Placenta and Pregnancy-Related Diseases

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Abstract

The placenta is unique among surgical pathology specimens in that it reflects the (patho)physiologies of two patients: the mother and the fetus. Placental examination may offer diagnostic, prognostic, and therapeutic information of clinical relevance to both neonates and their mothers. Pathological processes of relevance to future pregnancies may also be identified, facilitating preconception counseling as well as suggesting monitoring and potential intervention in subsequent gestations. In the setting of intrauterine or neonatal demise, the placenta may be the only, and often most useful, source of information regarding a potential cause of death. The following chapter describes the clinical and pathologic features of both common placental pathologies and uncommon lesions with important clinical implications with which the pathologist should be familiar.

Keywords

Placenta · Pathology · Obstetric

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15.1 Introduction

The placenta is unique among surgical pathology specimens in that it offers a chronicle of the intrauterine environment that reflects the (patho)physiologies of two patients: the mother and the fetus. Placental examination may offer diagnostic, prognostic, and therapeutic information of immediate clinical relevance to both neonates and their mothers. Pathological processes of relevance to future pregnancies may also be identified, facilitating preconception counseling as well as suggesting monitoring and potential intervention in subsequent gestations. In the setting of intrauterine or neonatal demise, the placenta may be the only source of information regarding a potential cause of death. This chapter describes the clinical and pathologic features of both common placental pathologies and uncommon lesions with important clinical implications with which the pathologist should be familiar.

15.1.1 Indications for Examination

The majority of gestations, deliveries, neonates, and placentas are normal, and for practical reasons, pathologic examination is not required for all placentas. The proportion of placentas submitted for examination depends on the acuity and complexity of obstetric care provided at the health center. A list of relevant indications for pathologic examination should be agreed upon by all stakeholders (pathologists, obstetricians, neonatologists) to maximize the clinical value of placental examination. The indications for examination endorsed by the College of American Pathologists guidelines provide a useful basis. These include pre-existing maternal diseases or gestationally significant health conditions, gestational diseases, abnormalities in the current pregnancy, pregnancy complications, fetal or neonatal abnormalities, or placental abnormalities (Table 15.1) [1].

In many laboratories serving routine and high-risk obstetric services approximately 10–20% of placentas are

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Table 15.1 Indications for placental examination

Maternal history
Pre-existing diabetes mellitus, vascular disease, or other gestationally significant medical condition
Substance abuse
Previous obstetric history
Prior recurrent pregnancy loss or late fetal/neonatal loss
Prior significant obstetric complication
Maternal conditions arising in pregnancy
Peripartum fever or suspected infection
Gestational diabetes
Preeclampsia or pregnancy-induced hypertension
Maternal trauma
Current pregnancy
Preterm labor or delivery (<37 completed weeks gestation)
Post-term delivery (≥42 completed weeks gestation)
Prolonged rupture of membranes (>24 h prior to delivery)
Excessive bleeding prepartum
Suspected placental abruption
Oligohydramnios or polyhydramnios
Placenta accreta/increta/percreta or previa
Meconium-tinged amniotic fluid
Termination for anomalies or suspected gestational trophoblastic disease
Fetal hydrops
Fetal demise in utero
Neonatal
Perinatal or neonatal demise
Need for resuscitation or ventilation, poor Apgar (<7), low cord blood pH
Neonatal anemia
Low birth weight (<10th percentile)
Macrosomia (birth weight >95th percentile)
Seizure
Sepsis or suspected infection
Admission to neonatal intensive care unit
Major congenital anomalies, including confirmed or suspected aneuploidy
Multiple gestation with discordant weight, premature delivery, and/or clinically significant question regarding chorionicity
Placental
Small or large placenta (either absolutely or relative to neonatal size)
Abnormal umbilical cord insertion (marginal or velamentous) or length (short or excessively long)
Abnormal umbilical cord vessels (single umbilical artery, suspected thrombosis)
Umbilical cord true knot
Discrete lesions of the disc (mass, hematoma, infarction)
Abnormal color (abnormal pallor, green-stained membranes)

Table adapted from [1]

submitted for pathologic examination. If resources allow, it is advisable to store unsubmitted placentas from all remaining deliveries for a period of time (1 or 2 weeks) to allow for placental examination if the need becomes evident postnatally. Refrigerated storage without formalin fixation preserves tissues sufficiently. In some jurisdictions, disposal of human tissues must be conducted by the laboratory regardless of whether medical examination is indicated.

The placental requisition for examination should include, at a minimum, the gestational age and the indication for examination. Some hospitals use purpose-designed placental requisitions with fields to record relevant obstetric details and indications for examination, which facilitates provision of relevant clinical history and appropriate requests for examination. Placentas are most commonly accessioned as surgical specimens under the maternal record; a special provision in the laboratory information system or reporting system ideally also makes the report available in the neonate's chart.

15.1.2 Gross Examination and Sampling

Placentas may be examined in the laboratory in the fresh- or formalin-fixed state. The advantages of formalin fixation include better characterization of some types of discrete lesions, decreased infection potential, less mess from unfixed blood, and better fixation of sampled blocks if processing is done on the same day as block sampling. On the other hand, even with large volumes of fixative, formalin permeates and fixes bloody tissues very slowly, mitigating some of the abovementioned advantages. Examination in the fresh state allows for sampling for specialized molecular genetic techniques that are incompatible with formalin, faster turnaround times, and use of considerably less fixative. The chosen examination protocol depends on the workflow and resources of the specific lab.

A placental gross examination should include descriptors of the umbilical cord, membranes, and disc including fetal surface, maternal surface, and parenchymal cut surface (Table 15.2). Use of standardized grossing templates facilitates thorough and reproducible examinations [2]. Explicit comparison of observed disc weight with gestational age-adjusted expected weight is recommended [3]. It should be noted that formalin fixation affects placental measurements, including increasing disc weight by up to nearly 8% [4]. It is often more useful to document macroscopic lesions photographically than it is to submit numerous sections of similar-appearing areas.

According to recently published consensus guidelines, minimum sections recommended for microscopic examination are roll of extraplacental membrane from the margin to the rupture site, two cross sections of the umbilical cord from different areas of the cord, three full-thickness sections of the placental disc, and representative samples of discrete lesions [5]. Increasing the number of grossly normal sections submitted for histologic examination will increase sensitivity; however, most grading schemes for common and clinically relevant pathological entities are based on examination of a

Table 15.2 Elements of a placental gross examination and description

Unique patient identifiers
Placenta received fresh or in formalin
Singleton or multiple gestation (see Sect. 15.12)
Umbilical cord
Attached or separate; number of segments
Number of vessels
Length and average diameter
Insertion (central, eccentric, distance to margin, marginal, velamentous, furcate, etc.)
Coiling (number of total coils or coils per 10 cm)
General descriptors (edematous, discolored, surface lesions, etc.)
Discrete lesions (varices, true knots, vessel thrombosis, etc.)
Membranes
Insertion into disc (normal, circummarginate, circumvallate)
Rupture site distance from margin
General descriptors (translucent, opaque, green, brown, hemorrhagic)
Velamentous vessels
Disc
Weight (after removal of membranes and umbilical cord)
Dimensions
Shape (round, oval, bilobed, accessory lobe, etc.)
Fetal surface
General descriptors (color, etc.)
Discrete lesions
Chorionic plate vessels (distribution, thrombosis, etc.)
Maternal surface
Completeness
Presence, size, and quality of hematomas
Discrete lesions
Cut surface of parenchyma
General descriptors (congested, pale, firm, mottled, etc.)
Discrete lesions (number, size, color, consistency, location, etc.)

set number of tissue sections, and increasing the sections submitted may lead to overestimation of grade. In general, submission of extra sections of grossly normal placenta should be restricted to specific indications requiring increased sensitivity (e.g., searching for maternal metastases).

Important gross findings and abnormalities are discussed in the sections below. The reader is also referred to other comprehensive resources on gross pathology of the placenta [6].

15.1.3 Standardized Reporting

The value of standardized reporting for improving clinical interpretation and research in cancer has been well established, and generally accepted cancer reporting protocols are now in widespread use. Considerable progress has been made in defining, refining, and standardizing many placental pathological processes [5], and placental pathology reporting could similarly benefit from this approach. Universally recognized placental reporting protocols do not presently exist; however, development of local reporting protocols may improve clinician understanding and facilitate research.

15.2 Placental Infection

Placental inflammation and infection may sometimes be used interchangeably, but they imply different disease states in the placenta. Placental infections can have inflammatory cells, but not all placentas with inflammatory cells have infections. Most inflammatory patterns in the placenta can be distinguished by location of the inflammatory infiltrate and cellular composition. This section deals with common and typical patterns of placental infections, and the section following covers inflammatory patterns not associated with infectious etiologies.

15.2.1 Ascending Intrauterine Infection

Ascending intrauterine infection is also referred to as amniotic fluid infection sequence or syndrome. The histopathologic descriptor chorioamnionitis should not be used interchangeably with these clinicopathologic terms.

Identifiable microbes are typically bacterial, and this type of placental infection has its sentinel declaration in the placental membranes, which are the first point of contact with the outside world. The closed cervical os and mucous plug act as natural barriers against outside contamination of the amniotic sac

15.2.1.1 Clinical Features

The incidence of ascending uterine infection is inversely associated with gestational age. There is an over 90% association of acute chorioamnionitis with spontaneous preterm delivery at 20 weeks; this association steadily decreases with increasing gestational age to 5.1% at term [7, 8].

The most common organisms are cervicovaginal bacteria from the lower genital tract. Common organisms include *Ureaplasma urealyticum*, *Escherichia coli*, *Gardnerella vaginalis*, and group B *Streptococcus* (GBS).

A requisition stating "query acute chorioamnionitis" is a common indication for placental examination when there is maternal fever or tachycardia. Other possible clinical findings include fetal tachycardia, uterine tenderness, foul-smelling vaginal discharge, and maternal white cell count increase. Common clinical scenarios are preterm rupture of membranes and prolonged premature rupture of membranes. Risk factors and contributors include many etiologies such as incompetent cervix, previous infection (such as bacterial vaginosis), cervical instrumentation such as cerclage, and vaginal hemorrhage. The clinical severity and histologic findings do not always correlate.

15.2.1.2 Gross Features

Color and opacity are both important descriptors of the placental membranes. Normal placental membranes are shiny and translucent, almost transparent. The neutrophilic exudate from an ascending intrauterine infection causes opacification of the membranes, making them thick and dull-white (Fig. 15.1). The neutrophilic exudate can also cause a green-brown discoloration; however, this is not a specific finding because meconium staining and biliverdin breakdown can also cause similar discoloration. Even in cases of severe inflammation, the gross findings may be relatively unimpressive.

15.2.1.3 Microscopic Features

The Amsterdam Placental Workshop Group Consensus Statement from July 2016 provides the latest standard in the diagnostic criteria for acute chorioamnionitis [5] (Table 15.3). There is consensus that location (staging) and composition of the inflammatory response should be documented. In addition, classification of the severity (grading), and separation of fetal from maternal inflammatory responses, is useful.

Maternal Inflammatory Response

See Table 15.3 for the recommended staging and grading system.

Stage 1: Acute subchorionitis or chorionitis includes acute inflammation in the form of neutrophils beneath the chorion, with minimal extension into the cellular chorion, without the presence of neutrophils elsewhere. This stage is considered an early response to an ascending infection. Strictly speaking, this is not a true chorioamnionitis (Fig. 15.2). *Stage 2: Acute chorioamnionitis* refers to a neutrophilic infiltrate within the chorion (above the cellular chorion), with or without early involvement of the amnion (Fig. 15.3). *Stage 3: Necrotizing chorioamnionitis* includes any cases with neutrophil karyorrhexis and/or overt necrotic damage to the amnion (Fig. 15.4).

Note that even severe/advanced chorioamnionitis can be surprisingly patchy, with relative or complete sparing of the chorionic plate or membranes in some fields.

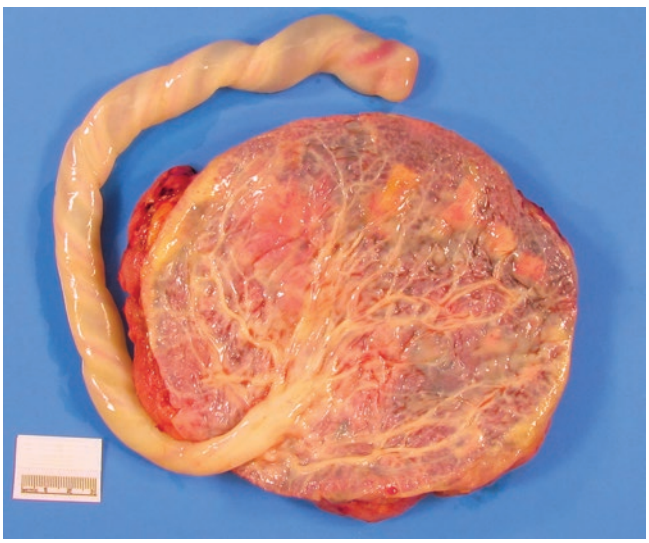

Fig. 15.1 In acute chorioamnionitis, the neutrophilic infiltrate can cause opacification of the membranes, chorionic plate, and Wharton's jelly surrounding the umbilical vessels

Table 15.3 Staging and grading of maternal and fetal inflammatory responses in ascending intrauterine infection

Maternal inflammatory response			
Stage 1	Acute subchorionitis or chorionitis	Grade 1	Not severe as defined
Stage 2	Acute chorioamnionitis; polymorphonuclear leukocytes extend into fibrous chorion and/or amnion	Grade 2	Severe: confluent polymorphonuclear leukocytes or subchorionic microabscesses
Stage 3	Necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia		
Fetal inflammatory response			
Stage 1	Chorionic vasculitis or umbilical phlebitis	Grade 1	Not severe as defined
Stage 2	Involvement of the umbilical vein and one or more umbilical arteries	Grade 2	Severe: near-confluent intramural polymorphonuclear leukocytes with attenuation of vascular smooth muscle
Stage 3	Necrotizing funisitis		

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Fetal Inflammatory Response

See Table 15.3 for the recommended staging and grading system.

Stage 1: Chorionic vasculitis or umbilical phlebitis describes fetal neutrophils migrating from the fetal circulation, out through the umbilical vein or chorionic vessels (Fig. 15.5). This inflammation is often seen to be chemotactically oriented toward the source of infection (the amniotic fluid). In the wall of the vein, early/sparse infiltrating neutrophils are best looked for in between the layers of vascular smooth muscle. *Stage 2: Umbilical arteritis* includes cases with neutrophilic inflammation of any two or more of the umbilical vessels (Fig. 15.6). *Stage 3: Necrotizing funisitis* refers to concentric neutrophilic inflammation within the ground substance (Wharton's jelly) around one or more umbilical vessels (Fig. 15.7).

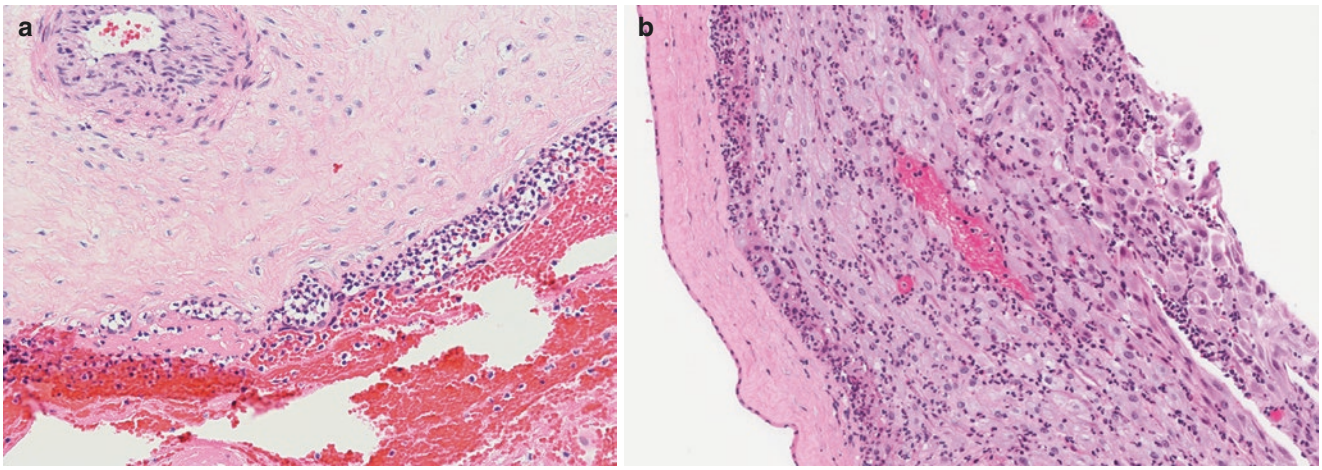

Fig. 15.2 Acute subchorionitis or chorionitis (maternal inflammatory response stage 1) denotes neutrophilic inflammation within subchorionic fibrin, beneath the chorion, with (**a**) no or (**b**) minimal extension into the cellular chorion (original magnifications 200×)

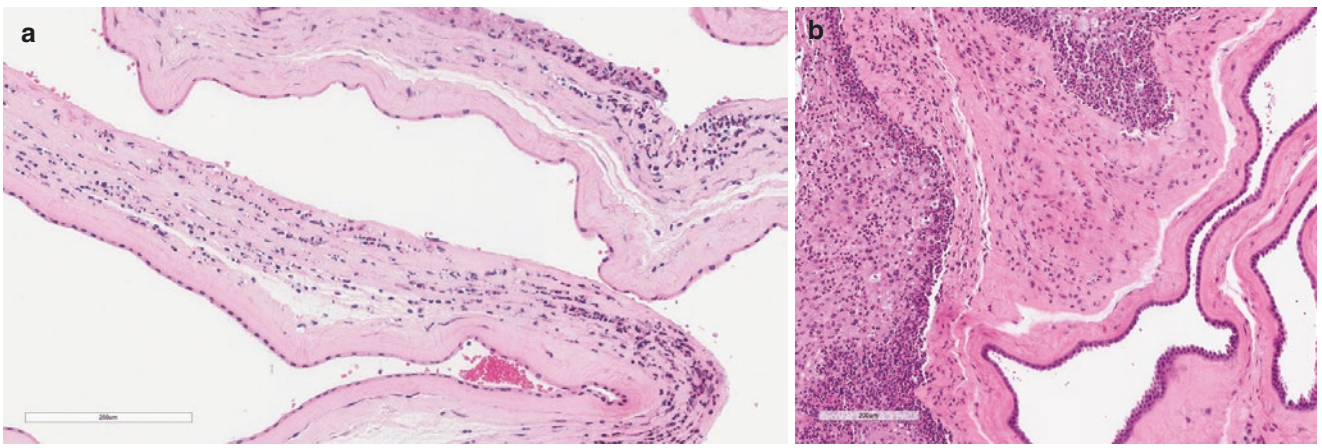

Fig. 15.3 Acute chorioamnionitis (maternal inflammatory response stage 2) refers to a neutrophilic infiltrate within the chorion, above the cellular chorion, with or without early involvement of the amnion, and can be graded as either (**a**) mild or moderate (grade 1) or (**b**) severe (grade 2) (original magnification 100×)

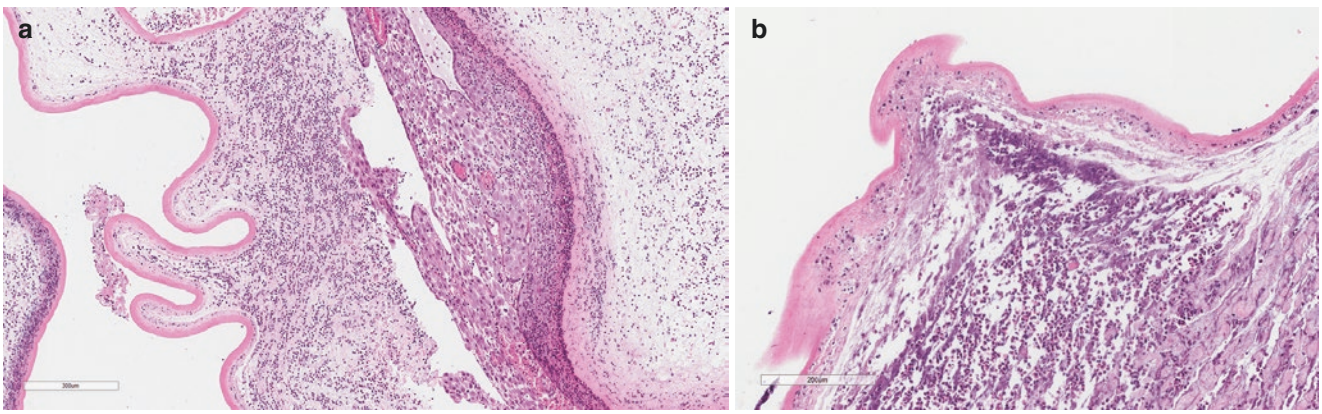

Fig. 15.4 Low- (**a**) and higher-power (**b**) views of necrotizing chorioamnionitis (maternal inflammatory response stage 3), with neutrophil karyorrhexis, amniocyte necrosis, and hypereosinophilia of the amnion basement membrane (original magnifications 40× and 100×)

Like the maternal inflammatory response, the inflammation can be variable and patchy in different parts of the fetal circulation. This is part of the reason for recommending at least two umbilical cord cross sections. In general, the fetal inflammatory response lags stagewise behind the maternal inflammatory response. The fetal inflammatory response

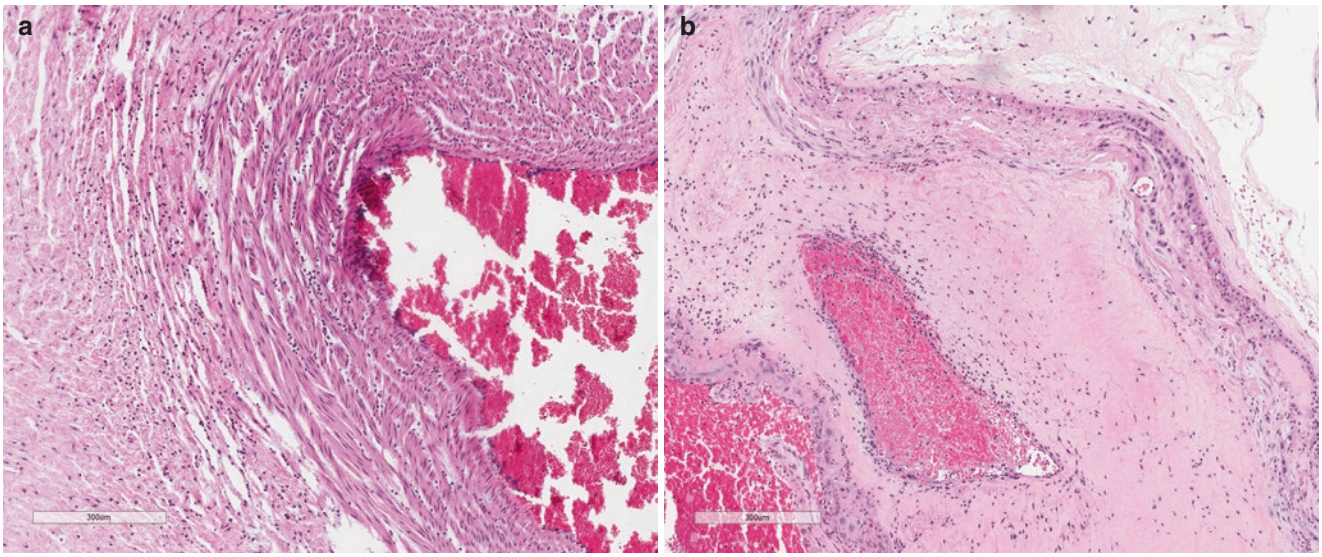

Fig. 15.5 (**a**) Umbilical phlebitis (fetal inflammatory response stage 1) with fetal neutrophils migrating from the fetal circulation via the umbilical vein. (**b**) Chorionic vasculitis (fetal inflammatory response stage 1) with fetal neutrophils migrating out through a chorionic plate vessel (original magnifications approximately 100×)

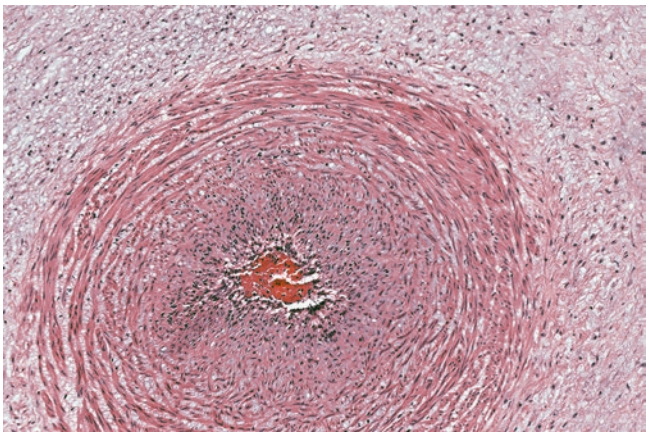

Fig. 15.6 Fetal inflammatory response stage 2, with neutrophilic involvement of an umbilical artery (original magnification 40×)

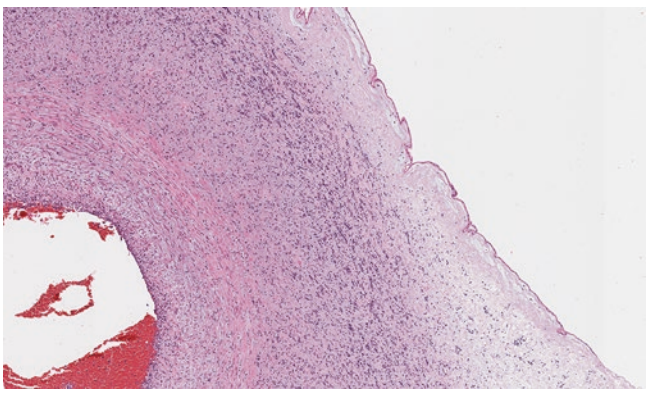

Fig. 15.7 In necrotizing funisitis (fetal inflammatory response stage 3), neutrophils form concentric rings in the ground substance surrounding umbilical vessels (original magnification 40×)

may be lacking or absent in second-trimester fetuses, who have immature immune systems. Despite being referred to as vasculitis/phlebitis, it is important to understand that the fetal inflammatory response is not true vasculitis.

15.2.1.4 Differential Diagnosis

The gross appearance of a placenta with bacterial infection is non-specific; cloudiness or discoloration of the membranes can be due to adherent villous or decidual tissue, excess subchorionic fibrin, meconium, or hemorrhage.

Neutrophilic inflammation in the placental membranes, chorionic plate, and umbilical cord is generally considered indicative of ascending bacterial infection. Identification of the specific infectious agent (by histology or culture) is not usually practical and is not required to guide empiric treatment of either the mother in labor or the potentially septic neonate. It has been noted that chorioamnionitis due to GBS may show unimpressive maternal inflammation, even in cases with significant fetal infection. Isolated subchorionitis may be seen in prolonged labor or induction of labor; in these settings subchorionitis likely represents early ascending infection secondary to rupture of membranes rather than a primary process.

