# Placental and Maternal Conditions in Perinatal Deaths

5

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## Contents



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K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2_6,

**Abstract**

The placenta provides information about the in utero environment. Abnormalities in the placenta are responsible for many cases of fetal or neonatal deaths, which, without the placenta, may go unexplained. This chapter describes how to examine and section the placenta to yield the best results. The placental abnormalities associated with prematurity, infection, intrauterine growth restriction, intrauterine fetal demise, maternal hypertensive disorders, and diabetes are described.

## Introduction

This chapter is designed to aid the evaluation of the placenta associated with a fetal demise or neonatal death, with emphasis on those maternal conditions that may have negative effects on fetal survival. The placenta is a "diary" of the intrauterine environment. Unfortunately, there are many different terms used when describing placental findings and differing opinions about the significance of some of these, which has resulted in confusion. There is no one finding that is diagnostic of a particular maternal or fetal condition. However, combinations of findings in the placenta can yield relatively consistent clinical pathological correlations.

## Basic Placental Examination

The gross examination of the placenta should include measurements of the various components and presence of both positive and negative findings. Generally important findings include trimmed weight, location of umbilical cord insertion, cord length and any abnormalities, cord diameter, color of membranes, presence of retroplacental clots, and parenchymal lesions. There are numerous placental textbooks and publications describing the important gross findings, including the guidelines published by the College of American Pathologists (Langston et al. 1997). In general, the placenta has three basic functions which include maternal blood flow, fetal blood flow, and permeability of the villi. If any of these functions is significantly altered, it can jeopardize the fetal well-being.

Adequate sections should be submitted to assure the identification of significant pathology, but in addition, normal tissues must also be examined. It is necessary to assess the development of the placenta in order to determine the significance of pathological features. In general, the placenta has built-in redundancy which allows the fetus to withstand the relative hypoxic intrauterine environment and the stress of labor. If the placenta is developmentally normal (normal weight with appropriate villous maturation), there is approximately a 30 % reserve capacity. However, if the placenta is developmentally abnormal (small for gestation, accelerated maturation), that reserve capacity is reduced to

**Table 5.1** Mean expected weight of placenta and length of umbilical cord

| Gestation | Mean weight (trimmed gm) | Fetal:Placental (F:P) weight (ratio) | Cord length (cm) | Cord diameter (cm) |
|---|---|---|---|---|
| 8 | 1.6 | | 6 | |
| 10 | 28.8 | | 10 | 0.32 |
| 12 | 56.1 | | 13 | 0.37 |
| 14 | 83.3 | | 16 | 0.51 |
| 16 | 110.5 | 1:1 | 20 | 0.65 |
| 18 | 137.8 | | 23 | 0.79 |
| 20 | 163 | 2.7:1 | | 0.95 |
| 22 | 189 | 2.9:1 | 28 | 1.09 |
| 24 | 190 | 3.4:1 | | 1.22 |
| 26 | 226 | 4.1:1 | 38 | 1.40 |
| 28 | 254 | 4.8:1 | | 1.43 |
| 30 | 314 | 5.2:1 | 50 | 1.62 |
| 32 | 338 | 5.9:1 | | 1.66 |
| 34 | 381 | 6.2:1 | 53 | 1.67 |
| 36 | 447 | 6.6:1 | | 1.65 |
| 38 | 493 | 6.9:1 | 57 | 1.58 |
| 40 | 510 | 7.2:1 | | 1.56 |
| 42 | 532 | 7.1:1 | 60 | 1.44 |

(Ref: Kalousek et al. 1990; Kraus et al. 2004)

as little as 10 %. Therefore the size, location, and type of lesions found within the placenta are important. A gross assessment of percentage of abnormal tissue noted needs to be correlated with the microscopic findings, as grossly normal tissue may also be abnormal. The expected placental weight is based on the disc only after the membranes and cord have been trimmed (Table 5.1).

## CAP-Recommended Placental Sections

- Two sections of the umbilical cord from separate areas
- A membrane roll to include the zone of membrane rupture
- Two full-thickness sections of nonmarginal, normal placenta
- Additional sections from abnormalities

The cord sections are primarily submitted to look for fetal inflammation, which may be focal (Katzman and Metlay 2010). There are often hematomas near the fetal end of the cord, secondary to clamping during delivery. These areas should be avoided, as they obscure inflammation. Cord diameter is representative of fetal fluid balance and growth. Thin, flattened, and abnormally spiraled cords are at increased risk of compression.

The zone of membrane rupture has a rolled appearance (Fig. 5.1). In a vaginal delivery, it is the portion of membranes over the cervix that is the most likely to be

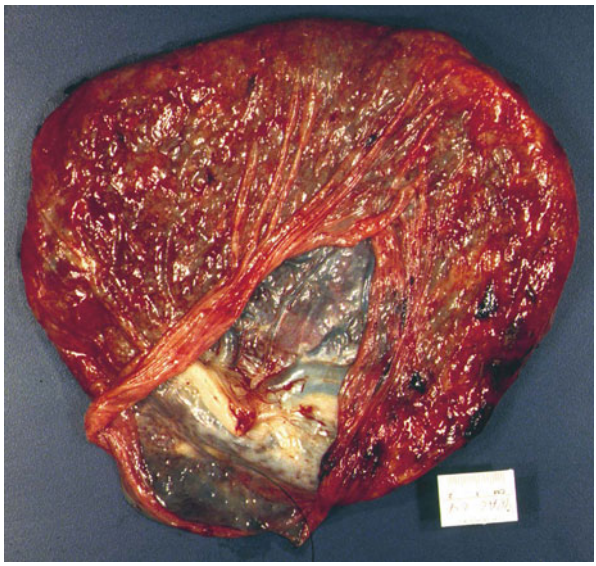

**Fig. 5.1** Asymmetric zone of membrane rupture, indicating a low-lying placenta

inflamed as the result of an ascending infection. The zone of membrane rupture is also a clue to the location of the placenta within the uterus. If the membrane rupture is at the placental margin, the placenta was low-lying. Of course, if the delivery is by C-section, the site of membrane rupture usually does not reflect either of these. It has been reported that four membrane rolls have a near-linear increased yield for both chorioamnionitis and maternal vasculopathy (Winters and Waters 2008). One might argue that if the findings are so focal, their significance is diminished.

Terminal villi are the functional unit of the placenta and a feature of a mature placenta. They become the dominant structure around 34 weeks gestation. Appropriate maturation of the placenta is paramount for appropriate transfer of oxygen and nutrients from the maternal to the fetal blood across the vasculosyncytial membranes. Villous development and maturation is a complex topic addressed elsewhere (Popek 1999). In general, throughout gestation, the villi become progressively smaller, there is a decrease in stromal cellularity, and the vessels become larger and move to the periphery to form the vasculosyncytial membrane. Assigning villous maturation is at best an estimate (Fig. 5.2a–d). There is variable maturation within every placenta; the marginal and subchorionic villi are generally less well perfused and appear more mature. The most significant abnormalities include generalized accelerated or delayed maturation.

While the CAP recommends only two full-thickness sections from nonmarginal normal-appearing placenta, many placental pathologists advocate that four sections of parenchyma result in a higher yield of abnormalities. Full-thickness sections show the dichotomously branching fetal vascular tree and the relationship of the villi overlying maternal vessels and are more useful than incomplete sections (Fig. 5.3).

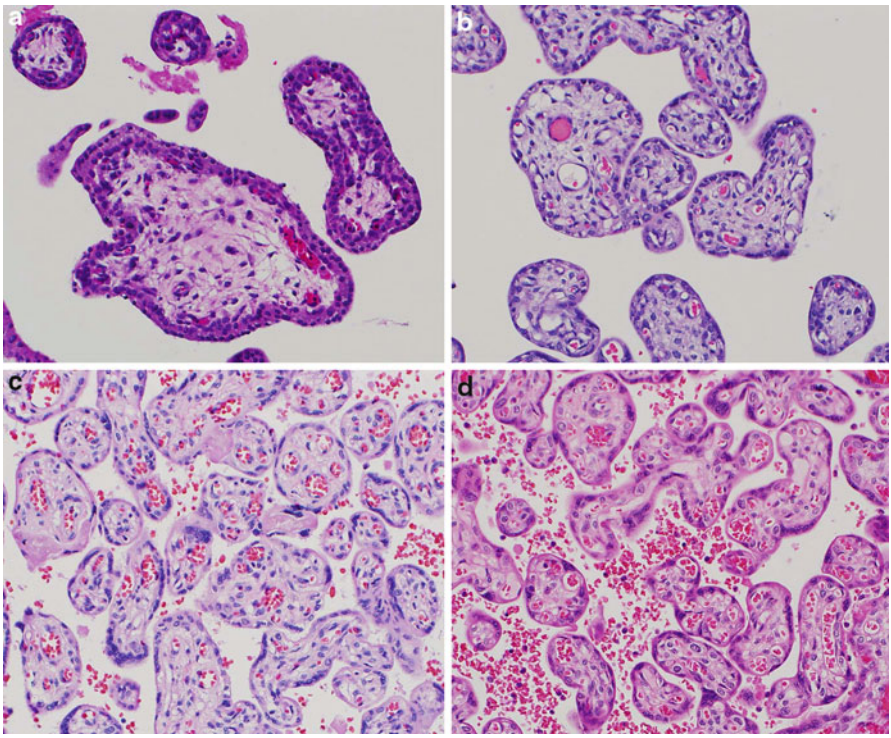


**Fig. 5.2** Villous maturation. (**a**) 10 weeks gestation, (**b**) 20 weeks gestation, (**c**) 30 weeks gestation, (**d**) 40 weeks gestation (Hematoxylin and Eosin, H&E × 20)

