# Overview of Placenta Pathology

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**Abstract**

The placenta is a very common, but often underappreciated, surgical pathology specimen. Gross examination of the placenta should be organized and routine, in order to efficiently identify abnormalities; only a proper gross examination will allow appropriate diagnosis. Gross findings and lesions discussed here include those of the umbilical cord (length, knots, coiling, insertion), membranes (discoloration, plaques, insertion), and disc (size, infarcts, abnormal shapes). The histologic findings are also discussed by site: cord (inflammation, thrombosis, remnants), membranes (pigment, lesions, chorionicity of twins, maternal arteriopathy), and disc (villous maturity, infarcts, hydropic change, villitis, specific infections). Finally, there is a discussion of the unifying diagnoses: maternal vascular malperfusion, fetal vascular malperfusion, and amniotic fluid infection sequence.

**Keywords**

Placenta · Infarct · Maternal arteriopathy · Villitis
Maternal vascular malperfusion · Fetal vascular malperfusion

## 14.1 Introduction

Placenta, Latin for flat cake, is a commonly encountered surgical pathology specimen. Unfortunately, the placenta is frequently overlooked as a specimen of little value. Much information can be gained from a focused examination of the placenta, both grossly and microscopically, when examined by a knowledgeable surgical pathologist.

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### 14.1.1 Fertilization, Fertilized Egg Development and Migration, and Implantation

Fertilization takes place in the fallopian tube 24–48 h after ovulation, creating a zygote. As the early embryo travels through the fallopian tube, the zygote becomes a morula (mass of 12–16 cells) and is encased in a nonadhesive protective coating called the zona pellucida. Once a fluid-filled cavity forms, the morula transitions to the blastocyst stage. This stage is also accompanied by cellular differentiation, with the surface cells becoming the trophoblast, which eventually gives rise to extraembryonic structures like the placenta, as the inner cells become the embryo. As the embryo finally enters the uterine cavity after its journey through the fallopian tube, it exposes the outer covering of syncytial trophoblasts within 72 h [1, 2].

About 6–7 days after conception, implantation occurs. This appears to occur in three distinct stages: apposition, stable adhesion, and invasion. The first step, apposition, occurs when the blastocyst adheres to the uterine wall, which occurs most often in the posterior fundus of the uterus. This initial weak adherence is followed by a complex series of incompletely understood changes which allow the next two steps, stable adhesion and subsequent invasion, to occur [1, 2].

By day 10 after conception, the blastocyst is completely embedded within the stroma of the endometrial lining, with uterine epithelium regrowing to cover the implantation site. Cytotrophoblasts invade the endometrial stroma, glands, vasculature, and myometrium [1, 2]. This step establishes the uteroplacental circulation, placing trophoblasts in direct contact with maternal blood [3].

### 14.1.2 Membrane and Placental Development

As the placenta develops, the entire blastocyst surface is initially covered by villi. To form the membranes, most of the newly formed villi regress and the intervillous space obliter-



W. Zheng et al. (eds.), *Gynecologic and Obstetric Pathology, Volume 2*, https://doi.org/10.1007/978-981-13-3019-3_14

ates, a process which spreads over the blastocyst surface. The chorion, obliterated intervillous space, villous remnants, and trophoblastic shell fuse, forming the smooth chorion. The small cells that line the inner surface of the trophoblast eventually form the amnionic epithelium. Early in gestation the amnionic mesoderm and the chorionic mesoderm fuse, but the fusion of the amnion and chorion is never complete, and the two membranes can always easily slide against each other [1, 2].

### 14.1.3 Twin/Multiple Pregnancy Development

This will be covered later in the chapter.

### 14.1.4 Chorionic Villi

Practically all maternofetal and fetomaternal exchange takes place at the chorionic villi, which have a dual blood supply from the fetal and maternal circulations. All tertiary villi have the same basic structure: an outer shell composed of syncytiotrophoblasts, which are bathed in maternal blood. The cytotrophoblasts are positioned between the outer syncytiotrophoblasts and the basement membrane of the villous structure. The villous stroma is composed of connective tissue cells (fibroblasts) and fetal vessels. The initial villous development from primary to secondary villi, and finally tertiary villi, has occurred by week 4 (when the heart begins to beat); tertiary villi contain fetal vessels, which will allow the villi to provide oxygen and nutrients to the developing embryo [1, 2].

There are five types of tertiary villi:

1. Stem villi: These villi are the thick-walled, fibrous villi that provide the initial branches and structure for the villous tree (Fig. 14.1a).
2. Immature intermediate villi: Bulbous in shape, with a trophoblastic cover and a distinctive loose stroma, these structures are the continuation of the stem villi.
3. Mature intermediate villi: These villi branch from the immature intermediate villi into longer and more slender structures. Their stroma is more dense and cellular, with increasing numbers of capillaries (Fig. 14.1b).
4. Terminal (free) villi: The final representation of the villous tree, these structures consist of grapelike outgrowths of the mature intermediate villi. They have scant connective tissue and a thin trophoblastic layer, which is in direct contact with sinusoidally dilated capillaries (Fig. 14.1c).
5. Mesenchymal villi: The precursors of all other villous categories, these villi are thought to sprout continuously throughout pregnancy, though most copiously in the first and second trimesters. Mesenchymal villi have a thick trophoblastic cover and poorly developed fetal capillaries, and make up very little of the term placenta (Table 14.1).

### 14.1.5 General Rules of Pathologic Evaluation

When approaching a placenta, it is helpful to use a systematic approach to inspect the three main components: the disc, the membranes, and the umbilical cord. The order is less important than a standard routine, although in practice it may be easiest to examine the cord and membranes prior to the disc as these will be removed before obtaining the placental weight. Additionally, it is important not to overlook any extraplacental tissue (such as a fetus papyraceus or large amounts of blood clot) that may be present [2, 4–7].

### 14.1.6 Fixation

Whether or not to fix a placenta before gross examination has been somewhat controversial, but it is generally believed that an initial fresh examination is preferable. The placenta can be palpated more easily, and gross assessment may become difficult following fixation due to the decreased pliability inherent to formalin fixation. For fresh placentas, dry storage in plastic buckets at 4 °C is recommended. After 72 h of dry storage, there may be changes in vascular architecture, and therefore the placenta should be fixed within 48 h if it cannot be examined macroscopically within that time. With fresh placental tissue, it is possible to perform microbiology studies such as bacterial cultures and karyotyping for chromosomal analysis, which may be useful in earlier gestations when the differential diagnosis can include a molar pregnancy, or if some form of placental mosaicism is clinically relevant. The weight of the placenta increases following fixation by up to 10% [2, 6, 8].

There are some benefits to examining the placenta after formalin fixation. Fixed placentas are less infectious, subtle areas of infarction are more apparent, and sections/blocks are easier to cut. Formalin is the preferred agent for fixing placentas; other fixatives may cause artifact, both grossly and microscopically [8].

## 14.2 Gross Features and Findings of the Placenta

### 14.2.1 Basic Gross Examination

#### 14.2.1.1 Integrity

One of the first things to note when examining the disc is integrity: Are the cotyledons complete and intact? Intactness

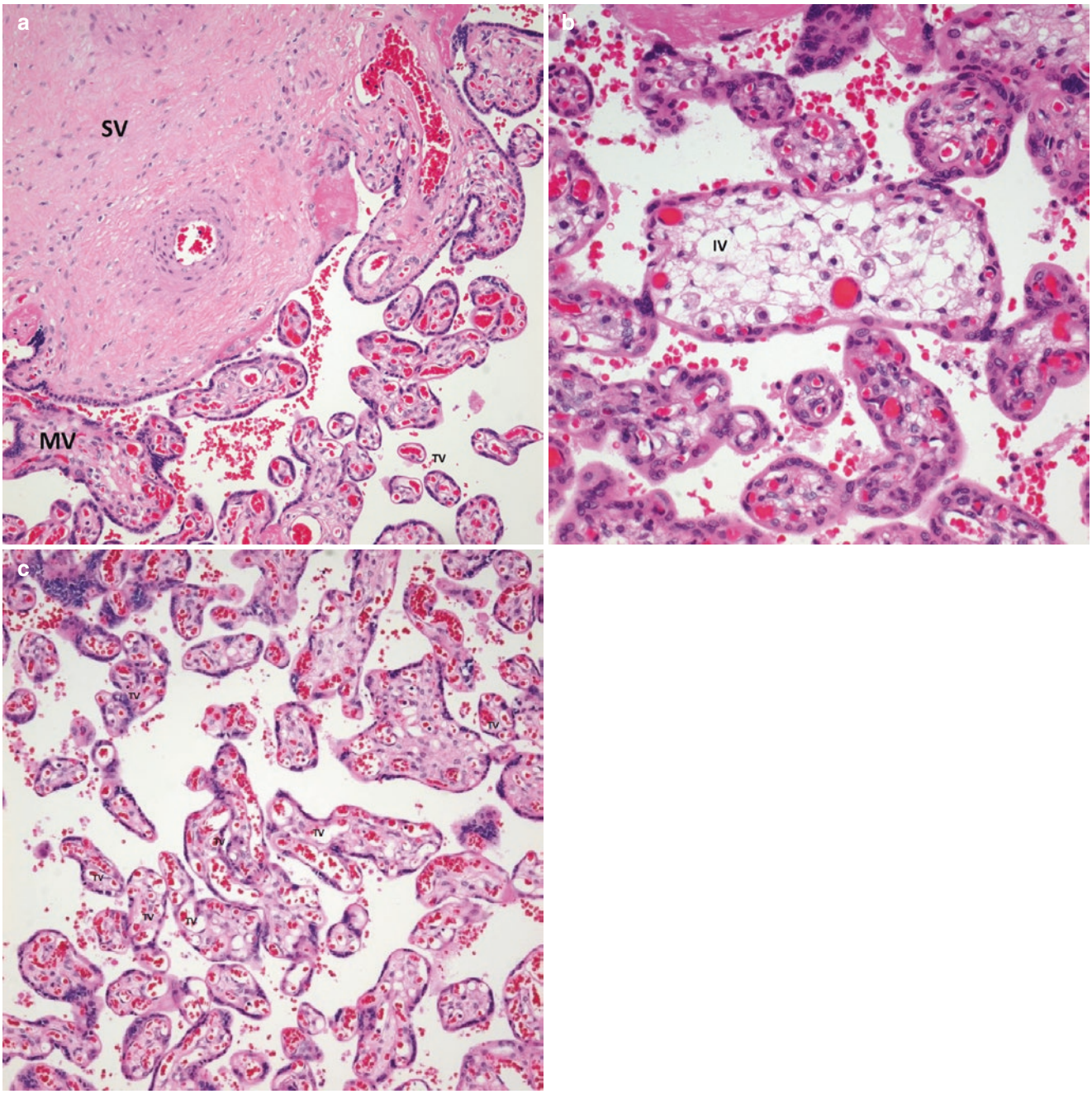


**Fig. 14.1** Tertiary chorionic villi. (**a**) Three types of villi are readily identified in this photomicrograph. The large stem villus (SV) is notable for its dense fibrotic stroma and large vessels. The mature intermediate villus (MV) has a dense cellular stroma, and over 50% of the volume is taken up by capillaries. Terminal villi (TV) are the smallest villi, and contain scant connective tissue, with more than 50% of the volume consisting of capillaries. (**b**) Immature intermediate villus (IV) with reticular stroma and fluid-filled channels. (**c**) Most of the villi in this picture represent terminal villi (TV). There is scant connective tissue and a thin trophoblastic layer, which directly contacts the dilated capillaries

refers to the presence or absence of disrupted cotyledons. In an intact placenta, the entire maternal surface will appear smooth and shiny due to the (thin) layer of decidua that is normally present. Areas of disruption appear roughened and reddish, due to exposed villi (Fig. 14.2a, b). Completeness refers to receipt of the entire placenta. Note that the cotyledons may be disrupted, but still comprise a complete placenta when pieced together, though this can be very difficult to determine with certainty (Fig. 14.3). Missing placental tissue affects accurate weight measurement and more importantly can indicate retained placental tissue within the uterus.

**Table 14.1** Five types of chorionic villi

| Villi type | Present | Maximum | % at term | Features |
|---|---|---|---|---|
| Mesenchymal | Throughout gestation | 0–8 weeks | <1 | Primitive stroma, thick trophoblastic cover, few vessels |
| Immature intermediate villi | 8 weeks to term | 14–20 weeks | 5–10 | Reticular stroma with fluid-filled stromal channels |
| Stem villi | 12 weeks to term | Term | 20–25 | Dense fibrotic stroma, myofibroblastic perivascular sheath, large vessels |
| Mature intermediate villi | Third trimester | Third trimester | 25 | Dense cellular stroma, >50% capillaries |
| Terminal villi | Third trimester | Term | 40–50 | >50% volume is capillaries |

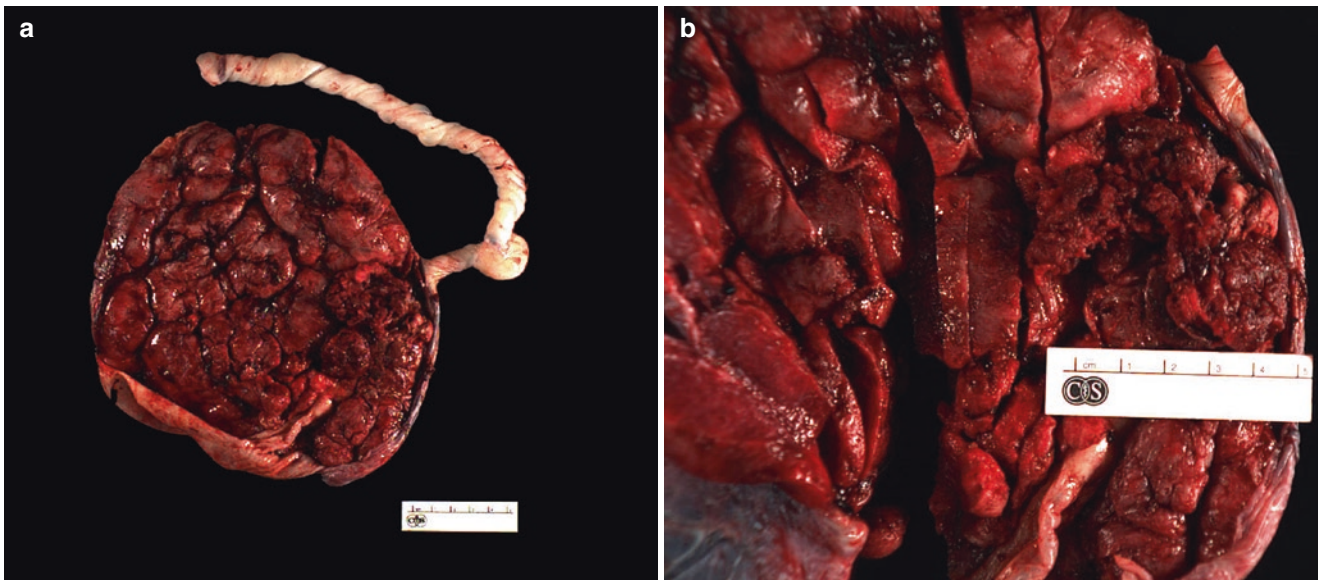


**Fig. 14.2** Integrity of the placental disc. (**a**) Maternal surface with mostly intact cotyledons, which are identified by their smooth, slightly shiny appearance. There is a focus of roughening, corresponding to exposed villi, near where the umbilical cord emerges. (**b**) The focus of disruption closer up. The roughened surface is clearly in contrast with the smooth, shiny intact cotyledons

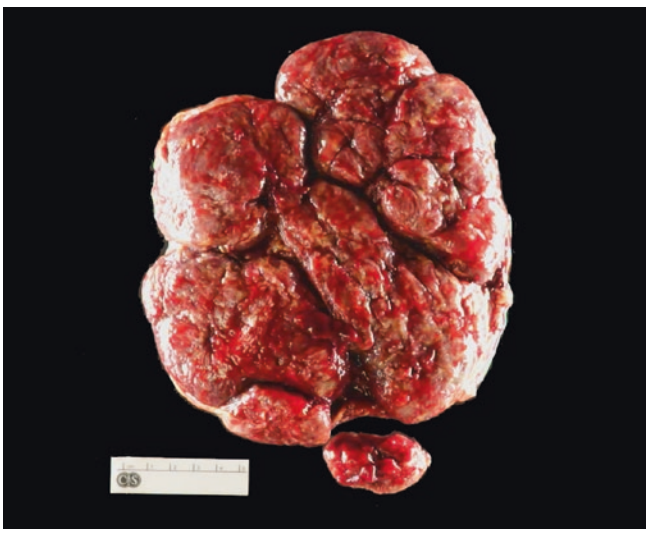

**Fig. 14.3** Completeness of the placental disc. This maternal surface is composed predominantly of intact cotyledons; however, one fragment is received separately (bottom of image). In this instance, the placenta is likely disrupted but complete

Another reason for a focally roughened maternal surface is adherent myometrium, which is seen in placenta accreta. Due to the abnormal implantation, these placentas often require manual removal which frequently results in disrupted cotyledons and a fragmented placenta/maternal surface for which completeness cannot be reliably determined (Fig. 14.4).

#### 14.2.1.2 Shape

While usually round to ovoid, placental shape is highly variable, and of not much importance as long as the overall growth/weight is appropriate. Uterine cavity abnormalities (i.e., septate uteri, scars, and leiomyomas) can result in unusual shapes. For example, should a placenta implant in the lateral uterine sulcus, a bilobate placenta can result, with a velamentously inserted cord between the lobes (Fig. 14.5).

In the early stages of placental development, the entire sac is covered by chorionic villi, most of which regress and flatten out to form the smooth fetal membranes. A succenturiate lobe (Fig. 14.6) results when an area away from the main placental disc fails to regress [7, 9].

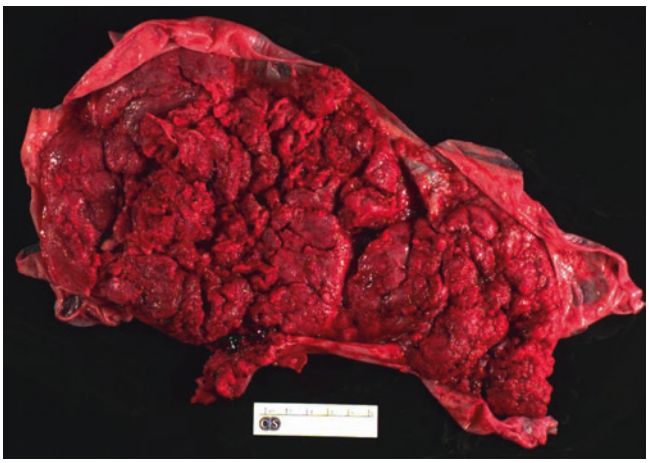

**Fig. 14.4** Disruption of the placental disc. This placenta required manual removal for presumed placenta accreta. The maternal surface is markedly disrupted; completeness cannot be assessed

#### 14.2.1.3 Color

Color of the villous tissue or placental parenchyma is mostly determined by the hemoglobin content, with immature placental parenchyma appearing significantly paler than discs at term. Color is not particularly specific, but may correlate with a clinical setting or suggest a diagnosis. Hydropic placentas, which are usually seen with hydropic infants and fetuses, will have a very pale color with coarse texture on cut section. Massive fetomaternal hemorrhage results in a remarkably pale placenta, often with an otherwise unremarkable exam, though intervillous thrombi are not unusual (Fig. 14.7). Very deep red placentas suggest increased blood content or congestion, such as in twin-twin transfusion syndrome [2, 5–7, 10] (Fig. 14.8).

