Placental Pathology

23

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Abstract

Preterm labor is a multifactorial syndrome that can lead to long-term complications for the child. Intrauterine inflammation (placental infectious disease) is commonly noted in preterm labor cases. Acute placental inflammation is classified into maternal and fetal inflammatory responses. Placental examination is mandatory in case of abortion, preterm delivery, fetal malformation, infection, growth restriction, preeclampsia, late intrauterine death, intra-partum hypoxia, and complicated twin pregnancy. The histological system recently proposed by Redline is widely used to assess the severity of placental inflammation, including maternal and fetal inflammatory responses. There is a significant association between the fetal inflammatory response and neonatal conditions. Further, many cases of spontaneous preterm labor leading to preterm birth appear to be caused by placental insufficiency, similar to the case of preeclampsia and intrauterine growth restriction/fetal growth restriction. Placental insufficiency has also been implicated in other causes of preterm labor, including placental abruption, chronic intrauterine hemorrhage, chronic villitis, and chronic intervillositis.

This chapter focuses on the pathological diagnostic features of preterm labor, including the placental inflammation severity and placental insufficiency. The use of placental pathology to understand intrauterine conditions can improve early gestation diagnostic testing and revolutionize preventative care for mothers and newborns.

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23.1 Preterm Labor and Placental Pathology

Preterm birth is a multifactorial syndrome that is associated with a variety of risk factors and long-term health consequences for the child. From a pathophysiological perspective, preterm birth is a highly complex syndrome that is not completely understood. Placental examination is mandatory in cases of abortion, preterm delivery, fetal malformation, infection, growth restriction, preeclampsia, late intrauterine death, intra-partum hypoxia, and complicated twin pregnancy. To perform a placental examination, a pathologist must receive a written request from the clinician, along with the pregnancy history, gestation week, weight of the baby, maternal health during pregnancy, and indications for referral.

Placental pathology provides important diagnostic information to ascertain the cause of preterm birth. Salafia et al. [1] studied the histological features of placentas from 539 preterm deliveries and 214 term deliveries. They found a significantly high incidence of umbilical or chorionic vasculitis (fetal inflammation), decidual vasculopathy, and chronic villitis/villitis of unknown etiology (VUE) among the preterm delivery cases. Placental lesions, umbilical-chorionic vasculitis, decidual vascular abnormalities, and chronic vasculitis/VUE were observed in 96% of births between 22 and 28 weeks, 54% of births between 29 and 32 weeks, and 46% of births between 33 and 36 weeks. Chisholm et al. [2] examined 102 placentas and found an association between intrauterine placental infectious changes, particularly umbilical vasculitis and chorionic vasculitis, and the severity of preterm (gestational age <34 weeks; birth weight <200 g) infant illness. Placental insufficiency is a known cause of several obstetric syndromes, including preeclampsia and fetal growth restriction (FGR). In addition, other conditions, such as placental abruption, chronic intrauterine bleeding, and chronic inflammatory disease, may cause preterm birth.

We reviewed the placental pathology findings in preterm labor cases (Table 23.1), and discuss the potential of using placental examination to improve early gestation diagnostic testing and preventative care for both the mother and child.

23.2 Intrauterine Infections

Prenatal infections are important aspects of placental pathology [3, 4] because they cause placental changes. Although these infections are common and varied, some are difficult to detect during placental examinations. Intrauterine infection can occur via two routes. Most commonly, the infection ascends into the amniotic sac from the vagina or cervix or via the decidua. In some cases, the infection is carried to the placenta by the maternal blood flow (hematologic infection). Acute chorioamnionitis

Table 23.1 The association between clinical diagnosis and histological findings of the placenta in preterm labor

Clinical diagnosis	Histological placental findings
Intrauterine inflammation	Chorioamnionitis
	Funisitis
Hypertensive disorders of pregnancy	Maternal (decidual) vasculopathy
	Infarction
Intrauterine growth restriction	Infarction
	Maternal (decidual) vasculopathy
	Fetal vessel thrombosis
	Villitis of unknown etiology
	Hemorrhagic endovasculitis/endovasculosis
	Chronic histiocytic intervillositis
Abruption	Retroplacental hematoma
Chronic abruption-oligohydramnios sequence	Diffuse hemosiderin deposition

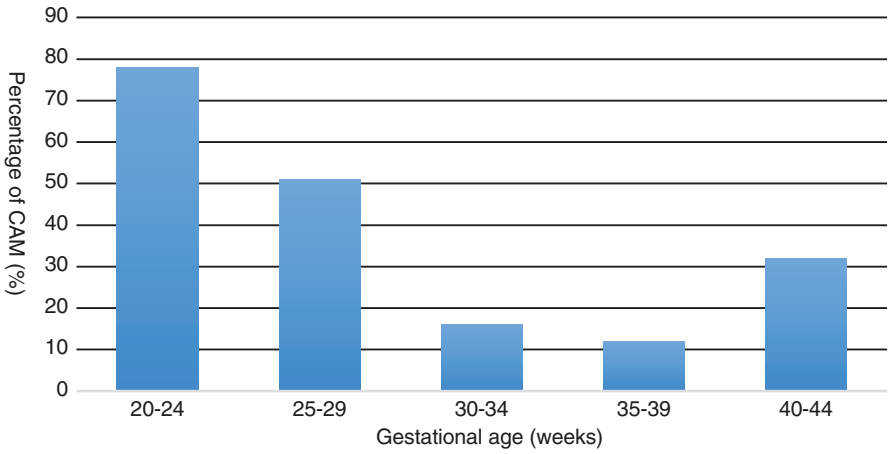

Fig. 23.1 The frequency of chorioamnionitis according to gestation age at the time of delivery

(CAM), membranitis, and funisitis indicate an ascending infection, whereas intervillositis or acute villitis indicates a maternal blood infection. Acute CAM is the most common diagnosis reported in placental reports and is generally considered to indicate the presence of intrauterine infection. The development of inflammation in the pregnant uterus involves several steps. First, the response to microorganisms is restricted to antigen non-specific cells, such as neutrophils and macrophages. Second, the inflammation tends to be confined to the peripheral area of the placenta, such as the membranes and terminal villi. Third, the fetal inflammatory response elicited by microbial antigens and other bacterial products damages fetal placental vessels and organs. CAM is associated with early delivery. Figure 23.1 shows the gestation age at the time of delivery in 522 cases of singleton pregnancies, wherein deliveries occurred after 20 weeks of gestation. The most deliveries occurred at a gestational age of 20–24 weeks (52/67 cases; 78%).