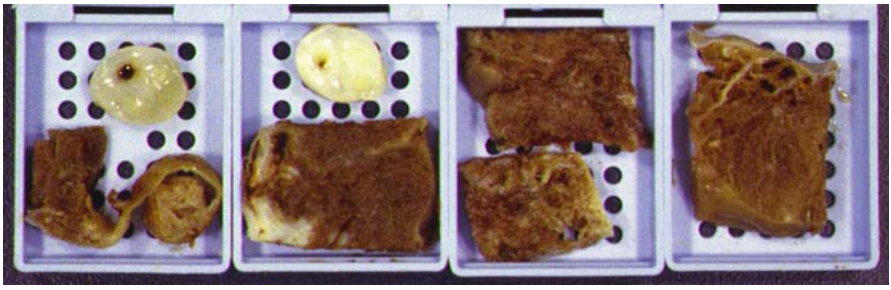

**Fig. 5.3** Suggested routine blocks of placental tissues

## Estimating Time of Fetal Demise by Placental Examination

Umbilical cord smooth muscle degeneration, villous capillary intravascular karyorrhexis, and intravascular and villous stromal fibroblast proliferation are features that occur after fetal demise but may also be found in live births and may

**Table 5.2** Placental changes after fetal demise

| Histologic feature | Postmortem interval | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <6 h | 6–12 h | 12–24 h | 24–36 h | 36–48 h | >48 h | >7 days | >14 days |
| Umbilical cord vascular degeneration | 0 | 33 % | 100 % | 100 % | 100 % | 100 % | 100 % | 100 % |
| Villous stromal karyorrhexis | 0 | 75 | 73 | 64–100 | 100 | 100 | 100 | 100 |
| Stem vessel luminal abnormalities | 0 | 25 | 7 | 21 | 67 | 20–60 | 50–100 | 100 |
| Villous stromal fibrosis | 0 | 0 | 0 | 0 | 0 | 20 | 50 | 100 |

(Ref: Jacques et al. 2003; Genest 1992)

be the etiology of fetal demise. There is significant overlap and very broad time intervals with regard to these findings. The most sensitive predictors include degeneration of cord vascular smooth muscle, villous intravascular karyorrhexis, stem vessel luminal obliteration, and villous fibrosis (Jacques et al. 2003; Genest 1992) (Table 5.2). These changes will be discussed more thoroughly in the section on fetal thrombotic vasculopathy. The placenta is the least reliable in estimating the duration of fetal demise.

## Umbilical Cord

The umbilical cord is the lifeline for the fetus (Fig. 5.4a–e). Cord accidents probably account for more cases of fetal demise than we can definitively document. Nuchal cord, looped around the neck, is present in at least 20 % of deliveries and most are not significant. Flattening on one side of the cord can sometimes be evident. Knots occur in 1 % of deliveries. As the baby descends during labor, a nuchal cord or knot can become progressively tighter. Cord length also increases throughout gestation and has some relationship to fetal movement (Table 5.1). Short cords are those less than 30–32 cm at term and may reflect neurological or musculoskeletal abnormalities. The cord diameter is a reflection of fetal growth and fluid balance. Thin cords are seen in intrauterine growth restriction (IUGR). Wrinkling of the cord surface is often an indication of decreased amniotic fluid. A thin cord may also be associated with a single umbilical artery (SUA), which is seen in 1 % of deliveries. Congenital malformations are present in 20 % of SUA. Cord spiraling is considered a reflection of fetal movement. The spiraling of the two pulsatile umbilical arteries around the vein also help move oxygenated blood to the fetus. Decreased spiraling, flattened cord, and decreased Wharton's jelly all are risk factors for cord compression. Increased spiraling is often associated with exceptionally long cords and has an increased risk of torsion or stricture and intrauterine fetal demise (IUFD).

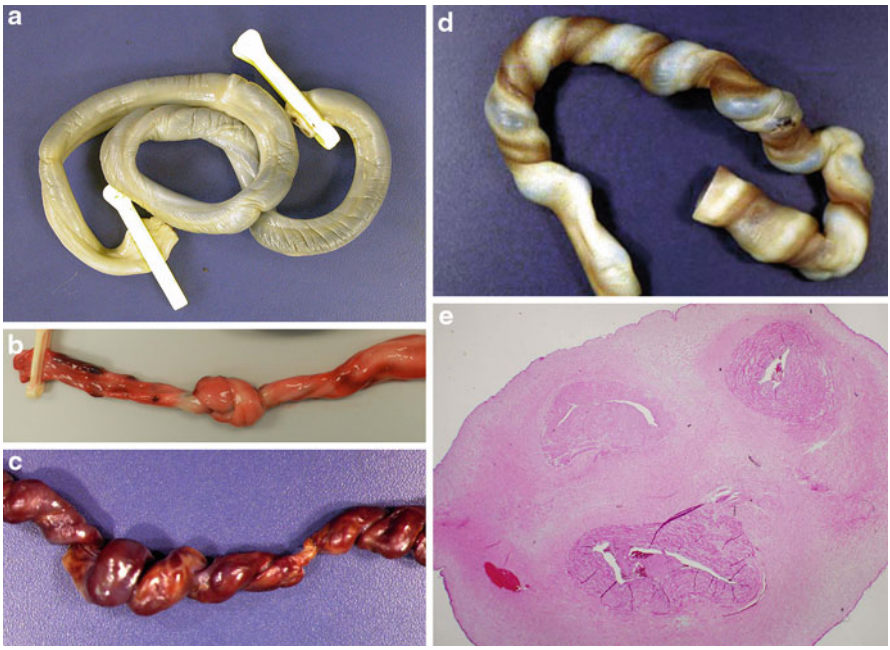


**Fig. 5.4** Cord abnormalities. (**a**) Nuchal cord x 3 with one side flattened, (**b**) Tight knot, but no differential congestion on the placental site, (**c**) Excessive spiraling with stricture in IUFD, (**d**) Recent umbilical artery thrombus, with extravasation of hemoglobin pigments, (**e**) Devitalized artery due to recent thrombosis (Hematoxylin and Eosin, H&E × 4)

## Preterm Delivery

Preterm delivery is defined as delivery less than 37 weeks gestation and complicates approximately 12–13 % of all births in the United States (USA) (Goldenberg et al. 2008). An increasing number of these, up to 20 %, are iatrogenic, with induced early delivery secondary to either maternal complication or nonreassuring fetal status. Spontaneous preterm births follow labor with intact membranes or after rupture of membranes. Risk factors of preterm births include a previous preterm birth, Black race, periodontal disease, bacterial vaginosis, short cervix, and low maternal body mass index.

Premature rupture of membranes complicates 4.5 % of pregnancies, accounting for 30–40 % of preterm births (Mercer et al. 2000; Menon and Fortunato 2007). In the majority of these cases, the membranes have been weakened by inflammation; however, the remaining have no inflammation, and the etiology of membrane rupture remains unknown. Latency between rupture of membranes and delivery is usually less than 5 days if inflammation is already present but can be weeks in the absence of infection.

Examination of the placenta in spontaneous preterm birth shows two nearly equal and distinct patterns of pathology in preterm delivery: infectious chorioamnionitis and maternal vascular abnormalities typical of hypertensive diseases of pregnancy (Arias et al. 1993; Faye-Petersen 2008).

## Infection

### Ascending Infection

Chorioamnionitis is the amniotropic migration of maternal neutrophils within the fetal membranes in response to microbial invasion of the amniotic cavity. The fetal inflammatory response within the umbilical cord and chorionic plate vessels is also amniotropic. Various definitions and grading schemes have been proposed, but in general, the diagnosis remains a descriptive one that includes the location and intensity of inflammatory cells (Redline et al. 2003). Maternal inflammation is progressive from the decidua-chorion-amnion. The time necessary for development of full-thickness membrane inflammation is several days, but a number of factors prevent precise timing, including virulence of the bacteria, bacterial load, and maternal immunocompetence. The higher within the membranes and the more severe the inflammation, the worse the outcome. Acute chorioamnionitis is evidence of an ascending infection and is not the result of fetal demise but can occur after fetal demise, as the cervix dilates for delivery. Acute deciduitis at the placental margin is a leading cause of abruption (Darby et al. 1989).

The fetal inflammatory response syndrome (FIRS) is a leading theory for the development of cerebral palsy in preterm infants (Yoon et al. 2007). A fetal inflammatory response is definitive evidence of viability at the time of infection. Caution must be used in interpretation of vasculitis in a severely macerated placenta, as degenerating smooth muscle nuclei may resemble multilobated neutrophils. As with chorioamnionitis, the fetal inflammatory response usually follows a sequential progression over time. The initial response is usually within the umbilical vein, progressing to the arteries. The chorionic plate vessels may be inflamed prior to inflammation of the cord or concurrent with the findings in the cord. The fetal cells begin by margination beneath the endothelium, progressing through the muscular wall out into the surrounding Wharton's jelly. The location and severity of the inflammation should be described, as there is increasing risk for fetal sepsis with increasing severity of the fetal inflammatory response.

Subacute necrotizing chorioamnionitis is a unique form of ascending infection commonly associated with extreme prematurity. Organisms responsible for this type of infection are not unique. It has been proposed that this form of infection has been present for up to 2 weeks, but why there has been a lag time between inflammation and delivery is not known (Ohyama et al. 2003). The gross and microscopic features are characteristic and are often accompanied by necrotizing funisitis (Fig. 5.5a–c).