#### 14.2.1.4 Weight

The placenta should be weighed with the membranes trimmed and the cord removed. As stated previously, fixation

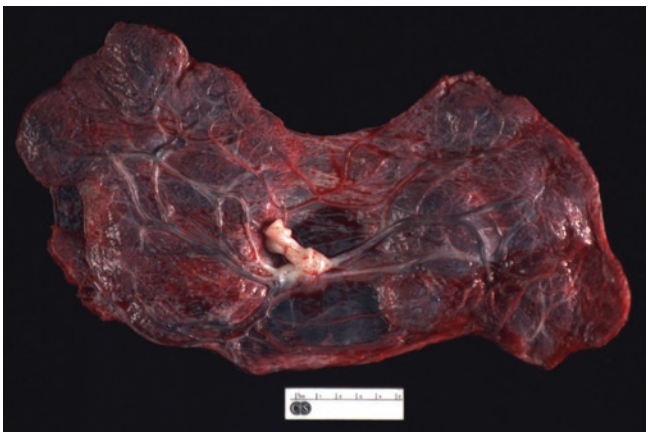

**Fig. 14.5** Placental shape. This is a bilobed singleton placenta with a membranously inserted umbilical cord located between the two discrete lobes

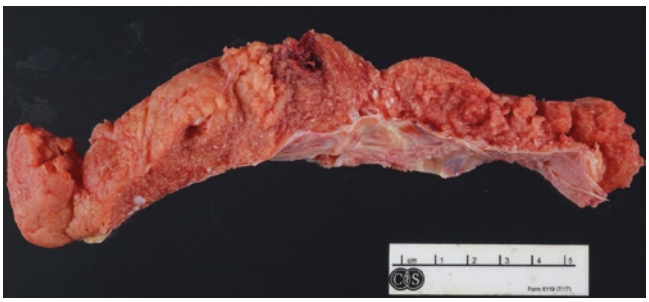

**Fig. 14.7** Placental pallor in a term placenta. This cross section of the parenchyma reveals notable placental pallor, as well as a small intervillous thrombus (top middle), but is otherwise normal. This is an example of massive fetomaternal hemorrhage (image courtesy of Stephanie Yagi, DO)

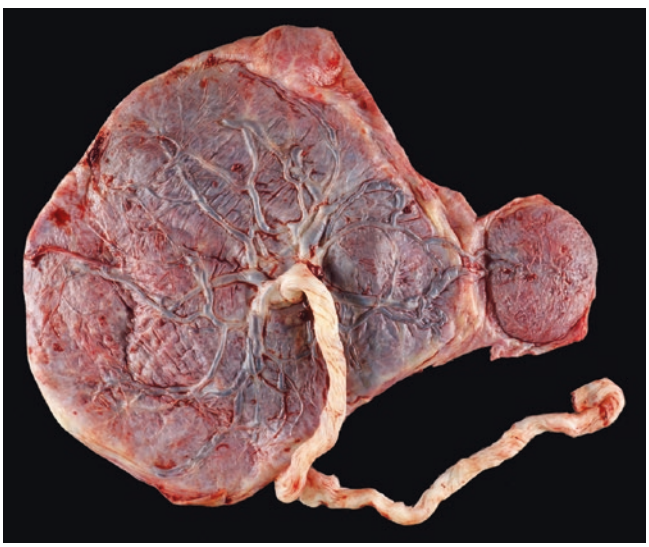

**Fig. 14.6** Succenturiate lobe. There is a separate island of well-developed placental parenchyma located away from the main disc. Note the large-sized vessels traversing the membranes to reach the accessory lobe

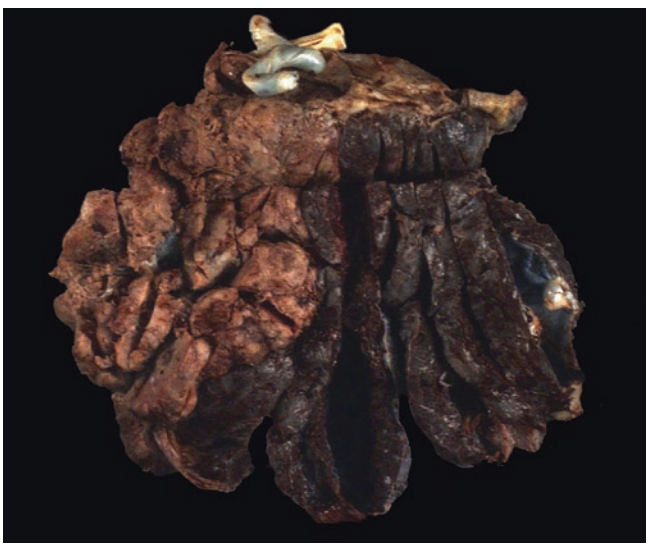

**Fig. 14.8** Twin-twin transfusion syndrome. The contrast between the markedly pale donor twin side and the very dark, congested, recipient twin territory is readily apparent

can increase the weight by up to 10%. There are established normal weight ranges for placentas, and small placentas (<10th percentile) and large placentas (>90th percentile) are associated with varying pathologies and maternal conditions. Ideally, weight norms should be established for the population in which the pathologist practices, though this is not always simple. Large-for-gestational-age placentas can be seen in diabetic pregnancies, maternal anemia, or retroplacental hematoma. Fetal factors leading to a large for gestation age can include states of fetal stress such as hypoxia or respiratory distress. Small-for-gestational-age placentas can be seen in cases of reduced uteroplacental blood flow, such as gestational hypertension or preeclampsia, as well as a variety of fetal conditions [2, 6, 7, 10, 11].

## 14.2.2 Umbilical Cord

The umbilical cord connects the developing fetus to the placenta. The cord contains three vessels: two umbilical arteries which carried deoxygenated blood from the fetus to the placenta, and a single, larger, umbilical vein, which carries oxygenated blood from the placenta to the fetus. The protective gelatinous connective tissue in which the vessels course is called Wharton's jelly; it is composed mainly of mucopolysaccharides with scattered fibroblasts and macrophages. At term, the umbilical cord is pearly white in color, about 60 cm in length, averages 1.0–1.5 cm in diameter, and is helical in shape, with an average of 1–3 coils for every 10 cm [12, 13]. The cord inserts into the fetal surface of the placenta disc [14]. When examining the umbilical cord, it is important to note color, length, diameter, coiling, insertion, and configuration, and to assess the vasculature both for number of vessels and for thrombi or hematomas.

### 14.2.2.1 Color

The normal cord is pearly white. If discolored, there will usually be a similar discoloration of the fetal surface and/or membranes. Green or brown discoloration is seen with meconium discharge before delivery. Yellowed cords are associated with maternal hyperbilirubinemia, or acute funisitis accompanying an ascending infection. Focal plaque-like discolorations of the cord are often noted in candidal infections of the amniotic fluid. Red discoloration can be iatrogenic but may also be due to necrosis, thrombosis, or hemolysis in the setting of fetal demise [12, 13, 15].

### 14.2.2.2 Length

The average length of an umbilical cord at term is 60 cm. A long cord is defined as one measuring over 70 cm, and short cords as 40 cm or less. It is important to note that calling a cord a "short cord" at the time of gross examination may not be accurate due to the fact that some length is left attached to the infant and more may be removed when retrieving cord blood, etc. [12, 13]. Long cords are associated with an increased incidence of cord entanglement, cord prolapse, true knots, excessive coiling, and constriction. Short cords are correlated with a range of neonatal problems (from fetal distress and low APGAR scores to depressed IQ and developmental anomalies). However, as cord length is thought to arise from fetal movement, it is unclear whether the short cord is a consequence or cause of these abnormalities [12, 13].

### 14.2.2.3 Cord Insertion

The umbilical cord may insert into the chorionic plate at any location; the insertion site is described qualitatively as central, eccentric (sometimes called paracentral), marginal, and velamentous (membranous). Central and eccentric insertions account for more than 90% of placentas. Velamentous is the least frequent (and most worrisome); the rest are marginal (Fig. 14.9).

Velamentous insertion is considered more susceptible to vessel rupture, and is associated with intrauterine growth restriction, stillbirth, and neonatal death. Interestingly, the incidence of velamentous insertion increases with maternal smoking, advanced maternal age, and diabetes mellitus, as well as in multiple gestations, congenital malformations, and pregnancies achieved with in vitro fertilization. The vessels of these cords are more vulnerable to injury because they lack the protective layer of Wharton's jelly as they course through the membranes to the disc (Fig. 14.10). Marginally inserted cords (those less than 1 cm from the disc edge) are similarly associated with adverse outcomes, though not as

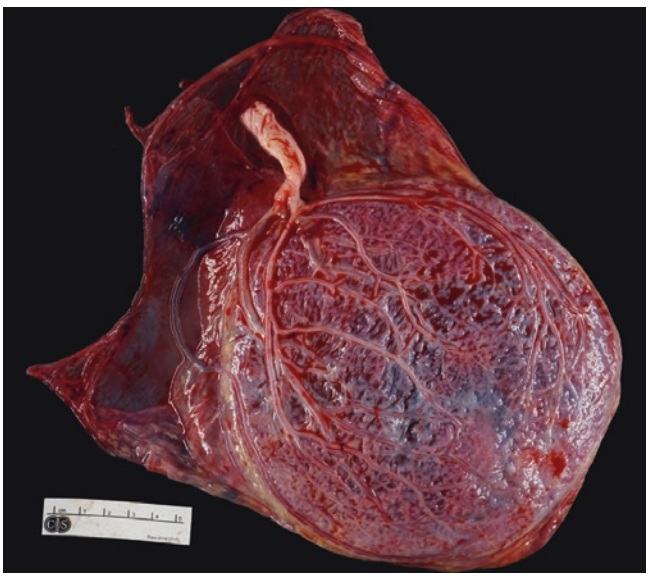

**Fig. 14.9** Marginal insertion of the umbilical cord. The cord insertion is directly at the disc edge. There is a vessel running unprotected through the membranes (left side); however, the cord itself does not insert into the membranes

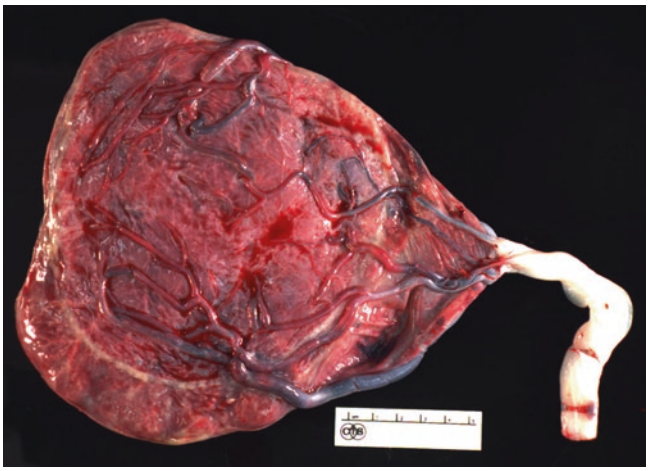

**Fig. 14.10** Velamentous, or membranous, cord insertion. The protective layer of Wharton's jelly ends as the cord inserts into the fetal membranes. The large vessels are easily identified coursing freely through the membranes to reach the placenta disc

clearly as a velamentous insertion, and the definition of marginal insertion varies considerably between studies [12–14].

#### 14.2.2.4 Coiling

The usual umbilical cord has a counterclockwise/left-turn coil. The average umbilical coiling index (UCI) is approximately 0.3 coils/cm (or about 1 coil every 5 cm) [16]. Both hyper- (>90th percentile) and hypocoiled (<10th percentile) cords are associated with adverse outcomes in the pregnancy, with hypercoiled cords associated with fetal growth restriction and hypocoiled cords associated with meconium staining, low Apgar scores, and NICU admission [17] (Fig. 14.11).

#### 14.2.2.5 Single Umbilical Artery

As stated previously, there are normally two arteries and one vein in the human umbilical cord. Initially, a second umbilical vein is present, but it atrophies during the second month of pregnancy [18–20]. Single umbilical artery (SUA) is the commonest true congenital anomaly of humans, with a prevalence ranging from 0.2% to 11%, depending on the population studied [18–20]. The loss of an umbilical artery is secondary to the thrombotic atrophy of a normal artery or, less commonly, due to primary agenesis of an artery. The vast majority of children with an isolated SUA grow and develop normally. However, the rate of chromosomal abnormalities and/or associated congenital malformations is increased in fetuses with SUA. Congenital malformations associated with single umbilical artery include neural tube and cardiac defects, as well as respiratory, gastrointestinal, musculoskeletal, and genitourinary anomalies [19].

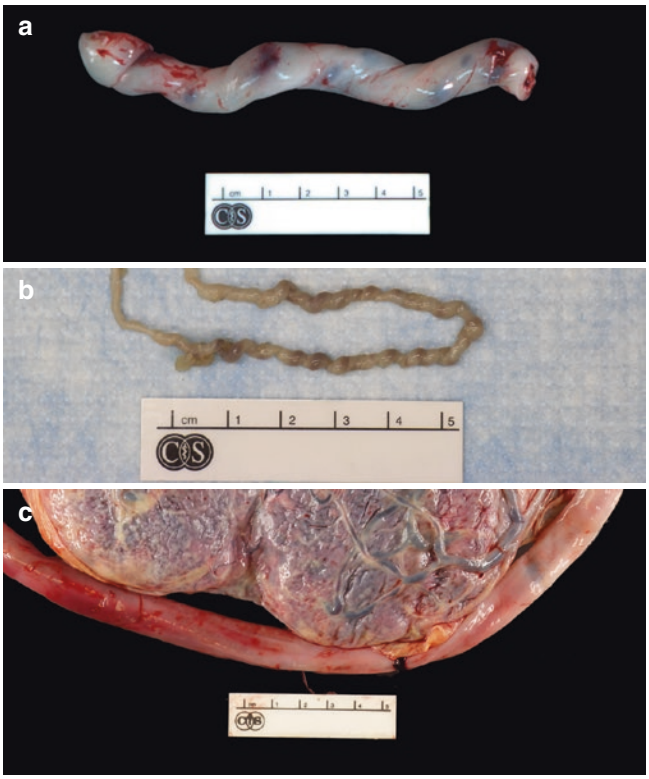


**Fig. 14.11** Cord coiling. (**a**) A normally coiled umbilical cord. (**b**) Hypercoiled umbilical cord (>3 coils per 10 cm) in a preterm gestation. (**c**) Hypocoiled umbilical cord (<1 coil per 10 cm). There is essentially no cord twist in this term cord

#### 14.2.2.6 Thrombi

Venous thromboses are more common than arterial thrombosis (with the latter being more often lethal). The cause is usually physical compression of umbilical vessels and/or damage to the vessel walls, but there may be an underlying cause (e.g., maternal diabetes, hypercoagulable state). Grossly, areas of thrombosis can show swelling and discoloration, and at times are visible on cut section; old thrombi may calcify [12, 13].

#### 14.2.2.7 Hematoma

While rare, true hematomas have serious consequences when they occur, and are associated with a 50% fetal mortality rate. They occur due to rupture of one or more umbilical vessels with varying underlying causes including short cords, trauma, inflammation, aneurysms, hemangiomas, and cord entanglement. Grossly, there will be elongated, fusiform swelling of the cord and marked dark red discoloration. It is important not to confuse this with iatrogenic cord hemorrhage associated with cord clamping. Cut sectioning will reveal hemorrhage throughout the cord. The cord surface may range from unstained (acute rupture) to red discoloration (in subacute to remote ruptures) [12, 13].

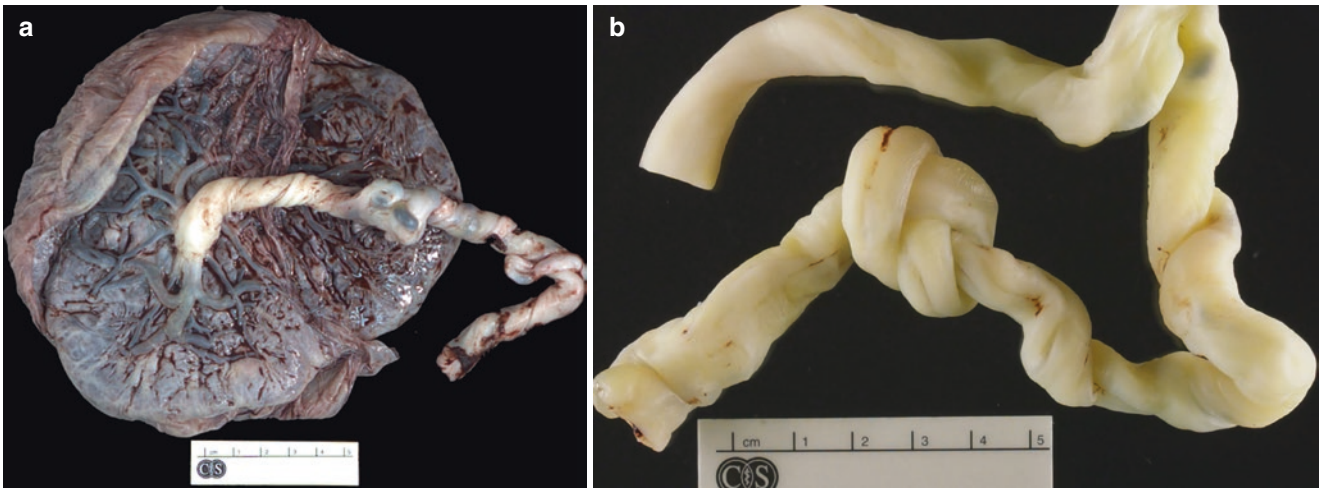


**Fig. 14.12** (**a**) False knot. Dilated umbilical vessels are present in the midportion of the cord. (**b**) True knot. This knot was easily reducible; note the absence of congestion or apparent constriction on either side of the knot

#### 14.2.2.8 Knots, True and False

False knots are formed by umbilical vessel redundancy, are very common, and are not pathologic, and gross assessment is sufficient. True knots, also a gross finding, are usually loose and inconsequential to the infant or fetus. If tight, true knots can lead to significant vascular compromise. Congestion of the cord on one side of the knot can be a sign of a tight true knot, as can marked thinning of the cord at the knot (which is visible when untied) [12, 13] (Fig. 14.12).

### 14.2.3 Membranes

Normal placental membranes are smooth, glistening, slightly translucent, and pinkish-tan in color. They insert at the outer margin of the placental disc, which typically coincides with the peripheral limit of the vascular plate [2, 5].

#### 14.2.3.1 Insertion

The usual membrane insertion pattern is called a "marginal" insertion. Circummarginate insertions are notable for a flat ridge of fibrin at the point the membranes contact the placenta surface, demarcating the extent of the vascular plate. It is generally believed to have no pathologic significance, although extensive cases may represent reduction of vascular plate that might affect fetal circulation. Similar to circummarginate, circumvallate placentas show a double-backed membrane fold where the membranes contact the placenta surface, and are associated with prematurity and chronic bleeding. The latter is because hemorrhage often occurs in this marginal region, presumably causing the membranes to separate from the disc and then later refold on themselves [2, 5] (Fig. 14.13).

#### 14.2.3.2 Color

Green-brown discoloration of the membranes can be due to meconium staining (the cord may be discolored too) or ascending infection. In cases of meconium staining, the membranes will also be slimy and edematous. Similarly, opaque membranes may be a sign of long-standing meconium or ascending infection. It is not unusual to see both meconium pigment and ascending infection in the same placenta. Red-brown discoloration of the membranes covering the fetal surface is a sign of old hemorrhage and results from small areas of decidual necrosis [2, 5].

#### 14.2.3.3 Amniotic Bands

If there is premature partial rupture of the amniotic sac (in which only the amnion is stripped away and the chorion stays intact) then amniotic bands can form. These will float in the amniotic fluid and can occasionally constrict parts of the growing fetus. In severe cases this leads to early amputations as the fetus grows beyond the vascular constraints of the constriction [21]. Grossly, thin adhesion-like threads and fragments are visible between parts of the fetal plate or between the fetal plate and umbilical cord, or sometimes even attached to the amputated fetal tissue [22] (Fig. 14.14).

#### 14.2.3.4 Other

Amnion nodosum consists of small, yellow-white, caseous, easily removed plaques that consist of sloughed keratin, hair, and other debris from the fetus. Amnion nodosum is a pathologic finding, usually associated with oligohydramnios [2]. Squamous metaplasia, on the other hand, consists of nodules/small plaques that are similar in color to the amnion nodosum, but are tightly adherent and not readily removed [2]. Squamous metaplasia is considered a normal finding at

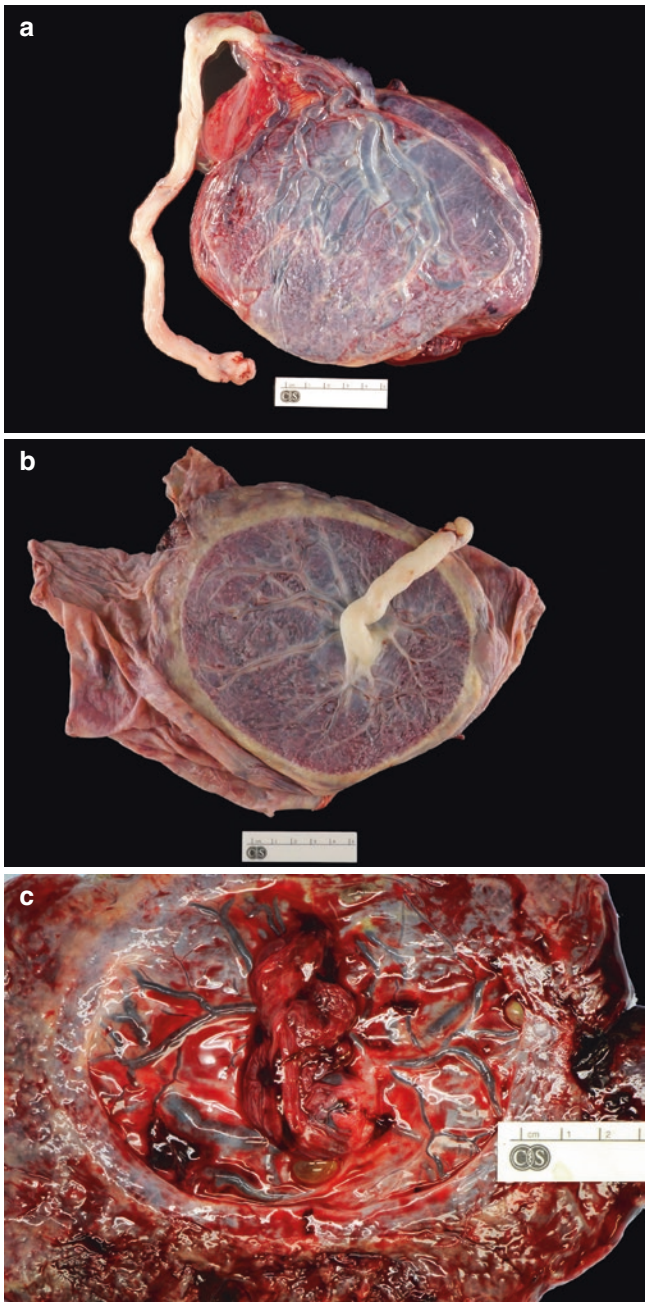


**Fig. 14.13** Membrane insertion. (**a**) Normal (marginal) insertion. Despite the abnormal cord insertion, the free membranes begin right at the margin of the disc. (**b**) Circummarginate insertion. There is a dense band of fibrin concentrically around the periphery, bringing the point where the membranes lift off closer to the center of the disc. (**c**) Circumvallate insertion. There is a dense band of fibrin located at the periphery of the disc, and in addition a flap is present at the bottom portion of the insertion. The flap consists of membranes folded back on themselves

term, and is noted most frequently near cord insertion. Occasionally, a yolk sac remnant is encountered. These are round, firm/calcified discs (~2 mm) within the membranes; they have no clinical significance. In multigestation concep-

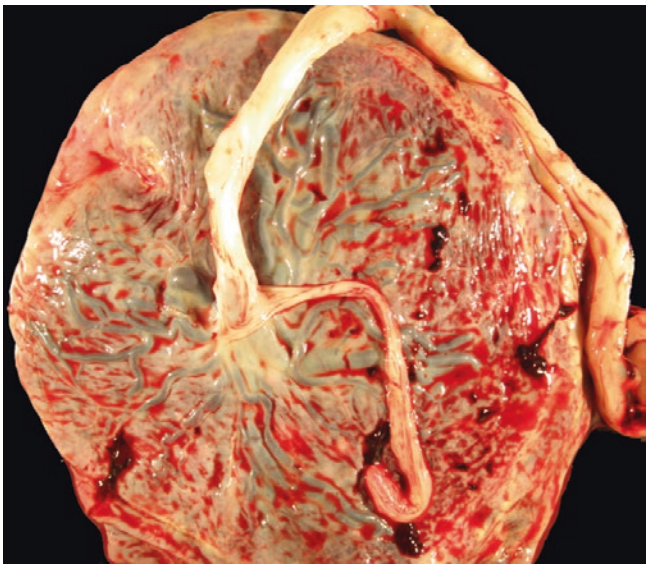

**Fig. 14.14** Amniotic band. The presence of free strips of amnion, seen here adjacent to the umbilical cord insertion site, indicates disruption of the amniotic sac. This example likely occurred at the time of delivery

tions with demise of one or more fetuses, the tissue may not be completely resorbed. In this situation, a firm mummified fetus papyraceous can be identified; depending on the gestational age of demise and time of delivery the tissue can range from very firm and sclerotic to semi-firm and necrotic. Placenta membranacea, also called placenta diffusa, is a rare developmental abnormality of the human placenta in which fetal membranes are covered diffusely by chorionic villi of varying thickness [2] (Fig. 14.15).