23.2.1 Chorioamnionitis

Typically, the CAM placenta is premature. Macroscopically, the color of the placenta and membranes appears to be normal in most CAM cases. If severe inflammation is present, the membrane may appear friable, edematous, opaque, and white-to-gray in color due to neutrophil exudation (Fig. 23.2). Long-term excess accumulation of leukocytic exudate causes the surface to become yellow. In addition, the membrane is typically more friable, and the decidua capsularis is frequently detached and hemorrhagic. These prematurely delivered placentas are often accompanied by acute marginal hemorrhage that originates from the deciduitis and undermines the edge of the placenta. In cases when CAM is detected in twin placentas, it is almost always the case that the cavity of twin A (first baby) is inflamed or contains the more severely inflamed portion. We have considered this to indicate that amniotic sac infections usually ascend through the cervical canal. Neutrophils are not normally present in the placental parenchyma or chorioamniotic membrane. The characteristic histological feature of CAM is the diffuse infiltration of neutrophils into the chorioamniotic plate or membrane. These leukocytes originate from two sources: the intervillous space (maternal leukocytes) and fetal surface blood vessels. Maternal neutrophils normally circulate in the intervillous space. In the presence of a chemotactic gradient, the neutrophils migrate toward the amniotic cavity, and the neutrophils in the subchorionic intervillous space mobilize in the chorionic plate of the placenta.

McNamara et al. [5] demonstrated that the neutrophils detected in CAM, with the exception of chorionic vasculitis, are of maternal origin by using fluorescence in situ hybridization (FISH) with probes for X and Y chromosomes. In contrast, Lee et al. [6] showed that the neutrophils in the umbilical cord and chorionic vessels of the placenta are of fetal origin. In addition, Sampson et al. [7] identified the neutrophils in the amniotic fluid to be of fetal origin.

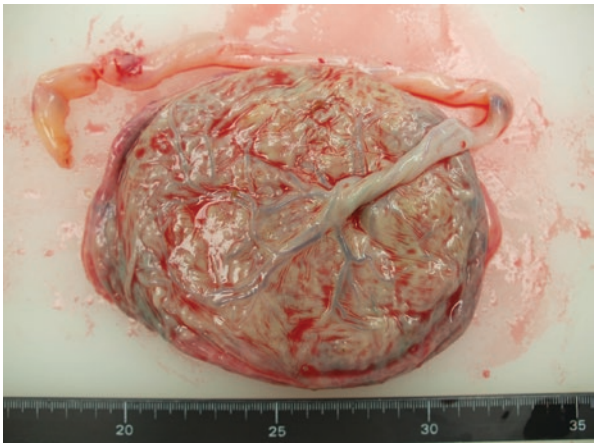

Fig. 23.2 Macroscopic appearance of chorioamnionitis. The amnion is white-to-gray in color

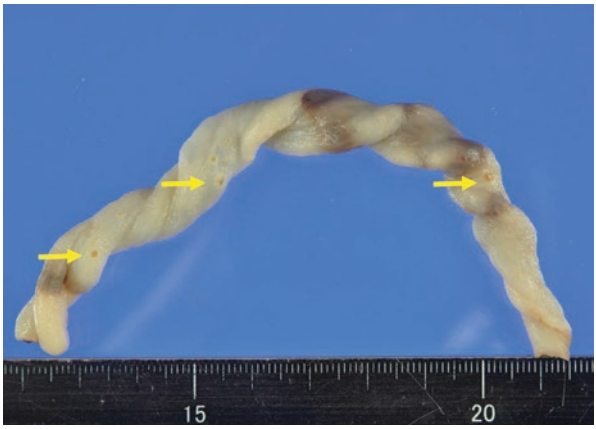

Fig. 23.3 Macroscopic appearance of *Candida* infection. Small white to yellow nodules can be seen (yellow arrows)

23.2.2 Funisitis

In early gestations, especially those prior to the 20th week of gestation, the neutrophils are mainly of maternal origin. By the midtrimester, the fetus is capable of producing leukocytes. Inflammation of the umbilical vessels begins in the vein (phlebitis), followed by involvement of the arteries (arteritis or funisitis). Neutrophil infiltration into the Wharton's jelly is common in acute funisitis. Tiny yellow-white nodules or plaques are observed on the umbilical cords infected with *Candida albicans* (Fig. 23.3). Microscopically, small accumulations of neutrophils with *Candida* hyphae are seen on the surface of the cord. Old exudate in the cord may accumulate in concentric perivascular rings. In cases of prolonged infection, mural thrombosis is frequently noted in the chorionic vessels. Thrombosis is noted in the umbilical cord in umbilical phlebitis, but is not commonly observed in umbilical arteritis.

23.2.3 Severity of Intrauterine Inflammation

Several grading and staging systems have been proposed to assess the severity of acute CAM. Histologically, intrauterine inflammation is generally divided into two categories: chorioamniotic membrane inflammation (maternal inflammation) and umbilical cord inflammation (fetal inflammation). Most systems that are designed to assess the severity of histological chorioamnionitis (CAM) have been based on the Blanc stage system [8]; however, this system has not been used to evaluate fetal inflammation. The classical CAM stage described by Blanc was found to be associated with chronic lung disease and intraventricular hemorrhage, but not with the occurrence of neonatal diseases after adjusting for gestational age [9].

Redline et al. [10] recently proposed a new histological system for grading both maternal and fetal inflammation according to the severity of the lesions (Table 23.2). They classified maternal and fetal inflammatory responses into stages and grades.

Table 23.2 Staging and grading system of acute chorioamnionitis and funisitis

	Maternal inflammatory response	Fetal inflammatory response
Stage 1	Chorionitis or subchorionitis	Umbilical phlebitis
Stage 2	Chorioamnionitis	Umbilical arteritis
Stage 3	Necrotizing chorioamnionitis	Necrotizing funisitis
Grade 1	Infiltration of individual or small clusters of neutrophils	Scattered neutrophil infiltration
Grade 2	Confluent neutrophil infiltration of at least 10–20 cells	Near-confluent neutrophil infiltration and/or degeneration of vascular smooth muscle cells

