Placental pathology: Findings potentially associated with neurologic impairment in children

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INTRODUCTION

In population-based studies, risk factors for birth of a neurologically impaired child include maternal infection, placental infection, intrauterine growth restriction, and a family history of cerebral palsy (CP) or related neurologic disorders. Immaturity and malformations of the central nervous system (CNS) are common causes of neurologic impairment among children born preterm. By comparison, few neurologically impaired children born at term have a clearly identifiable etiologic factor; causes include perinatal stroke, an inborn error of metabolism (eg, mitochondrial disorders), CNS infection, congenital hypothyroidism, and exposure to an exogenous (eg, mercury) or endogenous (eg, bilirubin) toxin. The contribution of intrapartum hypoxia to CNS injury in term newborns is controversial. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics have proposed essential criteria needed to define an acute intrapartum event that was sufficient to cause CP, as well as the collective criteria that suggest intrapartum timing (table 1) [1].

Histopathologic examination of the placenta may identify clinically overt or silent, pathophysiologic processes that may directly cause CNS damage, decrease the threshold for neurologic injury, or serve as markers for a deleterious in utero environment. Placental lesions associated with neurodisability have been found in the placentas of newborns at all birth weights and gestational ages but are most helpful for understanding unanticipated poor outcomes in term newborns.

The placenta should be submitted to the pathology department according to recommendations developed by the College of American Pathologists to ensure that valuable placental data are factored into an analysis of the cause of brain injury in a newborn [2,3]. It may also be necessary to discuss clinical findings and impressions with the pathology department to ensure that placentas are appropriately examined and sampled according to accepted guidelines so that important placental lesions are not missed. When perinatal complications occur, timely consultation with a perinatal pathologist with experience in evaluating cases of adverse neurologic outcomes can help identify placental lesions and explain their significance to the family soon after birth.

This topic will discuss acute and chronic conditions of the preterm and term placenta that may affect neurologic outcome in childhood. The terminology recommended by the Amsterdam International Working Group on Placental Nomenclature is used [4]. Other issues related to placental pathology are reviewed separately (see "Gross examination of the placenta" and "The placental pathology report"). Other issues related to children with neurologic impairment are also reviewed separately.

- (See "Etiology and pathogenesis of neonatal encephalopathy".)
- (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy".)
- (See "Cerebral palsy: Epidemiology, etiology, and prevention".)
- (See "Cerebral palsy: Classification and clinical features".)
- (See "Cerebral palsy: Overview of management and prognosis".)

LOW BIRTH WEIGHT NEWBORNS AND PRETERM PLACENTAS

In very low birth weight (VLBW; <1.5 kg) and extremely low birth weight (ELBW; <1.0 kg) newborns, central nervous system (CNS) damage is the major cause of long-term neurologic deficits, such as cerebral palsy (CP). CNS damage in this age group is primarily related to the inability of the immature developing brain and cardiopulmonary system to adapt to the changes incurred by the premature transition to extrauterine life [5,6]. However, placental lesions can be contributing factors that increase the risk for CNS injury and neurodisability. The risk is dramatically increased when the placenta has more than one lesion associated with adverse outcome [7-10]. These lesions include all of the lesions described below, plus long-standing chorioamnionitis with amnion necrosis (necrotizing chorioamnionitis), retroplacental hematomas with intraplacental extension (findings consistent with abruption placenta), and increased circulating nucleated red blood cells. (See "Cerebral palsy: Epidemiology, etiology, and prevention", section on 'Prematurity'.)

Infection and inflammation

- **Clinical and histologic chorioamnionitis (HCA) –** In preterm newborns, a meta-analysis found that clinical chorioamnionitis was associated with a nearly twofold increase in risk for CP (relative risk [RR] 1.9, 95% CI 1.4-2.5) and a threefold increase in risk for its precursor cystic periventricular leukomalacia (RR 3.0, 95% CI 2.2-4.0) [11]. HCA also appeared to be a risk factor for CP, but the confidence interval was wide and did not exclude a negative or minimal association (RR 1.6, 95% CI 0.9-2.7). Paradoxically, in the short-term, HCA has been associated with improved newborn survival and better short-term outcomes in a few reports [12,13]. (See "The placental pathology report", section on 'Chorioamnionitis'.)