## 14.2.4 Placental Disc

### 14.2.4.1 Maternal Surface

Examining the maternal surface starts with assessing for intactness of the cotyledons; incompleteness suggests the possibility of retained placental tissue (discussed earlier). A thick white layer involving the maternal surface is indicative of a maternal floor infarction, which is actually fibrin entrapping the basal villi, as opposed to a true infarction [2].

Retroplacental hemorrhage is found on the maternal surface, always overlies villous tissue, and is a sign of premature separation (corresponding to the clinical diagnosis of abruption). The gross appearance of retroplacental hemorrhage depends on how much blood is trapped, and for how long it has been present. A recent hemorrhage may show very little change, and may not be grossly apparent at all. Acute abruption is a clinical diagnosis that will not necessarily have any gross or histologic findings, though it can be associated with amniotic fluid infection ("inflammatory

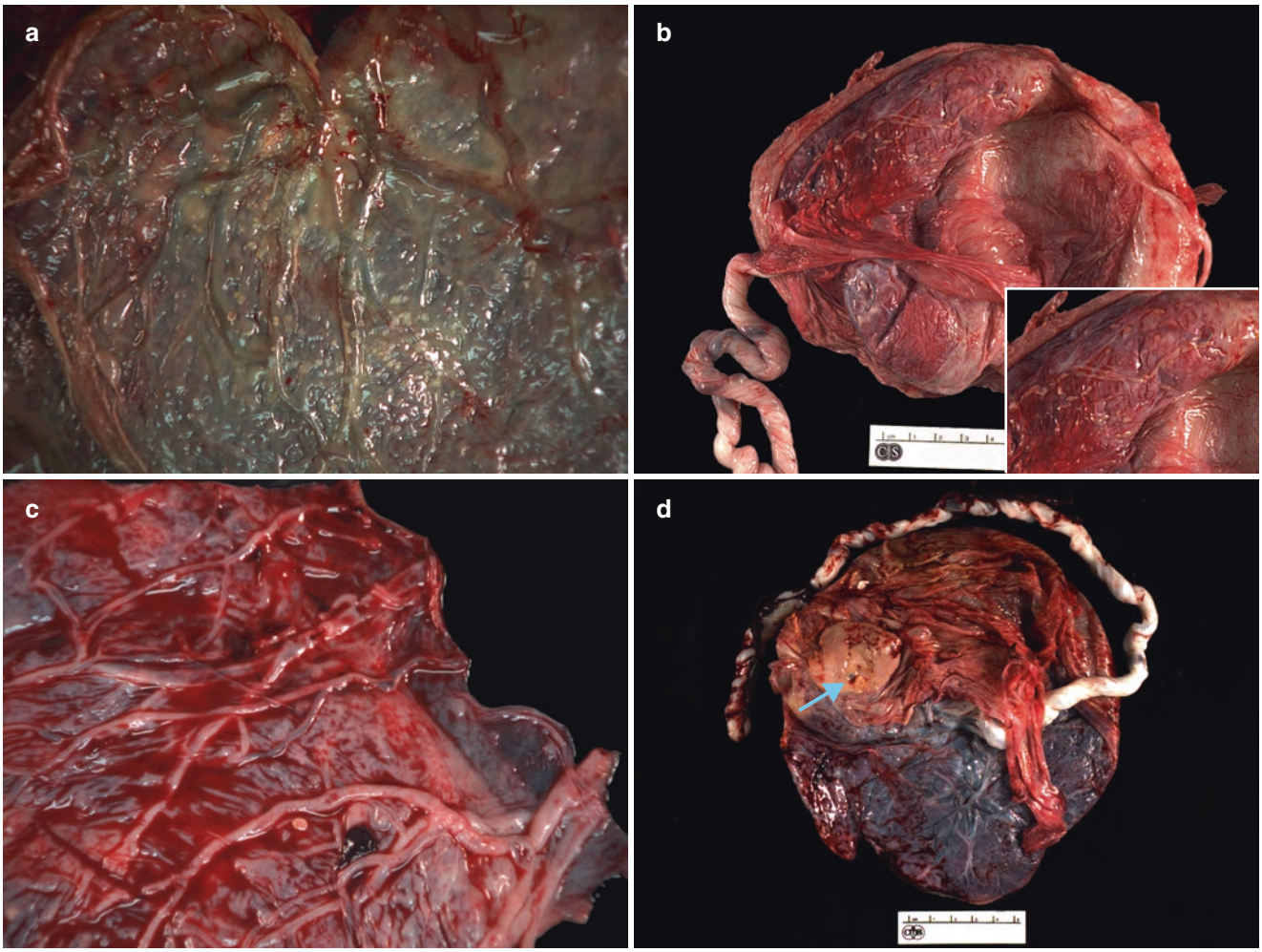


**Fig. 14.15** Plaques on the fetal membranes. (**a**) Squamous metaplasia. These small plaques are commonly seen in term placentas, especially near the umbilical cord insertion site. They are not removable. (**b**) Amnion nodosum. The plaques (upper left, inset) are pathologic and associated with prolonged oligohydramnios. They are removable. (**c**) Yolk sac remnant. Present as a single, firm nodule in the free membranes or fetal surface of the disc, this is a normal, if unusual, finding. (**d**) Fetus papyraceous. The dark pigment of the retina often stands out (arrow)

abruption"). If bleeding is confined behind the placenta for a significant amount of time, the overlying hematoma compresses the villous tissue and can lead to infarct, with notable thinning of the disc in that area (Fig. 14.16). Chronic marginal retroplacental hemorrhage can result in chorioamniotic hemosiderosis, which reflects hemorrhage into the amniotic fluid [2].

#### 14.2.4.2 Fetal Surface

The fetal surface is assessed for subchorionic fibrin and thrombotic material, both of which can increase through pregnancy. Patchy fibrin deposition is usually of little significance. A dull, opaque appearance to the fetal surface can be a sign of ascending infection, with more severe cases appearing more dramatic due to the numerous neutrophils and tissue necrosis (Fig. 14.17). Thrombosed fetal vessels are not rare, with chalky deposits representing calcified old thromboses [2, 5, 10]. In some cases, a cyst may be identified on prenatal ultrasound. The majority of these are not otherwise clinically significant and represent chorionic or subchorionic hemorrhage; the appearance can be relatively dramatic (Fig. 14.18).

#### 14.2.4.3 Parenchyma

Cut sectioning of the normal placental disc reveals a dark red, spongy surface. Serial sectioning of the disc at regular intervals (approximately 1–2 cm) is important to unveil any infarcts or thrombi.

Obstruction of the uteroplacental (maternal) circulation leads to placental infarcts, defined in part by villous necrosis. Minor infarcts are seen in about a quarter of placentas, but they are not of much clinical significance unless at least 30% of the placenta is involved. Single infarcts, especially at the placental margin, are not unusual in term placentas, but remember that *any* infarct in a preterm placenta is considered abnormal [2, 4, 5]. Compared to adjacent tissue, placental

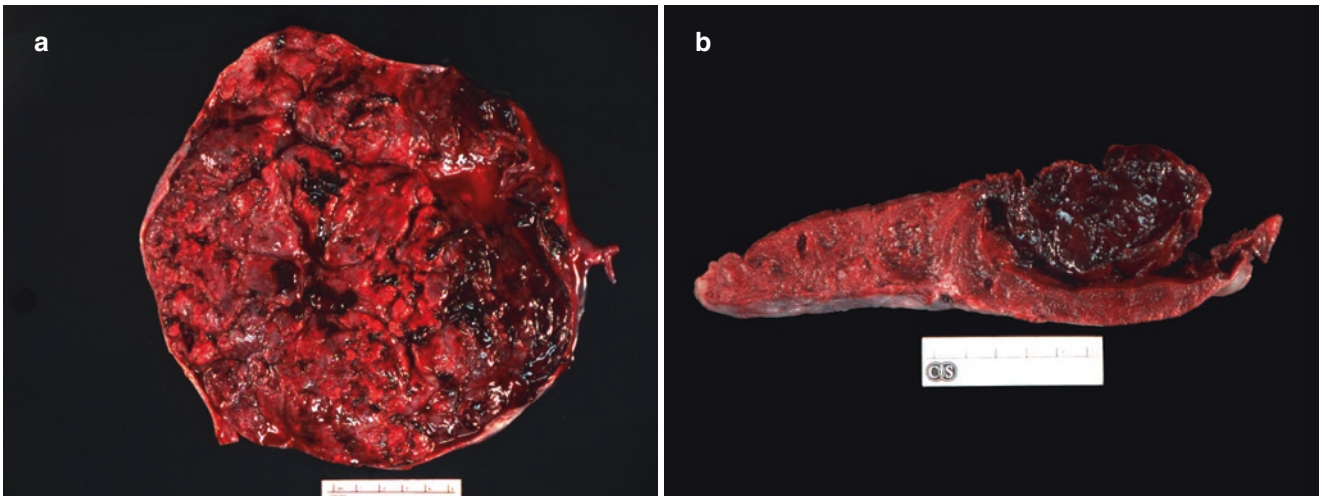


**Fig. 14.16** Retroplacental hemorrhage. (**a**) Maternal surface showing adherent blood clot, consistent with hemorrhage occurring prior to delivery. (**b**) Cross section of remote retroplacental hemorrhage; the underlying placental parenchyma is thinned due to the presence of the confined blood

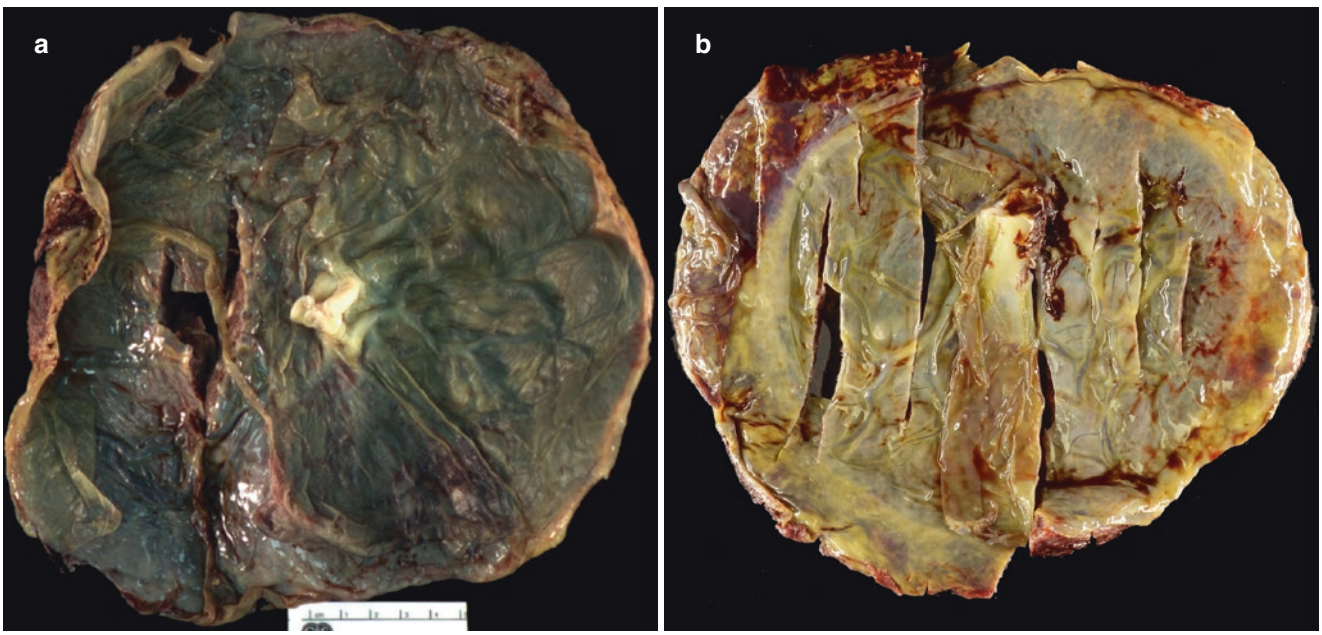


**Fig. 14.17** Discolored membranes. (**a**) Green-tinged membranes are suggestive of meconium staining. (**b**) Dull, opaque membranes are often associated with a significant acute fetal inflammatory response, such as to amniotic fluid infection

infarcts are firmer and granular; the appearance progresses from red and hemorrhagic to yellow to tan-white over time. Palpation can aid in detecting earlier infarcts, as can formalin fixation. Infarcts are more common at the periphery, with central infarcts more indicative of true pathology, especially if multiple [2, 5] (Fig. 14.19).

Clusters of avascular villi are caused by prolonged or recurrent occlusions within the *fetal* vasculature, which can eventually lead to a whole branch of the villous tree becoming avascular and atrophic. If there is a large enough focus of avascular villi, it may be visible grossly as an area of triangular pallor that retains the usual consistency of villous parenchyma (as contrasted with the denser firmness of an infarct). The base of the triangle is usually located at the basal plate and can sometimes be visualized more easily in a fixed specimen [23].

Intervillous thrombi are found within the parenchyma, expanding the intervillous space. Early thrombi are fresh red clots, which evolve to laminated thrombi, and eventually white lesions. They can be differentiated from infarcts by their shiny quality and lack of granularity [2, 5] (Fig. 14.20).

An entity that can be confused with infarcts and thrombi is the chorangioma, a firm fleshy lesion usually found under

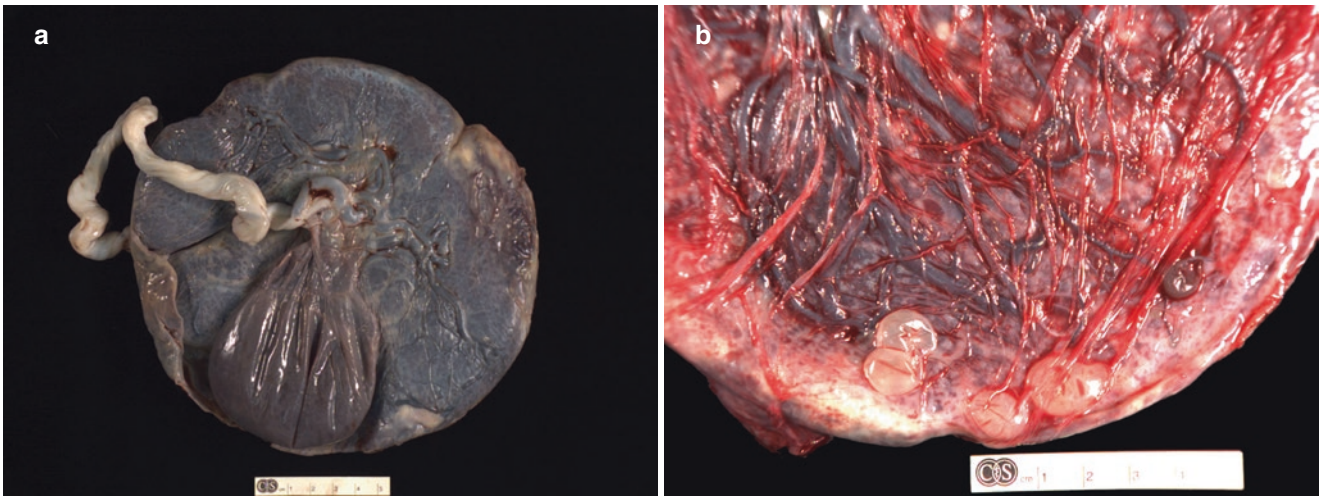


**Fig. 14.18** Placental surface cysts. (**a**) A relatively large subamniotic/subchorionic cyst, or hematoma. As here, this finding is most often seen near the cord insertion. (**b**) Multiple small amniotic and subamniotic/chorionic cysts, some with hemorrhage. These are of no clinical consequence

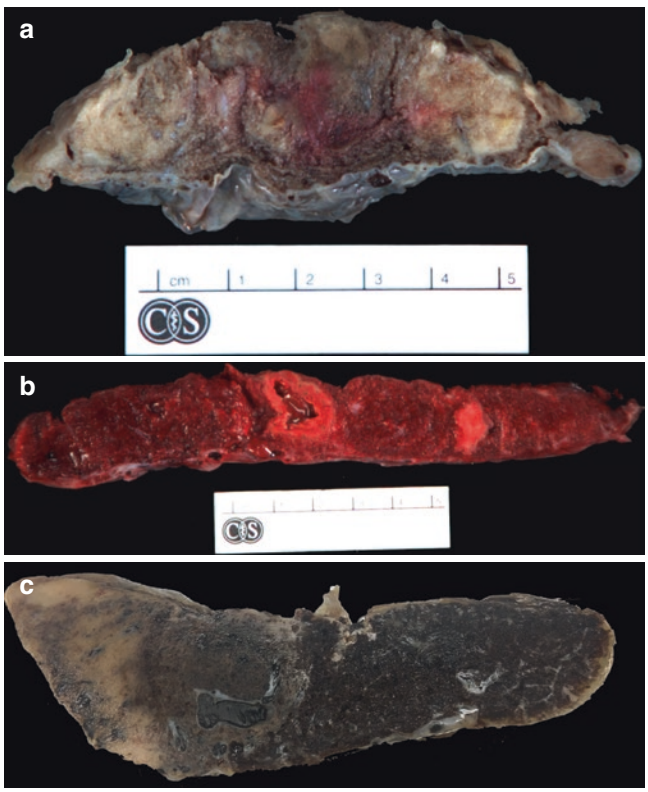


**Fig. 14.19** Placental infarcts. (**a**) Cross section of placenta showing multiple infarcts of various ages. There is very little normal parenchyma visible in this section; the small strip of parenchyma in the middle just deep to the fetal surface appears relatively uninvolved. (**b**) Two well-defined infarcts, one with unusual pseudocystic change. (**c**) The pale tan area on the far left is a more remote area of infarction, and just adjacent is a more recent infarct. Even the recent area of infarction has a sharp, well-defined border with uninvolved parenchyma

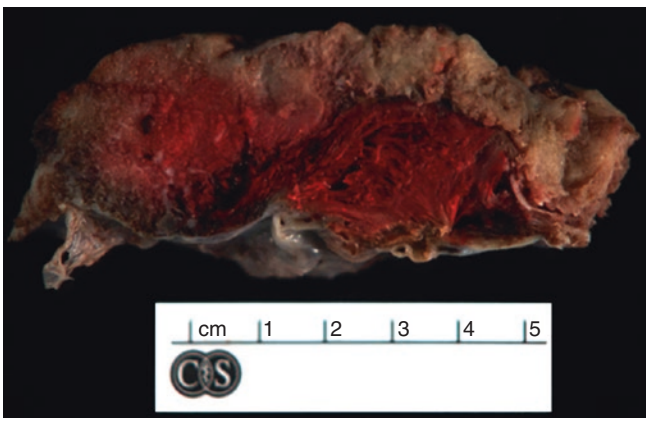


**Fig. 14.20** Intervillous thrombus. There is a large laminated thrombus in this preterm placenta, surrounded by pale parenchyma

the chorionic plate with varying degrees of hemorrhage and infarction [24] (Fig. 14.21). It is possible to see single or multiple reddish-brown well-circumscribed nodules often located in marginal or subchorionic region which suggests the possibility of a chorangioma (this will be discussed in greater detail in the histologic section of this chapter).

### 14.2.5 Twin/Multiple Gestation Pregnancy Development

With the rise in the use of fertility-enhancing therapies and an older average maternal age, the incidence of multiple births has increased dramatically over the past three decades.

