The placental pathology report

AUTHOR: Drucilla J Roberts, MD
SECTION EDITOR: Amy McKenney, MD
DEPUTY EDITOR: Vanessa A Barss, MD, FACOG

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Feb 07, 2023.**

INTRODUCTION

Placental examination provides insights about the intrauterine environment of the fetus, some of the fetal responses to acute and chronic disease, and the pathogenesis of adverse fetal and neonatal outcomes. It can provide useful information for diagnosis and treatment of sick newborns and is an essential component of the autopsy in cases of fetal or neonatal death. For these reasons, we believe that all placentas should have a minimal gross examination by the obstetric provider or clinical attendant at the birth. This examination should include color, length of umbilical cord, number of cord vessels, and weight of the trimmed placental disk. Histopathologic examination of the placenta should be obtained when clinically indicated by standard clinical criteria or the judgment of the clinician (table 1). (See "Gross examination of the placenta", section on 'Indications for a full examination'.)

Providing a clear and succinct report is essential for the clinician. The author strongly suggests that the placental pathology report be included in both the infant's and the mother's medical charts. Having a routine standard gross and histologic evaluation and report is extremely helpful for all clinicians involved in counseling the patient and improving neonatal care [1-3]. Reviewing all placental pathology reports may be particularly informative in cases of recurrent unexplained adverse pregnancy outcomes. An important secondary gain related to well-performed and reported placental examination is the avoidance of litigation [4]. Although some authors have recently questioned the relevance of placental pathology and expressed the view that very few obstetric providers understand the placental pathology report [5], we and others believe it provides useful information [6,7]. It should be

written to be clearly understandable by obstetric and pediatric providers and pertinent to the clinical situation.

This topic will provide a brief synopsis of the clinical significance of selected placental histopathologic findings that are reported by placental pathologists. A detailed discussion of placental histopathology is beyond the scope of this review. The normal anatomy and gross examination of the placenta are discussed separately. (See "Gross examination of the placenta".)

REPORT OVERVIEW

The placental pathology report describes the gross and microscopic placental findings to clinicians involved in maternal and infant care. Placental pathology should be reported as a usual surgical pathology specimen; therefore, reports should be available within several days. Standardized reporting is helpful for the clinician and should be followed [8]. These reports serve three broad functions: (1) providing information that helps to explain complications that occurred during the pregnancy, (2) providing information that should prompt immediate intervention (eg, previously unrecognized infection), and/or (3) providing information that is predictive of future maternal or offspring problems.

The language of the report should be direct and noninflammatory. Interpretation should be data-driven and not anecdotal; however, some expert opinion in a comment or a phone call, which is documented in a note, may be useful to help pull seemingly disparate findings together. Over-interpretation should be avoided.

Any findings with immediate clinical import should be brought promptly to the attention of the appropriate obstetric provider, and/or pediatric provider when appropriate. The rare diagnoses that require clinical intervention should be phoned to the clinician as a critical finding, and include such diagnoses as malignant neoplasms, specific infections, and inborn errors of metabolism. A list of gross and histologic critical placental findings is available in the appendix of the Atlas of Placental Pathology, 2021 [9].

Other important findings provide an estimate of risk for the neonatal and pediatric outcome, especially neurologic abnormalities, and include features associated with severe hypertensive disease (placental malperfusion), diffuse chorioamniotic hemosiderosis, fetal vascular malperfusion, fetal inflammatory response, meconium myonecrosis, diffuse villitis of unknown etiology (VUE), chronic histiocytic intervillositis, and massive perivillous fibrin deposition (maternal floor infarction) [9].

GROSS DESCRIPTION AND FINAL DIAGNOSIS

The placental pathology report should include a complete gross description and a final histopathologic diagnosis. In the author's opinion, the first sentence of the gross description should include two basic findings, the maturity of the placenta (immature or mature) and the placental weight (weight in grams and percentile for gestational age), followed by the diagnoses. (See 'Placental maturity and weight' below.)

Microscopic descriptions are variably included, but pertinent microscopic findings should be provided with the final diagnosis. Many histopathologic diagnoses are descriptors of unclear clinical significance, but pathologic nonetheless. Clinically important findings should be included with the descriptors. The clinician reading the pathology report should review the diagnoses and call the pathologist to clarify, if needed.

The following is an example of the diagnostic section of a placental pathology report:

Diagnosis:

- Immature placenta (215 g, approximately 10th percentile for reported gestational age of 28 weeks).
- Long hyper-coiled umbilical cord (cord length 75 cm; normally expect approximately 45 cm at 28 weeks).
- Fetal vascular malperfusion (multiple large regions of villous stromal-vascular karyorrhexis).
- VUE, low grade.
- Small placental infarct, usual type.

Comment: "The long hyper-coiled umbilical cord is the likely source of the fetal vascular malperfusion, as long umbilical cords are associated with slow flow, heart failure, and cord occlusive events."

FINDINGS

There are four major categories of placental pathology per the Amsterdam Criteria [10]:

- Maternal vascular malperfusion
- Fetal vascular malperfusion
- Acute chorioamnionitis
- Villitis of unknown etiology (VUE)

These and other patterns of placental injury are described in the following sections of the topic.

Placental maturity and weight

Maturity — Placental villi mature across gestation; full maturity is normally attained by mid-third trimester. The maturational level of the placenta correlates with the functionality of the placenta: villous maturation should be appropriate for gestational age.

Maturity is defined by histologic features in the terminal villi. As the placenta grows, the villi branch and bud off from the initial stem villi to secondary, tertiary, and terminal villi. Each successive branch/bud results in smaller villi, with the fetal vessels occupying more of the space in the stroma. The trophoblast thins, forms knots, and comes closely in apposition to the villous capillaries to make a vasculosyncytial membrane (picture 1). This maturation process facilitates oxygen and nutrient transport to meet the demand of the near-term fetus.

An immature placenta will have immature villi without abundant trophoblastic knots and vasculosyncytial membranes; this is a normal finding up to approximately the 32nd week of gestation. After approximately 32 weeks, the placental villi should have a predominance of small terminal villi with abundant knots and vasculosyncytial membranes.

Accelerated villous maturation is a sign of maternal vascular malperfusion. It is diagnosed when mature villi (small or elongated villi with increased intervillous space) are identified in a preterm gestation (ie, before 32 weeks) and the number of intermediate villi is decreased. It suggests placental ischemia.

Delayed villous maturation (also referred to as villous maturational arrest and distal villous immaturity) is diagnosed when immature villi are identified late in gestation (ie, at term) and suggests the placenta was less efficient in gas and nutrient exchange [11]. There is a paucity or absence of terminal villi, such that most of the villi are intermediate in size with increased numbers of centrally located capillaries and an absence or paucity of vasculosyncytial membranes (picture 2) [8]. This is an important diagnosis due to its association with maternal diabetes, anemia, opioid use disorder, and fetal mortality [12-14], even though the diagnosis can be quite subjective [15]. The link to fetal demise is possibly because the absence of vasculosyncytial membranes increases the distance (ie, decreases the efficiency) of oxygen/nutrient transfer to the fetus, resulting in decreased placental capacity to meet fetal demands [12].

Weight — The placental weight is a key part of the placental examination. It is a marker for placental development and capacity (reserve). Small placentas by weight are associated with less reserve/less capacity to support fetal needs. Standards for placental weights at different gestational ages are available and should be reported with the actual weight (table 2). The placenta must be weighed appropriately, trimmed of cord and membranes, for the percentiles and ratio to be reliable. (See "Gross examination of the placenta".)

The weight of the placenta should normally correspond to the weight of the fetus. A normal fetal/placental weight ratio at term is between 6 and 7; a ratio less than 6 is very unusual and suggests placental hydrops, and a ratio of ≥8 suggests placental insufficiency.

Fragmented placenta — If manual extraction of a retained placenta is performed, the placenta may be disrupted and the fragments sent to pathology. In these cases, it is difficult for the pathologist to determine whether there may be additional retained placenta based only on the weight and appearance of the placental fragments.

Placental accreta spectrum disorders may be the cause of retained placenta. In such cases, the pathologist may find basal plate myometrial fibers adherent on the placenta fragments, which should be measured and staged [16].

Umbilical cord — The umbilical cord is the lifeline of the fetus so any umbilical cord lesion that may interfere with blood flow (eg, cord hyper-coiling, knots, hemorrhage, tumors, thrombi) is clinically important. The umbilical cord also reflects the in utero environment (eg, meconium, infection, stress) and the fetal response to its environment (eg, vasculitis). However, some findings have no clinical significance, such as congenital remnants.

Umbilical cord gross and histopathologic findings are also reviewed in the following topics:

- (See "Gross examination of the placenta", section on 'Umbilical cord'.)
- (See "Umbilical cord abnormalities: Prenatal diagnosis and management".)
- (See "Velamentous umbilical cord insertion and vasa previa".)
- (See "Care of the umbilicus and management of umbilical disorders".)
- (See "Umbilical cord abnormalities: Prenatal diagnosis and management".)

Cord coiling — The normal umbilical cord coils a full 360 degrees over approximately every 5 cm of length, resulting in a cord coiling index (coils per centimeter) of approximately 0.2; the cord typically coils to the left.

Although the etiology of cord coiling is not completely understood, abnormal cord coiling is associated with antenatal complications. Flat umbilical cords have been associated with decreased fetal activity due to any etiology and thus have an association with neuromuscular abnormalities [17-19]. Hyper-coiled cords have been associated with sudden fetal death due to cord constrictions/flow obstruction. Four coiling patterns have been described: undulating, rope, segmented, and linked; the linked pattern is most associated with fetal morbidity (figure 1) [17]. Hypo- and hyper-coiled cords should be listed as a part of the diagnosis in the placental pathology report since they can be associated with adverse fetal outcomes.

Insertional anomalies — Marginal or membranous insertions of the umbilical cord are associated with an increased risk of adverse perinatal outcomes (eg, fetal growth restriction,

fetal death) and should be reported in the placental pathology report. (See "Velamentous umbilical cord insertion and vasa previa".)

Inflammation — Umbilical cord inflammation has different names, including funisitis and vasculitis. Inflammatory cells migrating through the fetal cord vessels (picture 3) or chorionic plate vessels are evidence of a fetal response and are diagnostic of systemic fetal inflammatory response syndrome [20]. Typically, the fetal inflammatory response starts by inflammatory cell migration to the periphery of the lumen of chorionic plate vessels, then transgressing through the endothelium, vascular muscular wall, and then into the mesoderm surrounding the vessel (chorionic plate mesoderm in the chorionic plate). With time, the umbilical vein becomes involved (umbilical cord phlebitis), Wharton's jelly in the umbilical cord, and finally the umbilical arteries.

An inflammatory infiltrate involving only the external surface of the cord and superficial Wharton's jelly originates from the mother; the maternal inflammatory cells (primarily neutrophils) migrate from the decidua to the amniotic fluid and then to the cord. This is characteristic of candida funisitis, candidal infection of the placenta, a grossly identifiable lesion of multiple variably-sized white plaques on the umbilical cord. It is a critical placental finding for the neonatologist.

The source (maternal or fetal) of the inflammatory response is important because there is a greater risk of neurologic compromise in offspring when the inflammatory response is fetal since fetal inflammation of the umbilical cord may be a marker for infection or possibly vascular inflammation elsewhere in the fetus [21,22]. A marked/severe fetal inflammatory response with prominent eosinophilia admixed with neutrophils in areas of fetal inflammation is particularly predictive of an adverse neonatal outcome, especially when preterm [23]. (See "Placental pathology: Findings potentially associated with neurologic impairment in children".)

Meconium staining — All fetuses after approximately 20 weeks of gestation can pass meconium. In preterm fetuses, meconium passage is considered a stress-related response. At term, and especially postterm, meconium passage may be physiologic and is not necessarily a stress response. Freshly passed meconium may coat the membranes, cord, and neonatal skin. Abundant meconium in the membranes at any gestational age is usually associated with a significant fetal insult.

A high concentration of meconium present for more than 12 hours can damage the umbilical cord by causing apoptosis of smooth muscle cells [24]. The histologic findings are an apoptotic-like degeneration of the arteries (usually) in a characteristic pattern that spares the centrally facing myocytes (picture 4). An inflammatory infiltrate is often present. The inflammation is fetal in origin, and the inflammatory cells migrate from the vessel lumen through the vessel wall into Wharton's jelly. In addition, meconium-induced vasoconstriction

has been documented in vitro, which may further compromise blood flow through the umbilical cord [25].

In retrospective studies, meconium-induced umbilical cord vascular necrosis has been associated with postterm pregnancy, oligohydramnios, low cord pH, low Apgar scores, and significant neurodevelopmental delay [24,26-28]. Fetal and neonatal morbidity is thought to be due to interruption of the normal blood flow in the cord from the meconium-induced vascular damage, causing intermittent or prolonged hypoxia. There are no prospective studies to establish whether this finding should cause concern and early postdelivery intervention, but the author typically notifies the infant's pediatrician of the finding.

Solid and cystic abnormalities — The most common mass of the umbilical cord is a hematoma (picture 5 and picture 6). These are usually a sequela of cord clamping and/or traction at delivery and are of no clinical significance.

Spontaneous cord hematomas are rare and clinically significant, as they are usually associated with fetal death due to exsanguination or to compression of umbilical cord vessels by the hematoma. The cause is generally not identifiable, although, in the author's experience, vascular damage (eg, meconium myonecrosis, inflammatory damage) is almost always present.

The umbilical cord is also host to other rare mass-like lesions, including mature cystic teratomas [29-31], hemangiomas [32-34] and angiomyxomas [35,36], and non-neoplastic intestinal-type polyps (ie, polypoid intestinal masses that probably develop within the vitelline duct remnant) [37]. If large, any of these masses can cause fetal morbidity or death in utero, due to compression/obstruction of the umbilical cord vessels.

Arterial and venous thrombosis — Umbilical artery and umbilical vein thrombosis are rare, but can compromise the fetal circulation [38-41]. Venous thrombosis occurs alone in approximately 70 percent of cases, both venous and arterial thrombosis occurs in approximately 20 percent of cases, and arterial thrombosis occurs alone in 10 percent of cases [42].

Arterial thromboses in one part of the cord can result in the appearance of a single umbilical artery (two-vessel cord) in another part of the cord. As long as one patent artery remains, the outcome is not lethal, but an adverse outcome may occur if the thrombus embolizes to the placenta and results in fetal thrombotic vasculopathy, which if significant, might result in fetal growth restriction or intrapartum hypoxemia or acidosis due to decreased placental reserve.

Umbilical vein thrombosis will be fatal if complete; partial thrombi can embolize to the fetus and cause cerebral or renal infarcts, or damage to other end-organs, including amputations of digits.

Possible causes of umbilical vessel thrombosis include mechanical obstruction (eg, hypertwisting or coiling causing kinking, knots, prolapse, amniotic bands, velamentous cord insertion, varices); fetal thrombophilia; meconium-induced vascular necrosis; severe inflammation (funisitis); and iatrogenic injury [40,43], but many cases remain unexplained.

Single umbilical artery — Single umbilical artery may be a developmental anomaly or result from remote thrombosis/occlusion. Its clinical significance is a somewhat weak association with congenital renal and cardiac anomalies. (See "Single umbilical artery".)

Congenital remnants — The proximal end of the umbilical cord (the end closest to the infant) often contains residual developmental structures, such as the allantoic (urachal) and vitelline (omphalomesenteric) ducts [44]. Allantoic duct remnants are common and have no clinical significance, except in rare cases where they are enlarged and a marker for a patent urachus. Vitelline duct and vitelline vessel remnants also have no clinical significance, except in rare cases where there is a direct connection to fetal bowel.

Nonbacterial infections — The umbilical cord is the site for some specific nonbacterial infectious organisms including candida (picture 7) [20] and toxoplasmosis [20]. Although much less common than bacterial infection, these organisms can sometimes be observed in the areas of inflammation. Candidal infection is frequently associated with neutrophilic microabscesses on the external surface of the umbilical cord. (See 'Candida' below.)

The only viral infection known to affect the umbilical cord in herpes simplex virus. In these cases, you might see a plasma cell infiltrate or cells with viral inclusions in Wharton's jelly.

Membranes — Gross and microscopic findings in the fetal membranes are critical aspects of the placental report. The membranes may show evidence of abnormal constituents of the amniotic fluid (eg, meconium, bacteria, inflammatory cells, blood), oligohydramnios, or fetal malformations (eg, gastroschisis, exstrophies, ectopia cordis).

Acute chorioamnionitis — Acute chorioamnionitis is one of the four patterns of placental injury per the Amsterdam Criteria [10]. Neutrophilic (acute) inflammation is probably one of the most common pathologic findings during placental examination and is present in as many as one-quarter of all term placentas. Contamination of amniotic fluid by vaginal/cervical flora [45] may result in a maternal inflammatory response; a fetal inflammatory response can also occur [46-48]. Acute chorioamnionitis should be diagnosed by staging and grading the maternal and fetal inflammatory response using the Amsterdam and Redline criteria or a modification of these criteria [8,21,49]. (See 'Chorioamnionitis' below.)

Chronic chorioamnionitis — Chronic chorioamniotic inflammation is characterized by a mononuclear cell infiltrate (ie, lymphocytes, histiocytes and plasma cells). Compared with the neutrophilic "acute" form, which is usually due to bacterial infection, immune mediated

inflammation has a different, and usually noninfectious, etiology [50,51]. It is often associated with chronic villitis, specifically villitis of unknown etiology (VUE) [51] and has the same clinical associations.

Meconium staining — All fetuses after approximately 20 weeks of gestation can pass meconium. In preterm fetuses, meconium passage is considered a stress-related response. At term, and especially postterm, meconium passage may be physiologic and is not necessarily a stress response. Freshly passed meconium may coat the membranes, cord, and neonatal skin.

Meconium pigment is derived primarily from the bile pigment it contains. This pigment varies from a fluffy, light brown material to a waxy, uniform, opaque pigment (picture 8) that is present in macrophages (or loosely on the membranes). These differences in macrophage appearance are not related to the exposure history or the clinical course.

Meconium appears to be toxic since it can cause amniotic epithelial necrosis, myocyte necrosis, and, in the author's opinion, a marked fetal inflammatory infiltrate in the fetal cord vessels and/or membranes in the absence of acute chorioamnionitis [24,27,28,52,53]. (See 'Meconium staining' above.)

Infant morbidity from meconium can occur from inhalation due to gasping in utero or at birth or from umbilical vascular damage due to prolonged exposure in utero. The degree of vascular damage relates to the length of exposure: it takes at least one hour for meconium pigment to be present in the amnion; three hours for the pigment to appear in the chorion; six hours to cause amniocyte necrosis; and more than 12 hours to cause myocyte necrosis [24,26-28,52,54-58].

Hemosiderin staining — Not all brown pigment in the membranes is meconium. Blood in the amniotic fluid from chronic abruption can cause hemosiderin deposition in the amniotic macrophages. This pigment differs from meconium because of its yellow-brown and crystalline hue, obviating the necessity for special stains in most cases. The author obtains iron stains when the clinical history suggests passage of meconium or in-utero stress or in suspicious cases, such as when the brown pigment is copper-colored or birefringent, pigment deposition is excessive, or when the gestational age is less than 30 weeks.