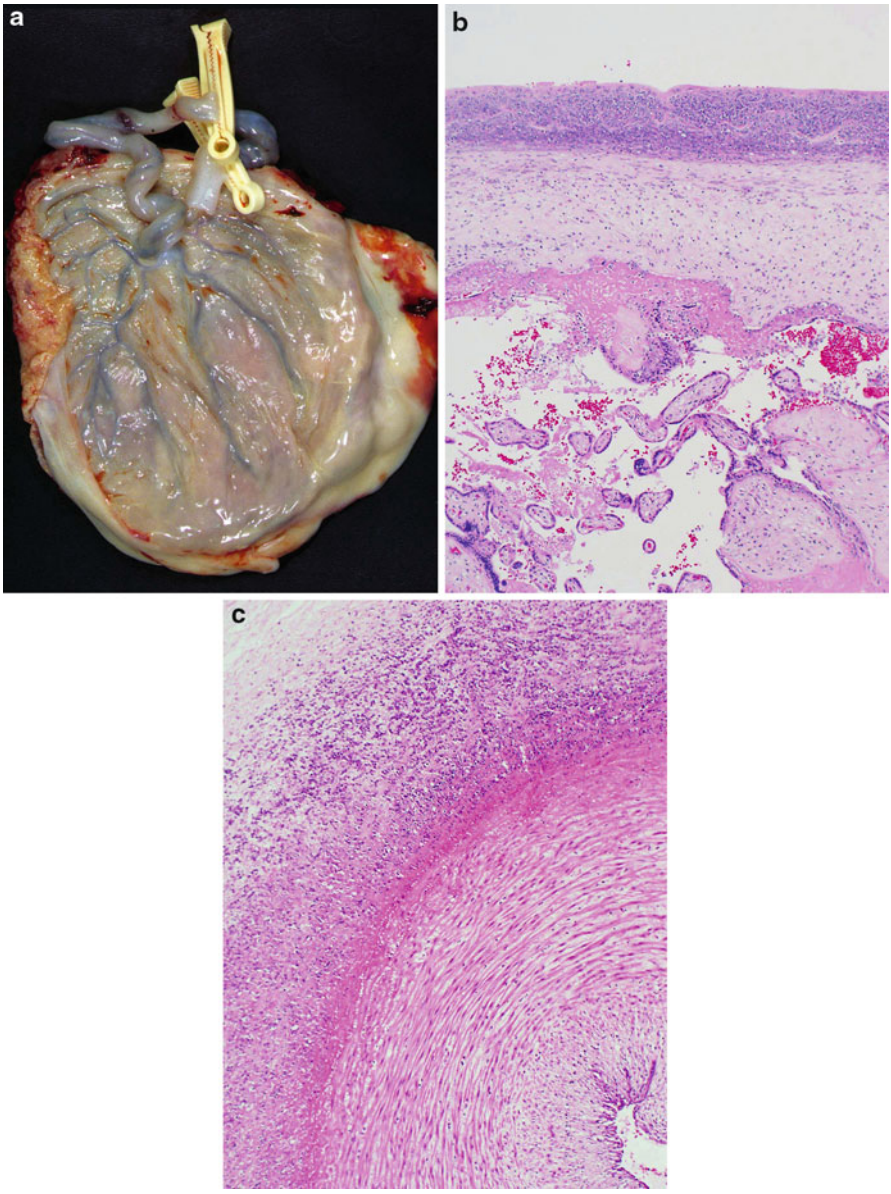


**Fig. 5.5** Subacute necrotizing chorioamnionitis. (**a**) Gross appearance, thick opaque membranes, (**b**) Marked necrotic inflammation at subamniotic region (Hematoxylin and Eosin, H&E × 10), (**c**) Necrotizing funisitis (Hematoxylin and Eosin, H&E × 20)

## Hematogenous Infection

Hematogenous infection occurs through maternal bacteremia, viremia, or parasitemia. It is much less common than ascending infection. The most common intrauterine viral infection is cytomegalovirus (CMV). There is a 1–2 % risk of CMV seroconversion during pregnancy. Fetal infection occurs in 35 % of primary infection. The earlier the infection, the more severely affected the baby, usually resulting in IUFD or neonatal death (Stagno et al. 1986). The placental hallmark of CMV infection is plasmacytic villitis often associated with hemosiderin-laden macrophages (Fig. 5.6a–c). CMV inclusions are uncommon, and immunohistochemistry is very useful for the diagnosis (Muhlemann et al. 1992).

Other potentially lethal viral infections can be identified by placental examination, but some are not associated with any pathology. Parvovirus B19 is usually associated with fetal anemia and hydrops fetalis. The intranuclear inclusions are easily identified within the nucleated red blood cells circulating within the villi. Immunohistochemistry is also very useful in highlighting the infected cells (Fig. 5.6d, e). Herpes simplex virus, rarely if ever, is a transplacental acquired infection and rarely has any abnormalities.

## Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy are a major cause of maternal and fetal morbidity–mortality. The incidence ranges from 3 to 7 %. The etiology is multifactorial, poorly understood, and beyond the scope of this chapter. The clinical diagnostic terms used to describe the presence of hypertension that occurs during gestation include pregnancy-induced hypertension, preeclampsia (mild or severe), and chronic hypertension with superimposed preeclampsia. The diagnosis is based on blood pressure elevation prior to or during gestation, degree of blood pressure elevation, and amount of proteinuria.

The basic abnormality identified within the placenta is failed or incomplete remodeling of the maternal spiral arteries at the implantation site of the placenta, resulting in decreased blood flow to the placenta. This is sometimes termed superficial implantation or disorders of deep implantation (Brosens et al. 2011). The spiral arteries are transformed from low-capacity, high-resistance vessels to high-capacity, low-resistance channels and are nearly five times the original diameter. By the end of the second trimester, nearly 90 % of central vessels have adapted, with higher rates near the center of the placenta. Defective vascular adaptation includes retained vascular smooth muscle, residual intraluminal trophoblast, incomplete reendothelialization, fibrinoid necrosis, lymphocytic vasculitis, and atheromas (Fig. 5.7a–e). The vascular lumens may be narrowed or obliterated by intimal proliferation, atherosis, fibrinoid necrosis, or thrombosis. The abnormal vessels are at the junction of the endometrium and myometrium and may not be delivered with the placenta and are often only found in a postpartum curretage (D&C) or placental bed biopsy.

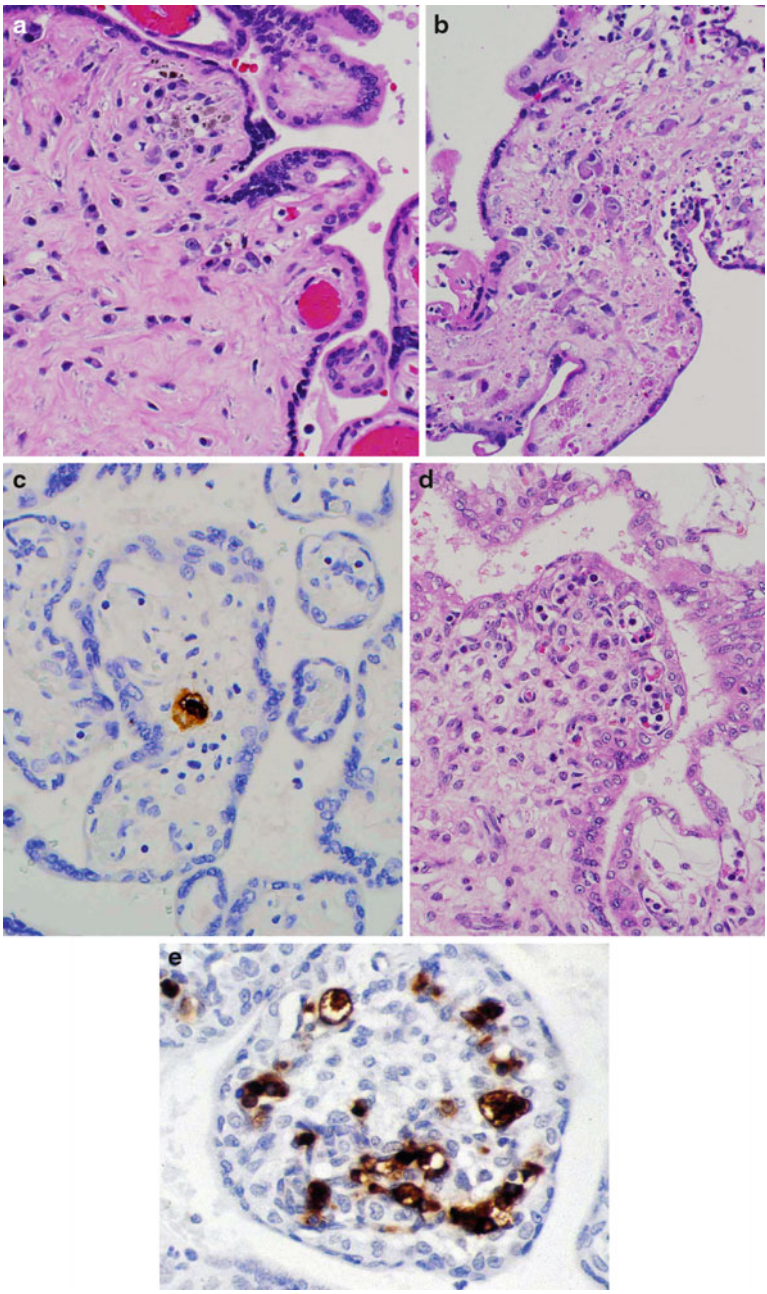


**Fig. 5.6** Villitis. (**a**) Lymphoplasmacytic villitis with hemosiderin, consistent with CMV, (**b**) Villous necrosis with CMV inclusions, (**c**) Immunohistochemistry for CMV, (**d**) Erythroblastosis with parvovirus B19 intranuclear inclusions, (**e**) Parvovirus B19 immunohistochemistry (Hematoxylin and Eosin, H&E × 40)

