and a thick strip of amniotic band associated with an area of stricture in the umbilical cord (arrow). Note the congestion of the umbilical cord adjacent to the area of stricture

the identification of the bands may be difficult requiring careful gross examination of the fetus to identify the delicate membranes surrounding fetal parts (Fig. 39.5). The differential diagnosis includes other syndromes in which limb reduction, facial clefts and abdominal defects are noted. Limb-body wall complex (LBWC) shares many of the abnormalities identified in amniotic band sequence and there is some doubt if they represent two separate entities or a unique disorder with different presentation. LBWC is associated with a short or constricted umbilical cord due to the approximation and entanglement of the fetus with more conspicuous strands and sheets of amnion.

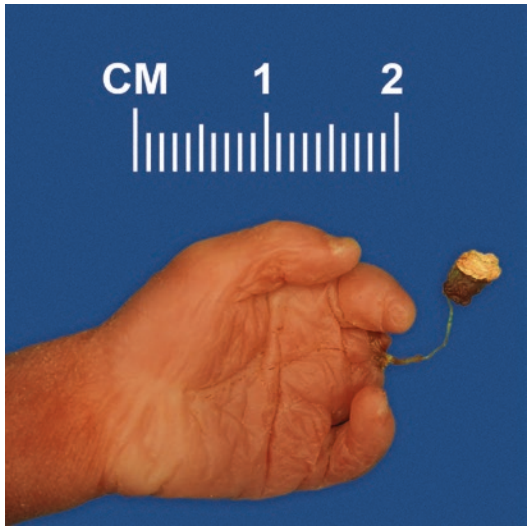

Fig. 39.3 Amputation of the third and fourth fingers at the level of the metacarpals and amputation of the second finger at the level of the middle phalanx. The necrotic amputated portion of the finger is still attached to the skin by a thin amniotic strand

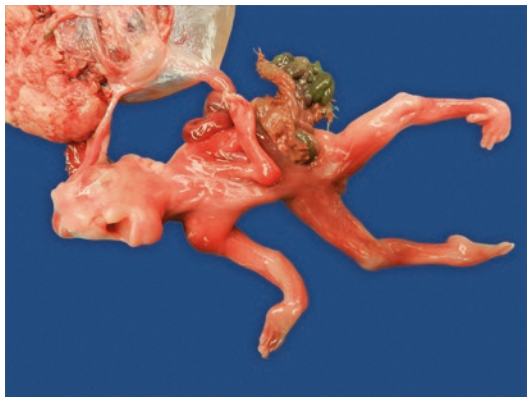

Fig. 39.4 Fetus with thick sheets attached to the head and abdomen leading to secondary anencephaly and gastroschisis. Note the amniotic band causing umbilical cord stricture in the mid portion of the cord

39.1.6 Histopathology

Histologic examination of the placental chorionic plate surface can confirm absence or discontinuity of the amnion epithelium with secondary changes of the chorion including chorion nodosum [6].

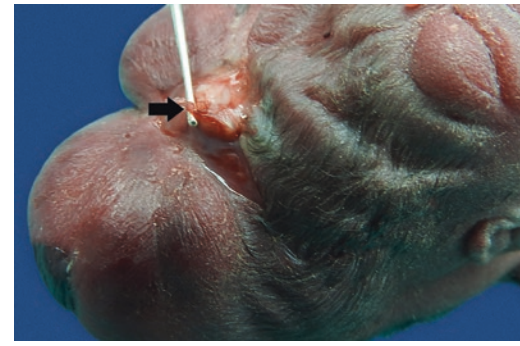

Fig. 39.5 Cranial deformity in a fetus due to amniotic band: careful examination of the fetus may reveal delicate strands of amniotic bands around the defects (arrow)

39.1.7 Immunohistochemistry

Immunochemistry is generally not applicable in the evaluation and diagnosis of amniotic band sequence.

39.1.8 Genetic Susceptibility

Although historically considered to be a sporadic occurrence, rare familial cases have been reported [2]. Recently, a mutation in the *IQCK* gene was demonstrated in a patient with the ABS/LBWC phenotype [7].

39.1.9 Prognosis and Predictive Factors

The prognosis depends on the severity of the fetal involvement. Most commonly, amputations in an asymmetric pattern will be noted in a live-born, otherwise normal baby. The most severe cases are often associated with intrauterine fetal demise. Elevation of amniotic fluid alpha-fetoprotein may occur [8]. The risk of recurrence is low although few familial cases are described [2]. The perinatal diagnosis is based on imaging findings of aberrant bands, characteristic fetal deformities, and restriction

of movement [9]. Fetoscopic amniotic band release may be used for limb salvage [10, 11]. Consideration should be given to mode of delivery as short umbilical cord may be associated with severe forms presenting with involvement of the fetal abdominal wall and additional complications.

39.2 Extra-Amniotic and Extramembranous Pregnancy

39.2.1 Introduction

Extra-amniotic and extramembranous pregnancy are rare events in which the fetus develops partially or completely outside intact membranes. Extra-amniotic pregnancy occurs with complete amnion rupture sufficiently early, or late, in gestation with no fetal sequelae of amniotic band formation. It results in a small, thick remnant of amnion remaining attached to the proximal umbilical cord within an intact chorionic membrane. Disruption of both amnion and chorion in early to mid-gestation results in extramembranous pregnancy associated with placental circumvallation and high fetal morbidity. Residual membranes are short and thick comprising a restrictive sac insufficient to contain the developing fetus. The aetiology of extra-amniotic pregnancy and extramembranous pregnancy remains unknown although antecedent abdominal trauma has been suggested as a potential pathogenic mechanism for both conditions.

39.2.2 Definition

Extra-amniotic pregnancy is persistent fetal development following rupture of amnion only. Extramembranous pregnancy is persistent fetal development in the uterine cavity following disruption of both amnion and chorionic membranes.

39.2.3 Synonyms

Extrachorial pregnancy (extramembranous).

Complete chorioamniotic separation (extra-amniotic pregnancy).

39.2.4 Epidemiology

Extra-amniotic pregnancy and extramembranous pregnancy are rare, although potentially under-recognized and under-reported. Extra-amniotic pregnancy may be diagnosed on prenatal ultrasonography with visualization of "floating amnion"; reports include examples occurring after amniocentesis [12]. Extramembranous pregnancy is typically documented upon delivery with examination of the placental membranes suggesting an interval of gestation following membrane rupture and distinct from preterm/premature rupture of membranes with abrupt delivery. Placental circumvallation is reported in 1–6.5% of placentas, of which only rare cases represent extramembranous pregnancy [13].

39.2.5 Gross Findings

Complete chorioamnion separation results in a contracted remnant of amnion attached to the base of the umbilical cord. The amnion remnant may appear fibrotic, oedematous, opaque or discoloured. At times, the remaining amnion may form an inconspicuous collar around the cord insertion or merely residual membrane strings requiring careful inspection of the fetal surface. The exposed chorion is relatively dull and may be thick and opaque. In extramembranous pregnancy, the placenta shows thick and shrunken membranes with a diminutive opening, a restrictive sac and a rolled membrane edge (Fig. 39.6). The membrane insertion is typically circumvallate and may be associated with fibrinous and/or haemorrhagic tissue around the insertion in the setting of maternal bleeding. The umbilical cord may be short and constricted by free membranes. Exposed fetal chorionic

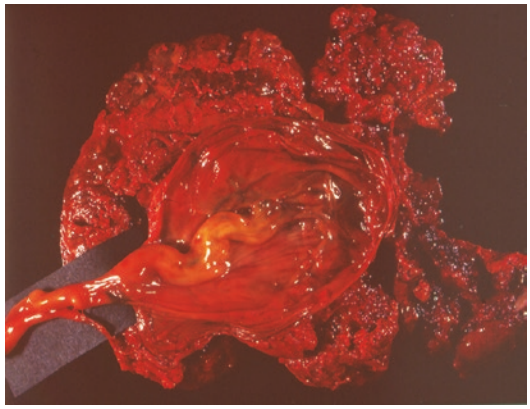

Fig. 39.6 Placenta and membranes from an extramembranous pregnancy: the placental opening is small and the placenta is circumvallate (courtesy of Dr. Yee Khong)

vessels should be carefully examined for disruption. Small rough lesions resembling amnion nodosum may be present on the denuded surfaces and exposed membranes due to adherent vernix.

39.2.6 Histopathology

In extra-amniotic pregnancy, sections of the fetal surface show chorion only. Separated amnion remnants may show epithelial cell degeneration. In extramembranous pregnancy, sections of the free membranes and fetal surface within the membrane sac are comprised of chorion with or without attached amnion. Peripheral sections of the fetal surface show the absence of membranes. Depending on the gestational age at delivery, adherent vernix may be present on the exposed membrane surfaces or between the membrane and exposed placental surface, so-called vernix granulomata [14]. Haemosiderin deposition may be present in cases with remote or chronic haemorrhage.

39.2.7 Genetic Susceptibility

Both conditions are considered sporadic with low risk of recurrence in subsequent pregnancies. Rare case studies of extra-amniotic pregnancy with concomitant fetal conditions, including restrictive dermopathy and connective tissue disorders, exclusive of amniotic band sequence, do exist raising questions of related pathogenesis [15, 16].

39.2.8 Prognosis and Predictive Factors

Disruption of the chorioamniotic membranes predisposes to ascending intrauterine infection, umbilical cord compromise and preterm delivery, all with increased fetal morbidity [17]. Extra-amniotic pregnancy with incomplete or fragmented remnants of amnion may result in amniotic band sequence with attendant morbidities depending on the gestational age (see also Sect. 39.1 above). Extramembranous pregnancy may present with amniorrhoea and is generally associated with a poor prognosis due to oligohydramnios, fetal compression and pulmonary hypoplasia.

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Part VI

Amniochorial Membranes: Microscopic Lesions

40 Amnion Transport: Histologic Features

Robert W. Bendon

40.1 Introduction

The amnion lines the fetal surface of the membranes. The surface epithelium demonstrates electron microscopic features (lack of tight junctions, many pinocytotic vesicles, and formation of pedicels on the basal border) that point to intense intercellular and transcellular transport of materials across the amnion [1]. A study comparing amnion epithelial ultrastructure among rat, guinea pig, monkey, and man found that all were similar and "the principal ultrastructural features appear to be adaptations to facilitated transfer of fluid rather than to synthesis or secretion" [2]. The amnion has a relatively thin, dense collagenous stroma and occasional mononuclear cells in the normal state. The transfer of materials from the amniotic fluid into the amnion is the basis of the pathological changes to be described in this section.

40.2 Definition

Morphologic changes in amnion epithelium reflect transport of substances in the amniotic epithelium including cell injury, intercellular water accumulation, and intracellular pigment accumulation. The transfer of pigments to deeper layers of the membrane can also be identified.

40.3 Epidemiology

The incidences of the amnion lesions presented in this chapter reflect those of the underlying fetal diseases or of the underlying pregnancy complications such as passing meconium.

40.4 Histopathology

The transport of bile pigments, red cell fragments, and lipids has all been identified microscopically within amnion epithelial cells (Fig. 40.1). Marked lipid vacuolization may occur with gastroschisis [3, 4], and this can be highlighted by staining of the unfixed amniotic epithelium with a lysochrome dye such as Sudan Black or Oil Red O.

Based on an in vitro study of meconium applied to placental explants, epithelial columnar change and pseudostratification can be a consequence of meconium exposure (Fig. 40.2) [5]. The histopathology can show elongated cells with thin stalks that appear to be crowded and stratified [6]. The intracellular spaces may be dilated. This finding may not be specific for meconium exposure.

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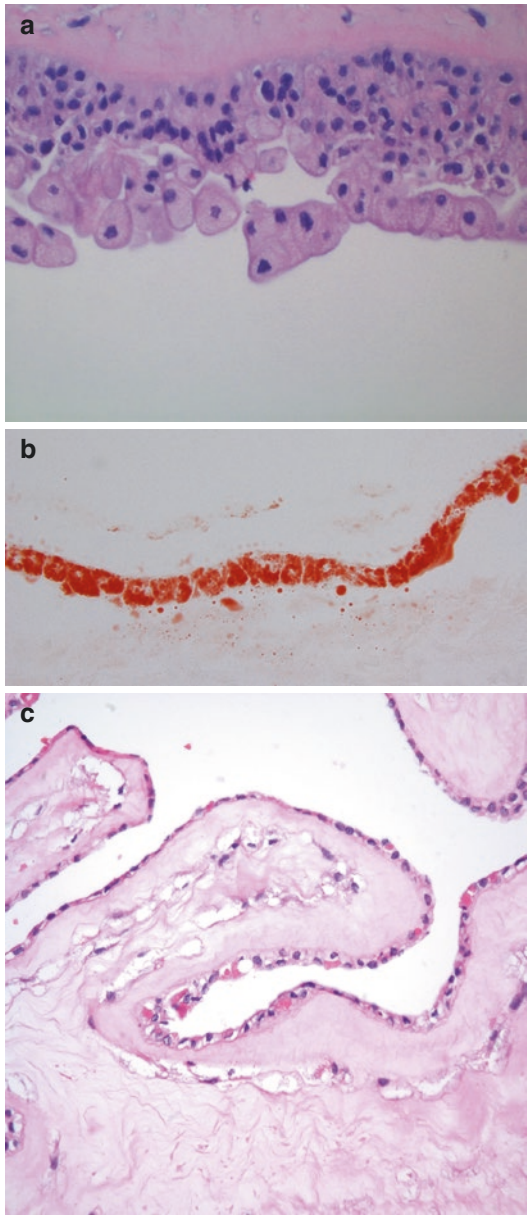

Fig. 40.1 (**a**) The amnion epithelium shows vacuolated, foamy cells in this membrane from an infant with gastroschisis. The cells show a piled up appearance with apical, pyknotic nuclei. (**b**) The amnion epithelium from an infant with gastroschisis demonstrates lipid staining with Oil Red O stain. (**c**) The amnion epithelium demonstrates intra- or extracellular red cells and fragments in the amnion epithelium

Meconium-laden macrophages and stromal cells in formalin-fixed, membrane connective tissue are identified by their brown-yellow-coloured

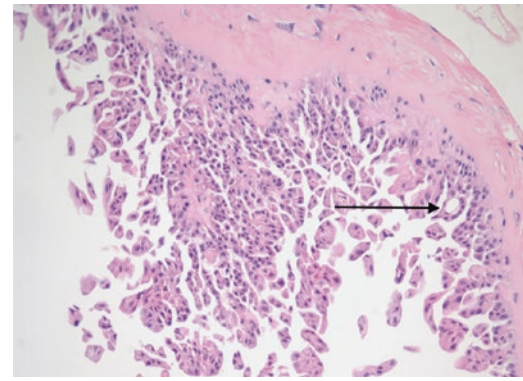

Fig. 40.2 The amnion epithelium shows loss of basilar nuclei, a piled up appearance, and increased intercellular space with focal goblet change from intercellular fluid (arrow). These changes can be associated with meconium, but there was not a history of meconium passage in this patient

cytoplasm on H&E staining (Fig. 40.3). The pigment may be either diffuse or in granules. The identity of the pigment can best be identified by the gross colour of the membranes. A gross green cast from bilirubin/biliverdin identifies the microscopic pigment as meconium. The green of meconium is persistent as demonstrated by serial amnioscopy in which it remained green for as long as 21 days [7]. Without bacterial breakdown, the bilirubin should not progress to the brown of stercobilin. Brown membrane discolouration may be from direct breakdown of haemoglobin into haemosiderin that can be identified by the blue reaction with the Perls' stain. The membrane pigment from bowel atresia often appears yellow-brown, but does not stain for haemosiderin, and likely is from regurgitated bile.

The duration of exposure to meconium has been correlated with the depth of the pigment macrophages starting at the amnion and progressing to the chorion and decidua. One study experimentally applied meconium at different concentrations (5–20%) to pieces of placenta in culture [5]. After approximately 2 h, pigment macrophages could be identified in the amnion connective tissue and in 3 h in the chorion connective tissue. A subsequent study using much more dilute meconium found few meconium macrophages in the amnion until 24 h and never

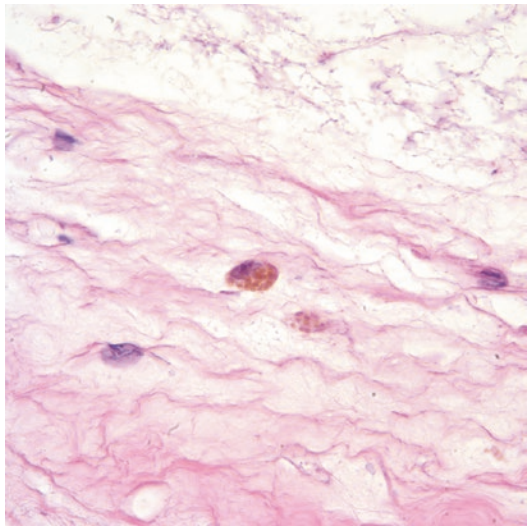

Fig. 40.3 The amnion connective tissue contains mononuclear cells with prominent brown pigment-filled vacuoles following prolonged exposure to meconium in the amniotic fluid

found them in the chorion layer even at 48 h [8]. They primarily assessed the depth of free meconium, but from the report it is unclear how this was identified. Another study evaluated meconium macrophages in women who initially had clear amniotic fluid but had subsequent passage of moderate to thick meconium [9]. They did not look at depth but quantity of macrophages. They comment that: "Our observation that meconium was present in the majority of the placental tissues analyzed within an interval as short as 10 min is puzzling." One explanation is that the terminal meconium had little amniotic fluid dilution and was intensely concentrated. A presented, but not published, study of 37 cases from our institution found that if meconium was known to be present for more than 1 h, there were pigment macrophages in the amnion or chorionic connective tissue in 11 out of 12 membranes [10]. In three patients with less than 1 h of meconium exposure, two had no pigment macrophages and one had pigment macrophages in the amnion. Surprisingly, three cases without recognized meconium had non-haemosiderin macrophages in the decidua but not in the amnion or chorion.

An estimate of the duration of meconium based on meconium macrophage depth is an imperfect measure. The evaluation is further confounded by the report that fluorescent lights in the room may substantially reduce the pigment intensity on the microscope slide [11].

40.5 Prognosis and Predictive Factors

The interpretation of pigment in the amnion needs to be correlated with the gross and clinical findings such as gastroschisis and bowel atresia.

There are no studies correlating the presence of lipid amount with morbidity of gastroschisis. However, some infants with gastroschisis exude more protein into the amniotic fluid and this has been associated with morbidity [3]. Amniotic vacuolization is highly sensitive for gastroschisis but is only highly specific for gastroschisis prior to 37 weeks gestation because of similar vacuolization in term placentas [12].

Mature infants commonly pass meconium, up to an incidence of 20%, during labour often near the time of delivery. This usually benign passage contrasts with the experimental passage of meconium in response to acute asphyxia [13]. A subgroup of infants with asphyxia likely accounts for the association of meconium passage in utero with markers of fetal asphyxia [14]. Neither the pathological measures of the duration of meconium in the amniotic fluid, nor even for the presence of meconium, have been proven to document the presence or the time of onset of fetal asphyxia in the individual fetus.

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Choriodecidual Haemosiderin Staining

41

T. Yee Khong and Jerzy Stanek

41.1 Introduction

The amniochorial membranes are normally translucent. Opacity or duskiness of the membranes is usually due to acute chorioamnionitis (Chap. 44), prolonged retention of stillbirth or prolonged rupture of the membranes. Discoloration due to the presence of pigment-laden macrophages in the amniochorial membranes can sometimes be evident grossly and is usually due to meconium (Chap. 40) or iron uptake by macrophages in the amniochorion. Haemosiderin is a breakdown product of red blood cells.

41.2 Definitions

Choriodecidual haemosiderin staining is defined as the presence of iron, preferably confirmed by using histochemical stains, in the amniochorial membranes or the chorionic plate.

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41.3 Synonyms

Iron pigment staining in the membranes and in the chorionic plate has been termed diffuse chorioamnionic haemosiderosis [1]. The objection to this term is that "diffuse" is not clearly defined and haemosiderosis by iron staining can be seen in about half of placentas examined [2] and thus may be normal (see below) [2, 3]. The presence of iron in the basal plate or placental membranes has been referred to as decidual haemosiderosis [4], albeit the basal place contains also the extravillous trophoblast.

41.4 Epidemiology

Some degree of iron pigment staining is seen in approximately 50% of placentas when unselected placentas were stained with an iron stain [2]. Previous studies with lower prevalences, 2.2% [1] and 4.2% [5], either excluded cases with history of meconium staining or histological finding suggestive of meconium [1] or performed iron stains following light microscopic determination of pigment in the membranes and chorionic plate [5]. Decidual haemosiderosis was seen in 43% of placentas <32 weeks gestation but only in 0.8% of term placentas [4]. Choriodecidual haemosiderosis (defined on haematoxylin- and eosin-stained slides without routine iron histochemistry stain)

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was seen in 5% of 3382 non-selected placentas from high-risk pregnancies [6]. Haemosiderosis in the amniochorial membranes, chorionic plate and/or basal plate is seen in approximately 50% of delivered placentas if they are stained for iron. There are no specific associations in low-risk cohorts [2].

However, placentas submitted to pathology for clinical indications do have specific associations in cases diagnosed with *diffuse chorioamnionic haemosiderosis*. Diffuse chorioamnionic haemosiderosis is an objective marker of chronic peripheral placental separation, clinically called the chronic abruption-oligohydramnios sequence. This finding is associated with circumvallate placentas, old peripheral clots, increased chorionic villous macrophages and green discolouration [1]. It also clusters with clinical and histological features of placental abruption [6]. It is not more common in chronic hypertension (4.7% vs 5.0%) and it is unclear whether preeclampsia affects this frequency [7, 8].

Diffuse haemosiderosis is more common with membrane laminar necrosis (8%), chorionic microcysts [9] and cord compromise [10]. Finally, diffuse haemosiderin deposits in the chorionic plate have been described in association with massive subchorial haematoma [11].

41.5 Gross Findings

A greenish-brown or "rusty" discolouration of the membranes may be seen, but it is essentially a microscopic diagnosis.

41.6 Histopathology and Special Stains

The differential diagnosis of pigment staining in the membranes can be due to haemosiderin deposition or meconium uptake by macrophages. Haemosiderin staining can be suspected by refractibility on haematoxylin and eosin staining [3] and confirmed by using an iron stain, such as Perls' Prussian blue, Gomori or Berlin blue.

Placentas are not usually routinely stained for iron. On haematoxylin and eosin staining, haemosiderin deposition is indistinguishable from deposition elsewhere in the body (Fig. 41.1). The iron deposition may be seen on histochemistry staining as a clustered stippling of dots, as a ring around nuclei or as a dark irregular spot (Fig. 41.2a–c). The staining is usually seen in the chorion laeve layer alone or in both the chorion and decidual layers. The cells in Fig. 41.2b resemble chorion laeve cytotrophoblast.

Based on histochemistry staining for iron, the extent of haemosiderin deposition is classi-

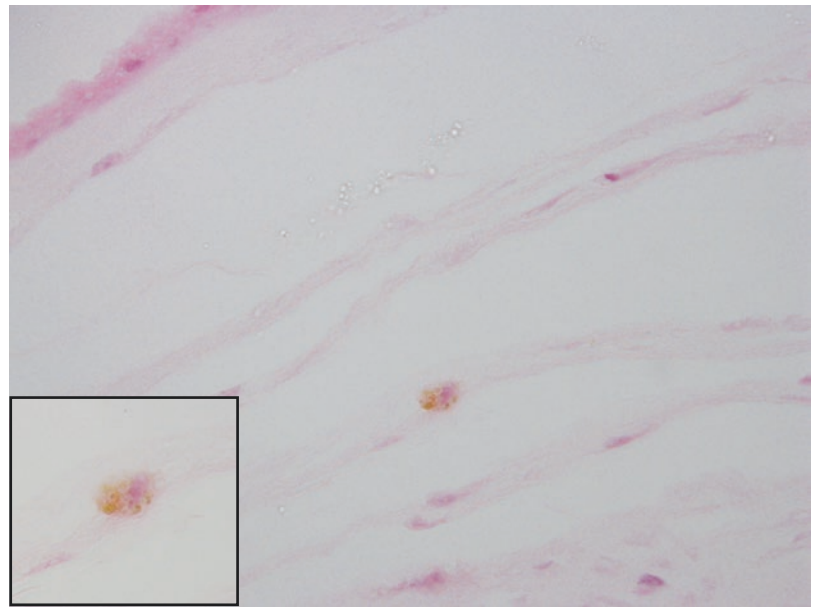

Fig. 41.1 Haemosiderin deposition in the amnion mesenchyme of the amniochorial membranes showing golden-brown granules phagocytosed by macrophage. (Haematoxylin and eosin-staining)

fied as diffuse when haemosiderin deposition is seen in five or more adjacent high-power fields (HPF × 20 objective lens) or as localised when present in fewer than five HPF. The density is defined as high when there are ten or more haemosiderin-laden cells or as low when there are fewer than ten haemosiderin-laden cells in one HPF (×20 objective lens). The haemosiderin deposition can be graded as mild, moderate or severe, based on the extent and density of haemosiderin deposition: sections with a localised and low density are graded as mild; sections with diffuse and high density are graded as severe and the rest as moderate (Fig. 41.3a–c) [2].

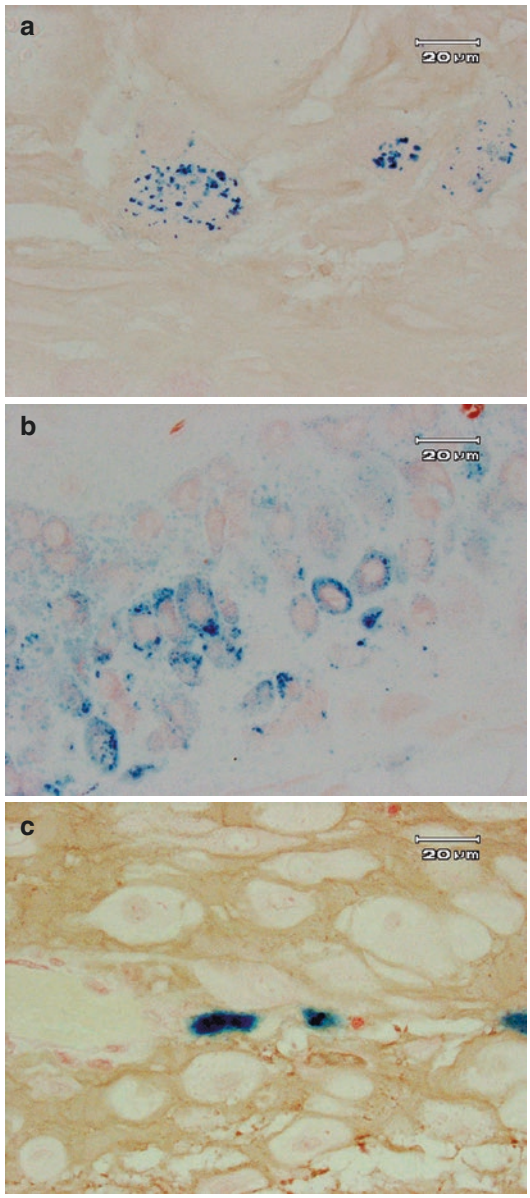

Fig. 41.2 Different patterns of iron deposition in the amniochorial membranes: (**a**) clustered stippling of dots, (**b**) perinuclear ring and (**c**) dark irregular spot (Perls' Prussian blue stain) (with permission from Pathology 2010;42:119–124)

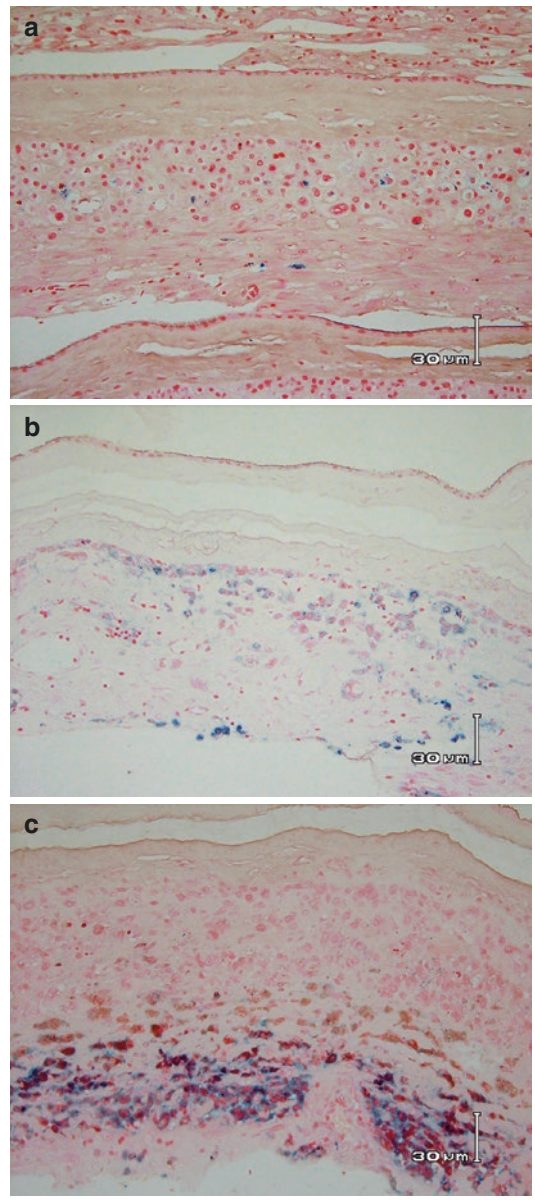

Fig. 41.3 Amniochorial membranes showing haemosiderin deposition graded as (**a**) mild, (**b**) moderate and (**c**) severe. (Perls' Prussian blue stain) (with permission from Pathology 2010;42:119–124)

Haemosiderin deposition can be observed not only in the extraplacental membranes but also in the chorionic plate and basal plate. Placental haemosiderosis is a wider term than choriodecidual haemosiderosis as iron deposition can be revealed in mineralization of basement membranes of chorionic villi or haemosiderin granules in the villi. Both can be diffuse as in retained stillbirth [12], aneuploid pregnancies, placental oedema or infections or lobular as in fetal vascular malperfusion (Chaps. 19, 21, 24) [3].