Diffuse chorioamniotic hemosiderosis is a dramatic histologic presentation of extensive hemosiderin typically involving the chorionic plate. It is a feature of chronic abruption [59,60] and has been associated with significant perinatal morbidity [61,62].

Solid and cystic abnormalities — No true neoplasms affect the fetal membranes, although extension of rare umbilical cord neoplasms can involve the adjacent chorionic plate. Cysts on the surface of the amnion may result from localized edema, and are not usually associated with clinical disease or sequelae. Cysts of the chorionic plate or septa are usually benign,

although multiple or large cysts are associated with increased fetal morbidity and mortality [63,64].

Remnants of the yolk sac are relatively common and benign. They present as one or more approximately 5 mm yellow-white, well-circumscribed calcified masses beneath the amnion.

Subamniotic hematoma is generally iatrogenic, such as from cord traction at delivery. Subchorionic hematoma results from intervillous (maternal) bleeding, usually from marginal (uterine) blood vessels, and is associated with an increased risk of miscarriage and preterm birth when large or associated with hemosiderin in the membranes [59,65].

Metaplasia of the amniotic epithelium (expanded cells with foamy microvesicular changes) may occur when fetal anomalies allow fetal viscera to make contact with the amnion (eg, exstrophies, ectopia cordis, gastroschisis) [66,67]. Other metaplasias (squamous, papillary, columnar) are common and of no clinical significance, but may indicate amniotic "irritation" as in acute chorioamnionitis or meconium exposure.

White, brown, or yellow nodules on the amnion may be due to amnion nodosum [66]. Amnion nodosum is caused by abrasion of the amnion with deposition of fetal squamous cells and acellular debris on the eroded areas (picture 9) in the setting of severe and prolonged oligohydramnios, and is usually associated with anhydramnios. The chorionic plate is most affected, while the umbilical cord is rarely affected.

Parenchyma — Parenchymal lesions can result from either a fetal or maternal source since both circulations perfuse the placenta, or may be unique to the placenta itself (eg, mesenchymal dysplasia [68]). Some parenchymal findings have been associated with neurologic impairment and cerebral palsy in children. (See "Placental pathology: Findings potentially associated with neurologic impairment in children".)

Villitis — Both neutrophilic (acute) and lympho-histiocytic (chronic) villitis are inflammatory infiltrates involving the placental parenchyma. The specific diagnosis is based upon the nature and type of inflammatory infiltrate and probable cause.

Acute villitis — Neutrophilic/acute villitis is a specific gross and histologic feature of micro/macro neutrophilic abscesses in the placental parenchyma and is often accompanied by neutrophilic chorioamnionitis (picture 10). It is typically associated with a bacterial infection, almost always secondary to listerial infections, but sometimes due to streptococci [24,27,28,52] and rarely others.

Lympho-histiocytic (chronic) villitis — Chronic villitis refers to a mononuclear (primarily lymphohistiocytic) cell infiltrate within or around the villi (picture 11) [69,70]. Most cases are not caused by infection, but the specific cause of these chronic villitis cases is

unknown, hence the term "villitis of unknown etiology." Villitis of unknown etiology (or VUE) is one of the four patterns of placental injury per the Amsterdam Criteria [10].

- **VUE –** VUE should be graded according to the Amsterdam criteria [8], as it is likely only high-grade VUE that is important clinically. High-grade VUE has been associated with fetal growth restriction, fetal death, abnormal brain findings on neonatal magnetic resonance imaging, and spastic quadriplegic cerebral palsy [62,71,72]. Therefore, severe diffuse VUE is an important diagnosis to report to both the obstetrician and the pediatrician. By contrast, focal or patchy VUE (picture 12) is a relatively common, usually nonspecific finding detected in approximately 5 to 10 percent of term placentas [50,73] and likely not clinically relevant in a placenta of normal weight.

  One hypothesis for VUE is that it is a response of the maternal host to the fetal/placental allograft. The mononuclear cells are mostly maternal in origin (a contribution from the fetal macrophages is present as well) and are probably responding to a fetal antigen expressed by the villi [74]. In some cases, the fetus is compromised by necrosis of the villi by maternal white cells; this process is commonly manifested clinically as fetal growth restriction [75,76]. It is also possible that products of villous inflammation enter the fetal vasculature and have a systemic effect on fetal growth [77]. This type of villitis has been associated with infertility, untreated neonatal alloimmune thrombocytopenia, and neonatal neurologic impairment (when associated with obliterative fetal vasculopathy) [75,78-80]. It recurs in future pregnancies in approximately one-third of cases [81]. There are no evidence-based treatments, but various treatment regimens have been tried (eg, low molecular weight heparin, low-dose aspirin, prednisone, intravenous immunoglobulin). Even with these treatments, outcomes have been poor (eg, severely growth-restricted live birth, recurrent demises). The best outcomes are with in vitro fertilization and use of a gestational carrier, which has produced good outcomes since this is an immunologic not genetic abnormality.

- **Infection-related villitis –** Infection is the definitive cause of a small (less than 5 percent) subset of cases of lympho-histiocytic villitis [82-84]. TORCH infections (ie, Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes) are the usual source. This type of villitis is associated with other abnormal pathologic or clinical findings, such as plasma cell deciduitis, stillbirth, fetal growth restriction, or hydrops. The diagnosis is made by routine hematoxylin-eosin or immunohistochemical stains for viral markers or spirochetes. When associated with TORCH infections, villitis is usually multifocal and may have some of the following histologic features:

  - Increased cellularity of the villi
  - Sclerosis of the villi due to collapse of the villous vessels
  - Clumping of the involved villi

- Fetal normoblastemia (circulating fetal immature nucleated red blood cells)
- Hemosiderin in the villous stroma
- Plasma cells in the villi

On low-power histopathology, these changes will appear as multifocal clusters of dark blue cellular avascular villi, often clumped together and surrounded by fibrin (picture 13). The inflammatory infiltrate in viral infections is typically mononuclear and typically contains histiocytes (sometimes multi-nucleate), lymphocytes, and plasma cells. The inflammatory cells are maternal in origin and may "spill out" of the villi to cause an intervillositis [74]. At higher magnification, a viral inclusion (eg, cytomegalovirus [CMV]) (picture 14), granuloma, or giant cells may be detected that help to determine a more precise etiology for the infection. Clinically, a small mature placenta with severe, diffuse, plasmacytic villitis associated with a small for gestational age neonate should prompt consideration of CMV infection primarily, and herpes simplex virus (HSV) or toxoplasmosis secondarily.

An infectious villitis in a liveborn is a critical finding to be reported urgently to the obstetrician and pediatrician. In a stillborn, it explains the loss and is therefore important to report.

Chorangiosis — Chorangiosis refers to a vast increase in the number of vascular channels in noninfarcted, nonischemic areas of the placenta [85]. When diffuse, it is uncommon and thought to be related to long-standing hypoxia. It is also seen with maternal tobacco smoking, high altitude pregnancies, multiple gestations, and maternal diabetes [11,86-88]. It has been associated with stillbirth, cord problems, and congenital anomalies [85,89-91]. Chorangiosis can be confused with placental villous congestion but, in the latter, the vessels are distended without an increase in number of vessels per villus.

Excessive fibrin deposition — Excessive fibrin deposition is a key finding in maternal floor infarction (MFI)/massive perivillous fibrin deposition (MPFD) and chronic histiocytic intervillositis (CHI). Both parenchymal disorders are associated with perinatal morbidity and mortality, and recurrence. They are probably related to, or part of, a spectrum of maternal immunologic dysfunction. However, a small amount of perivillous fibrinoid is a normal finding with advancing gestation.

Maternal floor infarction/massive perivillous fibrin deposition — The maternal floor corresponds to the anatomic region of the placental disk attached to the maternal surface of the uterine cavity. It includes the most basal villi, Nitabuch's membrane, the placental implantation site, and the decidual basalis. MFI refers to a process in which a thick band of fibrin is deposited along the maternal floor of the placenta, thereby obstructing maternal blood flow through the placenta to the fetal villi (picture 15). Thus, MFI is a misnomer, as the primary process is not infarction but abnormal interface fibrin deposition.

MFI is likely in continuum with MPFD; therefore, they are usually diagnosed with the single composite diagnosis MFI/MPFD [81,92,93].

The lesion has been associated with both an elevated maternal serum alpha-fetoprotein and recurrence in subsequent pregnancies. The fetal sequelae include fetal growth restriction, stillbirth, and neurologic injury [94,95] due to uteroplacental insufficiency.

The etiology of MFI/MPFD is unknown but is thought to be an extreme form of host versus graft reaction to the pregnancy [50,96-100]. Rarely, it is associated with infections, especially Coxsackie virus [101,102].

MFI/MPFD recurs in future pregnancies. The mother should be evaluated for a coagulopathy, particularly antiphospholipid syndrome [95,96,103], as a possible cause of MFI/MPFD, and other autoimmune disorders [81]. The author calls the obstetric provider with this diagnosis for these reasons.

Chronic histiocytic intervillositis — CHI is a critical diagnosis, and the obstetric provider should be called with this diagnosis. CHI refers to the presence of massive amounts of intervillous and perivillous fibrin associated with a marked maternal histiocyte infiltration (picture 16) usually in the absence of VUE [81]. This lesion is distinctive in the term placenta but is more commonly present in first- and second-trimester losses. It has been reported to recur in up to 80 percent of successive pregnancies, but the literature describing these cases is sparse [104-106]. CHI has been seen in some infectious pathologies as well, including malaria [107], Zika virus (in first-trimester placentas [108,109]), Dengue virus [110], and with acute inflammation in psittacosis [81,111].

CHI and MPFD have also been associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the placenta and may be a marker for congenital infection [112]. The characteristic placental pathology associated with SARS-CoV-2 placental infection (not transmission) has been termed "SARS-CoV-2 placentitis." It consists of a triad of placental findings diffusely involving the parenchyma, including increased perivillous fibrin, histiocytic intervillositis, and villous trophoblast necrosis (picture 17) [113]. This placentitis causes marked placental damage and can result in intrauterine fetal death [114]. Some authors have noted that just exposure (not infection of the placenta) is associated with either maternal [115] or fetal [116] vascular malperfusion.

Maternal vascular malperfusion — Maternal vascular perfusion is one of the four patterns of placental injury per the Amsterdam Criteria [10]. Maternal vascular pathology can reduce or completely interrupt the uteroplacental circulation, resulting in placental infarcts, placental abruption, ischemic lesions, and fetal death [117,118]. Classically, histopathologic findings associated with maternal hypertensive diseases have been attributed to malperfusion, although the damage may be more related to hypertensive injury (pressure

related) than to true malperfusion or ischemia [119-121]. Chronic maternal malperfusion of fetal villi often results in a small (eg, placental weight is <10th percentile) ischemic placenta [122-125].

Chronic malperfusion ultimately results in placental infarcts (picture 18). Infarcts consist of collapsed maternal intervillous spaces and necrotic villi, usually involving the maternal floor. These findings are nonspecific and can occur with maternal hypertensive disorders (preeclampsia, chronic hypertension), uterine anomalies, maternal cardiovascular disease, and maternal hereditary and acquired thrombophilias. Peripheral infarcts on the maternal side of the placenta are common at term and, if small, usually not clinically significant. Perinatal morbidity is associated with infarcts of more than 5 percent of the placental mass or greater than 3 cm in diameter [126,127]. Infarcts are considered clinically severe (eg, associated with fetal growth restriction/stillbirth) if 20 percent or more of the placenta is affected [128] or if the placenta is small by weight. Infarcts are rare in preterm gestations and are associated with malperfusion; therefore, they are more clinically relevant.

Specific histopathologic findings that correlate with maternal vascular malperfusion (MVM) include increased syncytial knots (>1 in 3 to 5 terminal villi and/or >10 nuclei per knot), large syncytial knots, villous agglutination (microinfarcts with villi collapsing on one another, especially in the center of the parenchyma not involving the maternal floor), distal villous hypoplasia (reduced numbers of intermediate villi resulting in increased intervillous space) (picture 19), increased intervillous fibrin (filling the slide), sclerotic narrowing of arteries and arterioles, and sheets of intermediate trophoblast along the basal plate [117]; although the significance of the findings and their relationship to clinical disease are unclear [129-131].

Calcification — Calcium deposits in fibrinoid in the floor and septa are a normal finding associated with diet and placental maturity at term and postterm. Villous calcification, however, is seen in villous necrosis and with excess perivillous fibrin deposition, which may be associated with pathologic disorders such as infarction, CMV infection, thrombosis, and fetal death. A unique subtrophoblastic mineralization often seen in stillbirths is also a characteristic of fetal/neonatal Bartter syndrome, and should be noted when present in livebirths [132,133].

When seen in preterm placentas, calcification in the floor and septa has been attributed to senescence and, therefore, considered a feature of placental insufficiency (MVM).

Langhans cells and Hofbauer cells — Villous Langhans and Hofbauer cells are significant when increased in number, as this has been associated with placental immaturity and congenital Zika infection [134]. (See 'Maturity' above.)

Fetal vascular malperfusion — Fetal vascular malperfusion is one of the four patterns of placental injury per the Amsterdam Criteria [10]. The pathology associated with vascular flow abnormalities on the fetal side of the placenta are known to be significant indicators of fetal well-being and outcome [118,135] and have been well-characterized and classified [86,136]. When diagnosing fetal vascular malperfusion (FVM), the Amsterdam criteria for grading should be employed [8].

Thrombi in fetal vessels — Organized mural occlusive or nonocclusive thromboemboli are occasionally noted in the fetal vessels of the placenta, including the umbilical cord, chorionic plate, and villi. FVM (also known as fetal thrombotic vasculopathy) is nearly always present in placentas from stillbirths, but also occurs not infrequently in live births. The differential diagnosis includes: anatomic obstruction (true knots of the umbilical cord, membranous vessels), inflammatory injury to vessels (as in the "phlebitis" present in some cases of neutrophilic chorioamnionitis and the small vessels compromised in neutrophilic or lympho-histiocytic villitis), toxic causes (meconium myonecrosis, infant of insulin requiring diabetic mother), sepsis with disseminated intravascular coagulation, polycythemia, cardiac failure, and inherited fetal coagulopathy (eg, factor V Leiden) and congenital vascular stroke [43,58,137-145].

The presence of chorionic plate vascular thrombi should raise suspicions of congenital viral infections, especially in the setting of premature delivery, hydrops, stillbirth, or villitis. Both CMV and HSV placentitis have an association with chorionic plate vascular thrombi [146].

Avascular villi — The villi become necrotic if the fetus stops perfusing them, but the maternal intervillous spaces are maintained since maternal blood flow is not affected. Avascular villi are usually the result of fetal vascular damage (eg, membranous cord insertion, severe chorioamnionitis with vascular involvement, chronic villitis) or fetal thromboemboli (picture 11).

Villous stromal-vascular karyorrhexis — Villous stromal-vascular karyorrhexis (VSK), also termed hemorrhagic endovasculitis, hemorrhagic endovasculopathy, or hemorrhagic endovasculosis, refers to a particular type of FVM in which the villous vessels are often occluded and contain extravasated and fragmented red blood cells (picture 20). This lesion is thought to be due to slow flow from the fetus, as in cardiac failure or polycythemia. This finding is common among stillbirths, although, in these cases, it is difficult to conclude whether the finding proceeded, and may have contributed to, the fetal death (unless the finding is unevenly distributed).

VSK is also seen in live births, and has been associated with neurologic injury in these cases [147]. It can be associated with other thrombotic lesions, and appears to be a form of FVM and a precursor of avascular villi. It has been proposed that the terms FVM and extensive avascular villi (and/or VSK) be reserved for placentas with 15 or more affected terminal villi

per section, and not include those with only scattered foci [148]. VUE with stem villitis and avascular villi (obliterative VUE) is a distinct process with substantial perinatal morbidity. (See "Placental pathology: Findings potentially associated with neurologic impairment in children", section on 'Chronic progressive placental disorders'.)

Mass lesions of the parenchyma — Parenchymal masses may be due to intervillous thrombi (IVT), chorangioma, metastatic neoplasms, as well as infarcts and abscesses.

Intervillous thrombi — IVT are laminated red blood cells and fibrin that fill the maternal space separating the villi (picture 21). Grossly, IVT appear as laminated jelly-like to firm lesions from pink/tan to dark red in color, depending on the age of the thrombus. These lesions are due to small volume fetal hemorrhage into the maternal space and are quite common and usually benign. However, they occur at higher frequency in pregnancies complicated by Rh and ABO incompatibilities [149-152] and with maternal diabetes [153]. Other signs of fetal anemia (eg, circulating immature red blood cells and hydrops) should be present in severe cases of chronic fetomaternal hemorrhage [154] but are not observed with acute hemorrhage. Three or more IVT or any IVT associated with a stillbirth warrant investigation for fetomaternal hemorrhage. (See "Spontaneous massive fetomaternal hemorrhage", section on 'Measuring the volume of FMH'.)

Chorangioma — Placental neoplasms are generally benign, such as chorangiomas (picture 22), which are either vascular neoplasms of the stem villi or hamartomas [89,155-164]. Teratomas and other much rarer lesions also may occur [165-169].

Chorangiomas (also called chorioangiomas) range from microscopic lesion(s) to large masses. Most chorioangiomas are benign incidental findings, but as size increases, there is an increasing risk of adverse outcome due to high output heart failure (cardiomegaly, polyhydramnios, increased velocity in the middle cerebral artery, fetal hydrops) from arteriovenous shunting, platelet trapping (consumptive coagulopathy), and iatrogenic preterm delivery. In a review of published cases including 161 pregnancies with chorioangiomas, adverse outcomes in pregnancies that did not undergo intervention included fetal or neonatal death (8.2 and 3.8 percent, respectively), small for gestational age (24.0 percent), preterm birth <37 weeks (34.1 percent), and composite neonatal morbidity (12.0 percent) [170]. For chorioangiomas ≥2, ≥4, ≥6, ≥8, and ≥10 cm, the frequency of fetal hydrops was approximately 15, 16, 20, 28, and 52 percent, respectively. However, as the data were derived from case reports, the findings are likely limited by ascertainment bias. Other factors could affect the relationship between size and morbidity as well, such as the size of the lesion in relation to gestational age.

Care should be taken in evaluation of the trophoblast associated with chorangiomas. The surface of a chorangioma is covered with villous trophoblast as these lesions are thought to arise in stem villi. Often the villous trophoblast is hyperplastic [86,171], suggesting the

diagnosis of an intraplacental choriocarcinoma; however, this diagnosis requires malignant trophoblast and is usually accompanied by necrosis [172].