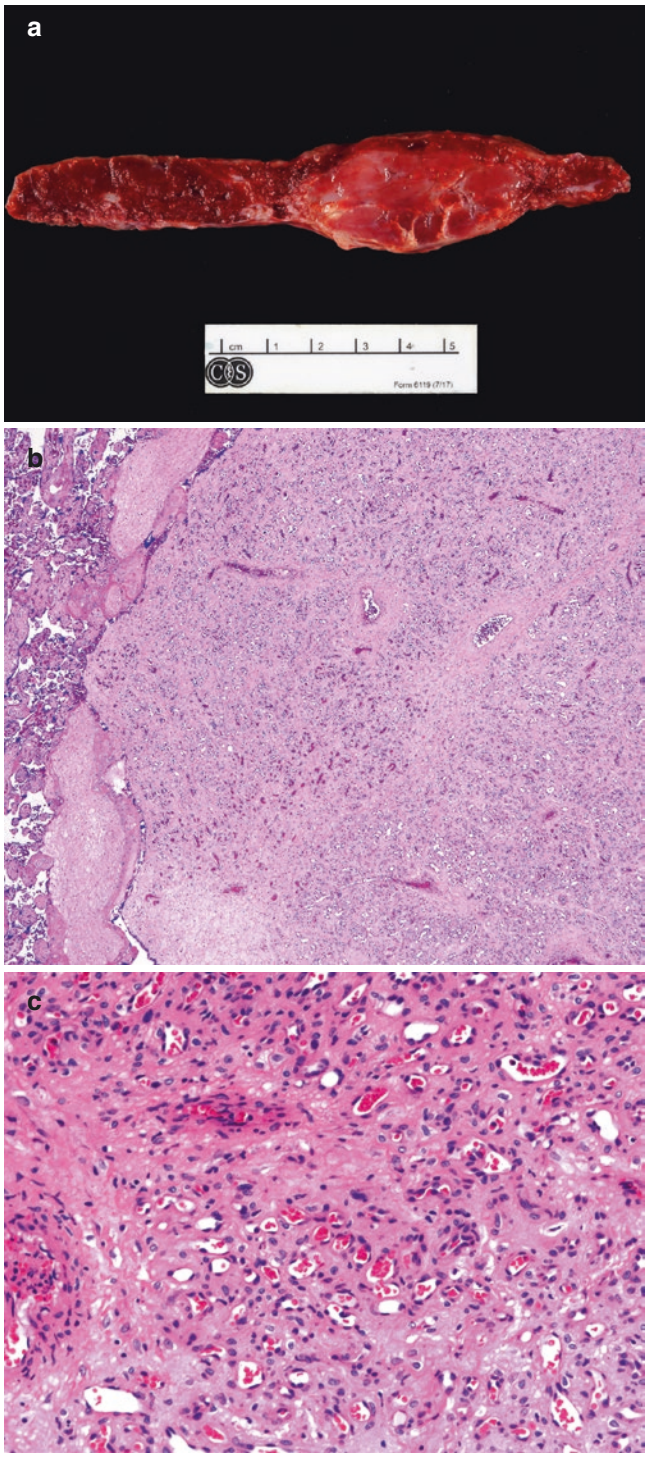


**Fig. 14.21** Chorangioma. (**a**) This mass lesion is well defined, multilobulated, and somewhat fleshy. (**b**) The lesion is clearly demarcated from the surrounding parenchyma. (**c**) On high power, the mass is composed of small, bland capillary-type vascular structures set within in a hyalinized stroma

Perinatal mortality of twins is roughly five times that of singletons, largely due to increased prematurity rates in the twin population. Monochorionic twins, in particular, have their own specific complications such as twin-to-twin transfusion syndrome, discordant growth restriction, and malformations [25].

A brief statement on the development of twin/multiple pregnancies: zygosity refers to the type of conception; twins can be either monozygotic or dizygotic. Dizygotic (fraternal/nonidentical) twins are more common and result from multiple ovulation with near-synchronous fertilization of two ova by two sperm cells. Monozygotic twins result from the fertilization of one ovum by two sperm cells and the subsequent division. The reasons why both monozygosity and dizygosity occur are not fully elucidated but are believed to be multifactorial [25].

Related to zygosity is the type of placentation, or chorionicity, of the resulting placenta. Dizygotic zygotes each develops its own amnion, chorion, and placental circulation. A fused placental mass (still with separate components) develops when the two blastocysts implant close to one another. Monozygotic pregnancies are not as straightforward, with the type of placentation depending on when the zygote divides, with early division (with the 3 days of fertilization) resulting in dichorionic placentas. Late division is defined as 8–12 days after fertilization and results in a monoamnionic-monochorionic placenta. Division in between those time periods results in diamnionic-monochorionic placentas. Division later than 12 days results in conjoined monoamnionic-monochorionic twins [25].

### 14.2.6 Gross Examination of the Twin and Multigestation Placenta

All twin and other multigestation placentas should be evaluated, at least macroscopically. The placentas should be labeled at the time of delivery to identify which cord belongs to which infant. As fixation may compromise any potential vascular injection studies (if indicated/possible), fresh examination of twin placentas is preferred.

#### 14.2.6.1 Chorionicity

One of the first things that should be assessed grossly is the chorionicity (how many discs are present) and amnionicity (how many amniotic sacs are present) of the placenta. Zygosity cannot be determined by placental examination, with the exception of monochorionic placentas, which occur only with monozygosity (taking care to exclude fused discs). Useful algorithms have been described previously regarding the assessment of twin placentation (histologic depictions of various membrane configurations are presented later in this chapter):

(a) Separate or fused discs: Separate discs (connected by only membranes) are diagnostic of diamniotic-dichorionic placentas. Fused discs are dichorionic and usually diamniotic

(see below). Single discs by definition are always monochorionic, and may be diamniotic or monoamniotic.

(b) Dividing membrane present or absent: In cases with a single disc or with fused discs, the placenta is examined for the presence of a dividing membrane. If no dividing membrane can be identified, it is suggestive of a monoamniotic-monochorionic placenta. It is important to remember that the dividing membranes may be stripped or disrupted, giving the false impression of a monoamniotic placenta. Fused placenta discs should always have started with a dividing membrane.

(c) Layers of the dividing membrane: Careful examination of the layers of the dividing membrane allows the prosector to differentiate between diamniotic-dichorionic and diamniotic-monochorionic placentas. A relatively thick, slightly opaque dividing membrane composed of 3–4 layers is indicative of diamniotic-dichorionic, providing that there are clearly separated chorionic vascular beds. Very thin, translucent, two-layered dividing membranes, less firmly attached to the chorionic plate, are seen in diamniotic-monochorionic placentas.

Twin placentas deemed dichorionic can be grossed as one normally does singleton placentas, with each placenta addressed separately. If the discs are fused, however, the placental weight should be combined (do not cut and weigh the portions separately!). Monochorionic twin placentas, on the other hand, have an increased rate of major complications, some of which have been associated with gross placental findings; these findings should be searched for and documented, specifically the type of cord insertion, degree of placental sharing, and presence or absence of artery-artery (AA) and vein-vein anastomoses (VV) [11, 25, 26].

#### 14.2.6.2 Anastomoses

Regarding inter-twin anastomoses, it is useful to note that chorionic arteries are identified by their tendency to run superficial to their accompanying veins (arteries travel over veins). AA and VV anastomoses are superficial and do not penetrate the chorionic plate, and are usually of minimal significance. Arteriovenous (AV) anastomoses, however, are deeper, occur at the villous capillary level, and cannot be seen when examining the chorionic plate. One can instead describe/sample the sites of an unpaired artery and vein in close proximity to one another [11, 25, 26] (Fig. 14.22).

Injection studies are not routinely needed, but may be pursued for academic purposes, at clinician/parent request, or in cases of laser ablation for twin-twin transfusion syndrome (TTTS). To perform an injection study, the umbilical cords are sectioned, with a stump left for cannulation of the vessels. Manual "milking" of the superficial vessels removes remaining intravascular blood. Umbilical catheters are inserted into the umbilical vein and arteries of each cord and dye is injected through these, allowing the examiner to visualize the anastomoses [11, 25, 26]. In practice, this is very rarely performed.

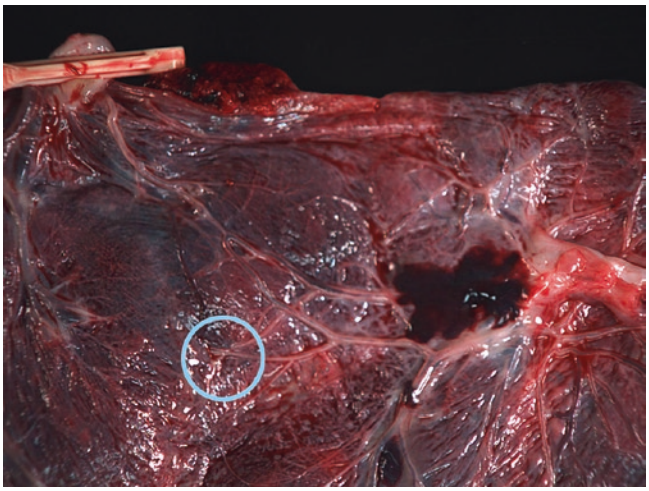

**Fig. 14.22** Anastomoses in a twin placenta. Vessels clearly traverse this monochorionic disc, from the area of one cord insertion to the other. Foci where an artery and vein enter the disc together are sites of possible arteriovenous anastomoses (circle)

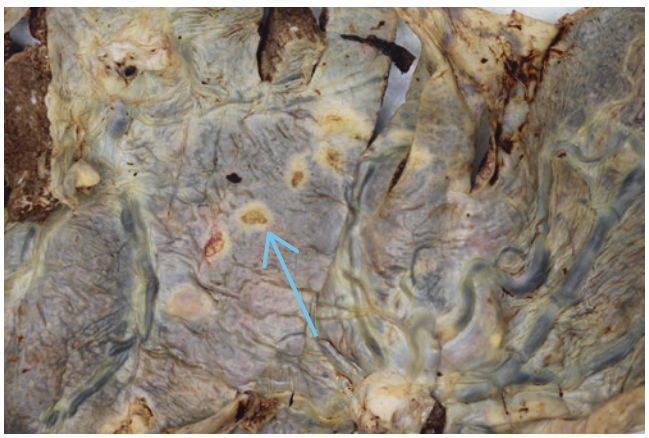

**Fig. 14.23** Laser ablation of anastomoses for twin-twin transfusion syndrome. The irregular to oval areas in the center (arrow) are the sites of in utero laser ablation

#### 14.2.6.3 Laser Treatment

In cases of severe chronic TTTS, possible prenatal treatments include serial amnioreduction, and fetoscopic laser coagulation (ablation) of the communicating vessels. Depending on the timing of the photocoagulation, gross findings range from hemorrhagic clotted vessels with interruption of dye filling (if examined within 1 month of photocoagulation) to absence of inter-twin anastomoses with subchorionic fibrin deposition [25] (Fig. 14.23).

#### 14.2.6.4 Fetus Papyraceus

When a fetus in a multigestation pregnancy dies in utero, it is either partially or completely reabsorbed. This results, in some instances, in a flattened, parchment-like state known as *fetus papyraceus*. In some instances a sclerotic placental component also remains.

### 14.2.7 Gross Examination of the Placenta in Fetal Demise

In instances of midgestation or term fetal demise, pathologic examination is incomplete without inclusion of the placenta; if an etiology of demise is identified, it is most often found there. Gross evaluation for these placentas is not much different than routine examination. Most critically, a proper review of clinical records is important in discerning areas of focus during analysis, but all placental components should be given fair attention. For example, if the Kleihauer-Betke test is positive (indicating fetal hemoglobin in the maternal blood), be sure to note if the parenchyma appears more pale than usual. If the mother has a history of preeclampsia, look carefully for infarcts. If the demise was relatively remote, the fetus will be macerated and the placenta firm and small for dates. Take care to look for discrete thrombi within the umbilical cord and fetal surface of the disc.

Fresh tissue may be saved for possible cytogenetics studies and culture for organisms, if indicated or requested; however these studies are rarely informative.

Specific findings that can be associated with fetal demise are discussed later in the chapter (see Constellation Disorders in particular).

## 14.3 Histologic Features and Findings of the Placenta

### 14.3.1 Umbilical Cord

Many umbilical cord findings are only identified grossly (knots, length, etc.).

#### 14.3.1.1 Basic Structure

Histologically, the vessels are surrounded by the mucoid extracellular matrix known as Wharton's jelly, and the cord is surfaced by a single layer of cuboidal amniotic epithelium. Microscopic examination of the umbilical cord consists primarily of looking for inflammation, and assessing the vasculature for thrombi and number of arteries.

Other normal structures that may be present within a cross section of the cord include developmental remnants. Not uncommonly, allantoic or vitelline duct remnants are identified (Fig. 14.24). In some cords, dilated small capillary-sized vessels are noted; the significance of this is unknown.

#### 14.3.1.2 Acute Inflammation

Funisitis is acute inflammation of the substance of the umbilical cord, and represents an acute fetal inflammatory response. Initially, the response tends to involve margination of neutrophils out of the umbilical vein (which is bringing oxygenated blood back from the placenta to the fetus) at the placental disc end of the cord, followed by involvement of the arteries, and finally the infiltrate extends into Wharton's jelly (at which point it is termed funisitis) [12, 13, 15] (Fig. 14.25). Though most often associated with amniotic fluid infection (see also the section on amniotic fluid infec-

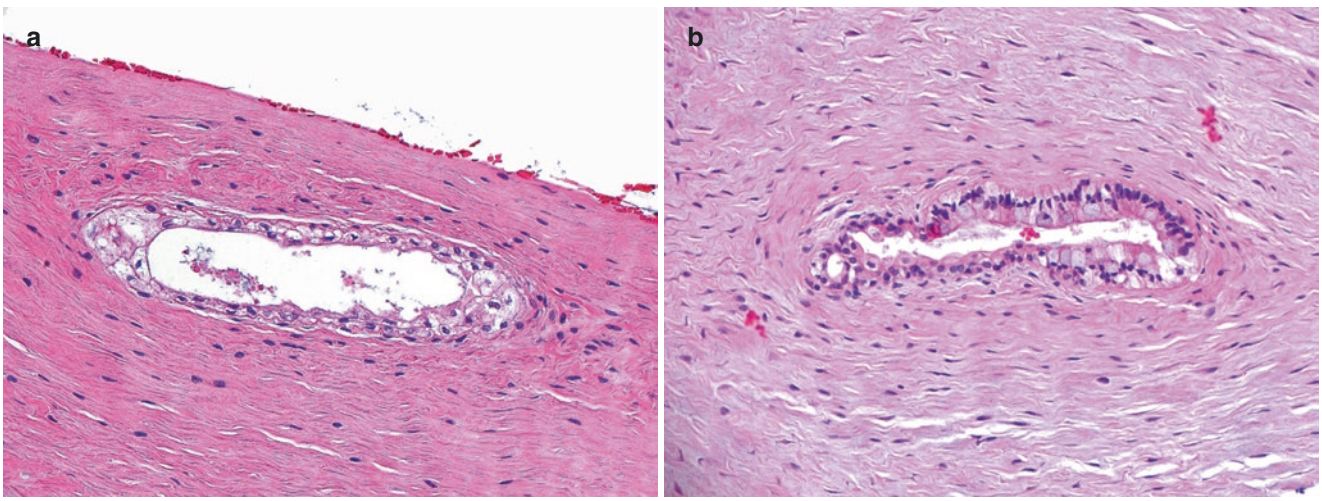


**Fig. 14.24** Embryologic remnants in the umbilical cord. (**a**) Allantoic duct remnant. These structures are lined by a cuboidal to flat epithelium, resembling transitional type epithelium or urothelium. A muscular wall is always lacking. (**b**) Vitelline (omphalomesenteric) duct remnant. As seen here, these are most often lined by mucin-rich epithelial cells, but rarely other tissue types are noted. A muscular layer or associated small vessels are occasionally seen

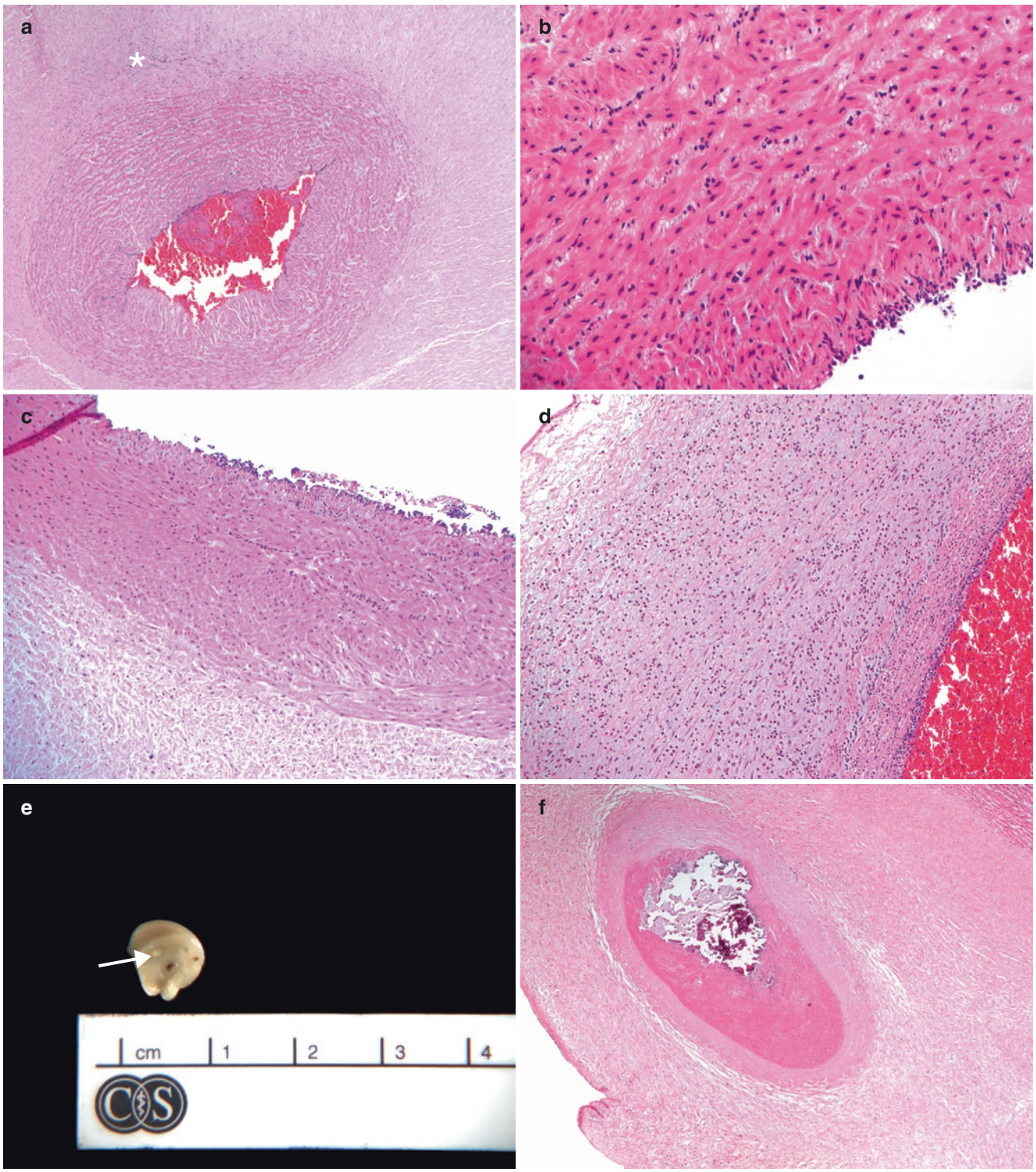


**Fig. 14.25** Acute inflammation in the umbilical cord. (**a**) Funisitis. Low power of the umbilical cord with acute inflammation marginating out of the vessel and spilling into Wharton's jelly (arrow). (**b**) Higher power of an umbilical vessel with neutrophils present between the muscle fibers. (**c**) Acute inflammation confined to the muscular wall of the umbilical vessel. (**d**) A robust neutrophilic infiltrate extending beyond the vessel and into Wharton's jelly (funisitis). (**e**) Gross appearance of a thrombosed umbilical artery (arrow). (**f**) Thrombosed and calcified umbilical artery

tion below), these findings can also be seen with in utero meconium exposure. When associated with meconium, the inflammation tends to be more pronounced in the umbilical cord than the chorionic plate, and meconium-laden macrophages should be identifiable histologically.

#### 14.3.1.3 Thrombi

Thrombi will show usual organization with alternating fibrin and clot within the lumen, as in any other vessel [12, 13, 27].

### 14.3.2 Membranes

When examining the membranes histologically (Fig. 14.26), the pathology to be evaluated ranges from pigment in the membranes to evidence of an inflammatory response and to searching for maternal arteriopathy within the decidua.