41.7 Prognosis and Predictive Factors

None known at present.

41.8 Further Studies

Choriodecidual haemosiderin staining, as defined, did not differentiate in which cells the iron staining was found. Transferrin receptors, which are needed to internalise iron into a cell, are expressed in macrophages [13] but not in chorion laeve cytotrophoblast [14]. Neutrophil gelatinase-associated lipocalin can bind and transport iron and has been localised to chorion laeve cytotrophoblast [15]. Studies on the role of iron transport proteins and homeostasis at the local level in the chorion laeve cytotrophoblast and macrophages in normal and abnormal pregnancy may reveal the clinical significance of choriodecidual haemosiderosis. Furthermore, the clinical significance of various stages and grades of choriodecidual haemosiderosis needs to be determined.

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42 Laminar Necrosis, Membrane Chorionic Microcysts and Chorion Nodosum

Jerzy Stanek

42.1 Laminar Necrosis

42.1.1 Introduction

Laminar necrosis (LN) of placental membranes is an acute hypoxic lesion (membrane infarction) [1]. The amnion is avascular and receives oxygen from the amniotic fluid while the deep decidua parietalis receives oxygen from maternal blood. The superficial decidua parietalis and the chorion are particularly susceptible for hypoxia and are affected thereby first. There is some pathophysiological analogy to the laminar necrosis seen in the brain [2].

42.1.2 Definition

A band of coagulative necrosis randomly distributed at the choriodecidual interphase may affect the decidua only (laminar decidual necrosis), the extravillous trophoblast (laminar trophoblastic necrosis) or both (mixed laminar necrosis). It is diagnostic if it comprises at least 10% of membrane roll(s), with or without leucocytoclastic reaction [2].

42.1.3 Synonyms

Membrane infarction [3].

42.1.4 Epidemiology

LN affects 10% of all pregnancies [1] and 21% of placentas from high-risk pregnancy [4], particularly in term pregnancy [5]. LN shows strong positive correlation with gestation age at delivery (Fig. 42.1) [6]. It is five times more frequent in association with than without maternal hypertension [2], almost two times more frequent in fetal growth restriction [7, 8] and more common in maternal diabetes mellitus [4] and umbilical cord compromise [9]. It is particularly significant when observed with maternal, fetal and neonatal conditions associated with hypoxia [2]. LN is two times more common than membrane chorionic microcysts (see below) [1] but tends to coexist with them and decidual clusters of multinucleate trophoblasts (acute-on-chronic membrane hypoxic lesion, overlap acute and chronic hypoxic lesion) [1, 10, 11].

42.1.5 Gross Findings

Grossly not visible.

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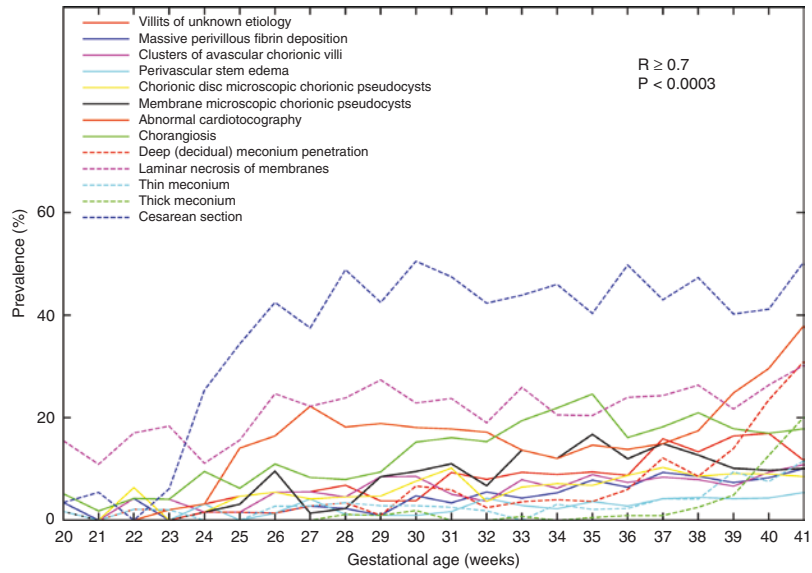

Fig. 42.1 Membrane laminar necrosis and chorionic microcysts, among other placental and clinical phenotypes, show strong positive correlation with gestational age at delivery

42.1.6 Histopathology

Trophoblastic or decidual ghost cells must be seen (Fig. 42.2a, b) [1]. Leucocytoclastic LN features focal neutrophil aggregates at the deep aspect of LN, not seen elsewhere in the membranes (Fig. 42.2c). The neutrophils are a reaction to necrotic tissue injury. The mechanism of accumulation of neutrophils in the leucocytoclastic LN is similar to other infarction-associated inflammation, as in myocardial or placental villous infarction [1]. LN must be distinguished from (1) the matrix-type fibrinoid or fibrinoid lamella, in which no ghost cells are present, and (2) acute necrotizing chorioamnionitis, which features liquefactive inflammatory necrosis, is usually diffuse and features trophoblastic accumulation of neutrophils. However, LN may also be seen in association with acute chorioamnionitis and is loosely associated with meconium staining [1]. Long-standing LN may undergo dystrophic calcification (Fig. 42.2d).

42.1.7 Immunohistochemistry

LN is positive for complement 9, a marker of necrosis (Fig. 42.3a), flanked by caspase-3 positivity, a marker of irreversible apoptosis (Fig. 42.3b), adjacent to positivity for nitrotyrosine residues, a marker of oxidative stress [2] (Fig. 42.3c) and is positive for hypoxia-inducible factor 2α (HIF2α), a marker of hypoxia [12–14] (Fig. 42.3d). The extent of the caspase-3 positivity and nitrotyrosine positivity is much larger than that of LN, the latter thus being a tip of the iceberg of the immunohistochemistry manifestation of membrane hypoxia ("aponecrosis") [2]. LN shows a characteristic temporal evolution: from positivity for nitrotyrosine residues, apoptosis, coagulative necrosis leucocytoclastic reaction to dystrophic calcification [15].

42.1.8 Genetic Susceptibility

Not applicable.

42.1.9 Prognosis and Predictive Factors

LN is a sensitive but nonspecific membrane lesion associated with acute in utero hypoxia, independent of its cause. Clinical conditions associated with the LN frequently have tendency to recur but the recurrence rate of LN itself is unknown. Diagnosing LN and membrane chorionic microcysts (see below) increases the

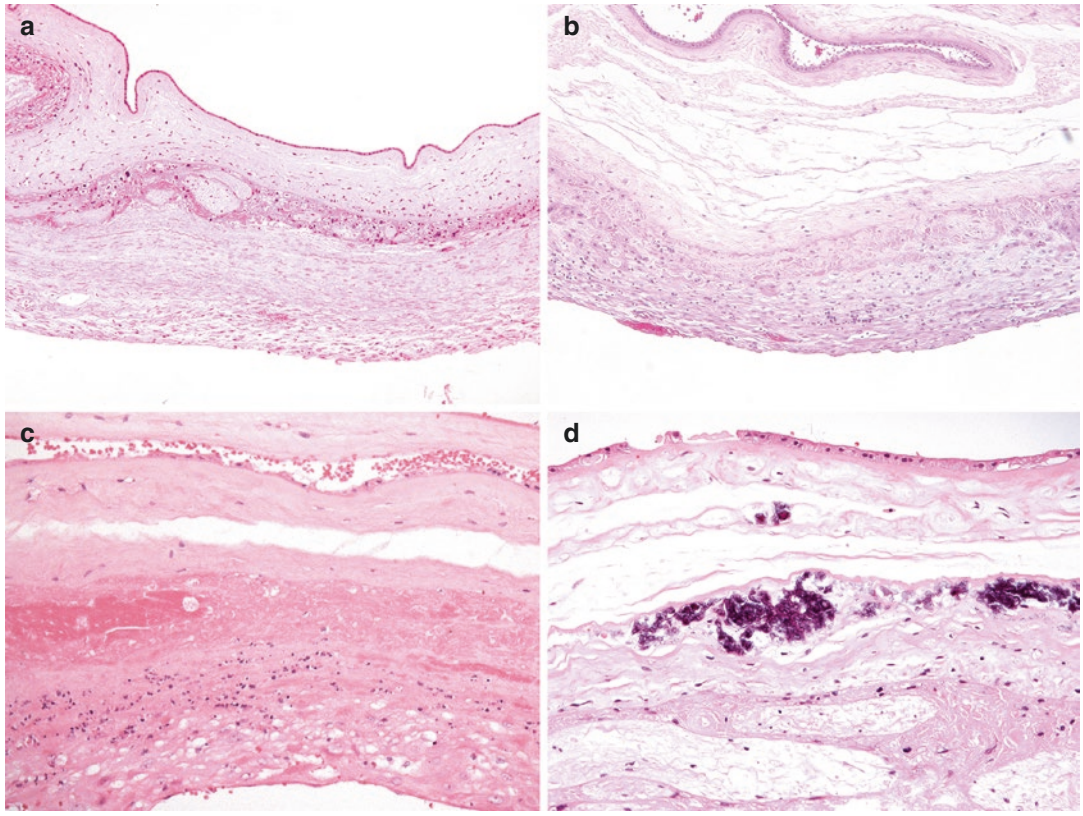

Fig. 42.2 Laminar necrosis of membranes. (**a**) Decidual necrosis. (**b**) Trophoblastic necrosis. (**c**) Leucocytoclastic mixed trophoblastic and decidual laminar necrosis. (**d**) Dystrophic calcification of presumed previous trophoblastic laminar necrosis

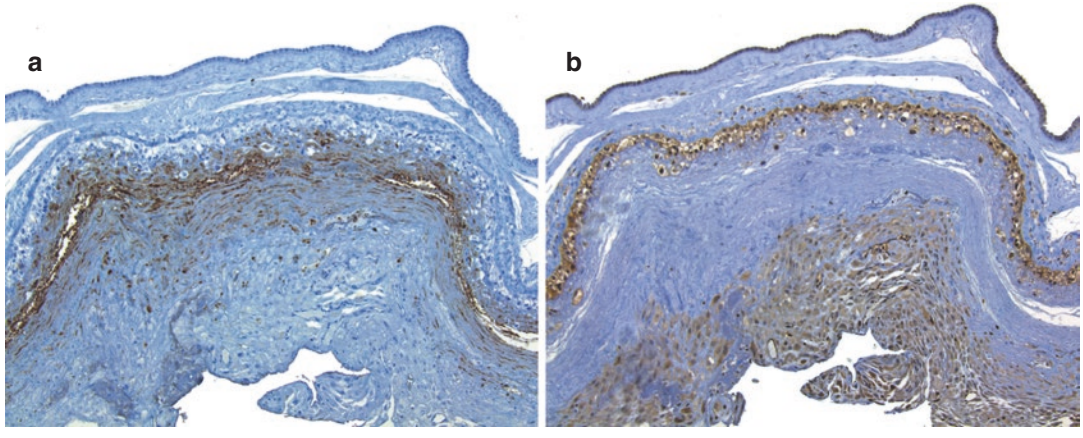

Fig. 42.3 Immunohistochemistry of laminar necrosis (LN). (**a**) LN stains positive for complement 9. (**b**) Viable cells adjacent to LN are positive for active caspase 3. (**c**) Areas underlying LN in the membrane roll are positive for nitrotyrosine residues. (**d**) Areas adjacent to LN are positive for HIF2α

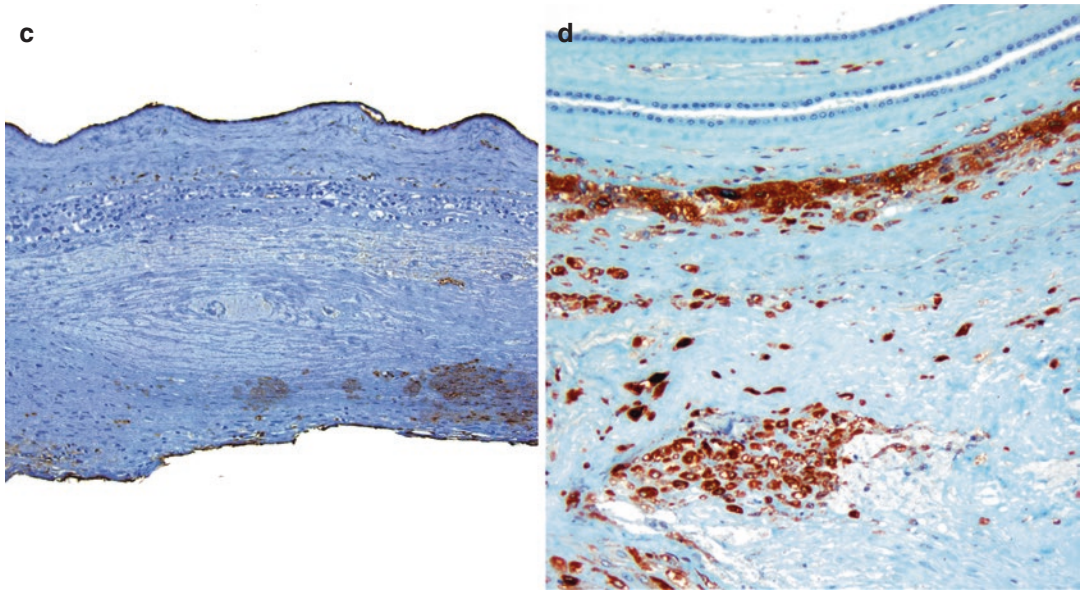

Fig. 42.3 (continued)

sensitivity of placental diagnosis for hypoxia by 15% [16]. Isolated LN may not have clinical significance [2]. However, in conjunction with other hypoxic lesions (overlap hypoxic lesions), it is a good retrospective evidence of in utero hypoxia [2, 10, 17].

42.2 Membrane Chorionic Microcysts

42.2.1 Introduction

Cystic degeneration and/or increased focal secretory activity of the migratory trophoblasts may lead to membrane chorionic microcyst (MCM) formation (extravillous trophoblast microcysts) [18]. MCM formation has the same aetiology, pathomechanism and clinical significance as in the chorionic disc (cell island/septal) microcysts [19]. Increased amount of extravillous trophoblasts with MCM formation may be a chronic hypoxia-driven lesion of extravillous trophoblast dysfunction [15, 20] or result from shallow placental implantation [21, 22].

42.2.2 Definition

MCM of chorion laeve are cysts lined by migratory extravillous trophoblasts. At least three MCM per membrane roll are regarded clinically significant [18].

42.2.3 Synonyms

Microscopic X-cell cysts, Microscopic X-cell pseudocysts.

42.2.4 Epidemiology

MCM can be seen in normal placentas (4.3%) [20] and in 9% of placentas from high-risk pregnancy [3]. They are more common in term pregnancies [8] and in mid third trimester [5, 20, 23]. MCM shows strong positive correlation with gestational age at delivery (Fig. 42.1) [6].

MCM are 2–3 times more common in both early-onset and late-onset preeclampsia (14.9%) [24], as preeclampsia itself is associated with excessive amount of extravillous trophoblasts

[25]. They are almost twice as common in diabetic pregnancies [20, 26] and fetal growth restriction [8].

MCM are frequently associated with other placental lesions/patterns such as decidual arteriolopathy, global hypoxic patterns of placental injury, chorangiosis, placental infarction, laminar necrosis, stem obliterative endarteritis, erythroblasts in maternal circulation, decidual hemosiderosis [20] and maternal floor multinucleate trophoblasts [11]. MCM are twice as common in patients with excessive extravillous trophoblasts in chorionic disc and chorionic disc microscopic pseudocysts [27].

42.2.5 Gross Findings

MCM are grossly inapparent. However, they can be visualized in pregnancy using optical coherence tomography [28].

42.2.6 Histopathology

MCM are filled with a homogeneous acellular granular material (Fig. 42.4a). They may be confluent, forming larger cysts (Fig. 42.4b). Some MCM in membrane sections feature ragged walls without any secretion. They are associated with thickened invasive rather than proliferative migratory trophoblastic layer, usually more than seven cells in thickness (Fig. 42.4c) [18]. MCM must be distinguished from sclerosed chorionic villi of chorion laeve frequently present in placental membranes (Fig. 42.4d) that feature rare fibroblastic nuclei rather than homogenous granular material [20].

42.2.7 Immunohistochemistry

The MCM content is strongly positive for dPAS, collagen type IV and fibronectin (Fig. 42.5a–c),

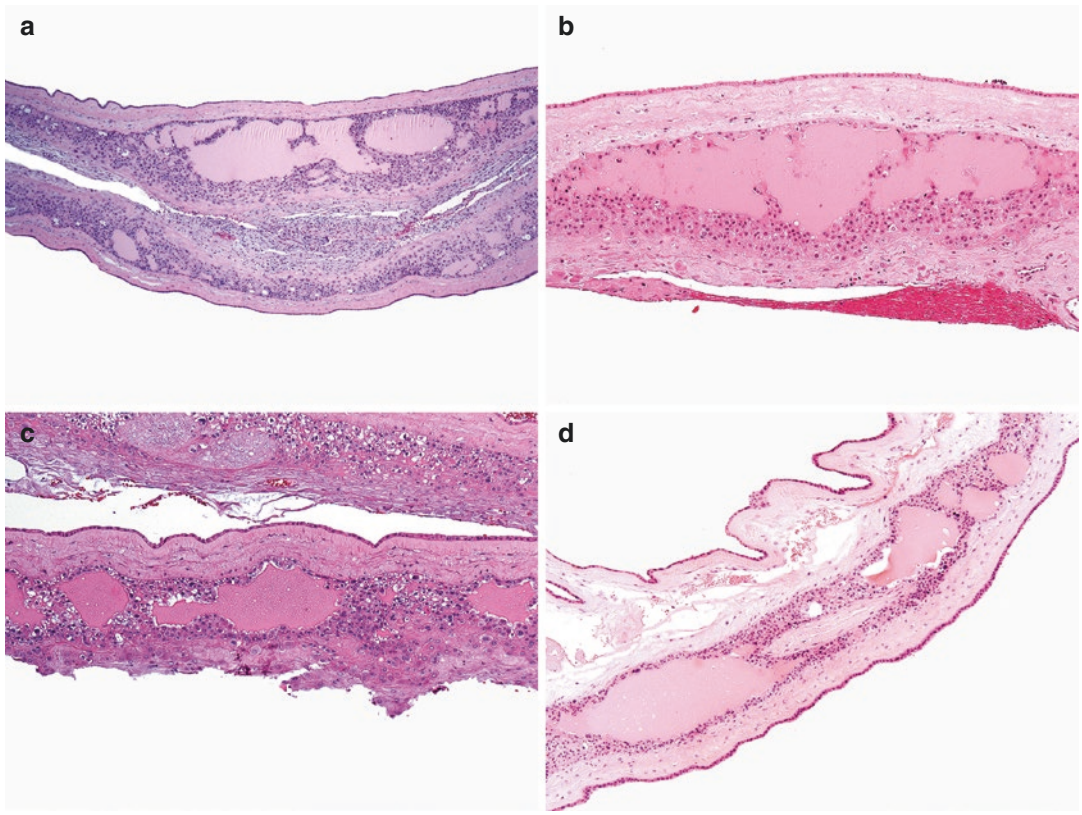

Fig. 42.4 Membrane chorionic microcysts (MCM). (**a**) MCM are filled with a homogeneous granular material. (**b**) MCM can form larger confluent lakes. (**c**) MCM are associated with thickened invasive extravillous migratory trophoblasts. (**d**) MCM in dividing membranes of dichorionic twin pregnancy; in the centre a sclerotic villous of the chorion laeve is seen

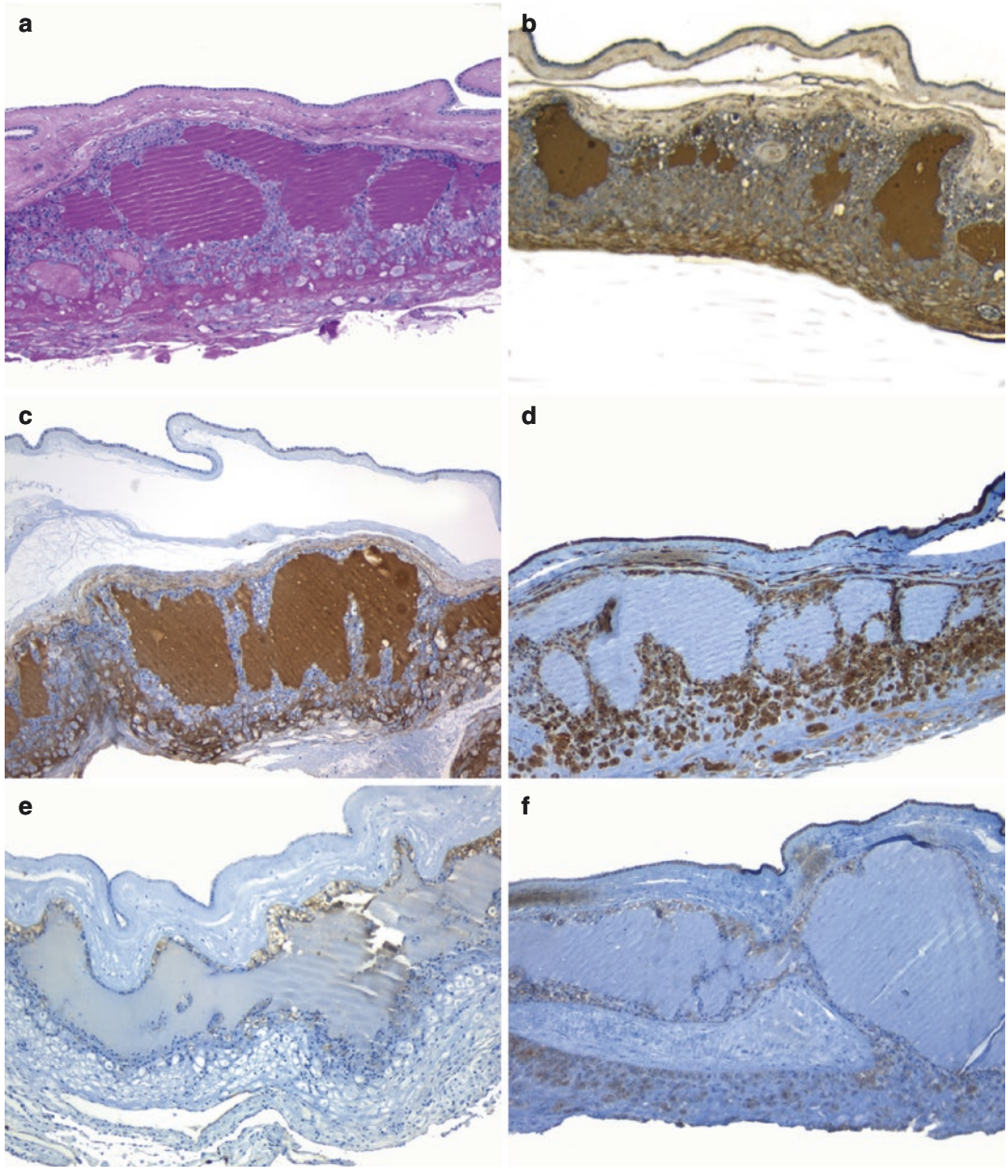

Fig. 42.5 Histochemistry and immunohistochemistry of MCM. (**a**) Microcyst content and extracellular matrix of invasive migratory trophoblasts are digested periodic acid-Schiff (dPAS) positive. (**b**) Microcyst content is collagen type IV positive but an atrophic villus of the chorion laeve in the centre is negative. (**c**) Microcyst content and extracellular matrix of invasive migratory trophoblasts are fibronectin positive. (**d**) Microcyst lining is positive for fascin. (**e**) Proliferative migratory trophoblast adjacent to MCM is positive for placental alkaline phosphatase. (**f**) E-cadherin stains the cytoplasm of the migratory trophoblast lining

weakly positive for human placental lactogen and negative for fibrin, thus representing the extracellular matrix of the migratory extravillous trophoblasts [29]. The lining of MCM is positive for fascin and weakly positive for E-cadherin and placental alkaline phosphatase (Fig. 42.5d–f) [20]. Unlike in LN, the degree of apoptosis, proliferation and maturation of the migratory extravillous trophoblast is not increased in MCM [20].

42.2.8 Genetic Susceptibility

Unknown.

42.2.9 Prognosis and Predictive Factors

MCM and placental disc microscopic chorionic pseudocysts share similar clinicopathologic correlations [19]. MCM is less commonly seen in respiratory distress syndrome in preeclamptic pregnancies [30]. Diagnosing placental membrane hypoxic lesions, including MCM, increases the sensitivity of placental examination [16, 17].

42.3 Chorion Nodosum

42.3.1 Introduction

Vernix of the amniotic fluid can be pasted on various surfaces being in direct contact with it, not only on amnion (amnion nodosum, see above) but also, for example, on the chorionic mesenchyme, chorion nodosum (ChN), pleura (pleura nodosa) [31] or mucoperiosteum of the middle ear [32]. The author has recently observed microscopic nodules similar to amnion nodosum on the visceral peritoneum exposed to amniotic fluid in amniotic wall disruption of the limb-body wall complex (peritoneum nodosum).

42.3.2 Definition

ChN is a vernix-containing nodule structurally similar to amnion nodosum as far as histological composition of its content is concerned but embedded in the chorionic mesenchyme of placental membranes or chorionic disc in areas denuded of amnion [33].

42.3.3 Synonyms

Vernix granuloma [34, 35].

42.3.4 Epidemiology

ChN is a rare placental lesion (only 0.1% of all placenta). It has a bimodal gestational age distribution: early second trimester in limb-body wall complex and term in extra-amniotic pregnancy [33]. ChN is associated with prolonged oligohydramnios or amniotic bands, the latter playing a main role in term ChN [36] and the former in the early vascular disruption of the severe early amnion rupture sequence, with direct contact of fetal body with the membranes denuded of amnion or a metabolic defect of the amniotic epithelium playing additional role. Some authors also mention amniotic disintegration due to inflammation or meconium damage in the pathogenesis of ChN [37].