- **HCA with acute fetal inflammatory response (FIR) –** In VLBW and ELBW newborns, the presence of HCA with an acute FIR has been associated with sonographically defined white matter lesions [14,15], but an association with development of CP-related neurologic processes is less clear. In one study of VLBW newborns, the combination of high-grade acute FIR or acute FIR with chorionic vessel thrombi plus HCA was weakly associated with development of CP-related forms of neurologic impairment [16]. By contrast, a study of ELBW newborns failed to find any association of HCA or acute FIR with either CP or abnormal neurocognitive testing in the group as a whole but did find that high-grade acute FIR predicted lower neurocognitive test scores in the subgroup with HCA [17].

  It is hypothesized that an acute FIR results in increased levels of circulating cytokines, which may damage immature oligodendroglia in the developing CNS [18,19]. Cytokine levels are highest when acute FIR affects all three umbilical vessels [20,21]. (See "The placental pathology report", section on 'Inflammation'.)

Maternal vascular malperfusion — Severe malperfusion of the maternal side of the placenta (previously called uteroplacental insufficiency) can result in vascular lesions such as infarcts, increased syncytial knots, and decidual arteriopathy (acute atherosis) that impact fetal growth. If fetal growth is severely compromised, fetal brain development may be affected as a result of fetal compensatory circulatory changes (eg, abnormal blood flow in the middle cerebral artery [22,23]), and CNS damage may occur.

This hypothesis is supported by several lines of evidence:

- Autopsy studies in stillbirths have shown a significant relationship between maternal vascular malperfusion (MVM; infarcts and increased syncytial knots) and neuronal necrosis in the stillborns [24-26].

- Large studies of small for gestational age and low birth weight newborns have demonstrated that they have an increased prevalence of CP and other neurodevelopmental disorders [27,28].

- In a study of ELBW newborns, placental lesions (increased syncytial knots, multiple villous infarcts, decidual arteriopathy [acute atherosis]) associated with MVM were strongly associated with CP [17]. A previous study in VLBW newborns had suggested a biphasic relationship, with less severe lesions correlating with better outcomes and more severe lesions correlating with worse outcomes [16].

- In a population-based study of placental infarction identified by macroscopic examination in singleton newborns at ≥35 weeks of gestation, placental infarcts were recorded in 2.0 percent of controls, 5.2 percent of newborns who subsequently developed CP (RR 2.5, 95% CI 1.2-5.3), and 8.4 percent of those who subsequently developed spastic quadriplegic CP (RR 4.4, 95% CI 1.8-10.6) [29]. Although lack of histologic confirmation is a limitation of this study, it suggests that placental infarction should be separated from other signs of MVM in future studies of the placenta and neurodisability. (See "The placental pathology report", section on 'Maternal vascular malperfusion'.)

Villous edema — Villous edema (diffuse multifocal edema having the appearance of large vacuoles or separation/clefting of the villous trophoblast from the villous stroma) affecting the immature intermediate villi of preterm placentas (picture 1) has been associated with an increased risk of neonatal death, CP, and chronic lung disease in VLBW newborns and lower neurocognitive scores at school age in ELBW newborns [8,9,17,24]. In one of these studies, villous edema was associated with neurocognitive impairment while placental lesions associated with MVM were risk factors for CP [17]. Placentas with villous edema, increased syncytial knots, and those with neither finding comprised nonoverlapping subgroups with distinct pathologic and perinatal characteristics: Among newborns with villous edema, those with neurologic impairment had lower gestational ages and more severe degrees of HCA.

TERM PLACENTAS

In term newborns, the underlying clinical risk factors for central nervous system (CNS) injury are less well-defined than in preterm newborns. However, many cases of cerebral palsy (CP) at term are preceded by neonatal encephalopathy and accompanied by basal ganglia injury, which may be related, at least in part, to acute and chronic inflammatory placental lesions [30,31]. Histopathologic examination of the placenta can identify the acute and chronic processes that directly contribute to neurologic impairment, as well as placentas with decreased functional reserve and with adaptive changes indicative of an abnormal intrauterine environment.

One report examined the effects of having more than one significant placental risk factor for CP and related neurologic conditions in term newborns [32]. It was shown that multiple

lesions acted synergistically and that each additional lesion significantly elevated the specificity of abnormal pathology for predicting adverse outcome. It was also found that lesions occurring at different time periods (eg, subacute superimposed on active chronic) were more strongly associated with outcome than lesions occurring at the same time. This sensitization or preconditioning might reflect the effects of later lesions on compensatory mechanisms invoked by the initial process.

Acute disorders that may be associated with perinatal asphyxia — Acute processes (ie, those occurring less than four to six hours prior to birth) associated with fetal hypoxia and subsequent neonatal encephalopathy include placental abruption, cord occlusion, and fetal hemorrhage. These processes generally are only detectable on placental histopathology if they result in detectable disruption and deformation of placental tissues. Typically, these acute insults are pathologically "invisible," but some features may be present to support the clinical diagnosis.