#### 14.3.2.1 Basic Structure

Histology of the extraplacental membranes consists of:

(a) Cuboidal amniotic epithelium, with its underlying basement membrane
(b) A hypocellular "spongy" layer with scattered fibroblasts, which is really a potential space
(c) Chorion, including the sclerotic villi of early gestation (chorion laeve) and trophoblasts
(d) Maternal decidua

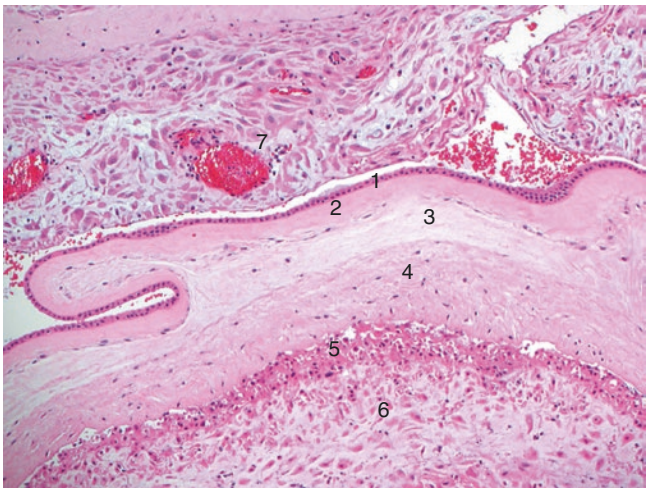


**Fig. 14.26** Fetal membranes. The membranes are composed of several layers, starting with the amniotic epithelium (1) with its underlying basement membrane and fibroblast layer (2). The spongy layer (3) is a potential space that divides the amnion from the chorion. The reticular layer of the chorion (4) contains fibroblasts, next to which is the basement membrane of the chorion and the chorionic trophoblasts (5). The final layer is decidua (6), which is the only maternal tissue component present, and is where spiral arteries are most easily identified (7)

#### 14.3.2.2 Meconium

Meconium, the bile-stained intestinal content of the fetus, is occasionally expressed at delivery or prior to delivery. If expelled into the amniotic fluid well prior to delivery, it can stain and irritate the fetal membranes, will be preserved within macrophages, and can therefore be identified histologically. Meconium expressed at the time of delivery will rinse off easily and won't be found within macrophages on histologic examination. Meconium-laden macrophages are large, are round to ovoid, have slightly granular yellow-brown material filling their cytoplasm, and are usually identified in the subamniotic spongy layer. If meconium has been present in the amniotic cavity for many hours, the amnionic epithelium may show degenerative changes, including vacuolization of the cytoplasm, heaping up of cells, hobnailing, dissociation, loss of cells, and necrosis. Meconium staining affects the amnion before the chorion, as the macrophages travel through the layers of the membranes (Fig. 14.27).

#### 14.3.2.3 Squamous Metaplasia

This is a finding that is present in more than half of term placentas. It is not a true pathologic finding, but a sign of placental maturity. The amniotic epithelium becomes stratified with focal keratinization of the epithelium, resembling squamous epithelium. It is most often identified near the umbilical cord insertion (Fig. 14.28a).

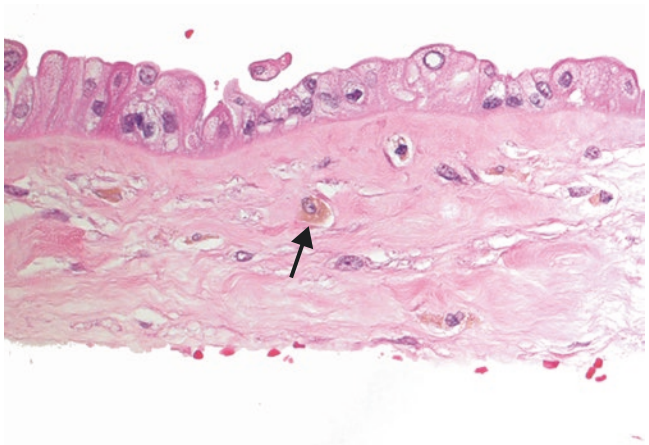

**Fig. 14.27** Pigment-laden macrophages in fetal membranes. The slightly granular brownish pigmented meconium is present in macrophages (arrow). The amniotic epithelium exhibits reactive changes, including heaping up, cytoplasmic vacuolization, and dissociation

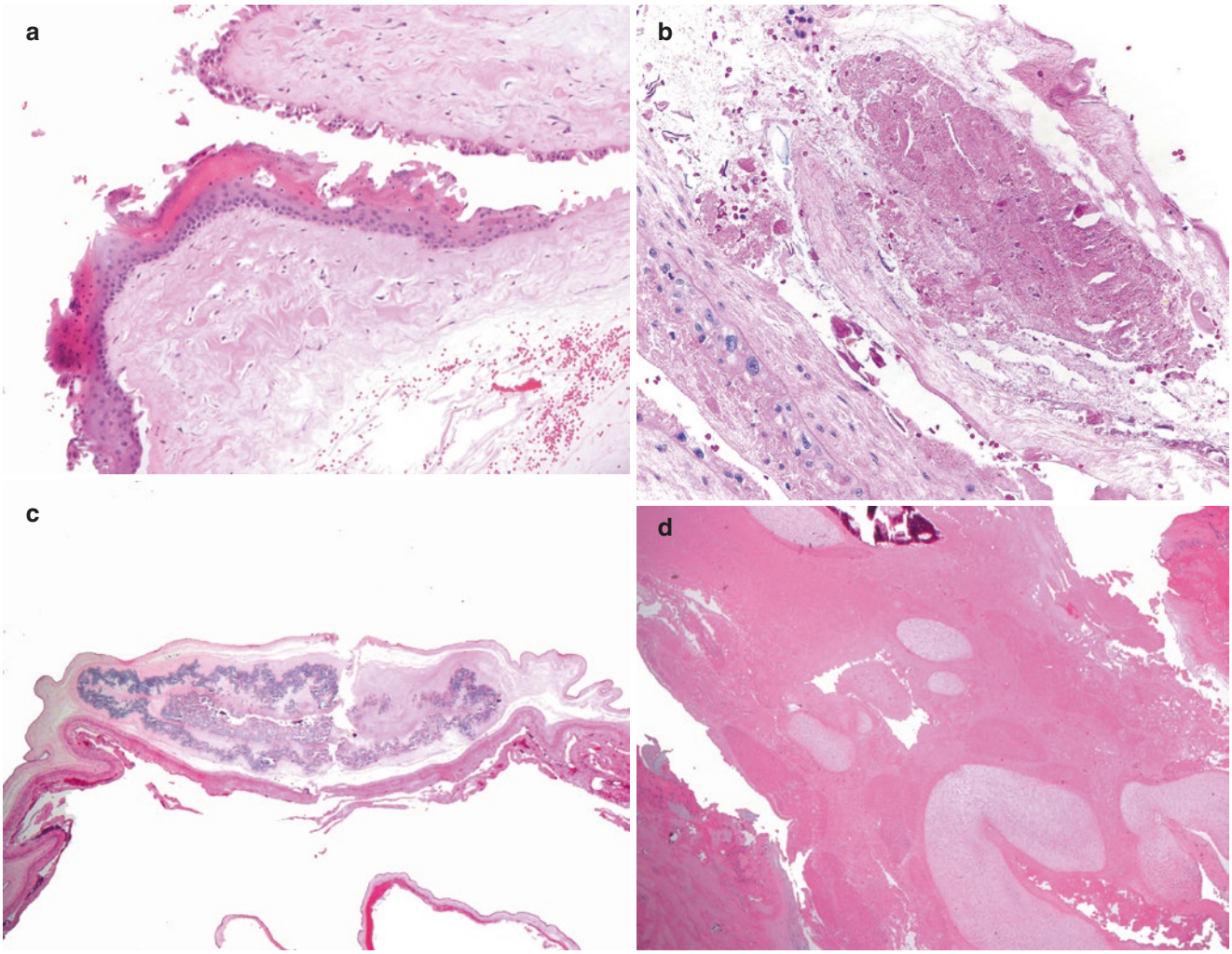


**Fig. 14.28** Fetal membranes. (**a**) Squamous metaplasia. Keratinizing epithelium is present, in contrast to the normal cuboidal amniocytes (upper right of image). (**b**) Amnion nodosum. Grossly identified plaques are composed of degenerated squamous cells, hair, and debris. (**c**) Yolk sac remnant. A well-defined, circumscribed, and calcified plaque, just under the amniotic epithelium. (**d**) Fetus papyraceous, with ghost outlines of devitalized and calcified fetal tissues

#### 14.3.2.4 Amnion Nodosum

This condition is associated with prolonged oligohydramnios of any cause, though the mechanism is not understood. Microscopically, the nodules are composed of sloughed fetal squamous cells and hair, mixed with hyaline and proteinaceous debris. There is no associated inflammation. The nodules are usually situated superficially on the amniotic surface, but sometimes extend through to the spongy layer (Fig. 14.28b). Other lesions such as yolk sac remnant and fetus papyraceous may be seen in Fig. 14.28c, d respectively.

#### 14.3.2.5 Amniotic Bands

Histologic sections show normal-appearing amnionic epithelium and underlying connective tissue. Inflammation is absent, and there are usually few signs of degeneration [21]. Amniotic bands need to be assessed grossly.

#### 14.3.2.6 Acute Chorioamnionitis

The pattern of pathologic findings commonly referred to as "chorioamnionitis" is most often indicative of ascending amniotic fluid infection. Its definition is the presence of neutrophils (PMNs) within the fetal membranes. Eosinophils may be present, especially in protracted infections, though chronic inflammatory cells are generally not a significant component of the response. PMNs may be present within the decidua and/or chorion, even in the absence of an infectious process. The term "acute chorioamnionitis" should be reserved for instances of inflammation extending into the subepithelial hypocellular space to involve all layers of the

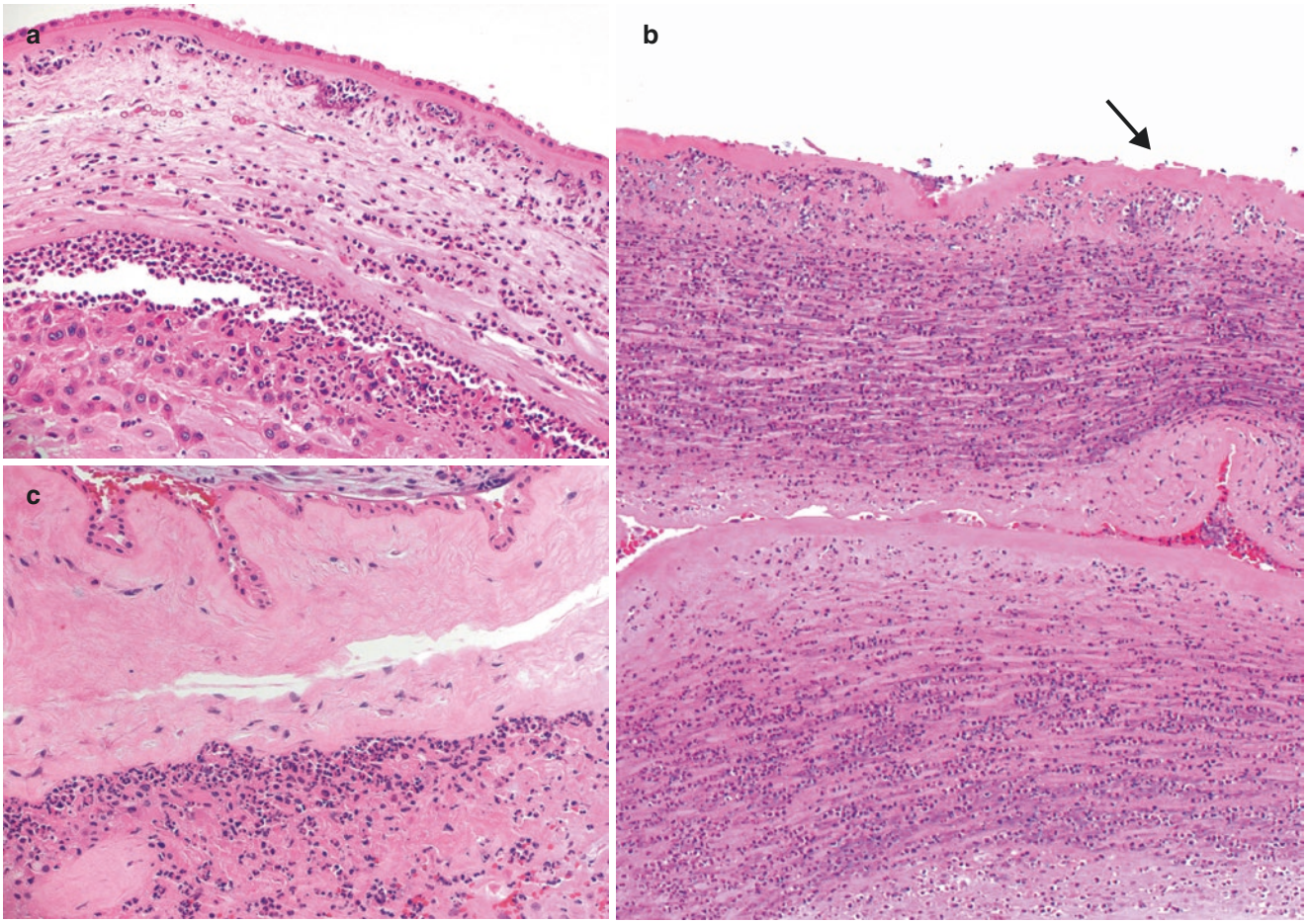


**Fig. 14.29** Acute chorioamnionitis. (**a**) Acute inflammation extends all the way up from the decidua (bottom of image) through the chorion and spongy layer into the amnion and is present just under the epithelium. (**b**) Necrotizing chorioamnionitis with confluent neutrophilic infiltrates and necrosis of the amniotic epithelium (arrow). (**c**) Chorionitis. The neutrophils are dense within the chorion, but have not yet crossed into the reticular or amniotic layers; chorioamnionitis should not be reported here

membranes [15, 23, 28] (Fig. 14.29). See also the section on amniotic fluid infection sequence.

### 14.3.3 Placental Disc

Findings within the parenchyma of the disc (and its compartments) are often related to lesions initially discovered upon gross examination, and to histological findings of the umbilical cord and membranes.

A brief discussion of villous maturation is merited before additional findings of the disc are elaborated. Various types of villi have been discussed previously; what follows is a summary of what to look for in terminal villi when assessing maturity.

1. Maturity mature terminal villi are found in the third trimester of pregnancy, and are the smallest versions of chorionic villi. These free villi are covered by a thin syncytiotrophoblastic layer, with a discontinuous cytotrophoblastic layer, which is in contact with sinusoidal capillaries. The dense collection of capillaries and sinusoids in terminal villi comprises at least 50% of the stromal volume in these small structures. Syncytial knots, which are aggregates of syncytiotrophoblast nuclei present along one surface of terminal villi, are also a sign of villous maturity (Fig. 14.30).
   (a) Hypermaturity: In instances of underperfusion, or placental hypoxia, the tertiary villi respond to decreased blood flow and poor oxygenation by exhibiting accelerated maturation. There is an increase in mature tertiary free villi (relative to gestational age), as well as an increase in syncytial knots (so-called Tenney-Parker change). It is generally agreed that knots in >20% villi preterm or >30% at term are considered increased, though this is a

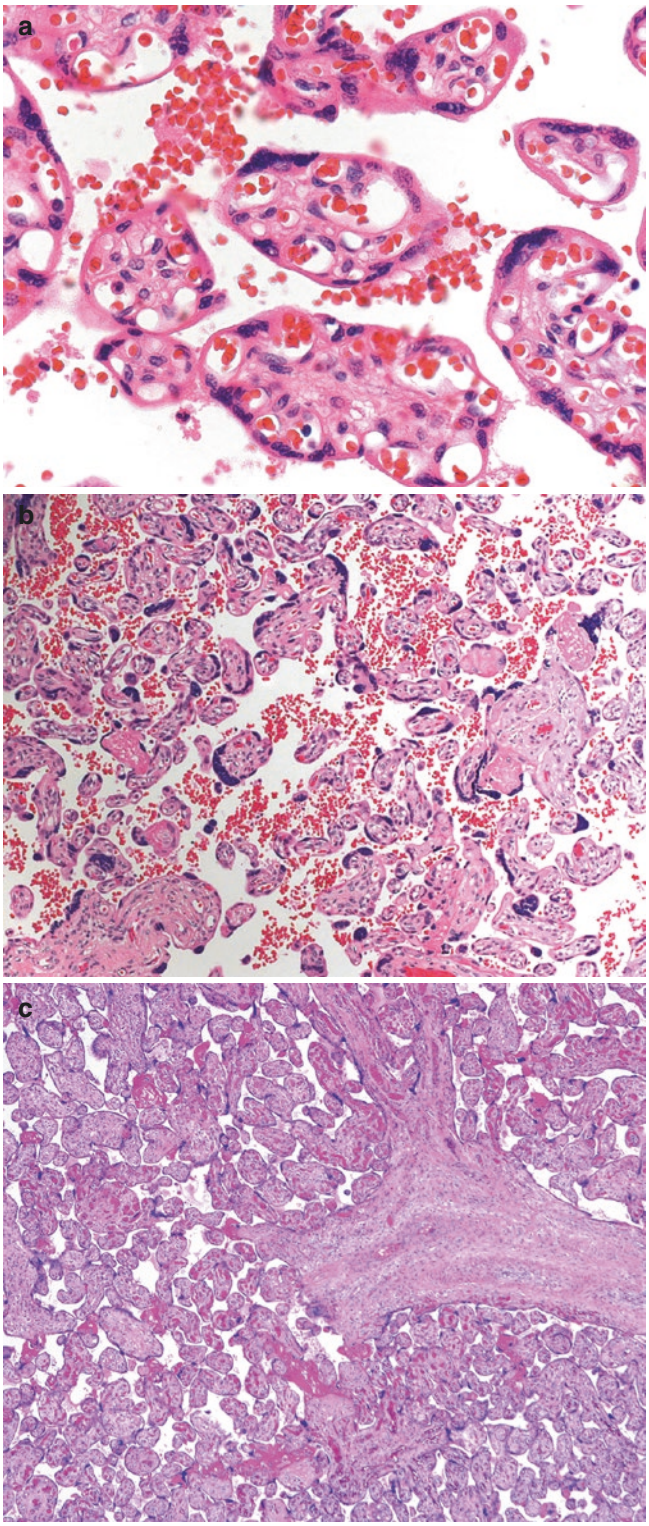


**Fig. 14.30** Villous maturity. (**a**) Mature terminal villi in a 39-week placenta with attenuated cytotrophoblastic surface layer; vessels take up the majority of the villous volume. (**b**) Hypermaturity in a 31-week placenta. The small size of the terminal villi and extensive syncytial knots are much more than expected at this gestational age. (**c**) Delayed villous maturation in a 40-week placenta. The large terminal villi with more centrally placed capillaries are typical of an earlier gestational age

very subjective measure. Hypermaturity is most easily appreciated in a second-trimester placenta with extensive mature terminal villi and prominent syncytial knots (Fig. 14.30a).

(b) Immaturity placental villous "immaturity," best termed *delayed villous maturation*, can be seen after 36 weeks gestation, and has been associated with diabetes mellitus, Beckwith-Wiedemann syndrome, and fetal demise. The features include clusters of intermediate-type villi (at least ten) with abundant stroma, and increased numbers of centrally located capillaries with a large diffusion distance (vessel-to-villous surface distance) (Fig. 14.30c). There will also be fewer tertiary villi than expected. Similar to the evaluation of hypermaturity, this assessment is very subjective, but should be considered only when the amount is significant (involving at least 30% of villi in one full section) [23].

2. Maternal Decidual Arteriopathy

During a normal gestation, the spiral arteries of the decidua undergo significant remodeling as trophoblasts invade and replace the maternal endothelial cells, resulting in ectatic, open vessels which are crucial for adequate perfusion of the placenta. Should this fail and the smooth muscle layer persist, maternal decidual arteriopathy occurs. This results in decreased blood flow to the placenta, apparently due to one, or a combination, of the following: overall lower supplied volume, higher pressure "jets" of blood that don't mix sufficiently, or intermittent vasoconstriction associated with the maternal vascular response to a variety of stimuli. Examination of the maternal decidual vessels shows small spiral arteries with intact smooth muscle walls. Fibrinoid necrosis of muscular wall (with a brightly eosinophilic, glassy appearance) with foamy macrophages can also be seen; in the past, this was termed the "severe" pattern, though this does not correlate well with severity of clinical disease (Fig. 14.31). Remember that this process is multifocal and does not affect every spiral artery. Arteriopathy is most easily identified in the membrane roll, which has the largest surface area in which to identify affected vessels [23]. See also the section on maternal vascular malperfusion below.

3. Acute Villitis

Rarely, neutrophils may be identified in fetal capillaries and the stroma of tertiary villi; if present, a diagnosis of acute villitis should be made. Acute villitis is an indicator of fetal sepsis. Occasionally, stains can highlight causative organisms, though this is not altogether reliable. Additionally, the medical record should be consulted to determine if the infant is being treated for possible sepsis. If the status of the infant is unknown, the obstetrician or pediatrician should be contacted right away [28].