42.3.5 Gross Findings

ChN is grossly inapparent.

42.3.6 Histopathology

ChN are nodules of amorphous, usually flat and buried directly into the chorionic mesenchyme of placental membranes and/or of the chorionic disc [33] (Fig. 42.6a, b). There is no granulomatous or other associated inflammatory reaction. They

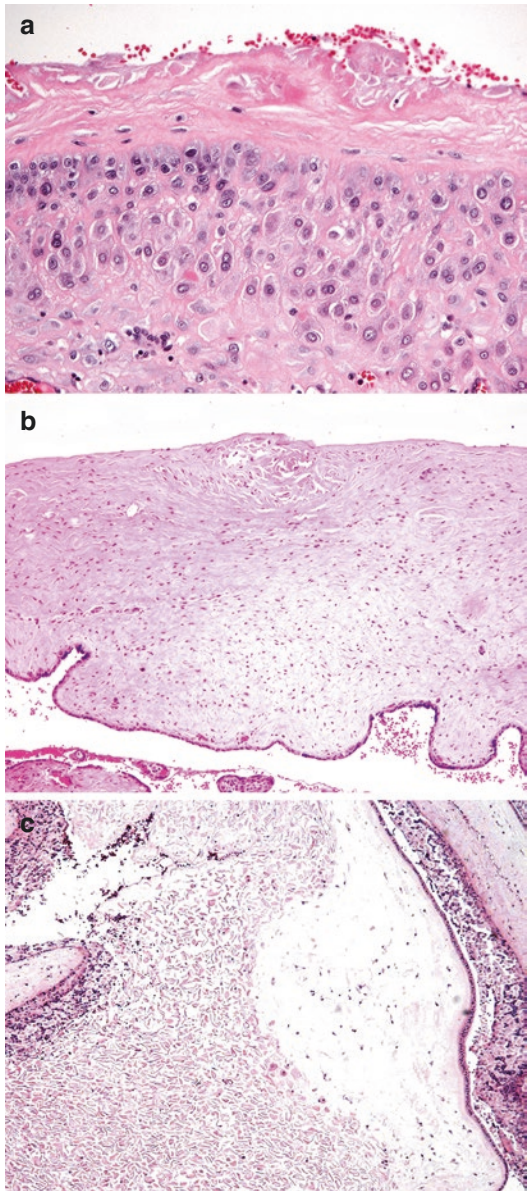

Fig. 42.6 Chorion nodosum. (**a**) Microscopic nodule containing vernix embedded into the chorionic mesenchyme of placental membranes; the trophoblastic layer of the chorion is visible underneath. (**b**) Microscopic nodule containing vernix is embedded into the chorionic mesenchyme of the chorionic disc. (**c**) Dissection of vernix between amnion and chorion of placental membranes featuring loose aggregates of squames and resulting from amnion rupture close to delivery has no diagnostic significance

should not be confused with dissection of vernix under amnion which are loose aggregates of squames from fetal skin seen in the spongy layer (Fig. 42.6c) [33].

42.3.7 Immunohistochemistry

Not relevant.

42.3.8 Genetic Susceptibility

None, as the limb-body wall complex and extraamniotic pregnancy are sporadic conditions.

42.3.9 Prognosis and Predictive Factors

When associated with the limb-body wall complex, the prognosis is poor because of usually lethal fetal intrinsic disruptions. Even without limb-body wall complex, the prognosis is guarded because of the prolonged oligohydramnios/anhydramnios-associated pulmonary hypoplasia and possible associated congenital malformations.

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Decidual Vasculopathy

43

Beverly B. Rogers and M. Halit Pinar

43.1 Introduction

Two histopathologic alterations in the placental membranes are associated with maternal malperfusion syndromes (e.g. preeclampsia) and chronic maternal hypertension: atherosis and mural hypertrophy of membrane arterioles. While atherosis is a relatively well-defined histopathologic alteration, medial hypertrophic terminology varies among studies. This chapter will delineate these differences and identify the prevalence and clinical associations of maternal vasculopathy when identified in placental membranes.

43.2 Definition

Maternal vasculopathy, by definition, is a pathologic condition of the maternal vessels, which may involve the spiral arteries in the placental bed (see Chap. 32) or the arterioles in the membranes. In histopathologic sections of placental membranes, maternal vasculopathy can be subdivided into atherosis and mural hypertrophy of membrane arterioles [1].

43.3 Synonyms

Atherosis, Acute atherosis, Hypertensive arteriopathy.

Hypertrophic decidual vasculopathy, Mural hypertrophy of membrane arterioles.

Membranous decidua, Parietal decidua, Decidua parietalis, Decidua attached to the placental membranes.

43.4 Epidemiology

The prevalence of atherosis and mural hypertrophy in the placental membranes varies depending on the number of membrane sections. The literature suggests atherosis is seen in roughly 10–40% of pregnancies complicated by early-onset preeclampsia and is also seen, but less frequently,

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in other maternal malperfusion syndromes like essential hypertension and early-onset fetal growth restriction.

43.5 Gross Findings

Atherosis and mural hypertrophy of arterioles in the decidua are not visible macroscopically.

43.6 Histopathology

Atherosis is seen histopathologically as degeneration of the smooth muscle in the media of the arterioles in the parietal decidua ("fibrinoid necrosis"), associated with an accumulation of dense eosinophilic material beneath the vascular endothelium containing foamy macrophages (Figs. 43.1 and 43.2). The vascular endothelium often demonstrates disruption, and lymphocytes are often seen surrounding or within the vascular wall. Vessels showing atherosis are more dilated than normal and may show marked dilatation.

Mural hypertrophy of membrane arterioles is defined based on the article by Redline et al. as thickening of the walls of an arteriole with a mean wall diameter of greater than 30% of the mean circumference of the arteriole (Fig. 43.3) [1]. The thickening can be "due to any combination of medial or subendothelial hyperplasia, hypertrophy, and interstitial matrix deposition".

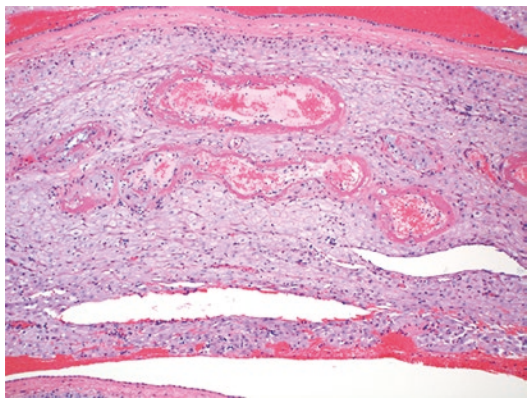

Fig. 43.1 Atherosis, low power: A histologic section of a placental membrane roll shows the parietal decidua with multiple dilated vessels containing dense, eosinophilic material (fibrinoid) in their walls. Histiocytes are seen embedded in the fibrinoid

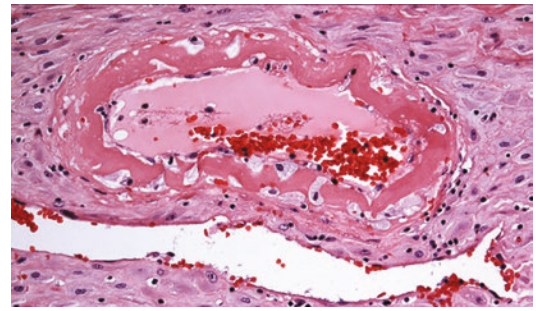

Fig. 43.2 Atherosis, high power: A higher-power view of a vessel affected by atherosis revealed eosinophilic fibrinoid replacing the vascular wall, with abundant foamy histiocytes. Note the disruption of the endothelium with absence of endothelial cells in multiple areas. Lymphocytes are seen within the wall, characteristic of atherosis. There is also a blood vessel in the field showing absence of a muscular wall and retention of an endothelial lining, which is normally what the vessels in the parietal decidua look like at term gestation

Atherosis and mural hypertrophy of arterioles of the decidua are both manifestations of maternal hypertension. Both are abnormal histopathologic changes in the maternal arterioles but have different pathologic findings. They are often seen in combination but may also be present individually in sections of placental membranes. The prevalence of the lesions is dependent on the number of membrane rolls sampled and the amount of decidua attached to the membranes.

The maternal vascular changes of atherosis are histopathologically identical regardless of whether they are seen in the parietal decidua, the basal decidua or a placental bed biopsy. While atherosis was well-described in the basal decidua and endometrial bed biopsies in the 1960s, Khong identified the lesion specifically in the parietal decidua when evaluating "two to three rolls of amniochorial membranes" [2]. He studied the histologic location of atherosis in 75 placentas from pregnancies complicated by the following disorders: preeclampsia, essential hypertension, small-for-gestational-age infants and diabetes mellitus. Atherosis was present in the parietal decidua in 8/19 (42%) pregnancies complicated by preeclampsia alone, and 4/24 (16.7%) pregnancies

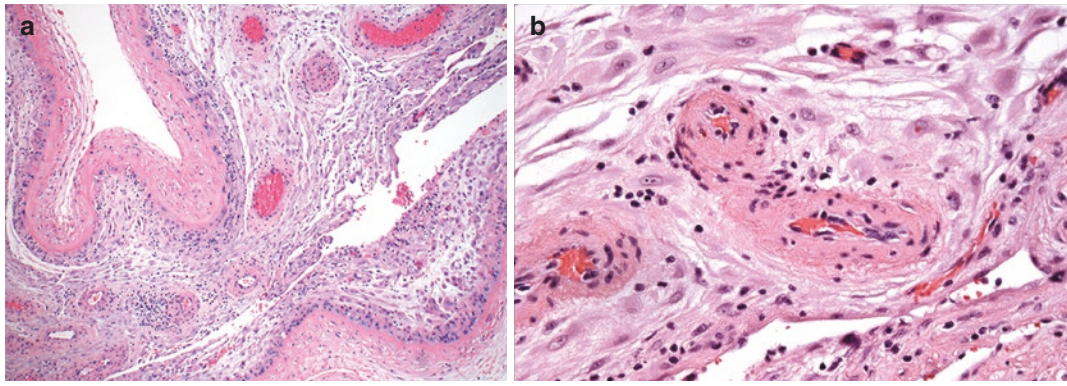

Fig. 43.3 Mural hypertrophy of arterioles: (**a**) A low-power view of the parietal decidua of a third trimester pregnancy complicated by preeclampsia shows multiple vascular profiles with thickened walls and perivascular lymphocytes. (**b**) A higher power demonstrates an arteriole with a thick wall and lymphocytes surrounding the vessel

complicated by preeclampsia, with or without essential hypertension, and small-for-gestational-age infants. Atherosis was seen more often in sections of the membranes (12/33 cases) than the basal decidua (7/33 cases). Pregnancies complicated by small-for-gestational-age infants with no associated maternal condition had atherosis in the basal plate in 10/26 cases (38%) but atherosis was not seen in the parietal decidua in any of the cases with isolated small-for-gestational-age infants. Atherosis was not seen in the parietal decidua, basal decidua or placental bed biopsies in placentas from 31 healthy pregnancy controls.

Kim et al. evaluated the frequency and topographic distribution of atherosis in placentas and placental bed biopsies from normal pregnancies and "those affected by the great obstetrical syndromes" [3]. The syndromes included preeclampsia, gestational hypertension, chronic hypertension, small-for-gestational-age infants, fetal death, spontaneous miscarriage, spontaneous preterm labour, preterm prelabour rupture of membranes and a group called "other". The authors evaluated one roll of chorioamniotic membranes and two sections of the basal plate, as well as endometrial bed biopsies from a subset of patients. As opposed to Khong, who identified atherosis in the parietal decidua in 42% of placentas from pregnancies complicated by preeclampsia without a small infant, Kim et al. reported a lower prevalence of 181/1779 (10.2%) in pregnancies complicated by preeclampsia. Atherosis was diagnosed in 326 placentas and the topographical location was the chorioamniotic membranes in 246/326 (75.5%), the basal plate in 235/326 (72.1%) and in either topographical location in 317/326 (97.2%) placentas. The authors did not discriminate between the topographical distributions of atherosis in the parietal decidua versus decidua from pregnancies complicated by small-for-gestational-age infants in the absence of preeclampsia, as Khong did [2].

Winters and Waters addressed the varying prevalence of microscopic lesions depending on the number of membrane rolls evaluated [4]. The authors assessed between one and four membrane rolls from 53 placentas submitted to the pathology department. Atherosis was identified in four placentas following review of all four membrane rolls from the 53 placentas. When evaluating one section of membranes, atherosis would have been identified in between one to three of the four placentas with the lesion, depending on which section was chosen for review. Review of two sections identified atherosis in two of the four cases and analysis of three samples identified the lesion in three of four.

Mural hypertrophy of arterioles is often seen in association with atherosis. The most precise definition of this lesion can be found from the consensus workgroup from the Society for Pediatric Pathology (SPP), where the authors differentiated mural hypertrophy of arterioles in

the parietal decidua from muscularization of basal plate arteries, both lesions being associated with atherosis [2]. The authors described the arteriolar changes in the parietal decidua as arterioles with thickened walls measuring greater than 1/3 of the mean circumference of the arteriole. The wall thickening was ascribed to any combination of changes, including medial or subendothelial hyperplasia, hypertrophy, and interstitial matrix deposition.

The SPP workgroup determined the interobserver reproducibility to identify these vascular abnormalities. Mural hypertrophy of the parietal decidual arterioles was one of the lesions most consistently detected by each of the pathologists. A group consensus was determined when greater than or equal to six of the eight pathologists agreed that a lesion was present or absent, and a group consensus was reached for mural hypertrophy of the parietal decidual arterioles in 90% of the cases with a kappa value of 0.43, indicating fair/moderate interobserver variability.

Spinillo et al. used the histologic criteria defined by the Society for Pediatric Pathology workgroup to investigate whether there was a correlation between placental pathology and fetal hypoxemia, as defined by a cerebroplacental Doppler ratio (CPR). The CPR is the ratio of pulsatility in the fetal middle cerebral artery to that of the umbilical artery, with a lower ratio indicating umbilical arterial constriction and cerebral arterial dilation, which increases cerebral blood flow, thus "sparing" the brain from hypoxia. Maternal arterioles were evaluated from 176 placentas submitted for evaluation due to fetal growth restriction and compared to the CPR of the fetus. Sections assessed for each placenta included three sections of the umbilical cord, one section of a placental membrane roll, and three sections of placental parenchyma. There was a significant association between mural hypertrophy of arterioles and a CPR less than 2.5%, with 51/87 (58.6%) of placentas associated with a low CPR showing mural hypertrophy. Muscularized arteries, seen in the basal plate, were present in 41/87 (47.1%) infants with a low CPR. Using logistic regression with CPR as the outcome to further define an association between histologic findings and CPR, mural hypertrophy of arterioles in the membranes had an associated odds ratio of 2.35, and muscularized arteries in the basal plate had an odds ratio of 3.14. When separated by gestational age, the odds ratio for mural hypertrophy was 2.94 at 34 weeks' gestation or younger, whereas muscularized arteries had an odds ratio of 5.28 in gestations over 34 weeks [5].

The association of mural hypertrophy of arterioles with diabetes has been debated, with early publications indicating that this lesion is found in association with diabetes. Subsequent studies have not corroborated this finding in diabetes without hypertension, and so the relationship is likely more aligned with hypertension complicating diabetes rather than diabetes alone.

The differentiation between mural hypertrophy of arterioles of the parietal decidua and muscular hypertrophy of the basal plate arterioles likely is more than just a semantic exercise but rather a reflection of the pathogenesis of the arteriolar alterations, which differs based on the location of the artery. Both are increased in pregnancies complicated by preeclampsia but they are in physiologically different areas of the placenta. The pathology of the muscularized arteries in the basal plate, which are associated with atherosis, is ascribed to a lack of vascular adaptation related to superficial invasion by extravillous trophoblast from the anchoring villi. It is curious that, while vascular adaptation by trophoblast does not occur in the placental membranes, muscularized arterioles are not identified in the membranes of normal term placentas, indicating that alteration of the muscular wall occurs despite adaptation by extravillous trophoblast (Fig. 43.3).

Smith et al. described early events of vascular remodeling of maternal vessels from the placental basal plate during the first trimester [6]. They identified an initial stage of vascular remodeling, consisting of disruption and disorganization of vascular smooth muscle and endothelial swelling and breaks associated with uterine natural killer cell activity. Fibrinoid was not detected in the vascular wall until luminal trophoblasts appeared, and so it is likely that the initial stages of vascular remodeling, including disruption of

vascular smooth muscle, occur for all uterine arteries, including those in the parietal decidua. These same findings were noted in an article by Craven et al. from evaluation of an ectopic pregnancy [7]. They noted spiral artery remodeling in the absence of vascular interaction with cytotrophoblasts.

43.7 Immunohistochemistry

Hecht et al. studied the vascular changes in the parietal decidua, away from areas of trophoblastic invasion, and proposed a sequence of endothelial injury using immunohistochemical staining for CD31, CD34, and desmin on sections of membrane rolls from six term and preterm placentas with decidual vasculopathy from pregnancies with a history of preeclampsia [8]. The definition of decidual vasculopathy was when the "mean wall diameter is about 30% of overall vessel diameter", which is slightly different from the description of hypertrophic decidual vasculopathy as defined by the Society for Pediatric Pathology workgroup. The authors compared the alterations in the hypertrophic arterioles in the parietal decidua of pregnancies complicated by preeclampsia to normal muscularized arterioles in the parietal decidua from elective terminations less than 16 weeks' gestation. In vessels with the early pathologic features of decidual vasculopathy, the endothelial cells were enlarged and variably detached from the vessel wall. The thickened media, seen by haematoxylin and eosin staining, revealed fragmented muscular walls, which had decreased desmin staining when compared to thick-walled vessels from normal pregnancies before 16 weeks' gestation. There were granular CD31 and CD34 deposits throughout the vascular wall of the vessels with decidual hypertrophy. Clinical associations were established, with the most significant amount of decidual vasculopathy in pregnancies with preeclampsia and small-for-gestational-age infants. The authors did not find decidual vasculopathy in cases of preterm labour or idiopathic small-for-gestational-age infants with Doppler abnormalities.

43.8 Genetic Susceptibility

This chapter will refer to Chap. 32, Decidual Vasculopathy of the Basal Decidua.

43.9 Prognosis and Predictive Factors

The prognosis and predictive factors of decidual vasculopathy will be the same as described in Chap. 32 (decidual vasculopathy of the basal decidua), with possibly one exception. Khong noted the lack of atherosis in the parietal membranes from pregnancies complicated by isolated small-for-gestational-age infants, but atherosis was present in the basal decidua. The location of atherosis, along with the presence of hypertrophic vasculopathy, may provide a clue to the pathogenesis of pregnancies complicated by isolated small-for-gestational-age infants.

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Acute Inflammation

44

Phillip Cox, Marta C. Cohen,
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44.1 Introduction

Acute inflammation of the amniochorial membranes is part of the spectrum of acute chorioamnionitis (intra-amniotic infection or amniotic fluid infection syndrome). Acute chorioamnionitis (ACA) commonly results from ascending microbial infection from the lower genital tract into the sterile amniotic cavity with the potential for subsequent invasion of the fetus [1, 2]. Clinically, infection of the amniotic cavity may result in a febrile illness and abdominal pain in the mother, tachycardia and fetal distress in the baby and the preterm onset of labour. Infection usually enters the amniotic cavity following rupture of the membranes but may cross closed membranes or gain access through small membrane breaches. Causative organisms include normal and abnormal endogenous vaginal flora and organisms colonising the vagina from the gastrointestinal tract (Group B β-haemolytic *streptococci*, *Listeria monocytogenes*, *Escherichia coli*, etc.) [3]. Occasionally, infective organisms can also reach the uterus through contiguous spread (from infections in the peritoneum, fallopian tubes or bladder) or by haematogenous dissemination (such as *T. pallidum*) [4].

44.2 Definition

Acute chorioamnionitis (ACA) is an inflammatory response in the chorionic plate of the placenta and amniochorial membranes usually in response to the presence of microorganisms in the amniotic fluid [3]. Acute inflammation involving the umbilical cord is dealt with in Chap. 55, whilst inflammation of the chorionic plate is discussed in Chap. 12.

44.3 Epidemiology

The incidence of histological ACA is inversely proportional to the gestational age, with a variation from 67% in less than 24 weeks gestational age to 24% at term [3, 5, 6]. In term placentas, the incidence of inflammation of the chorion and decidua has been reported to be 23.1% [5]. The use of molecular techniques has shown that in a subset of histological ACA cases, the culture does not demonstrate placental infection in term deliveries [7].

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Patients with histological ACA have a higher rate of nulliparity, longer duration of labour and rupture of membranes and received regional anaesthesia and oxytocin augmentation more frequently than those without histologic chorioamnionitis ($p < 0.001$ for each) [5].

Ascending microbial invasion from the lower genital tract seems to be the most frequent route for intra-amniotic infection. The risk factors for histological ACA include prolonged rupture of membranes, prolonged labour, multiple digital examinations with rupture of membranes, nulliparity, Group B streptococcus colonisation, bacterial vaginosis, alcohol or tobacco use, meconium-stained amniotic fluid, internal monitoring and epidural anaesthesia [8–14]. However, rupture of membranes is not necessary for bacteria to reach the amniotic cavity, as experimental evidence has shown that bacteria can cross intact membranes [2, 15].

Histological acute chorioamnionitis is more frequently seen in placentas of women who deliver after spontaneous labour than in the absence of labour. Intra-amniotic infection has been documented in cases of preterm labour with intact membranes, pre-labour rupture of membranes, cervical insufficiency, asymptomatic short cervix, idiopathic vaginal bleeding, placenta praevia and clinical chorioamnionitis at term [2]. Histological chorioamnionitis is common in second trimester pregnancy loss and, in many studies, the most common organism isolated is Group B streptococcus [16]. Women may present with recurrent cases of chorioamnionitis and miscarriage in the second trimester. Approximately 20% of pregnant women have vaginal colonisation with Group B streptococcus at any one time but carriage may be chronic, transient or intermittent. Histological acute chorioamnionitis regardless of amniotic fluid culture results is a risk factor of preterm delivery in cervical insufficiency [17]. Intrauterine infections caused by bacteria are the predominant cause of very early premature delivery [18]. Histological acute chorioamnionitis in preterm labour is associated with fetal growth restriction, acute neonatal morbidity and mortality, neurological impairment, chronic lung disease and thymic involution [19].

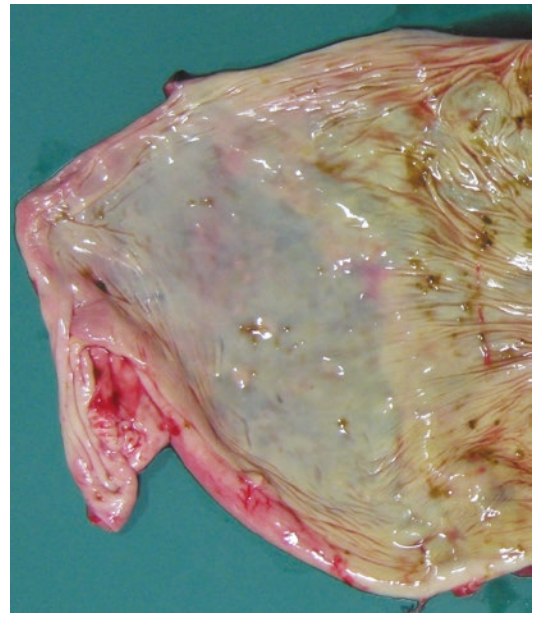

Fig. 44.1 Diffusely opaque, cream-colored amniochorial membrane as a result of severe chorioamnionitis

44.4 Gross Findings

The amniochorial membranes are made up of a thin, clear, shiny amniotic layer and a thicker chorionic layer. Both layers are avascular. A third layer of parietal decidua may be attached to the maternal side of the chorion. As with inflammation in the chorionic plate, acute inflammation leads to opacification of the membranes, with loss of the shiny surface of the amnion. The membranes may appear off-white, yellowish or greenish in colour (Fig. 44.1) and, if there has been prolonged rupture of the membranes, the surface may be dry or gritty suggesting amnion nodosum. Inflammation may be more prominent adjacent to the site of membrane rupture or around the site of insertion into the placental disc. White spots suggest Candida infection.

44.5 Histopathology

On histological examination the normal amniochorial membranes are composed of the amnion and the chorion, the former comprising a loose

connective tissue layer with a columnar epithelial covering on the side facing the amniotic cavity and the latter comprising a denser connective tissue layer with a layer of extravillous trophoblast on the maternal side. Tissue histiocytes are present within the connective tissue layers but neutrophils and lymphocytes are absent from normal membranes. Deep to the chorionic layer, there may be an incomplete layer of maternal decidua (the parietal decidua) containing maternal blood vessels.

Acute inflammation in the amniochorial membranes is of maternal origin, arising from the decidual vessels and emigrating towards the amniotic cavity. Thus, the earliest stage of inflammation is seen as accumulation of neutrophil polymorphs between the decidua and chorion (subchorionitis). This may be focal or diffuse and may appear as small numbers of neutrophils within the extravillous trophoblast layer or as microabscesses (Fig. 44.2a). There may also be acute inflammation in the parietal decidua. Extension of the inflammatory infiltrate into the chorionic layer (chorionitis) is followed by involvement of the amniotic layer (chorioamnionitis) (Fig. 44.2b). Inflammation may be most severe at the site of membrane rupture but may be diffuse, and severity varies from a mild infiltrate to dense inflammation, often associated with necrosis of the chorion and/or amnion (Fig. 44.2c). Following prolonged rupture of the membranes, amnion nodosum may be present (see Chap. 12).

The (maternal) inflammatory response may be graded and staged, although this is not regarded as essential by the authors of the recent Amsterdam Consensus Statement and may not relate to the clinical severity of the infection [20]. One suggested grading and staging protocol is shown in Table 44.1. When reporting chorioamnionitis it is, however, important to comment on the extent and severity of the inflammatory response, whether or not a grading/staging scheme is used.

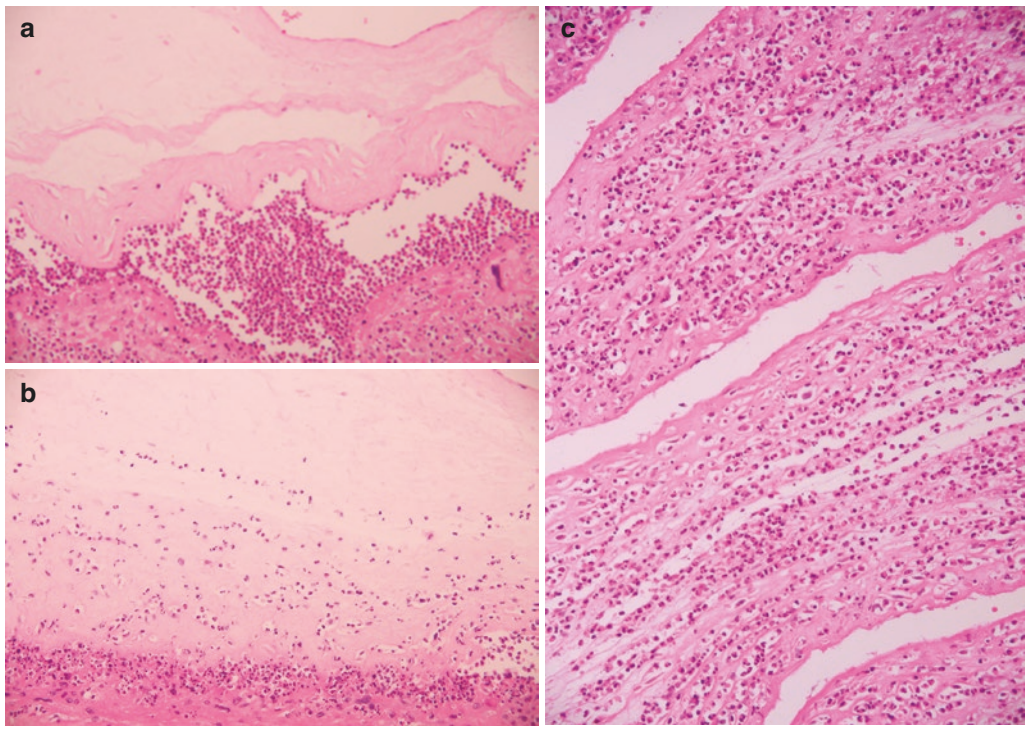

Fig. 44.2 Histology. (**a**) Acute subchorionitis with abscess formation (Stage 1, Grade 2); (**b**) extension of the inflammatory infiltrate from the chorion into the overlying amniotic membrane (Stage 2, Grade 1); (**c**) diffuse severe acute chorioamnionitis with necrosis in the amniotic membrane (Stage 3, Grade 2)

Table 44.1 Staging and grading of the maternal inflammatory response in ascending intrauterine infection

Maternal inflammatory response	
Stage 1—acute subchorionitis or chorionitis Stage 2—acute chorioamnionitis: polymorphonuclear leukocytes extend into fibrous chorion and/or amnion Stage 3—necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia	Grade 1—not severe as defined Grade 2—severe: confluent polymorphonuclear leukocytes or with subchorionic microabscesses

Ref. [20]

The causative organism may be demonstrated (see Chap. 12). Of note, some clinically severe infections, for example with Group B β-haemolytic streptococcus, may show only minimal or, even, no histological chorioamnionitis.