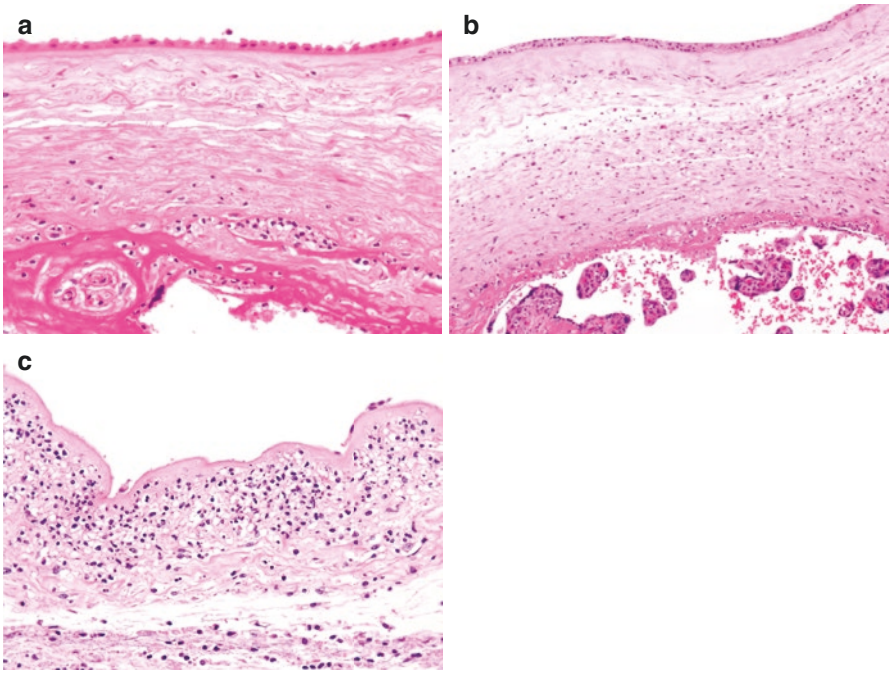

Fig. 23.4 Maternal inflammatory response stages. (**a**) Stage 1 (chorionitis or subchorionitis), (**b**) stage 2 (chorioamnionitis), (**c**) stage 3 (necrotizing chorioamnionitis)

Briefly, maternal stage 1 is characterized by the presence of neutrophils in the chorion (acute chorionitis) or subchorionic space (acute subchorionitis; Fig. 23.4a). Stage 2 refers to neutrophil infiltration in the amnion (acute CAM; Fig. 23.4b), and stage 3 is characterized by neutrophil infiltration and necrosis in the amnion (necrotizing CAM; Fig. 23.4c). Maternal grade 1 (mild to moderate) indicates the presence of individual or small clusters of neutrophil infiltration (Fig. 23.5a), and grade 2 (severe) involves confluent neutrophil infiltration comprised of at least 10–20 cells (Fig. 23.5b). Fetal stage 1 involves neutrophil infiltration in the chorionic vessel (chorionic vasculitis) or umbilical vein (umbilical phlebitis; Fig. 23.6a). Stage 2 involves neutrophil infiltration in the umbilical artery (umbilical arteritis; Fig. 23.6b)

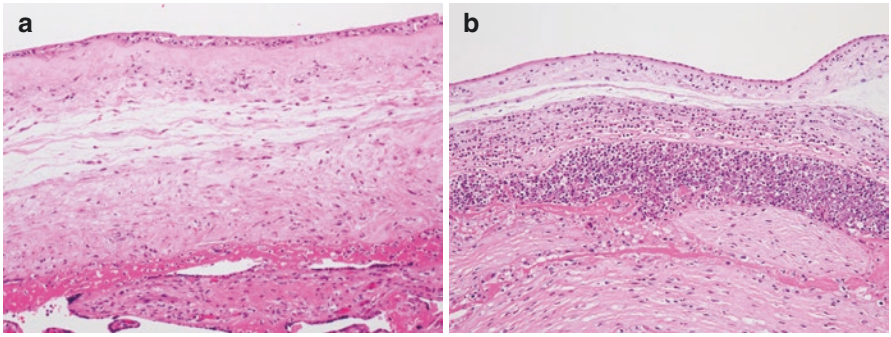

Fig. 23.5 Maternal inflammatory response grade. (**a**) Grade 1 (mild to moderate), (**b**) grade 2 (severe)

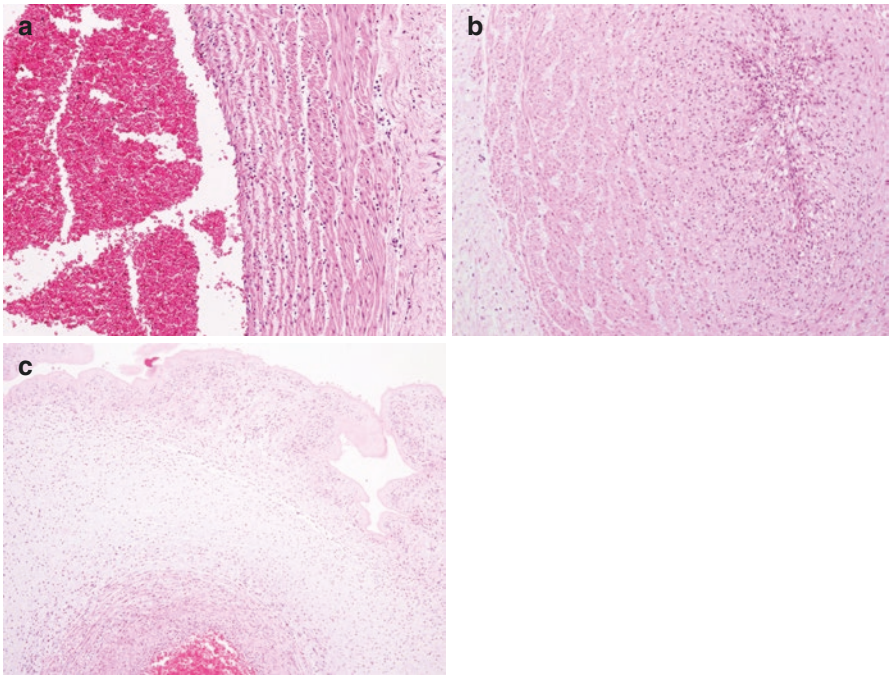

Fig. 23.6 Fetal inflammatory response stage. (**a**) Stage 1 (umbilical phlebitis), (**b**) stage 2 (umbilical arteritis), (**c**) stage 3 (necrotizing funisitis)

with or without phlebitis, and stage 3 is characterized by neutrophil infiltration with necrosis in the amnion (necrotizing funisitis; Fig. 23.6c). Fetal grade 1 (mild to moderate) is characterized by scattered neutrophil infiltration (Fig. 23.7a), and grade 2 (severe) is characterized by near-confluent neutrophil infiltration and/or degeneration of vascular smooth muscle cells (Fig. 23.7b). Zanardo et al. [11] reported that maternal stage 3 (necrotizing CAM) is associated with intraventricular