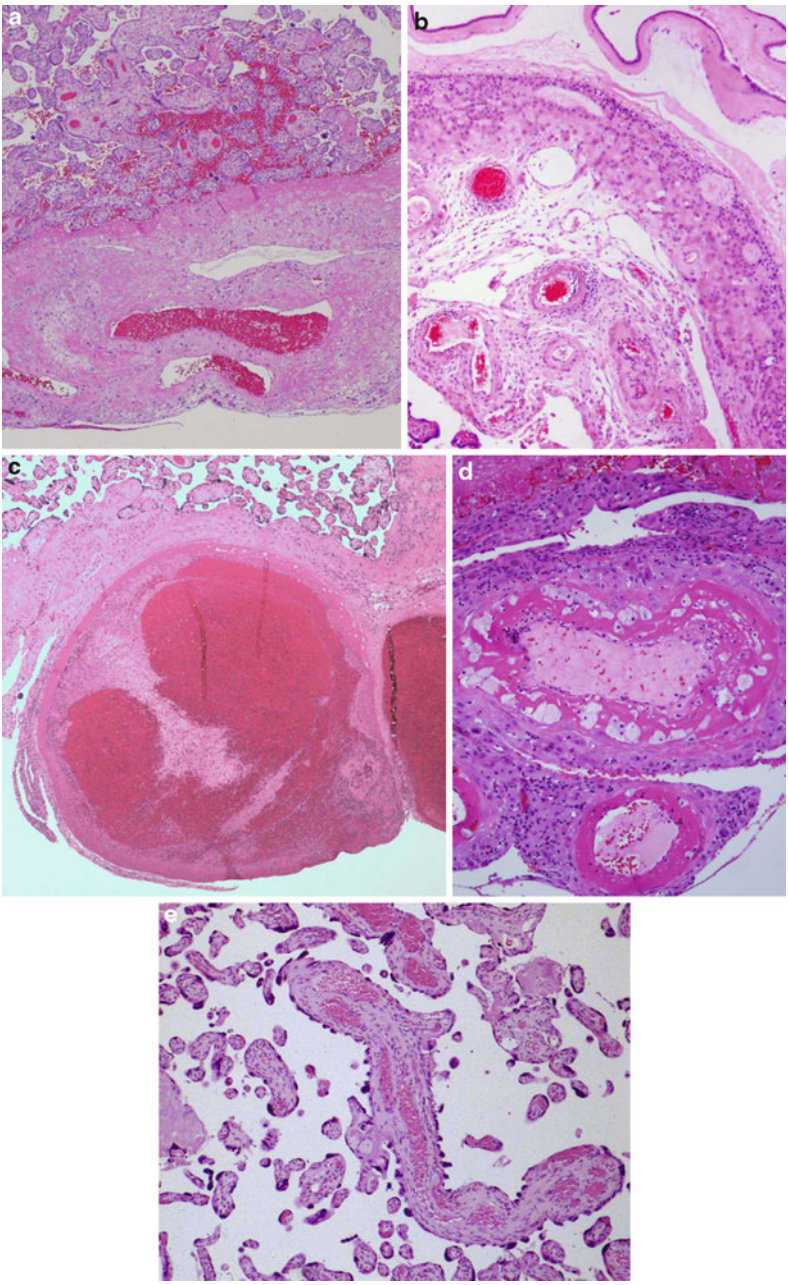


**Fig. 5.7** Maternal vasculopathy, (**a**) Normally adapted spiral arteries, (**b**) Fibrinoid necrosis with lymphocytic vasculitis in decidua parietalis, (**c**) Thrombosis, (**d**) Atheroma, (**e**) Accelerated maturation with serrated syncytial knots (Hematoxylin and Eosin, H&E, a, b, c, d × 10; e × 20)

Surrogate markers of poor uteroplacental blood flow, such as accelerated villous maturation or infarcts, are relied on in many cases.

The most severe changes are noted in cases of preterm preeclampsia, preeclampsia associated with IUGR, or abruption. Similar vascular changes with fewer involved arteries are seen in preterm delivery without preeclampsia and in second-trimester pregnancy losses (Khong et al. 1987). In term preeclampsia, the placenta may be completely normal; in fact, the placenta may be slightly heavier than expected for the gestational age. The placenta from preterm preeclampsia characteristically is smaller than expected for gestational age and for the size of the fetus. There are often multiple infarcts of different ages, including infarcts larger than 2 cm with central as well as marginal location. Some infarcts may have central hemorrhage, a particularly poor prognostic feature (Fig. 5.8a–f). The microscopic features include increased syncytial knots, villous agglutination, increased perivillous and intravillous fibrinoid, distal villous hypoplasia, increased invasive or multinucleated trophoblast at the basal plate, maternal vasculopathy, and chronic inflammation (Ghidini et al. 1997; Salafia et al. 1998; Redline et al. 2004a).

Scattered lymphocytes are a normal component of the decidua. Lymphocytes in the decidua are natural killer (NK) cells and have a role in attracting trophoblasts to the decidua and promoting remodeling of the spiral arteries. Increased decidual lymphocytes, extension of the lymphocytes into the chorion or amnion, and cuffing of maternal vessels is considered abnormal and is referred to as chronic chorioamnionitis (Gersell et al. 1991). Plasma cells within the decidua are always considered abnormal. Chronic chorioamnionitis is associated with approximately 37 % of cases of preterm labor or premature rupture of membranes and 23 % of preeclampsia and in 8–19 % of term placentas. It is associated with chronic villitis in approximately 37–70 % of cases (Jacques and Qureshi 1998). Chronic chorioamnionitis, like most chronic villitis, is thought to be an immunological reaction (Kim et al. 2010).

HELLP syndrome – hemolysis, elevated liver enzymes, low platelets – complicates approximately 3/1,000 pregnancies. There is overlap between preeclampsia and HELLP, with some suggestion that they are two different disorders. The major life-threatening complication of HELLP is hepatic hemorrhage and rupture.

## Abruption

Abruption occurs in 1–2 % of pregnancies and is the partial or complete separation of the placenta before delivery. Abruption is a clinical diagnosis based on two or more of the following: bleeding after 20 weeks gestation, retroplacental hematoma, uterine tenderness often with tonic uterine contractions, and nonreassuring fetal heart tracings or fetal demise. The etiology of abruption is multifactorial, and there are many risk factors or markers. The most important are preeclampsia, smoking, illicit drug use (cocaine), premature rupture of membranes, multiple gestations doubles the risk (usually affecting the second twin), polyhydramnios, and history of previous abruption increases the risk tenfold (Hladky et al. 2002). There is an association of abruption with inherited and acquired thrombophilias.

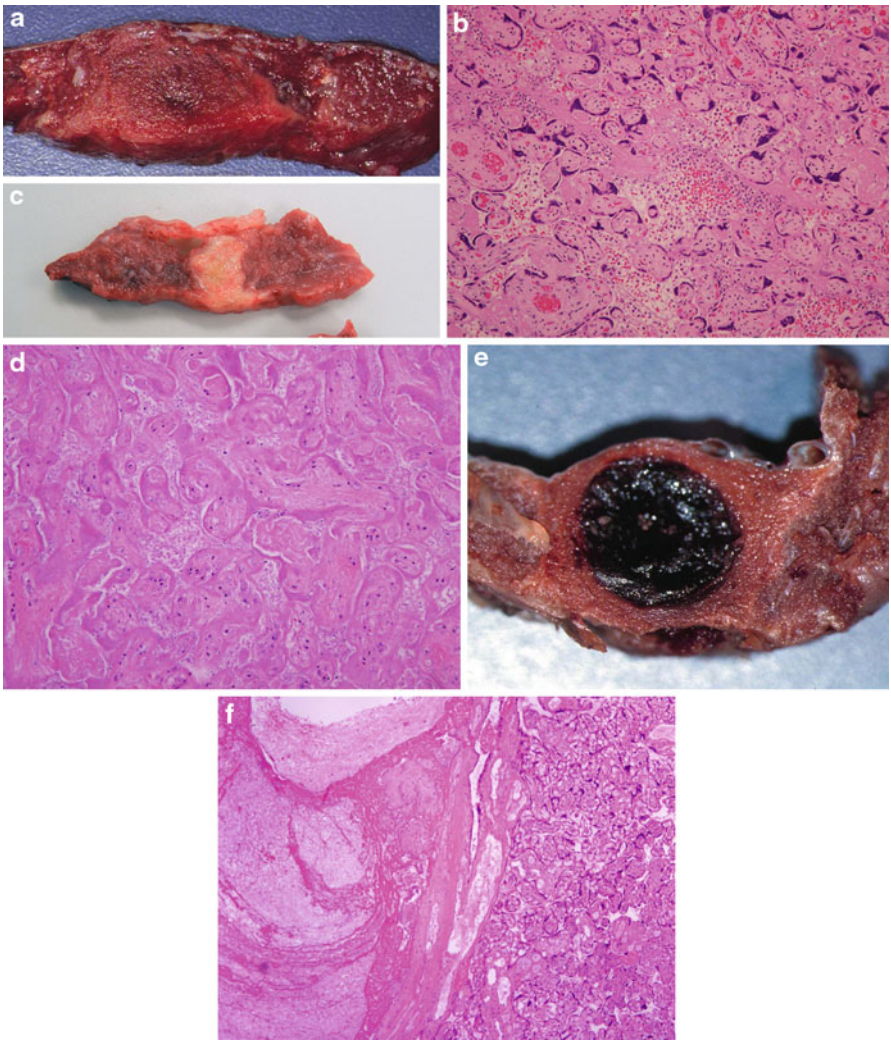


**Fig. 5.8** Infarcts, (**a**) Recent, *red* infarct, (**b**) Recent infarct with smudged syncytiotrophoblast and maternal inflammatory reaction to injured tissues, (**c**) Remote, *white* infarct, (**d**) Remote infarct with loss of nuclear chromatin basophilia, (**e**) Infarct with central hemorrhage, gross (Hematoxylin and Eosin, H&E; b, d × 20, f × 10)

Thrombophilias associated with an increased risk of abruption include homozygous methylenetetrahydrofolate reductase, heterozygous factor V Leiden mutation, and heterozygous prothrombin mutations (Tikkanen 2011). Trauma is responsible for abruption in 6 % of minor trauma and 20–25 % of major trauma. The abruption usually becomes manifest 4–6 hours after the trauma, but can occur up to 5 days later (Tikkanen 2011). Most abruptions are associated with major maternal injuries.