44.6 Immunohistochemistry

Immunohistochemistry is not necessary to diagnose acute chorioamnionitis. However, if herpes simplex or varicella infection is suspected, immunohistochemistry or molecular techniques may be employed to confirm the infection.

44.7 Prognosis and Predictive Factors

When accompanied by fetal vasculitis, histological acute chorioamnionitis in preterm labour likely plays a role in the development of necrotising enterocolitis [21]. Infections with highly pathogenic aerobic and facultative anaerobic bacteria such as Group B streptococcus, other *streptococci*, *Escherichia coli*, *Haemophilus influenza* and *Listeria monocytogenes* are more likely to spread to the fetus. Staging of the inflammation can be used to estimate the duration of the infection [22]; however, the clinical severity of the infection may not correlate with the degree of placental inflammation. Histological acute chorioamnionitis with fetal inflammatory response is associated with higher neonatal morbidity and mortality. In term infants, intrauterine infection is associated with neonatal encephalopathy and cerebral palsy [22].

Intrapartum antibiotic prophylaxis for all delivering women is not considered appropriate; however, giving intrapartum intravenous antibiotics to high-risk mothers (preterm delivery, intrapartum fever and prolonged rupture of membranes) is highly effective in preventing newborn disease [23]. Inadequate prophylaxis, however, may be responsible for neonatal disease [24].

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Chronic Inflammation

45

Suzanne M. Jacques and Faisal Qureshi

45.1 Introduction

Chronic chorioamnionitis is one of the chronic inflammatory lesions of the placenta, the involved placental compartment being the chorioamniotic membranes (extraplacental membranes) or membranes of the chorionic plate. Other chronic inflammatory lesions, VUE and chronic deciduitis, represent involvement of the villous tree and basal decidua, respectively, and are discussed in Chaps. 29 and 33. Chronic chorioamnionitis is a commonly identified lesion, and is frequently seen with villitis of unknown etiology [1–3] and with chronic deciduitis [1, 4], suggesting a common aetiology for the lesions. Of particular importance is the finding that chronic chorioamnionitis is the most common placental lesion of late preterm spontaneous delivery [1, 5]. As with the other chronic inflammatory lesions of the placenta, determining the aetiology of chronic chorioamnionitis is a challenge, but as with villitis of unknown aetiology, a growing body of evidence supports it as being the histologic manifestation of an immune process caused by maternal anti-fetal rejection (allograft rejection) in the majority of cases [6]. Subclinical infection must also be considered as an aetiology in some cases; however, the majority of cases do not show evidence of infection [2, 3].

The choriodecidual junction represents a large interface between the mother and the fetus, and alterations in fetal maternal tolerance can allow for maternal immune cells in the decidua to recognize fetal cells (chorionic trophoblasts) [6]. Chronic chorioamnionitis is associated with increased concentration of the chemokine CXCL10 in amnionic fluid and overexpression of CXCL9, CXCL10, and CXCL11 mRNA in the chorioamnionic membranes when compared to controls, and these T cell chemokines lead to a chemotactic gradient favouring migration of maternal T cells from the decidua into the membranes [1]. These dysregulated T cell chemokines also have anti-angiogenic properties and are involved in the migration of CXCR3+ activated T lymphocytes [1]. In addition to these features of cellular-mediated rejection, chronic chorioamnionitis is associated with features of maternal anti-fetal antibody-mediated rejection, including maternal anti-HLA antibodies specific against fetal antigens, and C4d deposition in the umbilical vein [4, 7]. It is further associated with higher positive rates of maternal IgG class I and II panel-reactive antibodies at delivery and higher seropositive conversion rates during pregnancy when compared to controls [4]. Chronic chorioamnionitis is also characterized by distinct alterations of the amnionic fluid proteome, notably with decreased amnionic fluid concentration of

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glycodelin-A, a molecule implicated in the maintenance of maternal tolerance against the fetus [8].

45.2 Definition

Infiltration of mononuclear inflammatory cells, predominantly lymphocytes, into the chorioamniotic membranes (extraplacental membranes) or, less frequently, into the membranes of the chorionic plate.

45.3 Epidemiology

Chronic chorioamnionitis is more frequently seen in preterm compared to term placentas, unlike villitis of unknown aetiology, which is more frequently seen in term placentas [1]. In one study, chronic chorioamnionitis was reported in 19% and 8% of term not in labour deliveries and term in labour deliveries, respectively, and in 34% and 39% of patients with spontaneous preterm labour and preterm prelabour rupture of membranes, respectively [1]. A separate study of preterm deliveries reported chronic chorioamnionitis to be the most commonly identified placental lesion, present in 20.8% of placentas and particularly common in the late preterm births, which represent the majority of preterm deliveries [5]. The frequency of chronic chorioamnionitis has also been reported to be notably higher in fetal deaths when compared to liveborn controls, with one study reporting chronic chorioamnionitis in 60% of cases of unexplained fetal death and further correlating the chronic chorioamnionitis with increased amniotic fluid levels of CXCL10 [9].

45.4 Gross Findings

No gross lesions are evident.

45.5 Histopathology

The inflammation seen in chronic chorioamnionitis is typically focal, but can be diffuse, with the extent and severity of the inflammation generally less than the neutrophilic infiltration seen with acute maternal inflammatory response (acute chorioamnionitis) [2, 3]. The foci of lymphocytes are most frequently seen in the extraplacental membranes and are present at the choriodecidual border of the chorioamnionic membranes (chorion laeve), this being the primary focus of interaction between the maternal cells (CD8+ T cells) and fetal cells (trophoblast) [1]. Chronic chorioamnionitis less frequently involves the membranes of the chorionic plate, this often occurring in the setting of chronic inflammatory lesions in other placental compartments. The CD8+ T cells may show only minimal invasion into the trophoblastic layer but cause trophoblast damage in the form of apoptosis, sometimes leading to thinning of the chorionic trophoblast layer and a "moth-eaten" appearance of the choriodecidual border [1]. Despite the often patchy and minimal invasion of lymphocytes into the trophoblastic layer, it has been shown that these placentas have significantly higher levels of amniotic fluid CXCL10 than those without chronic chorioamnionitis, indicating that even focal lesions are associated with intra-amniotic inflammation [1].

A staging and grading system has been proposed for chronic chorioamnionitis with the stage (location of lymphocytes) as follows: stage 1, lymphocytic infiltration limited to the chorionic trophoblast layer, sparing the chorioamnionic connective tissue (Figs. 45.1 and 45.2), and stage

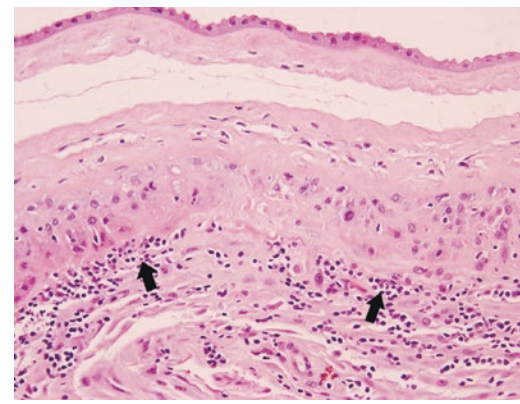

Fig. 45.1 Lymphocytes are seen within the chorionic trophoblastic layer (arrows) but do not extend into the chorioamniotic connective tissue (stage 1 chronic chorioamnionitis)

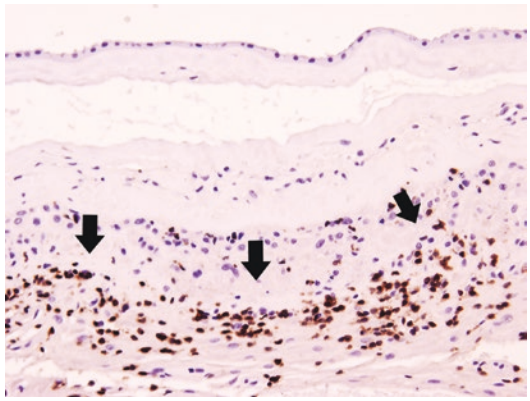

Fig. 45.2 Immunohistochemical stain for CD8 highlights the T lymphocytes in the chorion layer (arrows)

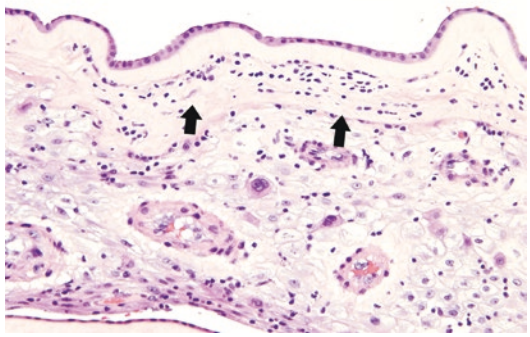

Fig. 45.3 Lymphocytes infiltrate into chorioamniotic connective tissues (arrows) (stage 2 chronic chorioamnionitis)

2, lymphocytic infiltration into the chorioamnionic connective tissues (Fig. 45.3) [1, 6]. The grade (intensity) is as follows: grade 1, more than two foci of inflammation or patchy inflammation, and grade 2, diffuse inflammation [1]. Increasing severity of inflammation has been demonstrated to correlate with higher amniotic fluid CXCL10 concentration [1]. Grading and staging are not currently advocated as routine but might be useful for research purposes.

45.6 Immunohistochemistry

Immunohistochemical staining for CD3 and CD8 will highlight the majority of lymphocytes, with CD4 highlighting smaller numbers [3]. B cells are essentially absent [3]. Immunohistochemical staining is generally not necessary for diagnosis.

45.7 Prognosis and Predictive Factors

Chronic chorioamnionitis is significantly more frequent in preterm prelabour rupture of membranes and preterm labour compared to term controls [1] and it is the most common placental lesion identified in late spontaneous preterm birth, suggesting a significant role for maternal anti-fetal rejection in these late preterm births [1, 5]. The association of chronic chorioamnionitis with unexplained fetal death suggests that some cases of fetal death may result from maternal anti-fetal rejection (i.e. allograft failure) [9]. The recurrence rate for chronic chorioamnionitis is not known.

Because chorioamniotic membranes cannot be biopsied during pregnancy, chronic chorioamnionitis cannot be used in the assessment or monitoring of anti-fetal rejection during pregnancy. However, chronic chorioamnionitis correlates with HLA panel-reactive antibodies and, although not currently used in clinical practice, these may in time prove to be a useful tool in monitoring humoral anti-fetal rejection [4]. Further investigation is required to clarify the association between chronic chorioamnionitis and other chronic inflammatory lesions, the association with cellular and antibody-mediated rejection and the association with adverse pregnancy outcomes, particularly late-term prematurity.

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Part VII

Umbilical Cord

Umbilical Cord Length

46

Rebecca N. Baergen

46.1 Introduction

The average cord length at term is reported to be from 51.5 to 61 cm [1–6]. Perinatal complications have been reported with both excessively long and excessively short umbilical cords. As measured in the fresh state, short cords have been defined as those less than 30–40 cm in length [5, 7], while long cords have been defined as those greater than 70 cm in total length [5, 7] at term. Short cords have an approximate incidence of 2% [8], while long cords are more common with a reported incidence of 3.7% [9]. Thus the distribution of cord length is slightly skewed toward longer cords. When evaluating cord length, it is important to distinguish between "absolute" and "functional" lengths. A cord that is excessively long but wound about the neck multiple times will be long in the absolute sense but short in the functional sense. Additionally, the entire cord is almost never submitted for pathologic examination as 5–7 cm is always left attached to the infant at delivery, some fragments may be discarded, and others are used for blood gas determinations or other testing. Furthermore, the length of the cord shrinks an average of 3% in the first few hours following delivery [10] and shrinks an average of 12% after 24–48 h of formalin fixation [10, 11]. Therefore, studies on cord length should include data on time of measurement and fixation status. Furthermore, the diagnosis of an excessively short cord must be made with caution, while the diagnosis of a long cord can be made but the overall incidence is likely underestimated. For these reasons, accurate recording at the time of delivery, although difficult to accomplish, is preferable.

46.2 Definition

Short cords are defined as those less than 35 cm in total length at term gestation. Long cords are defined as those above 70 cm in total length at term.

46.3 Epidemiology

Cord length seems to be determined by several factors—gestational age, genetics, and fetal movement. On the 41st day after conception, the developing cord has a mean length of about 0.5 cm. By the fourth month, the mean length is 16–18 cm, and by the sixth month, it is 33–35 cm. Most of the cord's length is achieved by the 28th week of pregnancy, but the cord continues to growth until delivery, albeit at a slower rate (Table 46.1). The presence of long cords in early abortion specimens suggests that length may be

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Table 46.1 Umbilical cord length as a function of gestational age

Gestational age (from last menstrual period)	Average cord length (cm)
12	12.6
13	15.8
14	18.8
15	21.5
16	24.0
17	26.4
18	28.7
19	30.9
20	33.0
21	35.0
22	36.9
23	38.7
24	40.4
25	42.0
26	43.5
27	45.0
28	46.4
29	47.7
30	49.0
31	50.2
32	52.0
33	53.0
34	54.0
35	54.9
36	55.7
37	57.2
38	57.9
39	58.5
40	58.5

Adapted from Benirschke K, Burton GJ, Baergen RN. Pathology of the Human Placenta, sixth ed. New York: Springer-Verlag, 2012

determined early in development [1, 11]. It has been opined that length is determined by tension on the cord produced with fetal movement [12–14]. Data to support that view come from studies in which fetal movement is restricted in some way resulting in short cords. For example, short cords are seen in fetuses who suffer from syndromes associated with diminished fetal movement, including Down syndrome [11], skeletal anomalies and dysplasias [15], long-term neurologic abnormalities [16], abdominal wall defects, gastroschisis, amniotic bands, and acardiac twins [1, 7, 11, 17]. Short cords are also seen in pregnancies associated with intrauterine constraint, such as uterine malformations [17] and twin gestations [18, 19]. Experimental studies seem to bear this theory out as administration of drugs to pregnancy animals that cause decreased fetal activity such as cocaine [20], alcohol [18], curare [12], and beta blockers [21] results in shortened cords. Studies in which fetuses are "tethered" to abdominal structures outside the uterus have also resulted in short cords [12]. However, data on cord length and oligohydramnios are conflicting. Some authors have reported oligohydramnios to be associated with short cords [12, 17], others have found oligohydramnios to be associated with long cords [22], and still others [23] have found no association of cord length. It is possible that oligohydramnios may lead to restriction of fetal movement in some but not all cases or cord length may be determined early in development, before oligohydramnios has developed. Further support comes from studies showing that "hyperkinetic" infants are associated with long cords [24, 25]. Recently, immunohistochemical studies have shown differences in the expression of several growth factors between long and short cords [26] supporting a molecular basis for the determination of cord length.

Parity has been positively correlated with cord length [27], suggesting that increasing parity causes increasing uterine enlargement allowing for increased fetal movement and longer cords. Long cords are more commonly associated with vertex presentation as opposed to breech presentation [6, 14], and perhaps a longer cord may allow the fetus to move into the more advantageous vertex position.

Evidence for a genetic predetermination of cord length is found in the positive correlations of umbilical cord length, birth weight, and placental weight [2, 3, 14]. Males, who are generally larger than females, also tend to have longer cords [6, 9, 13, 14]. These data suggest that growth of the umbilical cord, the placenta, and the body may share similar controls, some of which are likely genetic in origin. Additional evidence for a genetic component in determination of umbilical cord length comes from a large study on long cords [14] which showed an increased risk of a second long cord in women with a previous his-

tory of a long cord and the tendency for these women to have longer cords on the average. However, environmental factors may also play a role, as these fetuses would have a similar intrauterine environment. Other evidence for a genetic determination of cord length includes a positive correlation of cord length with maternal height and weight [9] and concordance of umbilical cord length in monozygotic but not dizygotic twins [4, 28].

46.4 Prognosis and Predictive Factors

It has been postulated that increasing cord length causes increased resistance to flow through the umbilical and placental vessels and that a longer cord would have decreased flow [14]. This in turn would lead to venous stasis, villous congestion, and distension of the branches of the umbilical vessels in the chorionic plate which would predispose the placenta to fetal vascular thrombosis [8, 14]. Previous studies have found a positive correlation of long cords with true knots [1, 5, 13, 29], cord entanglements [1, 5, 16, 29], prolapse [1, 7, 16], constriction, hypercoiling [1, 11, 14], and, as previously stated, thrombosis [14, 30, 31]. These cord problems can result in growth restriction or fetal demise which are significantly increased with long cords [1, 5, 7, 11, 14, 32, 33]. Other clinical associations with long cords include non-reassuring fetal status, fetal distress, and long-term neurologic impairment [1–5, 14].

Excessively short cords are also clearly correlated with neonatal problems, specifically with neurologic abnormalities. The essential question is whether the short cord resulted from prenatal neurologic problems leading to decreased fetal movements or whether the neurologic problems resulted from perinatal problems associated with delivery of an infant with a short cord. Short cords may be an issue during fetal descent, either during late pregnancy or during labour, and lead to increased traction on the cord. These include premature separation of the placenta (abruptio), cord haemorrhage or haematoma, cord rupture, uterine inversion, failure of descent, and prolongation of the second stage of labour [1]. Short cords have also been associated with fetal distress, low Apgar scores, depressed intelligence quotient (IQ), and developmental anomalies [1]. They are seen with certain congenital anomalies, particularly abdominal wall defects as well as amnionic bands. In these latter cases, the defects and the short cord are thought to be both the result of an embryonic developmental defect.

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Umbilical Cord Coiling

47

Peter G. J. Nikkels and Luiz Cesar Peres

47.1 Introduction

The umbilical cord is the sole communication between the fetus and placenta and is thus essential for delivery and removal of nutrients and waste products during intrauterine life. It is composed of one vein and either one or two arteries, which are surrounded by Wharton's jelly that is derived from embryonic myofibroblasts [1]. The umbilical cord has a characteristic coiling pattern with both arteries coiling around the vein. This coiling architecture is likely beneficial for proper blood flow between the placenta and the fetus.

47.2 Definition

Umbilical coiling index (UCI) is the number of coils/length of the umbilical cord [2, 3].

UCI follows a normal distribution with a tail to the right side of the curve (hyper-coiling). Normal UCI measurements were determined using fresh, unfixed, placentas with a mean and standard error of 0.2 ± 0.1 coils per cm [4, 5]. Abnormal cord coiling, i.e. UCI <10th centile (hypo-coiling) (<0.07) or >90th centile (hyper-coiling) (>0.30), is associated with adverse pregnancy outcomes [4, 6–9].

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47.3 Synonyms

Coils are also referred to as twists or spiral turns.

47.4 Gross Findings

Cord coiling should be measured using fresh placentas. The cord should be laid down straight on a flat surface to avoid stretching it. The numbers of coils are determined by counting how many times the complete 360° turns of the arteries are present in the whole length of the cord (Fig. 47.1). UCI is then calculated by dividing the number of coils by the length of the cord. Coiling may be quite irregular, with one segment hypo-coiled followed by a hyper-coiled segment.

Formalin fixation is associated with shrinking of the cord by an average of 12% after 24–48 h, and this may have an effect on determining the coiling index. Furthermore, conformational changes induced by formalin fixation can further alter the precise identification of coils, and as a result, UCI may vary between fresh and fixed states, leading to false-positive and false-negative UCI compared with "normal" metrics derived

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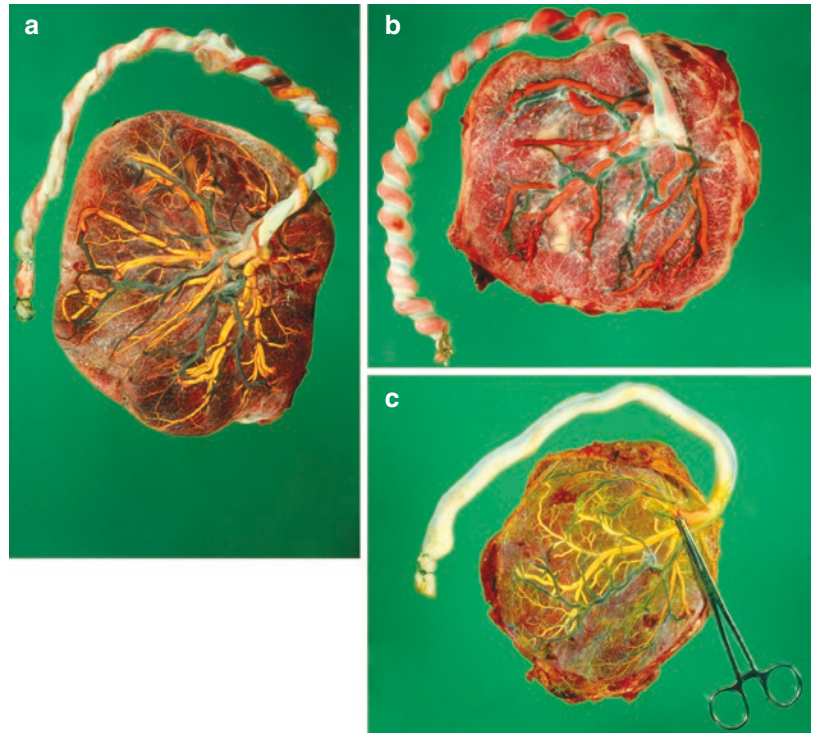

Fig. 47.1 (**a**) Term placenta with a cord of 55 cm and 12 coils (UCI 0.22): the vein was injected with orange and the arteries injected with a blue-coloured dye. (**b**) Term placenta of 47 cm with 18 coils (UCI 0.38). The neonate suffered from severe asphyxia after birth. (**c**) Placenta from 30 weeks of gestational age with a severely hypo-coiled cord, no coils in a 37-cm-long cord (UCI 0.0); the vein was injected with yellow and the arteries with a blue-coloured dye

from fresh placentas. Restricted segmental analysis may also lead to an over- or underestimation of UCI [10, 11].

The vessels are embedded in Wharton's jelly. Wharton's jelly consists of hyaluronic acid, chondroitin sulphate, and collagen. These molecules form a structure with thixotropic properties, i.e. this semi-solid gelatinous substance becomes liquefied after pressure. Presumably this feature prevents occlusion of the vessels during compression, torsion, or bending. Near the insertion at the placental surface, both arteries form anastomosis, the Hyrtl anastomosis, first described by Joseph Hyrtl (an anatomist in Vienna, 1810–1894) and recently demonstrated by angiography [12]. The amount of Wharton's jelly can be roughly the same between two adjacent coils (shallow indentations), sometimes imparting a rope-like appearance, or it can be markedly reduced (deep indentations), like a telephone receiver cord [13]. Deep indentations have been associated with histological evidence of chronic fetal vascular obstruction and stillbirth [13]. Strictures are sometimes associated with hypercoiled cords, usually seen at fetal end of the cord [9].

47.5 Histopathology

Thrombosis is a potential consequence of hypercoiling but it is rarely seen. Most of the histologic changes associated with hypo- or hyper-coiled cords are seen in sections of the placenta, including features of fetal vascular malperfusion.

47.6 Pathophysiology

The umbilical helix is well established by 9 weeks' gestation and coiling keeps pace with cord growth. In an umbilical cord of normal length of 50–60 cm, approximately 11 coils (turns of 360°) are found [3]. Many theories about why the cord coils have been postulated, but to date none of these have reached beyond speculation. Coiling may be the result of active or passive fetal movements [3], fetal haemodynamic forces [14], differential growth rates of the umbilical vessels [15], or a combination of factors [14, 16]. Coiling is left twist, or counter

clockwise, in 83% of cases and clockwise in 12%; 5% of cords show no coiling [15].

The precise influence of umbilical cord coiling on perfusion pressure is unknown but umbilical coiling may play a role in the venous return to the fetus, which is essential for oxygen and nutrient supply [17–20]. Hypo-coiled cords seem more susceptible to occlusion when traction is applied [21]. This in vitro model was supported by several computer models also showing disturbed blood flow through arteries and veins when the cord is not properly coiled [22, 23].

Abnormal cord coiling is associated with fetal demise, fetal intolerance to labour, fetal growth restriction, and acute chorioamnionitis [2, 4, 15, 18, 24, 25]. Fetal vascular malperfusion (FVM) has been associated with hyper-coiling in cases of fetal demise (Fig. 47.2) [4, 8, 26] and we have found signs of FVM in 18.2% of the intrauterine fetal deaths with umbilical hyper-coiling in our series compared with only 2.9% in normally coiled controls [9]. The rare association between hyper-coiling and thrombosis may be explained by larger values of wall shear stress, possible damage of the endothelium and stasis of blood

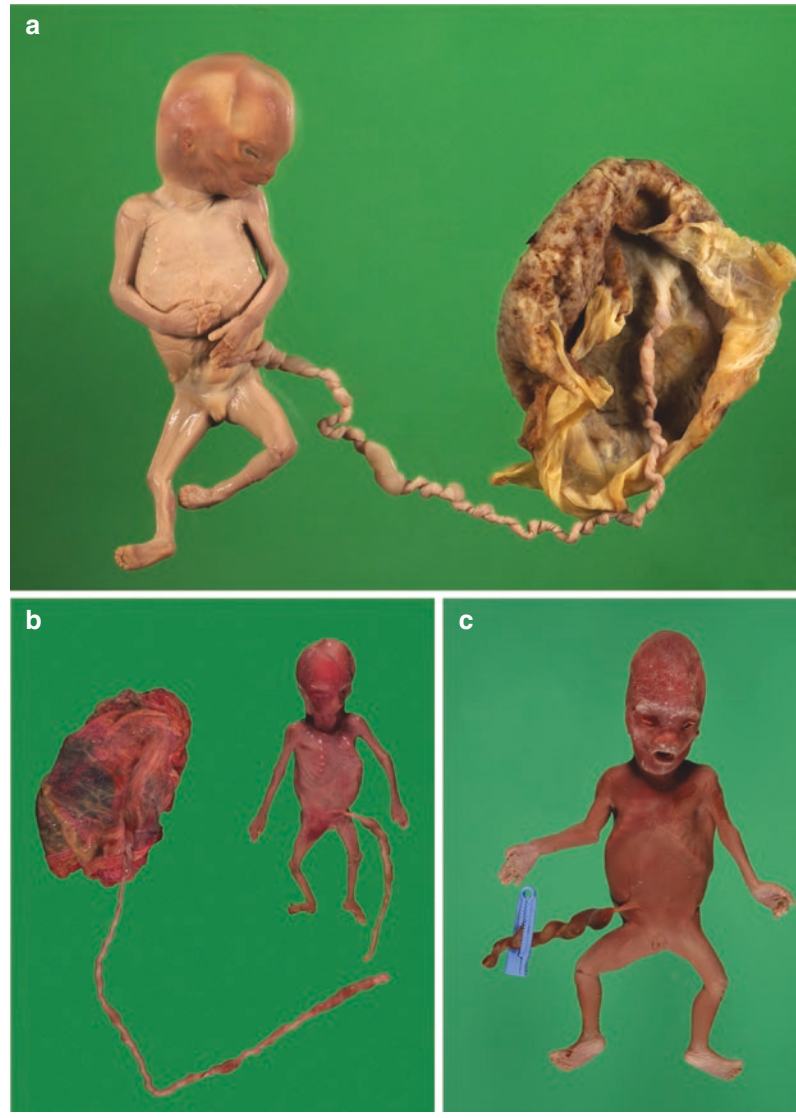

Fig. 47.2 (**a**) Fetal demise at 22 weeks of gestational age, no congenital anomalies, but there was severe fetal growth restriction with measurements comparable to 16–18 weeks of gestational age. Estimated time of death was approximately 2 weeks before birth. Placenta with a low weight (70 g) and a 25-cm-long cord with 45 coils (UCI 1.8). (**b**) Fetal demise at 19 weeks of gestational age. Placenta with normal weight and 28-cm-long cord with 31 coils (UCI 1.11). (**c**) Fetal demise at 24 weeks of gestational age, no congenital anomalies and mild asymmetric growth restriction. Placenta with normal weight and 35-cm-long cord with 19 coils (UCI 0.54) and stricture at fetal end of the cord

flow [22]. In a recent study, we demonstrated a significant negative correlation between the UCI and the gestational age of fetal demise [9]. A higher coiling index was found at younger gestational ages and a coiling index of 1.0 coil/cm or greater was only observed in cases less than 23 weeks of gestational age.