Metastatic neoplasms — Metastatic neoplasms can result from any hematogenously spread of malignant neoplasm [173-184]. Grossly, they appear as an infarct-like mass lesion on the maternal side of the placenta. In one review, 72 of 87 metastatic neoplasms involved the placenta only, 10 were metastatic just to the fetus, and 5 affected both the placenta and fetus [181]. The primary sites consisted of melanoma in 27 cases, breast cancer in 15, leukemia/lymphoma in 15, and lung cancer in 10. Fetal involvement was most common with metastatic melanoma (6 of 27), and 5 of these 6 infants died of the disease. No metastatic breast carcinomas affected the fetus. The author has seen lymphoma, intestinal, and breast cancer with their first presentation as a placental metastasis.

Fetal malignant neoplasms, such as neuroblastoma, can metastasize to the placenta, as well [184,185]. Benign (non-neoplastic) nevus cells can populate the villi, which is a dramatic microscopic finding of no clinical significance [186].

Choriocarcinoma — Choriocarcinoma has been detected on placental examination in otherwise unremarkable pregnancies [187,188]. It typically presents as small mass-like lesions grossly resembling infarcts or microscopic foci only. This is one of the reasons that the author believes that all grossly identified mass-like lesions in the placenta should be sampled for histology. Intraplacental choriocarcinomas (choriocarcinomas in situ) are often clinically silent, but often with widespread metastases, and they have been reported to metastasize to the fetus [187,189]. (See "Gestational trophoblastic disease: Pathology".)

Other rare masses — Leiomyomas and inflammatory myofibroblastic tumors are uterine masses that can be adherent to the placenta and appear grossly like a placental mass. Inflammatory myofibroblastic tumors are rare and apparently benign [190].

SELECTED DISORDERS OF PERINATAL AND MEDICOLEGAL IMPORTANCE

Some placental findings are of clinical importance either to the mother or fetus/infant. Many of these findings are significant enough to warrant an immediate phone call from the pathologist to the clinician.

Acute versus chronic stress/insult — The unstressed or acutely stressed gestation should have normal weight placenta for gestational age. Chronic stress often results in a small placenta (<10th percentile for gestational age) (table 2), but may produce a very heavy placenta (>99th percentile) in pregnancies complicated by maternal diabetes [11] or fetal hydrops. Placental weight should be obtained by trimming the umbilical cord and membranes off the disk. Normative standards for different populations are based on the

trimmed placental disk weight. The trimmed placental weight, therefore, is a critical parameter of in-utero well-being.

- Acute stress refers to stress of at least 1, but less than 24, hours duration. Placental pathologic findings include extensive meconium pigmentation (if less than 40 weeks of gestation) and acute villous edema [191,192]. When villous edema is severe, it may impair fetal oxygen delivery, resulting in fetal hypoxia and acidosis. Although some authorities believe that the fetus can release immature red blood cells (nucleated red blood cells) in as short a time as hours [191,192].

- Chronic stress refers to stress lasting days to weeks. The best indicator of chronic stress is a placental weight less than the 10th percentile; other findings include maternal or fetal vascular malperfusion (FVM) such as infarcts, amnion nodosum, erythroblastosis, hydrops placentalis, VSK, avascular villi, and villitis of unknown etiology (VUE) [71,193-195]. A heavy placenta associated with chronic stress may be due to chronic villous edema associated with syphilis, erythroblastosis fetalis, or any other cause of fetal hydrops.

Preeclampsia — The parenchymal finding most characteristically associated with preeclampsia is acute atherosis (ie, fibrinoid necrosis of the vessel wall with an accumulation of lipid-laden "foamy" macrophages and a mononuclear perivascular infiltrate) [137-142,196-201]. Vascular ectasia and thrombi may also be present. The histopathologic diagnosis is made by examination of vessels in the decidua parietalis (part of the extraplacental membranes). Other characteristic features of preeclampsia in the placenta include those of maternal vascular malperfusion (MVM) [202]:

- Distal villous hypoplasia
- Placental infarcts
- Small placenta by weight
- Acute or chronic abruption
- Decidual arteriopathy, with or without acute atherosis

MVM is particularly prominent in patients with preterm preeclampsia [203]. In the author's experience, most of the pathology related to MVM and preeclampsia is present in the preterm preeclampsia with severe features. Term preeclampsia often has no pathologic features of MVM.

Fetal growth restriction — The placenta can show a wide variety of findings in fetal growth restriction since this disorder has a wide variety of etiologies (see "Fetal growth restriction: Evaluation"). Features that have been correlated with idiopathic growth restriction include VUE, FVM, MVM, perivillous fibrin deposition that is excessive and located away from the margin and chorionic plate, extensive stromal fibrosis, and fetoplacental vascular

maldevelopment; however, all of these changes may not be present and the magnitude of change may be minor [204-206]. (See 'Maternal vascular malperfusion' above and 'Excessive fibrin deposition' above.)

Neurologically impaired infant — Examination of the placenta can provide information regarding the etiology of neurologically impaired infants and children [207]. (See "Placental pathology: Findings potentially associated with neurologic impairment in children".)

Recurrent preterm birth — A study of placental histology in recurrent preterm birth reported neutrophilic inflammation of the membranes, chorionic plate, and umbilical cord in 50 percent or more of pregnancies with recurrent spontaneous preterm birth [208]. Inflammation leading to thromboses in chorionic and umbilical vessels was not uncommon, possibly due to activation of the clotting cascade as a result of infection. The thrombosis began in the intima of chorionic veins and umbilical vessels, ultimately resulting in villous atrophy. Of note, this is an uncommon cause of thromboses of large placental veins, which is usually secondary to obstruction to venous return.

Other pathologies that recur and are often associated with preterm birth include maternal floor infarction/massive perivillous fibrin deposition and abruption. (See 'Maternal floor infarction/massive perivillous fibrin deposition' above and 'Placental abruption' below.)

Multiple gestation — Placental examination in multifetal gestation helps to determine zygosity, but may not be conclusive [209-211].

Placental abruption — In general, the diagnosis of acute placental abruption is made clinically. Histologic findings, such as diffuse retromembranous and/or intradecidual hemorrhages, irregular basal intervillous thrombi, and recent villous stromal hemorrhage, are not specific for the diagnosis and may rarely occur with normal placental detachment at delivery [212]. In some cases, intravillous hemorrhage (picture 23) can be identified in acute abruption due to rupture of the villous capillaries resulting in free blood in the intravillous stroma; however, intravillous hemorrhage is a nonspecific finding. An organizing retroplacental hematoma with overlying recent villous infarction is another pathologic finding in subacute to chronic abruption. Recent infarcts are characterized by preservation of villous stromal architecture, eosinophilic degeneration of the syncytiotrophoblast, and villous agglutination with scattered intervillous neutrophils. These infarcts take many hours to develop.

Several risk factors have been associated with abruption; history of a previous abruption confers the highest risk. However, most abruptions are idiopathic.

Inborn errors of metabolism — Storage material may accumulate in vacuolated placental cells in fetuses with inborn errors of metabolism [213]. The location and type of inclusion

varies depending on the disease. Diagnosis at placental examination will allow for early intervention and reproductive counseling.

Chorioamnionitis — Acute chorioamnionitis is one of the four patterns of placental injury. Neutrophilic inflammation of the chorion laeve and amnion (ie, acute chorioamnionitis) is the most frequent histopathologic result of ascending transcervical infection and occurs with both symptomatic and silent infections (picture 24 and picture 25 and picture 26 and picture 27) [214]. Isolated chorioamnionitis is characteristic of ascending infection while a hematogenous source displays greater inflammation of the villi (ie, villitis) and intervillous space (ie, intervillositis).

In one study of 1252 placentas from a high-risk population, histologic evidence of chorioamnionitis was found in 40 percent of patients with clinically apparent infection at delivery and in 15 percent of asymptomatic individuals [215]. Chorioamnionitis was diagnosed in 6 percent of 43,940 deliveries evaluated in the Collaborative Perinatal Project (CPP) [216]. The rate increased with decreasing gestational age: 15 percent at 28 to 32 weeks; 8 percent at 33 to 36 weeks; and 5 percent after 36 weeks of gestation. Similarly, another series describing the histopathology of 3928 placentas from pregnancies at 20 to 34 weeks of gestation found histologic chorioamnionitis in 31 percent [217]. The prevalence fell from 50 to 65 percent before 28 weeks to 16 percent at 34 weeks.

These studies are from high-risk pregnancies and used broad diagnostic criteria for the diagnosis of chorioamnionitis. The criteria for diagnosing histologic chorioamnionitis vary among pathologists [21,218]. Some definitions involve the number of tissues affected; other definitions have thresholds for the number of neutrophils observed. In the author's opinion, preterm neutrophilic chorioamnionitis is usually due to an acute infection. However, determining the duration of amniotic fluid infection by the severity of the histopathologic findings has proved unreliable [66,191]. Chorioamnionitis at term may be due to other factors including noninfectious entities (for example, epidural anesthesia [219]), and may be mediated by cytokines [214,220-223].

Chorioamnionitis can be either neutrophilic (frequently called acute) or lympho-histiocytic (chronic); neutrophilic chorioamnionitis is more common than lymphohistiocytic chorioamnionitis. Neutrophilic chorioamnionitis is usually mediated by bacteria, while lympho-histiocytic chorioamnionitis can be due to an abnormal immune reaction, a viral or protozoal infection, or, in most cases, an unknown etiology [50,51]. "Acute" chorioamnionitis is associated with an inflammatory infiltrate typically consisting of neutrophils or a mixture of neutrophils and mononuclear cells; eosinophils also may be present. The infiltrate involves one or more of the following:

- Chorionic plate
- Amnion of the placental membranes

- Fetal surface of the placental disk

An additional feature may include inflammatory infiltrate of the vascular portion of the umbilical cord or Wharton's jelly. There is a 70 to 90 percent correlation between the presence of leukocytes in the fetal membranes and associated placental and funic inflammation [224]. Fetal membranes also occasionally contain a large number of eosinophils; these are likely to be fetal inflammatory cells.

Inflammatory infiltrates in the maternal decidua and confined to below the chorionic epithelium can be normal. Decidua usually has an inflammatory infiltrate, typically neutrophilic or mixed neutrophilic/lymphocytic, during all stages of gestation, and labor may induce inflammatory cell migration into the chorion. By contrast, plasma cells are **not** normally present and should be considered pathologic. Inflammatory cells in the villi are also pathologic.

The clinical diagnosis of infection is not always confirmed by histologic or microbiologic studies. In one study of 139 pregnancies with clinical findings of presumed infection, histologic examination of the placenta did not support the clinical diagnosis in approximately one-third of cases [225]. The investigators suggested that noninflammatory events (eg, epidural anesthesia, abruption) could be responsible for maternal fever, tachycardia, uterine tenderness, or malodorous amniotic fluid. The author believes that clinically significant chorioamnionitis diagnosed histopathologically should be reserved for those cases with significant inflammation: diffuse or multifocal involvement of the membranes and/or chorionic plate with large numbers of inflammatory cells present. Minute foci of <10 neutrophils in the membranes should be ignored.

Conversely, histologic evidence of placental inflammation may not always be associated with microbiologic evidence of an infectious organism. Cultures of the amniotic fluid or membranes do not document a bacterial infection in 25 to 30 percent of placentas with histologic chorioamnionitis [219,224]. Negative cultures in the presence of histologic inflammation may be due to suboptimal microbiologic techniques for fastidious organisms such as Mycoplasma sp., administration of intrapartum antibiotics, or a noninfectious process.

Candida — Intrauterine candidal infections are rare. Unlike most ascending infections, intrauterine candidiasis often occurs without rupture of the fetal membranes. The specific maternal risk factors associated with intrauterine candidal infection include diabetes mellitus, sickle cell disease, presence of a cerclage, retained intrauterine contraceptive device, and immunocompromise.

Severe funisitis (ie, inflammation of the umbilical cord) and neutrophilic chorioamnionitis without villitis are the hallmarks of candidal infection. Grossly, the classic finding is multiple

small green and/or white abscesses on the surface of the umbilical cord. Microscopically, microabscesses with hyphae are usually present only on the cord's surface, but invasion into Wharton's jelly can occur (picture 28A-B). The presence of invasive hyphae in the cord is a risk factor for hematogenous dissemination to the fetus, in whom infection is rare and often catastrophic. Fungal organisms may be observed with routine or special stains.

Fusobacterium — This gram negative anaerobe has a strong association with neutrophilic chorioamnionitis and appears to play a role in the pathogenesis of spontaneous preterm birth, but is not a cause of neonatal sepsis [226,227]. Histopathology shows a severe, typically necrotizing, infiltrate (picture 29). Long filamentous fusiform bacilli can be readily identified with standard hematoxylin-eosin or bacterial stains.

Mycoplasma hominis and Ureaplasma urealyticum — The most common organisms identified in acute chorioamnionitis are mycoplasmas (*Ureaplasma urealysticum* [228] and *Mycoplasma hominis* [229]). They often present with a high stage and grade maternal and fetal inflammatory response.

Streptococcal infections — There are no specific placental histopathologic features of group B streptococcus (GBS) infection. Funisitis accompanies up to one-third of cases with neutrophilic chorioamnionitis. However, histopathology often does not show chorioamnionitis, despite well-documented cases of neonatal infection [230]. This may be due to the virulence of even short-term fetal exposure to GBS.

Group A streptococcus (GAS) can cause fulminant maternal infection and death [231]. GAS appears to invade the myometrium as a result of bacteremia associated with nongenital tract infection (eg, upper respiratory tract). The predominant histopathologic feature is neutrophilic purulent myometritis.

SUMMARY AND RECOMMENDATIONS

- **General principles**
  - **Rationale –** Placental pathology by a perinatal pathologist or a pathologist with some training in placental pathology provides information that (1) helps to explain complications that occurred during the pregnancy, (2) should prompt immediate intervention (eg, previously unrecognized infection), and/or (3) is predictive of future maternal or offspring problems. (See 'Introduction' above.)
  - **Basic examination –** All placentas should undergo a basic examination including color, length of umbilical cord, number of cord vessels and weight of the trimmed placental disk. (See "Gross examination of the placenta".)

Complete gross and histopathologic examination of the placenta should be obtained when indicated by standard clinical criteria or the judgment of the clinician (table 1). (See "Gross examination of the placenta", section on 'Indications for a full examination'.)

- **Weight and maturation** – The weight and maturational level of the placenta correlate with the functionality of the placenta. Standards for placental weights at different gestational ages are available. Villous maturation should also be appropriate for gestational age. Identification of mature villi in a preterm gestation (ie, before 32 weeks) suggests placental ischemia. Identification of immature villi late in gestation (ie, at term) suggests the placenta was less efficient in gas and nutrient exchange. (See 'Maturity' above and 'Weight' above.)

- **Specific diagnoses** – There are many placental diagnoses of clinical significance. They can be categorized most commonly into four major groups: Maternal vascular malperfusion, fetal vascular malperfusion, acute chorioamnionitis, and villitis of unknown etiology. Some common specific diagnoses and their clinical associations include:

  - **Funisitis** involving only the external/superficial surface of the cord and Wharton's jelly is most likely of maternal origin and strongly suggests candidal infection. Inflammatory cells seen migrating out through the fetal vessels in the cord are evidence of a fetal response and are diagnostic of systemic fetal inflammatory response syndrome(See 'Inflammation' above.)

  - **Acute/neutrophilic chorioamnionitis** is usually bacteria- or fungal-mediated and is the most common pathologic finding in placental examination. Chronic/mononuclear chorioamnionitis is characterized by a mononuclear cell infiltrate (ie, lymphocytes, histiocytes, and plasma cells) and often has a noninfectious etiology. (See 'Acute chorioamnionitis' above and 'Chorioamnionitis' above.)

  - **Meconium** may induce umbilical cord vascular necrosis, amniotic epithelial necrosis, myocyte necrosis, and a fetal inflammatory response. (See 'Meconium staining' above.)

  - **Neutrophilic and lympho-histiocytic ("acute" and "chronic") villitis** are inflammatory infiltrates involving the placental parenchyma, but are due to different etiologies. The specific diagnosis is based upon the nature and type of inflammatory infiltrate. Villitis of unknown etiology (VUE) is the most common chronic villitis and has a small recurrence risk. Villitis, when diffuse or present in a small placenta, can

be associated with fetal growth restriction and death. Focal chronic villitis is common and of no clinical significance. (See 'Villitis' above.)

- **Infarction –** Peripheral infarcts usually on the maternal side of the placenta at the margin are common at term and usually not clinically significant. Perinatal morbidity is associated with central infarcts of more than 5 percent of the placental mass or greater than 3 cm in diameter. Preterm placentas with infarcts are very rare and usually these placentas have other features of maternal vascular malperfusion. Infarcts are considered clinically severe (eg, associated with fetal growth restriction/stillbirths) if 20 percent or more of the placenta is affected (or less in a small placenta). (See 'Maternal vascular malperfusion' above.)

- **Severe diffuse villous edema** is a marker of acute fetal hypoxic insult. (See 'Acute versus chronic stress/insult' above.)

REFERENCES

1. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997; 121:449.
2. Gersell DJ. ASCP survey on placental examination. American Society of Clinical Pathologists. Am J Clin Pathol 1998; 109:127.
3. Spencer MK, Khong TY. Conformity to guidelines for pathologic examination of the placenta. Arch Pathol Lab Med 2003; 127:205.
4. Kraus FT. Perinatal pathology, the placenta, and litigation. Hum Pathol 2003; 34:517.
5. Polnaszek BE, Clark SL, Rouse DJ. Pathologic Assessment of the Placenta: Evidence Compared With Tradition. Obstet Gynecol 2022; 139:660.
6. Pinar H, Gordijn SJ, Grynspan D, et al. Pathologic Assessment of the Placenta: Evidence Compared With Tradition. Obstet Gynecol 2022; 140:341.
7. Redline RW, Roberts DJ, Parast MM, et al. Placental pathology is necessary to understand common pregnancy complications and achieve an improved taxonomy of obstetrical disease. Am J Obstet Gynecol 2023; 228:187.
8. Khong TY, Mooney EE, Ariel I, et al. Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. Arch Pathol Lab Med 2016; 140:698.
9. Roberts DJ, Polizzano C. Atlas of Placental Pathology, 2021. Vol 5.