Acute abruption — Acute placental separation due to abruption compromises transplacental fetal oxygen delivery and can result in perinatal asphyxia or death. The diagnosis of abruption is typically made clinically based on vaginal bleeding, abdominal pain, contractions, and uterine rigidity and tenderness. In patients who undergo cesarean birth, direct visualization of a large central retroplacental blood clot with indentation of the placenta or rupture of the basal plate is strong evidence of the disorder (picture 2). (See "Acute placental abruption: Pathophysiology, clinical features, diagnosis, and consequences".)

Histologic findings of abruption, such as diffuse retromembranous and/or intradecidual hemorrhages, irregular basal intervillous thrombi, and recent villous stromal hemorrhage (intravillous hemorrhage), may be detected on histopathologic examination but are less specific for the diagnosis [33]. (See "The placental pathology report", section on 'Placental abruption'.)

Acute umbilical cord occlusion — A tight knot, cord prolapse, or severe torsion related to cord entanglements or marginal/membranous cord insertion (picture 3) can result in acute total or near-total obstruction of umbilical blood flow and fetal oxygen delivery, resulting in perinatal asphyxia or death.

Histologic findings supporting acute cord occlusion include substantial differences in cord diameter, color, and vascular congestion on either side of the putatively obstructed area and dilation of large vessels in the chorionic plate and primary stem villi. Rarely, intravillous hemorrhage may ensue due to obstruction of villous vascular outflow and resultant congestion and rupture of villous capillaries. (See "The placental pathology report", section on 'Arterial and venous thrombosis' and "Nuchal cord", section on 'Possible sequelae' and "Umbilical cord abnormalities: Prenatal diagnosis and management".)

Severe acute fetal hemorrhage — Severe acute fetal hemorrhage can result in perinatal asphyxia or death from exsanguination. It is caused by placental vascular disruptions, most commonly involving the tearing of unsupported fetal vessels in the membranes (ie, ruptured vasa previa, ruptured velamentous cord) during labor or prelabor rupture of membranes. A rare type of catastrophic fetal hemorrhage involves subamnionic and umbilical cord hematomas caused by extreme stretching of an entangled umbilical cord during fetal descent through the birth canal. Because a small amount of fetal bleeding occurs quite commonly during the course of a normal birth, there should be evidence that bleeding has spread into adjacent tissues and the neonate is anemic before imparting pathologic significance to these placental findings. (See "Velamentous umbilical cord insertion and vasa previa" and "Umbilical cord abnormalities: Prenatal diagnosis and management", section on 'Hematoma'.)

Subacute disorders that may be associated with partial prolonged hypoxia — The concept of partial prolonged hypoxia is utilized by neurologists and neuroradiologists to describe specific patterns of brain injury related to sustained or repetitive periods of significant hypoxia or other systemic stress affecting the fetus over a period of many hours to days [34]. Partial prolonged hypoxia is more likely to be associated with various types of neurologic impairment (eg, CP) than with death and has many causes, as described below.

Infection and inflammation — As in preterm placentas, a meta-analysis found that clinical chorioamnionitis appeared to be a risk factor for CP (relative risk [RR] 4.7, 95% CI 1.3-16.2), but data were limited to two studies [11]. An association between histologic chorioamnionitis (HCA) and CP was also noted (RR 8.9, 95% CI 1.9-40.0), but data were limited to one study. Others have found that most grades and stages of HCA were equally prevalent in the placentas of term newborns with and without neurologic impairment, but high-grade acute fetal inflammatory response, defined by confluent neutrophilic infiltration of chorionic or umbilical vessel walls plus disorganization of vascular smooth muscle fibers and endothelial activation, when present, was a highly significant risk factor for CP and related forms of neurodisability [32,35]. (See "The placental pathology report", section on 'Inflammation'.)

Meconium-associated fetal vascular necrosis — Prolonged meconium exposure rarely leads to meconium-associated necrosis of vascular smooth muscle cells in the chorionic or umbilical vessels due to toxic effects of bile acids and other constituents of meconium [35,36]. This lesion is much more common in the placentas of term newborns with neurologic impairment and is a highly significant risk factor for this outcome (picture 4) [32,35]. By contrast, meconium-stained amniotic fluid is noted in 10 to 15 percent of term births. While the prevalence of meconium histiocytosis is somewhat higher in the placentas of infants with neurologic impairment, there is no significant association between meconium histiocytosis in the amnion or chorionic plate and adverse childhood outcome [32]. Other

authors have noted an association of meconium with white matter necrosis in stillbirths [24]. (See "The placental pathology report", section on 'Meconium staining'.)