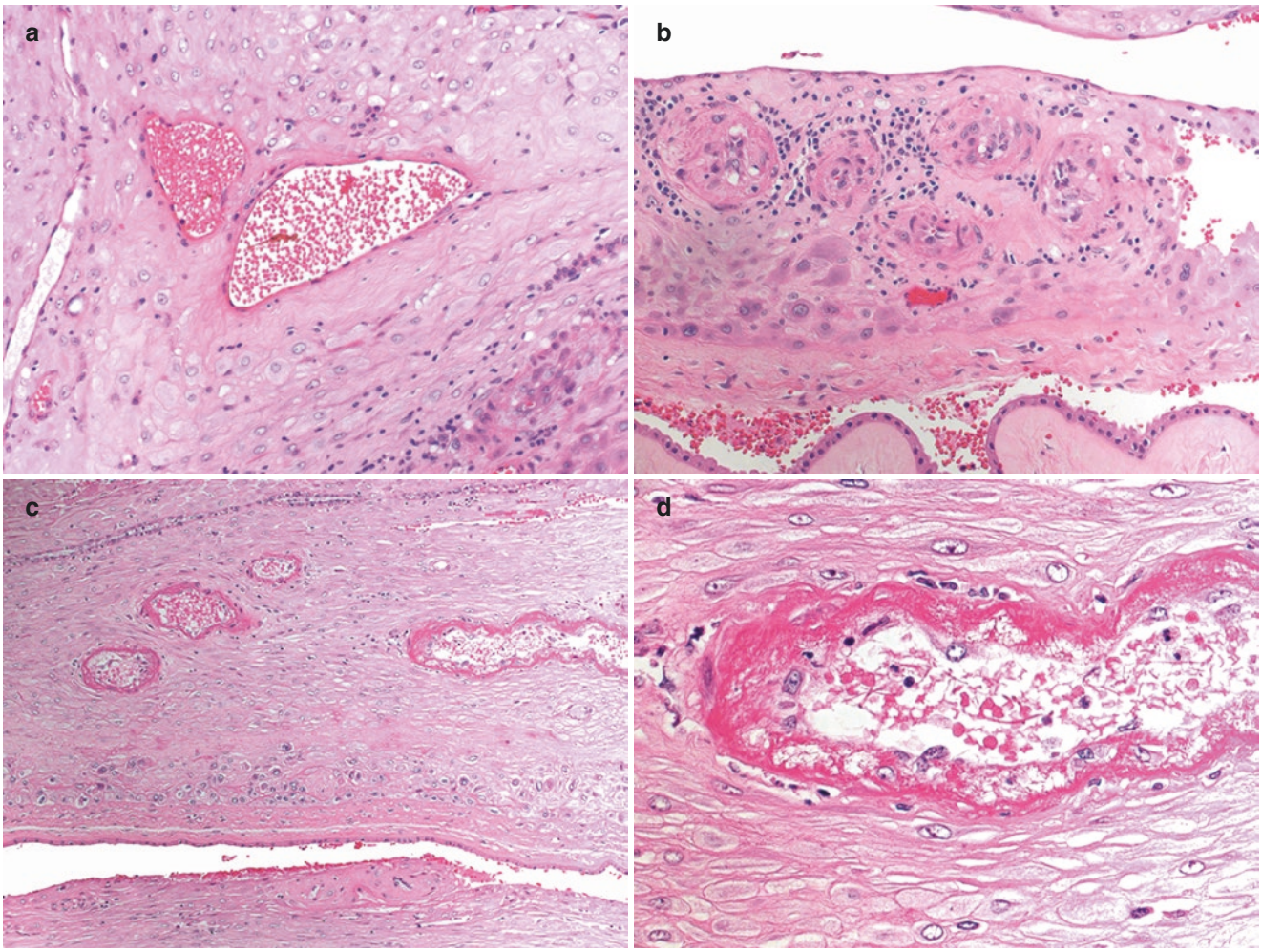


**Fig. 14.31** Maternal decidual arteriopathy. (**a**) Transformed vessels within the decidua; there is no discernable smooth muscle layer and the lumens are widely patent. (**b**) Decidual vessels with retention of the muscular wall. (**c**) Fibrinoid necrosis with acute atherosis. The brightly eosinophilic vessels stand out from the pale decidual cells in this example. (**d**) Fibrinoid necrosis with atherosis, higher power. At this power, the lipid-laden macrophages within the fibrinoid material are apparent

4. Villitis of Unknown Etiology
   Villitis of unknown etiology (VUE) is not an uncommon finding, and has been reported in 3–5% of placentas submitted to pathology. The histologic findings can range from cases in which chronic inflammation involves a small cluster of 5–10 villi to significant, diffuse, involvement. By definition, this diagnosis excludes any chronic villitis with an identified etiology, such as infection. The inflammatory component consists primarily of lymphocytes and histiocytes; significant numbers of plasma cells should not be present. A viral etiology should be considered if plasma cells are easily encountered. It is recommended that VUE be graded, since the association with adverse outcomes is much stronger with more extensive involvement. Low-grade lesions are those affecting fewer than ten villi per focus, with more than one focus required. Low-grade villitis is further classified as focal if it involves only one slide, and multifocal if it is identified in multiple slides. High-grade lesions are those involving more than ten villi in at least one focus. High-grade villitis is further classified as patchy when it is seen in one or more slides, and diffuses if at least 30% of the villi are affected (Fig. 14.32). The affected foci may be confined to the parabasal areas, paraseptal areas, scattered randomly throughout the parenchyma, or in any combination. Villitis confined to the basal and parabasal regions has been associated with pregnancies achieved with assisted reproductive techniques, but overall the significance of the variable distributions is unknown [23].
5. Infarct
   Histologic examination of remote infarcts shows pale, eosinophilic ghost villi, which is due to loss of nuclear basophilia. The intervillous space is obliterated by fibrin deposition as well as agglutination of the villi. Villous stromal fibrosis and cytotrophoblastic proliferation are

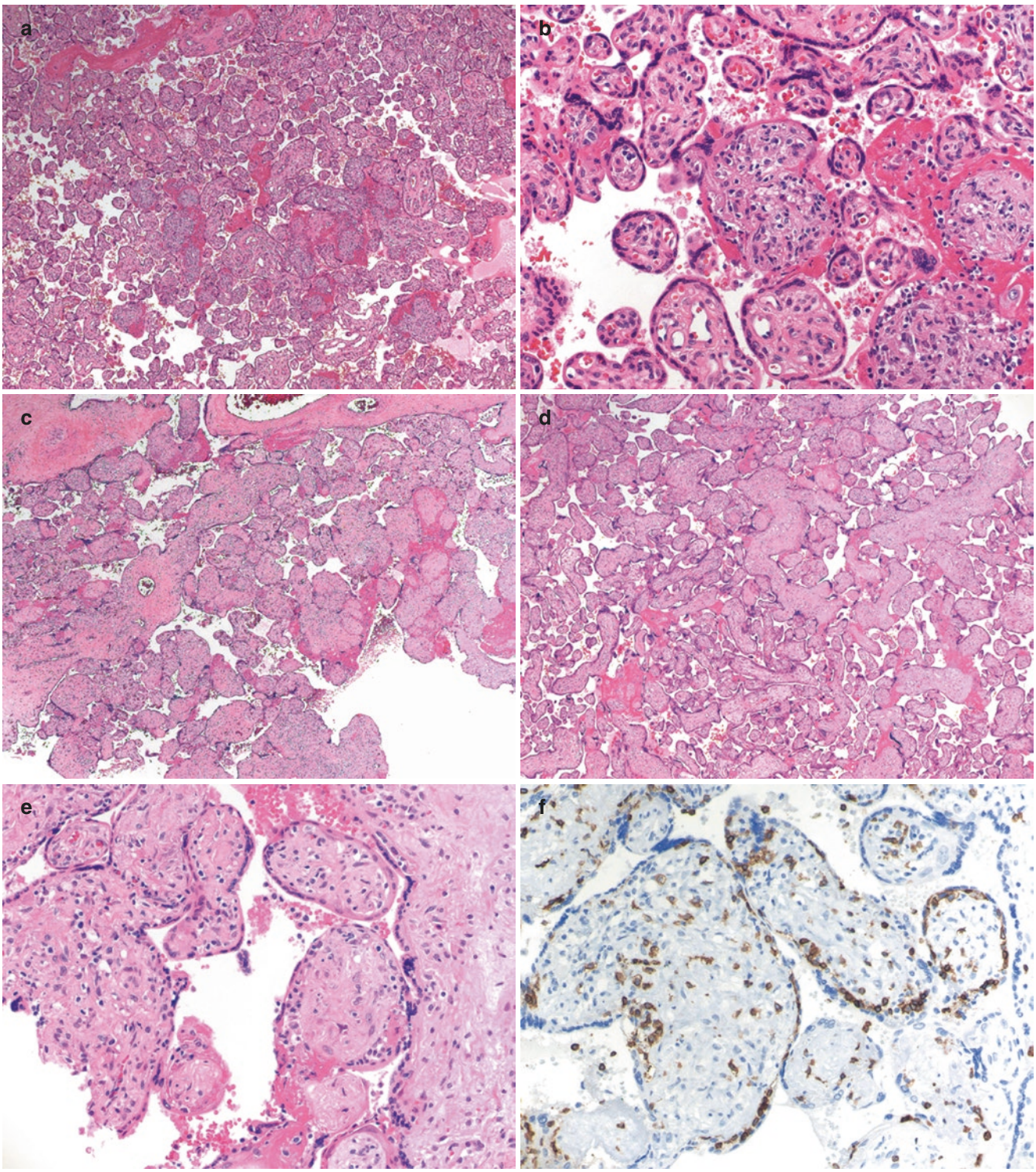


**Fig. 14.32** Villitis of unknown etiology (VUE). (**a**) Focal VUE. A cluster of hypercellular villi are present in the middle of the image. Though the finding is focal, this would be classified as high grade as >10 contiguous villi are involved. (**b**) On high power, the infiltrate is identified as lymphocytic. Also note the lack of villous capillaries in the affected villi. (**c**) High-grade VUE, diffuse pattern (involves >30% of one full-thickness section). (**d**) High-grade VUE, also a diffuse pattern. This example is relatively subtle; the top half of the image is composed of affected villi while the lower half is relatively spared. (**e**) Higher power appearance of the diffusely involved, sclerotic villi. (**f**) An immunohistochemical stain for CD3 (nuclear) confirms that the infiltrate is composed predominantly of lymphocytes

absent (Fig. 14.33). Foci of more recent infarction show more subtle changes, including villous crowding, congestion, a mild inflammatory response, and stromal karyorrhexis [4–6, 10]. It is important to distinguish infarcts from avascular villi.

6. Avascular Villi
   Clusters of avascular villi tend to be closely apposed to normal villi, and thus appear sharply demarcated from the surrounding parenchyma. This finding is differentiated from an infarct in several ways. First, the trophoblastic layer is still viable due to perfusion by maternal blood in the intervillous space. There may also be increased, or more prominent, syncytial knots, which retain their nuclear basophilia. In foci of avascular villi, the villous stroma is eosinophilic and hyalinized, and lacks stromal capillaries. Finally, the intervillous space is predominantly open and contains maternal blood; it is not obliterated as with an infarct [6, 10, 23] (Fig. 14.34).
7. Intervillous Thrombi
   If enough time has passed for the thrombus to be properly organized, it will have the usual appearance of an organized clot, with the alternating red and pink lines of Zahn. The red is composed of entrapped red blood cells and the pink is composed of fibrin. Grossly, it can be

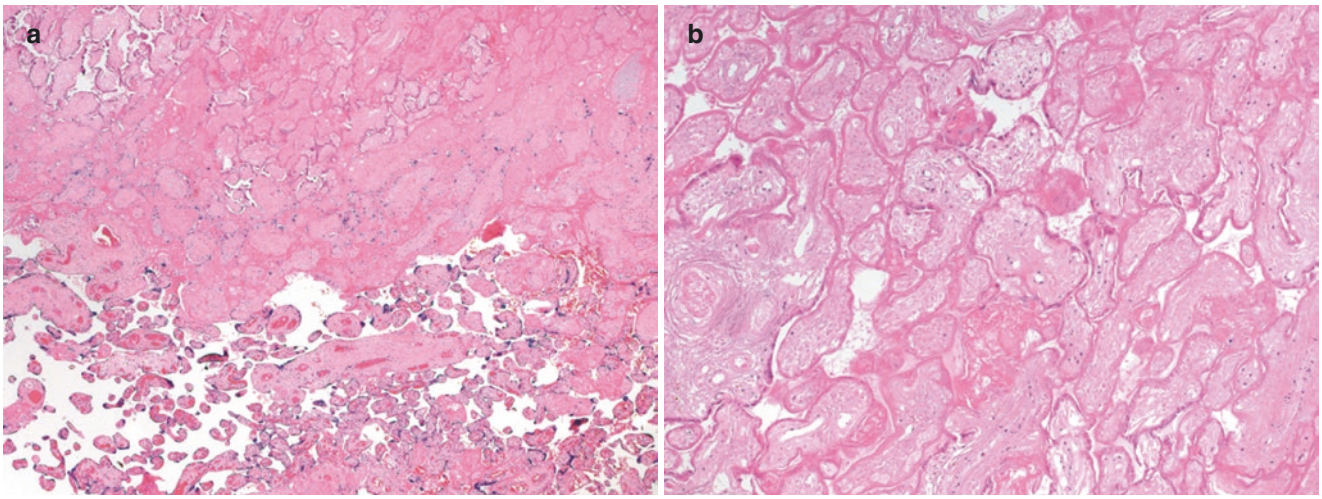


**Fig. 14.33** (**a**) Edge of a placental infarct. The infarcted villi (top) are bordered by a rim of ischemic parenchyma, including prominent syncytial knots. (**b**) The center of the infarct shows ghostlike villous structures with near-complete loss of nuclear basophilia

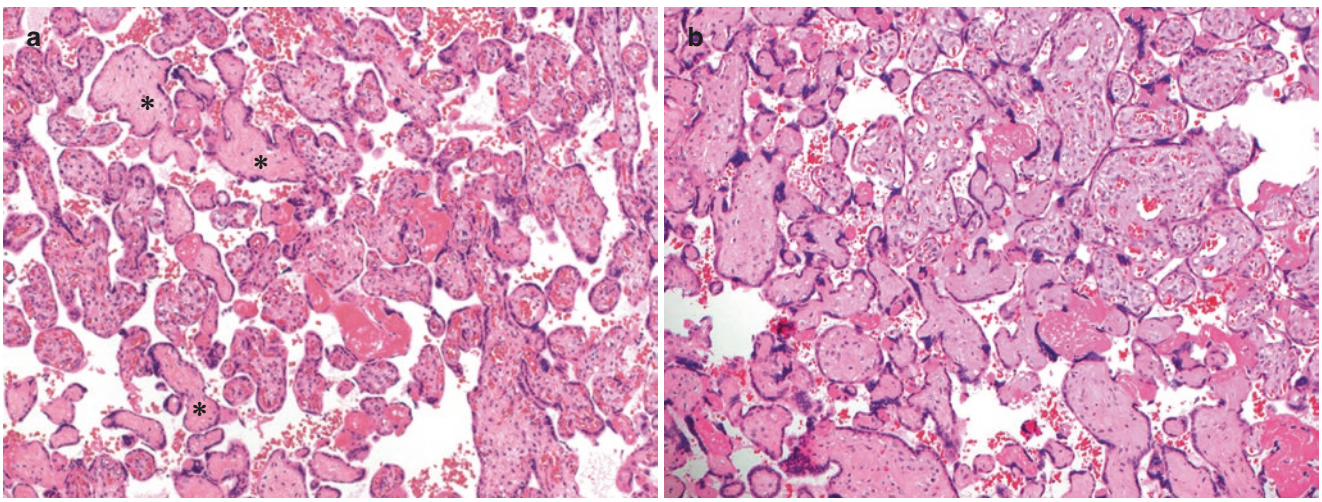


**Fig. 14.34** (**a**) The cluster of avascular villi (*) stands out from the background of unaffected villi due to its brightly eosinophilic hyalinized stroma. Note the lack of fetal capillaries, and retained nuclear basophilia of the trophoblasts. (**b**) A larger focus of avascular villi (left) contrasted with unaffected tissue on the right. Note the open intervillous space occupied by maternal blood, and the lack of significantly increased intervillous fibrin deposition

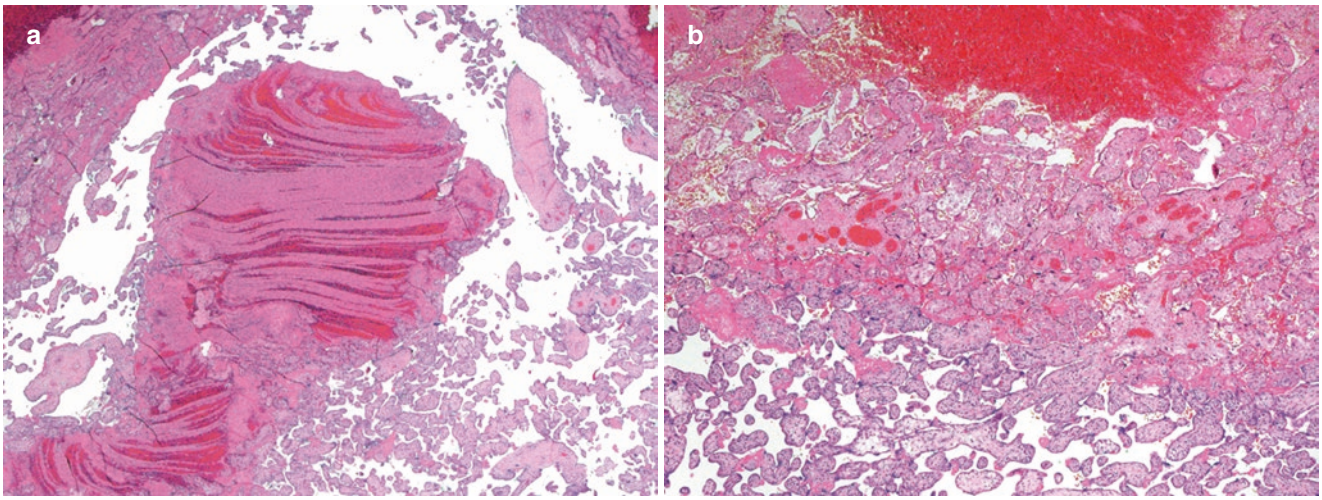


**Fig. 14.35** (**a**) Intervillous thrombus with prominent laminations (lines of Zahn). (**b**) The edge of a large intervillous thrombus. As shown here, the parenchyma just next to a thrombus can show evidence of ischemia, including increased fibrin deposition, prominent syncytial knots, and a mild chronic inflammatory response. Over time, the villi can become completely infarcted

difficult at times to distinguish these from infarcts but microscopic examination usually makes it clear which pathology is present (Fig. 14.35).

8. Meconium
   Meconium-laden macrophages can also be seen in the chorionic plate of the disc, under the amniotic epithelium, just as in the membranes. If there is a history of meconium-stained fluids or if the fetal surface has a green tinge, it may be prudent to carefully examine the specimen microscopically.
9. Hydropic Change
   This finding is usually noted in very early gestations, such as in therapeutic or missed abortion specimens. Swollen or dilated villi, with lightly basophilic hypocellular stroma and few to no residual vessels, are the hallmarks of hydropic change. These changes can be associated with degeneration due to fetal/embryonic demise, aneuploidy, partial hydatidiform mole (PHM), or complete hydatidiform mole (PHM). A brief overview of molar pregnancy is present below; more information on this topic is presented in Chap. 13.
   (a) Hydropic degeneration due to demise: In hydropic degeneration, a sign of lost pregnancy, there will be enlarged round to oval villi with edematous stroma, a few residual vessels, atrophy of the syncytiotrophoblasts, and evidence of embryonic or fetal tissue. While pseudocystic spaces may be seen, so-called inclusions (spaces lined by trophoblasts) within the villi will be absent, and trophoblastic hyperplasia will not be present. In instances of demise, there is often an admixture of variably sclerotic and edematous villi [5] (Fig. 14.36a, b).
   (b) Partial hydatidiform mole (PHM): In a well-developed partial hydatidiform mole, two relatively discrete villous populations can be seen. One population is composed of large hydropic structures, and the other of smaller, more normal-appearing villi. The hydropic villi have occasional central cisterns, exhibit areas of lacy trophoblastic hyperplasia (without atypia), and are notable for their unusual peripheral architecture. The hydropic villi of partial moles often have prominent invaginations of the surface, creating a scalloped appearance ("fingers and toes," or "coast of Norway"). There should also be evidence of fetal tissue, often noted in the form of nucleated red blood cells. Immunohistochemical staining for p57 will be positive within the villous stromal cell nuclei (Fig. 14.36c, d).
   (c) Complete hydatidiform mole (CHM): Well-developed examples of complete hydatidiform moles will have diffuse, rounded enlargement of the villi. Central cisterns and inclusions are easily identified, and lacy circumferential trophoblastic hyperplasia will be found. Prominent implantation site with notable trophoblastic atypia is often associated with CHM, but this can be a very subjective feature. No fetal tissues are present. CHM is due to uniparental (paternal) diploidy, and as such immunohistochemical staining for the maternally expressed protein p57 will be absent in the villous stromal nuclei. Staining can be seen in the extravillous trophoblasts, and does not exclude an interpretation as CHM (Fig. 14.36e–g).