Note is made here of an uncommon, but highly significant, pattern of umbilical cord inflammation. Peripheral/eccentric neutrophilic funisitis (which can appear grossly and/or microscopically on the umbilical cord surface as punctate microabscesses) correlates with candidal infection (Fig. 15.8). Although *Candida* spp. are common normal and pathogenic flora of the lower genital tract, they can rarely cause amniotic fluid infection. A high index of suspicion should be maintained with this pattern of inflammation, and

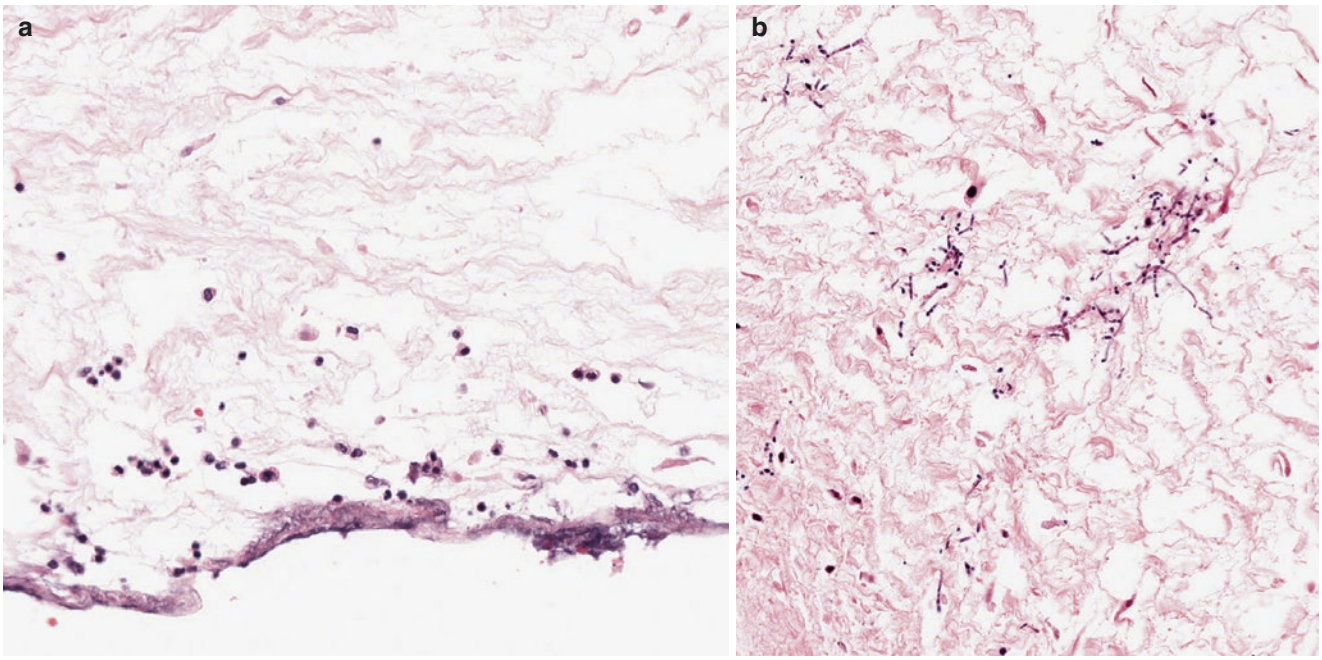

Fig. 15.8 (**a**) Neutrophil collection on the surface of an umbilical cord in a case of (**b**) *Candida* infection (original magnification 200×)

special stains ordered to identify invasive fungal organisms.

15.2.1.5 Prognosis

The outcome of ascending amniotic fluid infection depends on many clinical factors such as duration of infection, provision of maternal antibiotics intrapartum, severity of fetal sepsis, virulence of the etiologic organism, and especially gestational age of the newborn infant [8]. Chorioamnionitis is a contributing factor in a large minority of preterm deliveries. In general, potential fetal sepsis is of much more concern at young gestational ages, whereas term infants may manifest very little morbidity. In most cases, empiric antibiotics are provided whenever fetal infection is suspected. Histologic confirmation of chorioamnionitis is most clinically useful when provided to the neonatal care team within 48 h of delivery, since this may guide discontinuation or completion of a full antibiotic course regardless of the clinical picture.

15.2.2 Other Placental Infections

15.2.2.1 Acute Intervillositis

Acute intervillositis refers to neutrophils in the intervillous space with associated abscesses. It is most commonly associated with *Listeria monocytogenes*. The incidence of *L. monocytogenes* in pregnancy is 12 per 100,000 [9]. Pregnant women are at a much higher risk than the general population, where the incidence is 0.7 per 100,000 people.

Clinical Features

This is a food-borne illness, and in most jurisdictions, its diagnosis in pregnancy is a public health reportable disease. Maternal illness is most commonly mild, with either fever alone or a mild flu-like or gastrointestinal illness. Sometimes the mother is asymptomatic. By comparison, fetal infection is severe and rapidly fatal.

Gross Features

The gross findings are seen in both the placental membranes and the placental disc. The membranes can be opaque and thick. There may be outlines of septic infarcts in the placenta, characterized by geographical zones of pale yellow-white discoloration.

Microscopic Features

Listeria monocytogenes is a gram-positive rod but can often stain indeterminately on histologic Gram staining. The organisms are typically easily found, if not specifically identifiable, on histology, due to heavy colonization. The hallmark finding in this infection is neutrophilic infiltration throughout the intervillous space, membranes, and within villi (Fig. 15.9). Septic infarcts and abscesses may be seen (Fig. 15.10).

Differential Diagnosis

Maternal sepsis with other bacteria may produce identical acute intervillositis and villitis; however, bacteria are typically sparse and primarily located in the maternal blood

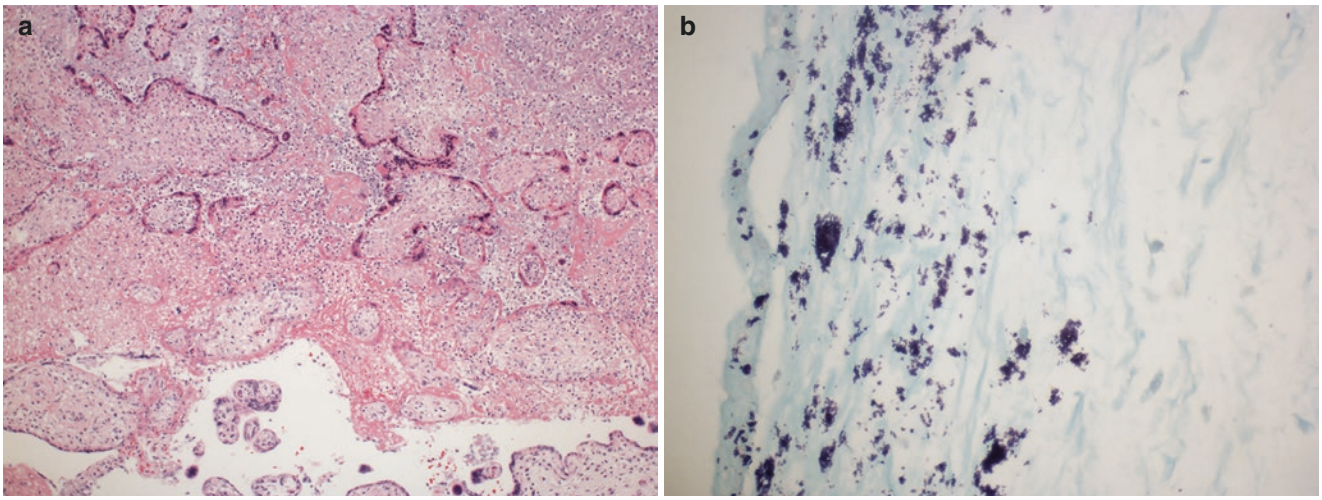

Fig. 15.9 (**a**) Acute necrotizing villitis and acute intervillositis, caused by *Listeria monocytogenes* infection (original magnification 100×). (**b**) Umbilical cord cross section showing colonies of *Listeria monocytogenes* (gram-positive rods) on its surface (gram stain; original magnification 400×)

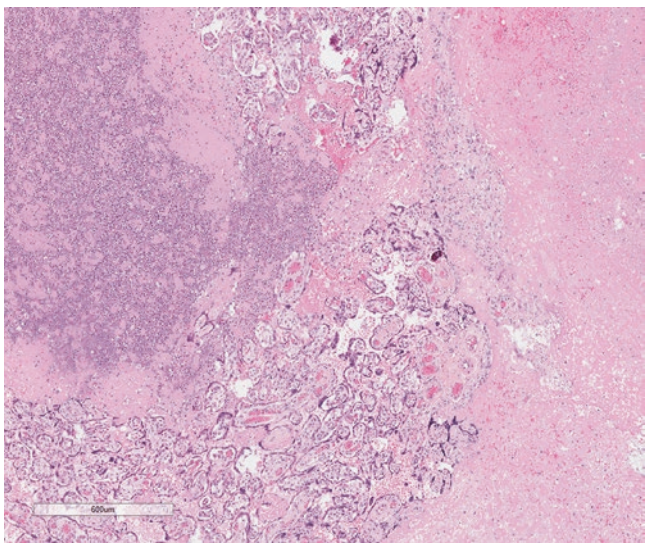

Fig. 15.10 Intervillous abscess in placental *Listeria* infection (original magnification 20×)

space. The clinical history is usually sufficient for differentiation.

Prognosis

Pregnancy outcome depends on the gestational age at time of infection. In the second trimester, fetal loss is common. The neonate remains vulnerable to *Listeria* sepsis and meningitis in the weeks following delivery.

15.2.2.2 Chronic Infectious Villitis

Clinical Features

The incidence is related to the two etiologic infectious agents associated with most of these cases: *Treponema pallidum* (causative agent of syphilis) and cytomegalovirus (CMV) (Fig. 15.11). Maternal disease may be asymptomatic, and symptoms partially depend on whether this is a new primary infection or a reactivation or later stage of disease. Primary infection is most likely to be passed across the placenta to the fetus. Another etiology of villitis is parvovirus B19, which can also cause potentially severe fetal anemia. Varicella zoster virus can be transmitted transplacentally, whereas herpes simplex virus is usually acquired during delivery through an infected lower genital tract.

Microscopic Features

See Table 15.4 for characteristic features of syphilis and CMV infection of the placenta.

Distinction between infectious villitis of this type and the much more commonly encountered chronic villitis of unknown etiology (VUE) is discussed below in the section on VUE.

15.2.2.3 Placental Parasitic Infections

Parasitic infections of the placenta are individually and collectively uncommon in North American practice. Two are worth mentioning for their specific clinical contexts and characteristic microscopic appearances.

Placental malaria is a significant public health concern in many parts of the world; in North America it is encountered mainly in immigrants and recent travelers. Malarial infection of the placenta occurs mainly within the maternal blood (intervillous) space and correlates with maternal parasitemia. The most common causative species is *Plasmodium falciparum*. The microscopic appearance is typically one of chronic histiocytic intervillositis with hemozoin pigment as well as organisms within maternal erythrocytes, although the histologic appearance and parasite burden depend on the timing and chronicity of infection (Fig. 15.12) [10, 11].

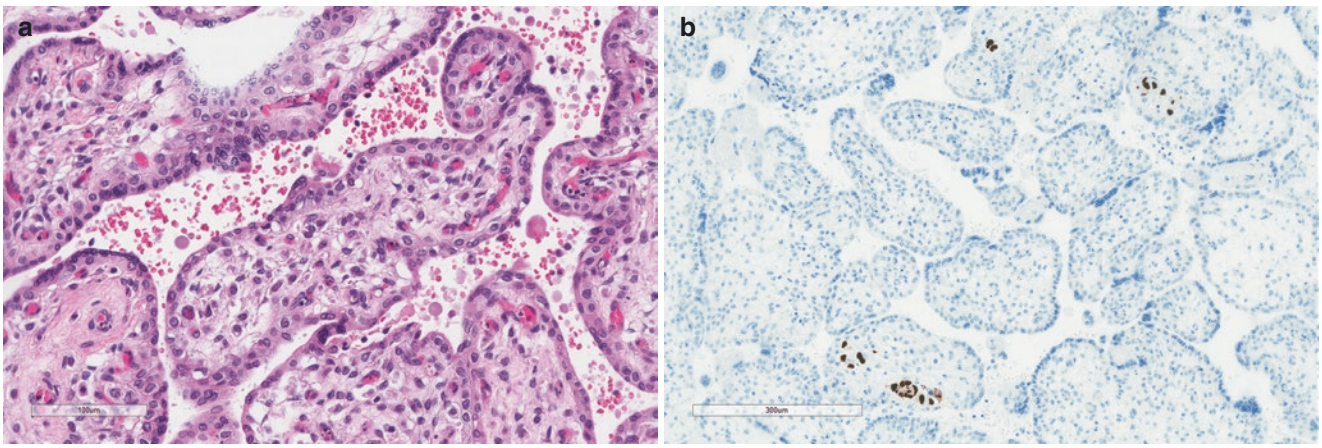

Fig. 15.11 Villitis caused by cytomegalovirus (**a**, original magnification 200×; **b**, immunohistochemical stain for cytomegalovirus showing nuclear positivity, original magnification 100×)

Table 15.4 Syphilis versus cytomegalovirus placental infection

Feature	Syphilis	Cytomegalovirus
Placenta size	Large placenta	Large and pale or small and fibrotic
Inflammatory cell	Histiocyte-predominant	Plasma cell-predominant
Location of inflammation	Villi	Villi
Other histologic features	Proliferative endovasculitis, necrotizing umbilical periphlebitis	Diagnostic intranuclear inclusions
Ancillary tests	Warthin-Starry histochemical stain	CMV immunohistochemical stain (nuclear)

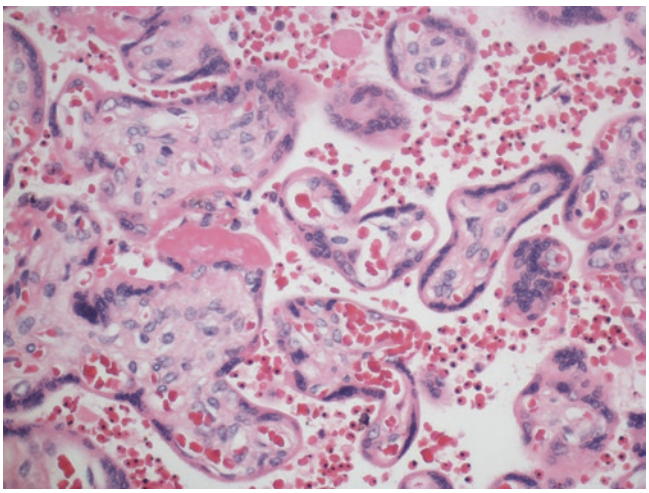

Fig. 15.12 Placental malaria with minimal inflammation but frequent organisms within maternal red blood cells (original magnification 400×)

Transmission to the fetus or neonate is relatively uncommon, but there is a significant risk of pregnancy loss and low birth weight neonates.

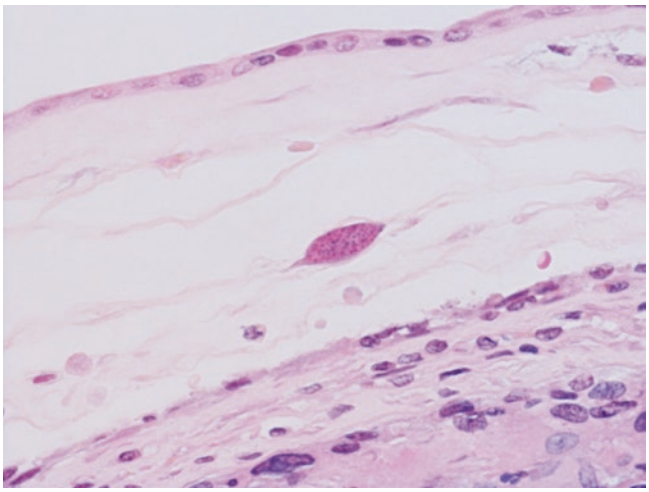

Fig. 15.13 *Toxoplasma* in placental membranes, with edema and chronic inflammation mimicking meconium exposure (original magnification 600×)

Toxoplasmosis of the placenta occurs only rarely despite the ubiquity of the causative organism (*Toxoplasma gondii*). The highest risk for transmission to the fetus occurs at later gestational ages, but infection can cause fetal loss at any stage of pregnancy [12]. The organisms appear within membranes or villi in the form of either tachyzoite-filled pseudocysts or bradyzoite-filled true cysts (Fig. 15.13). Congenitally infected neonates are at risk for low birth weight, as well as eye and brain damage.

15.3 Noninfectious Placental Inflammation

15.3.1 Chronic Histiocytic Intervillositis

This lesion is sometimes also referred to as chronic intervillositis (of unknown etiology; CIUE) or massive chronic

intervillositis. This term implies an unidentified noninfectious etiology that is thought to be immunologic.

15.3.1.1 Clinical Features

Chronic histiocytic intervillositis is seen in placentas of first- and second-trimester spontaneous abortions or from infants with severe growth restriction. There may be a history of recurrent pregnancy loss. There is an association with maternal autoimmune conditions (see Table 15.5) [13, 14].

15.3.1.2 Microscopic Features

The diagnostic feature is collections of histiocytes within the intervillous space (Fig. 15.14). These stain positively with CD68 immunoperoxidase (cytoplasmic). There is often increased perivillous fibrin deposition. These findings may be focal or diffuse. There may be associated chronic villitis, but in this diagnosis, the intervillous inflammation predominates.

15.3.1.3 Differential Diagnosis

A similar intervillous histiocytic infiltrate is typical of placental malaria. Other placental infections should also be considered in the differential diagnosis, although most of these present with either predominantly chorioamnionitis (usual ascending amniotic fluid infection, toxoplasmosis), neutrophilic intervillositis (*Listeria*), or chronic villitis (viruses, syphilis).

Table 15.5 Autoimmune conditions associated with chronic histiocytic intervillositis

Primary antiphospholipid syndrome
Raynaud's phenomenon
Pernicious anemia
Systemic lupus erythematosus
Celiac disease
Sjogren's syndrome

15.3.1.4 Prognosis

There is a high risk of recurrence with repeated pregnancy loss (>50% in some series) [15]. This should be mentioned in the report, for future pregnancy planning and management, since not all clinicians are familiar with the implications of this finding. Preventative treatments using aspirin or steroids have met with varying degrees of success.

15.3.2 Villitis of Unknown Etiology

Villitis of unknown etiology (VUE) is defined as chronic noninfectious lymphohistiocytic inflammation of the terminal villi that can result in fibrotic destruction of the villous stroma and capillaries.

15.3.2.1 Clinical Features

The prevalence of VUE varies widely depending on the diagnostic criteria used, selection of placentas for study, and the obstetric population [16]. In one study, a prevalence of 17.5% was reported in small for gestational age neonates, compared with 11.5% in normal-sized neonates [17].

15.3.2.2 Microscopic Features

A grading system first proposed by Redline is based on the number of villi involved per microscopic focus [18] (see Table 15.6). The inflammation tends to be patchy and can be detected at low to medium power as an area of increased villous cellularity (Fig. 15.15). There is often associated perivillous fibrin deposition and agglutination of villi. On higher power, the infiltrate is typically composed of predominantly maternal lymphocytes of the T lineage, as well as increased numbers of fetal and maternal histiocytes. Rare plasma cells and histiocytic multinucleated giant cells may also be seen; if prominent these should prompt a search for an infectious

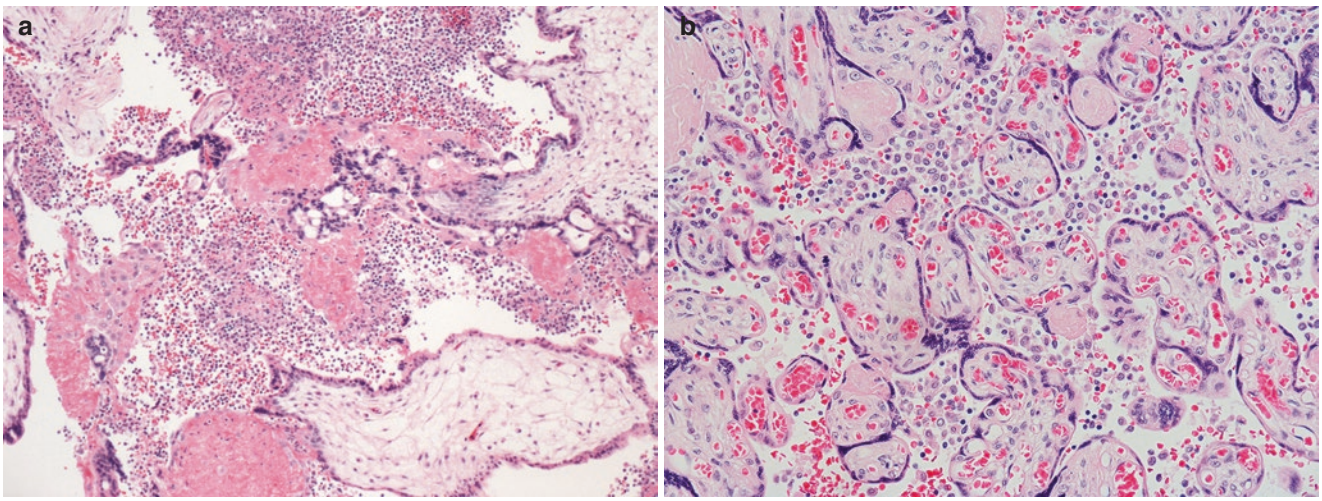

Fig. 15.14 Chronic histiocytic intervillositis in (**a**) early spontaneous abortion and (**b**) fetal demise at term (original magnifications 100× and 200×)

etiology. Evaluation of vessels is crucial to identify the presence of associated vascular damage (similar in appearance to that seen in fetal vascular malperfusion).

15.3.2.3 Differential Diagnosis

The most important consideration in the differential diagnosis of VUE is not to miss a significant placental infection. See Table 15.7 for distinguishing features.

15.3.2.4 Prognosis

High-grade chronic villitis of unknown etiology and villitis with associated vascular damage have been shown to be associated with poor outcome, in particular adverse neurological outcomes [19, 20].

15.3.3 Maternal Floor Infarction and Massive Perivillous Fibrinoid Deposition

Maternal floor infarction (MFI) and massive perivillous fibrinoid deposition (MPFD) are rare entities with overlapping phenotypes characterized by excessive deposition of perivillous fibrin and fibrinoid that obscures the maternal vascular space. The similarity of MFI and MPFD suggests they represent parts of a common pathogenetic spectrum. The underlying etiology of MFI/MPFD is unclear but is likely multifactorial and may involve aberrant maternal immune responses and/or coagulation abnormalities [21].

Table 15.6 Grading chronic villitis of unknown etiology

Low grade	Fewer than ten contiguous villi involved per focus
Focal	Only present on one slide
Multifocal	Present on multiple slides
High grade	At least one focus of inflammation with more than ten involved villi
Patchy	Multiple foci on one or more slides
Diffuse	Involving more than 30% of sampled distal villi

Table adapted from [5]

15.3.3.1 Clinical Features

MFI/MPFD typically presents with intrauterine growth restriction (in up to 100% of cases) and premature delivery (up to 60%); intrauterine demise may occur in up to 50% of affected pregnancies [21]. Oligohydramnios and elevated maternal serum alpha-fetoprotein may be associated prenatal findings. MFI/MPFD may be suspected by the combination of growth restriction, oligohydramnios, and echogenic placenta seen on prenatal ultrasound. There may be a history of infertility.

Table 15.7 Chronic villitis of unknown etiology versus villitis of infectious etiology

Feature	VUE	Infectious villitis
Prevalence	Common	Rare
Gestational age	Most common in third trimester	Any trimester
Inflammatory cells	Lymphocytes, especially T cells, and histiocytes	Histiocytes (including granuloma formation or giant cells) or plasma cells may predominate
Distribution	Patchy, often with basal predominance	Diffuse
Specific findings	None	Viral inclusions or microorganisms
Special stains	N/A	Viral and histochemical stains may be informative

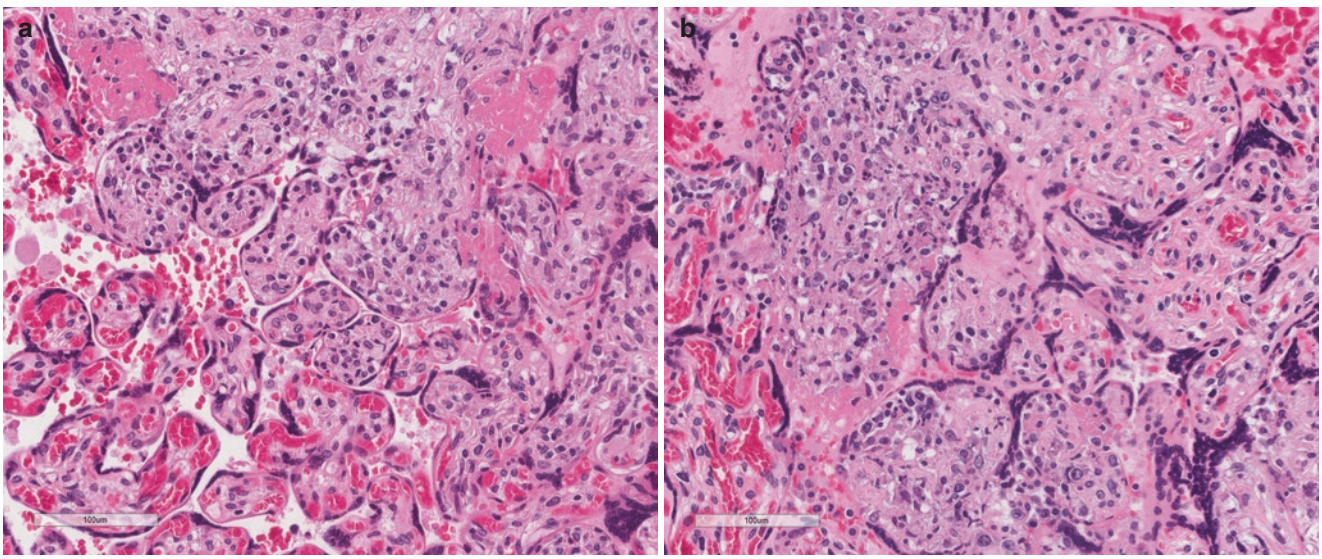

Fig. 15.15 In villitis of unknown etiology (VUE), lymphohistiocytic inflammation of the villi is typically patchy (**a**) and associated with agglutination of distal villi (**b**) (original magnification 200×)

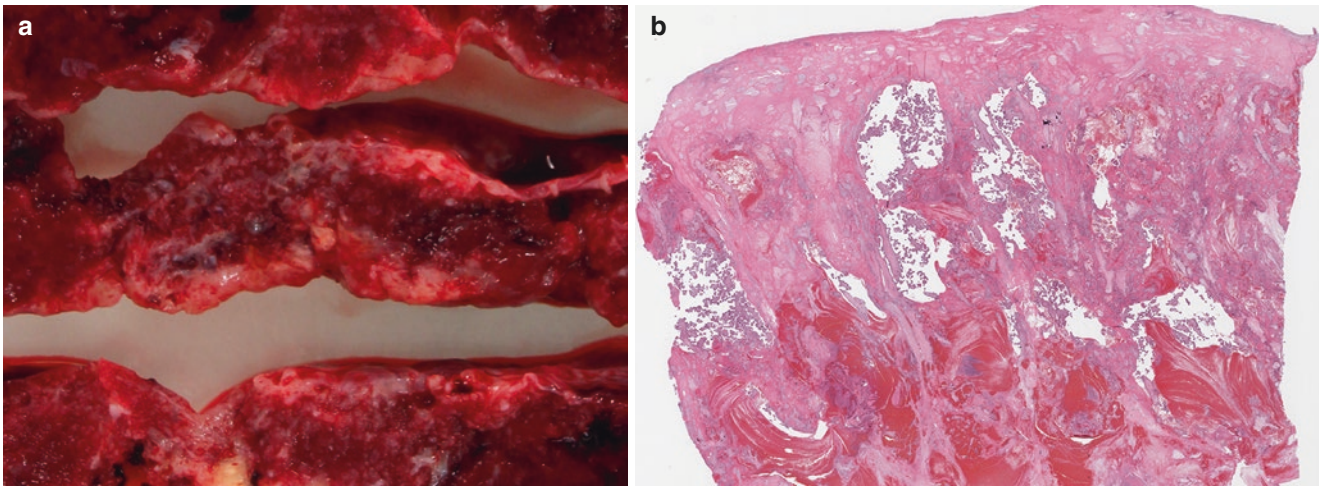

Fig. 15.16 (**a**) In massive perivillous fibrinoid deposition, excess fibrinoid appears and makes the placenta firm with a pattern of lacelike tan fibrinoid. (**b**) Low-power view showing excessive deposition of fibrinoid around villi (original magnification 10×)

15.3.3.2 Gross Features

Placentas affected by MFI/MPFD are usually small for gestational age but may be normal or even large by weight depending on the extent of fibrinoid deposition. Unfixed placentas are unusually firm and stiff, and the maternal surface appears pale. Sectioning reveals dense, firm, tan-white parenchyma in a distribution varying from conspicuous orientation along most or all of the maternal surface (the MFI pattern) to more discrete foci extending from the maternal surface to the chorionic plate and involving 50% or more of the placental disc volume (the MPFD pattern) (Fig. 15.16a).

15.3.3.3 Microscopic Features

Despite differences in distribution, MFI/MPFD both involve extensive perivillous deposition of fibrin and fibrinoid material that fills the intervillous spaces (Fig. 15.16b). Extravillous trophoblast within the fibrinoid material may be prominent. Encasement of villi produces regressive changes including loss of villous trophoblast, vessels, and stromal cells. Inflammatory cells, including lymphocytes and neutrophils, may be seen in the vicinity of degenerating villi. Mass effect disrupts local maternal blood flow leading to the features of maternal vascular malperfusion and development of intervillous thrombi in adjacent parenchyma. Semiquantitative diagnostic criteria for MFI/MPFD based on gross and microscopic findings have been proposed (Table 15.8).