Chronic partial intermittent umbilical cord occlusion — Chronic partial intermittent umbilical cord occlusion is difficult both to diagnose clinically and confirm by pathologic examination. Several studies implicating this process in infants with neurologic impairment have been published [37,38]. Placental findings suggestive of the disorder include the following [39,40]:

- Higher risk umbilical cord findings:
  - Long cord (>70 cm)
  - Hypercoiled cord (>3 coils/10 cm)
  - Thin cord (<8 mm diameter)
  - Marginal, membranous, or furcate insertion
- Intramural fibrin deposition (formerly intimal fibrin cushions) representing either insudation of fibrin or deposition of extracellular matrix in the walls of large fetal vessels. Intramural fibrin deposits can be difficult to distinguish from nonocclusive mural thrombi, especially when remote thrombi are re-endothelialized and incorporated into the vessel wall [41]. A lesion that projects into the vascular lumen suggests thrombotic origin.
- Dilation of large primary stem villous vessels (venous ectasia).
- Scattered small foci of degenerating terminal villi indicative of decreased fetal perfusion in the most distal portions of the fetoplacental circulation.

More severe umbilical cord occlusion can cause more extensive areas of villous stromal vascular karyorrhexis in the distal villous tree, a process also known as hemorrhagic endovasculitis [42]. Many of these cases also show an increase in circulating nucleated red blood cells (NRBC), indicative of significant fetal hypoxemia. (See 'Increased circulating nucleated red blood cells' below.)

Subacute abruption — Subacute abruption can be defined as an episode or episodes of placental abruption not leading to immediate delivery but potentially resulting in suboptimal fetal oxygenation. It has been associated with CNS injury [24]. The pathologic findings include an organizing retroplacental hematoma with overlying recent villous infarction. 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 approximately four to six hours to develop.

Subacute/chronic fetomaternal bleeding — Recurring episodes of intermittent fetal bleeding into the maternal circulation are rare but are important causes of severe fetal anemia, suboptimal fetal oxygenation, and CNS injury [43]. Clinically, it may be accompanied by decreased fetal movement and a sinusoidal fetal heart rate pattern. A positive Kleihauer-Betke or flow cytometric test identifying fetal red blood cells in the maternal circulation is the standard diagnostic test. (See "Spontaneous massive fetomaternal hemorrhage".)

Placental findings include a marked increase in circulating NRBCs within villous capillaries plus large or multiple intervillous thrombi in the placenta, particularly when accompanied by a low neonatal hematocrit and a sustained increase in the NRBC count in the first few days following birth [44,45]. (See "The placental pathology report", section on 'Intervillous thrombi'.)

Chronic progressive placental disorders — Active, chronic placental disease processes have their onset weeks prior to birth and are progressive, thus continuing to cause deterioration of placental function at an unpredictable rate until birth.

Severe fetal vascular malperfusion, segmental complete type — Severe fetal vascular malperfusion (FVM) of the segmental complete type has been strongly associated with neonatal encephalopathy, CP, and other related forms of neurologic impairment [35,46-49]. Brain injury may result directly from embolization of placental clots through the umbilical vein to the middle cerebral artery via the ductus venosus and foramen ovale or indirectly secondary to a fetal coagulopathy, sometimes accompanied by thrombocytopenia and thrombi in other fetal organs. (See "The placental pathology report", section on 'Fetal vascular malperfusion'.)

The lesion is characterized by multiple large foci of devascularized distal villi, in varying stages of degeneration, usually accompanied by identifiable organizing thrombi in upstream feeding vessels in the chorionic plate or large stem villi (picture 5) [50]. It is closely related to the condition previously referred to as hemorrhagic endovasculitis (picture 6) [42,51]. The total number of degenerating villi required for diagnosis must exceed an average of 15 per parenchymal section [52]. Depending on the duration of upstream vascular occlusion, distal villi either show stromal-vascular karyorrhexis (>24 hours) or become totally avascular and hyalinized (>7 days). Usually the latter predominate.

Disorders that may lead to FVM include pathologic abnormalities of the umbilical cord, cord entanglements, fetal thrombophilia, maternal antiphospholipid syndrome, and maternal diabetes mellitus [50,53-55].