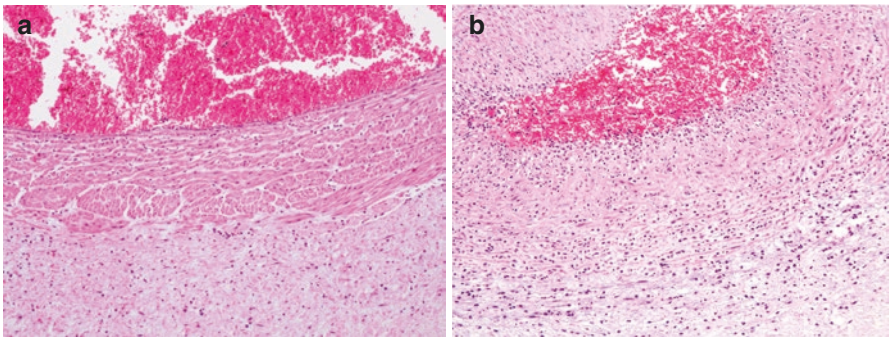

Fig. 23.7 Fetal inflammatory response grade. (**a**) Grade 1 (mild to moderate), (**b**) grade 2 (severe)

hemorrhage, and Lee et al. [12] showed that fetal inflammatory stage is associated with respiratory distress syndrome and bronchopulmonary dysplasia. We also used this system to assess placental findings in a study of 272 singleton neonates born at less than 34 weeks of gestation [13]. The incidence of sepsis, intraventricular hemorrhage, chronic lung disease, and necrotizing enterocolitis increased in a stepwise fashion with the severity of placental inflammation. After adjusting for gestational age, high grades of fetal inflammation were found to be significantly associated with chronic lung disease and necrotizing enterocolitis. Premature delivery is a major cause of perinatal mortality. Our study showed that higher stages and grades of maternal inflammatory responses were related to a shorter gestational age in CAM cases; in particular, the fetal inflammatory response was found to affect neonatal mortality.

23.2.4 Hematogenous Infections

Placental infection is rarely caused by infectious agents entering the organ via the maternal circulatory system. Generally, hematogenous infections involve the placental parenchyma rather than the membranes. Histologically, hematogenous infection is characterized by the presence of inflammatory lesions within the villous substrate, known as a villositis or villitis (Fig. 23.8). Villitis may be focal or diffuse. In acute villitis, the villi are infiltrated by neutrophils; however, in chronic villitis, lymphocytes, macrophages, or plasma cells are usually present.

23.3 Placental Insufficiency

Hypertensive disorders of pregnancy, typically defined as the de novo onset of hypertension and proteinuria after the 20th week of gestation, complicates approximately 2–8% of pregnancies [14]. The placenta in women with preeclampsia is smaller than that in women who have uncomplicated pregnancies. The overall

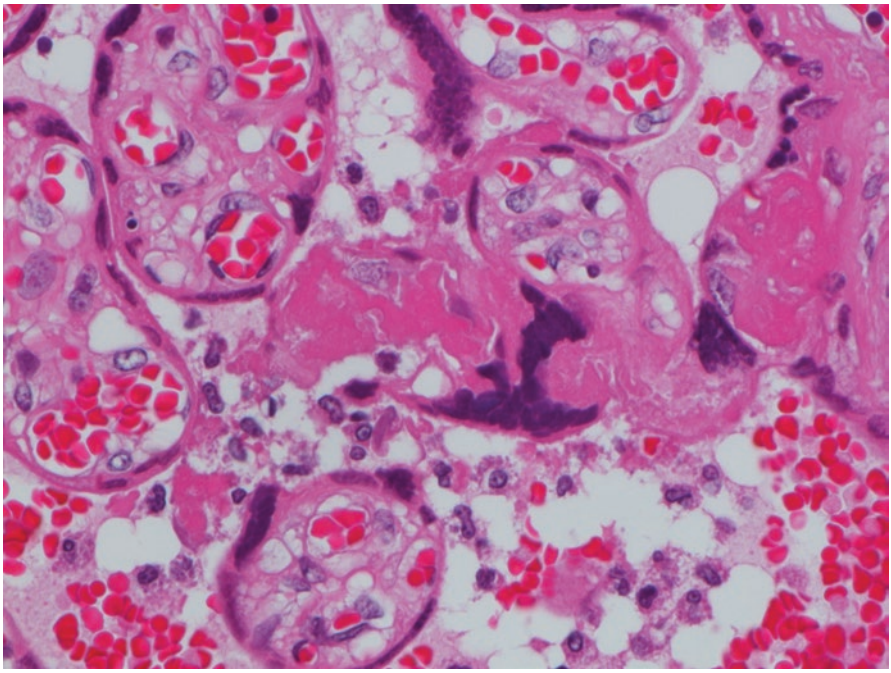

Fig. 23.8 Microscopic findings of hematogenous infection. Many neutrophils and macrophages are present in the intervillous space

incidence of placental infarction is much higher in preeclampsia cases than in uncomplicated pregnancies. The principal placental pathology changes in preeclampsia include maternal (decidual) vasculopathy, infarction in the central portion of the placenta, abruption, and Tenney-Parker change.

Intrauterine growth restriction (IUGR) or FGR manifests as low birth weight for a specific gestation period. IUGR is difficult to detect, and diagnosis usually involves a detailed assessment of maternal risk factors, including reproductive history, chronic conditions, pregnancy risk factors, and consecutive ultrasound findings. The placenta of babies with IUGR is small. Although IUGR is caused by several factors, reduced uteroplacental blood flow is a major cause. Further, primary intrinsic placental growth defects do not play a role in reduced placental growth. Placental insufficiency is a common cause of IUGR; however, fetal factors, including chromosomal abnormalities, congenital infections, and maternal risk factors, also contribute to IUGR.

Various pathological correlates, such as placental infarction, fetal vasculopathy/thrombosis, maternal vasculopathy, and chronic villitis, have been identified in IUGR cases [15]. In a previous study [16], we compared Japanese IUGR placentas (257 cases) with control placentas (normal growth pregnancies; 258 cases) and found the IUGR placentas to be smaller (296 g vs. 373 g, $P < 0.001$). With regard to histological findings, the prevalence of infarction (33% vs. 14%,

$P < 0.05$), fetal vessel thrombosis (22% vs. 6%, $P < 0.001$), and chronic villitis/VUE (11% vs. 3%, $P < 0.001$) was higher in the IUGR cases than in the controls. Other studies also demonstrated a high incidence of infarction, maternal infarction, and VUE in IUGR/FGR cases; however, acute CAM was not found to be associated with IUGR/FGR.