Histologic diagnosis of suspected molar pregnancies, particularly early in gestation, can be frustrating; it is not entirely sensitive or specific, and suffers from high inter-

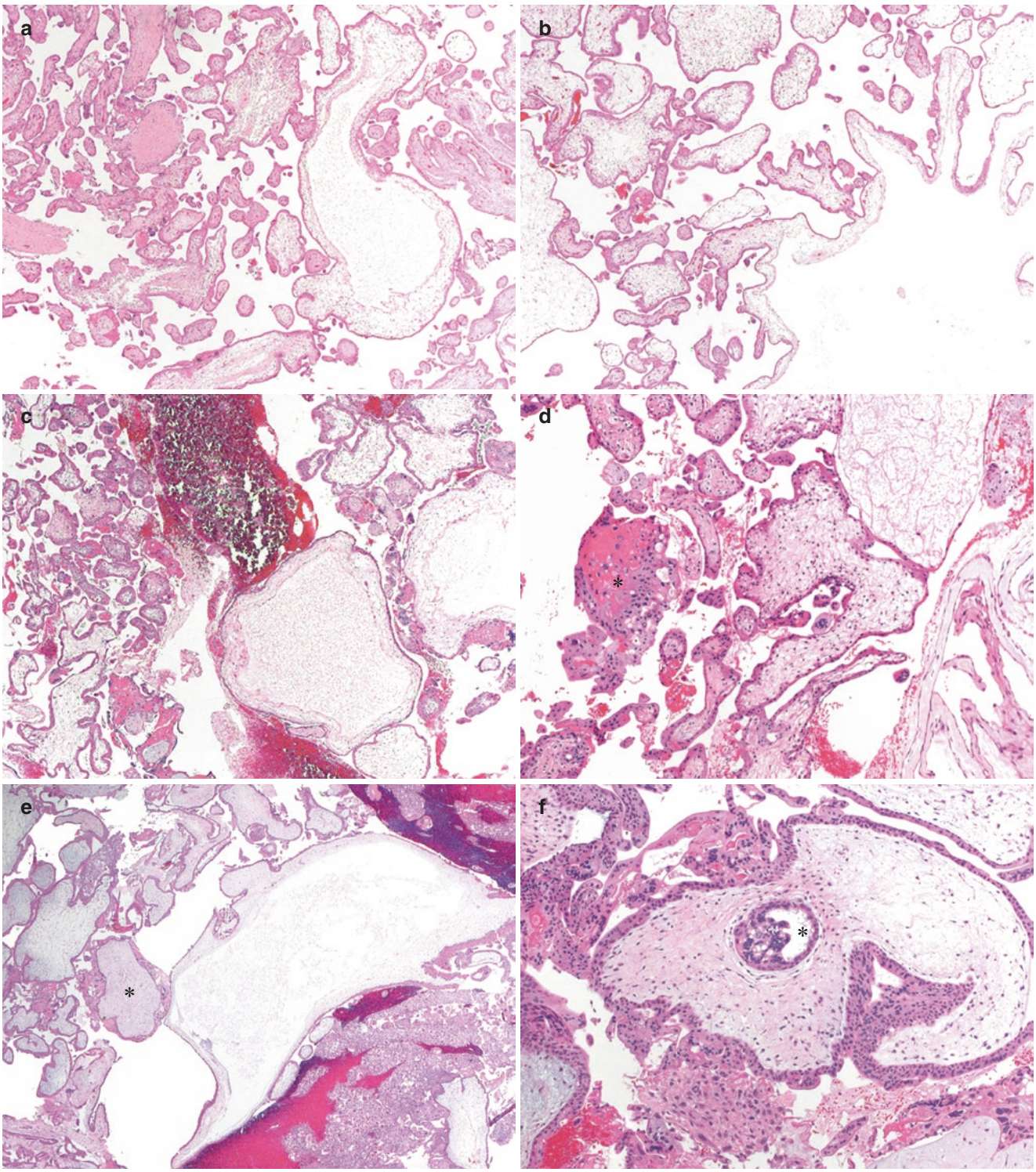


**Fig. 14.36** (**a**) Hydropic and sclerotic changes in a trisomy 16 conceptus. Central cisterns are present, but inclusions and trophoblast hyperplasia are absent. The edematous and sclerotic changes are present along a spectrum; a discrete dual population is not present. (**b**) Hydropic change in a trisomy 16 conceptus; note also the irregular villous contours *without* trophoblast hyperplasia. (**c**) Partial hydatidiform mole (PHM). Large edematous villi with central cisterns (right) are admixed with a second population of smaller, more typical-appearing (or fibrous) villi (left). Note the irregularly contoured villous in the lower left. (**d**) PHMs exhibit some degree of trophoblastic hyperplasia (*), but notable atypia is lacking and circumferential proliferation is absent. Villous contours tend to be complex and irregular. (**e**) Complete hydatidiform mole (CHM) showing edematous change of most villi, with prominent central cisterns. Circumferential trophoblastic hyperplasia is present (*). (**f**) Trophoblast inclusions (*) are a feature of CHM. (**g**) Trophoblastic hyperplasia with atypia in a CHM. (**h**) CHM. Immunohistochemistry for p57 shows *complete loss* of nuclear staining in the villous trophoblasts. Extravillous trophoblasts often show multifocal positive nuclear staining

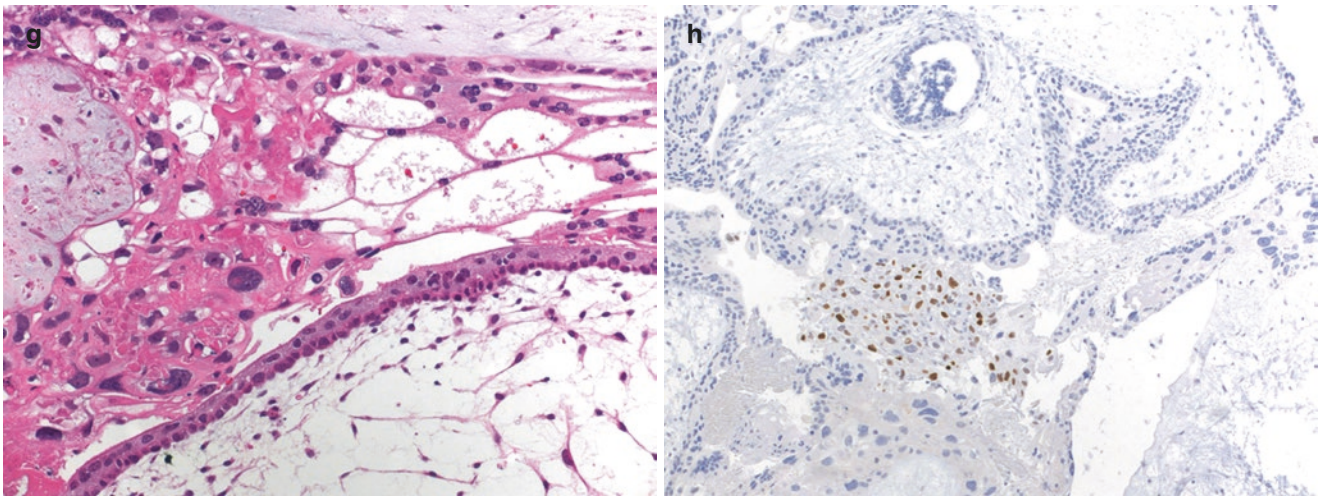


**Fig. 14. 36** (continued)

and intra-observer variability. Apart from immunohistochemical staining for p57 and clinical impression, there are few useful tools to assist in separating molar gestations from non-molar pregnancies. In particular, it can be challenging to distinguish a PHM from other types of aneuploid or hydropic gestations. In the clinical setting of a patient actively desiring pregnancy, the distinction can be immediately relevant.

Conventional karyotyping and ploidy analysis cannot distinguish between diandric triploidy and other triploid gestations, though a diploid result can exclude a partial mole (and karyotype can identify a trisomy, for example). More advanced genetic techniques may be of help, though they are not yet routinely in use at most facilities [5, 29].

10. Placental Mesenchymal Dysplasia

Placental mesenchymal dysplasia (PMD) is a rare, benign condition that is characterized by placentomegaly. It is associated with Beckwith-Weidman syndrome (in about a quarter of the cases), fetal growth restriction, and gestational hypertension. Clinically, PMD is easily mistaken for a molar pregnancy due to the striking cystic villous changes; however, unlike molar gestations, it can be associated with a viable, and even normal, fetus/infant.

On gross examination there will be an abundance of tissue, or a large-for-gestational-age placenta (Fig. 14.37). Grossly visible cystic structures and pale, friable zones are typically interspersed within an otherwise relatively normal-appearing parenchyma (Fig. 14.37a). In third-trimester or term placentas, the chorionic plate vasculature may be prominent, composed of dilated and tortuous vessels. Histologically, the changes of PMD vary somewhat with gestational age. Even in early gestation, PMD is most notable for the large, hydropic stem villi with central cisterns (not inclusions), myxoid change (in marked contrast with the more fibrous appearance of normal stem villi), and prominent fibromuscular vasculature with fibroblastic overgrowth. Trophoblastic hyperplasia is absent (Fig. 14.37b–d). As the pregnancy progresses, the abnormal vascular component may become more pronounced, and evidence of degenerative changes may appear [30].

11. Chorangiosis/Chorangiomatosis/Chorangioma

All three of the following conditions can be seen in cases of chronic placental underperfusion, and are thought to be an adaptive response:

(a) Chorangiosis: To diagnose chorangiosis, one needs >/= 10 fields of placental parenchyma with >/= 10 terminal villi, each with 10 or more capillaries per cross section. This is seen more frequently in diabetic and preeclamptic pregnancies, and the placenta is often large for gestational age. This is likely a normal finding at high elevations.

(b) Chorangiomatosis: This extremely unusual lesion can be either localized or multifocal, and consists of chorangioma-like lesions that, rather than forming a single nodule, extend into adjacent stem villi. The lesional vessels are surrounded by pericytes and there is increased stromal collagenization.

(c) Chorangioma: This is an intraparenchymal nodule composed of capillaries, stromal cells, and surrounding trophoblasts. A villous structure is expanded by the abnormal vascular proliferation, and there may be associated trophoblastic hyperplasia with pleomorphism and atypia. These lesions are usually located in the subchorionic or marginal zones of the disc, and there can be either a single nodule or (less often) multiple nodules. The majority of chorangiomas are incidental, but if large (>5 cm) they can be associated with complications including polyhydramnios, fetal thrombocytopenia, heart failure, and hydrops [24] (Table 14.2).

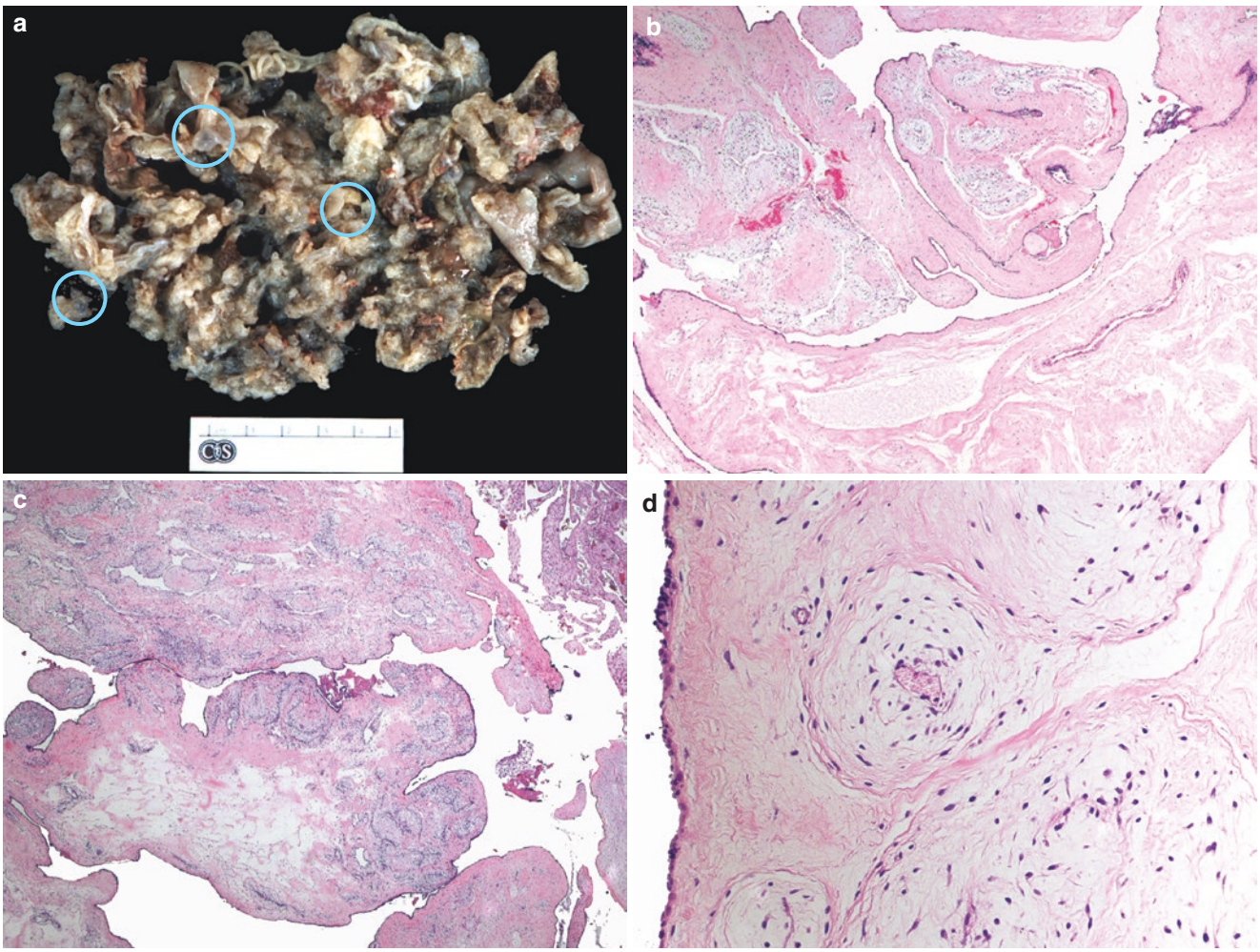


**Fig. 14.37** Placental mesenchymal dysplasia (PMD). (**a**) Gross appearance. This 13-week conceptus was clinically compatible with a complete mole; the specimen contained >70 g of tissue. There are many easily appreciated cystic structures (circled). (**b**) Edematous stem villi with cisterns are one of the hallmark findings in PMD. (**c**) Myxoid change with prominent vasculature and fibroblastic stromal overgrowth. (**d**) Higher power showing the unusual vascular changes

**Table 14.2** Hypervascular lesions

| | Gross | Microscopic | Clinical features/prognosis |
|---|---|---|---|
| Chorangiosis | – Not visible grossly<br>– Placenta may be LGA | – Formal definition rule of tens: At least 10 fields with at least 10 terminal villi which each contains at least 10 capillary profiles | – May be adaptive<br>– Unclear if it affects fetal outcome |
| Chorangiomatosis | – Not visible grossly<br>– No discrete nodules | – No discrete nodular foci (unlike chorangioma)<br>– Involves stem villi<br>– Lesional vessels surrounded by pericytes<br>– Increased stromal collagenization | – Associated with other vascular abnormalities<br>– Associated with AMA, preeclampsia, multiple gestation, preterm delivery, IUGR<br>– May be associated with platelet sequestration and DIC |
| Chorangioma | – Discrete nodule(s)<br>– Dark and soft (vascular) or firm and tan (fibrotic)<br>– Usually marginal or subchorionic | – Composed of capillaries, stromal cells, trophoblasts<br>– Expanded villous structure by vascular proliferation<br>– May show trophoblastic hyperplasia, pleomorphism, and atypia | – Never malignant<br>– Large lesions may be associated with complications |

*LGA* large for gestational age, *AMA* advanced maternal age, *IUGR* intrauterine growth restriction, *DIC* disseminated intravascular coagulation

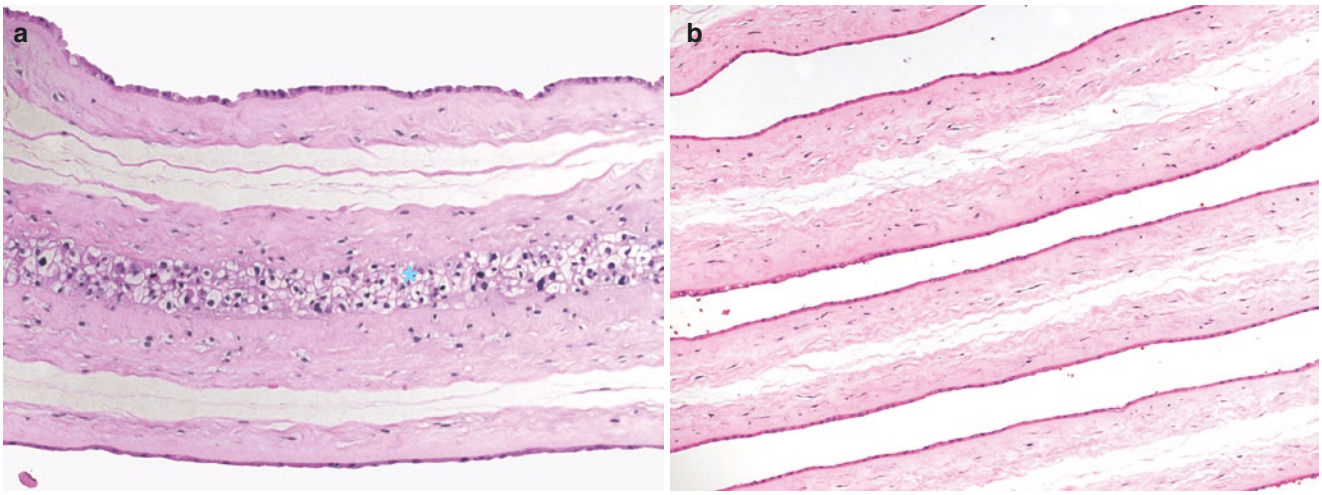


**Fig. 14.38** (**a**) Diamniotic dichorionic twin placenta. Chorion (*) is present between the two layers of amnion. (**b**) Diamniotic monochorionic twin placenta. The two layers of amnion are directly apposed

12. Microscopic Examination of the Twin Placenta
    Microscopically, twin placentas are examined in much the same fashion as singletons, with a major exception being confirming chorionicity when analyzing the layers of the dividing membranes. Dividing membranes from a diamniotic, dichorionic placenta (Fig. 14.38a) will have a trophoblast layer in the middle; monochorionic dividing membranes will have amnion directly apposed to amnion (Fig. 14.38b).
13. Lasers
    Laser-treated vessels show necrosis with focal hemorrhage, clusters of avascular villi, and fibrin deposition in the underlying parenchyma [25].

## 14.4 Constellation Syndromes

Constellation syndromes are a group of disorders that encompass findings in multiple parts of the placenta, both gross and microscopic, and are due to a single underlying etiology.

### 14.4.1 Maternal Vascular Malperfusion

The pattern of findings termed maternal vascular malperfusion (MVM) develops as a consequence of impaired, or insufficient, maternal blood flow to the placenta due to abnormal spiral artery perfusion. The abnormal blood flow is due, at least in large part, to problematic or incomplete remodeling of the maternal vasculature by trophoblasts. The cause of abnormal remodeling is still unknown, but is most strongly associated with preeclampsia/eclampsia and maternal hypertension; however, it is also seen with increased frequency in multiple gestations, and other types of abnormal implantation.

The pathologic findings of MVM include both gross and microscopic changes. Grossly, there is evidence of poor placental growth (a small [<10th percentile]-for-gestational-age disc), and evidence of maternal vascular disruption/occlusion such as infarcts and retroplacental hemorrhage (Fig. 14.39a).

The microscopic changes include confirmation of infarction, abnormal spiral arteries (maternal decidual arteriopathy), and features of placental hypoxia. The histologic findings of infarction and decidual arteriopathy are described above (Fig. 14.39b–d). Features of placental hypoxia include accelerated villous maturation (villous hypermaturity; see above) and distal villous hypoplasia. Distal villous hypoplasia is characterized by a notable reduction in distal/terminal villi in relation to the intermediate and stem villi. The remaining villi tend to be elongated, with prominent syncytial knots, and evidence of accelerated maturation. This finding is best appreciated on low power, and should involve at least 30% of one full-thickness section [5, 23].

### 14.4.2 Fetal Vascular Malperfusion

Fetal vascular malperfusion (FVM) refers to a group of findings that result from inadequate fetal blood flow to the placenta. The underlying causes of fetal vascular malperfusion are many, and similar findings can be identified in instances of intrauterine demise and live birth, which complicates interpretation in some cases; vascular changes are, of course, very common in the setting of demise. The underlying reason for fetal vascular malperfusion includes anything that would disrupt normal flow to the placenta, such as fetal vascular thrombosis, hypercoagulability, umbilical cord constriction, or fetal cardiac dysfunction, to name a few.