Chronic villitis, high-grade or with luminal obliteration and avascular villi — Chronic villitis (also known as villitis of unknown etiology [VUE]) has been associated with fetal growth restriction and recurrent pregnancy loss. In addition, when high grade and/or

accompanied by vascular obliteration and avascular villi, it has been strongly associated with CP, neonatal encephalopathy, and basal ganglia injury in term newborns [30,31,35].

Chronic villitis is a relatively common chronic inflammatory disorder (5 to 10 percent of term placentas), usually affecting only the distal chorionic villi (picture 7 and picture 8) [56,57]. The inflammatory infiltrate is primarily composed of maternal T lymphocytes, suggesting that this condition may represent a maternal host versus graft reaction [58]. Chronic villitis is considered high grade when groups of ≥10 contiguous villi with a lymphocytic villous infiltrate are present. In rare cases, inflammatory cells extend into more proximal villi and the chorionic plate where they can cause chronic vasculitis and luminal obliteration [52]. Downstream villi show a combination of inflammation and the degenerative changes, as described above for FVM. (See 'Severe fetal vascular malperfusion, segmental complete type' above and "The placental pathology report", section on 'Villitis'.)

Massive perivillous fibrin deposition (maternal floor infarction) — Massive perivillous fibrin deposition (maternal floor infarction) is a rare idiopathic placental disease process. It is often recurrent and can cause a variety of adverse outcomes including pregnancy loss before 20 weeks of gestation, preterm birth, fetal demise, and severe fetal growth restriction. One study showed a significant increase in adverse neurodevelopmental outcomes in newborns with placentas showing this finding [59]. Another study reported a significant association with CP and related neurologic conditions in term newborns [32].

The disorder is characterized by progressive obliteration of the intervillous space by a combination of fibrin and fibrinoid extracellular matrix material (picture 9) [60]. The etiology is unclear, with some studies suggesting an association with autoimmune disease, maternal thrombophilia, and hypertensive disorders [61-63]. (See "The placental pathology report", section on 'Maternal floor infarction/massive perivillous fibrin deposition'.)

Chronic peripheral placental separation (chronic abruption) — Chronic peripheral placental separation is the pathologic correlate of the chronic abruption-oligohydramnios sequence [64,65]. It is characterized clinically by repetitive episodes of vaginal bleeding, often in all trimesters of pregnancy. Sonographic evidence of so-called subchorionic hemorrhages may be detected in some cases. Pathologically, chronic peripheral separation is characterized by circumvallate membrane insertion, old degenerating marginal blood clots, and/or diffuse hemosiderosis of the placental membranes [66].

A clinical diagnosis of chronic vaginal bleeding was found to be a significant risk factor for CP in the Collaborative Perinatal Project conducted in the 1960s, and membrane hemosiderin deposition was an independent predictor of CP and related neurologic disorders in a study of term newborns [32,67]. However, chronic peripheral placental separation is more commonly recognized as a cause of preterm birth. Affected newborns show a specific pattern of lung

disease, but it has not been associated with neurologic impairment in preterm newborns [68].

Chronic static placental insufficiency — Chronic static placental insufficiency refers to conditions related to long-standing developmental processes affecting placental growth and villous efficiency. It has been estimated that the placenta has an approximately 30 percent reserve capacity to maintain maternofetal gas exchange during times of stress. Conditions that reduce reserve by decreasing the volume or efficiency of placental tissue do not directly cause brain injury, but they can decrease the ability of the fetoplacental unit to withstand significant stresses that occur during the course of normal labor and birth.

Reduced fetoplacental growth, maternal vascular malperfusion — Pathologic findings indicative of some degree of maternal vascular malperfusion (MVM; also known as uteroplacental insufficiency) are common, affecting 10 to 20 percent of all births. These findings are indicative of inadequate spiral arterial flow, generally due to abnormal trophoblast-dependent remodeling during the early stages of pregnancy [69]. Clinical conditions associated with MVM include pregnancy-related hypertension, fetal growth restriction, oligohydramnios, and abnormal pulsed flow Doppler studies.

Associated pathologic findings include decreased placental weight (placental hypoplasia), increased fetoplacental weight ratio, accelerated villous maturation (increased syncytial knots and intervillous fibrin), distal villous hypoplasia, a thin umbilical cord (<8 mm in diameter at term), villous infarcts (picture 10), and spiral artery abnormalities (decidual arteriopathy), including acute atherosis (fibrinoid necrosis with lipid laden macrophages), mural hypertrophy, and luminal thrombosis/fibrous obliteration [70,71]. While these changes are all suggestive of decreased placental reserve, by themselves, none are associated with CP or related neurologic abnormalities in term newborns.