10. Redline RW, Ravishankar S, Bagby CM, et al. Four major patterns of placental injury: a stepwise guide for understanding and implementing the 2016 Amsterdam consensus. Mod Pathol 2021; 34:1074.
11. Huynh J, Dawson D, Roberts D, Bentley-Lewis R. A systematic review of placental pathology in maternal diabetes mellitus. Placenta 2015; 36:101.
12. Higgins M, McAuliffe FM, Mooney EE. Clinical associations with a placental diagnosis of delayed villous maturation: a retrospective study. Pediatr Dev Pathol 2011; 14:273.
13. Rana S, Karumanchi SA, Levine RJ, et al. Sequential changes in antiangiogenic factors in early pregnancy and risk of developing preeclampsia. Hypertension 2007; 50:137.
14. Serra AE, Lemon LS, Mokhtari NB, et al. Delayed villous maturation in term placentas exposed to opioid maintenance therapy: a retrospective cohort study. Am J Obstet Gynecol 2017; 216:418.e1.
15. Al-Adnani M, Marnerides A, George S, et al. "Delayed Villous Maturation" in Placental Reporting: Concordance among Consultant Pediatric Pathologists at a Single Specialist Center. Pediatr Dev Pathol 2015; 18:375.
16. Hecht JL, Baergen R, Ernst LM, et al. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. Mod Pathol 2020; 33:2382.
17. Ernst LM, Minturn L, Huang MH, et al. Gross patterns of umbilical cord coiling: correlations with placental histology and stillbirth. Placenta 2013; 34:583.
18. Jessop FA, Lees CC, Pathak S, et al. Umbilical cord coiling: clinical outcomes in an unselected population and systematic review. Virchows Arch 2014; 464:105.
19. Patil NS, Kulkarni SR, Lohitashwa R. Umbilical cord coiling index and perinatal outcome. J Clin Diagn Res 2013; 7:1675.
20. Qureshi F, Jacques SM, Bendon RW, et al. Candida funisitis: A clinicopathologic study of 32 cases. Pediatr Dev Pathol 1998; 1:118.
21. Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2003; 6:435.
22. Redline RW. Placental pathology and cerebral palsy. Clin Perinatol 2006; 33:503.
23. Leviton A, Allred EN, Kuban KC, et al. Microbiologic and histologic characteristics of the extremely preterm infant's placenta predict white matter damage and later cerebral palsy. the ELGAN study. Pediatr Res 2010; 67:95.
24. Altshuler G, Arizawa M, Molnar-Nadasdy G. Meconium-induced umbilical cord vascular necrosis and ulceration: a potential link between the placenta and poor pregnancy outcome. Obstet Gynecol 1992; 79:760.

25. Altshuler G, Hyde S. Meconium-induced vasocontraction: a potential cause of cerebral and other fetal hypoperfusion and of poor pregnancy outcome. J Child Neurol 1989; 4:137.
26. Lewis SH, Gilbert-Barness E. The placenta and its significance in neonatal outcome. Adv Pediatr 1998; 45:223.
27. Naeye RL. Can meconium in the amniotic fluid injure the fetal brain? Obstet Gynecol 1995; 86:720.
28. Miller PW, Coen RW, Benirschke K. Dating the time interval from meconium passage to birth. Obstet Gynecol 1985; 66:459.
29. Kreczy A, Alge A, Menardi G, et al. Teratoma of the umbilical cord. Case report with review of the literature. Arch Pathol Lab Med 1994; 118:934.
30. Driscoll SG. Umbilical cord teratoma. Hum Pathol 1985; 16:1178.
31. Smith D, Majmudar B. Teratoma of the umbilical cord. Hum Pathol 1985; 16:190.
32. Ghidini A, Romero R, Eisen RN, et al. Umbilical cord hemangioma. Prenatal identification and review of the literature. J Ultrasound Med 1990; 9:297.
33. Kamitomo M, Sueyoshi K, Matsukita S, et al. Hemangioma of the umbilical cord: stenotic change of the umbilical vessels. Fetal Diagn Ther 1999; 14:328.
34. Søndergaard G. Hemangioma of the umbilical cord. Acta Obstet Gynecol Scand 1994; 73:434.
35. Carvounis EE, Dimmick JE, Wright VJ. Angiomyxoma of umbilical cord. Arch Pathol Lab Med 1978; 102:178.
36. Yavner DL, Redline RW. Angiomyxoma of the umbilical cord with massive cystic degeneration of Wharton's jelly. Arch Pathol Lab Med 1989; 113:935.
37. Lee MC, Aterman K. An intestinal polyp of the umbilical cord. Am J Dis Child 1968; 116:320.
38. Klaritsch P, Haeusler M, Karpf E, et al. Spontaneous intrauterine umbilical artery thrombosis leading to severe fetal growth restriction. Placenta 2008; 29:374.
39. Solano Sánchez SR, Baquera Heredia JJ, Reyes Cuervo H, Buen Abad EI. [Umbilical artery thrombosis. A report of a case and review of the literature]. Ginecol Obstet Mex 2005; 73:332.
40. Sato Y, Benirschke K. Umbilical arterial thrombosis with vascular wall necrosis: clinicopathologic findings of 11 cases. Placenta 2006; 27:715.
41. Afriat R, Bidat L, Fortier F, et al. [Prenatal diagnosis of spontaneous thrombosis of the umbilical artery during the third trimester of pregnancy. Two cases with surviving infants]. J Gynecol Obstet Biol Reprod (Paris) 1995; 24:411.

42. Heifetz SA. Thrombosis of the umbilical cord: analysis of 52 cases and literature review. Pediatr Pathol 1988; 8:37.
43. Ariel I, Anteby E, Hamani Y, Redline RW. Placental pathology in fetal thrombophilia. Hum Pathol 2004; 35:729.
44. Jauniaux E, De Munter C, Vanesse M, et al. Embryonic remnants of the umbilical cord: morphologic and clinical aspects. Hum Pathol 1989; 20:458.
45. Wigglesworth JS, Singer DB. Textbook of fetal and perinatal pathology, 2nd ed, Wigglesworth JS, Singer DB (Eds), Blackwell Science, 1998.
46. Newton ER. Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol 1993; 36:795.
47. Quinn PA, Butany J, Taylor J, Hannah W. Chorioamnionitis: its association with pregnancy outcome and microbial infection. Am J Obstet Gynecol 1987; 156:379.
48. Zhang JM, Kraus FT, Aquino TI. Chorioamnionitis: a comparative histologic, bacteriologic, and clinical study. Int J Gynecol Pathol 1985; 4:1.
49. Roberts DJ, Polizzano C. Atlas of Placental Pathology. American Registry of Pathology Press, expected 2021.
50. Gersell DJ. Chronic villitis, chronic chorioamnionitis, and maternal floor infarction. Semin Diagn Pathol 1993; 10:251.
51. Jacques SM, Qureshi F. Chronic chorioamnionitis: a clinicopathologic and immunohistochemical study. Hum Pathol 1998; 29:1457.
52. Mazor M, Furman B, Wiznitzer A, et al. Maternal and perinatal outcome of patients with preterm labor and meconium-stained amniotic fluid. Obstet Gynecol 1995; 86:830.
53. Grossman TB, Heller DS, Baergen RN. Isolated acute funisitis in the absence of acute chorioamnionitis: What does it mean? Placenta 2019; 75:42.
54. Altshuler G, Hyde SR. Clinicopathologic implications of placental pathology. Clin Obstet Gynecol 1996; 39:549.
55. Altshuler G. Role of the placenta in perinatal pathology (revisited). Pediatr Pathol Lab Med 1996; 16:207.
56. Mayer DC, Chescheir NC, Spielman FJ. Increased intrapartum antibiotic administration associated with epidural analgesia in labor. Am J Perinatol 1997; 14:83.
57. Simon C, Schröder H, Weisner D, et al. Bacteriological findings after premature rupture of the membranes. Arch Gynecol Obstet 1989; 244:69.
58. Stevens NG, Sander CH. Placental hemorrhagic endovasculitis: risk factors and impact on pregnancy outcome. Int J Gynaecol Obstet 1984; 22:393.
59. Ohyama M, Itani Y, Yamanaka M, et al. Maternal, neonatal, and placental features associated with diffuse chorioamniotic hemosiderosis, with special reference to

neonatal morbidity and mortality. Pediatrics 2004; 113:800.

60. Redline RW, Wilson-Costello D. Chronic peripheral separation of placenta. The significance of diffuse chorioamnionic hemosiderosis. Am J Clin Pathol 1999; 111:804.
61. Roescher AM, Timmer A, Erwich JJ, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: a systematic review. PLoS One 2014; 9:e89419.
62. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. Arch Pathol Lab Med 2000; 124:1785.
63. Brown DL, DiSalvo DN, Frates MC, et al. Placental surface cysts detected on sonography: histologic and clinical correlation. J Ultrasound Med 2002; 21:641.
64. Boulis TS, Rochelson BL, Williamson AK. Massive Subchorionic Placental Cyst and Poor Fetal Growth: A Case Report. J Reprod Med 2015; 60:458.
65. Alanjari A, Wright E, Keating S, et al. Prenatal diagnosis, clinical outcomes, and associated pathology in pregnancies complicated by massive subchorionic thrombohematoma (Breus' mole). Prenat Diagn 2013; 33:973.
66. Benirschke K, Kaufman P, Baergen RN. The pathology of the human placenta, Springer-Verlag, New York 2006.
67. Grafe MR, Benirschke K. Ultrastructural study of the amniotic epithelium in a case of gastroschisis. Pediatr Pathol 1990; 10:95.
68. Pawoo N, Heller DS. Placental mesenchymal dysplasia. Arch Pathol Lab Med 2014; 138:1247.
69. Boog G. Chronic villitis of unknown etiology. Eur J Obstet Gynecol Reprod Biol 2008; 136:9.
70. Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. Hum Pathol 2007; 38:1439.
71. Harteman JC, Nikkels PG, Benders MJ, et al. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. J Pediatr 2013; 163:968.
72. Nowak C, Joubert M, Jossic F, et al. Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillositis of unknown etiology and combined lesions: About a series of 178 cases. Placenta 2016; 44:104.
73. Althsuler G. Placental villitis of unknown etiology: harbinger of serious disease? A four month's experience of nine cases. J Reprod Med 1973; 11:215.
74. Redline RW, Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. Am J Pathol 1993; 143:473.
75. Labarrere C, Althabe O. Chronic villitis of unknown aetiology in recurrent intrauterine fetal growth retardation. Placenta 1987; 8:167.

76. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin: epidemiologic associations. Am J Obstet Gynecol 2005; 192:264.
77. Heyborne KD, McGregor JA, Henry G, et al. Interleukin-10 in amniotic fluid at midtrimester: immune activation and suppression in relation to fetal growth. Am J Obstet Gynecol 1994; 171:55.
78. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. Am J Obstet Gynecol 2005; 192:452.
79. Althaus J, Weir EG, Askin F, et al. Chronic villitis in untreated neonatal alloimmune thrombocytopenia: an etiology for severe early intrauterine growth restriction and the effect of intravenous immunoglobulin therapy. Am J Obstet Gynecol 2005; 193:1100.
80. Russell P, Atkinson K, Krishnan L. Recurrent reproductive failure due to severe placental villitis of unknown etiology. J Reprod Med 1980; 24:93.
81. Chen A, Roberts DJ. Placental pathologic lesions with a significant recurrence risk - what not to miss! APMIS 2018; 126:589.
82. Nakamura Y, Sakuma S, Ohta Y, et al. Detection of the human cytomegalovirus gene in placental chronic villitis by polymerase chain reaction. Hum Pathol 1994; 25:815.
83. Popek EJ. Granulomatous villitis due to Toxoplasma gondii. Pediatr Pathol 1992; 12:281.
84. Redline RW. Recurrent villitis of bacterial etiology. Pediatr Pathol Lab Med 1996; 16:995.
85. Altshuler G. Chorangiosis. An important placental sign of neonatal morbidity and mortality. Arch Pathol Lab Med 1984; 108:71.
86. Ogino S, Redline RW. Villous capillary lesions of the placenta: distinctions between chorangioma, chorangiomatosis, and chorangiosis. Hum Pathol 2000; 31:945.
87. Bentley-Lewis R, Dawson DL, Wenger JB, et al. Placental histomorphometry in gestational diabetes mellitus: the relationship between subsequent type 2 diabetes mellitus and race/ethnicity. Am J Clin Pathol 2014; 141:587.
88. Gupta R, Nigam S, Arora P, et al. Clinico-pathological profile of 12 cases of chorangiosis. Arch Gynecol Obstet 2006; 274:50.
89. Benirschke K. Recent trends in chorangiomas, especially those of multiple and recurrent chorangiomas. Pediatr Dev Pathol 1999; 2:264.
90. Benirschke K. Placenta pathology questions to the perinatologist. J Perinatol 1994; 14:371.
91. Benirschke K. Obstetrically important lesions of the umbilical cord. J Reprod Med 1994; 39:262.
92. Katzman PJ, Genest DR. Maternal floor infarction and massive perivillous fibrin deposition: histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. Pediatr Dev Pathol 2002; 5:159.

93. Faye-Petersen OM, Ernst LM. Maternal Floor Infarction and Massive Perivillous Fibrin Deposition. Surg Pathol Clin 2013; 6:101.
94. Adams-Chapman I, Vaucher YE, Bejar RF, et al. Maternal floor infarction of the placenta: association with central nervous system injury and adverse neurodevelopmental outcome. J Perinatol 2002; 22:236.
95. Devisme L, Chauvière C, Franquet-Ansart H, et al. Perinatal outcome of placental massive perivillous fibrin deposition: a case-control study. Prenat Diagn 2017; 37:323.
96. Bendon RW, Hommel AB. Maternal floor infarction in autoimmune disease: two cases. Pediatr Pathol Lab Med 1996; 16:293.
97. Mandsager NT, Bendon R, Mostello D, et al. Maternal floor infarction of the placenta: prenatal diagnosis and clinical significance. Obstet Gynecol 1994; 83:750.
98. Nickel RE. Maternal floor infarction: an unusual cause of intrauterine growth retardation. Am J Dis Child 1988; 142:1270.
99. Naeye RL. Maternal floor infarction. Hum Pathol 1985; 16:823.
100. Clewell WH, Manchester DK. Recurrent maternal floor infarction: a preventable cause of fetal death. Am J Obstet Gynecol 1983; 147:346.
101. Yu W, Tellier R, Wright JR Jr. Coxsackie Virus A16 Infection of Placenta with Massive Perivillous Fibrin Deposition Leading to Intrauterine Fetal Demise at 36 Weeks Gestation. Pediatr Dev Pathol 2015; 18:331.
102. Heller DS, Tellier R, Pabbaraju K, et al. Placental Massive Perivillous Fibrinoid Deposition Associated with Coxsackievirus A16-Report of a Case, and Review of the Literature. Pediatr Dev Pathol 2016; 19:421.
103. Sebire NJ, Backos M, Goldin RD, Regan L. Placental massive perivillous fibrin deposition associated with antiphospholipid antibody syndrome. BJOG 2002; 109:570.
104. Doss BJ, Greene MF, Hill J, et al. Massive chronic intervillositis associated with recurrent abortions. Hum Pathol 1995; 26:1245.
105. Jacques SM, Qureshi F. Chronic intervillositis of the placenta. Arch Pathol Lab Med 1993; 117:1032.
106. Fuke Y, Aono T, Imai S, et al. Clinical significance and treatment of massive intervillous fibrin deposition associated with recurrent fetal growth retardation. Gynecol Obstet Invest 1994; 38:5.
107. Ordi J, Ismail MR, Ventura PJ, et al. Massive chronic intervillositis of the placenta associated with malaria infection. Am J Surg Pathol 1998; 22:1006.
108. Martines RB, Bhatnagar J, de Oliveira Ramos AM, et al. Pathology of congenital Zika syndrome in Brazil: a case series. Lancet 2016; 388:898.

109. Martines RB, Bhatnagar J, Keating MK, et al. Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses--Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016; 65:159.

110. Ribeiro CF, Silami VG, Brasil P, Nogueira RM. Sickle-cell erythrocytes in the placentas of dengue-infected women. Int J Infect Dis 2012; 16:e72.

111. Hyde SR, Benirschke K. Gestational psittacosis: case report and literature review. Mod Pathol 1997; 10:602.

112. Schwartz DA, Morotti D. Placental Pathology of COVID-19 with and without Fetal and Neonatal Infection: Trophoblast Necrosis and Chronic Histiocytic Intervillositis as Risk Factors for Transplacental Transmission of SARS-CoV-2. Viruses 2020; 12.

113. Watkins JC, Torous VF, Roberts DJ. Defining Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Placentitis. Arch Pathol Lab Med 2021; 145:1341.

114. Schwartz DA, Avvad-Portari E, Babál P, et al. Placental Tissue Destruction and Insufficiency From COVID-19 Causes Stillbirth and Neonatal Death From Hypoxic-Ischemic Injury. Arch Pathol Lab Med 2022; 146:660.

115. Shanes ED, Mithal LB, Otero S, et al. Placental Pathology in COVID-19. Am J Clin Pathol 2020; 154:23.

116. Glynn SM, Yang YJ, Thomas C, et al. SARS-CoV-2 and Placental Pathology: Malperfusion Patterns Are Dependent on Timing of Infection During Pregnancy. Am J Surg Pathol 2022; 46:51.

117. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004; 7:237.

118. Kulkarni VG, Sunilkumar KB, Nagaraj TS, et al. Maternal and fetal vascular lesions of malperfusion in the placentas associated with fetal and neonatal death: results of a prospective observational study. Am J Obstet Gynecol 2021; 225:660.e1.

119. Cetin I, Foidart JM, Miozzo M, et al. Fetal growth restriction: a workshop report. Placenta 2004; 25:753.

120. Chaddha V, Viero S, Huppertz B, Kingdom J. Developmental biology of the placenta and the origins of placental insufficiency. Semin Fetal Neonatal Med 2004; 9:357.

121. Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. Eur J Obstet Gynecol Reprod Biol 2000; 92:35.

122. Fox H. Pathology of the placenta. Clin Obstet Gynaecol 1986; 13:501.

123. Rayburn W, Sander C, Compton A. Histologic examination of the placenta in the growth-retarded fetus. Am J Perinatol 1989; 6:58.

124. Rodriguez JG, Porter HJ, Andrews HS, Soothill PW. Placental lesions: is growth a predictor of bad outcome? Fetal Diagn Ther 1997; 12:163.

125. Salafia CM, Minior VK, Pezzullo JC, et al. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. Am J Obstet Gynecol 1995; 173:1049.

126. Fox H. The pathology of the placenta, 2nd ed, WB Saunders Co, Philadelphia 1997.

127. Naeye RL. Placental infarction leading to fetal or neonatal death. A prospective study. Obstet Gynecol 1977; 50:583.

128. Tettey Y, Wiredu EK. Autopsy studies on still births in Korle Bu Teaching Hospital: pathological findings in still births and their placentae. West Afr J Med 1997; 16:12.

129. Corrêa RR, Gilio DB, Cavellani CL, et al. Placental morphometrical and histopathology changes in the different clinical presentations of hypertensive syndromes in pregnancy. Arch Gynecol Obstet 2008; 277:201.

130. Vinnars MT, Wijnaendts LC, Westgren M, et al. Severe preeclampsia with and without HELLP differ with regard to placental pathology. Hypertension 2008; 51:1295.

131. Zhang P, Schmidt M, Cook L. Maternal vasculopathy and histologic diagnosis of preeclampsia: poor correlation of histologic changes and clinical manifestation. Am J Obstet Gynecol 2006; 194:1050.

132. Ernst LM, Parkash V. Placental pathology in fetal bartter syndrome. Pediatr Dev Pathol 2002; 5:76.

133. Maruyama H, Shinno Y, Fujiwara K, et al. Nephrocalcinosis and placental findings in neonatal bartter syndrome. AJP Rep 2013; 3:21.

134. Schwartz DA. Viral infection, proliferation, and hyperplasia of Hofbauer cells and absence of inflammation characterize the placental pathology of fetuses with congenital Zika virus infection. Arch Gynecol Obstet 2017; 295:1361.

135. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol 1995; 26:80.

136. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS 2018; 126:561.

137. Rayne SC, Kraus FT. Placental thrombi and other vascular lesions. Classification, morphology, and clinical correlations. Pathol Res Pract 1993; 189:2.

138. Redline RW, Wilson-Costello D, Borawski E, et al. Placental lesions associated with neurologic impairment and cerebral palsy in very low-birth-weight infants. Arch Pathol Lab Med 1998; 122:1091.

139. Sander CM, Gilliland D, Flynn MA, Swart-Hills LA. Risk factors for recurrence of hemorrhagic endovasculitis of the placenta. Obstet Gynecol 1997; 89:569.

140. Sander CH, Stevens NG. Hemorrhagic endovasculitis of the placenta: an indepth morphologic appraisal with initial clinical and epidemiologic observations. Pathol Annu 1984; 19 Pt 1:37.
141. Sander CH, Kinnane L, Stevens NG. Hemorrhagic endovasculitis of the placenta: a clinicopathologic entity associated with adverse pregnancy outcome. Compr Ther 1985; 11:66.
142. Sander CH, Kinnane L, Stevens NG, Echt R. Haemorrhagic endovasculitis of the placenta: a review with clinical correlation. Placenta 1986; 7:551.
143. Vern TZ, Alles AJ, Kowal-Vern A, et al. Frequency of factor V(Leiden) and prothrombin G20210A in placentas and their relationship with placental lesions. Hum Pathol 2000; 31:1036.
144. Kraus FT. Placental thrombi and related problems. Semin Diagn Pathol 1993; 10:275.
145. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Hum Pathol 1999; 30:759.
146. Iwasenko JM, Howard J, Arbuckle S, et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. J Infect Dis 2011; 203:1526.
147. Sander CM, Gilliland D, Akers C, et al. Livebirths with placental hemorrhagic endovasculitis: interlesional relationships and perinatal outcomes. Arch Pathol Lab Med 2002; 126:157.
148. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004; 7:443.
149. Batcup G, Tovey LA, Longster G. Fetomaternal blood group incompatibility studies in placental intervillous thrombosis. Placenta 1983; 4 Spec No:449.
150. Kaplan C, Blanc WA, Elias J. Identification of erythrocytes in intervillous thrombi: a study using immunoperoxidase identification of hemoglobins. Hum Pathol 1982; 13:554.
151. Hoogland HJ, de Haan J, Vooys GP. Ultrasonographic diagnosis of intervillous thrombosis related to Rh isoimmunization. Gynecol Obstet Invest 1979; 10:237.
152. Rolschau J. Infarctions and intervillous thrombosis in placenta, and their association with intrauterine growth retardation. Acta Obstet Gynecol Scand Suppl 1978; 72:22.
153. Basnet KM, Bentley-Lewis R, Wexler DJ, et al. Prevalence of Intervillous Thrombi Is Increased in Placentas from Pregnancies Complicated by Diabetes. Pediatr Dev Pathol 2016; 19:502.
154. Biankin SA, Arbuckle SM, Graf NS. Autopsy findings in a series of five cases of fetomaternal haemorrhages. Pathology 2003; 35:319.

155. Khalifa MA, Gersell DJ, Hansen CH, Lage JM. Hepatic (hepatocellular) adenoma of the placenta: a study of four cases. Int J Gynecol Pathol 1998; 17:241.

156. Soma H, Watanabe Y, Hata T. Chorangiosis and chorangioma in three cohorts of placentas from Nepal, Tibet, and Japan. Reprod Fertil Dev 1995; 7:1533.

157. Takayama M, Soma H, Yaguchi S, et al. Abnormally large placenta associated with Beckwith-Wiedemann syndrome. Gynecol Obstet Invest 1986; 22:165.

158. Chen CP, Chern SR, Wang TY, et al. Pregnancy with concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia. Hum Reprod 1997; 12:2553.

159. Sabhikhi AK, Chaudhury MC, Singh D, Raja LN. Chorangioma of the placenta with hydrops fetalis. Indian Pediatr 1996; 33:520.

160. Majlessi HF, Wagner KM, Brooks JJ. Atypical cellular chorangioma of the placenta. Int J Gynecol Pathol 1983; 1:403.

161. Kohler HG, Iqbal N, Jenkins DM. Chorionic haemangiomata and abruptio placentae. Case report and review. Br J Obstet Gynaecol 1976; 83:667.

162. Jones CE, Rivers RP, Taghizadeh A. Disseminated intravascular coagulation and fetal hydrops in a newborn infant in association with a chorangioma of placenta. Pediatrics 1972; 50:901.

163. Kim CK, Benirschke K, Connolly KS. Chorangioma of the placenta. Chromosomal and electron microscopic studies. Obstet Gynecol 1971; 37:372.

164. Sepulveda W, Alcalde JL, Schnapp C, Bravo M. Perinatal outcome after prenatal diagnosis of placental chorioangioma. Obstet Gynecol 2003; 102:1028.

165. Elagöz S, Aker H, Cetin A. Placental teratoma. A case report. Eur J Obstet Gynecol Reprod Biol 1998; 80:263.

166. Shimojo H, Itoh N, Shigematsu H, Yamazaki T. Mature teratoma of the placenta. Pathol Int 1996; 46:372.

167. Koumantakis E, Makrigiannakis A, Froudarakis G, et al. Teratoma of the placenta. A case report. Clin Exp Obstet Gynecol 1996; 23:268.

168. Wang L, Du X, Li M. Placental teratoma. A case report and review of the literature. Pathol Res Pract 1995; 191:1267.

169. Jaswal TS, Sen R, Singh S, et al. Teratoma of the placenta. J Indian Med Assoc 1995; 93:362, 345.

170. Buca D, Iacovella C, Khalil A, et al. Perinatal outcome of pregnancies complicated by placental chorioangioma: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2020; 55:441.

171. Khong TY. Chorangioma with trophoblastic proliferation. Virchows Arch 2000; 436:167.

172. Zanardini C, Papageorghiou A, Bhide A, Thilaganathan B. Giant placental chorioangioma: natural history and pregnancy outcome. Ultrasound Obstet Gynecol 2010; 35:332.
173. Eltorky M, Khare VK, Osborne P, Shanklin DR. Placental metastasis from maternal carcinoma. A report of three cases. J Reprod Med 1995; 40:399.
174. Baergen RN, Johnson D, Moore T, Benirschke K. Maternal melanoma metastatic to the placenta: a case report and review of the literature. Arch Pathol Lab Med 1997; 121:508.
175. Wang T, Hamann W, Hartge R. Structural aspects of a placenta from a case of maternal acute lymphatic leukaemia. Placenta 1983; 4:185.
176. Russell P, Laverty CR. Malignant melanoma metastases in the placenta: a case report. Pathology 1977; 9:251.
177. Sokol RJ, Hutchison P, Cowan D, Reed GB. Amelanotic melanoma metastatic to the placenta. Am J Obstet Gynecol 1976; 124:431.
178. Potter JF, Schoeneman M. Metastasis of maternal cancer to the placenta and fetus. Cancer 1970; 25:380.
179. Tsukamoto N, Kashimura Y, Sano M, et al. Choriocarcinoma occurring within the normal placenta with breast metastasis. Gynecol Oncol 1981; 11:348.
180. Choriocarcinoma of the placenta. By the OSMA Committee on Maternal Health. Ohio State Med J 1975; 71:144.
181. Alexander A, Samlowski WE, Grossman D, et al. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. J Clin Oncol 2003; 21:2179.
182. Altman JF, Lowe L, Redman B, et al. Placental metastasis of maternal melanoma. J Am Acad Dermatol 2003; 49:1150.
183. Pavlidis N. Lung cancer during pregnancy: an emerging issue. Lung Cancer 2008; 59:279.
184. Sebire NJ, Jauniaux E. Fetal and placental malignancies: prenatal diagnosis and management. Ultrasound Obstet Gynecol 2009; 33:235.
185. Anders D, Kindermann G, Pfeifer U. Metastasizing fetal neuroblastoma with involvement of the placenta simulating fetal erythroblastosis. Report of two cases. J Pediatr 1973; 82:50.
186. Sotelo-Avila C, Graham M, Hanby DE, Rudolph AJ. Nevus cell aggregates in the placenta. A histochemical and electron microscopic study. Am J Clin Pathol 1988; 89:395.
187. Lage JM, Roberts DJ. Choriocarcinoma in a term placenta: pathologic diagnosis of tumor in an asymptomatic patient with metastatic disease. Int J Gynecol Pathol 1993; 12:80.
188. Roberts DJ, Mutter GL. Advances in the molecular biology of gestational trophoblastic disease. J Reprod Med 1994; 39:201.

189. Mosher R, Genest DR. Primary intraplacental choriocarcinoma: Clinical and pathologic features of seven cases (1967-1996) and discussion of the differential. Journal of Surgical Pathology 1997; 2:83.

190. Makhdoum S, Nardi V, Devereaux KA, et al. Inflammatory myofibroblastic tumors associated with the placenta: a series of 9 cases. Hum Pathol 2020; 106:62.

191. Fox H. Pathology of the Placenta. In: Major Problems in Pathology, 2nd ed, WB Saunders Co, London 1997. p.488.

192. Benirschke K, Kaufman P. The pathology of the human placenta, 3rd ed, Springer-Verlag, New York 1995.

193. Khong TY. From delivery suite to laboratory: optimizing returns from placental examination in medico-legal defence. Aust N Z J Obstet Gynaecol 1997; 37:1.

194. Altshuler G. Placenta within the medicolegal imperative. Arch Pathol Lab Med 1991; 115:688.

195. Benirschke K. The placenta in the litigation process. Am J Obstet Gynecol 1990; 162:1445.

196. Khong TY. Acute atherosis in pregnancies complicated by hypertension, small-for-gestational-age infants, and diabetes mellitus. Arch Pathol Lab Med 1991; 115:722.

197. Pijnenborg R, Anthony J, Davey DA, et al. Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol 1991; 98:648.

198. Khong TY, Pearce JM, Robertson WB. Acute atherosis in preeclampsia: maternal determinants and fetal outcome in the presence of the lesion. Am J Obstet Gynecol 1987; 157:360.

199. Davies BR. Decidual vascular lesions of fibrinoid necrosis/atherosis. Am J Obstet Gynecol 1982; 144:118.

200. Soma H, Yoshida K, Mukaida T, Tabuchi Y. Morphologic changes in the hypertensive placenta. Contrib Gynecol Obstet 1982; 9:58.

201. Robertson WB, Brosens I, Dixon G. Maternal uterine vascular lesions in the hypertensive complications of pregnancy. Perspect Nephrol Hypertens 1976; 5:115.

202. Ernst LM. Maternal vascular malperfusion of the placental bed. APMIS 2018; 126:551.

203. Fillion A, Guerby P, Menzies D, et al. Pathological investigation of placentas in preeclampsia (the PEARL study). Hypertens Pregnancy 2021; 40:56.

204. Salafia CM, Vintzileos AM, Silberman L, et al. Placental pathology of idiopathic intrauterine growth retardation at term. Am J Perinatol 1992; 9:179.

205. Todros T, Sciarrone A, Piccoli E, et al. Umbilical Doppler waveforms and placental villous angiogenesis in pregnancies complicated by fetal growth restriction. Obstet Gynecol 1999; 93:499.

206. Krebs C, Macara LM, Leiser R, et al. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. Am J Obstet Gynecol 1996; 175:1534.

207. Anderson GM, Jacobs-Stannard A, Chawarska K, et al. Placental trophoblast inclusions in autism spectrum disorder. Biol Psychiatry 2007; 61:487.

208. Goldenberg RL, Andrews WW, Faye-Petersen O, et al. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol 2006; 195:792.

209. Baldwin V. Pathology of Multiple Gestation, Springer-Verlag, New York 1994.

210. Souter VL, Kapur RP, Nyholt DR, et al. A report of dizygous monochorionic twins. N Engl J Med 2003; 349:154.

211. Yoon G, Beischel LS, Johnson JP, Jones MC. Dizygotic twin pregnancy conceived with assisted reproductive technology associated with chromosomal anomaly, imprinting disorder, and monochorionic placentation. J Pediatr 2005; 146:565.

212. Chen AL, Goldfarb IT, Scourtas AO, Roberts DJ. The histologic evolution of revealed, acute abruptions. Hum Pathol 2017; 67:187.

213. Roberts DJ, Ampola MG, Lage JM. Diagnosis of unsuspected fetal metabolic storage disease by routine placental examination. Pediatr Pathol 1991; 11:647.

214. Hillier SL, Krohn MA, Kiviat NB, et al. Microbiologic causes and neonatal outcomes associated with chorioamnion infection. Am J Obstet Gynecol 1991; 165:955.

215. Beebe LA, Cowan LD, Altshuler G. The epidemiology of placental features: associations with gestational age and neonatal outcome. Obstet Gynecol 1996; 87:771.

216. Williams MC, O'Brien WF, Nelson RN, Spellacy WN. Histologic chorioamnionitis is associated with fetal growth restriction in term and preterm infants. Am J Obstet Gynecol 2000; 183:1094.

217. Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. Am J Obstet Gynecol 2004; 190:147.

218. Holzman C, Lin X, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. Am J Epidemiol 2007; 166:786.

219. Hillier SL, Martius J, Krohn M, et al. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med 1988; 319:972.

220. Aaltonen R, Heikkinen T, Hakala K, et al. Transfer of proinflammatory cytokines across term placenta. Obstet Gynecol 2005; 106:802.

221. Baergen R, Benirschke K, Ulich TR. Cytokine expression in the placenta. The role of interleukin 1 and interleukin 1 receptor antagonist expression in chorioamnionitis and parturition. Arch Pathol Lab Med 1994; 118:52.

222. Hagberg H, Wennerholm UB, Sävman K. Sequelae of chorioamnionitis. Curr Opin Infect Dis 2002; 15:301.

223. Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev 2007; 65:S194.

224. Dong Y, St Clair PJ, Ramzy I, et al. A microbiologic and clinical study of placental inflammation at term. Obstet Gynecol 1987; 70:175.

225. Smulian JC, Shen-Schwarz S, Vintzileos AM, et al. Clinical chorioamnionitis and histologic placental inflammation. Obstet Gynecol 1999; 94:1000.

226. Mikamo H, Kawazoe K, Sato Y, et al. Preterm labor and bacterial intraamniotic infection: arachidonic acid liberation by phospholipase A2 of Fusobacterium nucleatum. Am J Obstet Gynecol 1998; 179:1579.

227. Hill GB. Preterm birth: associations with genital and possibly oral microflora. Ann Periodontol 1998; 3:222.

228. Kikhney J, von Schöning D, Steding I, et al. Is Ureaplasma spp. the leading causative agent of acute chorioamnionitis in women with preterm birth? Clin Microbiol Infect 2017; 23:119.e1.

229. Romero R, Nores J, Mazor M, et al. Microbial invasion of the amniotic cavity during term labor. Prevalence and clinical significance. J Reprod Med 1993; 38:543.

230. Novak RW, Platt MS. Significance of placental findings in early-onset group B streptococcal neonatal sepsis. Clin Pediatr (Phila) 1985; 24:256.

231. Udagawa H, Oshio Y, Shimizu Y. Serious group A streptococcal infection around delivery. Obstet Gynecol 1999; 94:153.

Topic 2282 Version 51.0

GRAPHICS

Potential indications for examination of second and third trimester placentas

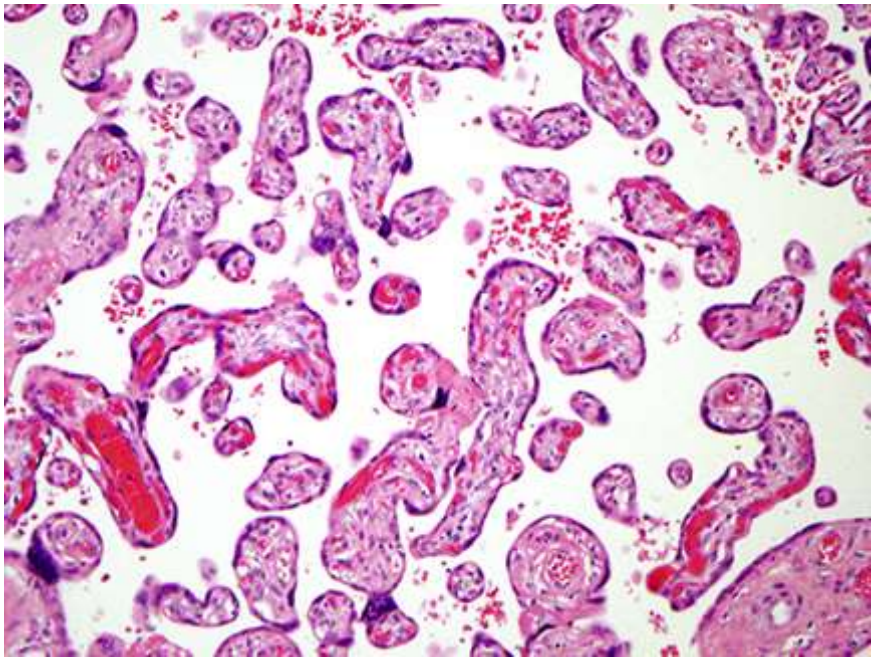
Maternal medical conditions with potential fetal effects
Preterm or postterm birth
Peripartum fever or infection
Third trimester bleeding or postpartum hemorrhage
Severe oligohydramnios or polyhydramnios
Invasive procedures with suspected placental injury
In utero fetal therapy
Placenta previa or abruptio placentae
Thick meconium
History of substance abuse or exposure to toxins
Maternal trauma during pregnancy
Prolonged premature rupture of membranes
Stillbirth or neonatal death
Maternal death
Depressed neonate
Hydrops fetalis
Neonatal seizures
Multiple gestation (including vanishing twin)
Small or large for gestational age neonates
Congenital anomaly
Umbilical cord abnormality
Placental abnormality
Neonatal hematologic abnormalities

Pathologic examination of the placenta can be omitted with normal delivery (vaginal or cesarean) of a healthy term infant from an uncomplicated pregnancy.

Data from: Langston C. Practice guideline for examination of the placenta. Archives of Pathology & Laboratory Medicine 1997; 121:449. Khong, TY. From delivery suite to laboratory: optimizing returns from placental examination in medico-legal defense. Aust N Z J Obstet Gynaecol 1997; 37:1. Kaplan, C, Lowell, DM, Salafia, C. College of American Pathologists Conference XIX on the Examination of the Placenta: report of the Working Group on the Definition of Structural Changes Associated with Abnormal Function in the Maternal/Fetal/Placental Unit in the Second and Third Trimesters. Arch Pathol Lab Med 1991; 115:709.