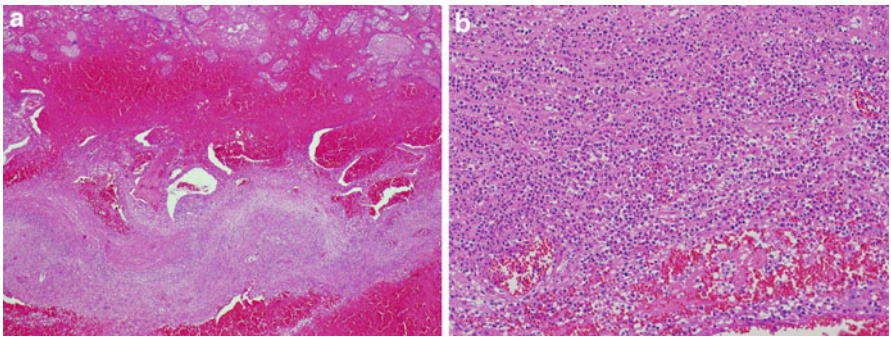


**Fig. 5.9** Abruption due to chorioamnionitis, (**a**) Acute hemorrhage into necrotic decidua (**b**) Acutely inflamed decidua (Hematoxylin and Eosin, H&E × 10)

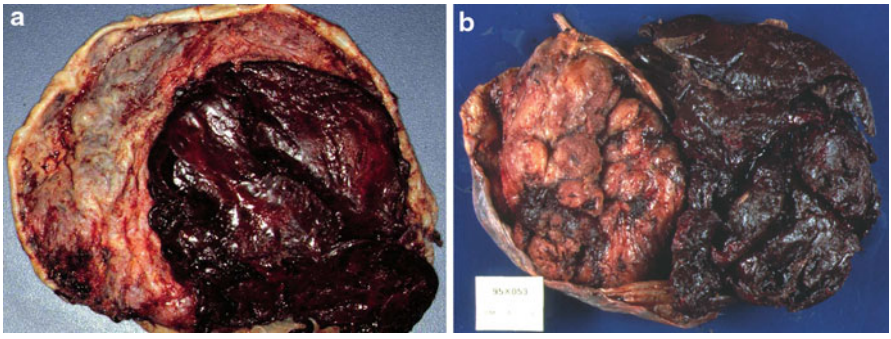


**Fig. 5.10** Abruption, (**a**) Retroplacental hematoma, (**b**) Retromembranous hematoma

The fetus can also be injured, and blunt or penetrating injury can be demonstrated. Approximately 25 % of abruptions remain unexplained.

There is a significant risk of preterm delivery, nearly 40 %, even with mild abruptions. IUFD is very common with 50 % separation (Ananth et al. 1999). The risk of abruption is highest at 24–26 weeks, and most occur before 37 weeks. As previously discussed, those mid-gestation abruptions are often related to decidual necrosis and chorioamnionitis (Fig. 5.9a, b). Chorioamnionitis may also be associated with abruption at term (Tikkanen 2011). Abruption is associated with a 15 times increase in fetal mortality compared to stillbirths from other causes (Ananth and Wilcox 2001). Abruption accounts for 10–20 % of all perinatal deaths (Tikkanen 2011; Ananth and Wilcox 2001). Stillbirth is highest when there is maternal PIH, shock, or DIC. Maternal mortality is seven times higher with abruption than with the other causes.

The pathological diagnosis is based on identifying abnormal bleeding at the basal plate of the placenta or sometimes behind the membranes (Fig. 5.10a, b). The more recent the abruption is to the time of delivery, the fewer changes there will be; therefore, a negative placental examination does not rule out a clinical abruption.

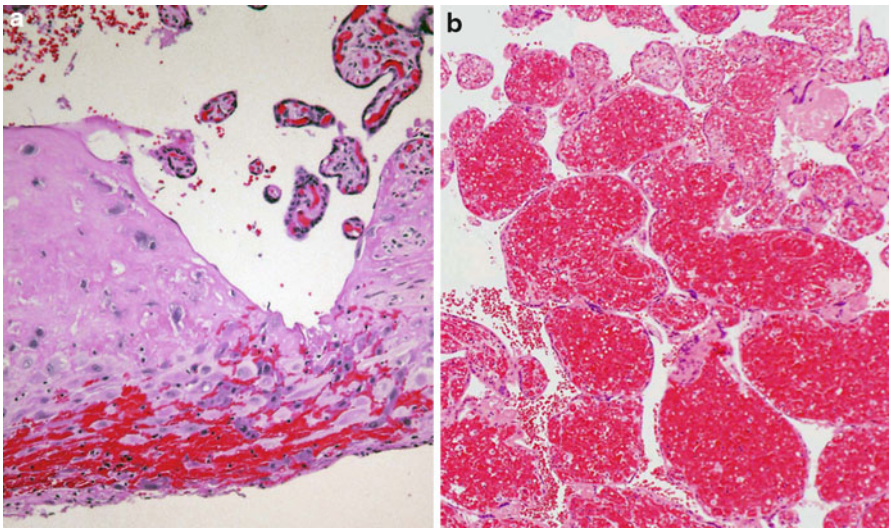


**Fig. 5.11** Abruption. (**a**) Blood actively dissecting into the basal tissues (Hematoxylin and Eosin, H&E × 40) (**b**) Intravillous hemorrhage (Hematoxylin and Eosin, H&E × 20)

In approximately one third of cases, there will be a gross retroplacental hematoma. Ultrasound will only identify approximately 50 % of retroplacental hematomas, as there is poor differentiation between recent hematoma and the placental tissue (Glantz and Purnell 2002). However, if the bleeding is allowed to escape the margin of the placenta, then vaginal bleeding will be seen, and there may not be any adherent blood on the maternal surface. A poorly formed retroplacental hematoma may only appear as increased blood in the specimen container, usually greater than 100 cc. Unfortunately sometimes, clots are discarded at the time of delivery. In another one third, there will be abnormal blood actively extending into the basal tissues or into the villi (Fig. 5.11a, b). Villous stromal hemorrhage occurs in abruption when the fetus reacts to the abruption by becoming hyperdynamic. The placental separation results in loss of maternal blood pressure in the intervillous space and rupture of the villous capillaries (Mooney et al. 1994). Less commonly, the blood dissects into the myometrium, resulting in a Couvelaire uterus, which is associated with a worse fetal outcome (Pitaprom and Sukcharoen 2006). The remainder of placentas will be normal, often with features of decreased uteroplacental blood flow.

The villi overlying a retroplacental hematoma will become ischemic and ultimately show characteristic features of infarction. A review of cases by Bendon compared the villous features with duration from abruption to delivery. Neutrophils marginated within decidua within 4 hours, smudged syncytiotrophoblast were found from 4 to 24 hours, and only after 24 hours were pale syncytiotrophoblast nuclei found (Bendon 2011). The timing of infarcts is divided into wide time spans. A very acute abruption will appear red and may only feel slightly firmer than the

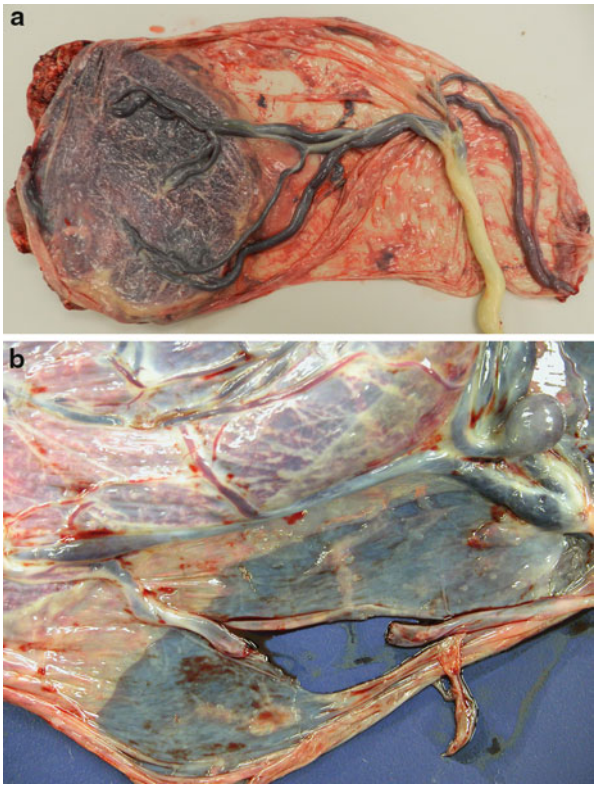


**Fig. 5.12** Intramembranous blood vessels. (**a**) Velamentous cord insertion in a "bucket handle" formation, with all vessels entering on the chorionic plate from the outside, (**b**) Disrupted intramembranous vessel, difficult to find after collapse of the thin walled vessels

surrounding tissue. Within 2–3 days, it will be pink, at 3–5 days tan, and greater than 7 days white. Decidual or stromal hemorrhage will eventually break down, and hemosiderin pigment will be present. Hemosiderin begins to appear at 72 hours and will remain present for months (Bendon 2011).

Other etiologies for antepartum vaginal bleeding should be considered. A placenta previa or low-lying placenta can result in painless vaginal bleeding. The origin can also be fetal with rupture of an intramembranous blood vessel, as can occur with a velamentous cord insertion and vasa previa (Fig. 5.12a, b). Careful examination of the fetal chorionic plate vessels should be performed.

## Villitis of Unknown Etiology

Villitis of unknown etiology (VUE) is seen in 8–12 % of term placentas, with 17 % incidence in placentas from IUGR (Pitaprom and Sukcharoen 2006; Bendon 2011). VUE is thought to be a heightened maternal immune reaction; it is a disorder usually of the third trimester (Gersell 1993). The inflammatory cells are a mixture of maternal and fetal T-lymphocytes. Maternal risk factors include obesity,

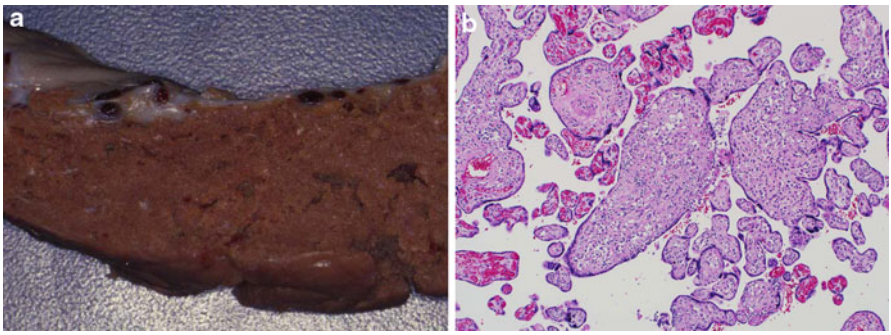


**Fig. 5.13** Villitis of unknown etiology. (**a**) Grossly coarse, granular appearance of the villi, (**b**) Lymphohistiocytic villitis (Hematoxylin and Eosin, H&E × 20)

increased parity, increased maternal age, and pregnancy-induced hypertension (Labarrere et al. 1990). There is a significant risk of IUGR and increased neonatal mortality. The abnormal outcome is directly proportionate to the amount of villous tissue involved, with increased severity in IUGR. Recurrence risk is 10–15 %, with increasing severity (Redline 2007). However, recent studies suggest that other factors such as cytokines must influence the IUGR, because even in severe cases, usually no more than 10 % of placental tissue is affected (Becroft et al. 2005; Redline 2007).