15.3.3.4 Differential Diagnosis

Focal perivillous fibrin and fibrinoid deposition accrue normally in all placentas and should not be overinterpreted as MFI/MPFD; application of diagnostic criteria avoids this potential pitfall. Chronic histiocytic intervillositis can be associated with development of extensive perivillous fibrin, but fibrinoid is not abundant, and intervillous histiocytic infiltrates are present. The gross and microscopic appearance of MFI/MPFD can resemble primary infarction; however, the villi in MFI/MPFD will be separated by abundant fibrin/fibrinoid. VUE and fetal vascular malperfusion may produce similar regressive changes in affected villi, but complete villus encasement by fibrinoid will not be present.

Table 15.8 Diagnostic criteria for maternal floor infarction/massive perivillous fibrin deposition

Pattern	Diagnostic criteria
Classic	Basal fibrinoid involving entire maternal floor At least one slide with fibrinoid thickness ≥3 mm
Transmural	Encasement of ≥50% of villi in at least one slide Non-basal (focal) fibrinoid distribution pattern
Borderline	Encasement of ≥25% to <50% of villi in at least one slide Non-basal (focal) fibrinoid distribution pattern

Table adapted from [21]

15.3.3.5 Prognosis

Although rare, MFI/MPFD is an important entity to recognize because it is associated with poor outcomes and has a significant risk of recurrence in future pregnancies. In addition to those described above, MFI/MPFD is also a risk factor for neonatal death and neurological impairment [22].

15.4 Meconium

Meconium is the sum of ingested amniotic fluid debris, exfoliated gastrointestinal epithelial tissue, and gastrointestinal excretions that can be expelled by the fetus or neonate per anus.

15.4.1 Clinical Features

Meconium release into the amniotic fluid can be associated with fetal stress; however, it also occurs in up to 15–25% of normal term births and is thus not a specific marker of fetal stress. The presence of meconium in the amniotic fluid is more likely with increasing gestational age, and it is a common finding in postdates delivery of both live-born and stillborn infants.

15.4.2 Gross Features

The meconium-exposed placenta may have particularly edematous ("slimy") membranes. Sloughing of the amniotic layer from the underlying chorion is common. Meconium may be apparent on the placental surface. The intensity of overt meconium staining, which appears brownish-green, is dependent on the volume of meconium released and the duration of exposure (i.e., the time interval between fetal passage of meconium and delivery) (Fig. 15.17).

15.4.3 Microscopic Features

Meconium appears microscopically as pale tan-brown amorphous material with a low refractive index within the chorioamniotic tissues. Meconium is caustic and induces reactive changes characterized by cytoplasmic vacuolization, atypia, and eventually necrosis of the amniotic epithelium and edema of the fibrous chorioamnion. It also elicits an inflammatory response, attracting phagocytic placental histiocytes (Fig. 15.18a). The amount of meconium present is generally proportional to the amount of meconium released and time of exposure, but this cannot be reliably inferred from histologic examination.

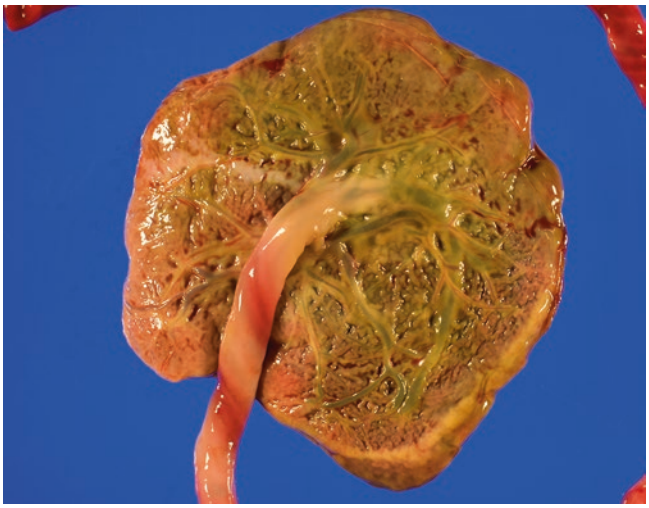

Fig. 15.17 Fetal surface of a placenta with meconium staining, from a case of fetal demise near term

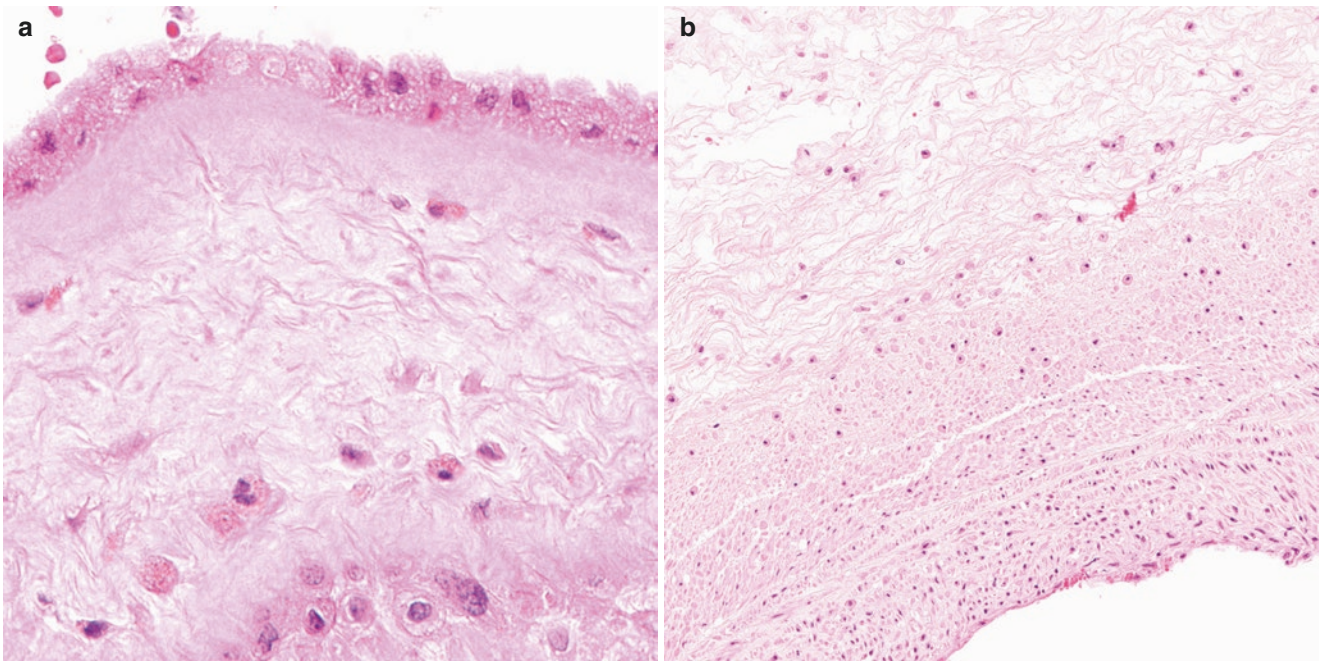

Fig. 15.18 (**a**) Meconium appears as tan, poorly refractile pigment within the chorioamniotic tissues and histiocytes. Amniocyte cytoplasmic vacuolization and edema, seen here, are commonly associated reactive changes (original magnification 400×). (**b**) Meconium extending to the umbilical vessels may induce smooth muscle vasospasm and necrosis (original magnification 100×)

The caustic nature of meconium may also induce vasospasm and vascular medial necrosis in umbilical and chorionic plate vessels, which may have serious consequences for the fetus (Fig. 15.18b). In this situation, meconium and vacuolated meconium-laden macrophages are seen in and around the media of umbilical and chorionic plate vessels.

15.4.4 Differential Diagnosis

Meconium can be differentiated from hemosiderin by the presence of the above-described reactive changes and negative iron special staining. Lipofuscin, which is not commonly encountered in the placenta, resembles meconium by light microscopy and cannot be definitively differentiated by special staining.

Meconium may be artifactually displaced in the potential space between the amnion and chorion after delivery. This can be differentiated from true meconium staining by its distribution, which may involve but is not restricted to the amniotic-chorionic cleft.

15.4.5 Prognosis

Most infants born with pre- or perinatal meconium exposure have no clinical sequelae. Although meconium can be associated with poor neonatal outcomes, it is not an independent predictor, and prognostically relevant placental abnormalities associated with meconium release should be sought. Prolonged intrauterine exposure to thick meconium can rarely result in meconium aspiration syndrome, a form of neonatal respiratory distress caused by massive meconium aspiration. Meconium aspiration syndrome cannot be reliably predicted by placental examination. Meconium-associated vascular necrosis is a significant risk factor for central nervous system damage and neonatal death [20].

15.5 Abnormalities of the Umbilical Cord

Commonly encountered intrinsic abnormalities of the umbilical cord include variance in length, diameter, and extent of coiling, localization of the cord insertion site, and the number of umbilical cord vessels present [23]. Extrinsic abnormalities that may involve the umbilical cord, such as the fetal inflammatory response of amniotic fluid infection syndrome, are considered elsewhere in this chapter. Most umbilical cords are not entirely submitted for examination, and it is important to recognize this limitation in assessment of umbilical cord abnormalities.

15.5.1 Umbilical Cord Length and Diameter

Umbilical cord length increases with gestational age with a normal range at 38 weeks gestation of approximately 35–70 cm [23, 24]. Unusually long umbilical cords pose an increased risk of fetal cord entanglement, true knot formation, and cord prolapse, all of which may obstruct umbilical blood flow with potentially disastrous consequences (Fig. 15.19). Short umbilical cords, especially when less than 10 cm, are associated with limb-body wall complex and fetal developmental abnormalities. Accurate assessment of umbilical cord length is frequently limited by submission of incomplete cords for assessment.

Umbilical cord diameter also increases with gestational age with a normal range of approximately 0.8–1.2 cm at 38 weeks gestation [25]. Ground substance (Wharton's jelly) surrounding the umbilical vessels provides a protective cushion that prevents vascular occlusion (Fig. 15.20a). Narrow umbilical cords have reduced ground substance and are at increased risk of vascular compression and fetal vascular malperfusion (FVM) (Fig. 15.20b). Increased umbilical cord diameter is usually the result of edema (Fig. 15.21). When umbilical cord edema is marked, it may appear as cystic spaces on prenatal imaging; however, these are almost always pseudocystic spaces. True umbilical cord cysts, which most commonly arise from the omphalomesenteric duct remnant, are rare.

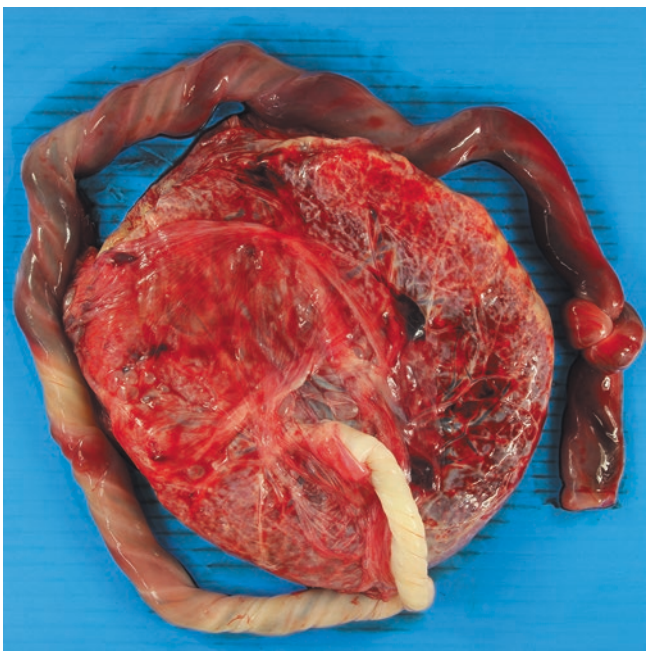

Fig. 15.19 True umbilical cord knot associated with long (84 cm) umbilical cord

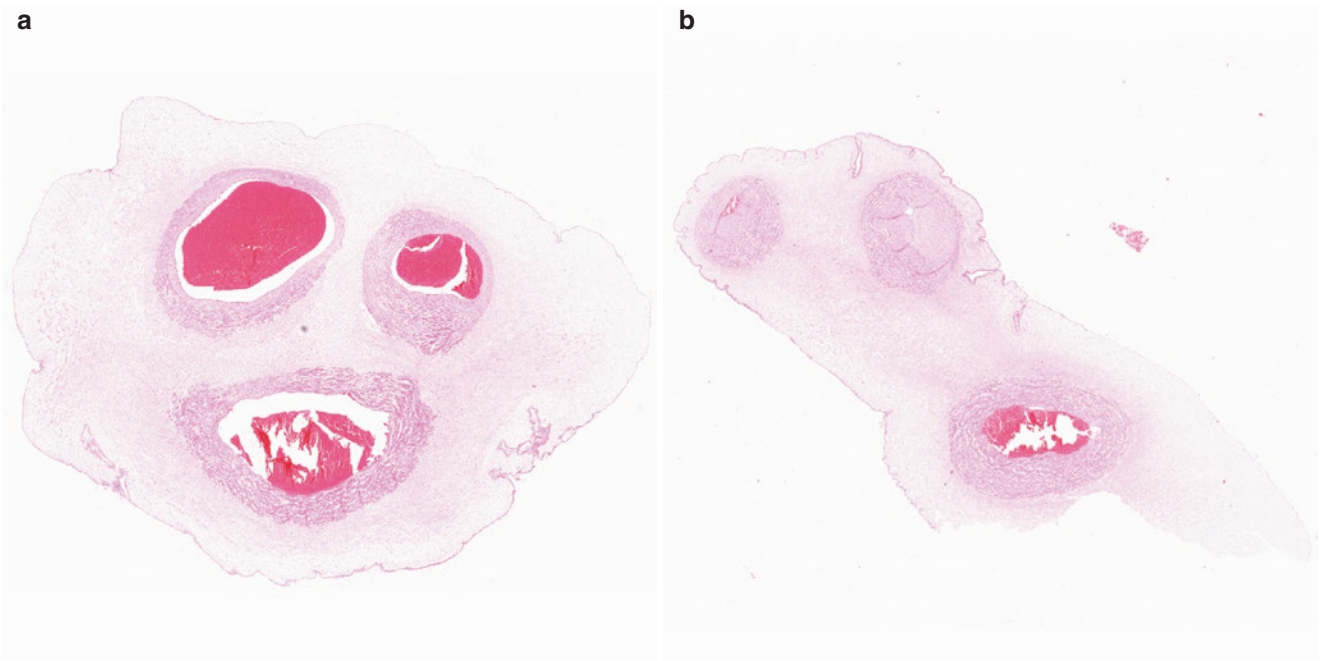

Fig. 15.20 (**a**) Connective tissue and ground substance surrounds and stents umbilical vessels. (**b**) Narrow umbilical cords (0.4 cm at 38 weeks, in this case) lack protective ground substance (original magnifications 100×)

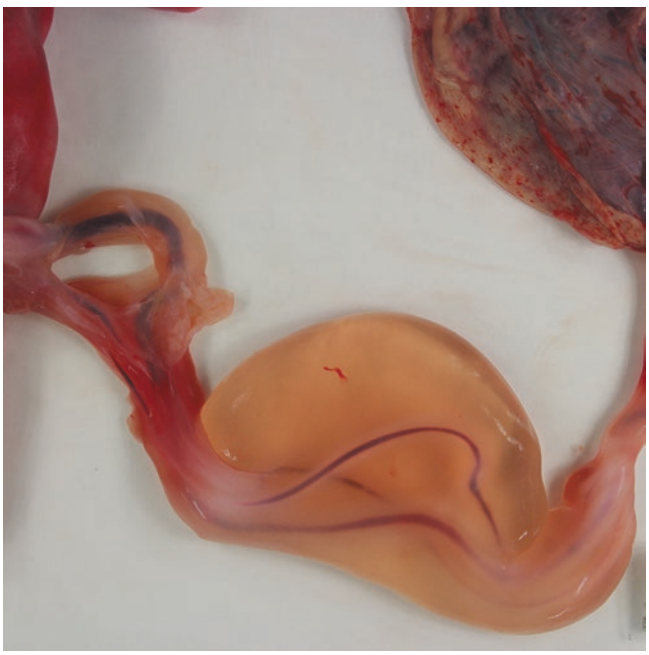

Fig. 15.21 Umbilical cord dilatation typically results from edema

15.5.2 Umbilical Cord Coiling

Like cord length, umbilical cord coiling increases with gestational age. At term, the average number of coils per centimeter (coiling index) is approximately 0.2 [26, 27]. An abnormal coiling index at term has been variably defined between 0.1 and 0.3–0.4; however, what truly constitutes abnormal coiling remains a topic of debate [28].

Both hypo- and hypercoiling are associated with poor outcomes, including fetal demise, developmental abnormalities, aneuploidy, and fetal hypoxia/ischemia [29]. Hypercoiling is associated with FVM, especially when umbilical cord ground substance is depleted allowing compression of adjacent umbilical cord loops (Fig. 15.22) [30]. Hypocoiling is thought to be an indicator of lack of fetal movement and may be associated with fetal abnormalities that inhibit movement, such as neuromuscular disorders.

Artifactual hypercoiling occurs after intrauterine demise and is especially prominent in the setting of moderate and advanced macerative change. Care must be taken when considering hypercoiling as a cause of intrauterine demise in this setting.

15.5.3 Umbilical Vessels

The most commonly encountered abnormality of the umbilical vessels is single umbilical artery. A single umbilical artery (Fig. 15.23) can be associated with developmental abnormalities of the renal and cardiovascular systems, aneuploidy, and increased risk of FVM and related abnormalities.

Fig. 15.22 Umbilical cord hypercoiling (coiling index 0.89 in this example) is a risk factor for fetal blood flow restriction

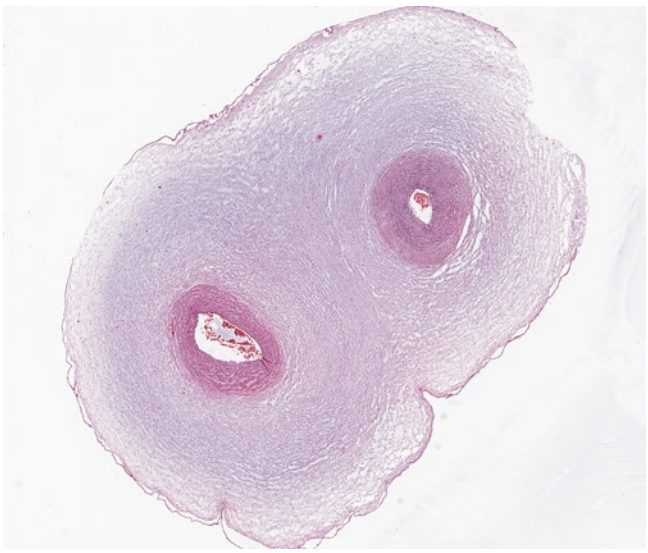

Fig. 15.23 Single umbilical artery

Persistence of the right umbilical vein is very rare and typically associated with multiple fetal anomalies. Umbilical vessel redundancies, which sometimes appear as false knots within the cord, are more common and should not be mistaken for additional umbilical vessels.

15.5.4 Umbilical Cord Insertion

The site of umbilical cord insertion into the placental disc is generally thought to initiate centrally and then "migrate" as the placental disc develops through trophotropism, although some have suggested localization of the umbilical cord insertion site is a stochastic event [31].

Regardless of the physiology, marginal cord insertions, which occur at the placental disc margin (Fig. 15.24a), and velamentous insertions, which terminate in the membranes (Fig. 15.24b), are risk factors for mechanical umbilical blood flow occlusion and FVM. A furcate umbilical cord is characterized by loss of the protective ground substance prior to the cord reaching the chorionic plate (Fig. 15.24c), which exposes the umbilical vasculature to increased risk of mechanical flow occlusion and FVM.

Velamentous and furcate cord insertions are also at increased risk of vascular rupture, which can lead to catastrophic fetal hemorrhage. Marginal and velamentous insertions occur more commonly in the setting of fetal developmental abnormalities and twin-twin transfusion syndrome; in the latter, release of angiogenic factors related to blood flow obstruction may play a pathogenetic role [32].

15.5.5 False Versus True Knots

False knots are outpouchings of the umbilical cord usually containing one or more umbilical vessels; they have no apparent functional significance, even when complex (Fig. 15.25). False knots are associated with vascular redundancy which may mimic extra umbilical vessels on cut sections.

True knots may or may not have functional consequences. True knots contain at least a "half-hitch" that can be tightened by applying traction on the ends. Thus, true knots have a potential of cord accident if the knot is so tight that the umbilical vessels collapse resulting in flow restriction. True knots may be completely asymptomatic; therefore, the identification of one during gross placental examination does not imply that there was a cord accident. Furthermore, cord accidents are dynamic phenomena that require clinical correlation for diagnosis. However, one observation that a true knot may have been sufficiently tightened to cause disruption in vascular flow is the presence of differential congestion on either side of the knot, with one side showing vascular congestion and the other side showing pallor (Fig. 15.26). True knots may also cause chronic vascular flow abnormalities and features of fetal vascular malperfusion.

15.6 Fetal Vascular Malperfusion

Fetal vascular malperfusion (FVM) is a diagnostic term that has been recommended to replace fetal thrombotic vasculopathy and fetal vascular flow restriction to describe abnormalities in fetal perfusion of the placenta [5, 33]. FVM is

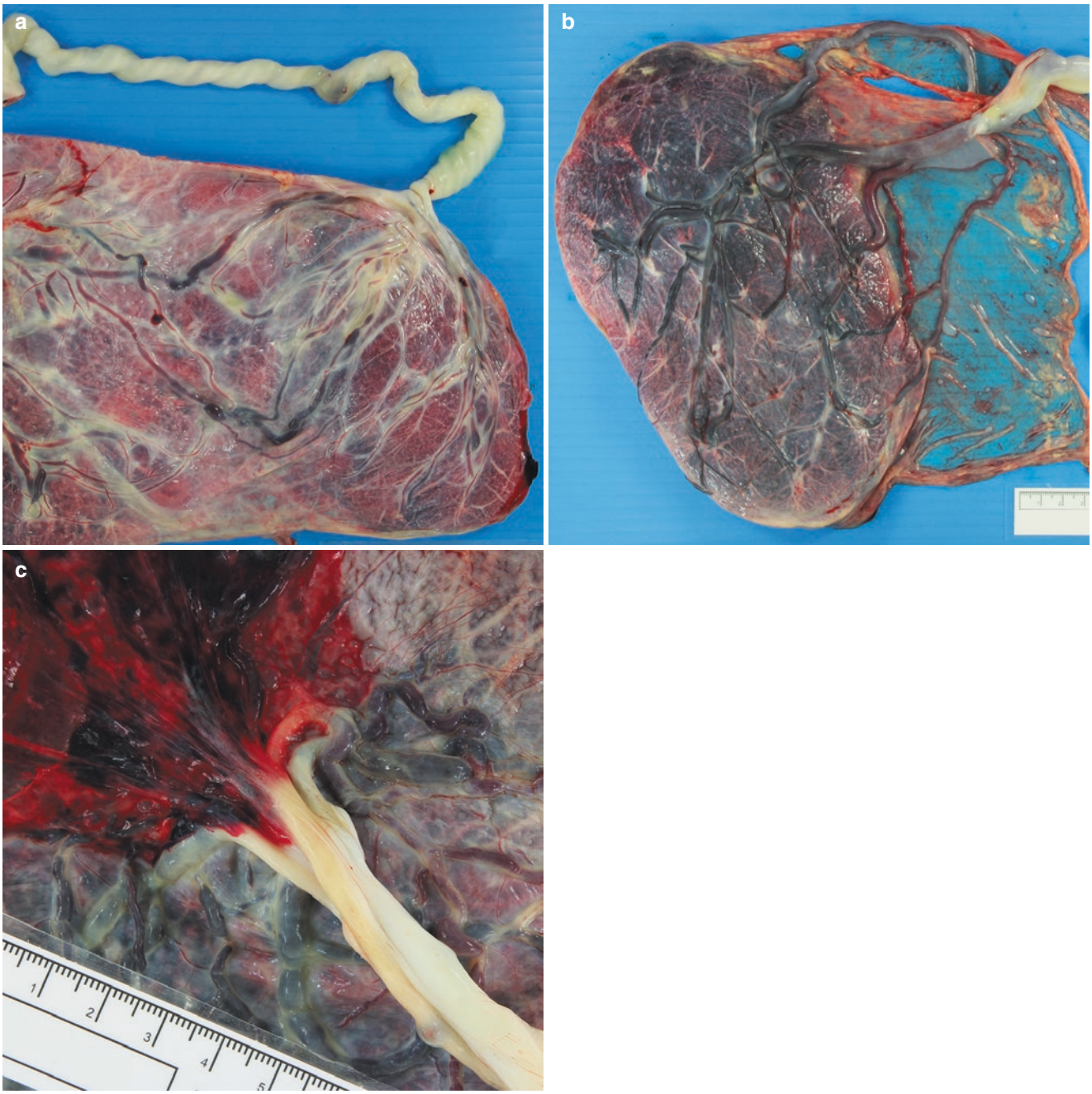

Fig. 15.24 (**a**) Marginal, (**b**) velamentous, and (**c**) furcate umbilical cord insertions are risk factors for mechanical obstruction of umbilical blood flow

defined by pathologic features of thrombosis or ischemia in the fetal vasculature of the placenta.

15.6.1 Clinical Features

Most causes of FVM fall within two groups: obstruction of umbilical cord blood flow and compromised fetal cardiac output. Of these, umbilical cord flow restriction is more common and is usually related to umbilical cord abnormalities (see previous section) and/or presence of oligohydramnios [34]. Compromised fetal cardiac output may be primary, as in structural cardiac defects, or secondary, such as in high-output failure secondary to fetal anemia.