Hyper-coiling may have an effect on placental development. We found a trend toward delayed formation of terminal villi with a normal amount of syncytio-capillary membranes (SCM) in the presence of hyper-coiling; we observed an inverse relationship between the mean number of SCM in the terminal villi and the UCI [27]. Higher arterial perfusion pressure stimulates placental villous angiogenesis [28], which means differences in cord coiling and therefore differences in resistance to flow may directly contribute to villous maturation.

Finally, in an unpublished study of term pregnancies, we compared the incidence of hyper-coiled cords in the placentas from normal pregnancy and normal vaginal delivery (NPVD, 439 cases), with normal pregnancy and elective caesarean section (NPEC, 105 cases), antepartum death (APD, 55 cases), intrapartum death (IPD, 21 cases), neonatal death (ND, 12 cases), and neonatal intensive care unit (NICU) survivors (80 cases). The placentas from all infants that died (APD, IPD, and ND cases) had a hyper-coiled cord incidence of 23–24% with an odds ratio (OR) of 14.1, 9.7, and 9.7, respectively. The incidence of hyper-coiling in placentas from neonates admitted to the NICU was 15% (OR 6.7). These incidences were significantly higher than the incidences of hyper-coiled umbilical cords in the NPVD group (2%) and the NPEC group (6%). In contrast, hypo-coiling was not associated with adverse outcomes at term in this study. There may be an increased risk of recurrence of abnormally coiled cords in following pregnancies [29] but more study is required.

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Cord Knots and Pseudo-Knots

48

Kenneth Tou En Chang and Sze Jet Aw

48.1 True Umbilical Cord Knot

48.1.1 Definition

A true umbilical cord knot is a mechanical lesion formed as a result of the fetus moving through a loop of umbilical cord (Fig. 48.1).

48.1.2 Epidemiology

Large prospective surveys have quantified the incidence of true umbilical cord knots at between 0.19% to 1.25% [1, 2]. Associations with a true umbilical cord knot include a long cord, polyhydramnios, increased fetal movements, multigravidity, monoamniotic twinning and male gender of the fetus [3]. True knots likely form early in gestation as the movement of the fetus through a loop of the umbilical cord is no longer possible later in pregnancy once the fetus is of a certain size. In some situations, the knot may be loose during pregnancy and tightens following delivery of the child when there is traction on the cord.

48.1.3 Gross Findings

True umbilical cord knots may be loose or tight. Loose knots likely are of no clinical significance if there is no obstruction to blood flow in the umbilical vessels. Tight knots feature compression of Wharton's jelly at the site of the knot. If the tight knot is longstanding, surface indentations or grooves corresponding to the site of knotting may be apparent following unknotting of the cord. Consequently, there will be a tendency for the cord to be kinked at the knot site. Tight knots cause vascular obstruction, manifesting as congestion on the placental side of the knot due to a greater degree of venous (compared to arterial) obstruction. This venous obstruction results in decreased venous return to the placenta. Longstanding venous obstruction may result in thrombosis of the umbilical vein or chorionic plate veins, and these features should be specifically looked for at the time of gross examination.

48.1.4 Histopathology

The site of a tight, true umbilical knot may show a decrease in the amount of Wharton's jelly.

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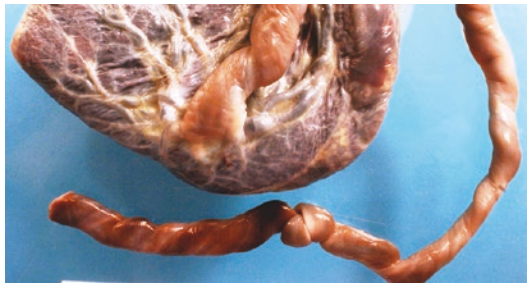

Fig. 48.1 Tight true umbilical cord knot

There may be vascular congestion or even haemorrhage into Wharton's jelly at the placental side of the knot. Vascular thrombi in umbilical and chorionic vessels should be sought. Longstanding thrombi may be associated with vessel wall calcifications.

48.1.5 Immunohistochemistry

Immunohistochemical stains are of limited value in the assessment of true knots.

48.1.6 Genetic Susceptibility

There is no known genetic susceptibility to the formation of true knots.

48.1.7 Prognosis and Predictive Factors

Antenatal identification of true umbilical cord knots is feasible using colour Doppler [4]. Loose true umbilical cord knots with no vascular obstruction are not associated with adverse outcomes. Tight true knots are a cause of intrauterine or intrapartum fetal death [5]. They are also associated with increased risk of prematurity, small-for-gestational-age infants, low Apgar scores, and need for neonatal intensive care [6].

48.2 Umbilical Cord Pseudo-Knot

48.2.1 Definition

An umbilical cord pseudo-knot is a nonmechanical lesion formed by focal redundancies or accentuation of the umbilical vessels or localized excess of Wharton's jelly (Fig. 48.2).

48.2.2 Synonyms

False knot of umbilical cord; Nodus spurious vasculosus (redundancy of vessels) or nodus spurious gelatinosus (redundancy of Wharton's jelly).

48.2.3 Epidemiology

Umbilical cord pseudo-knots are relatively common lesions.

48.2.4 Gross Findings

An umbilical pseudo-knot grossly mimics a true umbilical knot in its formation of a focal bulge or protuberance of the umbilical cord. However, no true mechanical looping and knot formation is evident. In the region of the bulge, the pseudo-

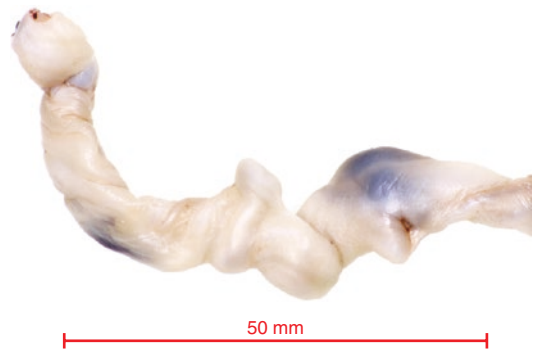

Fig. 48.2 Umbilical cord pseudoknot

knot comprises a localized redundancy of the umbilical vessels (usually an umbilical artery—personal observations) that form exaggerated varicosities or ectatic enlargements of the affected vessels. Alternatively, the pseudo-knot may comprise an area of excessive Wharton's jelly accumulation that may also be associated with a similar localized vascular redundancy.

48.2.5 Histopathology

Histopathological features include vascular ectasia and varicosities or localized accumulation of Wharton's jelly. Microscopy is helpful in excluding the presence of a vascular thrombus.

48.2.6 Immunohistochemistry

Immunohistochemical stains are of limited value in the assessment of a cord pseudo-knot. Vascular markers such as CD31 or CD34 will highlight endothelial cells lining the blood vessel profiles that may be increased in number.

48.2.7 Genetic Susceptibility

There is no known genetic susceptibility to the formation of cord pseudo-knots.

48.2.8 Prognosis and Predictive Factors

Umbilical cord pseudo-knots have no clinical relevance. Thrombosis or bleeding from a pseudo-knot is very rare.

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Umbilical Cord Tumours

49

Kenneth Tou En Chang and Sze Jet Aw

49.1 Cord Haemangioma

49.1.1 Definition

Haemangiomas are benign vascular lesions formed by vascular channels lined by benign endothelial cells.

49.1.2 Synonyms

Umbilical cord hamartoma.

49.1.3 Epidemiology

Cord haemangiomas are rare lesions.

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49.1.4 Aetiology

Haemangiomas are hamartomatous lesions that arise as a malformation of the angiogenic mesenchyme of the developing umbilical cord. Examples of haemangiomas connected with an umbilical vein or artery have been recorded; these may be considered as arteriovenous malformations [1]. Haemangiomas related to the major umbilical vessels may show extensive myxoid degeneration of Wharton jelly and are referred to as *angiomyxomas* [2]. Haemangiomas that bear no association with the umbilical vein or artery have also been recorded and may represent vascular proliferations of vitelline vessel remnants [3].

49.1.5 Gross Findings

Cord haemangiomas are rounded to fusiform swellings in the umbilical cord that may be very large, associated with myxoid change or pseudocyst formation (Fig. 49.1). An angiomyxoma weighing 900 g has been reported [4].

49.1.6 Histopathology

Haemangiomas consist of a ubiquitous proliferation of capillaries lined by bland, flattened endothelial cells, bearing resemblance to vascular malformations. These capillaries are held within

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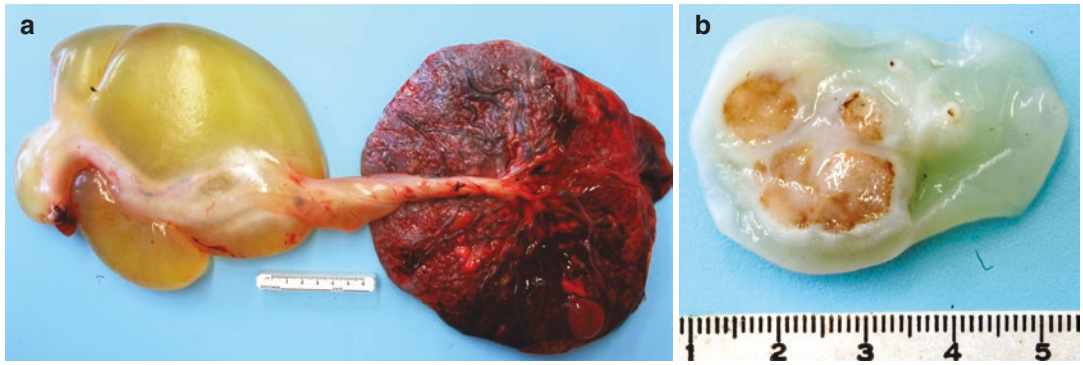

Fig. 49.1 (**a**) Angiomyxoma of the umbilical cord. (**b**) Cut section of angiomyxoma of the umbilical cord

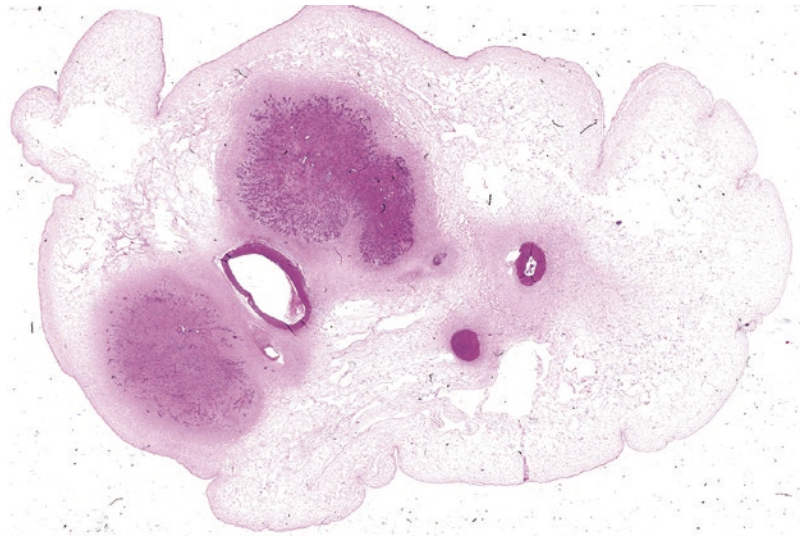

Fig. 49.2 Histological section of angiomyxoma of the umbilical cord

loose connective tissue that may have extensive myxomatous change or pseudocyst formation (Fig. 49.2).

49.1.7 Immunohistochemistry

The endothelial cells of the haemangioma show CD31, CD34 and GLUT1 [5] immunoreactivity.

49.1.8 Clinical Significance

Colour Doppler aids in distinguishing haemangiomas from other cord tumours through the demonstration of vascular flow [6]. Haemangiomas may be associated with elevated maternal serum alpha-fetoprotein levels and polyhydramnios and with fetal findings including haemorrhage, hydrops [7], cardiac failure, disseminated intravascular coagulation, structural anomalies and even death [8]. Cord haemangiomas have been reported in Klippel-Trenaunay-Weber syndrome [9] and with multiple cutaneous haemangiomas [10].

49.2 Cord Teratoma

Umbilical cord teratomas are extremely rare [11, 12] with fewer than 20 cases reported in the literature to date. Similar to teratomas arising in

other sites, teratomas are formed of tissue from one or more of the three germ layers. Early in gestation, the primitive gut evaginates into the umbilical cord, forming a possible route by which germ cells arising in the dorsal wall of the yolk sac migrate through the primitive gut wall into the mesenchyme of the umbilical cord where they then form a teratoma. Teratomas are distinguished from acardiac twins based on the absence of both an axial skeleton and separate umbilical cord attachment [13].

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50 Umbilical Cord Insertion Abnormalities

Kenneth Tou En Chang and Sze Jet Aw

50.1 Central and Eccentric Insertion

50.1.1 Definition

An umbilical cord insertion is measured from the edge of the cord nearest to the placental margin to the edge of the placenta.

A central insertion inserts at the epicentre of the fetal surface of the placental disc (Fig. 50.1). Beyond this region, but not extending to within 1 cm of the edge of the placental disc, the cord is said to have an eccentric (or paracentral) insertion.

50.1.2 Epidemiology

In the vast majority of placentas, the umbilical cord inserts into the placental disc centrally or eccentrically. In a study of placentas from 1000 consecutive singleton deliveries, the cord was inserted centrally in 308 (31%) cases and eccentrically in 620 (62%) cases [1].

50.1.3 Clinical Significance

Placentas with central and eccentric cord insertions have a normal cord insertion [1].

50.2 Marginal Insertion

50.2.1 Definition

Marginal cord insertions are defined variously. In 2016, the Amsterdam Placental Workshop Group Consensus Statement defined them as insertions less than 1 cm from the nearest placental edge [2]. However, a meta-analysis in 2017 on abnormal cord insertions showed that most studies defined marginal cord insertions as less than 2 cm from the placental margin [3] (Fig. 50.2).

50.2.2 Synonym

Battledore insertion.

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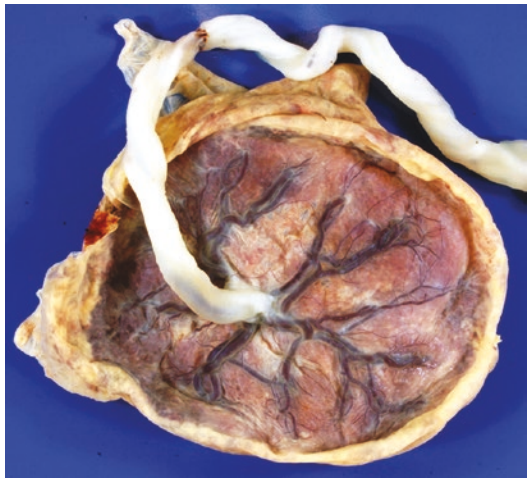

Fig. 50.1 Central umbilical cord insertion

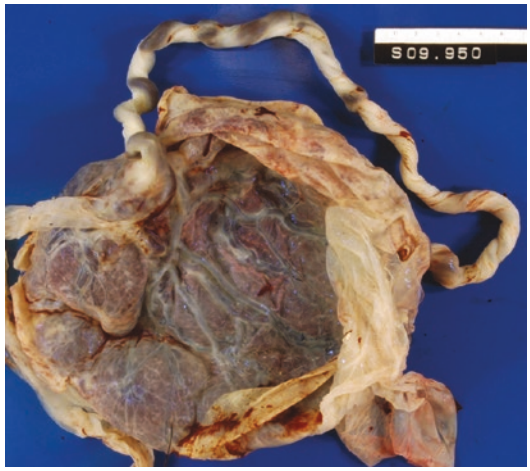

Fig. 50.2 Marginal cord insertion

50.2.3 Epidemiology

Umbilical cords have a marginal insertion in 5–7% of singleton placentas [4, 5]. The incidence in twin placentas is much higher and occurs in up to 22% in monochorionic twin placentas [6].

50.2.4 Clinical Significance

Marginal cord insertion appears to be associated with small for gestational age, low birth weight, and emergency caesarean section. However, it must be noted that the number of studies is small, and definitions varied between studies [3, 7].

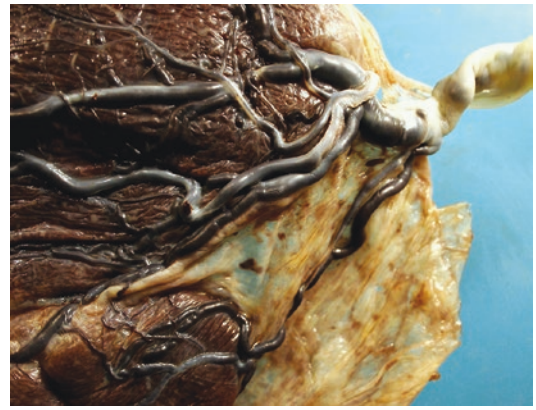

Fig. 50.3 Velamentous cord insertion: observe that the cord inserts into the fetal membranes, and run unprotected along the membranes to reach the chorionic plate

50.3 Velamentous Insertion

50.3.1 Definition

An umbilical cord with a velamentous insertion inserts into the fetal membranes rather than the placental disc and, thus, the vessels traverse between the amnion and chorion before reaching the placenta (Fig. 50.3).

50.3.2 Epidemiology

Velamentous cord insertion occurs in approximately 1% of singleton placentas [4]. It has an increased incidence in twin and multiple pregnancies, with the incidence increasing progressively in dichorionic separate, dichorionic fused, monochorionic twin pregnancies [7], and thence in triplet and higher multiple pregnancies. The incidence is also increased in cases of a single umbilical artery [8].

50.3.3 Pathogenesis

Two theories of pathogenesis have been described. The abnormal primary implantation (or polarity) theory states that a malpositioned blastocyst at the time of implantation has an aberrant body stalk-placental disc orientation. This results in velamentous cord insertion as the developing umbilical cord seeks its connection with the site

of placentation across the membranes that eventually form its site of implantation [9]. The trophotropism theory states that placental remodeling in response to a shift in the site of favourable vascular supply results in a net movement of the placental disc with the site of cord insertion being left behind in the membranes. This is a common phenomenon in placentas in uteri with structural defects [10].

50.3.4 Clinical Significance

Velamentous cord insertion is associated with in vitro fertilization [11] and maternal smoking and with an excess of obstetric and fetal complications including fetal growth restriction, preterm delivery, low Apgar scores at birth, and transferal to neonatal intensive care unit [5, 8, 12].

50.3.5 Complications

The exposed umbilical vessels unprotected by Wharton's jelly are at risk of physical damage with consequent haemorrhage and fetal exsanguination. The danger is most heightened in the clinical situation of vasa praevia, when the intramembranous vessels traverse the internal cervical os in advance of the presenting fetus.

50.4 Interpositional Insertion

50.4.1 Definition

A cord with interpositional insertion has a membranous insertion but retains its sheath of Wharton's jelly until it reaches its chorionic plate insertion (Fig. 50.4).

50.4.2 Synonym

Interposito velamentosa.

50.4.3 Epidemiology

This is a very rare condition.

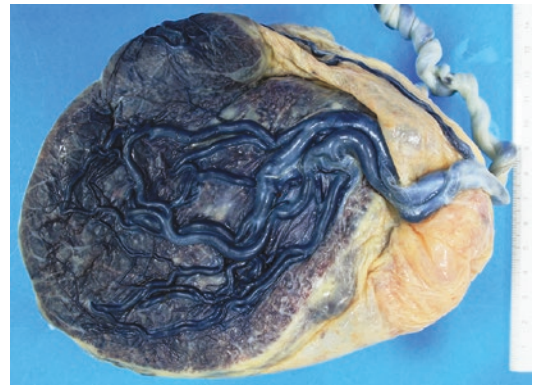

Fig. 50.4 Interpositional cord insertion: in contrast to a velamentous cord insertion, the umbilical vessels remain protected by Wharton's jelly as they course along the membranes to reach the chorionic plate

50.4.4 Clinical Significance

As the umbilical vessels remain protected by Wharton's jelly, interpositional insertion does not have the same clinical significance as velamentous insertion.

50.5 Furcate Insertion

50.5.1 Definition

A cord with a furcate insertion inserts normally onto the chorionic plate of the placental disc or velamentously in the membranes, with the umbilical vessels losing their protective covering of Wharton's jelly prior to the insertion (Fig. 50.5).

50.5.2 Synonym

Insertion funiculi furcata.

50.5.3 Pathogenesis

The pathogenesis of this very rare condition is not known and has been variously postulated as resulting from a developmental error or from local degeneration of Wharton's jelly at the site of insertion.

50.5.4 Clinical Significance

The exposed umbilical vessels unprotected by Wharton's jelly are subject to physical damage and subsequent fetal haemorrhage which may be fatal [13].

50.6 Tethered Insertion

50.6.1 Definition

A tethered cord insertion has amnionic webs that encase the umbilical cord at the insertion site (Fig. 50.6).

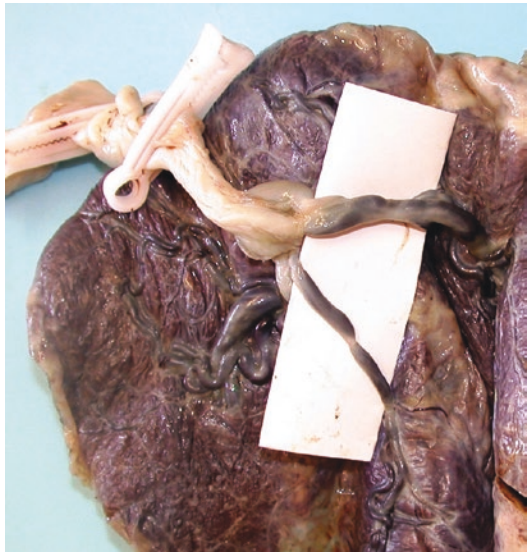

Fig. 50.5 Furcate cord insertion

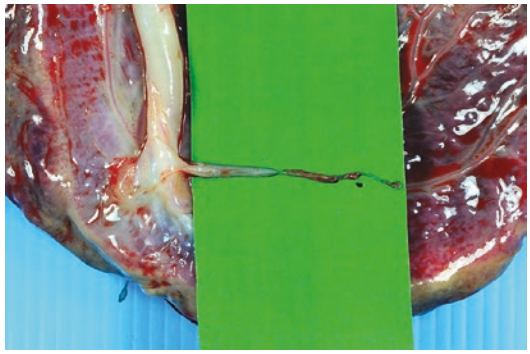

Fig. 50.6 Tethered cord insertion: a disrupted amnionic web binds the cord to the fetal surface of the placenta

50.6.2 Clinical Significance

A tight amnionic web may impinge upon the umbilical cord and cause blood flow obstruction in the umbilical vessels.

50.7 Recommendations and Future Research

A uniform approach with standardized definition for describing cord insertions would benefit future research. The term peripheral insertion has been used to describe combined marginal and velamentous cord insertions [1]; combined marginal, velamentous and paracentral cord insertions [14]; and insertions that are less than 3 cm from the nearest placental edge [15].

Research is needed to determine whether obstetric and neonatal outcomes are different if the definition of marginal insertion is at the edge, within 1 cm of the nearest edge or within 2 cm of the nearest edge. Sensitivities of differentiating between these three measurements (measurement of uncertainty) need to be considered. Furthermore, comparison studies need to define the population as whether the cord insertion is determined antenatally [16], where they may be of greater prognostic value, or by inspection of the placenta following delivery. In the meantime, we recommend retaining the term peripheral insertion to include the insertions that are less than 3 cm from the nearest edge.

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51 Embryonic Remnants and Pathology

Margaret J. Evans

51.1 Introduction

Embryonic vestigial structures are often found as incidental findings on routine light microscopic examination of the term placenta. These remnants, the allantois and vitelline ducts, represent extraembryonic ductal connections in the primitive umbilical stalk and date back to the early formation of the embryo [1]. At the end of the second week post ovulation, the secondary yolk sac is formed and shrinks as pregnancy advances [2]. By 9 weeks the yolk sac appears as a small remnant approximately 5 mm in diameter, which is connected to the midgut by the vitelline duct. The yolk sac has usually vanished by 20 weeks of gestation, and the vitelline duct is then obliterated and detached from the original midgut loop as it returns to the body cavity. In approximately 2% of adults, the proximal intra-abdominal portion persists as a diverticulum of the ileum (Meckel's diverticulum).

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The allantois appears on day 16 post ovulation. It forms a small out pouch or diverticulum protruding from the caudal wall of the yolk sac. It is involved with early blood formation and is associated with the development of the bladder. Its blood vessels become the umbilical vein and arteries. As the bladder enlarges, the allantois becomes the urachus but is progressively obliterated before 12 weeks post ovulation.

Occasionally they may present as large cystic structures.

51.2 Definition

- Vitelline duct—Connects the midgut lumen within the yolk sac to the developing fetus.
- Allantois—Represents the primitive extraembryonic urinary bladder and will eventually become the urachus which connects the fetal bladder to the yolk sac.

51.3 Synonyms

- Vitelline duct may also be referred to as omphalomesenteric or vitellointestinal duct.
- Allantois may be called the allantoic duct, urachal duct, or urachal remnant.

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51.4 Epidemiology

Vestigial remnants of the umbilical cord were identified in one series in 23.1% of umbilical cords on microscopic examination [3]. Remnants of the vitelline duct are less frequently seen than those of the allantoic duct; vitelline duct remnants occur in approx. 1.5% of cords, while allantoic duct remnants occur in up to 15% of cords [4]. The male to female ratio for vitelline duct remnants was 4.3:1 with a mean age of 2 months at presentation [5]. Allantoic or urachal remnant pathology has a male to female ratio of 1.2:1 [6]. Neither lesion shows a particular ethnic or geographic predilection.

51.5 Gross Findings

In most cases the remnants will be located at the fetal end of the cord (umbilical insertion) and may not be recognised on gross inspection though occasionally a cystic structure of the cord. The cysts vary in size from 0.4 to 6 cm diameter. The allantoic duct sits between the two arteries, whilst the vitelline duct is often surrounded by small vessels. Both will however require histological evaluation to assess origin (Fig. 51.1).