Villitis is rarely a gross diagnosis, but occasionally, the parenchyma may appear granular due to aggregation of the villi (Fig. 5.13a, b). There may also be increased fibrinoid material within the placenta or at the basal plate.

## Massive Perivillous Fibrinoid (Maternal Floor Infarct)

Massive perivillous fibrinoid is an uncommon placental abnormality, with an incidence of less than 1 %. It is characterized by deposition of eosinophilic material at the decidual plate and throughout the placenta surrounding otherwise normal villi (Fig. 5.14a, b). There may be hyperplasia of extravillous trophoblast within the material as a feature of chronicity. This is frequently mistaken for true infarct, which is a disorder of maternal blood flow. The fibrinoid material interferes with permeability of the villous resulting in IUGR, IUFD, and prematurity (Gersell 1993). There is a significant recurrence risk in some patients, with changes noted as early as 8 weeks gestation.

## Histiocytic Intervillositis

Histiocytic intervillositis is characterized by large numbers of macrophages within the intervillous space; some are clearly associated with areas of trophoblast injury.

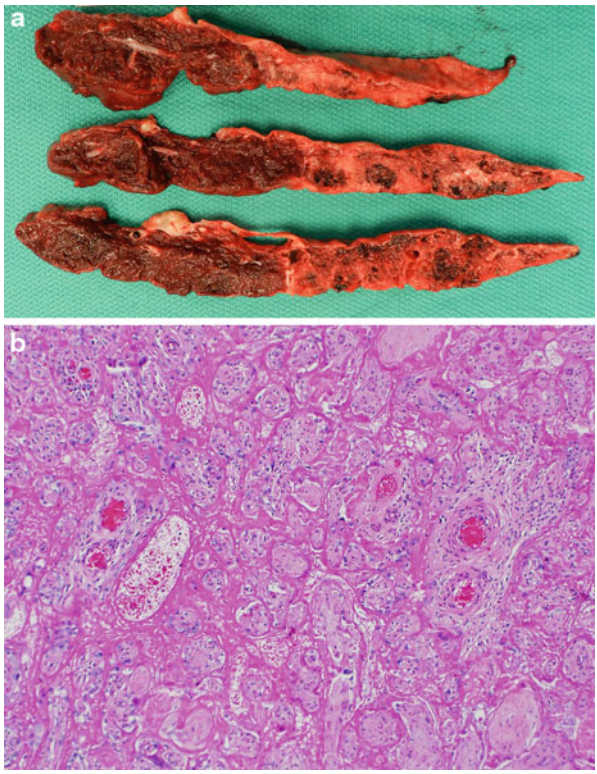


**Fig. 5.14** Perivillous fibrinoid. (**a**) Half of the placental surface is involved with perivillous fibrinoid, (**b**) Viable villi, surrounded by eosinophilic fibrinoid (Hematoxylin and Eosin, H&E × 20)

Some, but not all, cases are associated with actual villitis. It is associated with IUGR, prematurity, and IUFD. Recurrence rate in retrospective studies is similar to massive perivillous fibrinoid (Boyd and Redline 2000). Because of significant overlap in pathological features, histiocytic intervillositis and massive perivillous fibrinoid are thought to be ends of the same spectrum.

## Diabetes

Diabetes is the most common medical condition complicates 3–14 % of pregnancies. Gestational diabetes mellitus (GDM) is the onset of glucose intolerance during gestation, most commonly at the beginning of the third trimester. Diabetes, particularly pregestational, is associated with a significant incidence of congenital malformations, IUFD, and neonatal morbidity and mortality (Allen et al. 2007). The fetus receives all the glucose across the placental interface by passive diffusion. There is both placental and fetal overgrowth. The fetus produces increased insulin to control the hyperglycemia. Hyperinsulinemia results in acidemia and hyperglycemia in hypoxia, forming a relatively hypoxic intrauterine environment. The placenta in diabetes is large but has suboptimal function, which in conjunction with the hypermetabolic fetus plays a role in the approximately 6 % incidence of IUFD. There is increasing

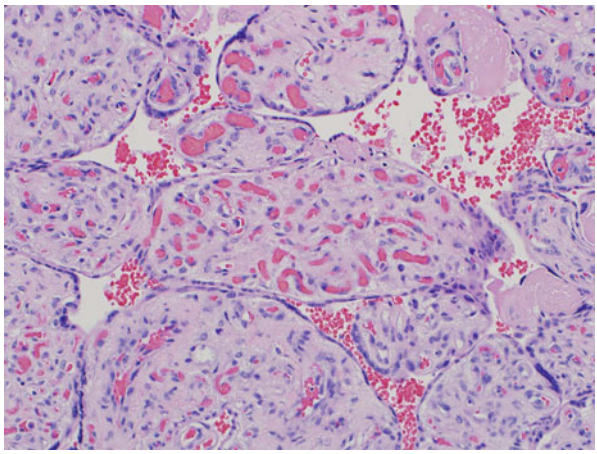

**Fig. 5.15** Chorangiosis, marked increase in number of capillaries within terminal villi (Hematoxylin and Eosin, H&E × 20)

evidence of increased oxidative stress in the diabetic placenta and fetus, and this may be important in the worse outcome for male infants (Rajdl et al. 2005).

Grossly, the placenta is large, having increased diameter and weight, for gestational age resulting in a decreased fetal:placental weight ratio. There appears to be generalized overgrowth of all portions of the placenta. There is an increased risk of fetal vascular thrombosis within umbilical cord and stem vessels in up to 25 % of diabetic placentas. Microscopically, the placenta usually has delayed villous maturation, edema, decreased calcifications, thickened trophoblast basement membrane, and hypervascularity (Makhseed et al. 2002). Chorangiosis is defined as diffuse increased villous vascularity when at 10 x magnification, there are greater than 10 vessels, in 10 terminal villi, in more than three nonischemic areas (Altshuler 1984) (Fig. 5.15). Chorangiosis is most commonly associated with diabetes but may also be seen in some cases of congenitally malformed and chromosomally abnormal fetuses in addition to some cases of decreased uteroplacental blood flow. The number of nucleated red blood cells is also increased to approximately double that of a nondiabetic (Green and Mimouni 1990). The placental abnormalities are in general worse with poor glucose control; but this is not universally true. Similar placental findings are noted in obesity without diabetes. Generalized vascular disease found in severe diabetes may also affect the placenta.

## Drug Use During Pregnancy

Cocaine and amphetamine use are both associated with abruptions, primarily related to vasoconstriction. The actual participation of these drugs to the pathology is confounded by other risk factors such as lack of prenatal care, smoking, increased risk-taking behavior, and increased chorioamnionitis. Cocaine and amphetamines produce their effects through inhibition of serotonin, norepinephrine, and dopamine transporters, the former two expressed on the syncytiotrophoblast. This is thought

to elevate serotonin and norepinephrine in the intervillous space and cause uterine contractions and vasoconstriction (Ganapathy 2011).

## Meconium

Meconium passage is found in approximately 15 % of term deliveries. It is considered to be a feature of fetal stress. Meconium is rarely passed prior to 32 weeks gestation. The more mature the fetus, the less stress is needed to result in passage, whereas at earlier gestation, the stressor is generally more severe. Meconium is most often passed secondary to chorioamnionitis, followed by uteroplacental blood flow issues and fetoplacental blood flow issues, usually cord compression (Incerti et al. 2001). Thick, particulate meconium is associated with significantly more morbidity and mortality. It is not always the meconium that results in the problems, but what caused the meconium passage in the first place. The mechanism for the injury is still unknown, but placental vasoconstriction seems to have been ruled out. Meconium aspiration syndrome occurs in 3–4 % of cases and is associated with significant respiratory distress, pulmonary hypertension, and neonatal mortality (Ahanya et al. 2004).

Grossly pigmented membranes may be secondary to severe chorioamnionitis, hemosiderin deposition, or meconium. Acute meconium is bright green and may only sit on the membrane surface. Subacute meconium is dark green and over time becomes more mucoid. Chronic meconium-stained membranes are dull, muddy brown (Kaspar et al. 2003). Meconium is phagocytized by macrophages in the membranes and is progressively removed from the amniotic fluid. Meconium-laden macrophages can be found within the amnion within 1 h of passage, the chorion in 2–3 hours, and in the decidua parietalis in 6 hours (Miller et al. 1985) (Fig. 5.16a, b). This time sequence is well accepted, but recent studies suggest that the process of uptake may take considerably longer (Funai et al. 2009).

A fetal acute vasculitis is not associated with maternal chorioamnionitis, when the presence of meconium is a feature of meconium aspiration syndrome. It is not the meconium on the placenta that elicits the fetal vasculitis but the presence of the meconium within the lung (Burgess and Hutchins 1996).

Prolonged exposure to heavy meconium may result in meconium-induced smooth muscle injury of the umbilical arteries. Altshuler noted that this feature was not seen in exposure less than 16 h (Wylie and D'Alton 2010) (Fig. 5.17a, b). I find meconium-induced smooth muscle necrosis in approximately 1 % of meconium-stained placentas, and cord ulceration is even less common. It is always associated with neurological injury, and the severity is proportionate to the vascular injury.