15.6.2 Gross Features

Thrombosis of fetal vessels may be partially or completely occlusive and in larger vessels may be seen grossly. Clusters

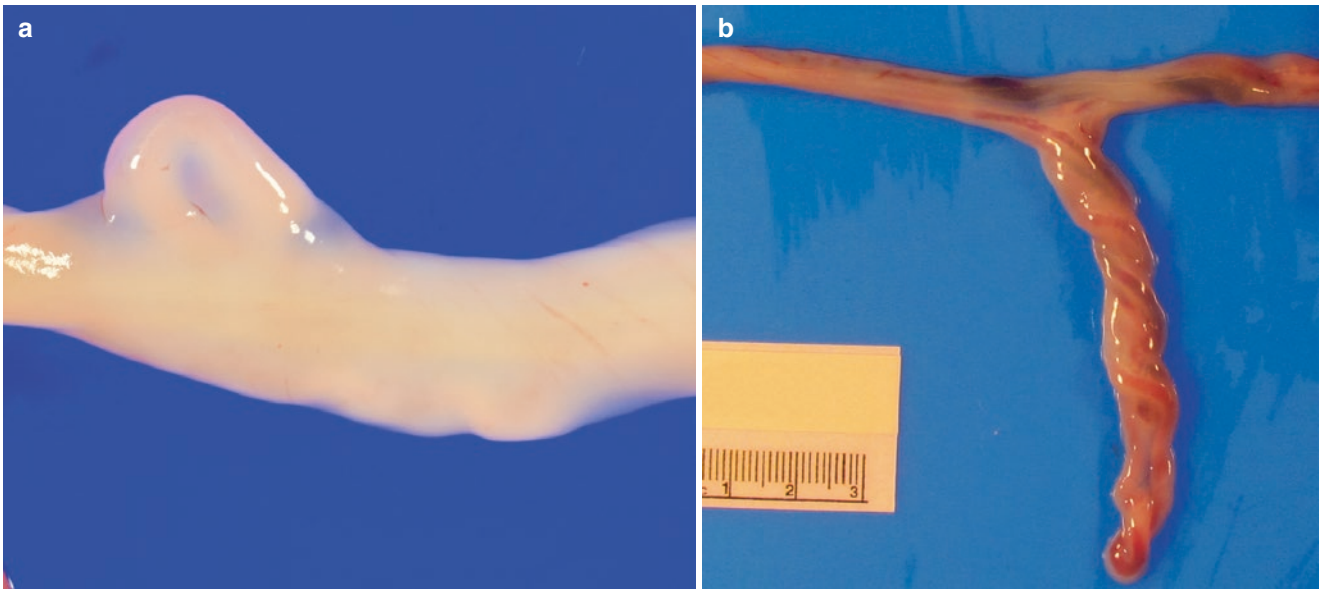

Fig. 15.25 Redundancies, outpouchings, or varices of umbilical vessels are sometimes referred to as false knots. They have no apparent functional significance, whether simple (**a**) or complex (**b**)

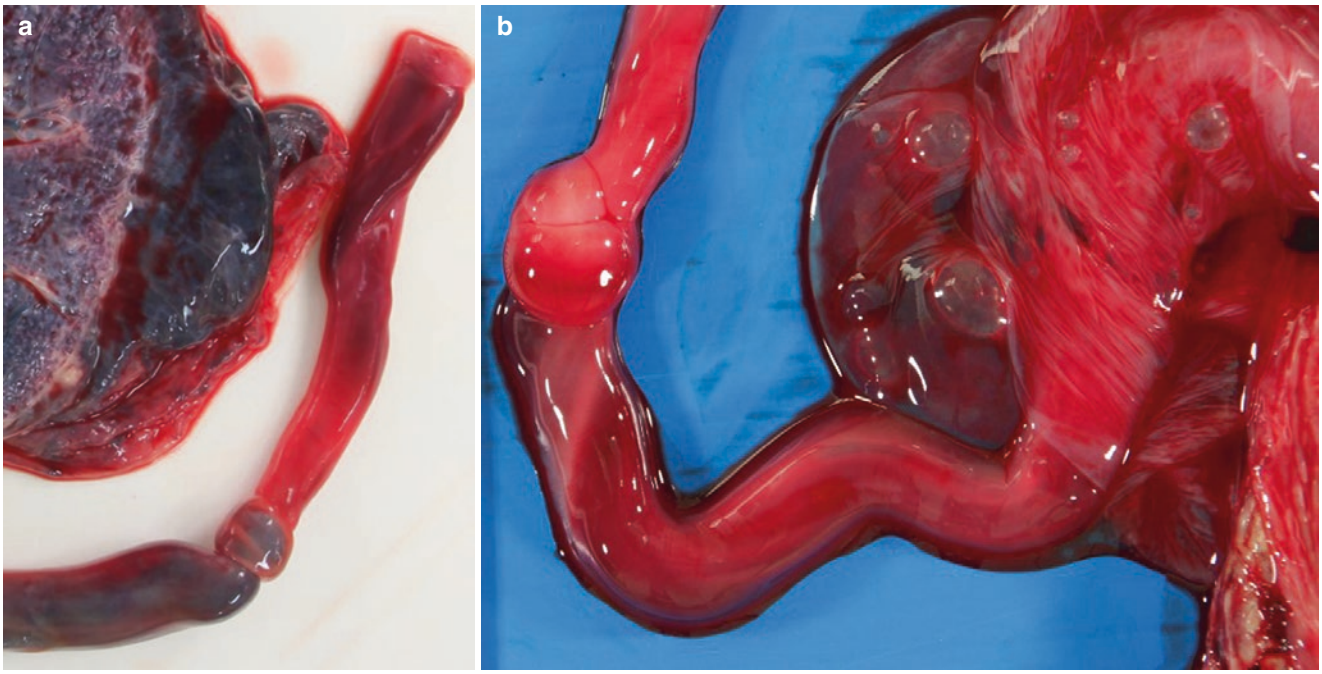

Fig. 15.26 Placentas from intrauterine fetal demises at (**a**) 36 weeks and (**b**) 20 weeks of gestation. Note the true knots in the umbilical cords with differential congestion of vessels on either side

of avascular distal villi may also be seen on gross examination as an area of pale parenchyma. Placentas with extensive FVM may be small for gestational age.

15.6.3 Microscopic Features

Fetal vascular thrombosis is more likely to be recognized on microscopic examination as fibrin layered against a vessel wall in the chorionic plate or stem villus. Histologic features of early true thrombosis include mural fibrin deposition (Fig. 15.27a) with loss of appreciable endothelium between the thrombus and vessel wall (Fig. 15.27b). Over time, nonocclusive thrombosis results in restoration of the vascular lumen and fibrin incorporated into the vessel wall (Fig. 15.28a), while occlusive thrombosis causes luminal obliteration with or without recanalization (Fig. 15.28b). Mural fibrin eventually calcifies, which is a sign of remote thrombosis (Fig. 15.28c).

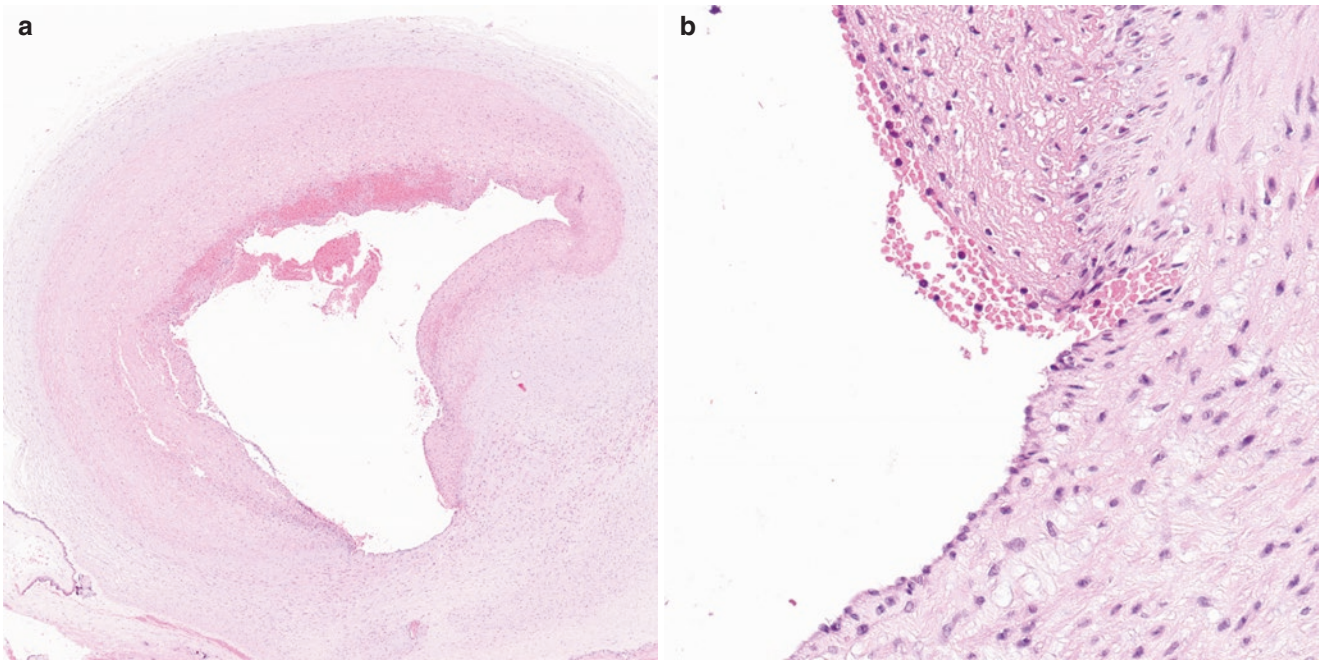

Fig. 15.27 Fetal vascular thrombosis and post-delivery or post-demise intravascular coagulation can both present as mural fibrin collections (**a**, original magnification 20×), but true fetal vascular thrombosis shows loss of intervening endothelium and extension of fibrin into the vascular intima (**b**, original magnification 200×)

Downstream stream effects of FVM present initially as villous stromal hemorrhage and karyorrhexis (Fig. 15.29a), which represent degenerative changes in villous capillaries. With time the villi become avascular (Fig. 15.29b). Hemosiderin resulting from villous stromal hemorrhage may be present in avascular villi. Foci of villous stromal hemorrhage, karyorrhexis, and avascular villi are usually sharply demarcated from adjacent unaffected villi (Fig. 15.30).

Intervillous thrombi can be seen in the setting of FVM where they arise from mixing of maternal and fetal blood related to stromal villous hemorrhage extending into the maternal blood space, but are not specific for FVM. A rare finding in FVM is erythropoietic islands arising in chorionic plate and stem villous stromal tissue adjacent to areas of fetal vascular thrombosis.

15.6.4 Differential Diagnosis

Mimics of FVM include amniotic fluid infection inflammation-related mural thrombi, but these are easily recognized by the intermixed acute inflammatory infiltrate (Fig. 15.31). Avascular distal villi may result from chronic villitis, which can be indistinguishable from avascular villi resulting from FVM. Differentiation of chronic villitis from FVM as the cause of avascular distal villi is based on the lack of an apparent vascular distribution and the presence of inflamed adjacent villi, if present.

Intrauterine fetal demise leads to fetal vascular changes similar to FVM. Pre-demise FVM can be recognized in the setting of fetal demise if temporally incongruous features of FVM are present (e.g., focal intramural fibrin, calcification), but making such a differentiation should be approached conservatively. See the section on late fetal demise, below, for an approach to this differential diagnosis.

15.6.5 Prognosis

The clinical significance of FVM is increased risk of stillbirth, fetal growth restriction, and development of neurological abnormalities [34–36]. Grading schemes have been developed in an attempt to quantify FVM for prognosis. The most recent grading scheme is summarized in Table 15.9. Aside from low and high grades, the findings can be described as either segmental (occurring in the distribution of a chorionic or stem villous vessel) or global (diffuse changes attributable to obstruction of flow to or from an umbilical vessel).

15.7 Maternal Vascular Malperfusion

In the normally developing placenta, uterine artery remodeling begins in the late first trimester, and placental perfusion commences around 12 weeks gestation. Arteries lose their muscular media and become thin-walled. The uterine spiral arteries therefore become a low-pressure arterial supply to the placental disc that is resistant to systemic vasoconstrictive signals. The term maternal vascular malperfusion refers

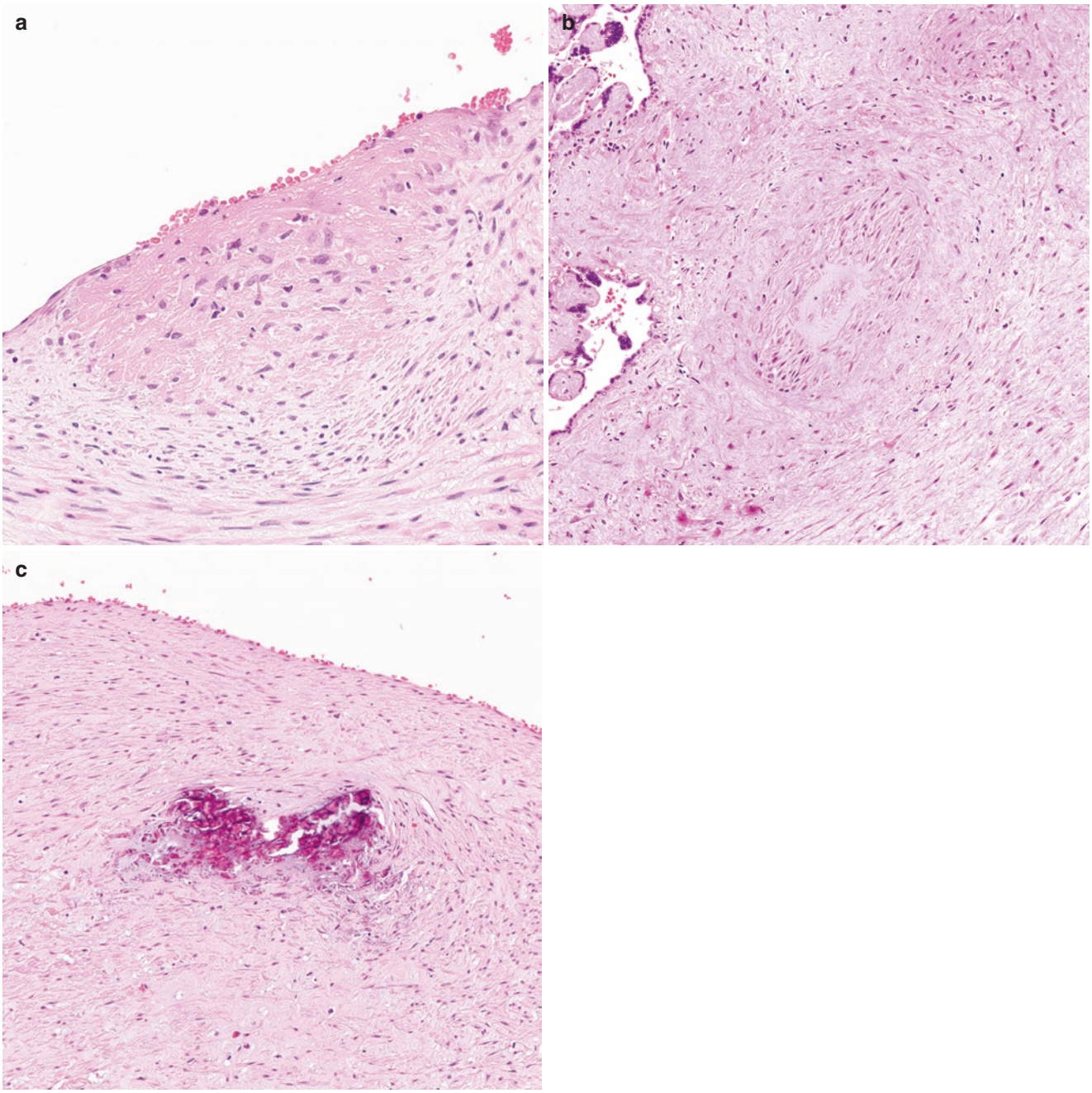

Fig. 15.28 (**a**) The intravascular component of nonocclusive fetal vascular thrombosis disappears with time, but fibrin incorporated into the vascular wall remains (original magnification 200×). (**b**) Occlusive thrombi lead to obliteration of the vascular lumen (original magnification 100×). (**c**) Calcification of intramural fibrin is a marker of remote fetal vascular thrombosis (**c**, original magnification 100×)

to both pathologies of the uterine (decidual) vessels and the downstream effects on placental development [5].

15.7.1 Clinical Features

Pre-existing hypertension, pregnancy-induced hypertension, acute hypertension/preeclampsia, and related disorders are the maternal clinical features typically associated with pathology of the decidual vessels. Hypertensive disorders affect approximately 5–10% of pregnancies and are relatively more common in young and older mothers.

The clinical presentation may reflect acute or chronic failure of adequate provision of oxygen and nutrients to the fetus, such as intrauterine growth restriction, fetal distress, or even fetal demise in utero. Placental abruption is associated with hypertensive disorders of pregnancy.

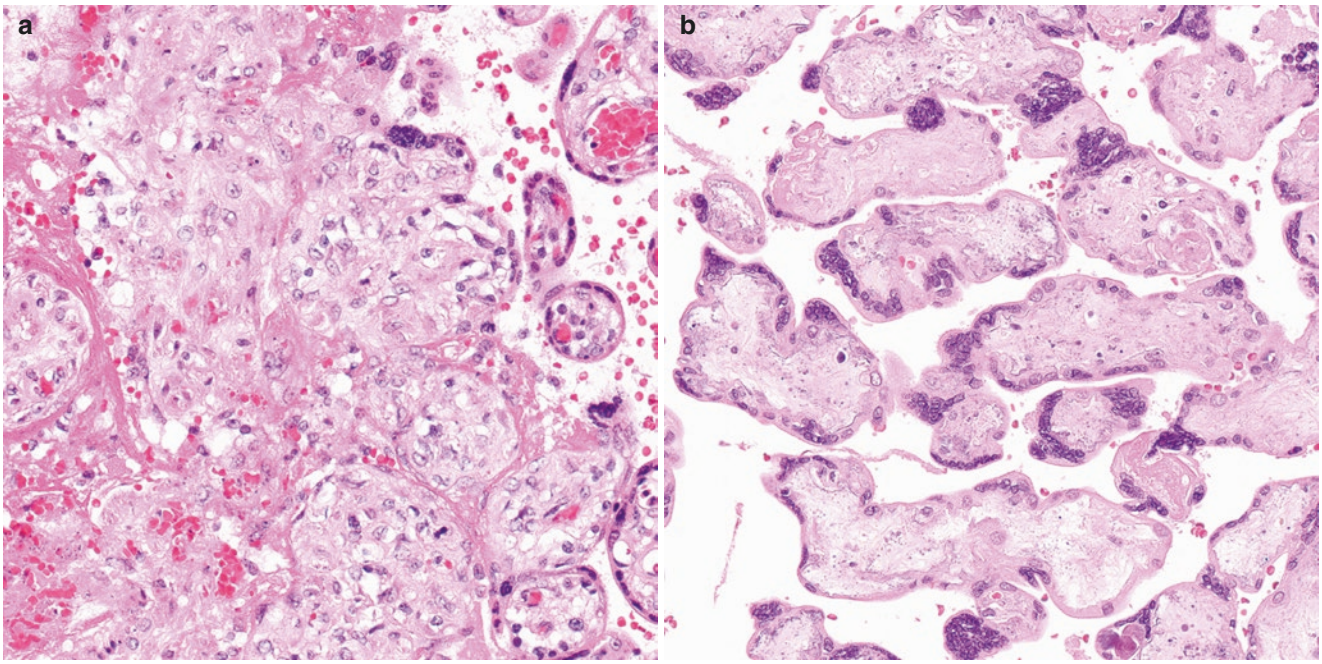

Fig. 15.29 (**a**) Upstream restriction of fetal blood flow results in degeneration of downstream distal villi vasculature. Initially this appears as villous hemorrhage and endothelial apoptosis (villous stromal karyorrhexis) (original magnification 200×). (**b**) Over time these degenerative debris are cleared leaving avascular villi (original magnification 200×)

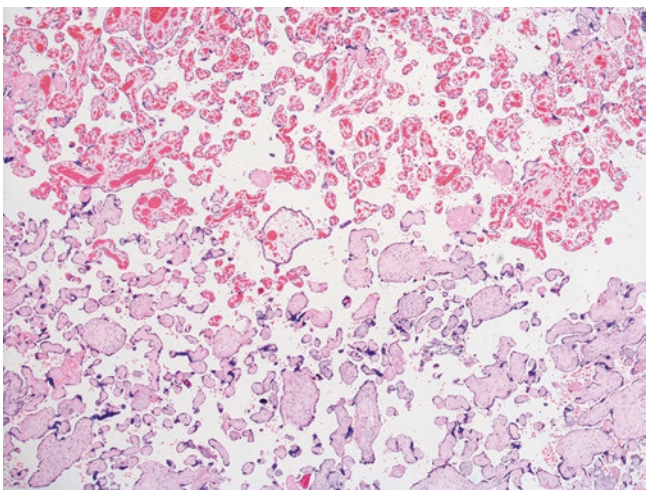

Fig. 15.30 A characteristic feature of fetal vascular malperfusion is a sharp distinction between avascular distal villi and adjacent uninvolved distal villi (original magnification 100×)

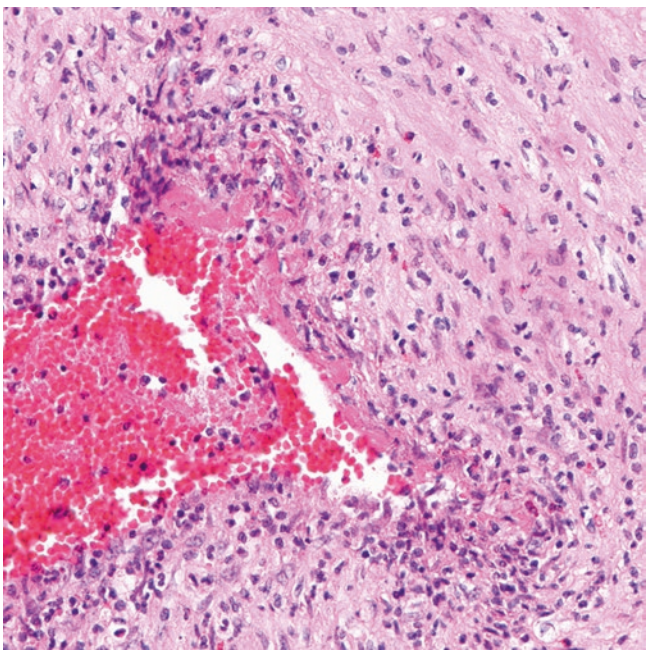

Fig. 15.31 Intense fetal inflammatory infiltrates in the placental chorionic plate vessels can mimic early true fetal vascular thrombosis; however, close inspection usually reveals intervening endothelium and a lack of intramural fibrin (original magnification 200×)

15.7.2 Gross Features

Decidual artery lumens can be identified, by careful inspection, as small dark indentations on the basal surface of the placenta. When choosing blocks of the placental disc for embedding, ideally the basal surface will include a layer of decidua with vessels.

Decidual vasculopathy cannot directly be observed macroscopically, but its downstream effects may be evident, such as placental hypoplasia and infarcts.

15.7.3 Microscopic Features

It should be kept in mind that the vast majority of the uterine arterial system remains unknown to the pathologist examining the placenta, and what few distal branches of the decidual vessels are incidentally included in routinely sampled blocks may provide only hints of occult significant pathology.

15.7.3.1 Normal Decidual Vessels

Normal decidual arteries of the membranous decidua can have very thin muscular walls throughout pregnancy (Fig. 15.32). Normal arteries of the basal decidua normally become more ectatic during the second trimester; trophoblast invasion may be seen. By the end of the third trimester, all arteries underlying the central part of the disc should be completely remodeled, with no identifiable muscular layer.

15.7.3.2 Decidual Vasculopathy

Decidual vasculopathy or arteriopathy includes a variety of abnormalities ranging from incomplete adaptation of vessels to more severe pathologies. Pathology of the decidual arteries correlates imperfectly with the presence of hypertensive disorders of pregnancy and fetal or placental growth restriction.

Table 15.9 Grading of fetal vascular malperfusion (FVM)

Low-grade FVM	One chorionic plate or stem villus thrombus and/or <45 avascular distal villi
High-grade FVM	Two or more chorionic plate or stem villus thrombi and/or ≥45 avascular distal villi, in at least two foci

Adapted from [5]

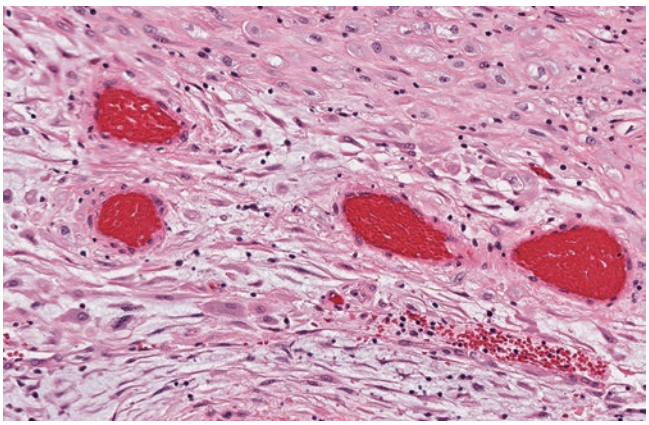

Fig. 15.32 Normal decidual vessels show appropriate adaptation for pregnancy, with complete loss of muscular layer or only a single inconspicuous layer of myocytes remaining (original magnification 200×)

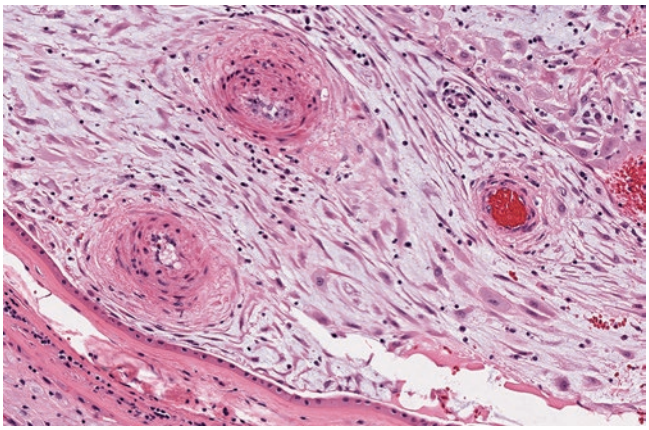

Fig. 15.33 Two decidual vessels with mural hypertrophy, a form of decidual vasculopathy. The muscular walls of the vessels comprise more than one-third the total vessel circumference. Contrast with the normal vessel on the right (original magnification 200×)

The presence of residual smooth muscle in basal decidual vessels near term, with or without persistence of invading trophoblast, indicates *incomplete adaptation for pregnancy*.

Decidual mural hypertrophy describes hypertrophic muscular layers in either membranous or basal decidual arteries and is pathologic. A muscular layer with thickness greater than one-third of the vessel diameter is a useful criterion (Fig. 15.33).

Acute atherosis refers to subendothelial foamy macrophages of an arterial wall in any part of the decidua and may be accompanied by acute fibrinoid necrosis (Fig. 15.34). Unremodeled arteries provide the substrate for the development of this acute lesion. Luminal thrombosis may be present.

Decidual vasculopathy is often accompanied by perivascular inflammation with lymphocytes, although this finding on its own is not diagnostic.

15.7.3.3 Histologic Sequelae

In addition to the vascular changes described above, the following accompanying histologic changes may be seen: accelerated villous maturation or distal villous hypoplasia, villous infarcts, and basal or retroplacental hematomas.

15.7.4 Prognosis

The outcome of pregnancies affected by decidual vasculopathy is variable and depends on severity and timing of pathology. The mechanism of poor fetal outcome is acute or chronic placental malperfusion. Adverse outcomes may include preterm delivery and its complications, fetal distress, placental abruption, perinatal asphyxia with potential long-term neurologic sequelae, growth restriction (classically asymmetric), and perinatal demise [37]. In severe cases of preeclampsia/eclampsia or HELLP syndrome, maternal death can occur [38].

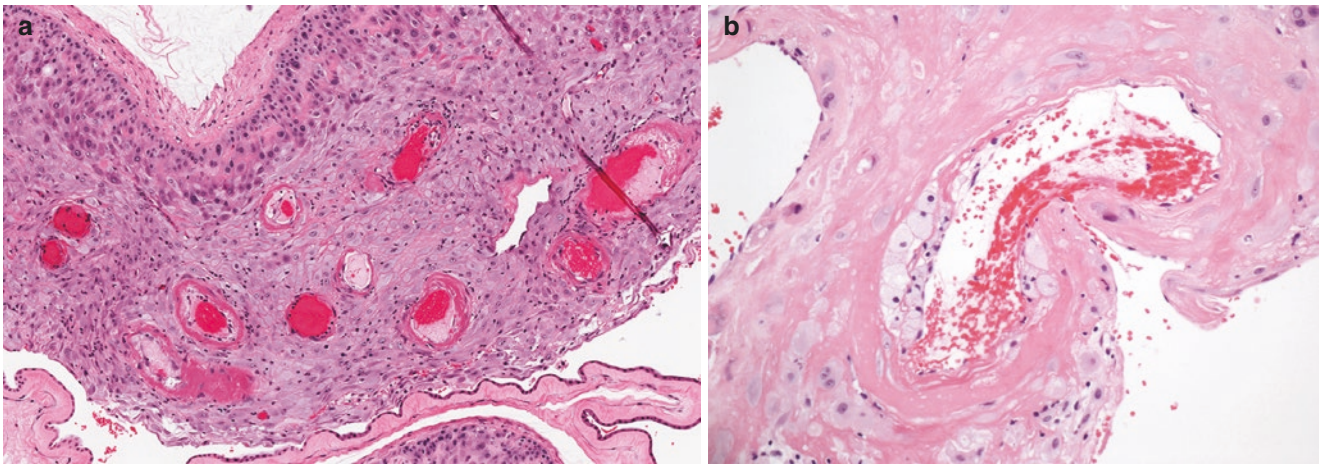

Fig. 15.34 (**a**) Acute atherosis of decidual vessels, with fibrinoid necrosis of the walls and (**b**) foamy macrophages (original magnifications 200×)

There is a risk of recurrence in subsequent pregnancies, especially if preeclampsia was severe or had preterm onset.

15.8 Placental Ischemia and Infarction

Villous ischemia results from inadequacy or interruption of maternal blood supply via the uterine spiral arteries. This is often due to the decidual vascular pathology described in the section above on maternal vascular malperfusion, but can also be caused by maternal conditions not necessarily affecting the arteries themselves. Premature separation of the placental disc from the uterine arterial supply (abruption) also causes ischemia of the supplied portion of the disc.

15.8.1 Clinical Features

The underlying cause may be a primary condition affecting maternal vascular health, such as pre-existing hypertension, diabetic vasculopathy, smoking, cocaine use, thrombophilia, or hemoglobinopathy. Maternal hypotension or shock can also cause ischemia of the placenta. The cause may be primarily a gestational one, as in decidual vasculopathy, or anatomically abnormal placental implantation (e.g., in the lower uterine segment or overlying a submucosal leiomyoma).