51.6 Histopathology

- Vitelline (omphalomesenteric) duct remnants tend to be sited at the cord periphery. Microscopically:
  - The duct is lined by cuboidal to columnar epithelium with an intestinal phenotype and often smooth muscle is often present within the walls (Fig. 51.2).
  - Rarely, liver, pancreatic, stomach, or small intestinal elements can be seen.
  - Frequently, paired or clustered vitelline vessels (without muscular walls) will be associated with duct remnants.
  - In some cases a small calcified nodule represents a "burnt-out" lesion.
- Allantoic (urachal) duct remnants are usually located between the umbilical arteries. Microscopically:
  - The duct is lined by low cuboidal epithelium and generally of transitional (bladder) type although mucin-producing epithelium may be found in some cases owing to its proximity to the yolk sac (Fig. 51.2).
  - The remnants are rarely accompanied by smooth muscle (Fig. 51.2).
  - Occasionally small vessels may be seen around the periphery of the duct remnant

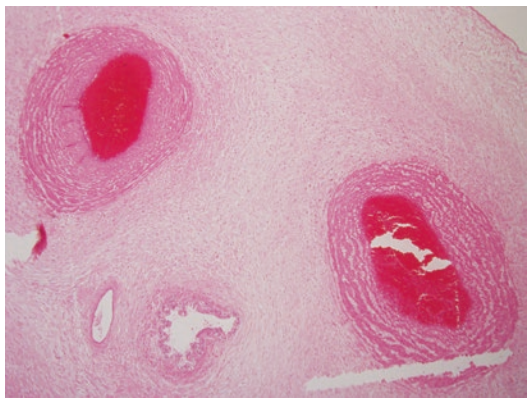

Fig. 51.1 An allantoic (urachal) duct remnant (left) adjacent to a vitelline (omphalomesenteric) duct remnant (right) between the two umbilical arteries

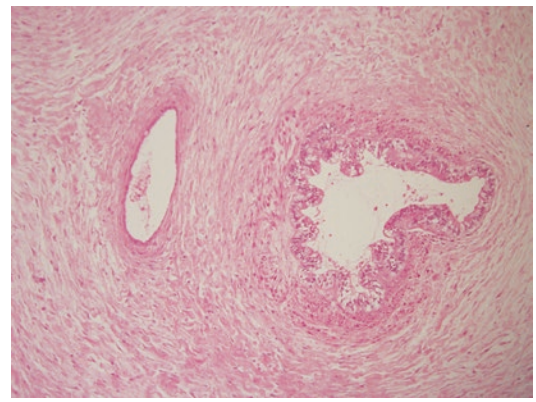

Fig. 51.2 Higher magnification showing the lack of muscle surrounding the allantoic duct remnant and the difference in epithelia between the two remnants

and very rarely extramedullary haematopoiesis is identified.
– In some cases a small calcified nodule represents a "burnt-out" lesion.

51.7 Immunohistochemistry

Immunohistochemistry is not routinely used in identifying these lesions [7]. Knowledge of the staining pattern of the embryonic elements may help in diagnosis of tumours derived from persistent urachal tissue. P63 and membrano-cytoplasmic β-catenin staining is consistently positive in uroepithelial urachal (allantoic) elements, with P63 also expressed in remnants with uroepithelial and glandular components. Expression of CK7 tends to be higher than CK20 in urothelial urachal elements.

No special stains are usually needed for the diagnosis of omphalomesenteric duct remnants.

51.8 Genetic Susceptibility

No specific genetic susceptibility has been noted for these conditions.

51.9 Prognosis and Predictive Factors

Generally, there are no specific signs and symptoms associated with omphalomesenteric duct remnant, either in the pregnant mother or in the developing fetus. However, in some cases problems will arise. The duct may be associated with intestinal atresia, Meckel's diverticulum and herniation of intestine though the umbilical cord which may lead to damage during clamping. The clinical features of other more common problems are indicated below.

- Patent omphalomesenteric duct: a communication between the ileum and the umbilicus. It presents in the neonate with the drainage of enteric contents, often with a prolapse of the duct and adjacent ileum from the umbilicus. Probing of the lesion documents the patent lumen. The condition should be suspected in cases of delayed separation of the cord or persistent, large, umbilical granulomas with associated drainage.
- Umbilical polyp: a small remnant of intestinal or gastric mucosa in the umbilicus. It presents as a bright red nodule in the umbilical dimple and may mimic an umbilical granuloma.
- Umbilical cyst: presents as a nodule deep to the umbilicus. It may be prone to infections.

Symptomatic allantoic (urachal) anomalies are uncommon and usually present in young children [8]. Though symptomatic remnants are often removed, it is unclear whether incidentally observed lesions require excision or if their presence in the cord merits further investigation of the child. The clinical features of the more common lesions are presented below.

- Patent urachus: persistence of complete communication between the bladder and umbilicus. Urine is noted to drain from the umbilicus. This may present with pyelonephritis or abscess formation.
- Urachal sinus: the blind-end opening of the urachal sinus is noted at the umbilicus either incidentally or because of drainage.
- Urachal cyst: a residual cyst without communication to the bladder or the umbilicus is found inferior to the umbilicus along the midline of the abdominal wall. It usually presents as a tender, swollen mass secondary to infection.

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52 Single Umbilical Artery, Supernumerary Vessels, Segmental Thinning of the Umbilical Cord Vessels and Vascular Calcifications in Umbilical Vessels

Margaret J. Evans

52.1 Introduction

The umbilical cord is formed when the body stalk and the ductus omphalo-entericus as well as the umbilical coelom are enveloped by the spreading amnion between 13 and 38 days after conception. It normally serves as the conduit for two umbilical arteries and one umbilical vein, derived from the allantois [1].

52.2 Single Umbilical Artery

In some cases only a single umbilical artery (SUA) is present. Although typically diagnosed in the third trimester, some report that it can be detected as early as 13 weeks of gestation [2]. The pathogenesis of SUA is uncertain and there has been much debate about the underlying mechanism. Martinez-Frias [3] suggests that single umbilical artery may be the result of several different and highly complex mechanisms.

- Failure or delay in the processes of formation of the definitive umbilical arteries occurring very early during normal embryo development, as evidenced by the very high specificity of association of SUA with cases with body stalk defects and those with some types of sirenomelia.
- Very early alteration in embryo development (during blastogenesis) that gives rise to defects that have a high specificity with the presence of SUA, such as oesophageal atresia, imperforate anus, other renal defects and vertebral defects.
- Defects in the primary developmental field including the umbilical cord are formed during the first 4 weeks of development (during blastogenesis), resulting in isolated CNS defects, cardiac defects and, possibly, unilateral renal agenesis and the association with SUA.
- An initial vascular pathogenic mechanism or secondary event due to the malformation itself leading to multiple congenital anomalies and their association with SUA.
- Secondary atrophy of one of the definitive umbilical arteries could explain the frequency of about 1% of non-malformed newborn infants with SUA.

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- Persistence of the primitive umbilical artery with failure of development of definitive vessels would be associated with hindgut atresias.

It is likely that all the proposed pathogenetic mechanisms occur but with different frequencies.

52.3 Supernumerary Vessels

Supernumerary vessels—are thought to arise from persistent umbilical veins or vitelline vessels, and more than three vessels are rare. The extra vessel may be an artery or a vein.

52.3.1 Supernumerary Vein: Umbilical Cord Presents Two Arteries and Two Veins

In normal development, the early venous system is represented by three symmetric paired veins: umbilical, vitelline and cardinal by the fourth gestational week. By the end of the sixth week of gestation, the entire right umbilical vein and the cranial segment of the left umbilical vein atrophy, whilst the caudal part of the left umbilical vein persists. It is the failure of the right to involute that results in persistent right umbilical vein. Usually it persists only in cases where the left umbilical vein is obliterated—however, much rarer is its persistence with a patent left umbilical vein, and it is this that gives rise to a four-vessel cord with two arteries and patency of both veins [4].

52.3.2 Supernumerary Artery: Umbilical Cord Presents Three Arteries and One Vein

At around the third week of embryogenesis, the umbilical arteries first appear as ventral branches of the paired dorsal aortas. With fusion of the paired dorsal aortas, the primitive umbilical arteries unite with the descending aorta, and the definitive umbilical arteries arise as two lateral branches from the caudal end of the descending aorta. At the same time, an arterial plexus develops around the allantois and coalesces to form a single artery which extends along almost the entire length of the body stalk. This allantoic artery becomes progressively shorter as the right and left umbilical arteries advance along the body stalk. It eventually fuses with the right and left umbilical artery to form the interarterial anastomosis usually at the site of cord insertion. An extra umbilical artery may arise:

- During the process where the umbilical arteries unite with the descending aorta.
- At the point where the arterial plexus fuses to form a single artery.
- At the time this allantoic artery unites with the right and left umbilical artery.
- At the time the umbilical artery splits into two as embryonic development advances.

52.4 Segmental Thinning of Umbilical Vessels

The aetiology of this lesion is unknown.

52.5 Vascular Calcifications in Umbilical Vessels

Two distinct patterns of vascular calcification may be seen within the umbilical cord:

- Sclerosis of the vessel wall.
- Obliteration of the vascular lumen.

Pathogenesis varies depending on the lesion. Inflammation secondary to intrauterine infection is thought to play a significant role in the sclerotic variant, whilst the obliterative type may arise due to partial calcification of an occlusive thrombus [5].

52.6 Definition

Single umbilical artery presents as a two-vessel cord with a single artery and a single vein; occasionally a hypoplastic artery may be present. The

term supernumerary vessels of the cord imply four or more umbilical vessels and may be due to an extra artery or vein. Segmental thinning of the umbilical vessels indicates focal thinning of an umbilical vessel due to virtual absence of the tunica media vasorum in at least one cord level and affecting an area, usually less than 30% of the vessel [6]. Vascular calcification of the cord may involve the arteries or the vein and may, as indicated above, lead to sclerosis of the wall of obliteration of the lumen.

52.7 Synonyms

Single umbilical artery may be referred to as a two-vessel cord. Supernumerary vessels of the cord may be referred to as a four-vessel cord, multi-vessel cord or persistent right umbilical vein with patency of the left.

52.8 Epidemiology

Single umbilical artery is diagnosed in approximately 0.2–2% of all pregnancies [7] though some series quote rates of up to 5% depending on the population studied and the mode of examination (gross examination v microscopic). It is more common in infants of diabetic mothers and those who smoke and more frequently seen in girls than boys [8]. The absence of the left artery is more frequent than the absence of the right artery, being identified in 73% of cases of SUA [9].

Supernumerary vessels are extremely rare in humans, and persistence of the right umbilical vein with patency of the left appears more commonly than an extra artery.

Segmental thinning of the umbilical vessels occurs in approximately 1.5% of all term placentas. The umbilical vein is most commonly affected (75% of cases). There is no racial, ethnic or geographic predilection. The same lesion may be seen to affect placental stem vessels.

Vascular calcifications of the umbilical cord are extremely rare as indicated by few reports in the literature.

52.9 Gross Findings

Single umbilical artery may be associated with atrophy of the placental territory of one umbilical artery leading in turn to abnormal placental insertion of the cord or placental trophotropism, a phenomenon where there is dynamic migration of the placenta to areas of good blood supply and nutrition.

Single umbilical artery and supernumerary vessels can be discerned on examination of cross sections of the cord. Several cross sections should be taken in order to ensure correct assessment, and it is recommended that sections should be taken away from the point of cord insertion as this may show only one artery due to anastomoses at this point or multiple vessels due to false knots. When assessing vessel number, it is important to be aware of looping of cord vessels which may also lead to overdiagnosis of supernumerary vessels.

Segmental thinning of the umbilical vessels is not usually seen macroscopically. It should be differentiated from segmental thinning of the cord itself which arises secondary to loss of supportive Wharton's jelly. Multiple sections of the cord may be required to identify the lesion.

Vascular calcifications of the cord may be identified on sectioning particularly if associated with thrombus. Where thrombus of the surface vessels is noted, it may be wise to take further sections of the cord.

52.10 Histopathology

Single umbilical artery—two vessels will be identified within the cord on routine microscopy (Fig. 52.1). If atrophy of artery occurs late in pregnancy, it may be represented by a tiny muscular remnant with or without calcification.

Supernumerary vessels—four vessels will also be readily identified on routine sections. Artery and vein can be distinguished by the presence or absence of an outer muscle wall (Fig. 52.2).

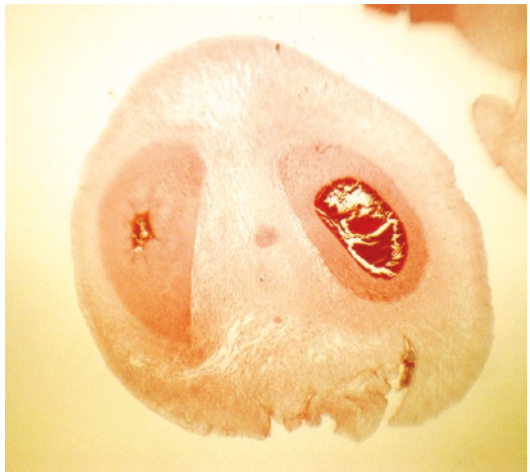

Fig. 52.1 Umbilical cord shows a single artery; the muscular remnant of the "vanished" second artery is seen in the centre of the image

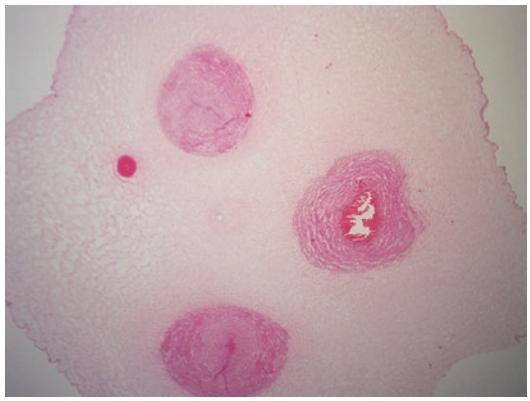

Fig. 52.2 The additional vessel appears thin walled with narrowed lumen. It lacks a thick outer muscle wall. This would suggest a persistent right umbilical vein rather than an additional artery

Segmental thinning of the umbilical vessels—this will be identified on routine microscopy. The affected vessel shows virtual absence of the muscular tunica media vasorum in at least one level of the cord (Fig. 52.3).

Vascular calcifications—these will be identified on routine microscopy. A distinction should be made between the two distinct types:

- Sclerosis of the vessel wall (Fig. 52.4).
- Obliteration of the vascular lumen (Fig. 52.5).

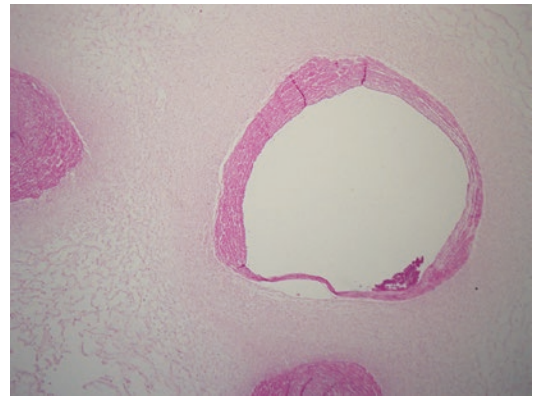

Fig. 52.3 Segmental thinning of the umbilical vein showing abrupt transition from normal to thinned segment (courtesy Dr. Yee Khong)

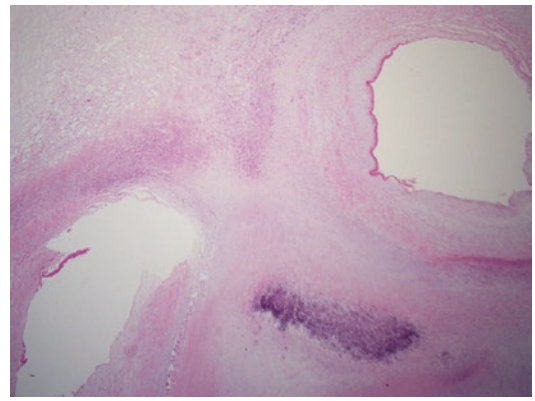

Fig. 52.4 Coarse calcification in Wharton's jelly with fine calcification in the media and adventitia of the umbilical arteries (courtesy Dr. Yee Khong)

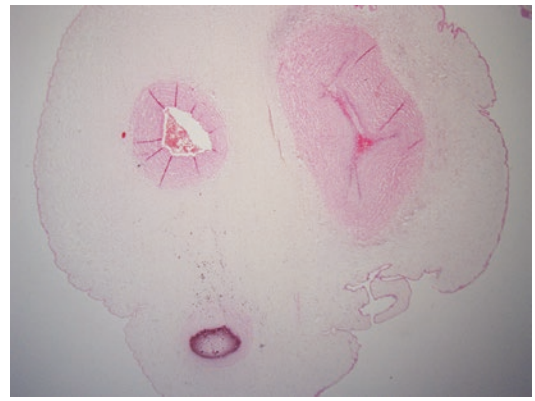

Fig. 52.5 Occlusion of umbilical artery lumen by calcification (courtesy Dr. Yee Khong)

52.11 Immunohistochemistry

None required.

52.12 Genetic Susceptibility

None known.

52.13 Prognosis and Predictive Factors

Both single umbilical arteries, supernumerary vessels and segmental thinning of umbilical vessels may be associated with an increased risk of congenital malformation and adverse pregnancy outcomes including preterm birth. Vascular calcifications have been noted to be associated with adverse outcome including stillbirth and fetal hydrops, but this may reflect the underlying aetiology—infection or thrombus.

The rate of associated fetal structural anomalies with single umbilical artery has been reported to range from 13% to 56% [9, 10]. Aneuploidy including triploidy, trisomy 18, 13, 21 and other chromosomal defects occurs in around 9% of cases [11]. Genetic syndromes that may feature an SUA include VATER complex (a group of congenital anomalies consisting of vertebral defects, imperforate anus, tracheoesophageal fistula and radial and renal dysplasia), Meckel-Gruber and Zellweger.

Nonchromosomal defects most specifically associated with SUA include bilateral renal agenesis, imperforate anus, intestinal atresia, unilateral renal agenesis and vertebral anomalies. Single umbilical artery was seen more frequently in cases of sirenomelia, caudal regression syndrome and body stalk anomalies. These structural defects may be seen on fetal anomaly or routine ultrasound scanning prior to birth. However, it would be wise to notify the paediatrician to the presence of a single umbilical artery in order that the infant may be screened for any hidden anomalies.

Various studies have shown that SUA in the absence of structural abnormalities, sometimes referred to as isolated SUA (iSUA), is independently associated with adverse pregnancy outcome, including placental abruption, true knot of cord, cord prolapse, lower Apgar scores and higher antenatal and postnatal perinatal mortality [12], an increased risk of fetal growth restriction, very preterm delivery and pregnancy-induced hypertension. Induction of labour and caesarean sections were also more common in these pregnancies [13–15].

As indicated above, supernumerary vessels are rare and the extra vessel may be an artery or vein. The extra vein arises where patency of normal left umbilical vein persists and may be associated with congenital anomalies: hydrops with hypertrophic cardiomyopathy [16], ectopia cordis, pulmonary stenosis, cleft lip and palate, bifid liver [17], situs inversus [18], tetralogy of Fallot and gastroschisis [19]. Whilst these may be diagnosed on ultrasound scan early in pregnancy, it is wise to alert the paediatrician to the presence of an additional vein in the cord although some authors suggest that the presence of additional vein does not always carry a dire prognosis [20].

The presence of an extra artery is extremely rare with few reports in the literature. Although its relation to stillbirth has recently been recorded as a single case report [21], others report no associated structural abnormality or adverse outcome [22].

Segmental thinning of umbilical vessels is associated with congenital anomalies including anencephaly, genitourinary tract abnormalities, cerebral palsy and fetal distress [6].

Vascular calcifications may be associated with macerated stillbirth and adverse pregnancy outcome. This may be secondary to the aetiology of the lesion with sclerotic lesions being the result of intrauterine infection with associated risk of spontaneous preterm labour. Though the obliterative type may indicate an underlying thrombophilic tendency, it may also be the result rather than the cause of the intrauterine demise. The

paucity of reports in the literature makes it difficult to precisely define its relationship with adverse outcome.

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Umbilical Cord Ulcer

53

Robert W. Bendon

53.1 Introduction

Umbilical cord ulcers can result in lethal intrauterine haemorrhage in infants with a bowel obstruction distal to the ampulla of Vater [1]. This is a recently recognized and highly specific association.

53.2 Definition

Umbilical cord ulcers are an erosion of the surface overlying the helix of the arteries, often with focal haemorrhages of the exposed arteries. The diagnostic term umbilical cord ulcer is usually restricted to those occurring in association with bowel atresia.

53.3 Synonyms

The cases of umbilical cord ulceration associated with bowel atresia have been called ulcerations or even simply haemorrhages. The "umbilical ulcer" has been used without specificity since at least 1876 [2]. An ulcer may rarely result from erosion caused by secretion from gastric mucosa in an omphalomesenteric remnant [3]. An ulcer-like lesion can occur with prolonged exposure of the cord to concentrated meconium in the amniotic fluid (Fig. 53.1) [4–6].

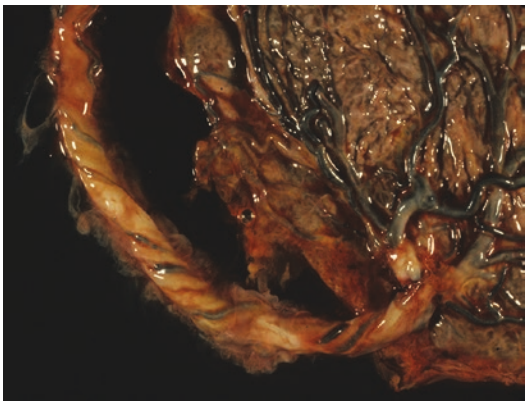

Fig. 53.1 The cord and membranes demonstrate intense meconium staining. The surface of the umbilical cord is denuded and the vessels are exposed

53.4 Epidemiology

Most reports of umbilical cord ulcers are single or small series. [1, 7–17] An updated review of the outcome of infants with congenital upper intestinal atresia found that of 121 infants, of which 71 had placental examinations, 13 had histological evidence of umbilical cord ulcer [18]. The incidence was higher with ileal atresia (26%) compared to duodenal atresia (4.6%). With umbilical cord ulcer, the mortality rate was 46%.

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53.5 Gross Features

The ulcers are typically linear overlying the helix of the arteries and may show small haematomas over the exposed artery. There is usually yellow to brown bile staining of the cord and membranes (Fig. 53.2). The placenta and chorionic vessels may appear pale from fetal haemorrhagic anaemia.

53.6 Histopathology

The ulcers show a bland undermining of Wharton's jelly over and under the artery, often with pigment macrophages present (Fig. 53.3).

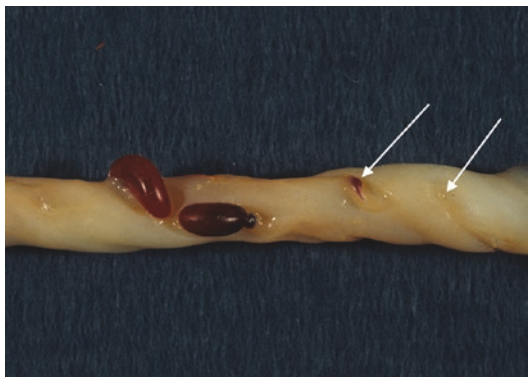


Fig. 53.2 This is a segment of an umbilical cord with ulceration above the arterial helix (arrows). On the left the undermined, bulging, thin walled arteries are exposed above the cord surface

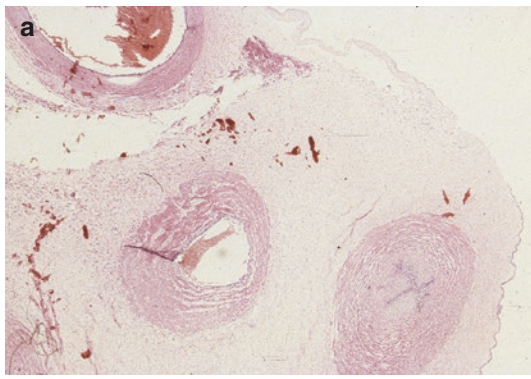
The arteries may be superficially thinned or necrotic. There are often scattered red blood cells in the ulcer bed. The umbilical vein may infrequently be involved.

53.7 Genetic Susceptibility

The lesion is associated with multiple aetiologies of bowel atresia that produce bile reflux into the amniotic fluid. Some cases have an associated non-genetic syndrome including trisomy 21, peritoneal band, polysplenia, and 13q deletion. A minority of cases are associated with familial congenital upper intestinal atresia, a likely autosomal recessive trait [19]. Epidermolysis bullosa is associated with bowel atresia, but no cases of umbilical ulcer have been reported with this syndrome [20].

53.8 Prognosis and Predictive Factors

Aside from complications of the bowel atresia and its aetiology, the major prognostic feature is recognition and treatment of fetal haemorrhage. From case experience, this haemorrhage may be prior to labour, may appear suddenly during labour, and, in one case, may occur in the diaper from the umbilical cord stump. The infants are often premature due to polyhydramnios.



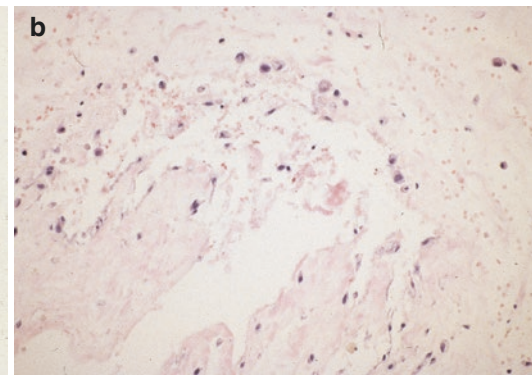


Fig. 53.3 (**a**) The artery in the upper left corner is dilated, has a hypereosinophilic, necrotic media, and is undermined by the ulcer. (**b**) An enlargement of the corner of the undermining ulcer demonstrates the mild infiltration of mononuclear cells, with pigment accumulation, and scattered red blood cells

The development of the lesion appears to be gradual prior until the sudden onset of severe haemorrhage. There are no prospective studies of the value of detecting the ulcers or dilated arteries by ultrasound [21] nor finding non-meconium bile, blood, or low pH in the amniotic fluid in order to predict or prevent potentially lethal haemorrhage.

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Umbilical Vascular Myonecrosis

54

Rebecca N. Baergen

54.1 Introduction

Meconium discharge at term and post term is relatively common. When the infant is mature, meconium discharge may be physiologic and merely a function of maturity. However, meconium discharge may also occur due to fetal distress, and prolonged exposure to high levels of meconium may lead to necrosis of the umbilical vascular smooth muscle (myonecrosis) [1].

54.2 Definition

Meconium-associated myonecrosis is characterized by damage and death of umbilical vascular smooth muscle associated with prolonged meconium passage in utero.

54.3 Synonyms

Umbilical vascular myocytolysis, meconium vascular necrosis, meconium-induced myocyte necrosis.

54.4 Epidemiology

Meconium is the bile-stained intestinal content of the fetus. It is present in the fetal intestines early in gestation but is usually not eliminated until after birth. Its chemical composition is variable but is known to contain mucus, mucopolysaccharides, blood group antigens, enzymes and a small amount of protein [2]. Meconium discharge in utero is a common event at term (~20% of placentas submitted to pathology), less common in preterm deliveries, and more common in postdate deliveries (~30%) [2, 3].

54.5 Gross Findings

Acute meconium will show particles of meconium on the fetal surface of the placenta without green staining. Within a few hours, the fetal membranes and fetal surface will be stained, and after many hours, the umbilical cord may be stained. Studies of the timing of meconium staining and uptake in the placenta have shown variable results with estimates from 1 to 48 h [4, 5] (Chap. 40).

54.6 Histopathology

Microscopic examination will reveal pigment-filled macrophages in the fetal membranes, but due to the paucity of macrophages in Wharton's

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jelly, they are difficult to identify in the umbilical cord (Fig. 54.1). Meconium pigment is slightly translucent and yellow brown in colour. In some cases with clear gross meconium staining, macrophages may be present without pigment, as the pigment fades with exposure to ambient light [6]. Damage to the amnionic epithelium may occur with degenerative changes, piling up of the epithelial cells, and loss of the epithelial layer. In the umbilical cord, meconium-associated myonecrosis will manifest as characteristic rounding up of the most peripheral muscle fibres, with increased eosinophilia and shrunken, pyknotic, or absent nuclei (Fig. 54.2).