Graphic 71399 Version 2.0

Term placenta

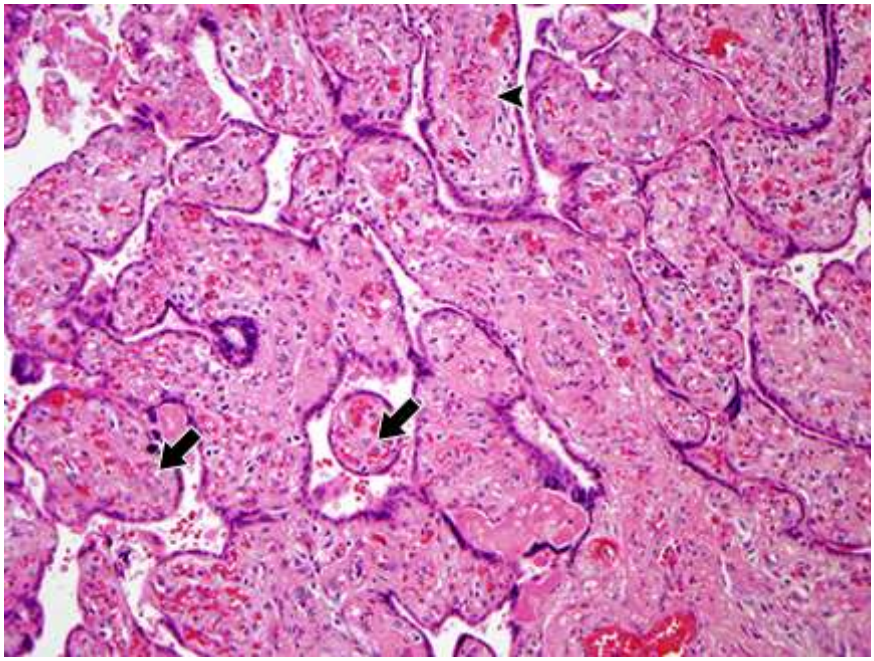


Normal term placenta showing a spectrum of villous sizes with terminal villi predominating.

Courtesy of Drucilla J Roberts, MD.

Graphic 62758 Version 1.0

Villous maturational arrest



A term placenta from a recently delivered fetal demise showing large villi without vasculosyncytial membranes (arrows), hemorrhagic endovasculitis (arrowhead) and a paucity of small villi, syncytiotrophoblastic knots, and vasculosyncytial membranes.

Courtesy of Drucilla J Roberts, MD.

Graphic 72450 Version 3.0

Placental weight standards

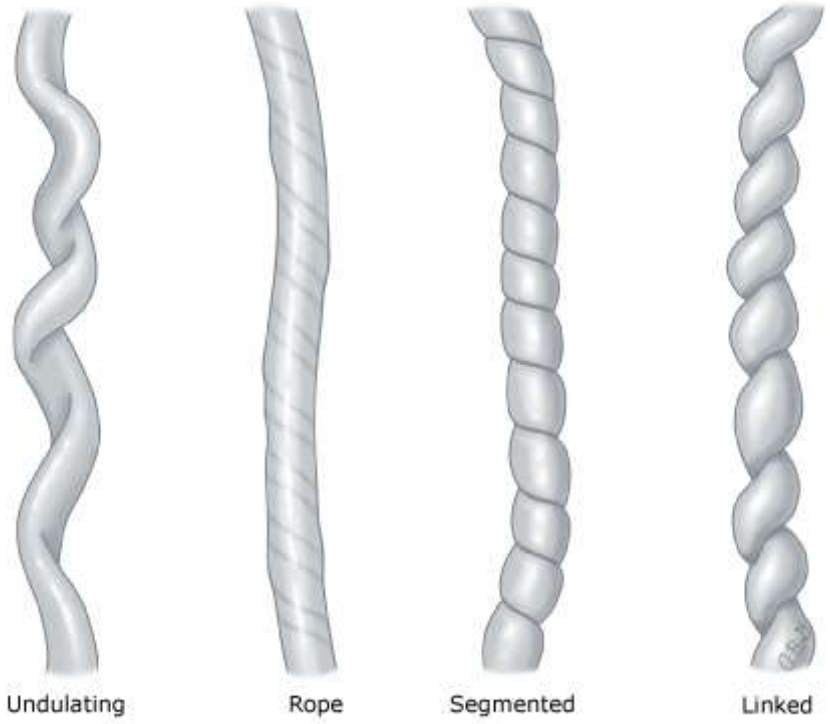
Gestational age	Singleton					Twin				
	Percentiles					Percentiles				
	10	25	50	75	90	10	25	50	75	90
12			56							
14			83							
16			110							
18			137.8							
20			145			166	190	218	245	270
22	122	138	157	176	191	191	219	251	282	310
24	145	166	189	212	233	232	267	307	346	382
26	175	200	227	255	280	284	330	380	430	475
28	210	238	270	302	331	345	401	464	527	584

30	249	281	316	352	384	409	478	554	631	700
32	290	325	364	403	438	472	554	644	734	815
34	331	369	411	453	491	531	624	727	830	923
36	372	412	457	501	542	582	684	798	912	1014
38	409	452	499	547	589	619	728	850	972	1082
40	442	487	537	587	632	638	753	879	1005	1118

Data from: Pinar H, Sung J, Oyer CE, Singer DB. Reference values for singleton and twin placental weights. Pediatr Pathol Lab Med 1996; 16:901.

Graphic 72177 Version 2.0

Umbilical cord coiling patterns

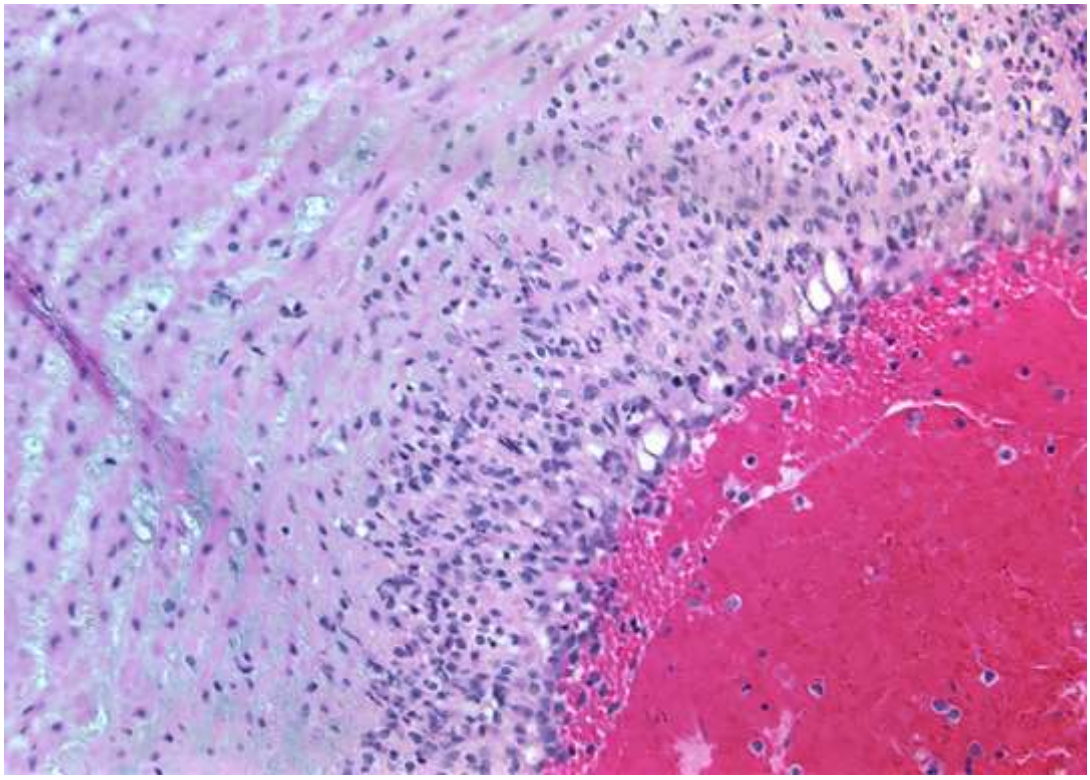


Schematic representation of the four gross umbilical cord coiling patterns.

Modified from: Ernst LM, Minturn L, Huang MH, et al. Gross patterns of umbilical cord coiling: correlations with placental histology and stillbirth. Placenta 2013; 34:583.

Graphic 93966 Version 2.0

Funisitis

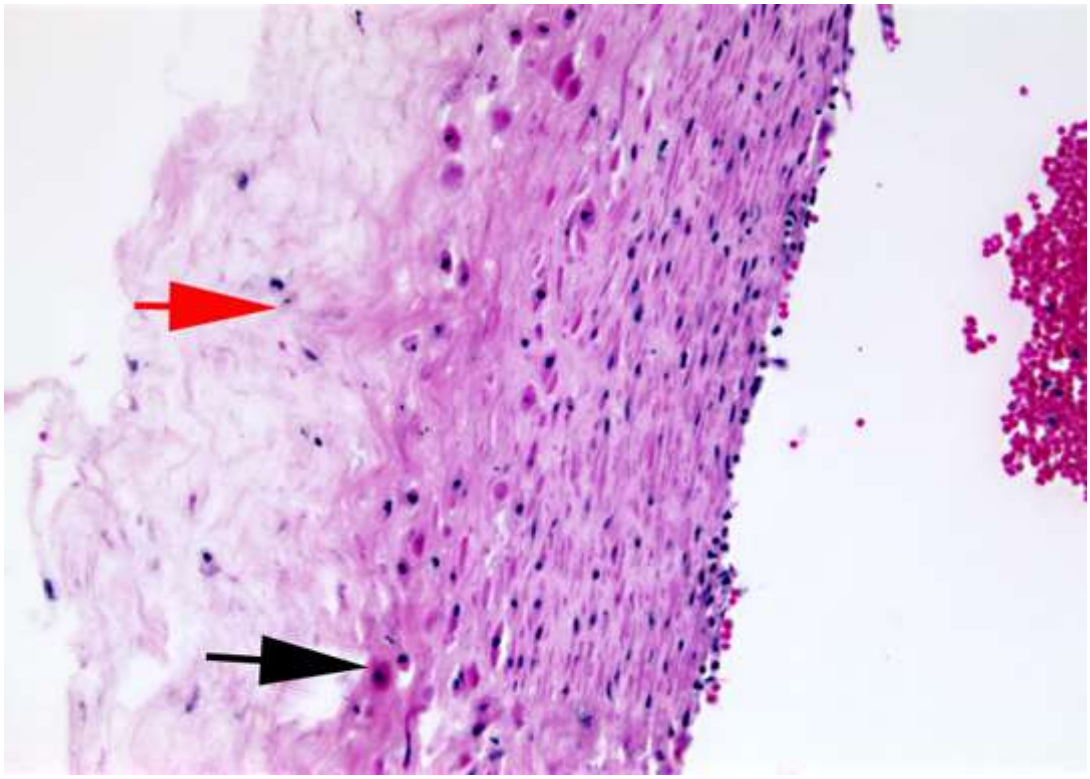


High power photomicrograph of an umbilical vein with migration of fetal inflammatory cells into the inner third of vein wall.

Courtesy of Drucilla J Roberts, MD.

Graphic 74438 Version 3.0

Meconium myonecrosis

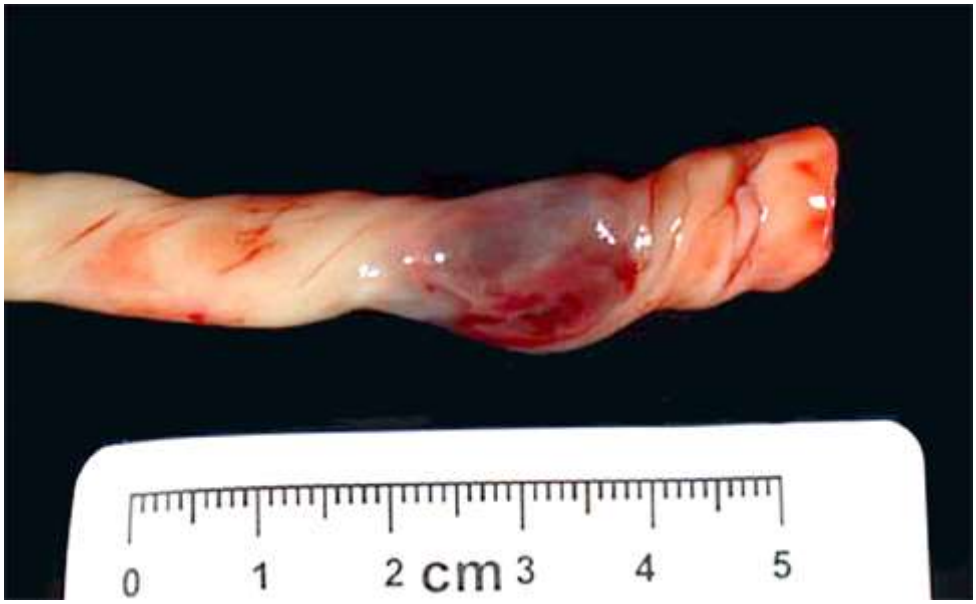


Black arrow shows orangophilic apoptotic smooth muscle cell, and red arrow shows meconium pigment.

Courtesy of Drucilla J Roberts, MD.

Graphic 67487 Version 3.0

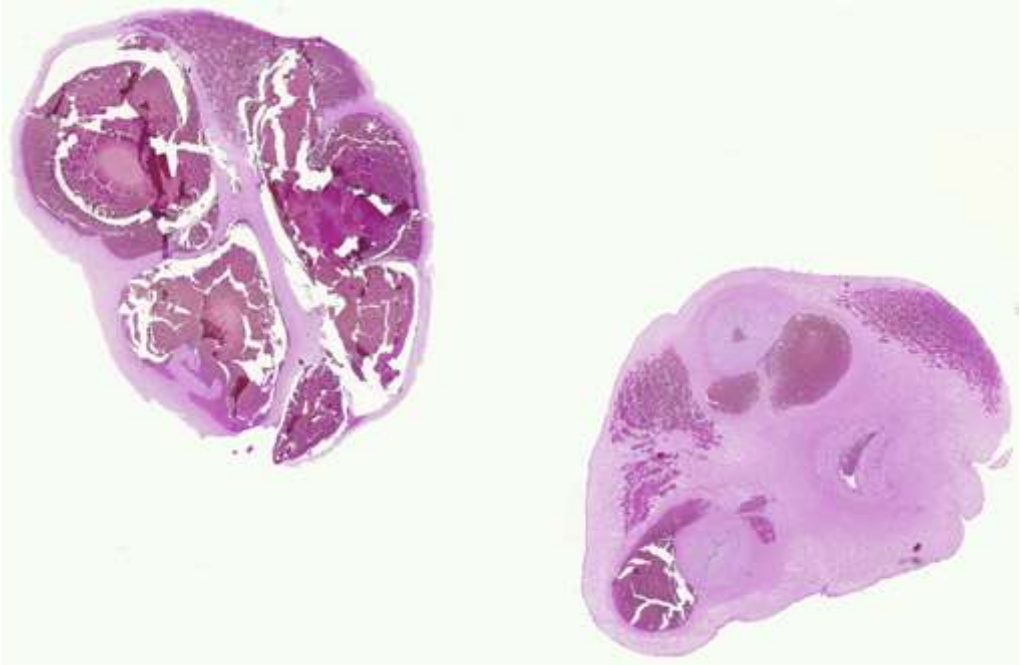
Hematoma umbilical cord



Gross section of umbilical cord revealing localized hematoma.

Graphic 70927 Version 3.0

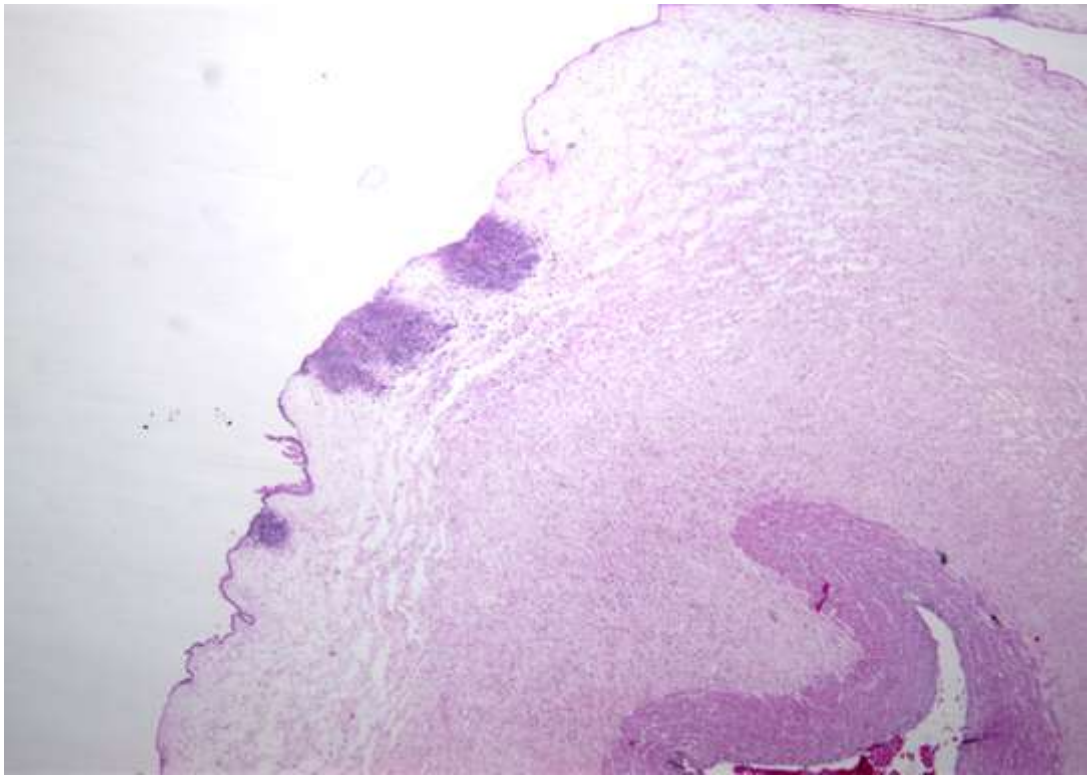
Microscopy cord hematoma



Microscopic section through localized umbilical cord hematoma revealing extravasated blood surrounding the umbilical vein.