Excessive fetoplacental growth, delayed villous maturation — Placentomegaly (weight greater than the 90th percentile for gestational age) and delayed villous maturation with long umbilical cords and FVM (increased villous stroma and decreased vasculosyncytial membranes) are pathologic changes associated with excessive levels of fetal insulin or other fetoplacental growth factors [72,73]. These changes may be seen in pregnancies complicated by maternal diabetes, obesity, excessive weight gain, and fetal Beckwith-Wiedemann syndrome. (See "The placental pathology report", section on 'Placental maturity and weight'.)

The combination of excessive demand due to increased fetoplacental mass and inefficient villous gas exchange due to villous immaturity decreases placental reserve and has been associated with stillbirth and other perinatal complications. While these changes may impair the placental capacity to withstand stress, no direct evidence of a link to CP and related neurologic conditions has been reported.

ADAPTIVE CHANGES POTENTIALLY ASSOCIATED WITH FETAL HYPOXIC STRESS

The fetus and placenta undergo a number of adaptive changes triggered by persisting alterations in the delivery of critical substrates from the maternal circulation. Unlike the disorders described above, they are indicators of intrauterine status, not causes of placental insufficiency and fetal hypoxia. In theory, these adaptations could improve placental function, but there is no evidence that they do so. (See "The placental pathology report", section on 'Acute versus chronic stress/insult'.)

Increased circulating nucleated red blood cells — Exposure of the bone marrow and other sites of fetal hematopoiesis (eg, liver) to persistent and significantly decreased levels of oxygen results in the release of erythropoietin (via hypoxia-inducible factor 1 [HIF-1 alpha]), which stimulates increased production and premature release of nucleated red blood cells (NRBC) into the peripheral circulation [74]. The ability to detect increased circulating NRBCs in placental sections corresponds to a level of approximately 2500/mm^3 in the neonatal peripheral blood count.

Widely divergent estimates of the time required to detect such an increase in the level of NRBCs (2 to 48 hours) have been reported; however, in vivo animal experiments agree with the clinical experience of many placental pathologists that it takes between 6 and 12 hours [75]. Higher NRBC levels (>10,000/mm^3) and elevations lasting several days after birth probably take 24 to 48 hours or longer to develop, but this estimate is not based on any experimental data.

Causes of fetal hypoxemia associated with increased NRBCs include both decreased oxygen tension and decreased oxygen delivery due to anemia (eg, blood group incompatibility or fetomaternal hemorrhage). It is important to stress that, while significantly associated with cerebral palsy (CP) and related neurologic disorders, increased NRBCs are not causally related to them [32].

Villous chorangiosis — Villous chorangiosis is characterized by an increased number of capillaries observed in cross sections of distal villi, which probably reflect increased angiogenesis in the third trimester (picture 11). The classic definition of this lesion is more than 10 capillaries in more than 10 villi in several areas of the placenta, but most cases have far more than 10 capillaries in some villi [76,77]. Several reported associations support the hypothesis that this placental finding is a chronic adaptive change to decreased oxygen delivery, possibly triggered by vascular endothelial growth factor (VEGF-1), another HIF-1 alpha inducible gene. These associations include high altitude, maternal anemia, and heavy smoking [78-80]. Unlike increased NRBCs, there are no experimental data linking this adaptive change to CP and related conditions. Some data suggest that it is equally common

in placentas submitted for other indications [81]. (See "The placental pathology report", section on 'Chorangiosis'.)

MONOCHORIONIC PLACENTAS IN MULTIPLE GESTATIONS

Studies have consistently shown that the risk of cerebral palsy and neurodisability is increased in multiple gestations [82]. This risk is greatest in pathologically confirmed, monochorionic twin placentas. The suggestion that increased risk, at least in part, relates to episodes of circulatory imbalance with transient hypotension in one or both twins is supported by the very high prevalence of central nervous system lesions following fetal demise of one twin in pregnancies with monochorionic placentas [83] and in twin-twin transfusion syndrome. No studies have systematically evaluated other placental lesions that might increase the risk of neurodisability in multiple gestations. (See "Twin pregnancy: Management of pregnancy complications", section on 'Death of one twin' and "Twin-twin transfusion syndrome: Management and outcome", section on 'Neurodevelopmental impairment'.)

SUMMARY AND RECOMMENDATIONS

- **Value of placental pathology** – Placental pathology can identify a number of conditions with specific relationships to development of cerebral palsy and related neurologic disorders in children. While necessarily indirect, these findings can provide important insights into adverse antenatal environments (table 1) that can impact susceptibility to brain injury. (See 'Introduction' above.)