Because the normal term placenta has significant excess capacity, small infarcts near or at term, especially near the disc margin, rarely cause problems.

15.8.2 Gross Features

The macroscopic appearance of an infarct, as in other organs, depends on the age of the lesion. Acute infarcts may appear darker than surrounding parenchyma, whereas older infarcts become paler, firmer, and more homogeneous (Fig. 15.35). This tinctorial and textural difference is more evident in the fixed than in the fresh state. They usually involve the basal portion of the disc with variable extension toward the fetal surface.

The size and/or quantity of infarcted parenchyma should be estimated in the gross description, either in absolute terms or as an approximate percentage of placental disc volume. The location should also be noted, as small marginal infarcts are not uncommon at term. It is not necessary to exhaustively sample infarcted parenchyma if the macroscopic appearance is typical; if multiple lesions appear grossly similar, one representative block often suffices. Sampling of surrounding apparently unaffected parenchyma is often more informative.

In general, central infarcts are abnormal since this should be an area of optimized maternal blood supply. Additionally, large infarcts (>1–2 cm), multiple infarcts, and any infarcts in the preterm or undersized placenta indicate inadequacy of utero-placental perfusion.

The placenta may have other gross features of maternal vascular malperfusion, most notably hypoplasia and/or gross evidence of abruption.

15.8.3 Microscopic Features

Histologically, early villous infarcts appear as crowding or collapse of the villous architecture with loss of the intervening intervillous maternal blood space (Fig. 15.36). Infiltration by neutrophils may be a prominent, though transient, feature (Fig. 15.37). As the infarct matures, there is progressive loss of nuclear staining in the villous stromal cells. The syncytiotrophoblastic nuclei usually first appear smudged and eventually also lose their nuclear staining (Fig. 15.38). A remote infarct is a good example of coagulative or white infarction (despite the dual blood supply of the placenta), in which

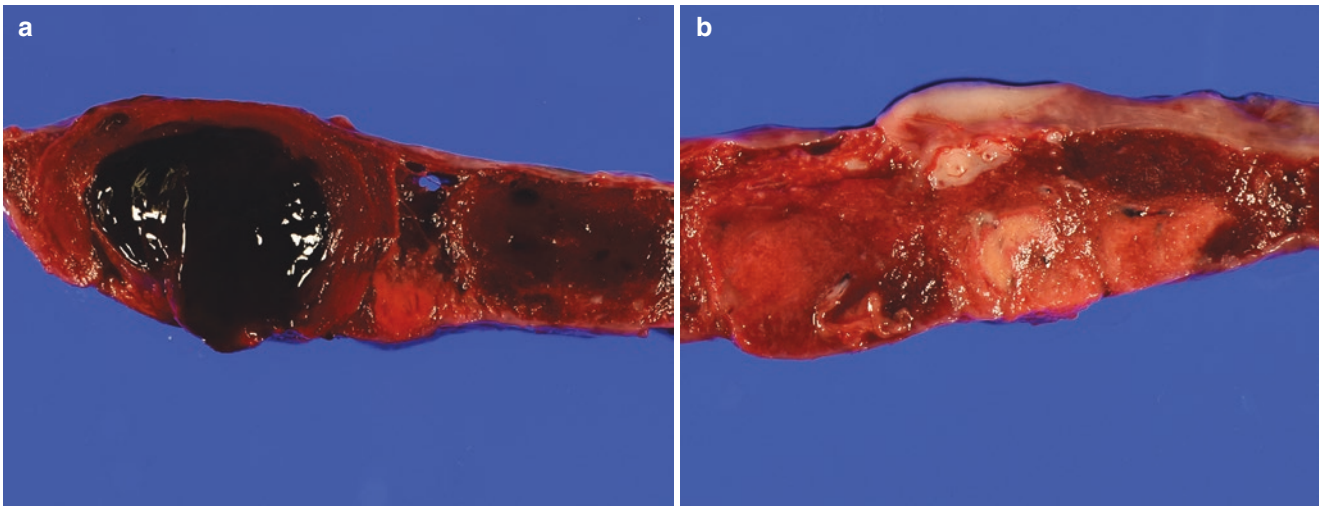

Fig. 15.35 Placental disc cross sections showing multiple infarcts at varying stages, from (**a**) recent (dark red and hemorrhagic) to (**b**) remote (pale and firm)

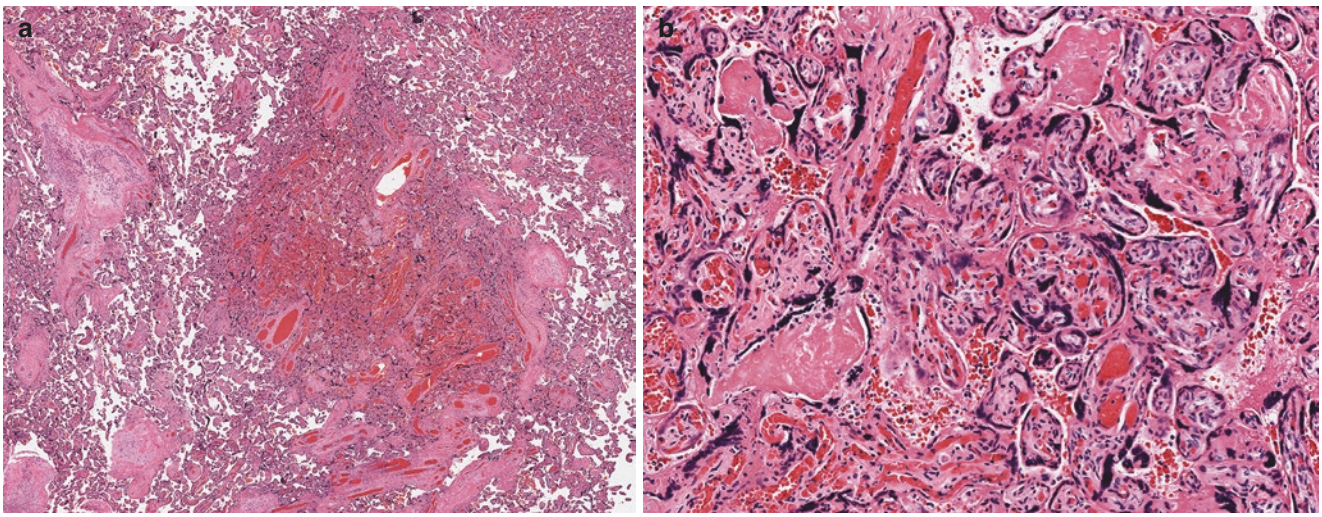

Fig. 15.36 (**a**) At low power, early villous infarcts appear as localized areas of villous condensation and congestion with collapse of the intervillous space (original magnification 10×). (**b**) At higher power, increased syncytial knots and nuclear smudginess are apparent (original magnification 200×)

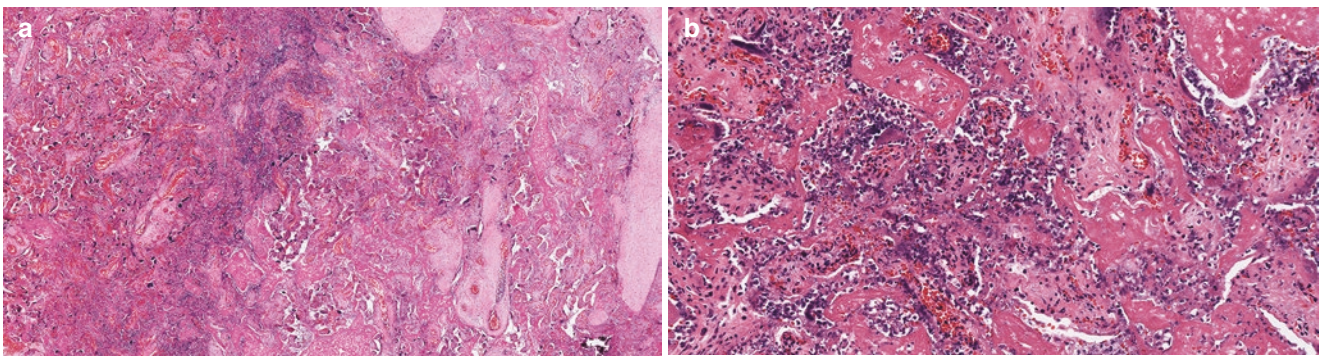

Fig. 15.37 (**a**, **b**) Infarcts may be transiently surrounded by a rim of infiltrating neutrophils which quickly undergo karyorrhexis (original magnifications 10× and 200×)

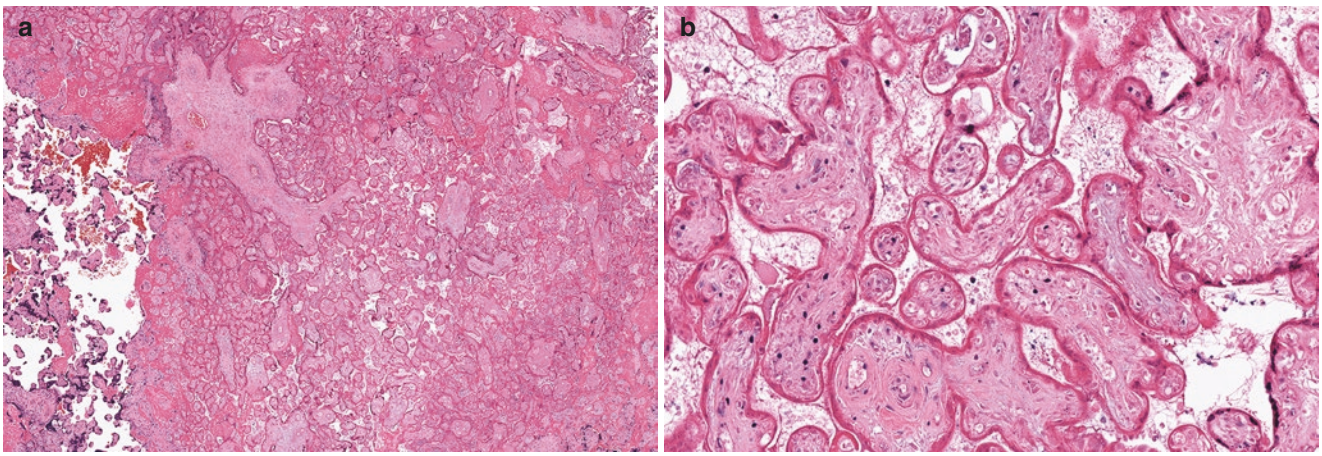

Fig. 15.38 (**a**) Remote infarcts appear as well-defined areas of agglutinated pale villi (original magnification 20×). (**b**) At high power, villous outlines are maintained but nuclei are faded (original magnification 200×)

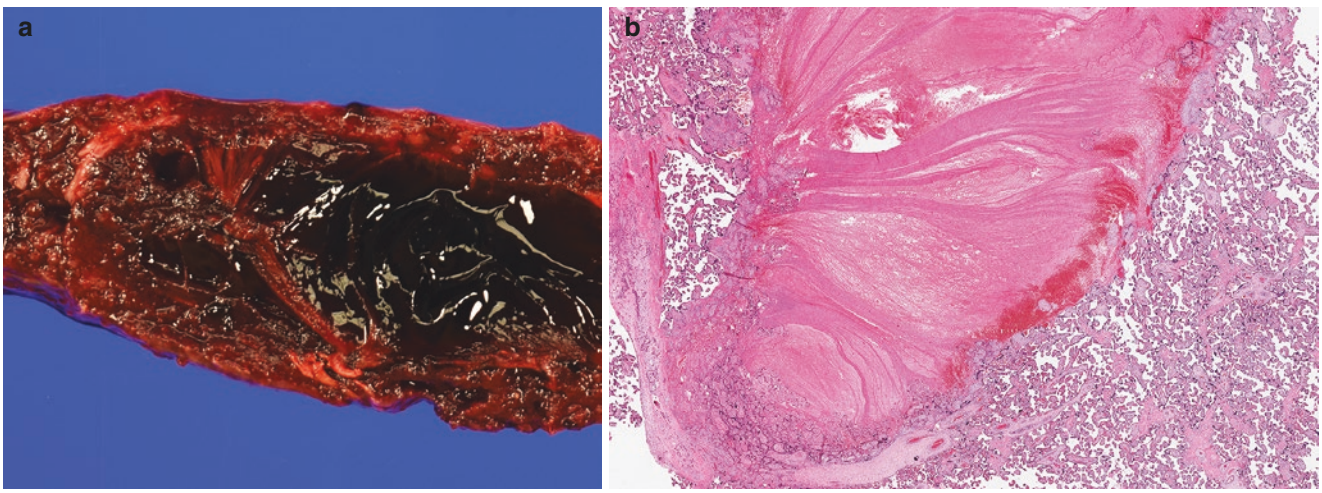

Fig. 15.39 Intervillous thrombi are common discrete parenchymal lesions that can mimic infarcts. On gross (**a**) and microscopic (**b**) examination, however, they can be seen to not involve villi (except peripherally) and have characteristic lines of Zahn (**b**, original magnification 20×)

nuclear detail is lost but architectural outlines of villi remain (so-called ghost villi).

Aside from frank infarction, the villi in an affected placenta may elsewhere show changes of acute and/or chronic ischemia on the basis of inadequate perfusion of the placenta. In severe cases of chronic underperfusion, distal villous hypoplasia may be evident (described in next section). Other changes attributed to ischemia include increased syncytial knots and/or prominent protrusion of syncytial knots on villous surfaces (Tenney-Parker change). Villous agglutination and perivillous fibrin deposition are non-specific features of villous injury that may precede histologic evidence of infarction.

Examination of sampled decidual vessels may or may not disclose evidence of decidual vasculopathy.

15.8.4 Differential Diagnosis

Another relatively common discrete gross parenchymal lesion is the intervillous thrombus (IVT). These are localized areas of intervillous hemorrhage, composed most often of both maternal and fetal blood. They can be distinguished macroscopically from infarcts in that they are often polygonal instead of round, are not typically basally located, and are composed of laminated layers. On microscopic examination they can be seen to be composed of alternating layers of red cells and fibrin with platelets (lines of Zahn). Ischemic or infarcted villi may be present at the periphery, but there are no ghost villi within the center of the lesion (Fig. 15.39).

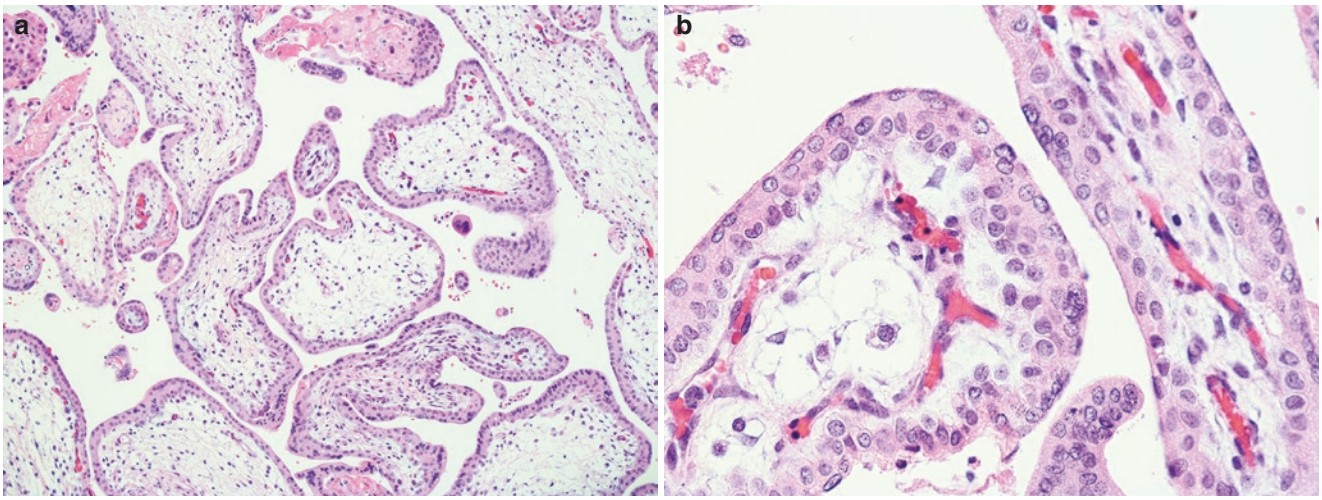

Fig. 15.40 Chorionic villi in the late first trimester are relatively homogeneous in size, shape, and appearance. There are distinct layers of synctiotrophoblast and cytotrophoblast lining the villi, which have edematous-appearing stroma. Developing fetal vessels contain nucleated red blood cells (**a**, original magnification 100×, **b**, original magnification 400×)

15.8.5 Prognosis

The larger the affected portion of the placental disc, the higher the likelihood of adverse fetal or neonatal outcome. Adverse outcomes that can be attributed to acute or acute-on-chronic ischemia include fetal distress, abnormal umbilical blood flow on Doppler ultrasound, perinatal asphyxia, and fetal demise. There may be concurrent clinical evidence of chronic ischemia including fetal growth restriction and gross placental hypoplasia.

15.9 Disorders of Villous Maturation and Development

A reasonably accurate clinical estimate of gestational age must be provided to the pathologist evaluating a specimen. In order to objectively assess disorders of villous maturation, one must be familiar with the range of villous shapes, sizes, and vascularity in the normally developing placenta.

15.9.1 Normal Villous Development

Several texts explain normal development of the villous tree in detail, including the typical appearances, functions, and relationships between the five developmental types of villi: mesenchymal villi, immature intermediate villi, stem villi, mature intermediate villi, and terminal (or distal) villi [39, 40]. For the purposes of this text, we will summarize the expected morphologies in each trimester.

15.9.1.1 Villi in the First Trimester

The very earliest stages (the first few weeks postconception) of placental development will not be covered here, as these specimens rarely produce clinically recognized abortions sent to surgical pathologists. The chorionic villi most often encountered in first-trimester products of conception are from mid- to late-first trimester (Fig. 15.40). The villous sizes at this stage are more similar to each other than the greater variability seen in later gestation. The villi are lined by abundant syncytiotrophoblast and a continuous recognizable layer of underlying cytotrophoblast cells. The stroma is loose and edematous-appearing with few mesenchymal cells. Early developing vessels may be inconspicuous or may contain abundant nucleated fetal red blood cells.

15.9.1.2 Villi in the Second Trimester

Over the course of the second trimester, the villous stroma becomes less edematous and more collagenized, with progressively more vascularization (Fig. 15.41). As the villous tree branches, there is more variability in villous size.

15.9.1.3 Villi in the Third Trimester

In the third trimester, the population of smallest (most distal) villi becomes more numerous, and the average size of distal villi becomes smaller (Fig. 15.42). The nuclei of the syncytiotrophoblast tend to pile up in so-called syncytial knots; the cytotrophoblast is inconspicuous. These distal or terminal villi eventually contain numerous capillary cross sections. At term, a typical distal villus contains numerous capillary cross sections comprising more than half of its total area, as well as multiple vasculosyncytial membranes, where capillaries abut

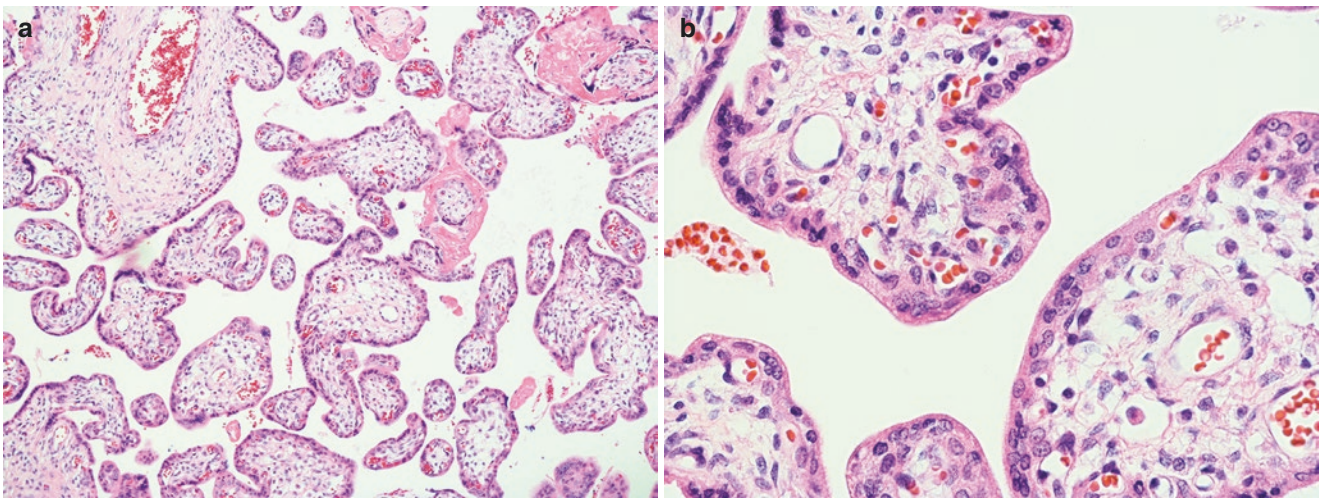

Fig. 15.41 Villi in the second trimester undergo further branching, resulting in greater variability of size. Villi become more collagenized and more vascularized (**a**, original magnification 100×, **b**, original magnification 400×)

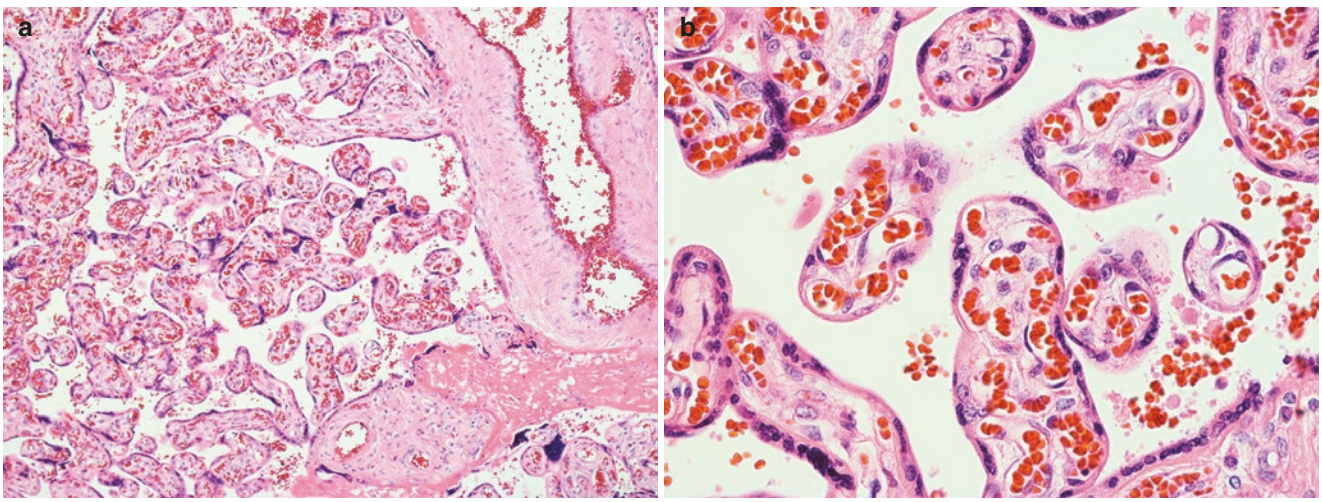

Fig. 15.42 These term villi are mostly small distal villi with abundant capillaries and vasculosyncytial membranes. Larger villi are stem villi containing conducting vessels (**a**, original magnification 100×, **b**, original magnification 400×)

the thinned syncytiotrophoblast directly (the site of maternal-fetal gas and nutrient exchange). The larger villi are stem villi containing conducting venous and arterial branches with no vasculosyncytial membranes; these often become lined by a layer of fibrin rather than syncytiotrophoblast.

15.9.1.4 Assessment of Villous Maturation

Villous maturity cannot be assessed in a single field, but instead is a gestalt based on multiple complete disc cross sections. Appearance of the villi at the margin and immediately under the chorionic plate may give a false impression of accelerated maturation. Likewise, maturation should not be assessed immediately adjacent to a discrete pathologic lesion.

It is important to remember that the changing appearance of various villous types exists on a spectrum; even occasional immature villi may be encountered at term. One should be familiar with the expected villous populations seen across a range of gestational ages, in order to recognize aberrations of development or maturation.

The most helpful way to assess villous development is by comparison with whole-slide normal age-matched controls. Single textbook figures usually do not suffice to show the full range of villous morphologies and sizes at any gestational age.

15.9.2 Delayed Villous Maturation (Distal Villous Immaturity)

The pathophysiologic mechanism of this disorder of placental development is not clear. The paucity of mature vasculosyncytial membranes typical of the term placenta is thought to impair oxygen and nutrient exchange required by the fetus approaching term. The diagnosis of delayed villous maturation/distal villous immaturity is usually reserved for immature-appearing placentas at or near term (>34 weeks)

15.9.2.1 Clinical Features

The most important maternal risk factor for this finding is diabetes, either pre-existing or gestational [41]. See below for a discussion of the effects of diabetes on placental development. Villous immaturity can also be seen with maternal obesity and/or excessive weight gain in pregnancy (possibly indicating occult hyperglycemia not diagnosed as gestational diabetes).

15.9.2.2 Gross Features

These placentas are often (but not always) large for gestational age. Although the neonate is often large, the placenta may be relatively even more so, with a decreased fetal-placental weight ratio. The cord may also be thick.

15.9.2.3 Microscopic Features

The villi overall appear immature relative to the documented gestational age (Fig. 15.43). Specifically, there will be too many immature intermediate villi and not enough mature distal villi with well-developed capillarization. The distal villi that are present are on average larger than normal. The villous stroma may appear edematous and/or hypercellular.

In some placentas delayed villous maturation is accompanied by chorangiosis, which is defined as diffusely hypercapillarized distal villi (≥10 capillary cross sections per terminal villus, seen in ≥10 villi in ≥10 fields over 3 sections) (Fig. 15.44).

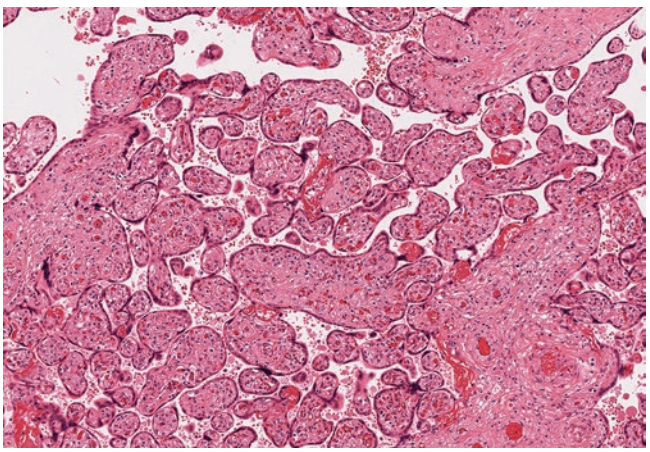

Fig. 15.43 Delayed villous maturation/distal villous immaturity: this term placenta shows a deficiency of mature distal villi with vasculosyncytial membranes (original magnification 100×)

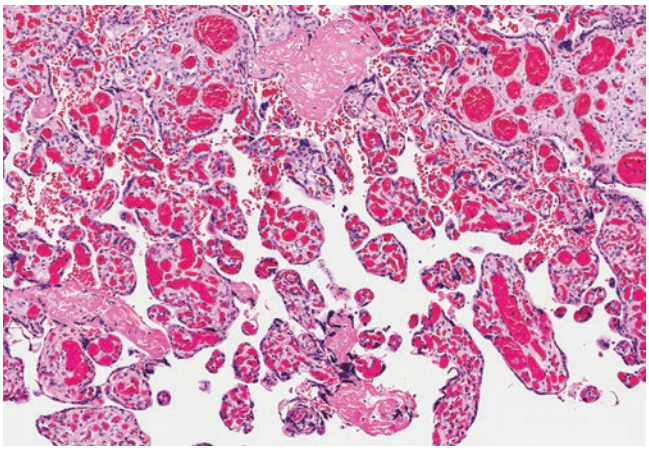

Fig. 15.44 Chorangiosis refers to diffuse hypercapillarization of distal villi, usually defined as at least ten capillary cross sections per distal villus, seen in at least ten fields in at least three different sections (original magnification 100×)

15.9.2.4 Differential Diagnosis

The differences may be subtle and in general diagnostic reproducibility is poor [42]. The differential diagnosis should always include incorrect documented gestational age.

15.9.2.5 Prognosis

Delayed villous maturation is typically (but not exclusively) seen in combination with large-for-dates or frankly macrosomic fetuses. These large but immature fetuses of diabetic mothers have increased risk of demise in utero near term and a small risk of neonatal death [41]. Distal villous immaturity is probably not an independent risk factor for poor outcomes, once maternal and fetal factors are taken into account.