Graphic 56907 Version 3.0

Candida placentitis

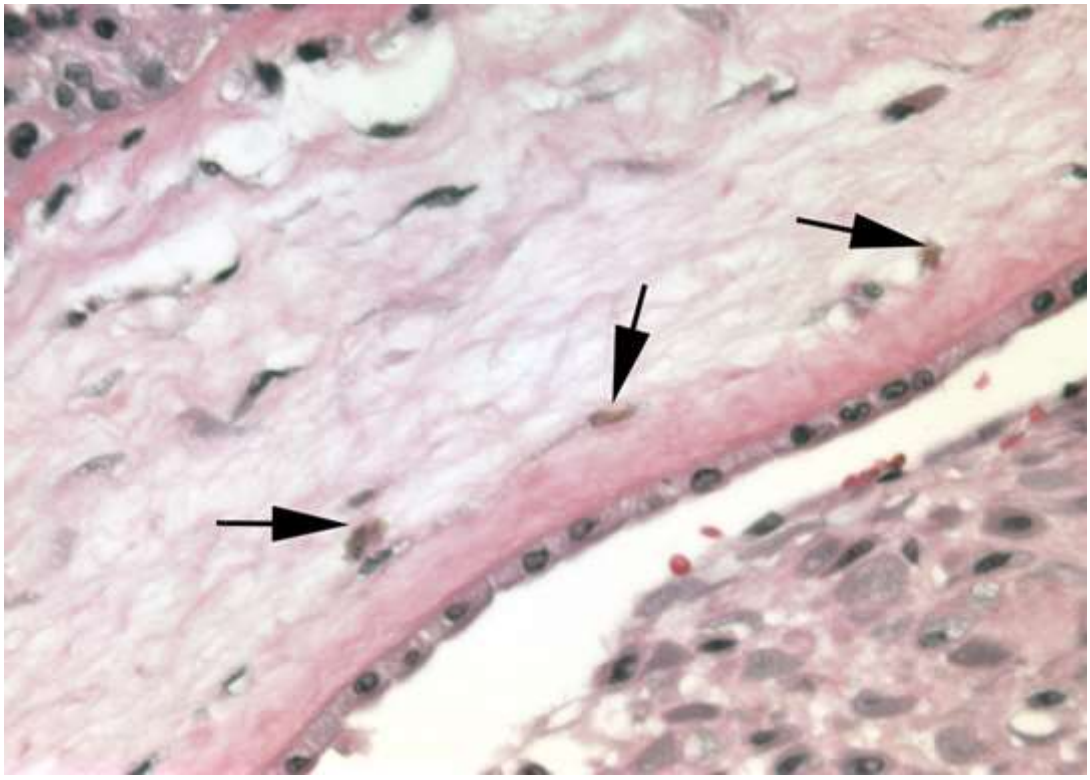


Low power photomicrograph showing microabscesses on the surface of the umbilical cord in a case of candida placentitis.

Courtesy of Drucilla J Roberts, MD.

Graphic 53199 Version 2.0

Meconium stained fetal membranes

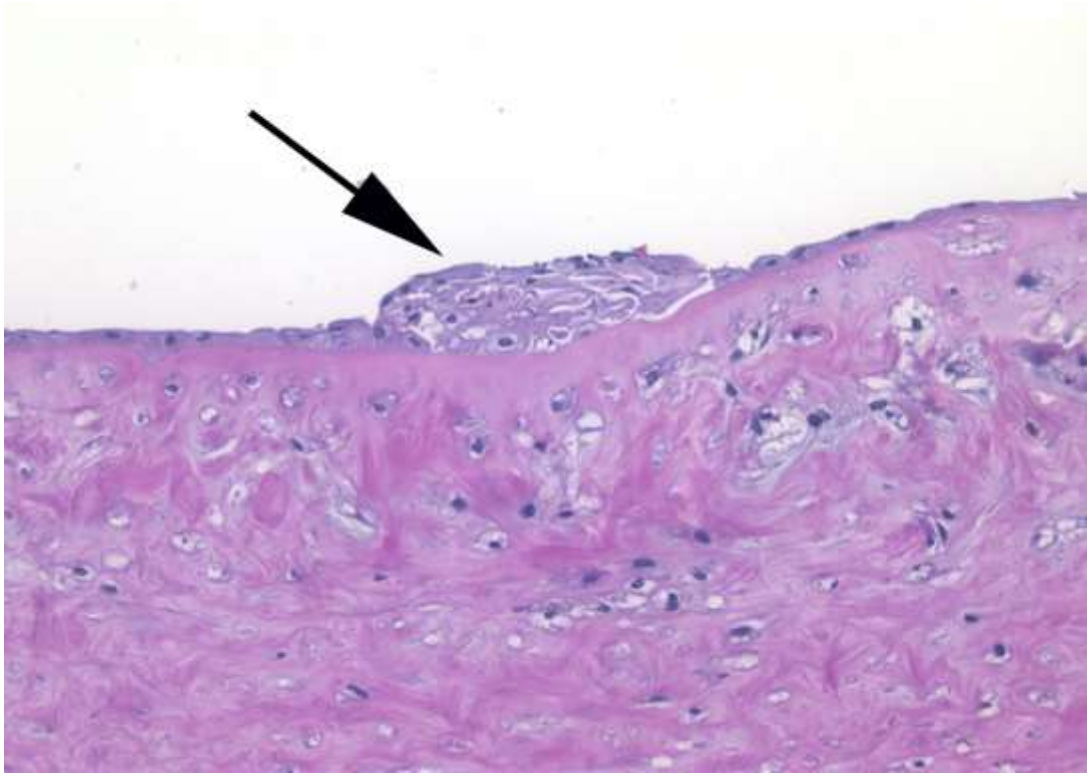


Arrows point to meconium pigment in membranes.

Courtesy of Drucilla J Roberts, MD.

Graphic 53101 Version 2.0

Amnion nodosum

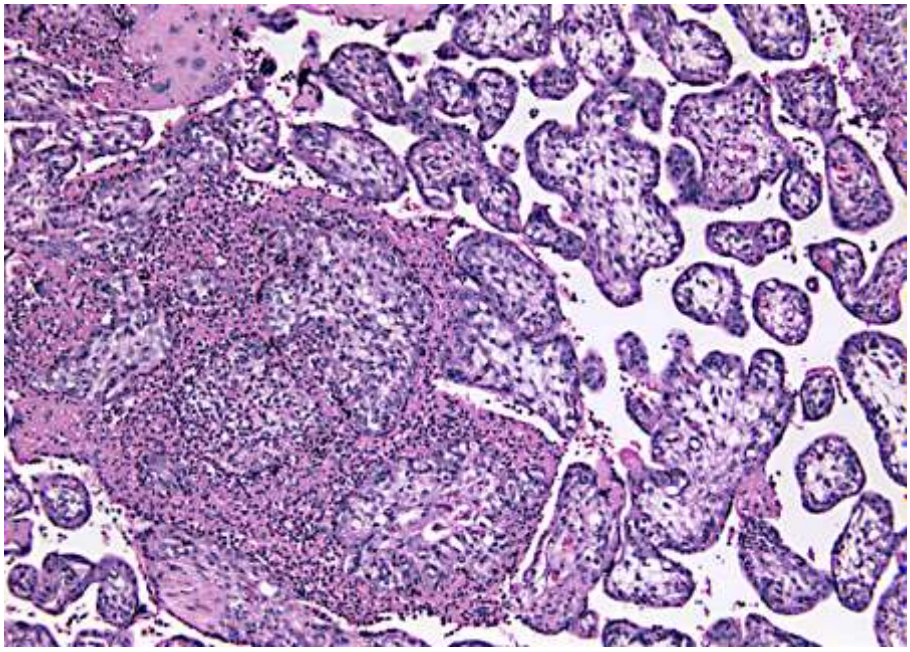


Arrow points to amnion nodosum on the membranes in a case of bilateral renal agenesis.

Courtesy of Drucilla J Roberts, MD.

Graphic 78284 Version 2.0

Neutrophilic villitis and abscess

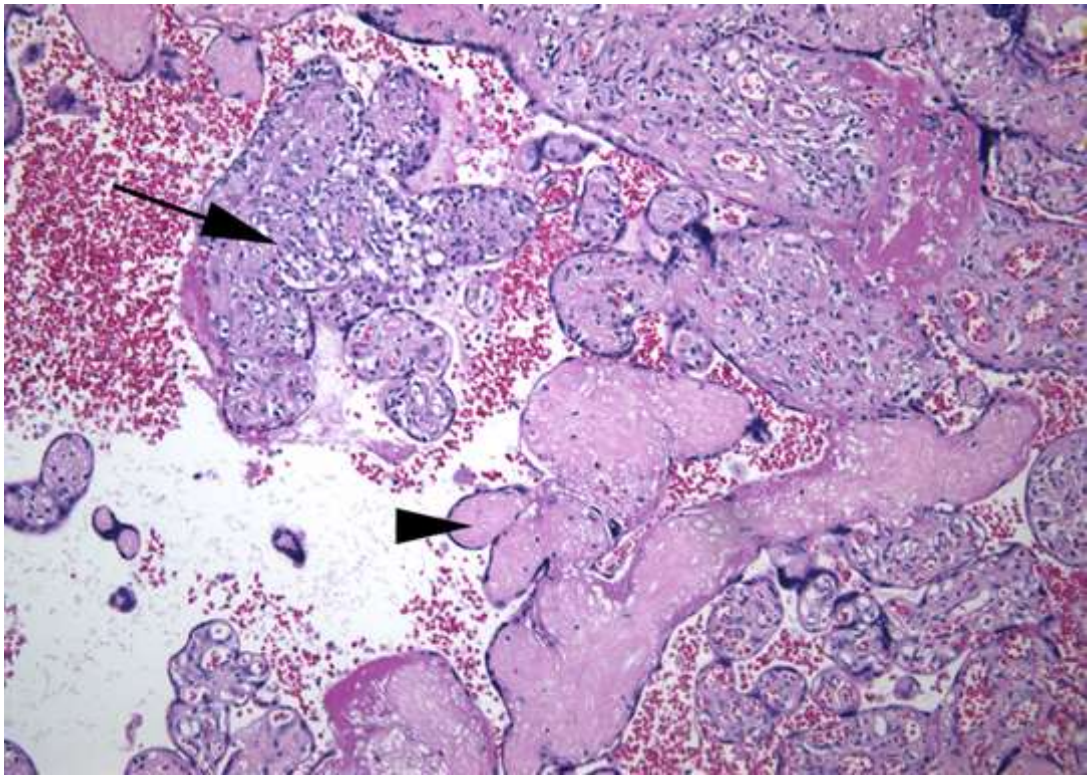


Neutrophilic (acute) villitis and abscess in a case of streptococcal placentitis.

Courtesy of Drucilla J Roberts, MD.

Graphic 56641 Version 3.0

Lymphohistiocytic (chronic) villitis



Arrow points to a mononuclear inflammatory infiltrate in a term placenta. Pregnancy was complicated by fetal growth restriction. Arrowhead shows avascular villi presumably due to the vascular damage from the lymphohistiocytic villitis "upstream."

Courtesy of Drucilla J Roberts, MD.

Graphic 77237 Version 4.0

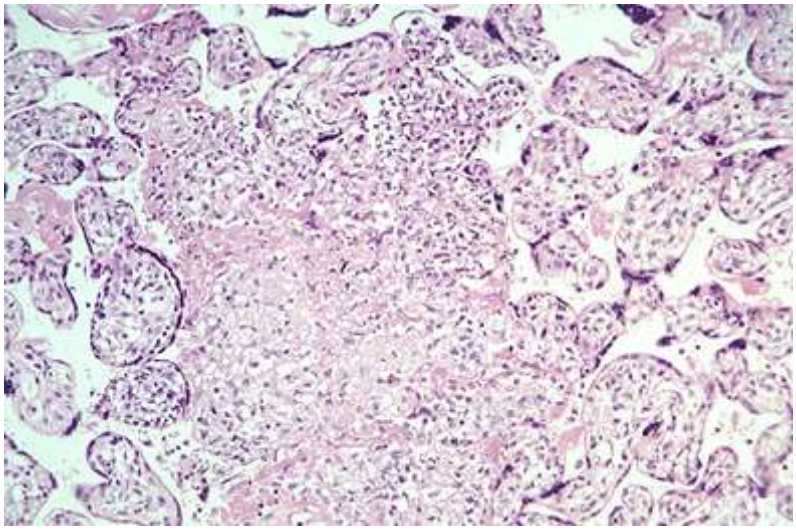
Villitis of unknown etiology

Patchy mild villitis of unknown etiology.

Courtesy of Drucilla J Roberts, MD.

Graphic 95039 Version 1.0

Chronic villitis (VUE)

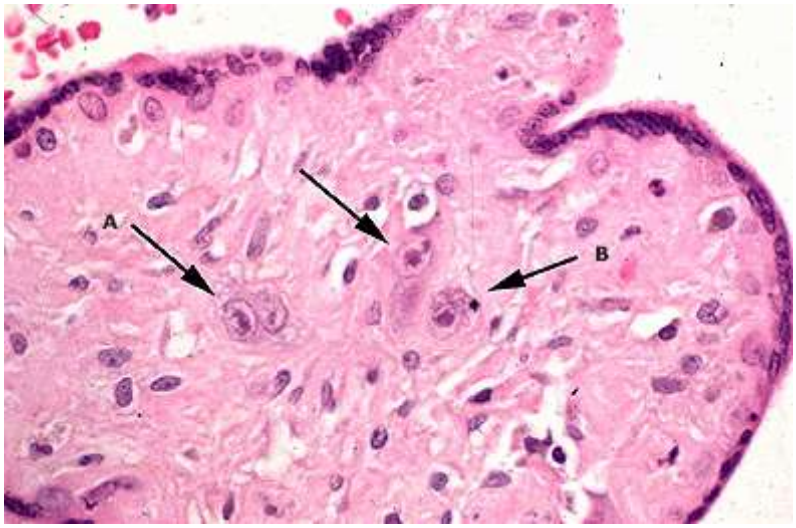


There is increased cellularity of the villi with sclerosis of the villi due to collapse of the villous vessels and clumping of the involved villi.

Courtesy of Drucilla J Roberts, MD.

Graphic 64413 Version 4.0

Cytomegalovirus infection of placenta

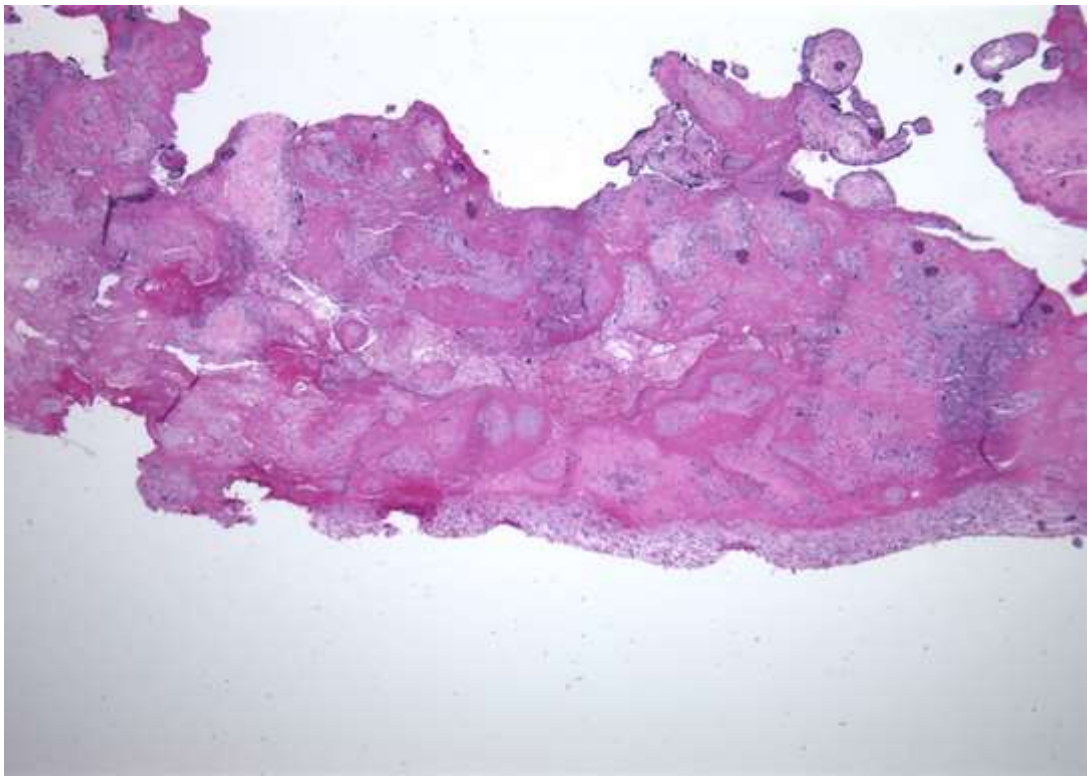


Light micrograph illustrating placental cytomegalovirus infection. Arrows point to cells with nuclear inclusions.

Courtesy of Drucilla J Roberts, MD.

Graphic 70713 Version 3.0

Massive perivillous fibrin deposition (maternal floor infarction)

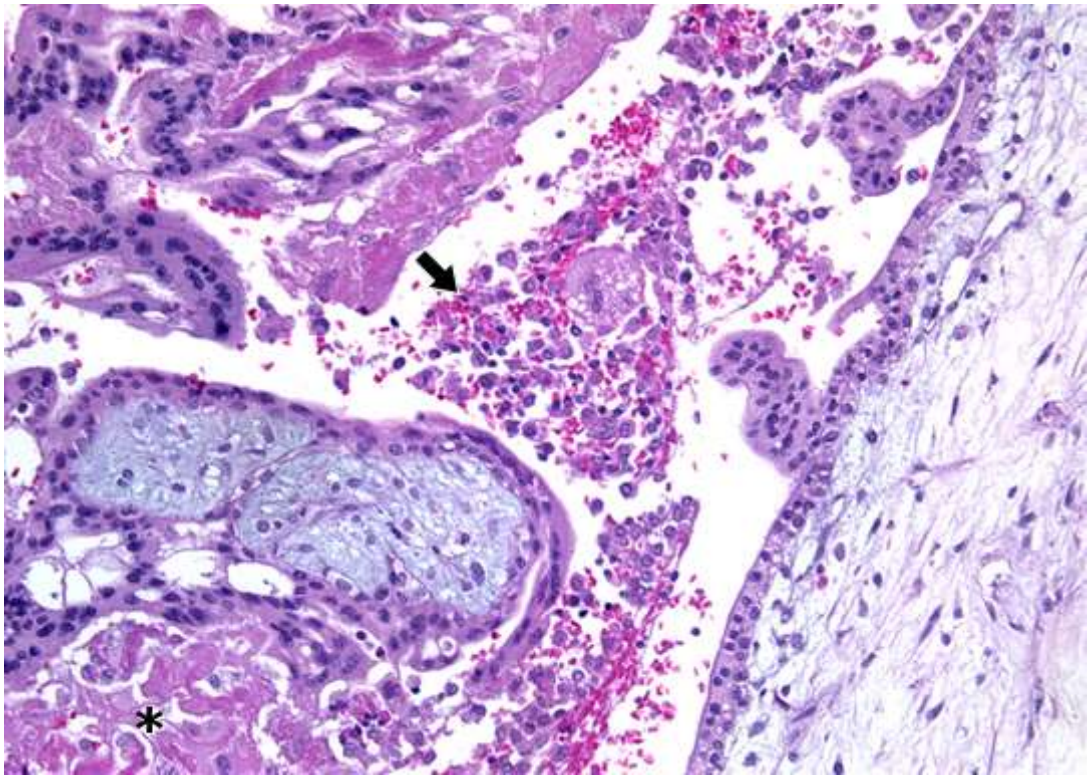


Band of fibrinoid material along maternal floor of placenta causing "strangulation" and necrosis of the villi.