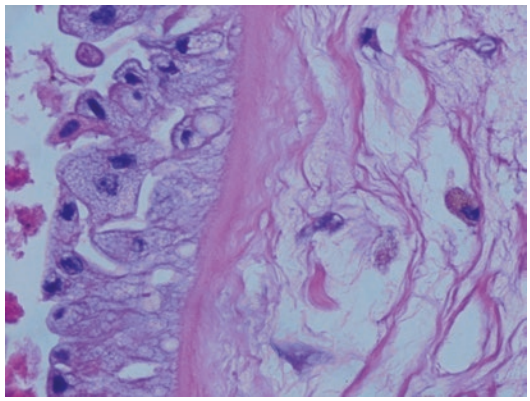

Fig. 54.1 Amnionic epithelium with several macrophages, including one that contains meconium pigment

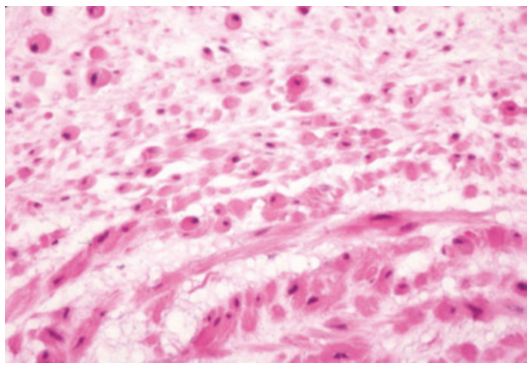

Fig. 54.2 Umbilical artery with meconium-associated myonecrosis. Smooth muscle cells contain small, dark, pyknotic nuclei, and many of the dead smooth muscle cells have completely lost their nuclei and show further evidence of cytoplasmic degeneration

54.7 Prognosis and Predictive Factors

Meconium discharge has been implicated as a marker for fetal hypoxia as it may be discharged by the fetus prematurely in the presence of intrauterine hypoxia. However, meconium may be discharged physiologically without fetal distress or evidence of hypoxia [2]. Furthermore, fetuses may die in utero without ever discharging meconium [2]. It is unclear whether meconium is a cause or effect of fetal hypoxia; it may be both [2, 7, 8]. Umbilical vascular myonecrosis has been associated with intra-amniotic infection, fetal growth restriction, low Apgar scores, fetal demise, and adverse prognoses, including fetal growth restriction, neurologic impairment and cerebral palsy [9–16].

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Inflammation

55

Suzanne M. Jacques and Faisal Qureshi

55.1 Introduction

Acute inflammatory lesions of the umbilical cord, along with acute inflammation of the chorionic surface blood vessels (acute chorionic vasculitis), represent the histologic hallmark of the fetal inflammatory response syndrome [1], a condition characterized by elevated fetal plasma levels of interleukin-6 (IL-6) and associated with preterm labour, perinatal morbidity with multiorgan involvement, and long-term sequelae [2]. This fetal inflammation results from a chemotactic intraamniotic gradient and is frequently associated with microbial invasion of the amniotic cavity but may in some cases also represent sterile inflammation [3]. Acute chorioamnionitis is discussed in Chaps. 12 and 44.

55.2 Definition

Acute funisitis is an acute inflammatory response in the umbilical cord, characterized by infiltration of fetal neutrophils into the umbilical vein (acute phlebitis), umbilical arteries (acute arteritis) and/or Wharton's jelly. Peripheral funisitis is a distinct pattern of umbilical cord inflammation, which is most frequently associated with *Candida* species [4].

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55.3 Epidemiology

Acute funisitis has been reported in 25% of preterm deliveries, those with funisitis having lower gestational age at birth than those without [5]. Acute funisitis has been reported in 4–6% of term or near term deliveries [6, 7]. *Candida* funisitis has been reported in 0.14% of placentas [4].

55.4 Gross Findings

Most funisitis is not grossly apparent but necrotising funisitis is sometimes grossly identifiable with chalky white concentric arcs partially surrounding umbilical blood vessels, imparting a characteristic "barber's pole" appearance and resulting from bands of degenerating inflammatory cells and calcification. *Candida* funisitis is characterized by diffusely scattered yellow-white 1–2 mm plaques on the cord surface [4].

55.5 Histopathology

The stage (extent or location of neutrophils) in acute fetal inflammatory response is as follows: stage 1, umbilical phlebitis or chorionic

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vasculitis (neutrophils seen within the wall of the umbilical vein or a chorionic surface blood vessel); stage 2, umbilical phlebitis and umbilical arteritis (neutrophils present in the wall of one or both arteries); and stage 3, necrotising funisitis (bands of degenerating neutrophils and cellular debris forming concentric arcs partially surrounding one of more umbilical blood vessels, sometimes with calcification) (Figs. 55.1 and 55.2) [8]. The grade (intensity) is as follows: grade 1, not severe as defined, and grade 2, near-confluent intramural neutrophils with attenuation of vascular smooth muscle [8]. While funisitis and phlebitis are established terms, the pattern of inflammation seen reflects neutrophil migration, rather than a true primary vasculitis. Neutrophils migrate from the fetal circulation with the inflammation beginning in the umbilical vein, followed by the arteries, making the presence of arteritis evidence of more advanced fetal inflammatory response [9] and making qualification of the term "funisitis" with location and severity of inflammation in the pathology report important. The acute funisitis can be patchy, beginning as separate foci of inflammation along the umbilical cord that merge with progression of the inflammation [9].

Candida funisitis is characterized by triangular subamnionic microabscesses containing neutrophils and a variable number of budding yeasts and pseudohyphae, generally identified in every cord section (Fig. 55.1) [4]. *Candida* funisitis is accompanied by acute chorioamnionitis and vasculitis of cord vessels, frequently with necrotising funisitis (Fig. 55.1) [4]. Special stains are helpful in demonstrating the fungal elements (Fig. 55.3). A similar pattern of cord inflammation may rarely be seen with other microorganisms.

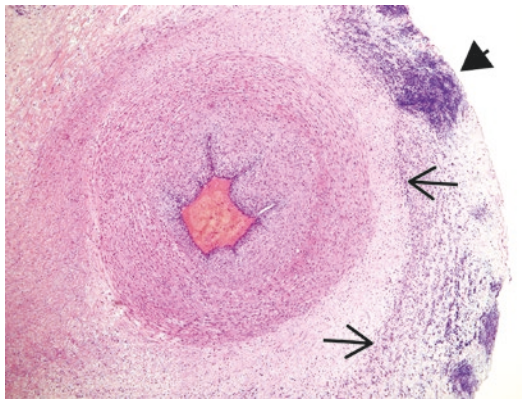

Fig. 55.1 Necrotising funisitis and *Candida* funisitis (peripheral funisitis): a band neutrophils partially surround an umbilical artery, characteristic of necrotising funisitis (long open arrows), and in addition there are variably sized subamnionic microabscesses, characteristic of *Candida* funisitis (short closed arrow)

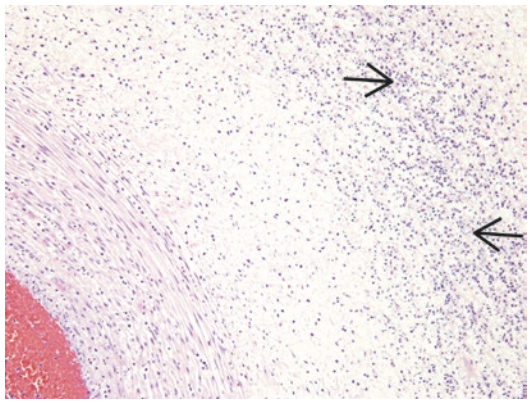

Fig. 55.2 Necrotising funisitis: bands of neutrophils, including degenerating neutrophils and cellular debris, form an arc partially surrounding the umbilical artery (arrows)

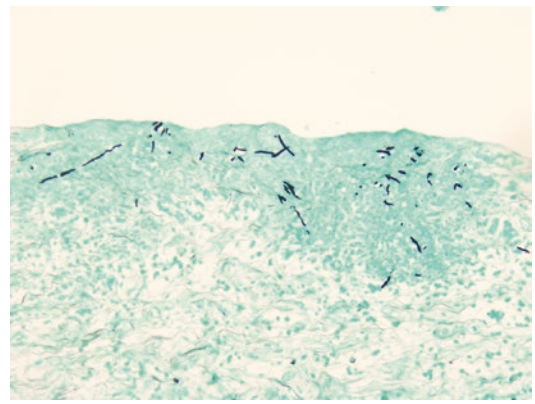

Fig. 55.3 *Candida* funisitis: Gomori's methenamine silver stain demonstrates the typical pseudohyphae and yeast forms of *Candida* species

55.6 Prognosis and Predictive Factors

Preterm neonates with microbial invasion of the amniotic cavity are more likely to have acute funisitis compared to term neonates with microbial invasion of the amniotic cavity [10]. The acute funisitis in the preterm neonates more frequently includes acute arteritis (stage 2) [11] and this correlates with elevated fetal IL-6 levels [12, 13] compared to acute phlebitis only (stage 1). Acute funisitis in preterm neonates is also associated with higher risk of congenital sepsis [5] and cerebral palsy compared to term neonates [14]. However, term neonates with acute funisitis are also more likely to have adverse clinical outcomes [6] and positive amniotic fluid culture [7] when compared to term neonates without acute funisitis. Severe (grade 2) fetal inflammation, particularly in chorionic surface blood vessels, can lead to vascular damage and thrombi and is a predictor of neurologic impairment in both preterm and term neonates [15, 16].

Necrotising funisitis (stage 3) is associated with preterm birth, prelabour rupture of membranes and high perinatal mortality and morbidity including stillbirth [17]. Initial studies suggesting that necrotising funisitis is specific for congenital syphilis [18] have not been borne out with subsequent studies finding it to be a nonspecific lesion resulting from a wide range of infections [17, 19]. Causative infections include herpes simplex virus [20], *Actinomyces* [21] and *Candida* species [4], among others.

Candida funisitis is associated with preterm delivery, intrauterine contraceptive devices, and cervical cerclage [4]. In one series of *Candida* funisitis, congenital candidiasis was documented in 16% of cases; therefore a diagnosis of *Candida* funisitis should prompt careful inspection for neonatal infection [4].

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Part VIII

Clinical Correlation, Reporting and Frontiers

56 Constellations of Pathology in the Placenta and How They Relate to Clinical Conditions

Sanne J. Gordijn, Alexander E. P. Heazell, Eoghan E. Mooney, and Theonia K. Boyd

56.1 Introduction

Histopathologic assessment of the placenta involves quantitative and qualitative examination for the presence of various individual features on gross and microscopic evaluation. These features may be grouped together in different ways. From a pathologic perspective, individual placental features may be combined into the different diagnoses as described in this book. In addition, these features may be viewed from a clinical perspective as being associated with specific pregnancy conditions such as maternal hypertension, fetal growth restriction or sepsis. In this chapter, we propose that these features may be grouped, as stars can be, into constellations, such that a pattern can be seen and useful information obtained.

However, due to the variation present in the mother, the fetus and the placenta and the complex interplay between them, few pregnancies exhibit a full range of maternal/fetal symptoms/signs and associated placental characteristics. Thus, for optimal clinico-pathologic interpretation, a full clinical history is required to provide context for the interpretation of results of the histopathological examination of the placenta. Ideally, before conveying information to patients, results should have been interpreted by a multidisciplinary team (e.g. obstetrician, pathologist, geneticist, midwife).

To illustrate the concept of clinico-pathologic correlation, we have highlighted the clinical and pathologic features of two disorders, namely, hypertensive disorders of pregnancy and preterm birth with preterm rupture of membranes. This is not meant to be a comprehensive analysis of the wide range of all pregnancy complications that have recognized clinical and pathologic features. Rather these are examples of how information regarding the patterns of abnormality may be important when providing information for

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parents about the causes of disorders leading to pregnancy complications, their likely etiopathologic pathways, the estimated recurrence risks and possible interventional strategies to be considered in future pregnancies.

56.2 Hypertensive Disorders of Pregnancy

The hypertensive disorders in pregnancy form a major problem in obstetric care affecting 5–10% of pregnancies and have a spectrum of disease severity. Hypertensive disease in pregnancy is currently classified according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) into chronic hypertension, gestational hypertension, preeclampsia and white coat hypertension (which will not be explored further in this chapter). Chronic hypertension is defined as hypertension (systolic blood pressure of >140 mmHg and/or diastolic blood pressure >90 mmHg) before mid-pregnancy (<20 weeks). Gestational hypertension and preeclampsia are defined as new-onset hypertensive disease after 20 weeks of pregnancy [1]. Although chronic hypertension and gestational hypertension are generally considered to be less severe hypertensive disorders, they can progress to preeclampsia in up to 25% of cases [2] and can carry a risk of (severe) maternal and/or fetal complications [3]. In the absence of preeclampsia, gestational hypertension is associated with increased fetal weight rather than fetal growth restriction.

Preeclampsia is defined by hypertension combined with organ failure based on endovascular disease. Classically, the latter was defined by proteinuria of at least 300 mg/24 h. However, although this restrictive definition is practical for research purposes, it does not sufficiently cover the wide variation of the clinical syndrome of preeclampsia. Consequently, preeclampsia was redefined by ISSHP in 2014 to include symptoms of endovascular disease in other organs as well as proteinuria (Table 56.1). This definition incorporates the more severe forms of preeclampsia (including eclampsia and HELLP syndrome) [1] and covers the broad variety of symptoms. The broad spectrum of abnormalities evident in preeclampsia emphasizes the need to provide detailed clinical information to the pathologist, such that relevant clinical diagnoses are not overlooked in placental pathology interpretation.

56.2.1 Clinical Management of Preeclampsia

Preeclampsia carries high maternal and fetal risks for adverse outcomes [4, 5]. The disease can be critical enough to necessitate termination of pregnancy for maternal reasons.

In the remote from term period, considerations of fetal and maternal well-being may conflict with respect to delivery decisions. If severe preeclampsia occurs in the previable period, perinatal death is the usual consequence. In the viable preterm period, a temporizing management strategy may be employed in high-care settings, provided that the severity of symptoms and signs does not dictate imminent delivery. This approach reduces the rate of neonatal complications without compromising maternal outcome [6]. Prolongation of pregnancy places the mother at risk with a small but significant chance

Table 56.1 Definition of preeclampsia (ISSHP 2014)

Gestational hypertension plus one of the following:	
1. Proteinuria	Spot urine protein/creatinine >30 mg/mmol (0.3 mg/mg) or at least 300 mg in a 24-h portion, or at least 1 g/L (“2+”) on dipstick testing
2. Other maternal organ dysfunctions	Renal insufficiency, liver involvement (elevated transaminases; at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurological complications (including eclampsia), haematological complications (platelet count below 150,000/dL, DIC, haemolysis)
3. Uteroplacental dysfunction	Fetal growth restriction

DIC disseminated intravascular coagulation

of severe maternal morbidity and of unanticipated fetal death on the one hand and of improved neonatal outcome, despite the morbid associations of prematurity, on the other hand. Maternal condition is monitored, blood pressure is reduced by antihypertensive medication, and anticonvulsive medication (magnesium sulphate) is provided to reduce the risk of eclampsia in cases of suspected imminent eclampsia. In the meantime, fetal well-being is monitored by regular ultrasounds including Doppler measurements to determine vascular resistance in the placenta (umbilical artery Doppler), fetal brain (middle cerebral artery Doppler) and when growth restriction is present before 32 weeks' gestation by assessment of blood flow in the ductus venosus [7]. A description of abnormalities in these waveforms would provide the pathologist with additional information about possible placental pathology.

In late pregnancy (≥36 weeks' gestation), an interventionist approach aiming for expedited delivery may be most practical. Severe maternal complications are rare, but consequences from prematurity are also more benign. Even though there are no clinically significant differences in outcomes of babies and mothers, this approach reduces the caesarean section rate, likely by preventing progression to more severe maternal signs/symptoms and interventions that follow from it [8]. If delivery is anticipated before 34 weeks, corticosteroids should be administered for lung maturation.

Hypertensive disorders of pregnancy share many risk factors with cardiovascular diseases in later life. This is shown by an increased risk of maternal chronic hypertension, ischaemic heart disease, cerebrovascular disease, renal disease, diabetes mellitus, thromboembolism, hypothyroidism and even impaired memory [9]. Importantly, conditions which predispose to the development of MVM (which is the most frequent placental abnormality seen in hypertensive disease) include pre-existing maternal disease such as diabetes, hypertension, renal disease, connective tissue disorders such as scleroderma and various autoimmune conditions, most notably the lupus anticoagulant family of disorders (e.g. systemic lupus erythematosus). A history of placental abruption is a risk factor for recurrence, and women who were themselves born SGA have an increased risk of placental abruption [10].

56.3 Fetal Growth Restriction

Hypertensive disorders are an important risk factor for fetal growth restriction (FGR) in early-onset disease, but FGR often occurs independently, particularly in late-term gestation. FGR is defined as the inability of the fetus to reach its optimal/genetic growth potential. The underlying pathophysiology for FGR is that the placenta is not able to provide the adequate exchange (nutrients, oxygen and waste products) to and from the fetus. This organ failure is multifactorial and relates to a wide variety of placental lesions that may be vascular, immunologic, inflammatory or genetic in origin, e.g. VUE, genetic lesions and vascular lesions.

The dominant cause of FGR (particularly in early-onset cases) is impaired flow in the uteroplacental unit, most frequently as a consequence of maternal vascular malperfusion (MVM). Other disruptors to optimal exchange may be found in disturbed placental-fetal unit flow, as in fetal vascular malperfusion (FVM), with increased diffusion distance for exchange as seen in villous maturation disorders, and in inflammatory conditions reducing the optimum diffusion capacity as in chronic histiocytic intervillositis, villitis of unknown aetiology and massive perivillous fibrin deposition. Infections such as rubella, malaria and Zika virus can cause multiple processes that result in FGR, including those acting directly through the placenta: impaired placental vascularization, altered production of growth hormones and immunologic milieu [11]. Lastly, FGR can also be caused by genetic disorders that affect placental function. These include chromosomal abnormalities involving the fetus such as triploidy or trisomy 18, or anomalies confined to the placenta such as confined placental mosaicism [12].

Table 56.2 Consensus definitions of FGR based on non-customised growth charts [13]

Early FGR
Gestational age <32 weeks, in the absence of congenital anomalies
AC/EFW <p3 or AEDF in the umbilical artery
Or at least two out of three of the following:
1. AC/EFW <p10 *combined with*
2. PI in the uterine artery >p95 and/or
3. PI in the umbilical artery >p95
Late FGR
Gestational age >32 weeks, in the absence of congenital anomalies
AC/EFW <p3
Or at least two out of three of the following:
1. AC/EFW <p10
2. crossing centiles of more than 2 quartiles on growth centiles
3. CPR <p5

AC abdominal circumference, *EFW* estimated fetal weight, *PI* pulsatility index, *CPR* cerebroplacental ratio

It is difficult to define abnormal growth for the individual fetus. FGR cannot simply be defined by dichotomising growth between normal and abnormal based on a threshold of size on a reference chart [13] (Table 56.2). In general there are two approaches to compare fetal size to reference values. The first approach is to relate optimal fetal size to size for a given gestational age in a healthy population. The INTERGROWTH-21st studies have shown that the variation of fetal growth between populations of different ethnic backgrounds is smaller than the variation within populations [14]. The second approach is to customise for maternal individual factors, as surrogate markers for genetic growth potential like maternal height, weight and ethnicity, to assess expected fetal or neonatal sizes [15]. Irrespective of which clinical approach is taken, deviation of growth centile or growth below a certain threshold of the reference is defined as abnormal. However, it does not stop there. FGR is a functional placental problem and a sound definition also encompasses functional variables. The current international definition was developed in international expert consensus, both for clinical practice and research purposes.

56.3.1 Clinical Management of Fetal Growth Restriction

Not only is it difficult to determine the benchmark of optimal growth, there is also considerable difficulty in how to monitor fetal growth during pregnancy. Fetal growth is measured by biometric measurements obtained by ultrasound and is hampered by several variations stemming from variability in observer, software, maternal and fetal characteristics. Additionally, due to the fact that growth is not a static but a dynamic process, complete assessment requires more than one measurement. In many countries, routine obstetric care does not involve multiple ultrasounds, and an ultrasound is performed only when signs or symptoms of pregnancy complications such as preeclampsia occur or when FGR is suspected. Although sequential measurements are required to measure growth, it is possible to estimate whether fetal growth is optimal or not on a single occasion by a combination of biometric measurements and measurements of functional parameters. These include Doppler flow profiles of uterine artery, umbilical artery and ductus venosus [7] in early FGR (<32 weeks of gestation) and middle cerebral artery flow [16] in late FGR (>32 weeks of gestation) [13]. Due to overlap with the syndrome of preeclampsia and associated maternal vascular malperfusion, similar research is performed to arrive at functional predictive and/or diagnostic parameters in the area of angiogenic and anti-angiogenic factors and of radical oxygen species (ROS) biomarkers [17]. Nevertheless, a summary of ultrasound findings and, if relevant, a clinical diagnosis of FGR should be provided to the pathologist prior to examination of the placenta.

Currently, the only known intervention is optimal timing of delivery [18]. For prevention of FGR, aspirin is used as this is associated with a reduction in severe early-onset preeclampsia and FGR in high-risk populations. Many prevention and intervention strategies are under research at the moment, such as sildenafil, growth factor substitution and statins [19].

56.4 Pathologic Changes Related to Preeclampsia and FGR

The gross and microscopic changes are discussed in more detail in the individual chapters and are summarized in Table 56.3.

Preeclampsia and FGR are two complications of pregnancy to which the term "Great Obstetrical Syndromes" has been applied. The others are preterm labour, preterm premature rupture of membranes, late spontaneous abortion and placental abruption [20]. They are characterised by disease of the placental vascular bed and are a feature of early-onset (<34 weeks, rather than late onset, >34 weeks) preeclampsia. There is suboptimal, notably shallow, implantation leading to maternal vascular malperfusion (MVM) and ischaemia. The lesions seen are arterial lesions (unconverted spiral arteries) leading to acute atherosis (which are prone to thrombosis) and prone to damage resulting in abruption. Reduced uteroplacental blood flow can lead to infarction of placenta. Depending on the timing of the insult, there may be recent or remote or combination of lesions. Placental weight and/or size may be affected. As a result of these changes, placental adaptation can be seen in the form of accelerated villous maturation. Secondary lesions frequently coexist: hypoxic stress to the fetus secondary to MVM may be manifested as meconium staining of the membranes and as an increase in nucleated red blood cells within the fetal circulation. A threefold increase in the incidence of fetal vascular malperfusion (FVM) has been documented in cases with MVM compared with controls [21].

Other placental findings frequently reported in preeclampsia include VUE. There is a view that VUE, together with other inflammatory lesions in the placenta such as chronic histiocytic intervillositis and massive perivillous fibrin deposition, has an alloimmune basis. If so, this could be a maladaptation of the immunological interplay between the mother and fetus. Shallow implantation may in part reflect poor preconditioning of the endometrium prior to conception, with a significant immunologic contribution.

Placental findings in preeclampsia can be varied, and the placenta can, indeed, display no overt pathological features, particularly in late-onset disease. Furthermore, it is possible that clinical

Table 56.3 Pathophysiology and constellation of pathology findings in preeclampsia

Pathophysiological event	Pathological effect and findings
Maladaptation of immune response to pregnancy	Inadequate extravillous trophoblast migration Villitis of unknown aetiology Chronic deciduitis Chronic chorioamnionitis
Inadequate extravillous trophoblast migration	Unconverted placental bed spiral arteries Intraluminal endovascular trophoblast in third trimester Increased multinucleate trophoblast cells in basal plate
Absence of physiological vascular change	Acute atherosis
Acute atherosis	Uteroplacental thrombosis Infarction Abruption
Decreased uteroplacental vascular perfusion	Accelerated villous maturation (increased syncytial knots) Membrane chorionic microcysts Laminar necrosis of membranes Diffuse decidual leukocytoclastic necrosis
Intrauterine (intervillous) hypoxia	Persistence of villous cytotrophoblast Presence of fetal nucleated red blood cells in villous vessels Chorangiosis Meconium effects

intervention may alter the pathological manifestations, the most obvious being that early delivery will have altered the natural history of the disease.

56.5 Preterm Birth and Preterm Rupture of Membranes

Preterm birth, the delivery of an infant before 37 completed weeks' gestation, has an incidence of approximately 10% in high-income countries. The earlier the gestation at delivery, the worse the prognosis. Preterm birth is responsible for the majority of neonatal mortality and morbidity worldwide and may occur spontaneously (~66%) or be iatrogenic (~33%), with intervention indicated by deteriorating maternal or fetal conditions (e.g. preeclampsia or FGR). Spontaneous preterm birth may be due to preterm labour or following preterm prelabour rupture of membranes (PPROM). Risk factors for preterm birth include a history of spontaneous preterm birth, short cervix, Afro-Caribbean ethnicity, short inter-pregnancy interval, multiple gestations and uterine anomalies (e.g. bicornuate uterus) [22].

The pathways leading to spontaneous preterm birth are incompletely understood and are beyond the scope of this chapter. Inflammation plays a key role in normal labour as well as abnormal labour, and shifts to pro-inflammatory profiles are thought to be key in sensitizing the myometrium to become contractile. One third of cases of preterm labour are associated with intra-amniotic infection that is usually subclinical, i.e. there are no clinical features of chorioamnionitis or systemic sepsis. When microorganisms are involved, the infectious, usually bacterial, organisms are thought to enter the uterus from the maternal genital tract. Why this happens in some women is unknown; it may be that cervical shortening and microbiome alterations in the vaginal mucosa are key processes leading to ascending intrauterine bacterial infection. It is thought that activation of inflammation, particularly lytic enzymes, weakens the extraplacental membranes, resulting in rupture.

Several strategies to prevent preterm birth have been investigated, including administration of progesterone and cervical cerclage placement. Although widely used in high-income settings, tocolysis is not associated with improvement in neonatal survival and is not used where there are concerns for fetal or maternal well-being (e.g. in the presence of antepartum haemorrhage/sepsis). When preterm birth is anticipated, a course of corticosteroids for lung maturation is indicated, as this reduces neonatal mortality and morbidity prior to 34 weeks. The primary reason to use tocolysis is to gain time for the steroids to have an effect. In the presence of PPROM, women may receive antibiotic treatment (usually erythromycin), which has been demonstrated to prolong pregnancy and to reduce short-term infection [23]. In the case of PPROM, women are screened for signs of infection, using clinical signs and body temperature and on indication of a mixture of genital tract microbiological swabs, white cell count and C-reactive protein. If fever and/or a rise in inflammatory markers is present, without another focus than the intrauterine environment (chorioamnionitis), delivery is indicated. Where a fetal response is detected and an organism identified, this information should be given to the perinatal/neonatal team caring for the baby in order for antibiotic therapy to be modified as appropriate.

56.6 Pathologic Changes Related to Preterm Labour

The predominant identifiable pathologic condition associated with preterm labour and PPROM is amniotic fluid infection. However, often no responsible organism can be identified, and in low-risk women at term, histologic chorioamnionitis was much more common than infection [24]. Amniotic fluid infection refers to infectious organisms which usually inhabit the perineum and/or vagina, which gain access to the uterine cavity, with or without associated membrane rupture. The amniotic fluid infection constellation is restricted to cases that meet the histologic criteria

for chorioamnionitis, with or without clinical chorioamnionitis, but that are due to ascending infection. While there are pregnancies with clinical but no histologic chorioamnionitis and cases of histologic chorioamnionitis without identifiable infectious organisms, discussion of those conditions is not within the scope of the amniotic fluid constellation disorder. Clinical chorioamnionitis is diagnosed with maternal uterine tenderness and fever and/or maternal tachycardia, usually together with PPROM and/or contractions. The diagnosis is difficult, especially during (preterm) delivery, when many women have epidural anaesthesia that reduces uterine sensation and increases maternal temperature by interfering with the hypothalamic thermal regulation centre and subsequently increases maternal heart rate and fetal heart rate.

Amniotic fluid infection is suspected in the presence of a number of predisposing conditions, which are identified by clinical history and potentially by ultrasound [25]. These include premature/prolonged membrane rupture, preterm labour, prolonged labour, prolonged intrapartum cervical dilatation, ± intact membranes, cervical shortening (spontaneous and/or due to prior surgical intervention), prior history of chorioamnionitis, multifetal gestation, history of urinary tract infection(s), history of vaginal colonization (bacterial vaginosis, Group B streptococcus, Candida), young maternal age and primigravid pregnancy [26].