23.3.1 Maternal Vasculopathy

Maternal or decidual vasculopathy comprises a group of related pathological changes in the spinal arteries of the maternal decidua, including acute atherosis, hyalinization, and mural or occlusive thrombosis. Acute atherosis and preeclampsia placentas maybe of a normal size, but they are often smaller than average. Infarcts are common. Microscopically, smooth muscle cells of the vascular media persist. Acute atherosis is characterized by mural fibrinoid necrosis and the accumulation of large, foamy, lipid-filled macrophages and neutrophils (Fig. 23.9). Occlusive and mural thrombi are common. Ultrastructural studies of the placental bed vessels reveal endothelial injury. Distinct alterations are commonly seen in the villi of placentas associated with maternal preeclampsia and other states of maternal vascular perfusion.

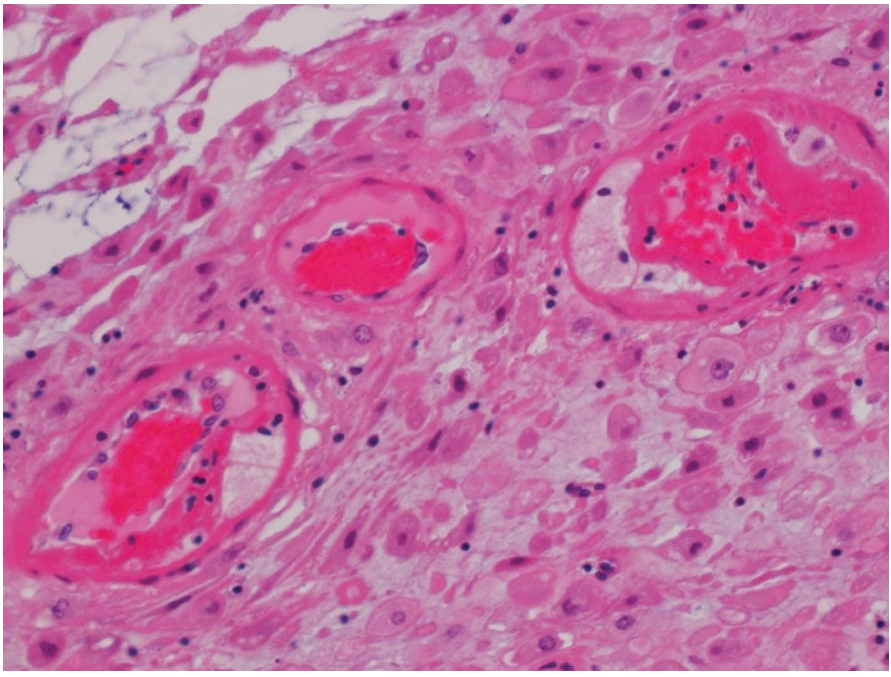

Fig. 23.9 Microscopic appearance of acute atherosis. The arteries show fibrinoid degeneration and accumulation of foamy macrophages

23.3.2 Infarction

Placental infarctions are localized regions of ischemic necrosis of the villi. Macroscopically, infarctions are circumscribed and firmer than the adjacent placenta. Recent infarctions appear dark red with only slight induration, and have a homogeneous or solid-appearing cut surface. These infarctions can be distinguished from living tissue by their firmness and lack of a spongy texture. Older infarctions are more indurated and demarcated, and progressively turn brown, tan, and finally white in color. Microscopically, necrosis of the villi is noted in the infarcted area (Fig. 23.10). In acute infarctions, villi are clustered together and are attached to one another by fibrin strands. The extreme ischemia also produces prominent trophoblastic knots. In old or chronic infarctions, the nuclear membranes of the trophoblasts and stromal and endothelial cells disappear. Phagocytosis of necrotic cells, organization, and fibrosis are observed.

23.3.3 Tenney-Parker Change

Tenney-Parker change (aggregation of syncytiotrophoblastic nuclei) is often noted in cases of placental insufficiency, such as preeclampsia or FGR. The placental stem villi are often slender with reduced branching; the terminal villi are very small and

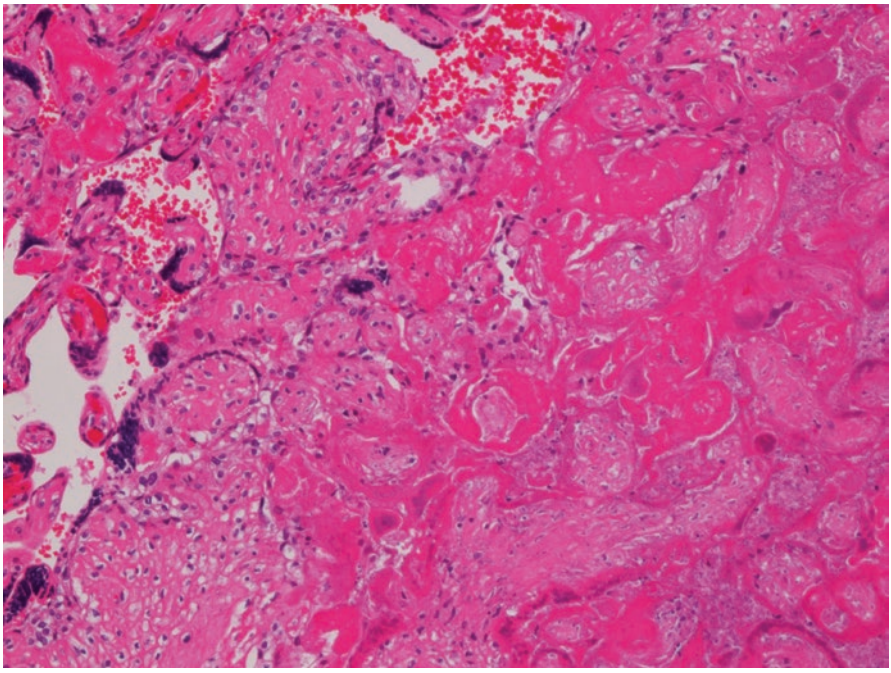

Fig. 23.10 Microscopic appearance of infarction. Coagulative necrosis of the villi (nuclei loss) is noted on the right side, and Tenney-Parker change is observed on the left side

produce a stunted or atrophic-appearing pathological pattern. This combination of findings has been termed as accelerated maturation.