Courtesy of Drucilla J Roberts, MD.

Graphic 59608 Version 6.0

Massive chronic intervillositis

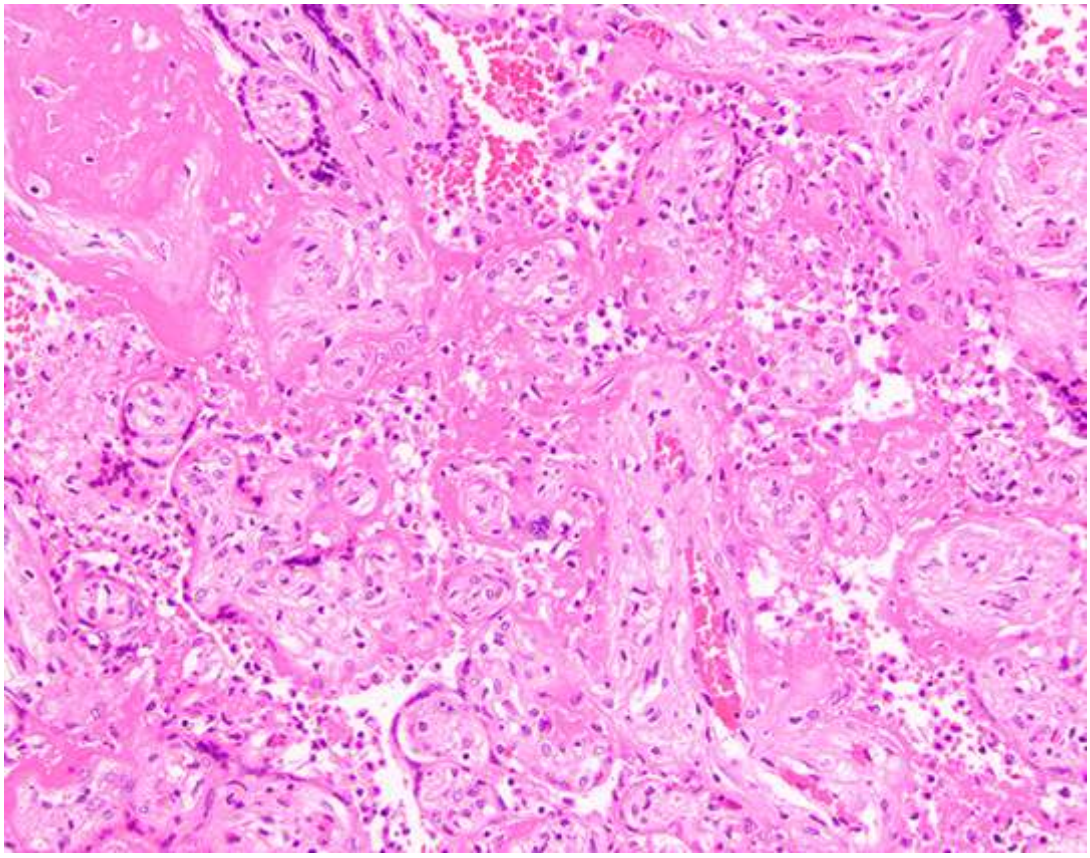


High power of a second trimester placenta with mixture of maternal histiocytes (arrow) and fibrinoid material (asterisk) in a case of massive chronic intervillositis.

Courtesy of Drucilla J Roberts, MD.

Graphic 58193 Version 2.0

SARS-CoV-2 placentitis

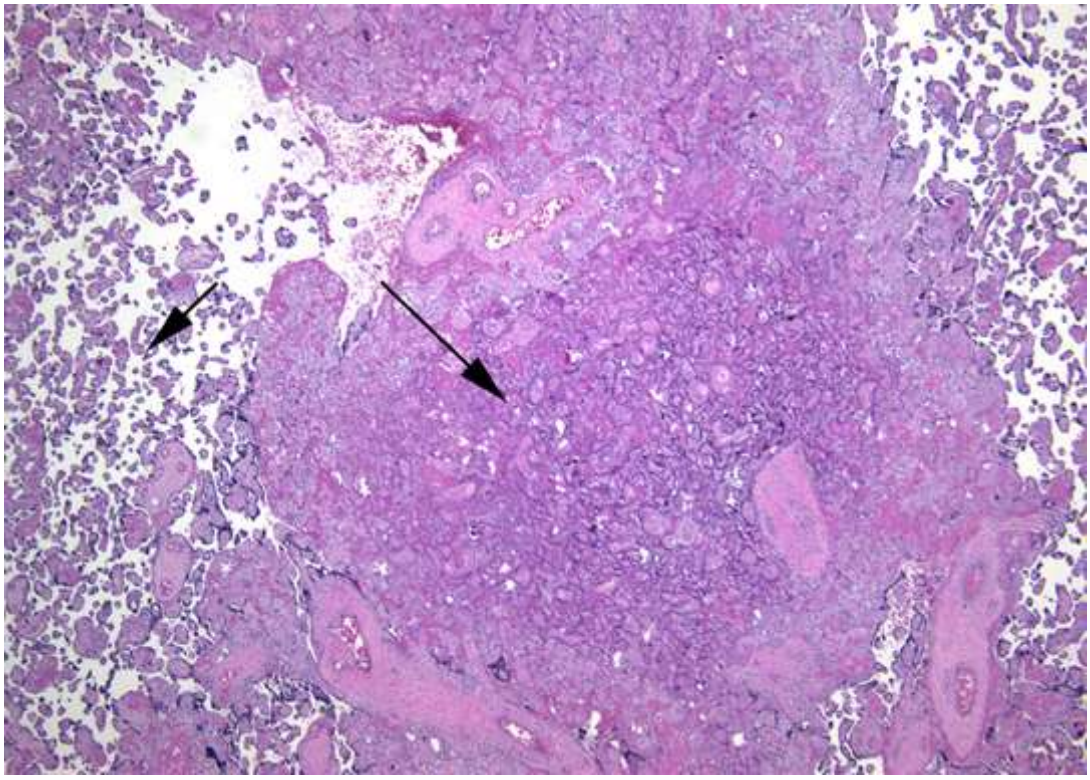


Hematoxylin and eosin stained section of the placenta at 20×-magnification showing SARS-CoV-2 placentitis. Noteworthy characteristics include increased intervillous fibrin, histiocytic intervillositis, and villous trophoblast necrosis. These findings are usually diffuse but can be focal in earlier gestations.

Courtesy of Drucilla Roberts, MD.

Graphic 134823 Version 1.0

Maternal vascular malperfusion

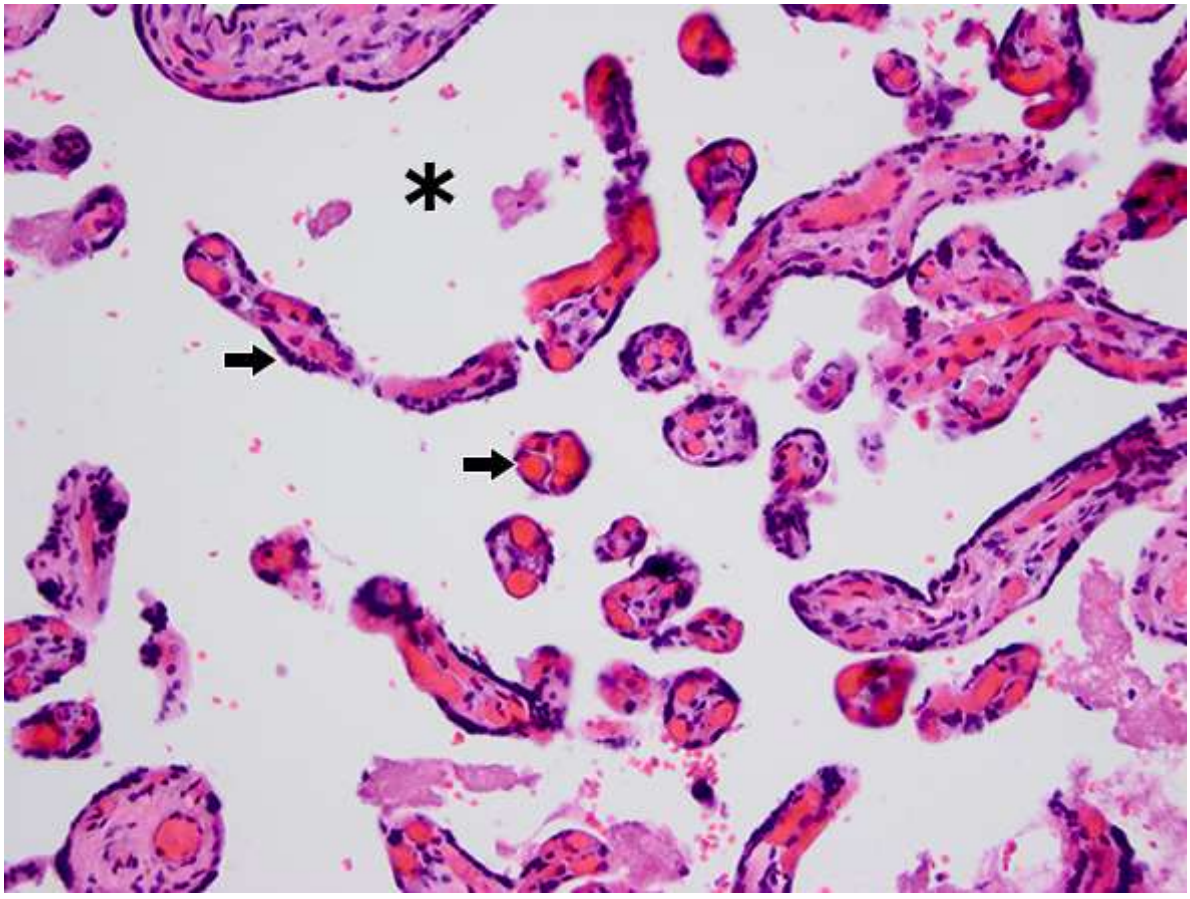


Preterm placenta from a pregnancy complicated by severe preterm preeclampsia. The arrows show areas of accelerated maturity of the villi (short arrow) and a central infarct (long arrow).

Courtesy of Drucilla J Roberts, MD.

Graphic 51550 Version 3.0

Distal villous hypoplasia

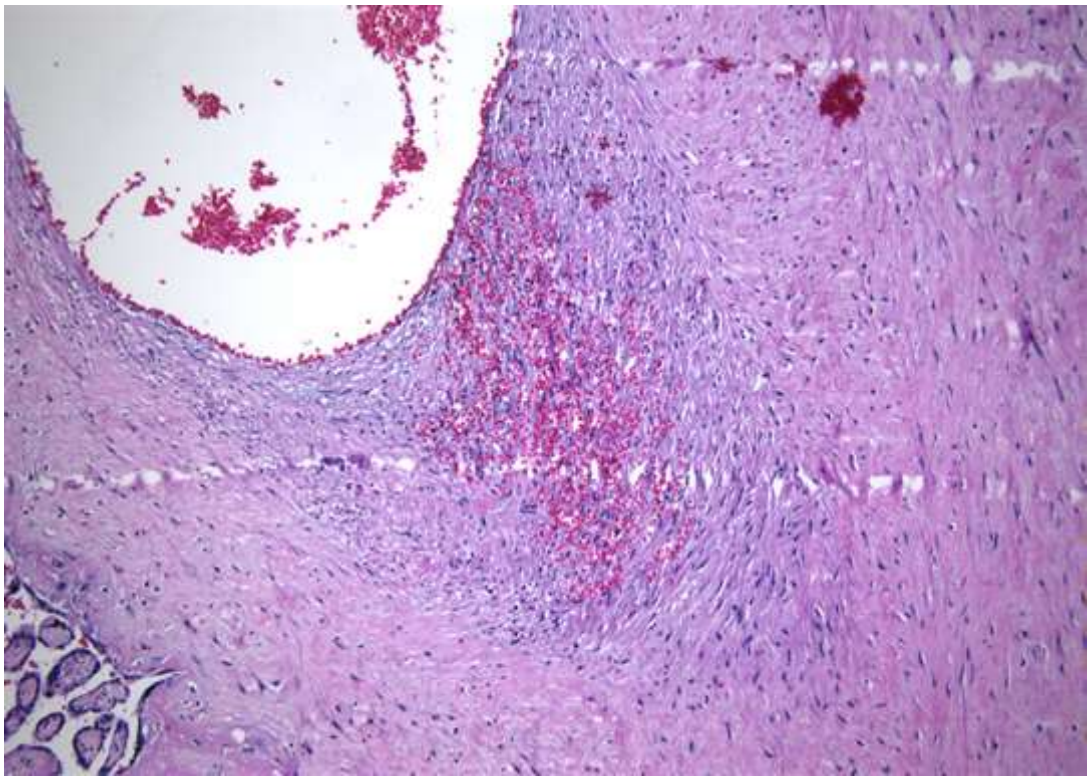


Arrows point to a long thin villi and a small round villi. The asterisk is in the expanded intervillous space.

Courtesy of Drucilla J Roberts, MD.

Graphic 94964 Version 1.0

Fetal stem/chorionic vessel obliteration (fetal vascular malperfusion)

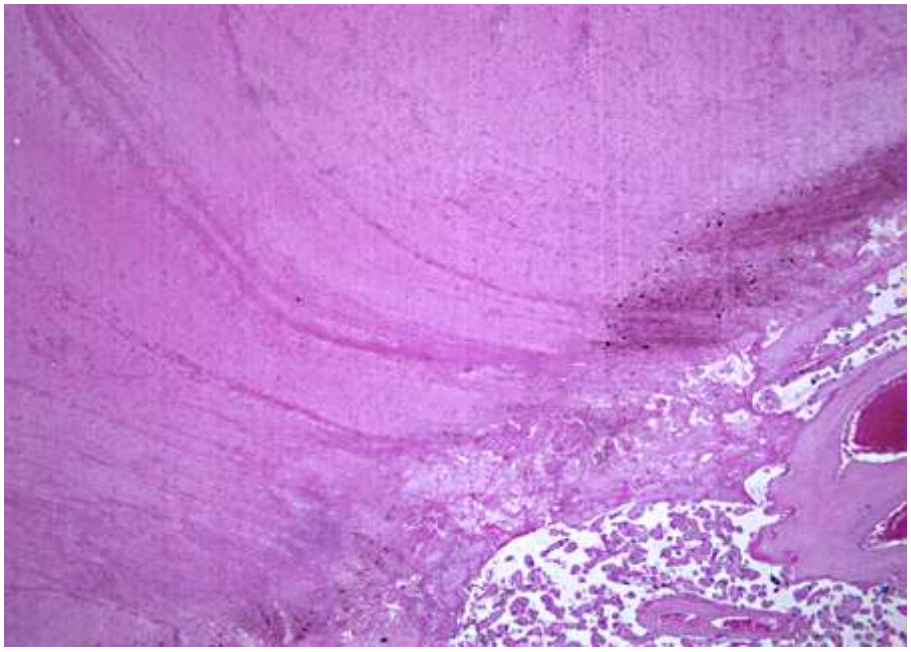


Hemorrhagic endovasculitis in the stem villus of a live born infant with cardiac failure.

Courtesy of Drucilla J Roberts, MD.

Graphic 50997 Version 4.0

Laminated intervillous thrombus



A laminated intervillous thrombus filling slide.

Courtesy of Drucilla J Roberts, MD.

Graphic 74960 Version 3.0

Chorangioma

Arrows point to vessels within the mass.

Courtesy of Drucilla J Roberts, MD.

Graphic 67130 Version 2.0

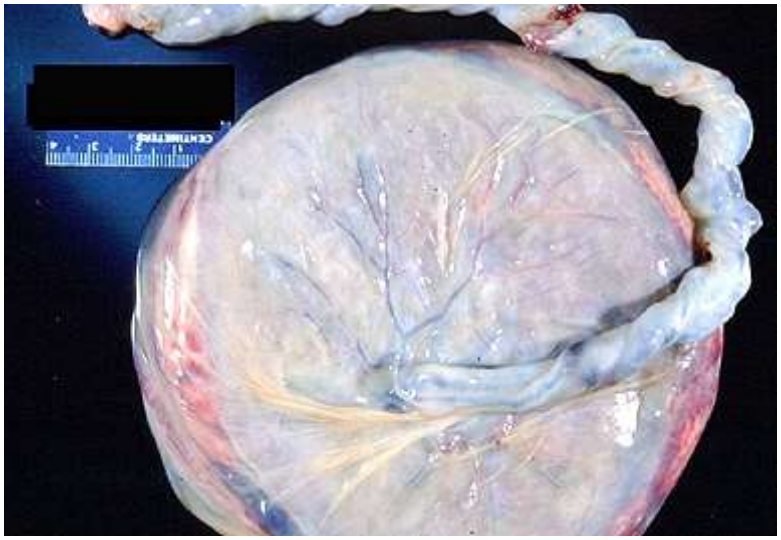
Intravillous hemorrhage

Arrows point to villi with blood filled stroma. An asterisk indicates red blood cells located appropriately within the villous vascular space.

Courtesy of Drucilla J Roberts, MD.

Graphic 94965 Version 1.0

Chorioamnionitis



Gross photograph of the umbilical cord and fetal surface of the placenta illustrating opaque membranous surfaces characteristic of inflammation from chorioamnionitis.

Courtesy of Drucilla J Roberts, MD.

Graphic 56454 Version 2.0

Chorioamnionitis 3

Gross photograph of the umbilical cord and fetal surface of the placenta illustrating yellow, opaque membranous surfaces characteristic of inflammation from chorioamnionitis.

Courtesy of Drucilla J Roberts, MD.

Graphic 77902 Version 2.0

Severe neutrophilic (acute) chorioamnionitis

Arrow points to amniotic epithelium. Yellow asterisk shows inflammation in severe neutrophilic (acute) chorioamnionitis.

Courtesy of Drucilla J Roberts, MD.

Graphic 50692 Version 3.0

Normal membranes

(A) Normal chorioamniotic membrane.

(B) Light micrograph illustrating leukocytes extending through the full thickness of chorioamniotic membrane.

Courtesy of Drucilla J Roberts, MD.

Graphic 51447 Version 4.0

Candidiasis of umbilical cord

(A) Gross candidiasis of umbilical cord.

(B) Microscopic view of umbilical cord candidiasis.

Courtesy of Drucilla J Roberts, MD.

Graphic 58878 Version 3.0

Candidal hyphae in cord

Courtesy of Drucilla J Roberts, MD.

Graphic 74230 Version 2.0

Fusobacterium chorioamnionitis

Fusobacterium chorioamnionitis with severe, necrotizing infiltrate (arrow). Bacilli are not visualized at this low power.

Courtesy of Drucilla J Roberts, MD.

Graphic 53331 Version 3.0

Contributor Disclosures

Drucilla J Roberts, MD Other Financial Interest: American Registry of Pathology [Placental pathology]; Cambridge University Press [Placental pathology]. All of the relevant financial relationships listed have been mitigated. **Amy McKenney, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Vanessa A Barss, MD, FACOG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→