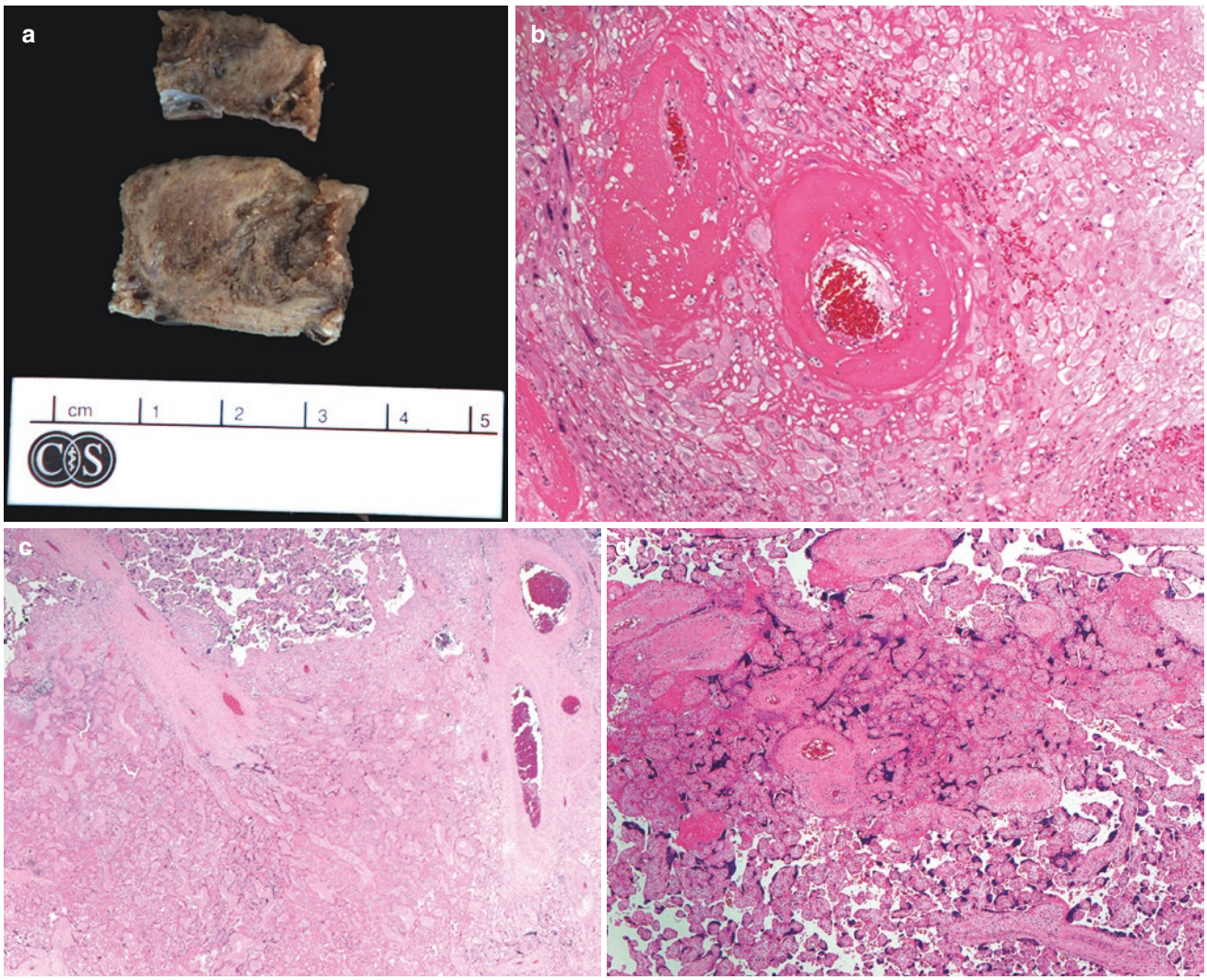


**Fig. 14.39** Maternal vascular malperfusion in a placenta from an intrauterine fetal demise at 31 weeks. (**a**) Gross appearance of multiple central infarcts. (**b**) Maternal decidual arteriopathy with fibrinoid necrosis. (**c**) Low-power appearance of a large infarct (bottom of image), contrasted with the hypermature villi (for 31 weeks) in the upper portion of the image. This could be seen immediately adjacent to an infarct, but this change was present diffusely throughout the placenta. (**d**) A smaller "microinfarct" which was not appreciated grossly. The agglutinated focus of villi in the top middle of the image shows nuclear smudging and loss of fetal capillaries

The established findings of FVM are predominantly microscopic, but relevant gross findings include the presence of an umbilical cord thrombus, thrombi within the chorionic plate vasculature, or a tight umbilical cord knot. The principal finding microscopically is clusters of avascular villi, as described previously. To be identified as a "cluster" there should be at least 3–4 villous structures affected, with large foci including 10 or more villous cross sections; at least 3 separate foci should be identified to qualify as a diagnosable lesion (Fig. 14.40d–e).

Fetal vascular malperfusion can have variable distribution patterns. If associated with obstructive umbilical cord lesions such as hypercoiling or stricture, abnormal placental insertion site, or long-standing fetal entanglements, the overall histological features are suggestive of globally increased venous pressure and poor circulation. The changes are identified in the most distal portions of the villous tree, resulting in randomly scattered small foci of avascular villi (Fig. 14.34).

The other pattern, which is due to segmental/complete occlusion of a large fetoplacental vessel (often by thrombus), leads to larger, more discrete foci of degenerating downstream villi. These villi initially show degenerative changes (villous stromal karyorrhexis, vascular remodeling) and eventually lose all of their vessels, which results in a large focus of avascular villi (Fig. 14.40f). When extensive, this pattern has been termed fetal thrombotic vasculopathy and has been associated with increased risk of fetal CNS injury, as well as other adverse outcomes.

The associated vascular changes, other than a well-developed unequivocal thrombus, are more subtle and controversial. Additional vascular lesions that may be important

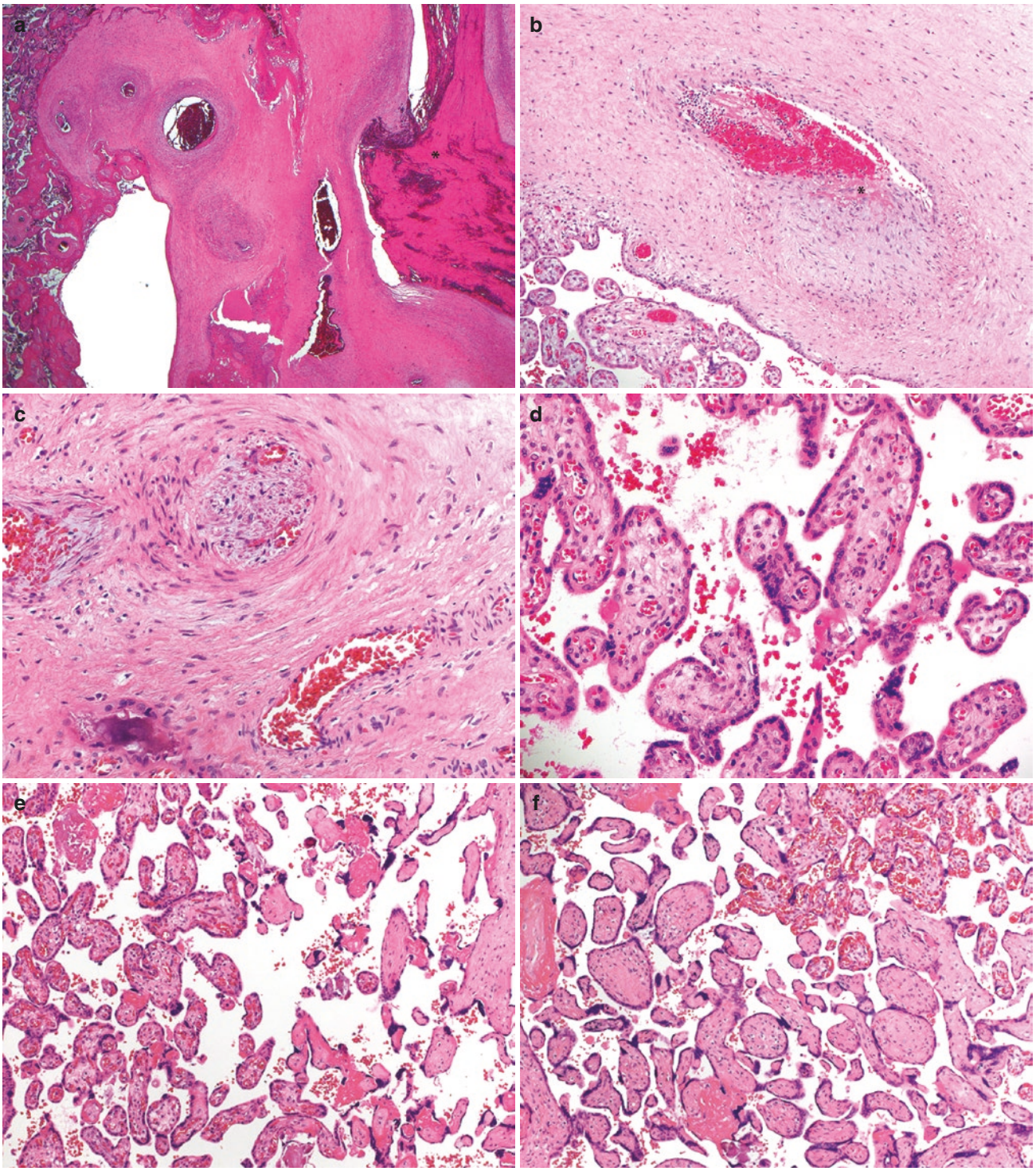


**Fig. 14.40** Global fetal vascular malperfusion in the setting of a tight umbilical cord knot. (**a**) A large, organizing thrombus is present in a chorionic plate vessel (*). (**b**) Downstream from the large thrombus, foci of intramural fibrin deposition are present (*). (**c**) Partially obstructive vascular changes in a stem villous. (**d**) Villous stromal karyorrhexis. Thought to be an early sign of fetal vascular malperfusion, karyorrhectic debris with extravasated/fragmented red blood cells are present in the villous stroma. (**e**) A cluster of avascular villi (right side of image) are present adjacent to uninvolved villi. (**f**) A larger zone of avascular villi; uninvolved villi are present at the upper right

to identify include vascular ectasia (large fetal vessels dilated to four times the size of adjacent similar vessels), intramural fibrin deposition (formerly termed "intimal fibrin cushion"), and stem vessel obliteration. Intramural fibrin deposition is characterized by deposition of fibrin within the vessel wall, often admixed with fragmented red blood cells, or in long-standing lesions, calcification. Stem vessel obliteration refers to the presence of notable thickening ("fibromuscular hyperplasia") of the stem villous vessels, which results in luminal obliteration. Remember that in instances of fetal demise, the changes of decreased fetal blood flow will begin quickly; diffuse changes involving nearly all of the parenchyma are more likely a result of demise than evidence of an etiology. Even in a background of diffuse change, it may be possible to identify earlier, more well-developed lesions. Organized thrombi are always considered premortem events, but loose, myxoid changes to the fetal vessels that can resemble remodeling are nearly always diffuse or multifocal and are due to demise [5, 23, 31]. Diffuse vascular changes are nearly always a consequence of demise, rather than the cause of it.

### 14.4.3 Amniotic Fluid Infection Sequence

The amniotic fluid infection sequence (AFIS) describes the acute maternal and fetal inflammatory response to ascending infection of the amniotic fluid, usually due to cervicovaginal flora. *E. coli* and group B streptococci are some of the most common causes of ascending amniotic fluid infection.

The response can be considered as two parts: the maternal inflammatory response and the fetal inflammatory response. The maternal response is seen most easily in the membranes, where the inflammation originates from the decidual blood supply (deciduitis, subchorionitis), and moves into the chorion (chorionitis), and finally into the hypocellular zone just beneath the amniotic epithelium (chorioamnionitis). The maternal response can also be identified on the fetal surface of the placenta, where neutrophils migrate from the intervillous space, through the chorion, and into the amnion. Fetal inflammation is noted initially in umbilical vein, and then progresses to involve the umbilical arteries and finally Wharton's jelly (funisitis). Sections of umbilical cord taken closer to the fetal end demonstrate inflammation earlier in the course of infection than sections closer to the placental disc (Fig. 14.41).

Though it is understood that the clinical and histologic severity does not correlate well, there still may be some value in staging and grading the histologic response (Table 14.3). In particular, attention should be paid to the presence and extent of the fetal response, which is more likely to indicate clinical disease, and to accurate documentation of the location of inflammation. Neutrophils confined to the subchorionic space or the chorion, for example, should not be diagnosed as chorioamnionitis. Necrotizing inflammation, meaning karyorrhectic neutrophils, often with evidence of tissue damage (such as amniocyte necrosis), represents the final stage of inflammation. The grade refers to the presence (Grade 2) or absence (Grade 1) of confluent neutrophils and/or microabscess formation [23].

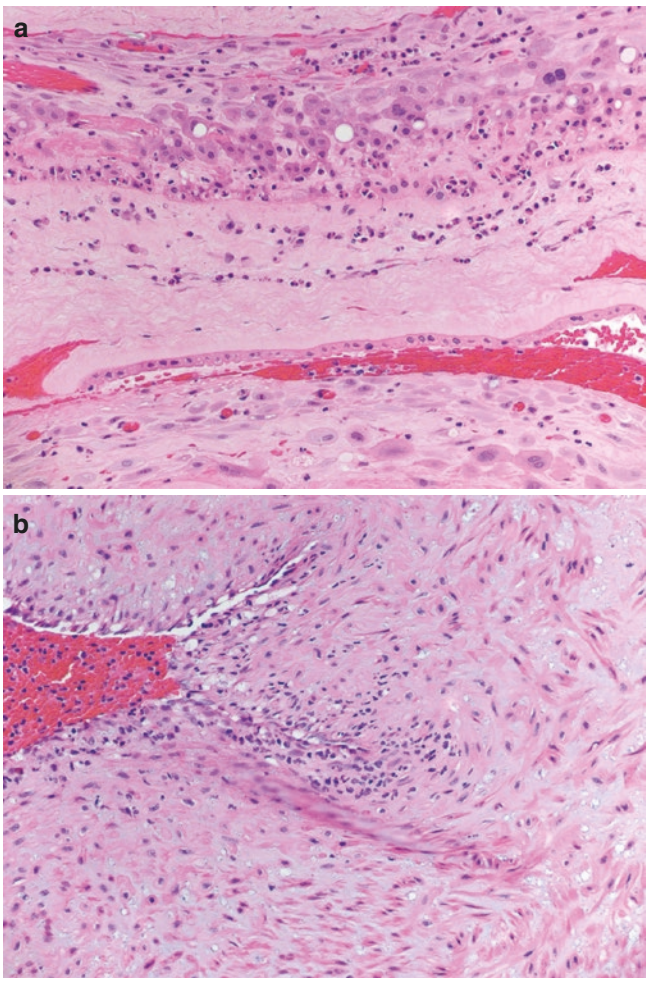


**Fig. 14.41** Amniotic fluid infection sequence. (**a**) The maternal acute inflammatory response is chorioamnionitis; neutrophils are present within the amnion of the fetal membranes. (**b**) The fetal inflammatory response is identified in the umbilical cord and chorionic plate vessels; neutrophils are marginating out of the lumen and into the vessel wall

**Table 14.3** Grade and stage of the inflammatory response to ascending amniotic fluid infection (Amsterdam Placental Workshop Group Consensus Statement [23])

| Stage | Grade |
|---|---|
| Maternal inflammatory response<br>(Evaluated in the membranes) | |
| 1. **Acute chorionitis or subchorionitis**: *Neutrophils within subchorionic fibrin, subchorial intervillous space, or at the choriodecidual interface*<br>2. **Acute chorioamnionitis**: *Neutrophils extend into fibrous chorion and/or amnion*<br>3. **Necrotizing chorioamnionitis**: *Karyorrhexhis of neutrophils, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia* | 1. Not severe<br>2. **Severe**: *Confluent neutrophils or subchorionic microabscesses* |
| Fetal inflammatory response<br>(Evaluated in the large fetal vessels of the umbilical cord and placental surface) | |
| 1. **Chorionic vasculitis or umbilical phlebitis**: *Neutrophils are present within the vessel wall*<br>2. **Involvement of umbilical vein, and at least one artery**: *Neutrophils are present in the walls of at least two umbilical vessels*<br>3. **Necrotizing funisitis**: *Neutrophils extend through a vessel wall into Wharton jelly, associated with karyorrhextic/necrotic debris* | 1. Not severe<br>2. **Severe**: *Confluent or near-confluent neutrophils within a vessel wall, with vascular smooth muscle attenuation* |

## 14.5 Specific Infections

### 14.5.1 Candida

The presence of Candida is very common; at least 20–50% of pregnant women are colonized; 50% of infants will be colonized, and 10% of these infants will develop systemic disease. The incidence of candidal colonization is higher in women with a cerclage in place. The vast majority of infections (80%) are due to *Candida albicans*. Premature delivery (prior to 28 weeks) is associated with increased incidence of disseminated disease, and has a high risk of neonatal mortality. Evidence of candidal infection, particularly in a premature placenta less than 28 weeks, is a critical finding and should be communicated to neonatology immediately [32].

Grossly, the umbilical cord may show yellow-white plaques, which are characteristic of this infection. Histologically, the plaques are revealed to be subamnionic microabscesses; associated necrotizing funisitis and acute chorioamnionitis can also be seen. Organisms (Fig. 14.42a) are usually very difficult to see without special stains, but are easily identified with routine fungal stains (Fig. 14.42b). Yeast forms with pseudohyphae are present within the microabscesses of the umbilical cord, and may or may not be identified within the inflammation seen on the membranes. Villous edema may be present, but granulomatous inflammation and inflammation involving the intervillous space are not usually associated with candidal infection [32, 33].

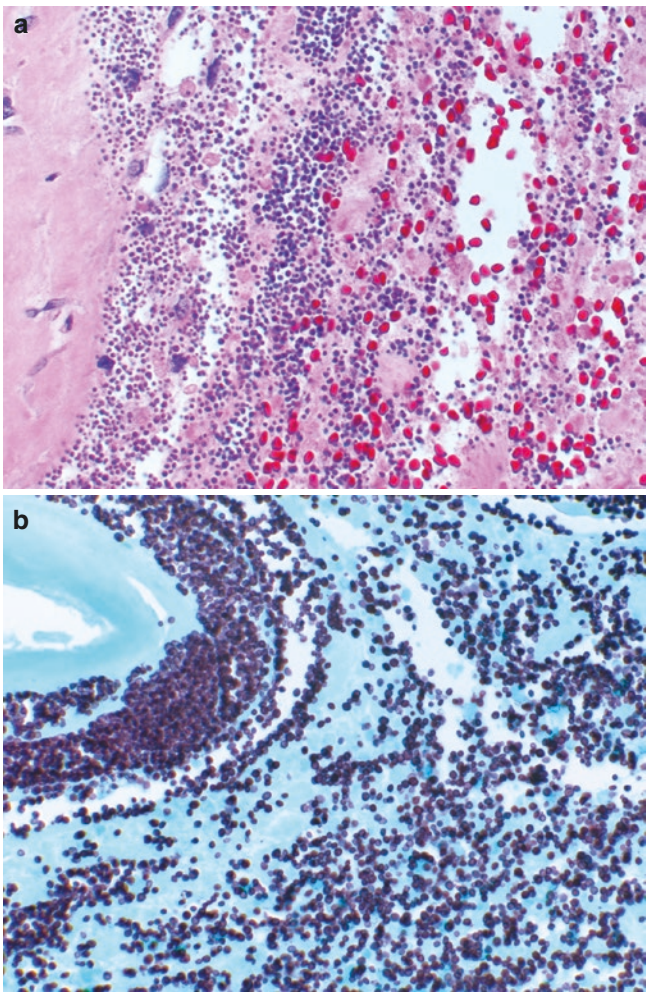


**Fig. 14.42** Candida infection. (**a**) Section of a membrane roll reveals numerous yeast forms, some with signs of budding. (**b**) GMS stain of the same placenta highlights the organisms

### 14.5.2 Listeria

*Listeria monocytogenes* infection occurs in approximately 9/100,000 pregnancies, and about 20% of these infections result in fetal or perinatal demise. Grossly, the amniotic fluid appears meconium stained (even in premature deliveries unlikely to have passed meconium), and on cut section small white nodules can be identified scattered throughout the placental parenchyma. Histologically, the hallmark of listeriosis is the presence of prominent acute intervillositis with microabscess formation, which is what forms the white nodules

seen grossly. The villi themselves are relatively spared from inflammation, as this is a hematogenously spread infection that is acquired via the maternal blood. Organisms are usually appreciable with a gram stain [6, 28].

### 14.5.3 Toxoplasmosis

Infection with toxoplasmosis can have severe consequences, with 5–15% of infections resulting in stillbirth. Among surviving infants, though most will appear asymptomatic, at least 85% will develop chorioretinitis if they are not treated. Grossly, there are no specific features of this protozoal infection in the placenta. Histologically, the intracellular organisms are found in amniotic epithelial cells, stromal cells between amnion and chorion, and villous stromal Hofbauer cells. Pseudocysts and true cysts may occasionally be seen, which harbor many organisms. Rupture of these cysts results in a lymphohistiocytic or granulomatous villitis with multinucleated giant cells and necrosis [6, 28].

### 14.5.4 Cytomegalovirus

Cytomegalovirus (CMV) is the most common congenital viral infection, occurring in 1–2% of newborns. Congenital CMV acquired early in gestation can lead to prematurity, hydrops, growth restriction, and fetal demise. Grossly, the placenta may appear hydropic. Histologic findings are most often present only in cases with severe clinical findings. The histologic features include lymphoplasmacytic villitis, hyalinized villi, or avascular villi with hemosiderin-laden macrophages. Viral inclusions, when present, can be found in villous stromal Hofbauer cells and endothelium. Immunohistochemical stains for CMV may be helpful [34, 35].

### 14.5.5 Herpes Simplex

The rare placenta infected with herpes simplex virus (HSV) is almost always both grossly and microscopically unremarkable. Rarely, features including necrotizing lymphoplasmacytic villitis, villous fibrosis and calcification, chronic inflammation surrounding fetal vessels, or HSV inclusions (in villi, the cord, and membranes) are noted. Necrotizing funisitis has also been described [36, 37].

### 14.5.6 Syphilis

While about two-thirds of infants infected with *Treponema pallidum* are asymptomatic at birth, about one-third are stillborn. There is also a high incidence of prematurity and intrauterine growth restriction. Grossly, the placenta affected by syphilis is thick, friable, and frequently pale. In about half of the cases, the umbilical cord has a "barber pole" appearance with chalky white necrotic debris surrounding the vessels. Histologically, the "barber pole" appearance is due to severe necrotizing funisitis, with a prominent (mostly degenerated) acute inflammatory cell infiltrate in Wharton's jelly; spirochetes may be identified with silver stains if antibiotic therapy had not yet been initiated. The villi may show chronic lymphoplasmacytic villitis, increased nucleated red blood cells, villous edema, and increased numbers of Hofbauer cells [6, 15, 38].

### 14.5.7 Zika

Infection with the Zika virus has recently become a widespread topic of interest as a significant congenital infection. While not all mothers who have been exposed to the virus will give birth to affected infants, the recent surge in incidence and awareness has certainly made it a consideration for obstetricians. Serologic testing of the mother and infant is the mainstay of diagnosis, but there are reports of placental pathology associated with congenital infections. The histologic changes, when present, tend to be mild, and are nonspecific. The villi are enlarged, partly due to villous edema, but also due to increased numbers of Hofbauer cells in the villous stroma. Interestingly, no significant acute or chronic villitis has been noted. RNA probes for the virus will highlight the villous stromal/Hofbauer cells, indicating the presence of Zika within them [39].

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