56.6.1 Macroscopic Placental Changes

The placenta may have an opaque fetal surface, with the opacity extending to the extraplacental membranes. The placenta and membranes may also be discoloured (yellow, tan, off-white, green-tinged). The extraplacental membranes may be diffluent (slimy). There may be many pinpoint white umbilical discolorations (surface microabscesses) in the event of umbilical inflammation, and there may be evidence of marginal/retroplacental bleeding (which can be termed "inflammatory abruption"). In addition to these visual changes, the placenta may have a foul odour.

56.6.2 Microscopic Placental Changes

There may be evidence of an inflammatory response in both the maternal and fetal compartments. The maternal inflammatory response progresses temporally from acute subchorionitis, acute chorionitis and acute chorioamnionitis, culminating in necrotizing acute chorioamnionitis ± deciduitis. The maternal changes may be accompanied by a fetal inflammatory response which may be evident as umbilical vasculitis ± perivasculitis and/or chorionic vasculitis ± perivasculitis. In addition, there may be normoblastaemia, meconium, meconium-associated vascular necrosis, vasculitis-associated chorionic/umbilical thrombi and villous oedema.

56.6.3 Prognosis, Predictive Factors and Potential Recurrence Risks

The prognosis for fetuses/neonates affected by amniotic fluid infection depends on a range of factors including gestational age, organism virulence, duration of infection, extent of fetal vasculitis, superimposed vasculitis-associated fetal thrombosis and coexisting complications such as meconium aspiration and the presence of congenital/neonatal sepsis. Predictive factors with respect to an increased risk of adverse fetal or neonatal outcome include the presence of fetal vasculitis, particularly when advanced [27], prematurity, concomitant meconium and congenital/neonatal sepsis [25].

Recurrence risks for amniotic fluid infection are those in which the predisposing conditions persist from one pregnancy to another. These include cervical shortening due to a prior surgical intervention, a prior history of chorioamnionitis, a history of urinary tract infection(s) and a history of vaginal colonization by organisms known to be associated with ascending infection.

56.7 Conclusion

The critical role of the placenta in determining the likelihood of pregnancy outcome means that placental examination is one of the most useful investigations to perform in the presence of a potential or known adverse outcome. Placental abnormalities are observed in 11–65% of stillbirths, and examination of the placenta reduces the likelihood of unexplained stillbirth [28]. Critically, the value of placental examination is optimized with information shared among obstetric and neonatal teams and the pathologist. Understanding the clinical presentation, results of investigations and how this data fits informs placental phenotypes is important, so that placental abnormalities can be placed in context and their potential significance appreciated [29].

Clinical interaction is critical to ensure that relevant diagnoses are recorded and appropriate interventions are considered in future pregnancies. It is anticipated that understanding the interrelationship between clinical factors and placental phenotypes (such as with placental constellation disorders) will facilitate this process. Links between clinical and placental conditions in which key pathologic lesions are identified and the information is conveyed to clinicians, while spurious lesions or incidental findings are recorded but do not prompt inappropriate diagnoses or action, are the aim of clinically informative placental diagnosis.

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The Placental Pathology Report

57

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57.1 Introduction

From its appearance in adulthood to its rapid growth to its transience, the placenta is, in many respects, an unusual organ. Three additional features not common among other human organs have fostered complications in interpreting placental pathology and in communicating these findings to clinicians. First, the placenta changes (matures) on almost a week-by-week basis throughout pregnancy. As a consequence, normal can only be assessed in reference to the gestational age. Second, the normal range for the histology of the placenta is wider than typical for other organs. The proportions of individual villous types are surprisingly variable, even within a specific gestational age, and the histology of the placenta can differ substantially across the individual lobules and across the placenta as a whole. These two issues create uncertainty in distinguishing normal from abnormal and have often resulted in poor concordance between pathologists. Lastly, even placentas from clinically uncomplicated pregnancies can have evidence of damage on pathologic examination. Peripheral infarcts are not uncommon at term, for instance. Given these complexities, expressing placental diagnoses in binary fashion may omit important subtleties. Many placental pathologies are perhaps best considered as falling along spectra, with thresholds dividing normal from abnormal. In this context, the construction of the placental pathology report may be crucial to conveying to the clinicians the significance of the placental pathology without generating needless confusion. This chapter will discuss the fundamentals of the placental pathology report. Since the focus of this chapter is the report itself and not the details of placental pathology diagnosis, specific lesions, particularly microscopic lesions, will be addressed minimally if at all.

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57.2 What Is of Clinical Interest?

Clinicians read placental pathology reports to find answers to any of multiple different questions. They may simply hope to confirm a clinically suspected diagnosis, such as acute chorioamnionitis. They may seek the aetiology for an intrauterine complication, such as clinically detected fetal growth restriction resulting

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from maternal vascular malperfusion. They expect the pathologist to detect unsuspected diagnoses that may affect the health of the baby, such as *Candida* infection of the placenta or evidence of a fetal metabolic disorder. They similarly expect the pathologist to alert them to pathologic entities that may affect subsequent pregnancies. Lesions with high recurrence rates, such as massive perivillous fibrin deposition and chronic histiocytic intervillositis, fall into this category. In litigious regions of the world, they may scour reports for exculpation in potential medicolegal cases. Finally, given the abundant recent evidence demonstrating the importance of the in utero environment for later life disease susceptibility, placental pathology reports may hold important clues for the long-term health of the mother and child [1]. The placental pathology report should answer all of these questions, and many more, while maintaining an informative yet easily digestible format.

57.3 Basic Structure of a Placental Pathology Report

There are several essential elements for each placental pathology report. The patient's name, date of birth, other identifiers, and the surgical pathology accession number are generally the most crucial details for this section. A section for the mother's clinical history is required. At least a minimal history of the pregnancy and delivery should be included. This section also may include the names of the doctors to whom the pathology report should be sent. For the pathologist, a macroscopic section, usually termed the gross description, is important to give an objective and reproducible description of the placenta. Finally, the diagnoses should be provided in a short, precise, and easily understandable construction.

Other sections of the report may be desirable but not necessarily mandatory. Particularly common is a comment or discussion section. This section is generally used to correlate the macroscopic and microscopic findings with the given clinical information, allowing the findings to be interpreted in a pathophysiologic context. This section is especially suited to discussions of differential diagnoses when the findings are indeterminate. A microscopic description may also be included in the report, although these are uncommonly used. Some institutions employ a separate section for reporting immunohistochemical staining, although others include these results in the microscopic description or even the final diagnoses. Finally, at least in the USA, there is always a series of disclaimers included for medicolegal reasons. These are generally presented in a smaller size font near the end of the report.

57.4 Specific Structural Elements of the Placental Pathology Report

57.4.1 Clinical History

In general, a patient's medical history is not well provided on pathology request forms [2]. While this problem plagues all fields in pathology, it seems especially problematic for placental pathology. One of the most necessary items of clinical information is the gestational age at delivery. Maturation disorders are among the more important findings on placental examination, and their diagnosis relies critically on knowing the gestational age at delivery. Maternal systemic disorders also may impact the pregnancy and the conceptus. Finally, it is helpful to learn if the placenta has been submitted for pathologic examination solely for an event that arose during delivery, such as clinical acute chorioamnionitis, meconium staining of the amniotic fluid, or a fetal bradycardic episode.

One of the best means for obtaining timely and accurate clinical information is through open lines of communication with the clinicians. Interdisciplinary communication between the pathologist and clinicians rapidly disseminates critical information, minimizes misinterpretation of findings, and deepens each field's appreciation for the other [2–5].

An important counterargument to the plea for more clinical information from the submitting obstetricians is that any clinical information

available to the pathologist introduces bias into the report. This problem may be particularly significant for placental pathology. For many major obstetrical conditions, such as preeclampsia or diabetes, the range of potential placental pathologic changes is wide, with many placentas in fact appearing entirely normal. This circumstance increases the likelihood that placental pathology will be overdiagnosed. While any experienced placental pathologist will be aware of this pitfall, this cognizance may be insufficient to counteract the introduced bias. This is an understudied problem in placental pathology.

57.4.2 Macroscopic Description

The macroscopic description typically includes a wealth of detail about the placenta (see also Chap. 4). This can take the form of a dictated narrative description (often following a guide) or, more commonly, a synoptic style fillable template. Assessing and measuring by compartments help to minimize gaps in the recorded parameters. An exhaustive formulation of the parameters to be evaluated is beyond the scope of this chapter (and is instead covered in Chap. 4), but a brief outline with specific reference to the pathology report will be included. The first consideration is the state of fixation of the placenta. Most organizations have a uniform policy regarding when the placenta is fixed and either choice (fixation immediately after delivery in the labour and delivery suite or in pathology after examination) has its advantages. Immediate fixation inactivates pathogens early in the process but also precludes ancillary studies such as culturing for organisms or growing cells from the placenta for karyotype. Fixation of the placenta also affects its weight, adding 3–6% [6]. The next consideration is the placental weight. The placenta may be weighed with the umbilical cord and extraplacental membranes attached, or weighing may be delayed until after these structures have been removed (trimmed placental weight). The advantage of an untrimmed weight is that very large databases of untrimmed placental weights have been published, with accompanying percentiles [7]. Fewer weight charts of trimmed placentas are available, and the ones that have been generated contain far fewer placentas. The absence of the cord and membranes may improve the precision of the weight, though, since the umbilical cord length (and the length received in pathology) may vary considerably among placentas. The placental weight should be accompanied by a percentile range on the report to help put the weight in context.

The first structure to be examined is often the umbilical cord [8]. Description of the umbilical cord should include the cord length and average diameter. Its point of insertion is documented, and employing a limited, consistent set of descriptors may help the clinicians. Common choices include central/paracentral, eccentric/peripheral, marginal, and velamentous. Establishing criteria for a marginal insertion (e.g., an insertion within 10 mm of the placental periphery) is helpful. Determining the degree of umbilical cord coiling is often performed. While this measurement can be obtained from a small segment, it is little more effort to assess the entire cord length. Despite the ubiquity of this measurement recommendation, recent evidence suggests that the results may be less useful than previously assumed [9].

The extraplacental membranes are normally evaluated next. Colour and clarity are examined (keeping in mind that areas of opacity in the extraplacental membranes may represent adherent decidua). Areas of circumvallation or circummargination are estimated (expressed as a percent of the disc perimeter). Completeness of the membranes should be assessed. Measurement of the distance from the site of membrane rupture to the disc periphery has typically been recommended, but this effort is of limited utility. This measurement was primarily used to assess for placenta praevia (any membrane distance between the site of rupture and the placental periphery argued against praevia). Given the ubiquity of ultrasound examinations in modern obstetrics, cases of unexpected placenta praevia are rare.

The placental disc is evaluated. Parenchymal defects due to prior sampling of the placental parenchyma or disruption of the basal plate

should be noted. The placenta should be measured in three dimensions. Macroscopic lesions should be measured and described. One important discrimination is between central/paracentral and peripheral lesions. The total parenchymal volume occupied by each type of lesion should be estimated. If limited in number, all lesions may be sampled. If too many lesions are present, then at least one lesion of each appearance should be taken, giving preference to central lesions. The temptation to diagnose lesions macroscopically should be resisted.

The maternal surface of the placenta should be examined for evidence of retroplacental haemorrhage, including adherent blood clot and/or indentation of the parenchyma. Any such lesions should be measured (in at least two dimensions) or the percentage of maternal surface area involved. The location (central vs. peripheral/marginal) should be recorded. Accompanying clotted blood should be either weighed or measured (in three dimensions).

A slide key should be appended to the macroscopic description section. Ideally, each slide should receive a description characteristic enough to differentiate it from the other slides. "Representative sections in three cassettes" does not suffice. "Random full-thickness central section" provides much more useful information. Similarly, sections of lesions deserve a comparable attention to detail. "Section of 30 mm firm white peripheral lesion" allows the pathologist to distinguish this lesion from others; "Lesion" does not.

57.4.3 Microscopic Description

A written microscopic description is not obligatory for a typical placental pathology report and, in fact, microscopic narratives have largely fallen out of favour in some institutions. Nevertheless, when confronted with unusual microscopic findings, particularly when of uncertain pathogenesis or diagnostic significance, the inclusion of a microscopic description may be prudent. Not uncommonly in these circumstances, the comment section is alternatively used as the location for a brief, focused microscopic description.

In the USA, at least, the microscopic description is generally replaced by a medicolegal disclaimer indicating that the evaluating pathologist did specifically examine the microscopic slides.

57.4.4 Immunohistochemistry and Special Stains

Immunohistochemical and special stains are likely used less frequently in placental pathology than in many other areas of pathology, but their results can prove critically important in some cases. Among the most frequent uses include immunostains detecting antigens from *Cytomegalovirus*, herpes simplex virus, *Parvovirus*, toxoplasma, or *Treponema pallidum* in cases of possible infectious chronic villitis. Staining for iron to confirm haemosiderin pigment deposition is also common. Immunostaining for lymphocyte and macrophage markers may assist in cases of chronic villitis of unknown aetiology (VUE), chronic histiocytic intervillositis, or chronic chorioamnionitis.

The location of the immunostain results within the pathology report is usually specified by each institution. A separate section, often in table format, provides for easy identification of the immunostains tested and the results of the staining. This format also simplifies coding and billing efforts. When not set apart in an independent section, the results of these stains are generally either included with the final diagnoses or incorporated into the microscopic description.

57.4.5 Diagnosis

The diagnosis section appears superficially to be the simplest. After thorough gross and

microscopic examinations, the only remaining task is to list the diagnoses. However, this section is particularly susceptible to misinterpretation [10], an issue that is exacerbated in the placenta by the complexities of distinguishing normal from abnormal. Broadly, there are several methods for organizing and reporting placental pathology diagnoses. The least effort for the pathologist is simply listing all of the individual diagnoses. This method relies on highly informed clinicians capable of interpreting the individual findings. A comment tailored to the specific findings may assist the clinicians in their interpretation. Alternatively, the diagnostic lines may be limited only to the major pathologic diagnoses for each placenta. The individual pathologist may choose the precise diagnostic categories (and the specific terminology), or a placental classification scheme may be employed [11]. Survey data suggest robust acceptance of and preference for at least one placental classification scheme [12]. Consistency in reporting major diagnoses within an institution is clearly helpful to clinicians. For systems reporting major placental diagnoses, the inclusion of minor diagnoses that are likely to be inconsequential or of uncertain significance is optional. One may reasonably list these diagnoses in a separate subheading of the diagnosis section, clearly indicating that they are different from the major diagnoses and likely to be of little or unclear significance.

57.4.6 Comment

The comment or discussion section is one of the most important for a placental pathology report. If placental diagnoses are simply listed, then this section is essential for providing context for the individual diagnoses. Even when the diagnoses are stratified into major and minor subsections, the comment may be used to provide additional relevant clinical information. Recurrence risk and long-term risk to the baby may be helpful to the clinicians, particularly for uncommon entities.

57.5 Pathology Report Optimization

Pathologists generally expend substantial effort on the details of their reports, crafting precise diagnoses and comments to convey the findings with a high degree of accuracy. Much less commonly considered, however, is the impact that the structure of the report can have on a clinician's understanding of the content. Various clinical specialties read pathology reports differently [2, 4, 10], so, while a report cannot be optimized for everyone, it should be usable by all. Based on data from fields outside of medicine, recommendations have been made for improving the readability and comprehension of pathology reports [10]. These include using headlines to emphasize key findings, maintaining layout continuity, optimizing information density for readers, and reducing clutter in reports. Specific suggestions include eliminating diagnostic lines consisting of all capital letters, minimizing text and font changes, and segregating information (such as diagnoses) into small, logical groups.

Finally, one important and often overlooked consideration is the fact that many clinicians now view pathology reports exclusively online in their hospital's electronic medical record system. Electronic medical record systems frequently discard some or all of the formatting, potentially resulting in compressed diagnostic lines with inapparent line divisions. Tables seem to fare particularly poorly in these conversions [10]. A pathology report should be inspected as presented in the electronic medical record system, and, if possible, the formatting adjusted to improve readability (Figs. 57.1 and 57.2).

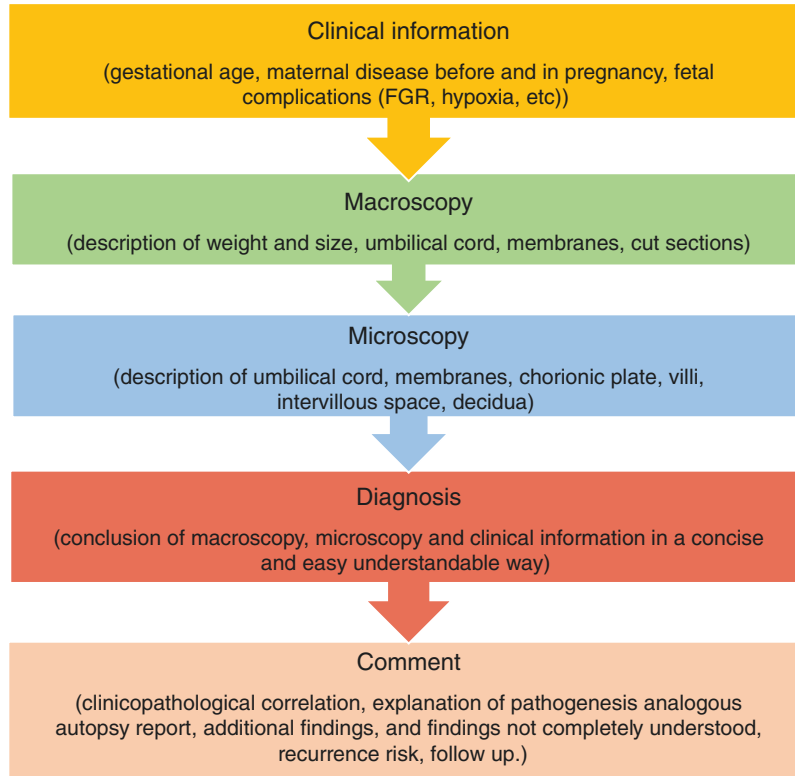

Fig. 57.1 Principle of a pathological placental diagnosis report

Demographics	Patient name, medical record number, birthdate Surgical pathology report number
Clinical	34 – year old primigravida, Diabetes mellitus type 1, HELLP syndrome, urgent
information	cesarean section in gestational week 38+1. Child's weight 4010g, Apgar 9-10.
Macroscopy	Placenta with 656 g net weight, basal area 282 cm^2. Umbilical cord length 62 cm, diameter 1 cm, 3 vessels, centrally inserted, right hand coiling, 2 coils each 10 cm. Normal chorionic surface, no fetal vessel thrombosis. Membranes with normal opacity. Cut sections each 1-1.5 cm show normal parenchyma without mass lesions. Decidua without any signs of bleeding.
Microscopy	Umbilical cord with 3 vessels without inflammation. Membranes without meconium macrophages, no inflammation. Intermediate villi of medium size with loose reticular stroma and numerous fetal capillaries predominate. Minimal vasculosyncytial membrane formation. Trophoblast with increased syncytial sprouts and knots. Intervillous space with mild fibrin deposition. Focal villous collapse.
Diagnosis	Macrosomic placenta with villous maturation disorder.
Comment	The placenta's net weight is >90^{th}-percentile for 38 weeks gestational age (50^{th} %ile : 460g, 90^{th} %ile: 605g). The prominent excess of intermediate villi with infrequent terminal villi and few vasculosyncytial membranes indicates a maturation disorder. Maturation disorders of different types are seen most commonly in maternal metabolic disorders, but they are not necessarily diagnostic of such disorders. The pathogenesis underlying maturation disorders is still not completely understood. In this case the maternal type I diabetes mellitus may explain the fetal and placental macrosomy. The additional findings of increased syncytial knots and intervillous fibrin suggest the onset of maternal vascular malperfusion, correlating with the clinically diagnosed HELLP syndrome. The recurrence risk may depend on the degree of control of the maternal diabetes.

Fig. 57.2 Example of a placenta pathology report

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Frontiers in Placental Pathology

58

Terry K. Morgan

58.1 Introduction

Placental pathology is an autopsy of the pregnancy and provides useful gross and histopathologic information to help explain why the pregnancy was complicated. Many of the authors of this book met in Amsterdam, The Netherlands in 2014, Portland, OR, USA in 2016, and again in Dublin, Ireland in 2018, to discuss diagnostic criteria and frontiers in placental pathology. Undoubtedly, there will be many other frontiers, but a few that we discussed are briefly summarized in this chapter:

1. Prognostic information about short- and long-term health implications.
2. Morbidly adherent and invasive placentas.
3. Early pregnancy detection of placental pathology.
4. Placental in vitro assays to study developmental impacts of exposures.
5. What is normal?

To answer these questions, there are many opportunities for placental pathologists to collaborate with placental scientists, developmental biologists, clinical obstetricians, and obstetric researchers. A pathologist's experience and expertise classifying gross and microscopic features provide useful structural analysis to correlate with function measured by imaging, biomarkers or related outcomes.

Right now there is a growing interest by funding agencies to *invigorate placental research* to study placental structure and function in real time and relate these insights to clinical outcomes [1, 2]. When asked about the role of pathologists in placental research, Dr. David Weinberg, project coordinator for the *Human Placenta Project* at the *National Institutes of Health* (NIH), said, "I think it's pretty fair to say that pathologists provide critical expertise to move this project forward. One important way that pathologists can help is by informing the technology folks, who may know very little about the placenta". Similarly, Dr. Catherine Spong, who at the time was acting director of the National Institute of Child Health and Human Development (NICHD) at the NIH, commented, "Pathologists have an intimate understanding of the consequences of placental development gone awry. They provide insights into cell types and microstructure that we cannot get from imaging or other techniques. The contributions that pathologists make to the *Human Placenta Project* are not just unique, but vital" (Fig. 58.1).

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Fig. 58.1 The *Human Placenta Project* reinvigorated placental research in the USA dedicating funds from the *National Institute of Child Health and Human Development*. Placental pathology provides prognostic and mechanistic information, but much more work needs to be done. Figure provided courtesy of the NIH

58.2 Prognosis

Intrauterine exposures affect an individual's susceptibility to adult onset of chronic diseases like obesity, cardiovascular disease, and some cancers [3]. This makes sense. The availability of various nutrients or exposures to various toxins, during the embryonic and fetal period, influences gene expression, organ development, and long-term epigenetic "programming" of organ function. Numerous epidemiologic studies in humans and various animal models have now shown that the placenta plays a key role in developmental programming linked to intrauterine exposures. The placenta regulates nutrient delivery to the fetus and shows a remarkable ability to adapt to adverse situations. Variance in placental adaptive responses related to long-term clinical outcomes in the mother and child needs to be further studied. For example, what is the implication of chorangiosis (adaptive response to increased fetal demand relative to placental supply, which is more commonly seen in twin or multiples than in singleton pregnancies) to the long-term mental health of the child (in addition to the risk for cerebral palsy)? How do placental features of insufficiency, including placental size, shape, presence of infarctions, and villous architecture, correlate with the long-term risk for cardiovascular disease in mother and child?

To get to the bottom of issues, we must first "get serious about the placenta" as described by Dr. Raymond Redline [4]. We need uniform grossing, sampling and reporting protocols for multicentre studies. Placental pathology reports must be linked to both the mother's and child's electronic medical records (Chap. 57).

We need to stop wasting placental data! Dr. Carolyn Salafia argues that "placental gross features do not develop in a vacuum; they vary, and they vary in relation to and depending on each other". A better understanding of relationships between placental shape, vascularity and umbilical cord development is a frontier that needs to be explored [5, 6]. Similarly, where the placenta is sampled for study makes a big difference. We all agree the edge of the placenta has a number of "artefacts", or could the edge of the placenta provide a more sensitive region to detect phenotypes associated with outcomes? Chorionic villous morphology near the chorionic plate is different to morphology at the decidua basalis. Placental lobule histology varies across the placental bed. Indeed, placental heterogeneity may contribute to its plasticity and adaptive capacity. How do we capture these data in a few microscopic sections?

Uniform grossing, uniform sampling and uniform nomenclature are essential to improve reproducibility and accuracy for prognostic studies [7].

58.3 Morbidly Adherent and Invasive Placenta

Abnormally adherent and invasive placentation is a multifactorial spectrum disorder that may present as subtly as basal plate myometrial fibres (Chap. 34)

or as grossly devastating as bladder invasion (not covered in this book) [8]. It is currently not known whether these extremes represent entirely different mechanisms or if they represent two ends of a spectrum. Indeed, it seems to be a problem with the seed and the soil—the placenta is either abnormally "hyper-invasive", or the maternal decidua/paracrine environment is abnormally receptive to placental invasion, or both. Prior caesarean delivery increases the risk of abnormal adherence, perhaps related to disruption of the protective decidual lining; however, differences in the invasiveness of extravillous trophoblasts cannot be ignored [9]. The next frontier is a better understanding of the early pathophysiology of this spectrum disorder and diagnostic approaches to more reliably detect it before delivery.

58.4 Early Pregnancy Detection of Placental Pathology

New imaging approaches to measure uteroplacental blood flow or to test for abnormal invasion remain in the early stages of technical development [10, 11]. Monitoring placental health in vivo will require liquid-based biomarkers from these cells in maternal blood [12] that could be followed throughout pregnancy, correlated with pregnancy outcomes, and validated using first trimester elective termination specimens (limited availability). Chorionic villous sampling would not be representative of the placental bed while extravillous trophoblasts detected in cervical cytology samples are unlikely to be representative of the placenta. But these approaches require more study. There is a lot of work ahead of us to develop early detection testing in pregnancy. Human studies, animal models and in vitro assays will all play a role.

58.5 Placental In Vitro Assays to Study Developmental Impacts of Exposures

There is a paucity of in vitro human placental cell lines able to appropriately model this organ. Recent work has shown that human pluripotent stem cells can be used to model placental development in culture; a method for step-wise differentiation of stem cells into terminally differentiated multinucleated hCG-secreting syncytiotrophoblasts and invasive HLA-G positive extravillous trophoblasts has been developed [13]. This provides a platform to study the impact of environmental exposures on these specific placental cell types.

58.6 What is Normal?

Placental pathologists do not have a clear understanding of what is "normal" placenta. There are a lot of data about normal gross placental weight but even these values may be out of date because of an increasing prevalence of maternal obesity around the world. After weighing (and sometimes measuring) normal placentas, they are disposed of as waste. In contrast, the placentas submitted to pathology laboratories are from complicated pregnancies, which lead to a clear selection bias for abnormal phenotypes.

We need a large multicentre, multi-racial series of normal term deliveries to create a normal term placenta database so we can begin to answer questions like what is the prevalence of various lesions in normal term placentas? This is an important question as they may point to the underlying causes of those lesions, as for example, how much of chronic villitis is related to maternofetal genotypes or to infectious disease exposures.

What is the normal histology of third trimester chorionic villi? This is an important question related to accelerated villous maturation (AVM), which is a common histopathologic feature associated with complicated pregnancies (e.g. pre-eclampsia, fetal growth restriction, non-infectious spontaneous preterm labour). AVM studies tend to use fetal anomalies or intra-amniotic infection as an approach to control for villous architectural changes related to gestational age [14] but they do not entirely account for the potential impact of fetal development and placental inflammation on chorionic villous maturation. Rare collections like those managed at the *Centre for Trophoblast*

Research at Cambridge University, UK, provide some insight into normal uteroplacental histopathology but their cohort size and available tissue for molecular studies are limited [10]. Instead, most of what we are currently learning about normal term placenta is based on molecular and microbiome studies [15, 16].

58.7 Summary

The few examples illustrated here are only the tip of the iceberg. The placenta is a stealth organ with many mysteries. It is like an invasive neoplasm that regulates its immune microenvironment and stimulates regional angiogenesis. It impacts maternal metabolism and releases metastatic "sprouts" into the maternal circulation that implant in the mother's lungs and live for years after delivery. (Are these multinucleated syncytiotrophoblasts sprout an essential component of normal postpartum well-being?) Relationships between placental size, architecture, and fetal development are only beginning to be explored. There are so many interesting and clinically significant questions that impact the health of all of us. Our frontier is vast and inviting.

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