23.3.4 Fetal Vessel Thrombosis

Fetal vessel thrombosis is associated with placental insufficiency, such as in the case of FGR, or stillbirth. Mural thrombi occur frequently in the superficial placental vessels and stem vessels, but occlusive thrombi are rare. Macroscopically, thrombotic occlusion areas on the chorionic or stem vessels with avascular villi (fetal thrombotic vasculopathy [FTV]) appear rough or sharply pale. Mural fetal vessel thrombosis is common, but FTV is rare.

Microscopically, fetal vessel thrombi are usually mural thrombi with some degree of organization (Fig. 23.11). Mural thrombi attach to the vascular wall without endothelial cells, and fibrous intimal thickening (endothelial cushion) is occasionally noted. Such thrombi often calcify over a prolonged duration. Old thrombi may get completely obliterated, and they may be difficult to detect among completely organized thrombi with fibrin strands. If the large thrombi have been occlusive for a prolonged duration, the entire villous tree may become avascular and atrophic and undergo fibrosis (FTV). However, avascular villi are occasionally

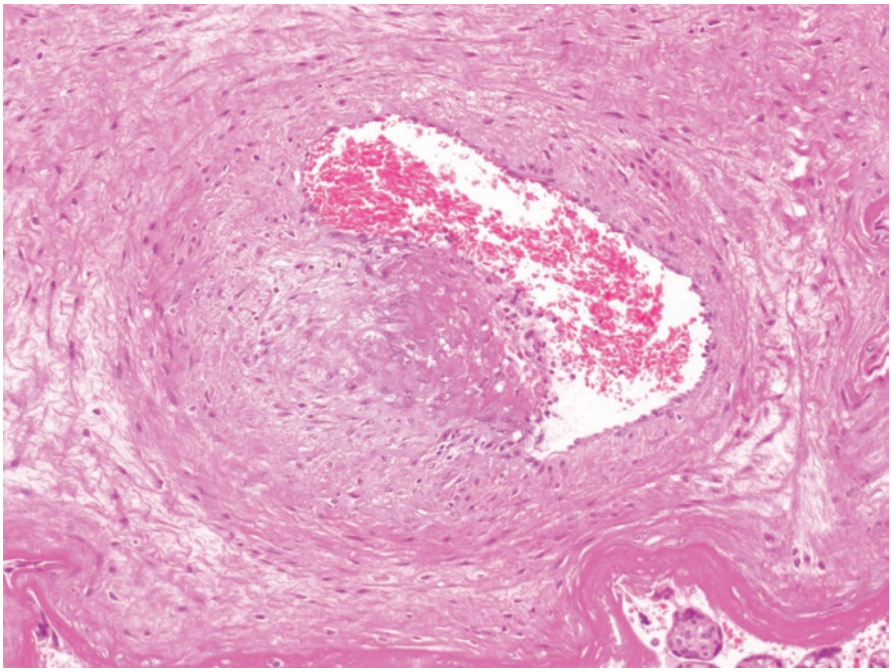

Fig. 23.11 Microscopic appearance of fetal vessel thrombosis. Mural thrombosis with organization (endothelial cushion) is present in the fetal vessel

found in many diseases and otherwise normal placentas. Redline and O'Riordan [17] proposed that the minimal criterion for FTV was the presence of ten or more small foci of three to five avascular villi.

Fetal vessel thrombi are variably located across the fetal surface within the placenta, and are only occasionally present in the umbilical cord. The thrombi are usually found in the umbilical vein associated with the intrauterine infection but have been reported to occur in the umbilical arteries as well. We previously reported on 11 cases of umbilical artery thrombosis [18]. In that study, the majority of umbilical artery thrombi were found in one artery, and atrophy of the umbilical arteries and mural ischemic degeneration of the vascular wall were noted. These thrombi were found to be associated with severe FGR or fetal mortality.

23.3.5 Hemorrhagic Endovasculitis/Endovasculosis

According to Sander et al. [19, 20], this fetal vessel abnormality is characterized by various degrees and combinations of stem vessel wall disruption with erythrocyte fragmentation, obliteration of villous capillaries, and thrombi in the stem vessels (Fig. 23.12). This fetal vessel disease is reportedly associated with a majority of stillbirth cases (>80%). However, placentas from liveborn infants also have this focal lesion, and it is usually associated with VUE, chorionic thrombi, or infarction.

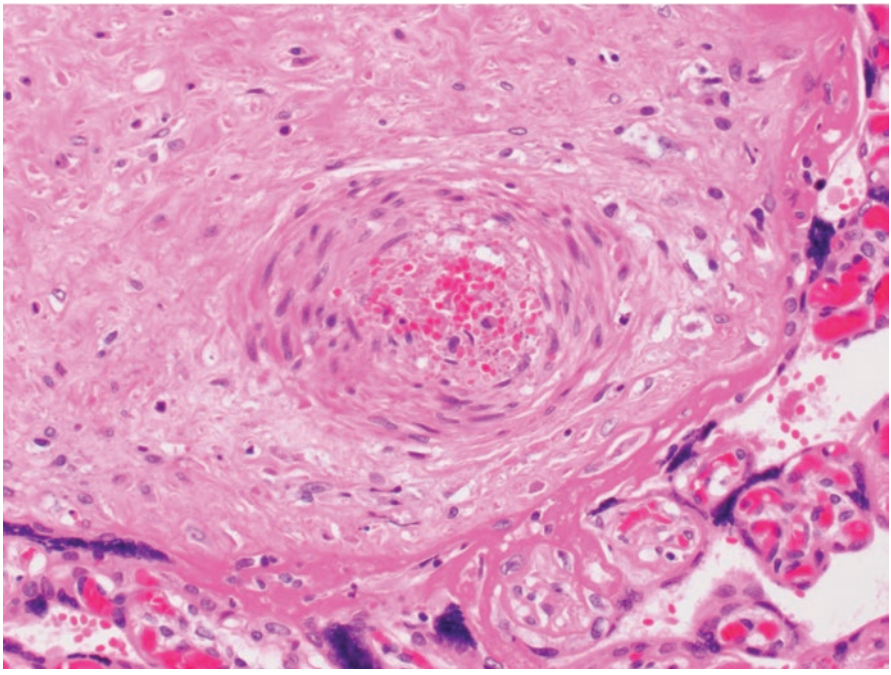

Fig. 23.12 Microscopic appearance of hemorrhagic endovasculitis/endovasculosis. The stem vessel exhibits obliteration with erythrocyte fragmentation

23.4 Intrauterine Hemorrhage

Intrauterine hemorrhage (placental abruption/retroplacental hematoma and diffuse hemosiderin deposition) is associated with preterm labor. Other intrauterine hemorrhage lesions are known as massive subchorionic thrombosis or intervillous thrombosis. We will focus on placental abruption/retroplacental hematoma and diffuse hemosiderin deposition.