## Fetal Maternal Transfusion

Massive fetal maternal transfusion (FMT) occurs in 0.3 % of pregnancies and results in perinatal mortality in 1 in 1,000 deliveries. Throughout gestation, fetal

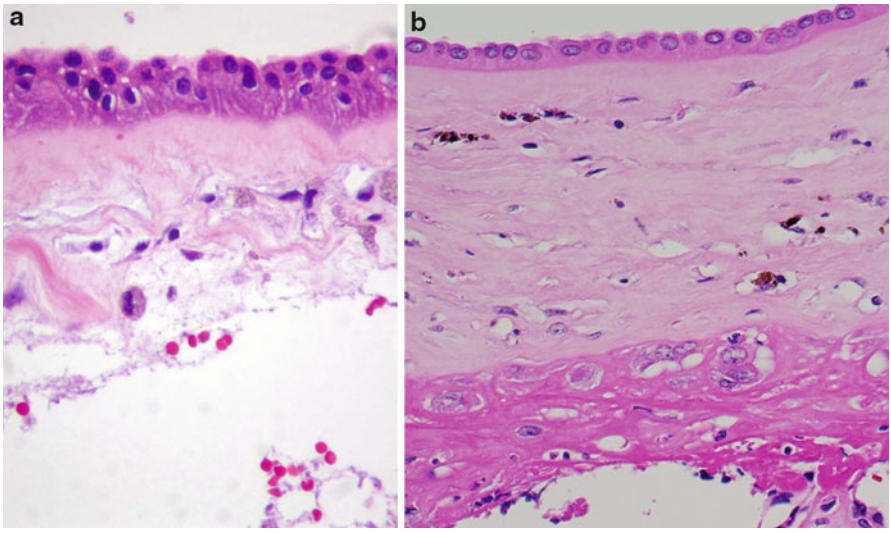


**Fig. 5.16** Pigmented macrophages. (**a**) Meconium-laden macrophages in the amnion with mild amnion hyperplasia, (**b**) Hemosiderin-laden macrophages, with more granular appearance (Hematoxylin and Eosin, H&E × 40)

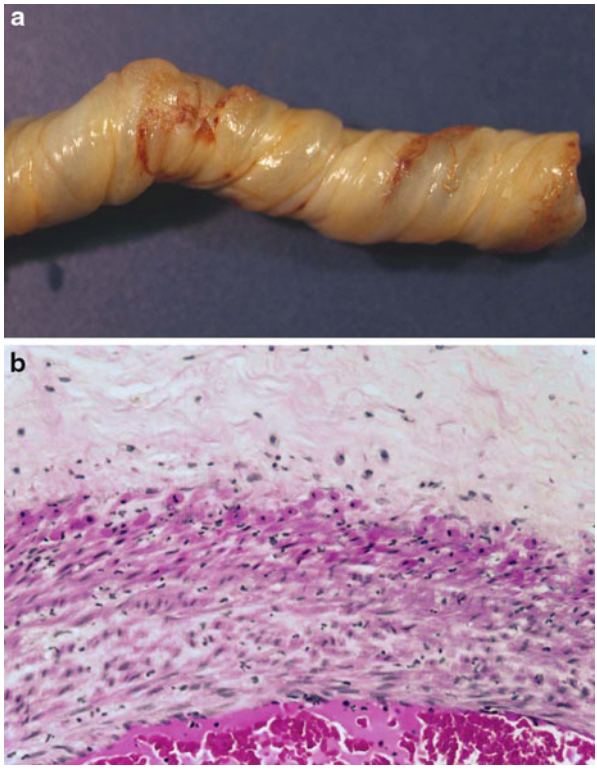


**Fig. 5.17** Meconium-induced smooth muscle injury of umbilical cord, (**a**) Superficial ulceration of cord over the arteries, (**b**) Meconium-laden macrophages in Wharton's jelly: rounded up smooth muscle with pyknotic nuclei and vasculitis (Hematoxylin and Eosin, H&E × 40)

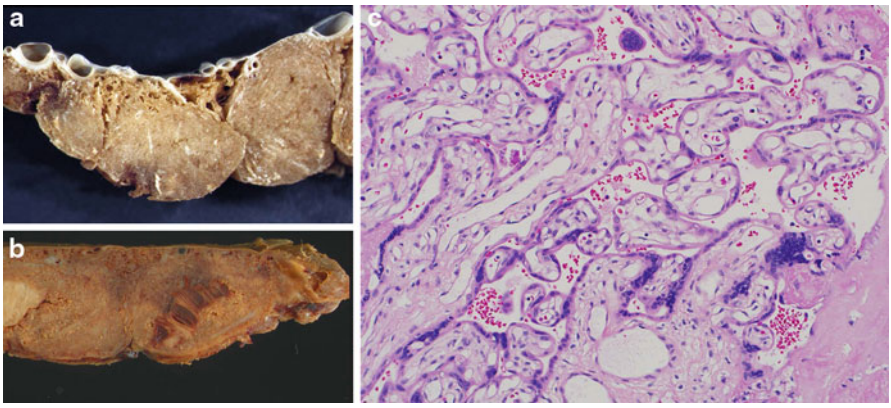


**Fig. 5.18** Massive fetal maternal transfusion. (**a**) Pale anemic appearing placenta, with distended chorionic plate vessels, (**b**) Multiple intervillous hematomas, (**c**) Empty fetal capillaries (Hematoxylin and Eosin, H&E × 20)

nucleated and red blood cells gain entrance into the maternal circulation, although their numbers are very small. It is likely that the majority, if not all women, have some fetal red blood cells within their circulation after delivery, which is usually less than 0.5 mL. It is slightly more with C-sections and after placental abruption, particularly if traumatic. The cutoff for "massive" transfusion is variable, ranging from 30 mL to 150 mL.

If the FMT occurs close to the time of delivery or results in immediate fetal demise, the placenta may look completely normal. A Kleihauer-Betke stain performed on maternal blood is the only way to identify circulating fetal cells. If there has been equilibration of the fetal blood volume, the placenta has a characteristic pale appearance with dilated but empty chorionic plate vessels (Fig. 5.18a–c). The villi will also contain increased circulating nucleated red blood cells, within a relatively low hematocrit-appearing blood. In utero equilibration occurs in 4–6 h, much quicker than would occur in a newborn, because of rapid reaccumulation of fluid volume through the placenta (Brace and Cheung 1990).

Fetal anemia must be severe and prolonged before the fetus or placenta becomes hydropic. There is controversy as to whether hydrops occurs within the placental villi before or after the fetus. In my experience, villous edema precedes the onset of fetal hydrops. Severity of the FMT is related to the amount of fetal blood loss, rate of loss, and whether the loss is acute or chronic. Rapid loss of 30 % blood volume is lethal in a high percentage of animal studies, while a greater loss over a longer period of time can be tolerated (Brace and Cheung 1989). In review articles, perinatal death of 36.6 % occurred with hemorrhage above 150 mL, which would be approximately 50 % of the term blood volume (Sebring and Poleksy 1990).

The fetal blood volume changes with gestation. At 20 weeks gestation, the fetal blood volume is approximately 35 mL, while at term, it is approximately

85 mL/kg fetal weight. The placental vasculature will also contain additional fetal blood; at term, this amount is approximately 50 mL. Not only is the amount of fetal blood loss important, whether the loss is over a short or long period of time will also affect the fetal outcome. An estimate of the amount of fetal blood within the maternal circulation can be calculated by using the % of fetal cells from the Kleihauer-Betke stain and multiplying by 5,000 (estimated total maternal blood volume). It is not uncommon to have more than the total blood volume present within the maternal circulation, which may be due to placental blood or indicate some degree of chronicity. Flow cytometry is now being used to automatically measure fetal HbF-containing cells, which is much quicker and more accurate. Delay in testing maternal blood may result in negative results if an ABO incompatibility is present, where maternal blood type O would result in lysis of fetal type A cells.

The placenta may show features of abruption. Other etiologies include chorangiomas and intervillous hematomas/thrombi. Most placentas associated with massive FMT have no lesions. Staining recent and remote intervillous hematomas with immunohistochemistry for fetal hemoglobin can be useful, as is finding fetal nucleated red blood cells within the maternal intervillous space. The placenta may show features of abruption. Other etiologies include chorangiomas and intervillous hematomas/thrombi. Most placentas associated with massive FMT have no lesions.

## Fetal Thrombotic Vasculopathy

Fetal thrombotic vasculopathy (FTV) is the result of stasis, hypercoagulability, and vascular damage within the fetal vasculature of the placenta. The lesions can be in any level of the system from the umbilical cord to the villous capillaries. Originally, these lesions were identified in placentas from IUFD and were thought to be secondary to retention of the placenta that is still being perfused by the maternal circulation. However, it is also found in live-born babies with IUGR, neonatal thrombocytopenia, elevated liver enzymes, increased nucleated red blood cells, and neonatal and long-term neurologic deficits. At autopsy, thromboemboli may be found in a small number of cases. The extent of FTV within the placenta to result in morbidity or mortality is unknown, but in some studies, even small lesions were associated with morbidity (Redline and Pappin 1995).

The most common etiology of FTV is obstruction to blood flow through the umbilical cord due to mechanical lesions, velamentous insertion, hyperspiraling, knots, and tight nuchal cord. In the absence of a mechanical lesion, hypercoagulable states such as in an infant of a diabetic mother, and inherited thrombophilias should be considered.