15.9.3 Accelerated Villous Maturation

Accelerated villous maturation is a term sometimes applied to placentas with a subjective appearance of accelerated maturation, but falling short of the criteria for distal villous hypoplasia (see below) (Fig. 15.45). Features that may be abnormal for gestational age include predominance of inappropriately small distal villi and increased syncytial knots.

15.9.4 Distal Villous Hypoplasia

This villous phenotype is the result of chronic malperfusion (from any cause). It is thought that the fundamental

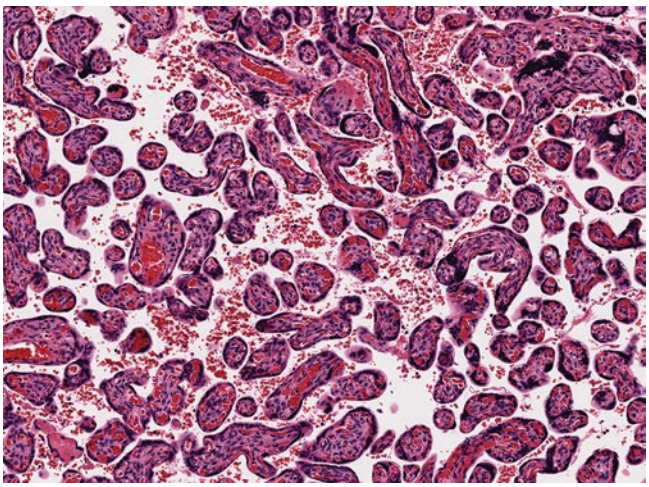

Fig. 15.45 Accelerated villous maturation: in this 30-week gestation placenta, the distal villi appear similar to term distal villi (original magnification 100×)

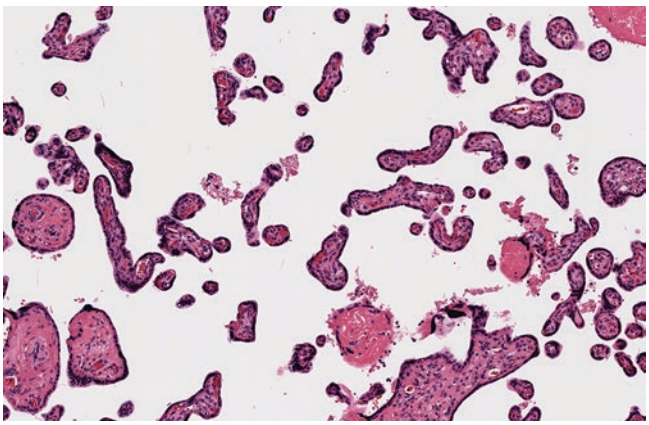

Fig. 15.46 Distal villous hypoplasia in a grossly hypoplastic near-term placenta. The villi are small and sparse (original magnification 100×)

development problem is one of deficient branching of the developing villous tree [43].

15.9.4.1 Clinical Features

In its well-developed form, distal villous hypoplasia (DVH) is strongly associated with severe preeclampsia with preterm onset. Other hypertensive disorders of pregnancy are also risk factors. This phenotype has also been associated with autoimmune disorders, severe malnutrition, and smoking.

Distal villous hypoplasia is often associated with fetal growth restriction, particularly early-onset growth restriction, which may be severe. There may be abnormal umbilical arterial Doppler studies and fetal distress with indicated preterm delivery.

Distal villous hypoplasia may be a discordant feature in twin or multiple gestations. In monochorionic twins complicated by twin-to-twin transfusion, the donor twin's placental villi may appear hypoplastic. In dichorionic twins with discordant growth, the smaller twin may have a disadvantaged placental implantation site with poorer perfusion and DVH.

15.9.4.2 Gross Features

These placentas are most often small for gestational age. They may have other stigmata of acute or chronic ischemia or preeclampsia, including infarcts and retroplacental or marginal hematomas. In cases associated with inadequate perfusion due to non-ideal anatomic site of implantation, the umbilical cord insertion may be marginal or velamentous.

15.9.4.3 Microscopic Features

The distal villi appear very small and sparse (Fig. 15.46). Frequently seen are long skinny distal villi studded with hob-nailed syncytial knots. Stem villi appear relatively more prominent due to the paucity of distal villi. Side-by-side comparison with an age-matched normal control will frequently highlight the differences. In normal placentas, an appearance similar to DVH can often be seen immediately below the chorionic plate, due to the relative hypoxia in this part of the maternal circulation. The diagnosis of distal villous hypoplasia should be reserved for those cases in which the findings are diffuse or, at minimum, involve a large area (>30%) of one slide.

Associated findings may include ischemic villous changes, infarcts, and other features of maternal vascular malperfusion or preeclampsia.

15.9.4.4 Prognosis

There is a significant risk of perinatal morbidity and mortality, resulting from the combination of low birth weight and prematurity.

15.9.5 Villous Development in Chromosomally Abnormal Placentas

Except in the case of molar pregnancies, the gross and microscopic features of chromosomally abnormal (aneuploid) placentas are non-specific and have poor interobserver diagnostic concordance [44–46]. Hydrops is not uncommon in some aneuploidies, but is non-specific; see the section on hydrops, below. Gestational trophoblastic disease is discussed in another chapter.

15.9.5.1 Clinical Features

These placentas may be encountered in a variety of clinical scenarios, including termination of pregnancy for fetal anomalies with or without prenatally confirmed aneuploidy, unexpected fetal demise in any trimester, or unexplained fetal growth restriction. Examination of the fetus by complete postmortem examination and chromosomal studies will

usually be more informative than placental examination in isolation.

15.9.5.2 Gross Features

Placentas may be either very small for gestational age (which is typical for trisomy 18 and digynic triploidy), small-to-appropriate for gestational age (trisomy 21), or large for gestational age (monosomy X with hydrops, molar pregnancy).

15.9.5.3 Microscopic Features

Villi may appear completely normal. Not uncommonly, villous development is diffusely but non-specifically altered. In general, clues to aneuploidy include accelerated *or* delayed villous maturation, variable villous morphology in different areas ("villous dysmaturity"), villous edema, villous stromal hypercellularity, complex villous outlines, predominance of intermediate villi, trophoblast (pseudo)inclusions, and stippling of trophoblast basement membranes (Figs. 15.47 and 15.48). None of these features have individually been shown to predict aneuploidy (and all are occasionally seen in diploid gestations), but in the correct clinical setting, the gestalt may be useful in suggesting chromosomal testing to explain a pregnancy loss or anomalous fetus.

15.9.6 Placental Mesenchymal Dysplasia

Placental mesenchymal dysplasia is a specific placental phenotype sometimes referred to as "pseudo-mole" [47]. It is usually characterized grossly by large placental size, large-caliber thick-walled and tortuous chorionic plate vessels, and hydropic villi (Fig. 15.49). Some of the microscopic features (edema and cisterns) resemble those of molar pregnancy, but rather than trophoblastic hyperplasia, abnormal vascular development predominates, including thick-walled stem vessels as well as chorangiomatous capillary proliferations (Fig. 15.50). This type of placental maldevelopment is classically associated with Beckwith-Wiedemann syndrome, although other genetic, imprinting, and chromosomal etiologies have been described [48].

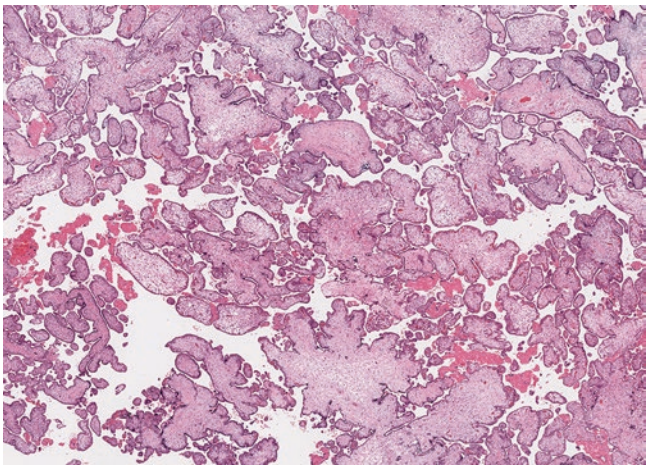

Fig. 15.47 Aneuploid placenta (trisomy 18) at mid-gestation, with immature convoluted villi (original magnification 20×)

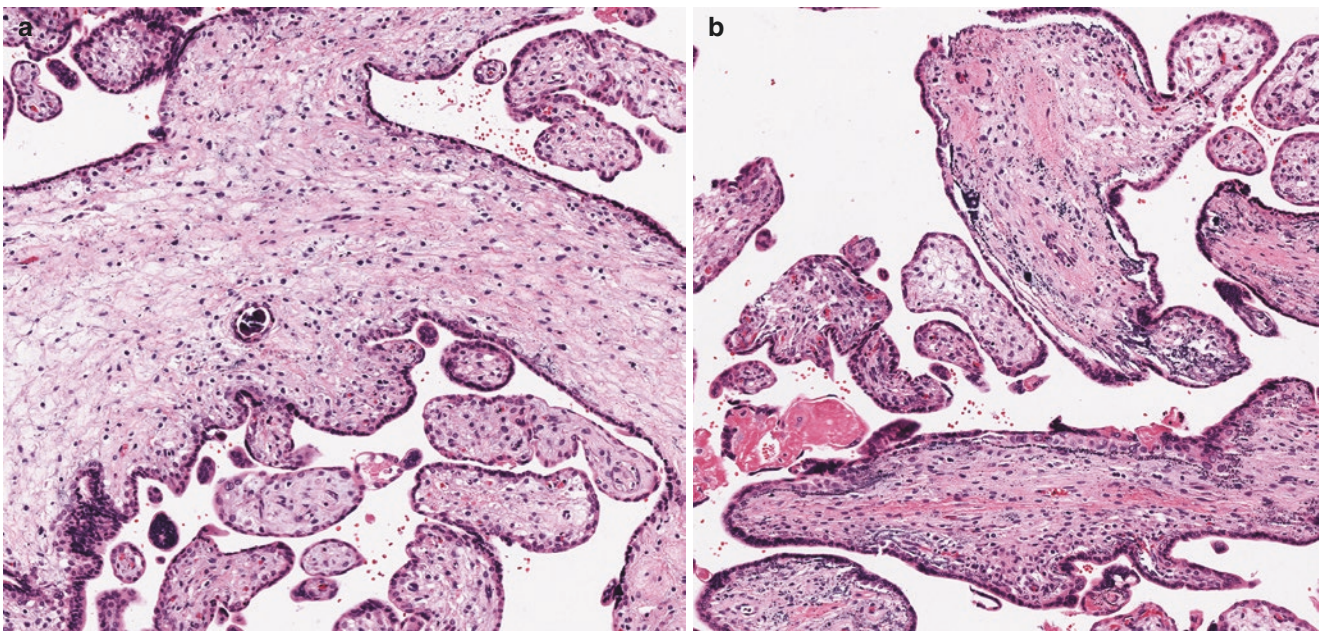

Fig. 15.48 Non-specific features that can be seen in aneuploid placentas are (**a**) trophoblast pseudo-inclusions and (**b**) stippling and edema (manifested as clefting beneath the trophoblast basement membrane) (original magnifications 100×)

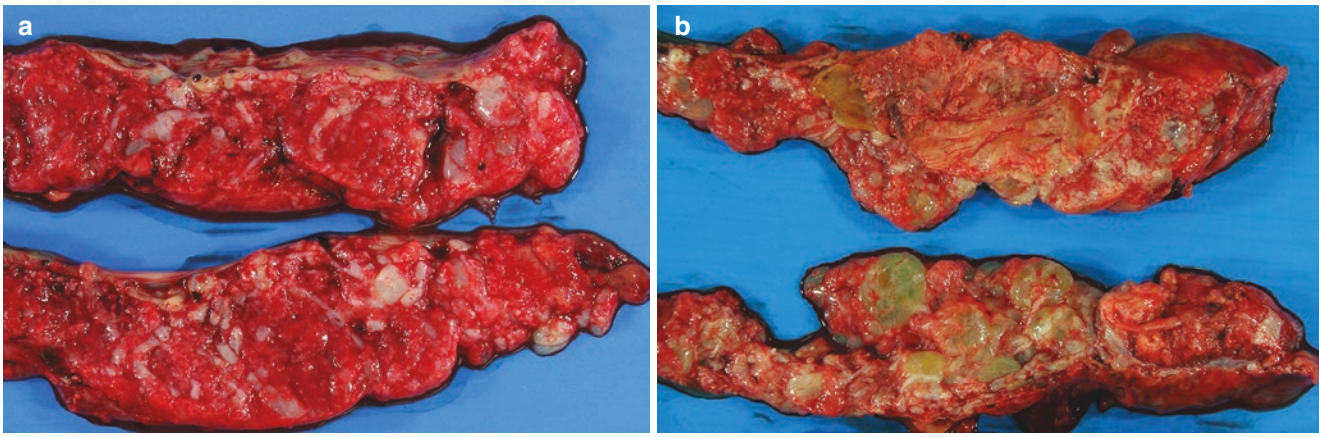

Fig. 15.49 Two cases of placental mesenchymal dysplasia with abnormal vessels and cyst-like masses, at (**a**) 32 weeks and (**b**) 35 weeks. Both neonates had congenital anomalies, but neither had genetically confirmed Beckwith-Wiedemann syndrome

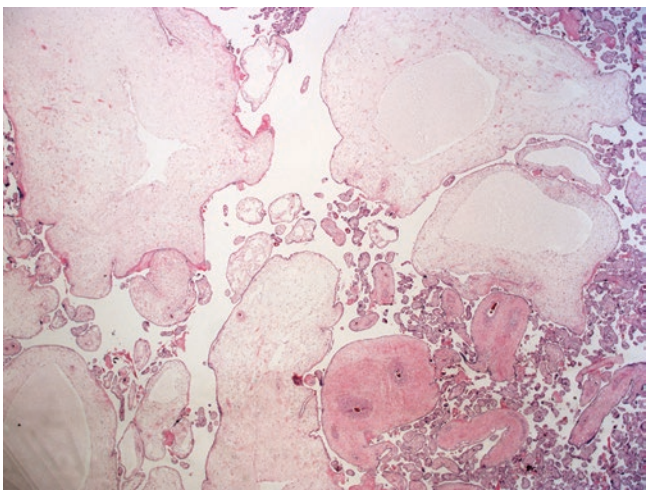

Fig. 15.50 Placental mesenchymal dysplasia. The cystic lesions seen grossly correspond to edematous stem villi (original magnification 20×)

15.9.7 Effects of Maternal Diabetes on Placental Development

15.9.7.1 Clinical Features

Diabetes in pregnancy is either pregestational type 1 diabetes mellitus, pregestational type 2 diabetes mellitus, or gestational (pregnancy-induced) diabetes mellitus. The effects on placental and fetal development depend on duration of disease, degree of chronic diabetic visceral vasculopathy, glycemic control during pregnancy, and whether there is also hypertension. Maternal diabetes causes structural and functional changes in the placenta; none of these are sensitive nor specific.

15.9.7.2 Gross Features

The most common gross alteration is increased placental weight and central thickness, which are commonly observed in placentas of mothers with either pregestational diabetes or gestational diabetes [49]. Good insulin control can mitigate the excessive placental weight [50]. Placentas from women with long-standing diabetes with significant end-organ damage may however be small for gestational age. Single umbilical artery has also been associated with diabetic gestations [51].

15.9.7.3 Microscopic Features

Placentas from diabetic mothers show increased angiogenesis and distal villous immaturity/delayed villous maturation [49]. Chorangiosis is also common. See description of both of these patterns above (Sect. 15.9.1).

15.9.7.4 Prognosis

Fetuses of diabetic mothers are at increased risk of macrosomia, congenital anomalies, neonatal respiratory distress, neonatal hypoglycemia, early spontaneous abortion, as well as late (term or post-dates) stillbirth. A long-term implication for the maternal patient diagnosed with gestational diabetes is an estimated 50% risk of developing type 2 diabetes within 20 years [52].

15.10 Abruption

Placental abruption refers to premature separation of the placenta from the decidua, and can be divided into three categories based on the associated pathological findings and clinical context: acute, subacute, and chronic.

15.10.1 Clinical Features

Maternal risk factors for abruption include eclampsia/preeclampsia, vasoactive drugs (e.g., cocaine), and trauma. Acute and subacute abruption classically present as

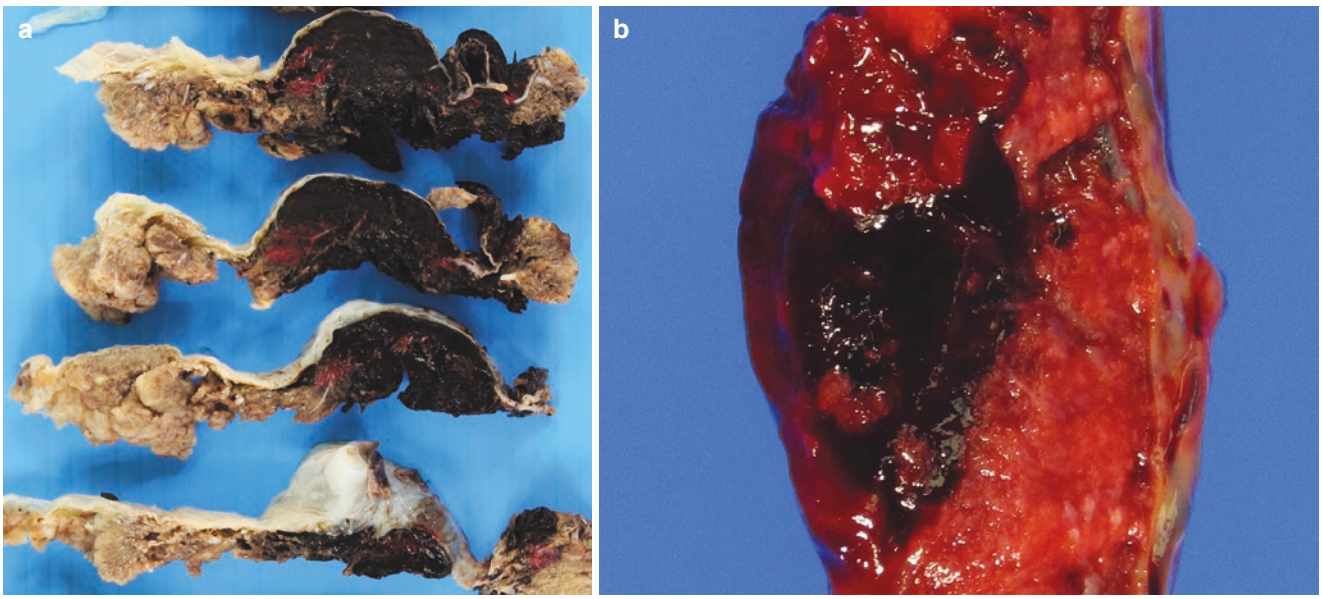

Fig. 15.51 Acute placental abruption is associated with retroplacental hematoma formation that deforms the maternal surface (**a**, formalin-fixed, **b**, fresh)

acute abdominal or back pain and tetanic rigidity of the uterus. The bleeding, which is of maternal origin as the decidual arteries bleed into the retroplacental space, may be overt or concealed. Abruption may also be asymptomatic in the mother but manifest as unexplained fetal distress or preterm labor. Ultrasound can be useful for the diagnosis and follow-up of abruption in the non-emergent setting [53].

Chronic abruption differs from acute/subacute abruption in that it is not severe enough to prompt spontaneous or iatrogenic delivery. Chronic abruption usually has a history of excessive, persistent, or intermittent vaginal bleeding without the other symptoms and signs of acute abruption.

15.10.2 Gross Features

Deformation of the maternal surface of the placenta by a retroplacental hematoma is virtually pathognomonic of acute or subacute abruption (Fig. 15.51), but is not a sensitive marker. Chronic abruption may be recognized grossly as fibrin collections typically seen around the disc margin (Fig. 15.52). Hemosiderin discoloration of the placental membranes may be apparent and when prominent and diffuse should prompt diagnosis of diffuse chorioamniotic hemosiderosis (Fig. 15.53), which is thought to be related to chronic periplacental separation and related hemorrhage [54].

15.10.3 Microscopic Features

Acute abruption does not produce specific histopathological changes, which by definition take time to develop.

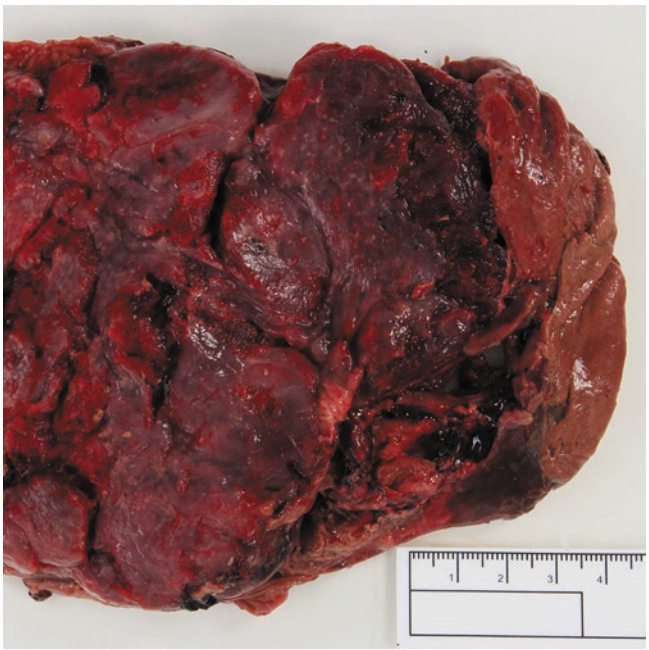

Fig. 15.52 Chronic abruption-associated marginal thrombus demonstrating the typical friable maroon-tan appearance

Subacute abruption is defined by the presence of histopathological features of early placental infarction in the clinical setting of acute abruption. Microscopic features of early placental infarction include terminal villous aggregation, loss of syncytiotrophoblast chromatin detail, and increased syncytiotrophoblast cytoplasmic eosinophilia (Fig. 15.54).

Chronic abruption is characterized by periplacental hemorrhage(s) showing degenerative changes including

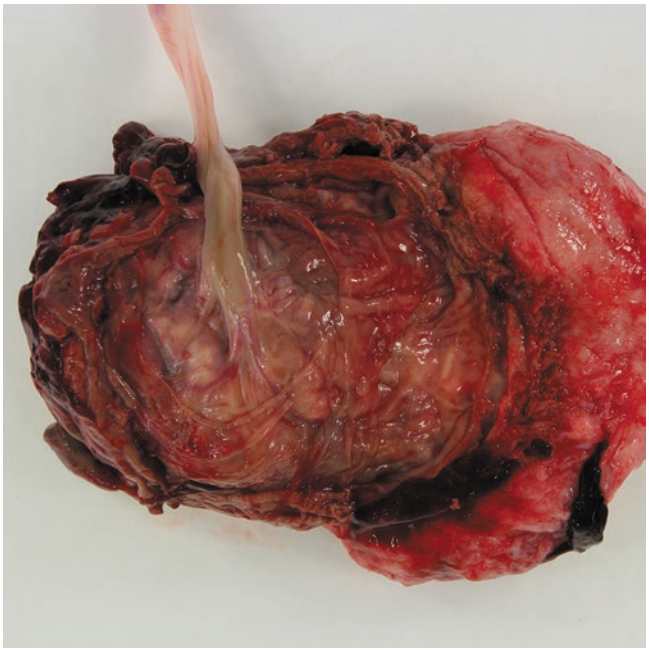

Fig. 15.53 Extensive chronic abruption leads to grossly visible heme breakdown products that stain the placental membranes green-brown (diffuse chorioamniotic hemosiderosis). Marginal thrombus is a typical concurrent finding and is present in this example

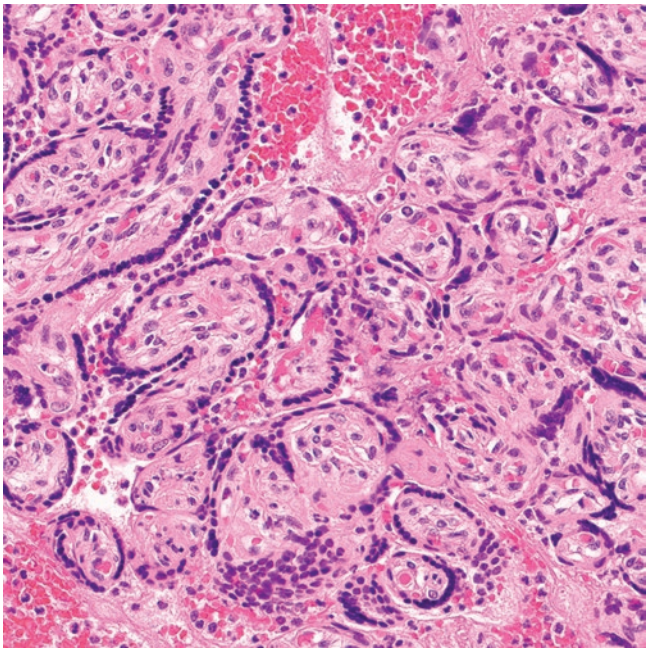

Fig. 15.54 Early ischemic changes associated with subacute abruption include loss of nuclear chromatin detail and cytoplasmic eosinophilia in affected syncytiotrophoblast (original magnification 200×)

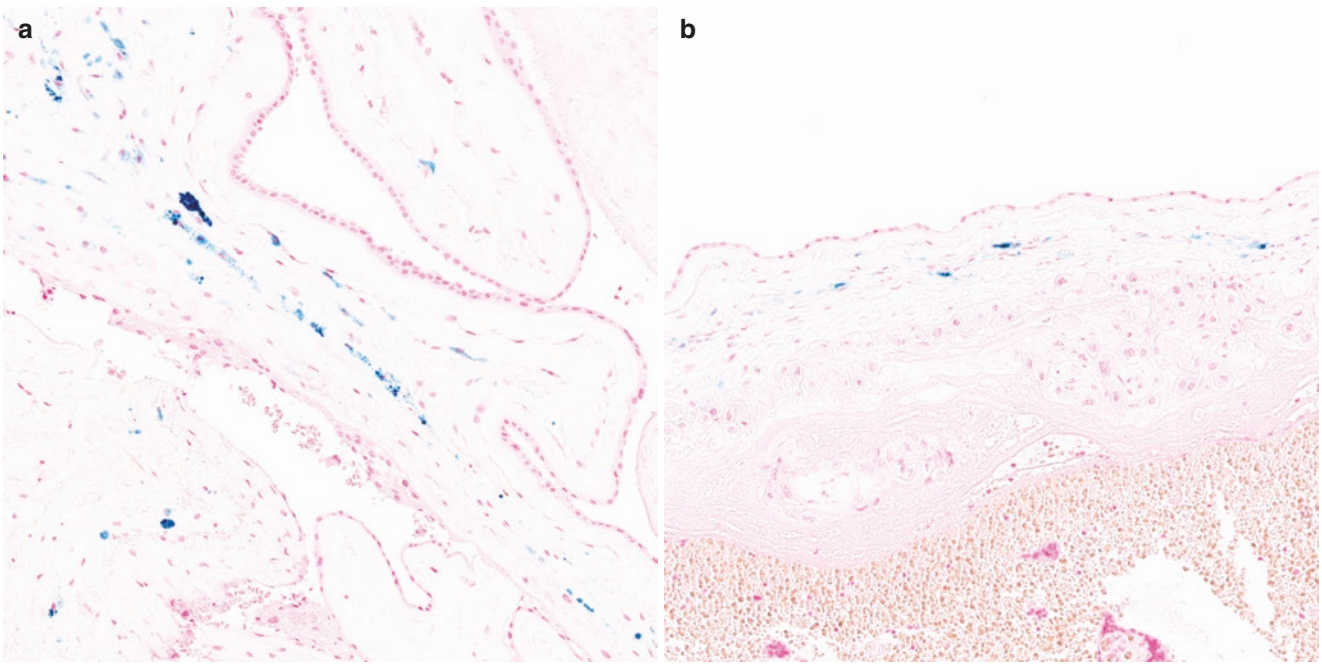

Fig. 15.55 Characteristic microscopic findings in chronic abruption include hemosiderin in the (**a**) membranous tissues and (**b**) chorionic plate (Perls' Prussian blue stain; both original magnifications 100×)

retromembranous degenerating blood, retromembranous thrombus, and hemosiderin-laden macrophages and hemosiderin deposits (Fig. 15.55a). Hemosiderin deposits in the chorionic plate are also seen in chronic abruption and may conform to the juncture of the amnion and chorion, implying bleeding into this potential space (Fig. 15.55b). Small areas of remote infarction related to areas of chronic abruption may be present, particularly at the disc margin (Fig. 15.56).