23.4.1 Placental Abruption/Retroplacental Hematoma

Retroplacental hematoma occurs between the basal plate of the placenta and the uterine wall. Placental abruption refers to the clinically symptomatic state of premature placental separation with pain, bleeding, and accelerated uterine enlargement in the mother. Symptomatic placental separation may be extensive and occur suddenly. In classical abruption, the placenta has fresh clot attached at the maternal surface (Fig. 23.13). Older retroplacental hematomas are firm and brownish in color; further, the overlaying placenta is usually infarcted if the hematoma is large. The villous tissue is usually compressed by the hematoma and infarction, or ischemic changes of the villous tissue are noted. Maternal vasculopathy may also be observed.

23.4.2 Chronic Abruption-Oligohydramnios Sequence/Diffuse Hemosiderin Deposition

Abruption placenta is acute placental hemorrhage, leading to acute breakdown of placenta functions, such as fetal blood oxygenation. In contrast, chronic placental hemorrhage is not lethal to the fetus, and the pregnancy period can be prolonged with the administration of appropriate medication. Chronic placental hemorrhage is associated with oligohydramnios, as is termed as chronic abruption-oligohydramnios sequence (CAOS), which typically results in preterm delivery at approximately 28 weeks of gestation.

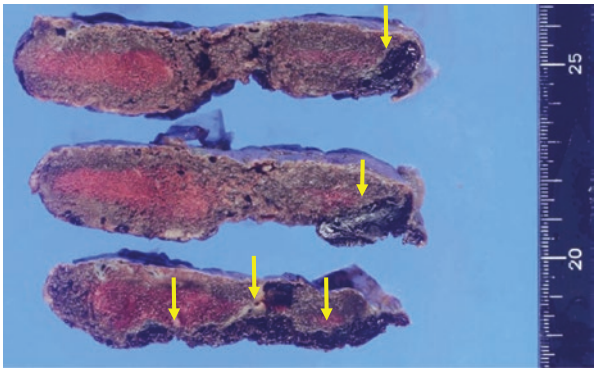

Fig. 23.13 Macroscopic appearance of a retromarginal hematoma. The hematoma compresses the parenchyma of the placental tissue

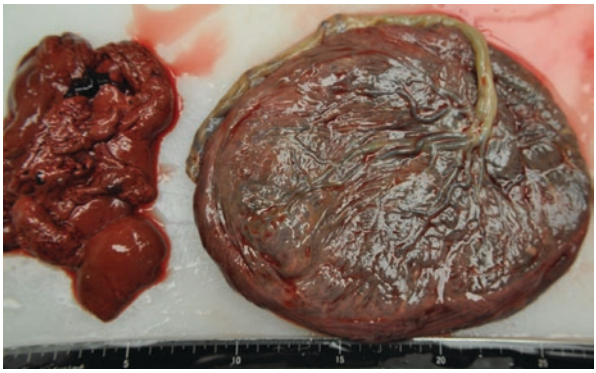

Fig. 23.14 Macroscopic appearance of diffuse hemosiderin deposition. The amnion is gray to greenish in color

Redline and Wilson-Costello [21] described the diffuse iron-stain positive pigment deposition in the chorioamniotic layers of the chorionic plate and/or membranes as diffuse chorioamniotic hemosiderosis (DCH). They reported a correlation between DCH and circumvallation and old peripheral blood clots, and proposed that DCH is an objective indicator of chronic peripheral separation and clinical CAOS. Ohyama et al. [22] analyzed DCH placentas and reported macroscopic findings of old peripheral blood clots (DHC: 46% vs. control: 8%), subchorionic hematoma (20% vs. 1%), and circumvallation (13% vs. 1%). With regard to microscopic findings, amniotic necrosis was significantly more frequent in the DHC group (63% vs. 24%). The incidence of recurrent episodes of vaginal bleeding (70% vs. 11%) and oligohydramnios (59% vs. 8%) was significantly higher in the DHC group.

The DCH placenta is brown to green in color in the amniotic membrane and exhibits circumvallation and old peripheral blood clots (Fig. 23.14). Microscopically, diffuse marked hemosiderin deposition is noted in the chorioamniotic plate or membrane, which is caused by the phagocytosis of hemoglobin or the products of hemoglobin breakdown by macrophages. Marked degeneration or necrosis of the amnion is also noted.

23.5 Chronic Inflammation of Unknown Etiology

Chronic inflammation lesions of the placenta are characterized by the infiltration of chronic inflammatory cells (lymphocytes, plasma cells, and/or macrophages), and may result from infections or be of unknown etiology (probably due to immunological reasons such as maternal anti-fetal rejection). Chronic inflammation lesions of the placenta that have an unknown etiology are known as VUE and chronic histiocytic intervillositis (CHI).

23.5.1 Villitis of Unknown Etiology

VUE is a T-cell-mediated disorder targeting the distal villous tree. It is characterized by chronic cellular inflammation of the villous stroma (villitis), intervillous space (intervillositis and perivillous fibrin deposition), and stem villous vessels

(obliterative fetal vasculopathy) [23]. VUE is a common lesion and occurs in approximately 3–5% of all term placentas. Immunohistochemical and in situ hybridization studies have shown that VUE represents a maternal immune response occurring within the fetal tissue, and the infiltrating lymphocytes are primary maternal T lymphocytes [24]. Clinically, VUE is associated with IUGR/FGR [23]. Antenatal fetal abnormalities are more common in pregnancies with diffuse VUE. The incidence of diffuse VUE is significantly higher in the placentas of term infants with cerebral palsy and other forms of neurogenic impairments.

Macroscopically, almost all placentas with VUE are normal, but some placentas are small for the gestational age and may exhibit a pale discoloration. In VUE, the microscopic findings include an infiltration of maternal T cells and an increasing number of fetal macrophages in the intermediate and terminal villi (Fig. 23.15); this is noted more commonly in the basal villous tissue (approximately 50% of cases). Basal villitis involves the anchoring of villi to the basal plate, and this type is frequently associated with chronic deciduitis. The proximal type occurs in 30% of cases and involves the proximal stem villi; this type is associated with obliterative vasculopathy and fetal vascular thrombo-occlusive disease, which results in hyalinized avascular villi. The histological grading of VUE is based on the number of affected chorionic villi [23]. Approximately two-thirds of VUE cases involve small clusters of five to ten villi in either a single (focal) or multiple (multifocal) slides.