The gross lesions may be seen as firm distended chorionic plate vessels, often with white fibrin thrombi (Fig. 5.19a–d). The stem vessels are frequently distended

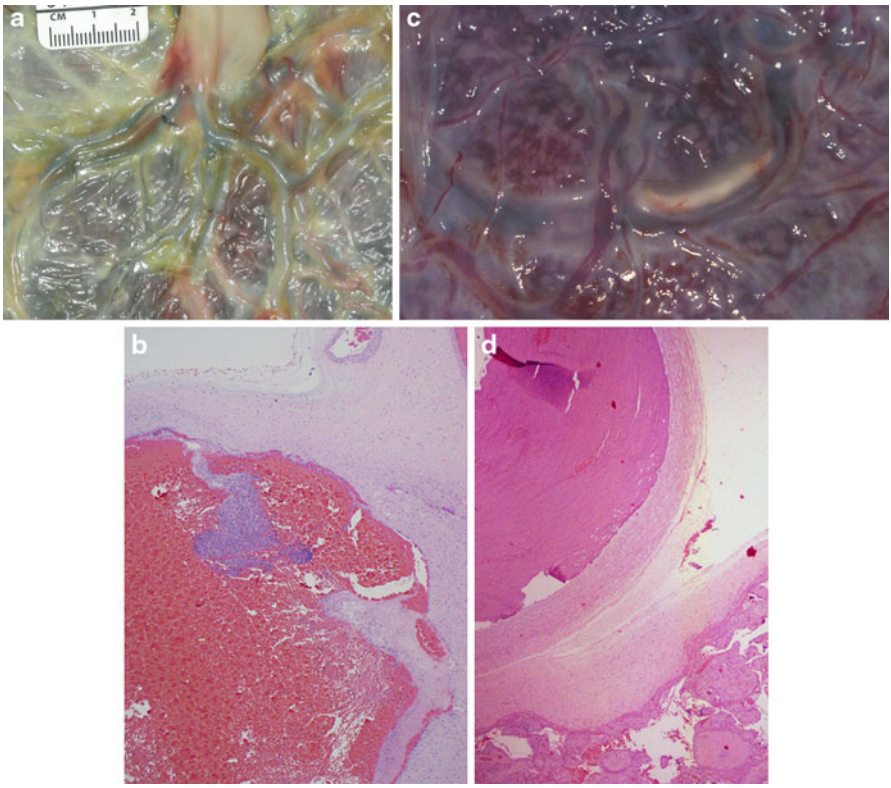


**Fig. 5.19** Fetal thrombotic vasculopathy. (**a**) Acute thrombosis of chorionic plate vessels with minimal extravasation of hemoglobin pigments, (**b**) Acute thrombosis with fibrin attached to endothelium, (**c**) Remote thrombosis of chorionic plate vein (arteries cross over veins), (**d**) Remote laminated thrombus (Hematoxylin and Eosin, H&E × 10)

as well. Areas of avascular villi are pale in comparison to the surrounding parenchyma. Microscopic lesions within larger vessels include fibrin thrombi, usually eccentric nonocclusive, frequently with calcification (Fig. 5.20a–d). The stem vessels frequently have varying degrees of fibroblast proliferation, to complete luminal obliteration, and extravasation of red blood cells. Both chorionic plate and stem vessels frequently have eccentric fibroblast proliferation, "cushion" lesions, that can have fibrinoid necrosis, overlying fibrin and inflammation. These may represent vessel branch points in some cases. Villous capillaries show stromal and vascular karyorrhexis, fragmentation, and extravasation of red blood cells and ultimately are completely avascular (Redline et al. 2004b) (Fig. 5.21a–c). These villous lesions are often termed hemorrhagic endovasculosis. It may be possible to distinguish the premortem villous injuries from those that occur after demise by variability of hemosiderin-laden macrophages within villi that were progressively injured prior to fetal demise (Stanek 2010).

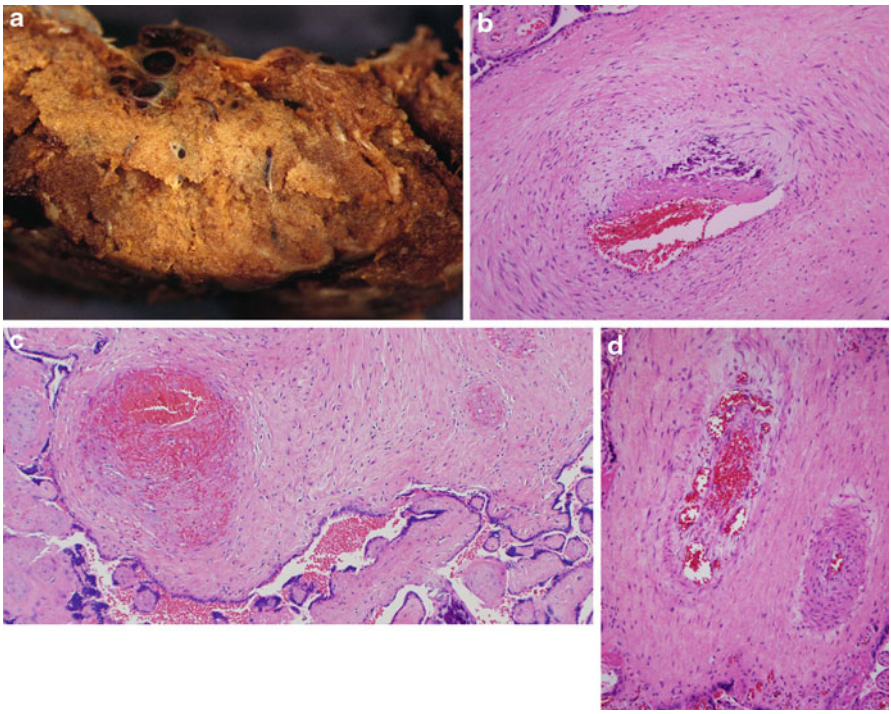


**Fig. 5.20** Fetal thrombotic vasculopathy. (**a**) Thrombosed stem vessels, surrounded by pale avascular villi, (**b**) Stem vessel with cushion lesion, fibrinoid, and calcification, (**c**) Stem vessel with fibroblast proliferation and red blood cell extravasation, (**d**) Stem vessel with recanalization (Hematoxylin and Eosin, H&E × 10)

## Acquired and Inherited Thrombophilias

Normal pregnancy alters coagulation factors that promoted coagulation, decreased anticoagulation, and inhibit fibrinolysis. There is a marked increase in most of the coagulation factors and a decrease in physiological anticoagulants. There is a significant increased risk of venous thromboembolism (VTE) during pregnancy and the 4–6 weeks postpartum. VTE accounts for approximately 20 % of maternal deaths.

The most common acquired thrombophilia is antiphospholipid syndrome (APS). APS is a heterogeneous syndrome both clinically and in the laboratory. There are several different criteria for the clinical and laboratory diagnosis of APS. Thrombosis may be arterial, venous, or small-vessel. Complications during pregnancy include recurrent early and mid-gestation pregnancy loss and early onset preeclampsia (<34 weeks).

Inherited thrombophilias are usually autosomal recessive, single gene mutations that may lead to a hypercoagulable state. These include factor V Leiden G1691A (FVL), factor II (prothrombin G20210A PGM), methylenetetrahydrofolate

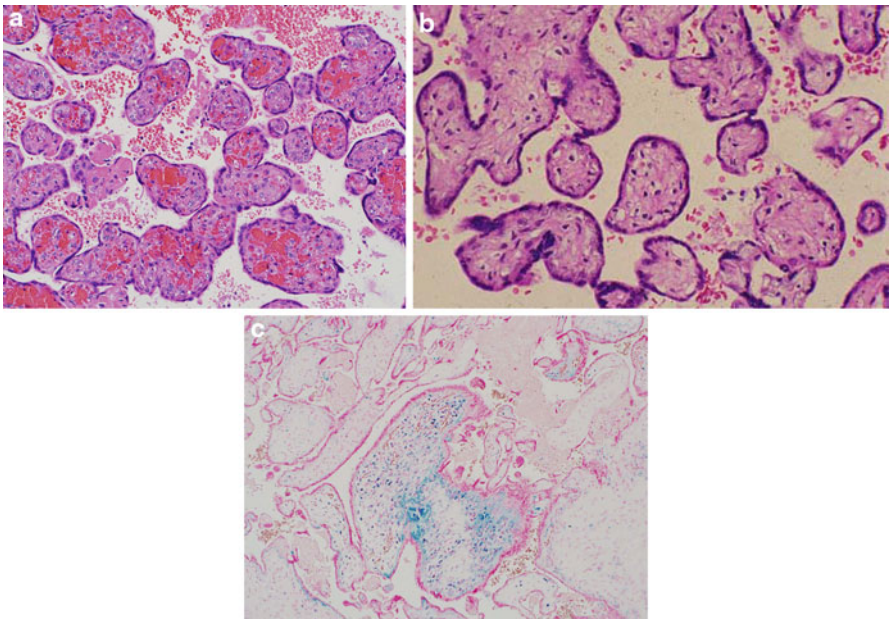


**Fig. 5.21** Hemorrhagic endovasculosis. (**a**) Villi with capillary nuclear debris and extravasated red blood cells, (**b**) Avascular villi, (**c**) Variable amount of hemosiderin within villi of a live-born baby with FTV (a, b Hematoxylin and Eosin, H&E × 20; c Perls × 20)

reductase C677T mutation (MTHFR), and protein S and protein C deficiency. With exception of MTHFR, these factors increase the risk of VTE. Most of these are also associated with abnormal pregnancy outcome including early pregnancy loss (MTHFR), late pregnancy loss (protein S deficiency, FVL), preeclampsia (homozygous FVL), abruption, and intrauterine growth restriction (Pierangeli et al. 2011).

Placental pathology includes a small placenta, thrombi in the maternal vasculature, and possibly altered trophoblast interface, resulting in decreased feto maternal oxygen exchange (Pierangeli et al. 2011). The placenta in 105 women, heterozygous for FVL mutation, was found to have increased syncytial knots and increased hypervascular villi. Fifty infants heterozygous for FVL mutation had increased avascular villi (Rogers et al. 2010).

## Placenta Without a Baby

Most placentas are passed within 30 minutes of a vaginal delivery. However, there are instances where a woman presents to an emergency department with vaginal bleeding and is found to have a retained placenta, yet no baby is present, and in most cases, its existence is denied. The facts noted above can be helpful to assess gestational age, confirm the presence of a fetus, such as a fetal inflammatory response, and identify abnormalities that could be responsible for fetal demise.

## Conclusions

Placental examination is an important part of the evaluation of poor outcome in pregnancy and can yield information concerning a number of questions important to the forensic evaluation of a fetal/neonatal/maternal death: (1) gestational age, based on placental size and maturity of the villi; (2) viability of a fetus also based on gestational age and presence of vital reactions such as fetal inflammatory response; (3) etiology of fetal loss; and (4) assessment of maternal disorders that contribute to poor outcome of both mother and baby.

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