Chronic abruption-oligohydramnios sequence (CAOS) describes chronic abruption associated with oligohydram-

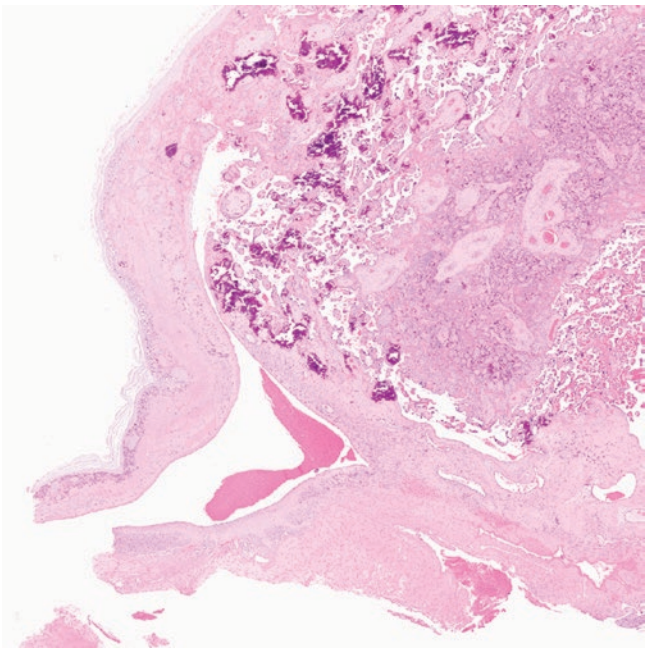

Fig. 15.56 Marginal chronic abruption may be associated with adjacent placental infarction (original magnification 10×)

nios. Microscopic features of chronic abruption are extensive, and hemosiderin is prominent. Oligohydramnios is thought to arise from abruption-related membrane ischemia, necrosis, and rupture. CAOS is frequently complicated by amniotic fluid infection syndrome.

15.10.4 Differential Diagnosis

Care must be taken not to confuse delivery-related adherent blood as acute abruption; non-specific adherent blood can be recognized by the lack of associated placental deformation and easy removal from the disc maternal surface. Microscopic features of subacute abruption may be found in early infarction related to maternal vascular malperfusion and prolonged placental retention after induction of labor; correlation with clinical history is important to discern between these possibilities. Hemosiderin of chronic abruption may be confused with meconium; positive special staining for iron will identify hemosiderin.

15.10.5 Prognosis

Acute and subacute abruption can be associated with preterm birth, birth asphyxia, stillbirth, and maternal hemorrhage. Chronic abruption, when diffuse chorioamniotic hemosiderosis is present, is an independent risk factor for development of cerebral palsy [55]. CAOS is associated with increased risk of amniotic fluid infection and poor outcomes, including long-term neurological damage [56].

15.11 Abnormal Placental Implantation

15.11.1 Placenta Accreta, Increta, and Percreta

Pathologically invasive trophoblast, in which villi and basal fibrin are found adjacent to or within myometrium, without intervening decidua (endometrium altered for pregnancy), has been divided into three anatomically defined types with associated increasing severity of clinical consequences. *Placenta accreta* refers to deficiency of decidua without obvious thinning or invasion of the myometrium. *Placenta increta* is used to describe extension of villi into the myometrium, which can also be seen as thinning of the myometrium. *Placenta percreta* is the situation in which villous tissue extends through the myometrium to the serosa of the uterus or adjacent structures (e.g., bladder), with or without gross uterine perforation.

15.11.1.1 Clinical Features

These lesions occur most often when the placenta implants in a uterus with pre-existing deficiency or alteration of the endometrium. The most common risk factor by far is previous Cesarean section. Not unexpectedly, increasing rates of Cesarean section have contributed to a significant increase in the incidence of placenta accreta and associated conditions, most recently estimated to occur in nearly 1 in 500 deliveries [57, 58]. The risk increases significantly after two or more previous such surgeries. Other clinical risk factors include other types of uterine surgery, for example, myomectomy for leiomyoma or endometrial curettage or ablation.

Placenta accreta can also occur when the placenta implants anywhere with suboptimal, relatively deficient decidua, such as in the lower uterine segment (in which case it is usually associated with placenta previa), the uterine cornu, or overlying a submucosal leiomyoma.

Placenta accreta/increta/percreta has variable presentation depending on gestational age and severity. It can be detected on prenatal ultrasound imaging with fair sensitivity and high specificity and further characterized as necessary with MRI [59]. It may present unexpectedly in the immediate postpartum period as postpartum hemorrhage and/or as delay or failure of placental separation.

When diagnosed prenatally, significant placenta accreta/increta/percreta requires management by a specialized obstetrics service to make decisions about timing of delivery, type of delivery, surgical approaches, and to anticipate the need for hysterectomy. In cases of placenta percreta detected in mid-gestation, gravid hysterectomy prior to fetal viability may be required.

15.11.1.2 Gross Features

In the most common scenario encountered by the surgical pathologist, the specimen is a manually delivered placenta with no obvious macroscopic abnormalities related to abnor-

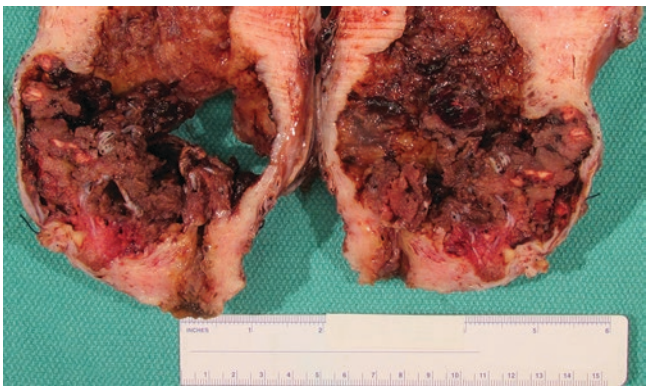

Fig. 15.57 Placenta increta in the lower uterine segment and cervix in a hysterectomy specimen

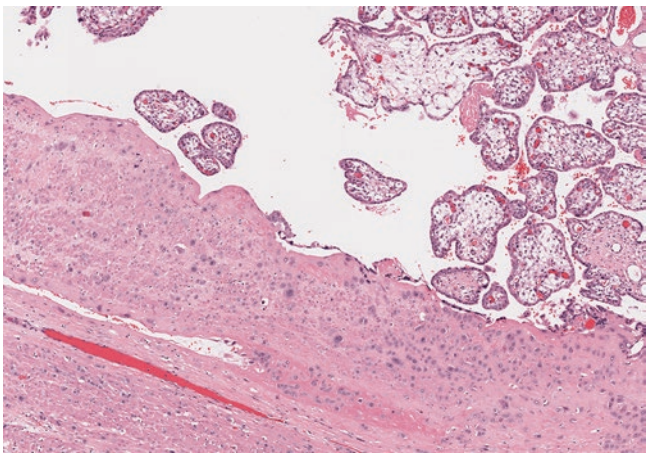

Fig. 15.58 Placenta accreta with chorionic villi implanted immediately above a layer of extravillous trophoblast and myometrium, without intervening decidua (original magnification 40×)

mal implantation. Rarely grossly evident adherent myometrium is evident.

In more severe cases, hysterectomy may have been required either after placental delivery due to persistent hemorrhage, or the hysterectomy specimen may be received with the placenta still attached (Fig. 15.57). In this case, it is helpful to approach the examination and sampling similarly to that used for invasive endometrial cancers; that is, the following should be documented: anatomic location of implantation (fundal, anterior/posterior, lower uterine segment, cervix), relationship to parametrial and paracervical resection margins, depth of invasion (on cross section), thickness of uninvolved myometrium, and involvement of serosal surface. Photographs are helpful. A standardized protocol has been published [60]. Principles of standard placental examination also apply.

15.11.1.3 Microscopic Features

In the case of a delivered placenta not accompanied by a uterus, microscopic examination is probably insensitive for confirming a clinical suspicion of placenta accreta. This is in part due to the fact that the diagnostic features may be hidden in retained products. Furthermore, considering the very limited sampling typical for placental pathology (three blocks from a 400 to 500 g organ), it is not unexpected that diagnostic microscopic fields may be missed simply due to extremely limited sampling of the maternal surface.

When myometrium is present on the basal surface in a microscopic section, there is most often an intervening layer of basal fibrin and extravillous trophoblast underlying villi, as opposed to villi lying immediately upon myometrial cells (Fig. 15.58). Immunohistochemical stains can be used to differentiate decidua and trophoblast if necessary: decidual cells are CD10 positive (cytoplasmic/membranous) and keratin negative (cytoplasmic), whereas extravillous trophoblast stains oppositely.

The significance of incidentally seeing the histologic picture of placenta accreta in a patient without clinical evidence of abnormal implantation is debated. Some have referred to this finding as occult placenta accreta or basal plate myometrial fibers (Fig. 15.59); there is a plausible connection and case-control evidence that this finding is associated with placenta accreta in subsequent pregnancies [61, 62].

In placenta increta, gross myometrial thinning will also be evident microscopically, and the absence of decidua can be confirmed. Note that the myometrium of the lower uterine segment is physiologically very thin in late pregnancy (comparison with a section of uterine wall not underlying the placental disc provides a control). The microscopic picture of placenta percreta may be less clear as frank serosal perforation will often be accompanied by hemorrhage and/or disruption due to surgical dissection off an adjacent structure (Fig. 15.60).

15.11.1.4 Prognosis

Abnormal placental implantation is a risk factor for preterm delivery, perinatal mortality [58], indicated Cesarean section, postpartum hemorrhage, delayed placental delivery, hysterectomy, and even maternal mortality. The recurrence risk in subsequent pregnancies for women who do not undergo hysterectomy is high.

15.11.2 Placenta Previa and Vasa Previa

Placenta and vasa previa describe placental implantation over the inner cervical os. In placenta previa, the placental disc covers the os, while in vasa previa, the disc regresses leaving placental membrane with velamentous umbilical vessels covering the os (Fig. 15.61). Placenta and vasa previa predispose to abruption; features of chronic abruption are typically found. Occasionally, large hematomas with evidence of recurrent bleeding may be present. Associated disc infarction and atrophic regression may also be seen. Since

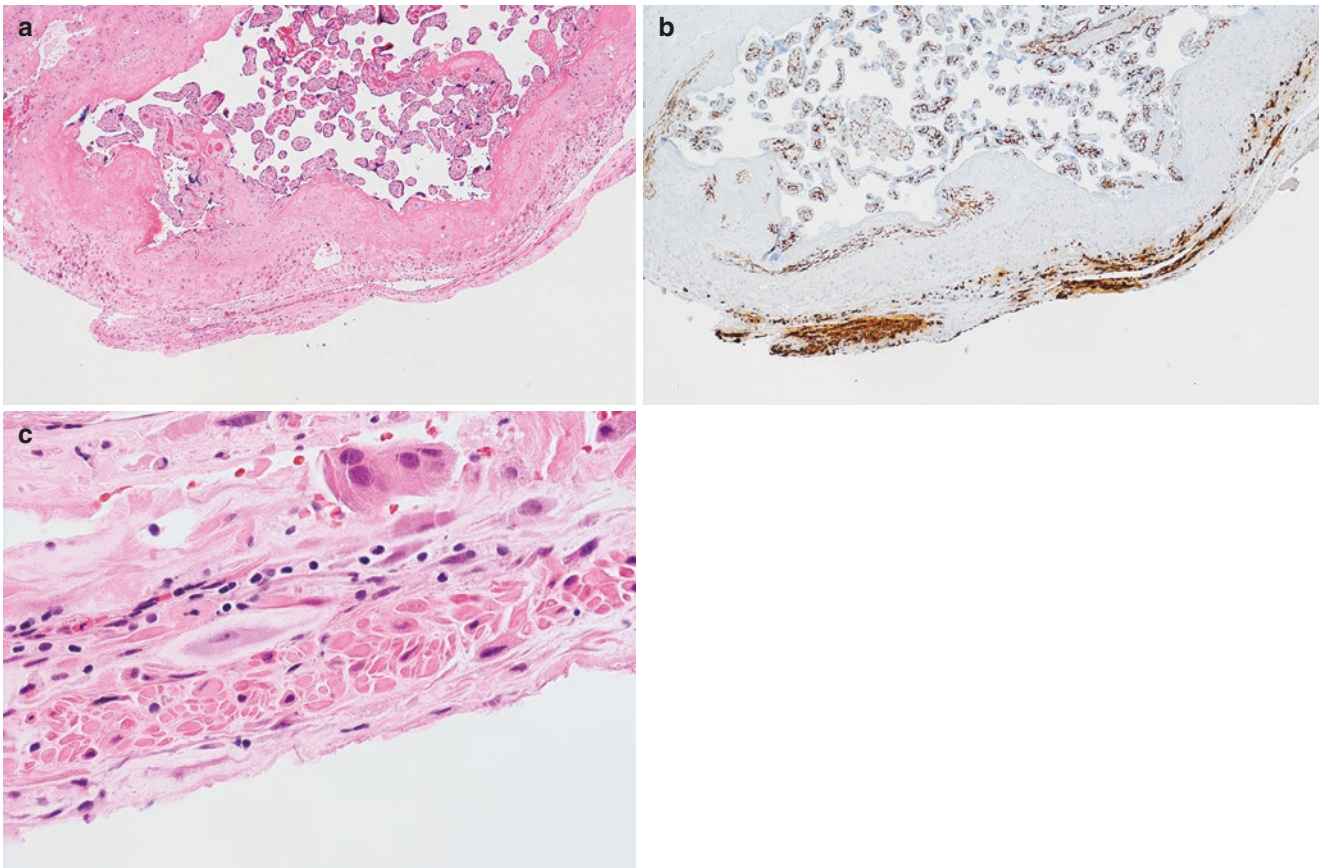

Fig. 15.59 Myometrial cells can be seen adherent to the basal surface of the placenta, with only rare decidual cells intervening between them and the basal trophoblast (**a**, original magnification 100×, **b**, same field and magnification with desmin immunohistochemical stain, **c**, original magnification 400×)

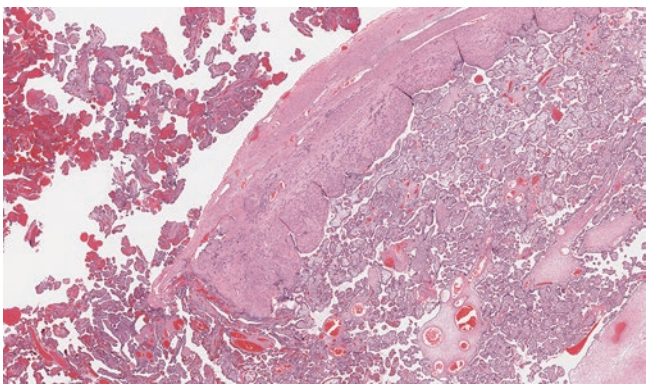

Fig. 15.60 The right side of the picture demonstrates increta, with thinning of the normal uterine wall thickness, and the left side of the picture shows percreta, with chorionic villi invading into extrauterine space (original magnification 20×)

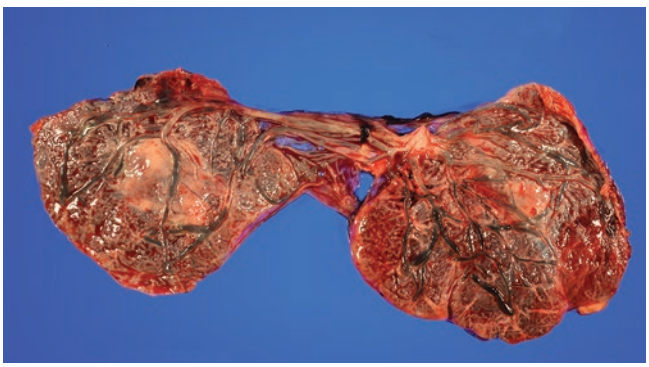

Fig. 15.61 A case of delivered placenta previa with vasa previa. The section of velamentous vessels with deficient parenchyma overlaid the cervical os

the placenta is implanted over the adjacent lower uterine segment, features of maternal vascular malperfusion and placenta accreta/increta/percreta may also be present. Vasa previa is also at risk of fetal vascular flow restriction and vascular rupture.

15.12 Multiple Gestation

15.12.1 Clinical Features

In North America, data from 2014 to 2015 record approximately 33 twin births out of every 1000 total births. Triplet

and higher-order multiples are around 300 times less frequent than twins [63, 64].

Risk of multiple gestation is increased in some ethnic groups, with advancing maternal age, with higher parity, and with a personal or family history of prior twins or multiples. An increasingly important contributor to multifetal pregnancy rates is the use of assisted reproductive technologies [65]. Many pregnancies that begin as multiple gestations have asymptomatic occult spontaneous abortion of one twin prior to the second trimester (so-called vanished twin).

15.12.2 Gross Features

The gross description of multiple gestation placentas involves specialized terms. *Chorionicity* of the placenta refers to the number of chorionic sacs present. *Amnionicity* refers to the number of amniotic sacs contained within a chorionic sac.

A placenta composed of a single chorionic sac is known as *monochorionic*. Within the chorionic sac, there may be a single or multiple amniotic sacs (*monoamniotic, diamniotic, triamniotic*, etc.). In this type of placentation, the fetuses share a single placental bed. These fetuses are by definition monozygotic, i.e., arising from a single zygote that undergoes twinning.

Frequently, twin and higher multiple gestations are characterized by each fetus having its own gestational sac with amnion, chorion, and placental bed. In this situation, fetuses do not share a placental bed. These fetuses may be monozygotic, arising from a single zygote that undergoes early twinning, or dizygotic, arising from two separate eggs fertilized by separate sperm. Such gestations are denoted by "dichorionic," "trichorionic," etc.

Commonly encountered twin scenarios include:

Dichorionic, diamniotic: These consist of two discrete placental discs each with its own amnion and chorion. Each fetus resides in its own amniotic and chorionic sacs, and the dividing membrane consists of two core layers of chorion flanked by two layers of amnion. This membrane is grossly opaque. The discs may be separate or fused.

Monochorionic, diamniotic: This placenta consists of a single placental disc with one chorion and two amniotic sacs. Each fetus resides in its own amniotic sac, and the dividing membrane consists of two layers of amnion only. The membrane appears thin and translucent.

Monochorionic, monoamniotic: This placenta consists of a single placental disc with a single chorion and single amnion. Two fetuses reside together in the same amniotic sac. There is no dividing membrane. There is a high risk of cord entanglement [66].

In addition to routine observations made for any gross placental description, several multiple-gestation-specific details should be noted (see Table 15.10).

Table 15.10 Specific details to include in gross description of a multiple gestation placenta

Whether cords have been matched to specific neonates (e.g., "cord clamp on twin B")
Chorionicity (monochorionic, dichorionic, trichorionic, etc.)
Amnionicity: within each chorionic sac, how many amniotic sacs are present (monoamniotic, diamniotic)?
Description of dividing membrane (opaque versus translucent)
Number of discrete placental discs? If multiple, separate, or fused?
Separate discs: weigh each separately Single or fused disc: weigh together (To be compared against multiple gestation-specific normal values)
Intercordal distance (distance between cord insertions)
For monochorionic placentas, placental share (percentage of the fetal surface covered by each twin's chorionic plate vessels)

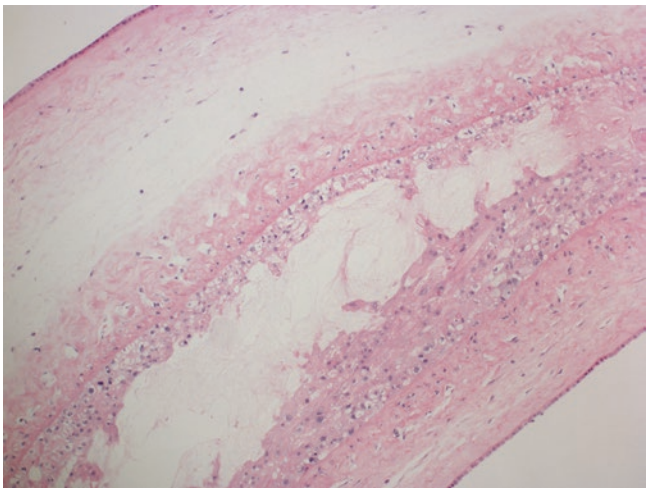

Fig. 15.62 Separating membranes of a dichorionic, diamniotic twin placenta. The middle of the separating membranes is composed of two apposed layers of chorion (one from twin 1, one from twin 2). The chorion from each twin's placenta is surfaced by a layer of amnion, which faces their respective amniotic cavities. There are four total tissue layers depicted in this photomicrograph. From left to right: amnion 1, chorion 1, chorion 2, amnion 2 (original magnification 100×)

15.12.3 Microscopic Features

Chorionicity can be confirmed microscopically by evaluating the tissue layers of the dividing membrane. The dividing or separating membrane refers to the wall of the gestational sac separating the fetuses. In dichorionic placentation, the dividing membrane is composed of four layers: amnion 1, chorion 1, chorion 2, and amnion 2 (Fig. 15.62). In monochorionic placentation, the separating membrane is composed of two layers: amnion 1 and amnion 2 (Fig. 15.63).

When assessing the placenta from a multiple birth, one should compare the villous development of each placental disc (if multichorionic) or each infant's "side" of the disc (if monochorionic). Discrepant villous development may help

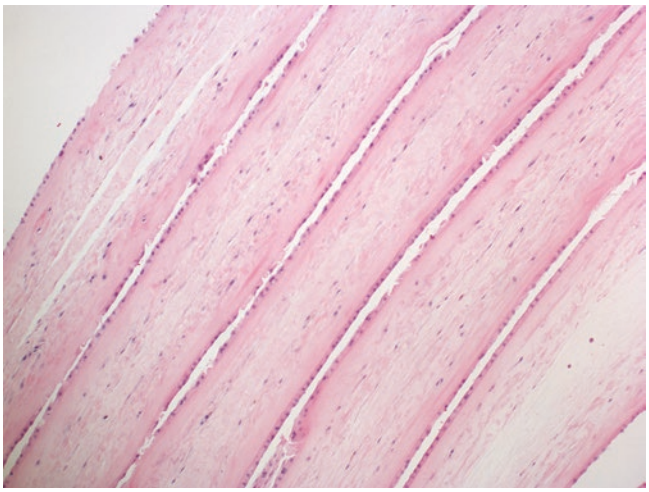

Fig. 15.63 Separating membranes of a monochorionic, diamniotic twin placenta, consisting of two layers of amnion with the deep surfaces apposed. The amniotic epithelium faces the amniotic cavity (original magnification 100×)

to explain discordant birth weights (i.e., differences of >10% between birth weights).

15.12.4 Prognosis

The risk of adverse obstetric and neonatal outcomes for twins and especially higher-order multiples is well-documented [65]. Obstetric risks include increased risk of hypertensive disorder, spontaneous abortion or fetal demise, and preterm labor. Risks to the fetuses and neonates include higher rates of congenital anomalies as well as predictable complications arising from low birth weights and prematurity. There are unique risks associated with monozygotic twins, one of which is discussed below.

15.12.5 Twin-to-Twin Transfusion

15.12.5.1 Clinical Features

Twin-to-twin transfusion syndrome (TTTS) is a condition primarily affecting monozygotic twins sharing a monochorionic, diamniotic (MCDA) placenta. In MCDA placentation, the placental vascular circuit is shared by the twins. Complications can arise when one twin receives more blood flow than the other twin, resulting in a recipient and a donor twin. The Quintero system is commonly used to stage the severity of the condition by ultrasound (Table 15.11). Hydrops results either from fetal anemia (donor twin) or high-output cardiac failure from volume overload (recipient twin) [67, 68].

Development of TTTS depends on the existence of inter-twin vascular anastomoses at the vascular equator. An inter-twin vascular anastomosis is presumed to occur when placental vessels from each twin enter and exit the same cotyledon. The opposing vessels are presumed to share a capillary bed in the distal chorionic villi. Therefore, the condition is not seen in dichorionic twins, in which two discrete placental discs are formed with no vascular connections between the discs [69]. TTTS has been rarely reported in monochorionic, monoamniotic, twins. It should be noted that although inter-twin vascular anastomoses are commonly seen in MCDA twin placentas, only a subset of MCDA twins develop TTTS. Therefore, vascular anastomoses are a prerequisite, but not a guarantee of TTTS development. In fact, there is some evidence that certain types of inter-twin anastomoses (namely, artery-to-artery) may be protective against the development of TTTS [70, 71].

Table 15.11 Quintero staging system for twin-to-twin transfusion

Stage I: DVP <2 cm in donor and >8 cm in recipient
Stage II: Cannot visualize donor bladder
Stage III: Critically abnormal Doppler studies (umbilical artery absent or reversed end-diastolic velocity, reversed ductus venosus flow, pulsatile umbilical vein flow)
Stage IV: Hydrops in either fetus
Stage V: Death of one or both fetuses

DVP Deepest vertical pocket of amniotic fluid. Adapted from [68]

Since symptomatic TTTS can lead to death or severe morbidity in one or both fetuses, techniques have been developed to disrupt the anastomoses and separate the fetal circulations. Selective laser ablation targets and coagulates vascular anastomoses deemed physiologically abnormal, which are identified by fetoscopic visualization and intraoperative Doppler studies [67]. More recently, a technique called Solomonization has been introduced, in which a laser line is drawn across the vascular equator to coagulate it [72, 73], with the aim of separating/isolating the respective twin circulations. Laser ablation of vascular anastomoses is performed on eligible individuals during the second trimester. Complications include bleeding/infection, premature rupture of membranes, demise of one or both twins following the procedure, and conversion of the procedure to selective reduction of a twin if conditions are unfavorable to perform laser ablation.

15.12.5.2 Gross Features

The placenta associated with twin-to-twin transfusion syndrome is typically a MCDA twin placenta (Fig. 15.64).

The separating membranes have no relationship with the orientation of the vascular equator. Examination of the fetal vessels of the chorionic plate is facilitated by entirely removing the reflected membranes and fetal surface amnion. The vascular equator is the imaginary line where the vessels from both twins meet. It is in the center of the disc if the placental share is equal. In cases of uneven placental share, the vascular equator is skewed toward one end of the disc.

The integrity of intact anastomoses can be tested by injecting air using a syringe into the fetal surface vessel from one twin (near the equator), then gently massaging the air bubble into the parenchyma, and observing the bubble appearing in an adjacent fetal surface vessel from the other twin. A highly sensitive technique for identifying vascular anastomoses during gross pathology examination has been developed by a group in the Netherlands [72–74]. This technique involves injection of different-colored pathology dyes into one artery and one vein of the umbilical stumps of each twin. This allows for identification of anastomoses involving vessels too thin to inject with air. For detailed information on this technique, the reader is directed to the technical paper [74]. Air and dye injection maneuvers require a relatively intact placenta. Fragmented placentas cannot be successfully injected. A case in which one or more fetuses died in utero may be challenging to inject.

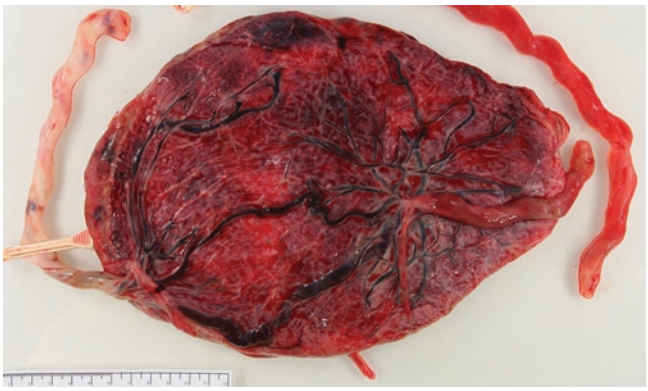

Fig. 15.64 Monochorionic, diamniotic twin placenta at 25 weeks of gestation. The pregnancy was complicated by twin-to-twin transfusion syndrome and intrauterine demise of the twin on the right at 24 weeks. The twin on the left was live-born at 25 weeks. Laser ablation was not performed in this case. There are at least seven surface vascular anastomoses at the vascular equator identified by visual inspection, including vein-artery, artery-vein, artery-artery, and vein-vein

Identifying inter-twin vascular anastomoses can provide an explanation for in utero hemodynamic variations/abnormalities in the twins. Another purpose of identifying anastomoses is to evaluate the quality and success of laser ablation. The gross appearance of ablation sites depends on the time elapsed between ablation and delivery. Initially they may not be visible, but as the ablated parenchyma ages, the sites become firm, fibrotic, and yellow, similar to subchorionic infarction or fibrin deposition (Fig. 15.65a).