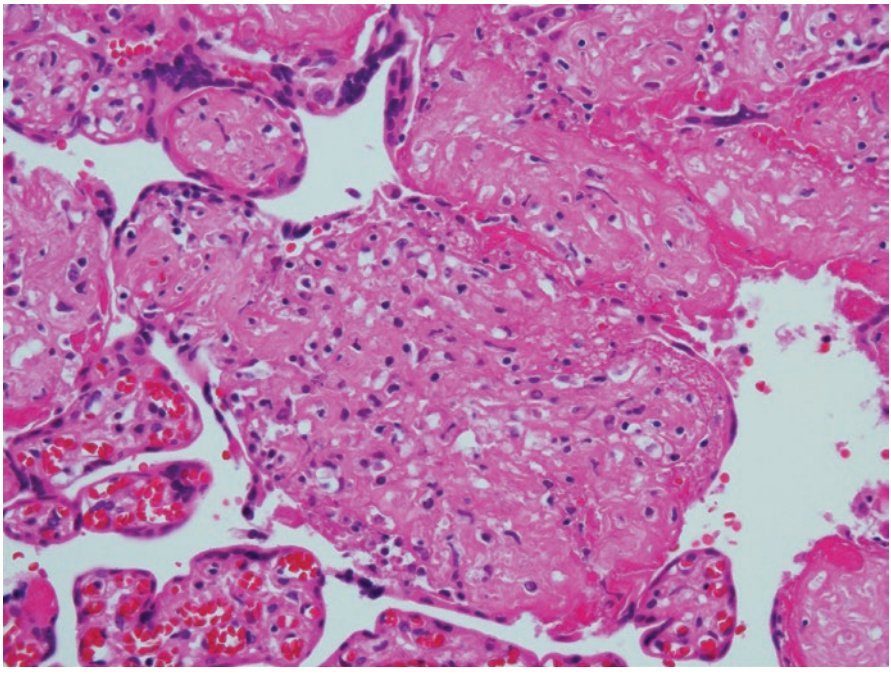

Fig. 23.15 Microscopic appearance of villitis of unknown etiology. Many chronic inflammatory cells infiltrate the terminal villi. The villi exhibit fibrosis and capillary loss

These low-grade patterns are usually clinically silent. The remaining cases involve larger (more than ten villi) foci (patchy) and diffuse involvement of all sections (diffuse). A strong relationship has been demonstrated between these high-grade patterns and FGR and other clinical complications.

23.5.2 Chronic Histiocytic Intervillositis

CHI is a rare placental lesion characterized by marked infiltration of maternal chronic inflammatory cells into the intervillous space, which can be accompanied by varying degrees of intervillous fibrin deposition. This entity, first described by Labarrete and Mullen in 1987 [25], consists of recurrent lesions and is associated with a poor pregnancy outcome; however, despite anecdotal reports of successful immunomodulatory treatment, no effective treatment is available [26]. The reported incidence of CHI is 4.4% in first trimester miscarriages with a normal karyotype and is quite rare in the second or third trimester. The true incidence of CHI, however, is still unknown. The mechanism underlying these associations is still unclear. Further, a hypothesis of immune conflict was proposed, but is yet to be proven [27] (Fig. 23.16).

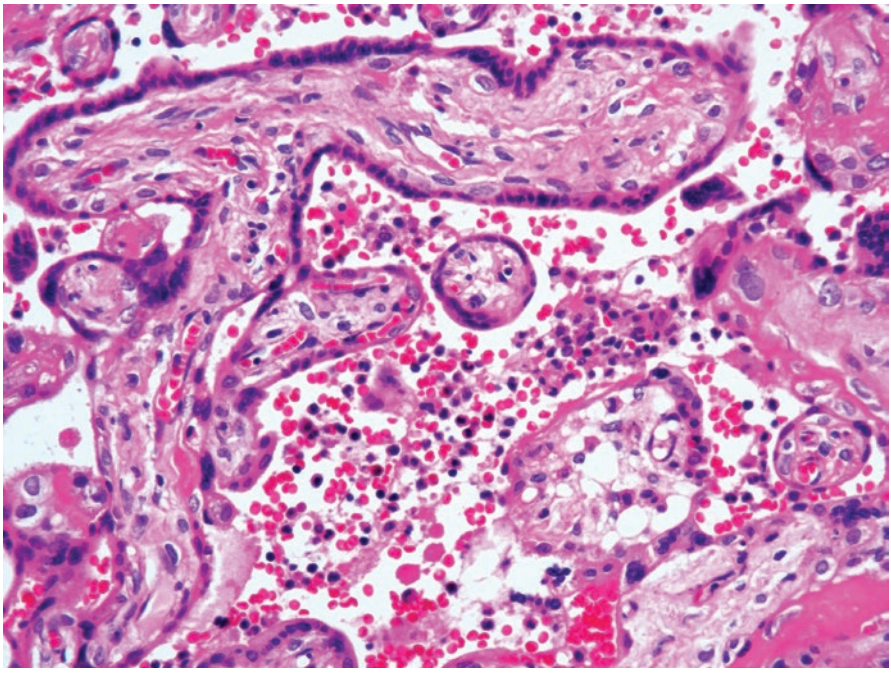

Fig. 23.16 Microscopic appearance of chronic histiocytic intervillositis. Many macrophages are present in the intervillous space

CHI produces no symptoms during pregnancy. Diagnosis is established exclusively postnatally on the basis of histology, but there is no final consensus on the diagnostic criteria. Heller [28] analyzed the CD68-positive cell count in CHI cases and control cases and found that the mean CD68 cell count per high-power field was 88 in the CHI cases and eight in the controls ($P < 0.01$). Capuani et al. [29] showed that, in CHI, inflammatory cells made up the predominant component (80%) of histiocytic cells apart from T cells (20%). The ratio of CD4 to CD8 cells was close to 1.

The frequent associations between VUE and CHI and the incidence of recurrence of both conditions make it difficult to establish a clear difference between the two. CHI is associated with a higher morbidity rate (intrauterine fetal death and IUGR) as compared to VUE, but the morbidity associated with combined lesions was similar to that of VUE.

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