Symptomatic TTTS may be associated with congested parenchyma on the recipient twin's side and pale parenchyma on the donor twin's side (Fig. 15.65b). The twin placenta associated with TTTS could include demise-related changes if one or both twins undergo demise (Fig. 15.66).

15.12.5.3 Microscopic Features

The separating membranes are monochorionic and diamniotic. Without dye-injection studies, it is not possible to determine from a histologic section which vessels came from which twin. If there was differential congestion of the two sides, similar findings may be seen microscopically. The chorionic villi may appear edematous if the fetus was hydropic. There may be accelerated villous maturation and

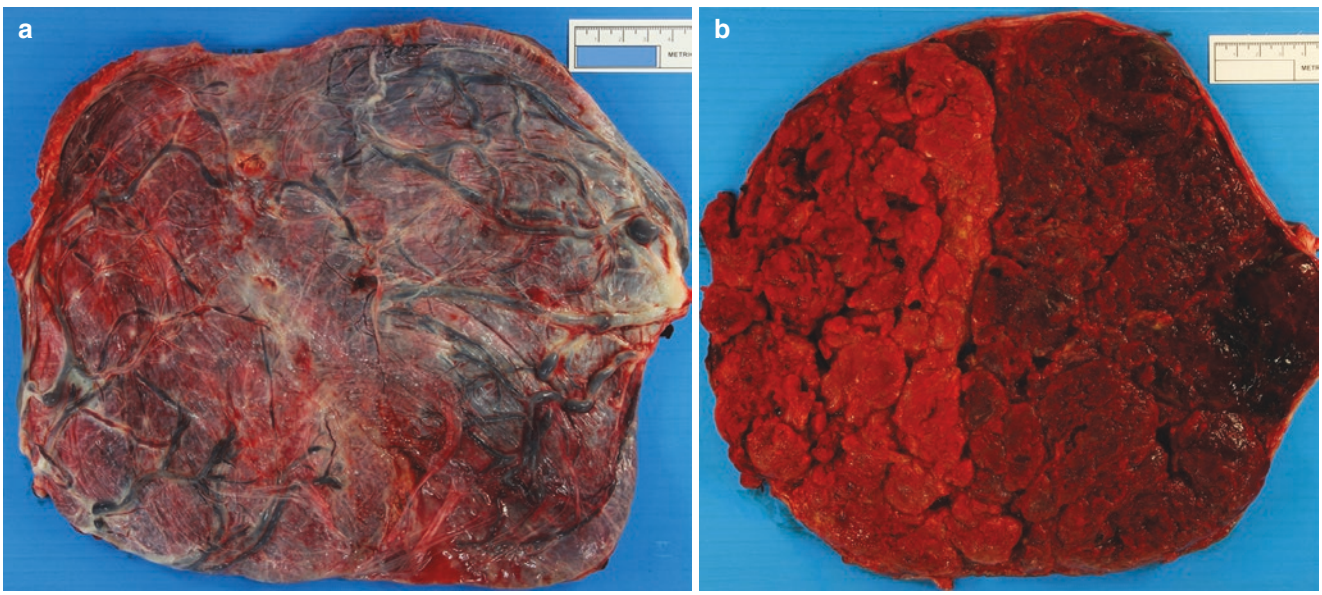

Fig. 15.65 (**a**) Monochorionic, diamniotic twin placenta delivered at 36 weeks of gestation. Selective fetoscopic laser ablation was performed at 23 weeks of gestation. Both twins were live-born. Gross examination shows no residual intact vascular anastomoses at the vascular equator by visual inspection or by air injection technique. Some firm yellow patches are visible where the laser was applied. These resemble infarcts microscopically. (**b**) Same placenta, demonstrating maternal surface with differential congestion

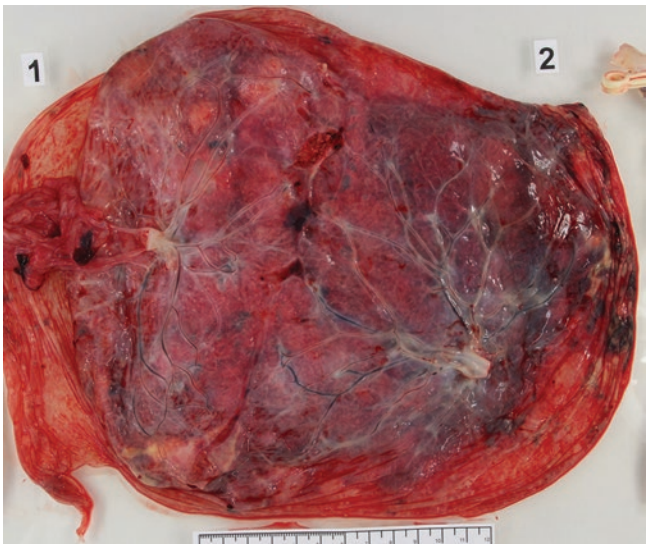

Fig. 15.66 Monochorionic, diamniotic twin placenta from a pregnancy complicated by twin-to-twin transfusion syndrome. Selective fetoscopic laser ablation was attempted at 16 weeks, but pregnancy was complicated by extreme preterm labor and delivery at 22 weeks resulting in demise of both twins. Ablation sites at the vascular equator are visible as subchorionic hemorrhagic patches. No residual vascular anastomoses could be demonstrated by air injection technique or by visual inspection

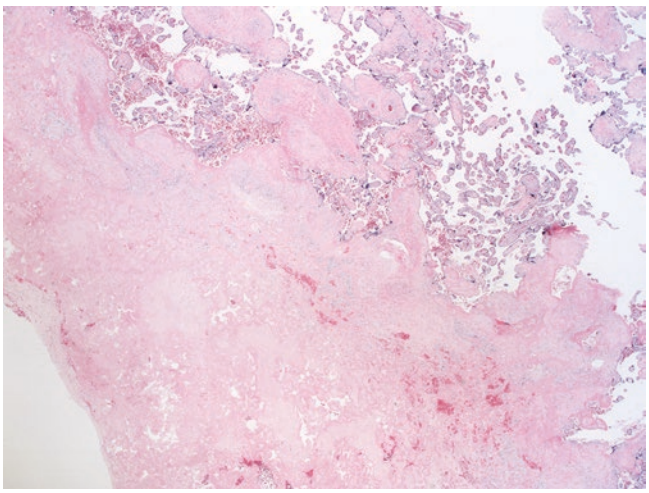

Fig. 15.67 Laser ablation of twin-to-twin transfusion syndrome; villi with infarct-like changes with increased perivillous fibrin deposition (original magnification: 20×)

fetal normoblastemia due to chronic hypoxia and/or fetal anemia. The histology of ablation sites is non-specific and is related to tissue damage and repair [75]. The histology depends on the interval between laser ablation and delivery. There may initially be a thrombohematoma that becomes a remote organized thrombus. Infarcted villi, avascular villi, and subchorionic fibrin deposition are also seen (Fig. 15.67). Coexisting findings may include chorioamnionitis if there is premature rupture of membranes secondary to the ablation procedure and diffuse demise-related changes if there is demise of one or both twins.

15.12.5.4 Differential Diagnosis

Not all discordant growth in twins is attributable to TTTS. In either mono- or dichorionic gestations, twins may be discordant for intrauterine growth restriction because of suboptimal placental implantation of one twin or have different amniotic fluid volumes due to rupture of only one twin's amniotic sac. In dichorionic gestations, twins may have discordant size or hydrops due to one but not both twins being affected by a genetic, chromosomal, or anatomical anomaly.

15.12.5.5 Prognosis

Outcome depends on severity (including Quintero stage) of the hemodynamic imbalance. In general, the earlier in pregnancy the condition is detected, the more severe its potential consequences. There is high mortality particularly for TTTS presenting in the second trimester, if left untreated, with excess mortality for the donor rather than the recipient twin.

15.13 Fetal Hydrops

15.13.1 Clinical Features

Hydrops fetalis is defined as the accumulation of fluid in two or more body compartments [76, 77]. Development of fetal hydrops can be associated with development of maternal edema, in a complication known as mirror syndrome (Ballantyne syndrome). There are many possible underlying etiologies, which are briefly discussed below.

15.13.2 Gross Features

The placenta is large for gestational age by weight and three-dimensional size, owing to fluid retention in chorionic villi. The cut surface of the placenta is pale, and the texture of the chorionic villi may be boggy and friable [78]. If the underlying etiology is a placental tumor, it may be grossly detected as a space-filling lesion.

15.13.3 Microscopic Features

In a hydropic placenta, there is diffuse or focal chorionic villous edema. The affected chorionic villi are expanded by fluid and enlarged. Edematous villi are especially prominent in third-trimester placentas, when villi are normally expected to differentiate into small terminal villi with reduced stroma and numerous close-packed profiles of capillary vessels. Edematous villi show capillaries that appear small in caliber

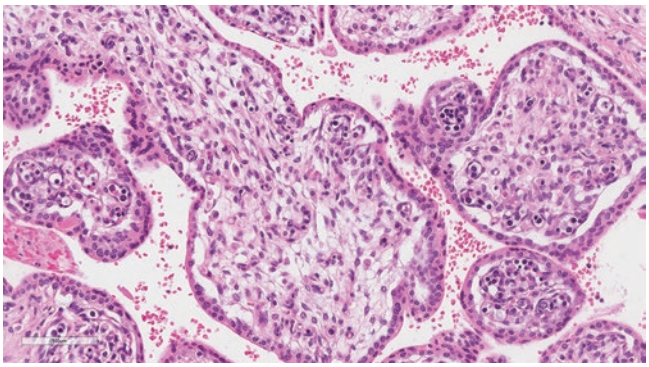

Fig. 15.68 Chorionic villi from a placenta infected by human parvovirus B19. There are increased circulating nucleated red blood cells, some of which contain viral inclusions. The villi are hydropic, characterized by increased empty spaces between villus stromal cells and lifting of the villus trophoblast from the stroma (clefting) (original magnification: 100×)

and spaced apart. Villous stromal cells are dispersed by edema. There may be an increase in Hofbauer cells (villus stromal macrophages). When fetal anemia is present, within villous capillaries there may be increased circulating fetal nucleated red blood cells (normoblasts) or more primitive erythroid precursors (erythroblasts). There may be separation of the villous trophoblast from the stroma leading to a cleft-like space. Mineralization of the villous trophoblast may occur.

The presence of viral cytopathic effect, possibly accompanied by infectious villitis, can reveal an underlying infectious etiology for the hydrops (Fig. 15.68). Stromal cells with foamy cytoplasm and vacuolated trophoblast may point to an underlying storage disorder. Review of maternal and fetal/neonatal history and laboratory investigations is necessary to narrow down the differential diagnosis.

15.13.4 Differential Diagnosis

Red cell alloimmunization (development of maternal antibodies to circulating fetal red blood cell antigens) leads to fetal hydrops if maternal antibodies cross the placenta and destroy enough fetal red blood cells to cause clinically significant fetal anemia (hemolytic disease of the newborn). Maternal antibodies can develop against rhesus antigen (D antigen) in Rh-negative mothers and less commonly to minor red cell antigens. Hydrops secondary to maternal sensitization to D antigen is now rare due to routine administration of anti-D immune globulin during pregnancy in eligible Rh-negative mothers. Maternal antibodies against major blood group antigens (ABO incompatibility) rarely occur, as the IgM antibody is too large to cross the placenta into fetal circulation. Nonetheless, cases of fetal hydrops due to development of maternal antibodies against fetal A or B antigens have been reported in the literature [79].

Table 15.12 Causes of nonimmune fetal hydrops

Infection
Parvovirus
Cytomegalovirus
Zika virus [82]
Other TORCH infections
Aneuploidy
Monosomy X
Trisomy 21
Congenital or acquired fetal anemia
Parvovirus infection
Thalassemia
Chronic feto-maternal hemorrhage
Fetal lymphatic abnormalities [83]
Noonan syndrome
Trisomy 21
Monosomy X
Fetal cardiac dysfunction
Maternal systemic lupus erythematosus with fetal heart block
Fetal right-sided cardiac structural abnormalities (e.g., tricuspid atresia, Ebstein malformation)
Fetal myocarditis
Fetal rhabdomyoma
Fetal hepatic dysfunction
Inborn errors of metabolism, e.g., Niemann-Pick [84], MPS VII [85]
Fetal renal dysfunction
Congenital nephrotic syndrome
Placental tumors
Giant chorangioma [86–88]
Choriocarcinoma in situ [89]
Metastatic maternal and fetal tumors [90]

MPS VII Mucopolysaccharidosis type VII

When red blood cell alloimmunization is clinically excluded, the condition is specified as nonimmune hydrops fetalis (NIHF). NIHF now account for the majority of fetal hydrops cases. There are multiple categories of underlying causes, including congenital infections, fetal aneuploidy, congenital or acquired fetal anemia, fetal high-output heart failure, fetal structural congenital heart disease, fetal liver dysfunction, fetal renal dysfunction, and fetal tumors. Other etiologies include primary placental tumors and metastases from mother or fetus to the placenta. Table 15.12 summarizes the very broad differential diagnosis [80, 81]. Hydrops that develops in one twin in monozygotic pair is discussed in the section on twin-to-twin transfusion syndrome.

15.13.5 Prognosis

Outcome depends partially on the underlying etiology of hydrops, as well as its prenatal severity. In general, outcomes are poor for prenatally diagnosed hydrops [91].

15.14 Fetal Demise

15.14.1 Early Pregnancy Loss

15.14.1.1 Clinical Features

Spontaneous abortion [92] (miscarriage) in the first trimester is extremely common, affecting an estimated 10–20% of clinically recognized pregnancies and an even greater proportion of those not diagnosed prior to the first missed menstrual period. The etiologies are myriad; the earlier the miscarriage, the more likely the cause is one of nonviable chromosomal complement. When examining these products of conception, a few things should be kept in mind. One may be able to answer specific clinical questions such as approximate gestational age or gross features of aneuploidy. Laboratories should have policies in place to determine indications for chromosome testing, as well as type of testing and who coordinates it (clinician or laboratory).

15.14.1.2 Gross Features

Gross description of first-trimester and fragmented second-trimester products of conception should include at minimum the amount of material received (often easiest recorded as an aggregate weight) and a list of grossly identifiable components (villi, gestational sac with or without embryo, fetal parts, umbilical cord, clot, decidua). Villi should be described specifically if they are abnormal (e.g., hydropic). If no villi are identified after careful gross search, this should be explicitly noted. Absence of identifiable gestational sac or fetal components is not uncommon, even when one has been documented on ultrasound.

Examination of the embryo or fetus can be as detailed as size and practical constraints allow. For embryos, recording of the crown-rump length suffices. For fetuses, foot length is the single most useful measurement to correlate with gestational age. Obvious fetal anomalies should be noted, although artifacts of surgical curettage or extraction are common.

15.14.1.3 Microscopic Features

One should confirm the presence of villi and/or trophoblast invasion into decidua. If no villi are identified grossly or microscopically in a spontaneous or iatrogenic abortion specimen, this should be reported to the responsible physician as a potential missed ectopic pregnancy [93]. Villi should be assessed to confirm generally appropriate development for gestational age, especially to rule out the presence of molar pregnancy-associated findings. Many early miscarriages will have diffuse mild hydropic change; trophoblast proliferation is limited; depending on the interval to evacuation, villi may instead appear fibrotic. Necrosis, hemorrhage, and inflammation of the decidua are common. Because these specimens are often fragmented and degenerated, one can only rarely make a specific diagnosis suggestive of etiology of pregnancy loss (e.g., viral placentitis, histiocytic intervillositis).

15.14.2 Placental Changes in Late Fetal Loss

15.14.2.1 Clinical Features

Fetal demise becomes less likely as gestation proceeds. For this reason, for unexpected fetal loss in the second half of pregnancy, one is more likely to be asked clinical questions about etiology, fetal, and placental abnormalities. In the ideal scenario, a consented complete postmortem examination with indicated chromosomal testing should be at least considered in all cases of unexplained fetal demise, as well as for selected cases of terminations for unexplained fetal anomalies. Many of the placental pathologies discussed in this chapter can result in fetal demise; their specific features are discussed in appropriate sections. This section focuses on expected postmortem placental changes after demise in utero.

15.14.2.2 Gross Features

Examination of the placenta should follow the general principles outlined in the introductory section. One may consider taking extra sections when the suspected cause of death is placental.

Chromosome testing (molecular aneuploidy detection, chromosomal microarray, or karyotype) generally requires sampling of fresh tissue. In most cases fetal tissue proper is preferred to placental tissue (which may be contaminated with maternal material). When fetal-placental chromosomal discrepancy is a diagnostic possibility, one may consider taking samples from each.

Placentas from demised fetuses tend to undergo stereotypic degeneration the longer they are retained in utero, with preserved maternal but not fetal circulation. The placenta may appear diffusely pale. The umbilical cord is often darkly discolored with loss of vascular tone. Careful examination of the cord is indicated. If labor has been induced or augmented, artifactual hematoma suggestive of abruption may be present.

15.14.2.3 Microscopic Features

The placenta from a very recently demised fetus may show no postmortem changes. After just a few hours of in utero retention, one may begin to see intravascular karyorrhexis. Stem vessels then begin to show involutional changes including endothelial disintegration, fibrous luminal organization, and red cell extravasation; these are similar to those changes that can be seen in fetal vascular malperfusion (Fig. 15.69a). No fibrin thrombi or calcification of vessel walls should be seen in purely postmortem change. Eventually (after a period of days to weeks), as the fetal vascular tree involutes, the capillaries of the distal villi likewise involute, and eventually

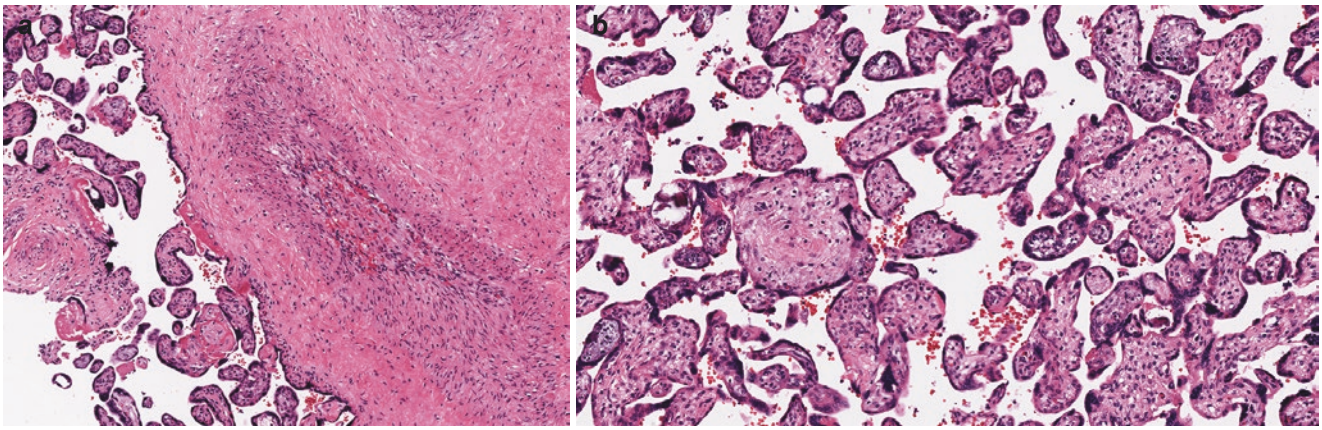

Fig. 15.69 Changes following intrauterine fetal demise include involution of large fetal vessels, (**a**) stem vessels, and (**b**) distal capillaries (original magnifications 100×)

Table 15.13 Postmortem vascular changes versus premortem fetal vascular malperfusion in stillbirth

Feature	Postmortem vascular involution	Premortem fetal vascular malperfusion
Umbilical cord	Non-specific; darkly discolored after long period of retention	Gross cord lesion such as true knot, tight fetal entanglement, organized thrombus
Anatomic distribution	Random, diffuse	Segmental, suggesting a specific vascular distribution
Temporal distribution	All changes at similar stages	Temporally heterogeneous, especially with respect to apparent timing of demise
Large vessel changes	Non-specific	Intramural fibrin; calcified thrombi

distal villi are avascular and fibrotic [94] (Fig. 15.69b). The villous stroma and trophoblast layer are maintained by the maternal blood supply.

15.14.2.4 Differential Diagnosis

The findings of placental examination in the setting of unexplained stillbirth should be combined with those of fetal postmortem examination as well as ancillary and clinical information in order to provide the most useful information to the clinician and patient. The placental examination provides evidence of a cause of death in many such cases, but these findings must be interpreted in the correct clinical context. Any of the diagnostic entities discussed in this chapter in placentas of live-born infants may be seen in stillbirth cases; one should be familiar with expected postmortem changes in order not to miss significant, nor overinterpret artifactual, findings.

The lesion most likely to be confused with or obscured by postmortem fetal vascular involution is fetal vascular malperfusion, including those cases attributable to umbilical cord pathologies and accidents [95] (Table 15.13).

15.15 Tumors of the Placenta

15.15.1 Chorangioma

Chorangiomas are the most common tumor encountered in the placenta. Their etiology is unclear, but they are more commonly encountered in the setting of placental hypoxia suggesting a reactive pathogenetic mechanism. Chorangiomas are benign but can attain very large sizes where they may compromise fetal cardiac output and be associated with deleterious mass effects.

Grossly chorangiomas appear as a red to tan solid mass (Fig. 15.70a). Infarction is common and may give the lesion a more homogenous gray appearance. Microscopically chorangiomas are a mass of fetal capillaries with a lobular architecture circumscribed by chorionic tissue and syncytiotrophoblast (Fig. 15.70b). The vascular features may be partially or completely obliterated by infarction.

Chorangiocarcinoma, sometimes also called as atypical chorangioma, is variant of chorangioma that consists of typical chorangioma surrounded by proliferative trophoblast. Despite its name, chorangiocarcinoma appears to be benign.

15.15.2 Choriocarcinoma

Choriocarcinoma may occur as primary tumor of the placenta, although this is exceedingly rare [96]. The histopathological features are the same as in choriocarcinomas elsewhere and include distinct malignant appearing cytotrophoblastic and syncytiotrophoblastic components (Fig.15.71). Primary placental choriocarcinomas are at high risk of maternal metastasis.

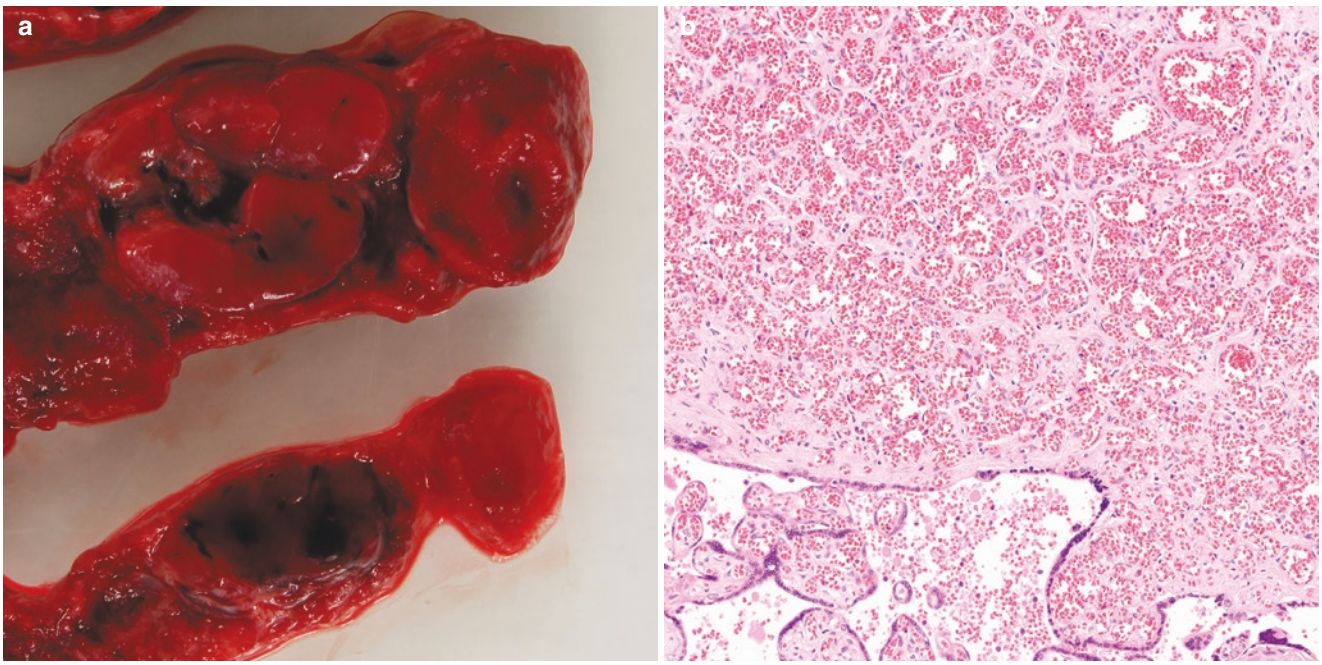

Fig. 15.70 Chorangiomas typically appear as (**a**) round or lobulated red-tan masses, (**b**) microscopically comprised of lobules of capillaries within chorionic tissue histologically similar to adjacent villi (original magnification 100×)

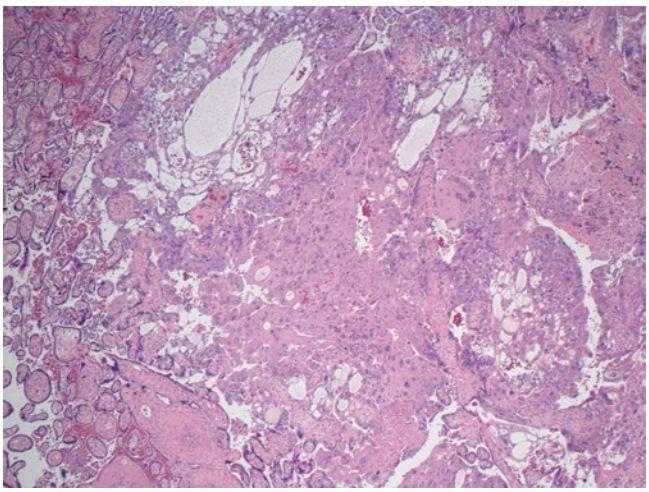

Fig. 15.71 Primary placental choriocarcinoma with cytotrophoblastic and syncytiotrophoblastic components (original magnification 40×)

15.15.3 Placental Metastasis

Metastases of maternal malignancies to the placenta are exceedingly rare. Melanoma is most common; carcinomas (e.g., breast) occur less frequently. Placental tumor deposits may metastasize further to the fetus with disastrous consequences. Fetal metastases to the placenta are also rare and comprised of tumors that may present congenitally such as neuroblastoma and leukemia. These typically appear histologically as limited to circulating tumor cells in the fetal vasculature. Metastasis from fetus to mother has not been reported.

15.16 Other Obstetric Disorders

Previously, we have discussed common maternal conditions with variably specific placental phenotypes, including infection (Sect. 15.2), preeclampsia and other hypertensive disorders (Sects. 15.7, 15.8, and 15.9.3), and diabetes (Sects. 15.9.1 and 15.9.6). There are some uncommon obstetric disorders that, while not associated with specific placental stigmata, bear mentioning because of significant risk of maternal or fetal complication.

15.16.1 Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) typically presents in the third trimester with maternal pruritus, liver dysfunction, and increased serum bile acids [97]. The pathogenesis of ICP is unclear but appears to be complex with pregnancy hormones and genetic susceptibility playing central roles. ICP is characterized by an increased risk of perinatal complications, particularly preterm birth and stillbirth, which is related to the level of maternal serum bile acids. The etiology of fetal distress has not been defined but likely includes the direct toxic effects of increased bile acids on the fetal heart [98]. Meconium staining of the fetus and placenta is a common finding in ICP. Specific placental features of ICP have not been identified, although ICP may be associated with MVM-like changes [99, 100]. Interestingly,

treatment of ICP with ursodeoxycholic acid has been reported to protect the placenta including a decreased incidence of VUE [99, 100].

15.16.2 Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy presents as rapidly progressive maternal acute liver failure, which may include severe manifestations such as hepatic encephalopathy, coagulopathy or disseminated intravascular coagulation, or hypoglycemia [101]. It is fortunately rare, occurring in fewer than 1 in 5000 pregnancies. Maternal and fetal mortality are high. The placenta may appear normal or may show effects of preeclampsia, a commonly associated condition [39].

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