- **Placental examination** – In order to ensure that valuable placental data are factored into an analysis of the cause of brain injury in a neonate, we suggest the following (See 'Introduction' above.):

  - Submit the placenta to the pathology department according to recommendations developed by the College of American Pathologists.

    It may also be necessary to discuss clinical findings and impressions with the pathology department to ensure that placentas are appropriately examined and sampled according to accepted guidelines so that important placental lesions are not missed.

  - Consult a perinatal pathologist with experience in evaluating cases of adverse neurologic outcomes to help identify placental lesions and explain their significance to the family early after problem births.

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Topic 2285 Version 24.0

GRAPHICS

Markers of an acute peripartum or intrapartum hypoxic-ischemic event

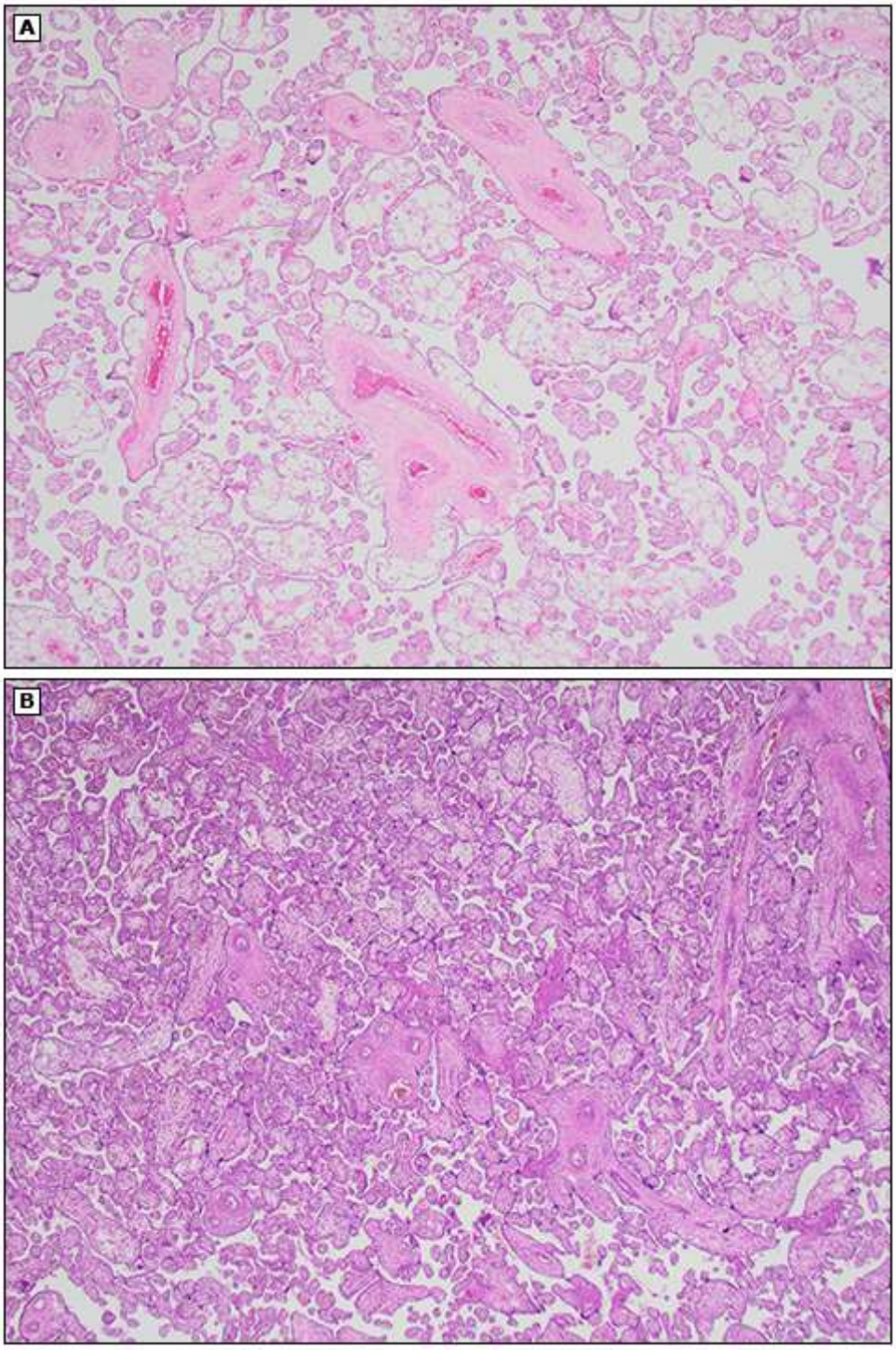
Neonatal signs consistent with an acute peripartum or intrapartum event:
▪ Apgar score of <5 at 5 minutes and 10 minutes ▪ Fetal umbilical artery acidemia – Fetal umbilical artery pH <7.0, or base deficit ≥12 mmol/L, or both ▪ Neuroimaging evidence of acute brain injury seen on brain MRI or MRS consistent with hypoxia-ischemia ▪ Presence of multisystem organ failure consistent with hypoxic-ischemic encephalopathy
Type and timing of contributing factors that are consistent with an acute peripartum or intrapartum event:
▪ A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery: • Ruptured uterus • Severe abruptio placentae • Umbilical cord prolapse • Amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia • Maternal cardiovascular collapse • Fetal exsanguination from either vasa previa or massive fetomaternal hemorrhage ▪ Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event, particularly a category I fetal heart rate pattern on presentation that converts to one of the following patterns: • Category III pattern • Tachycardia with recurrent decelerations • Persistent minimal variability with recurrent decelerations ▪ Timing and type of brain injury patterns based on imaging studies consistent with an etiology of an acute peripartum or intrapartum event. Well-defined patterns on brain MRI typical of hypoxic-ischemic cerebral injury in the newborn are: • Deep nuclear gray matter (ie, basal ganglia or thalamus) injury • Watershed (borderzone) cortical injury ▪ No evidence of other proximal or distal factors that could be contributing
Developmental outcome is spastic quadriplegia or dyskinetic cerebral palsy:
▪ Other subtypes of cerebral palsy are less likely to be associated with acute intrapartum hypoxic-ischemic events ▪ Other developmental abnormalities may occur, but they are not specific to acute intrapartum hypoxic-ischemic encephalopathy and may arise from a variety of other causes

MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy.

Source: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol 2014; 123:896.

Graphic 96192 Version 2.0

Diffuse villous edema



(A) Diffuse multifocal villous edema in placenta at 24 weeks of gestation. This entity is strongly associated with adverse outcome in offspring, including neurodevelopmental abnormality.

(B) Normal placenta at 25 weeks of gestation.

Courtesy of Raymond Redline, MD.

Graphic 119324 Version 1.0

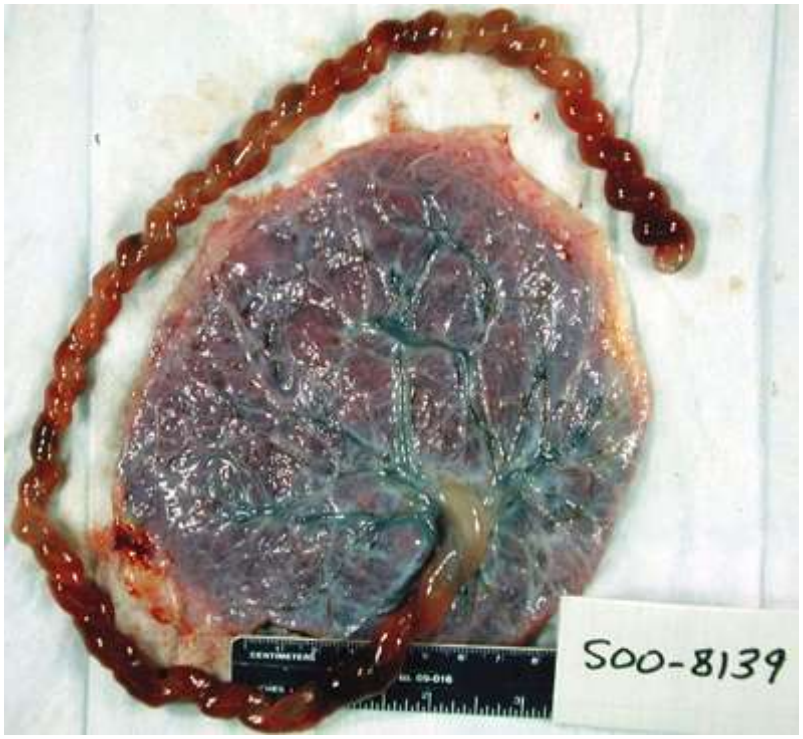
Abruptio placenta

A large retroplacental hematoma derived from rupture of a spiral artery separates the placenta from the underlying uterus and indents the basal plate of the placenta.

Courtesy of Raymond W. Redline, MD.

Graphic 60258 Version 1.0

Umbilical cord obstruction

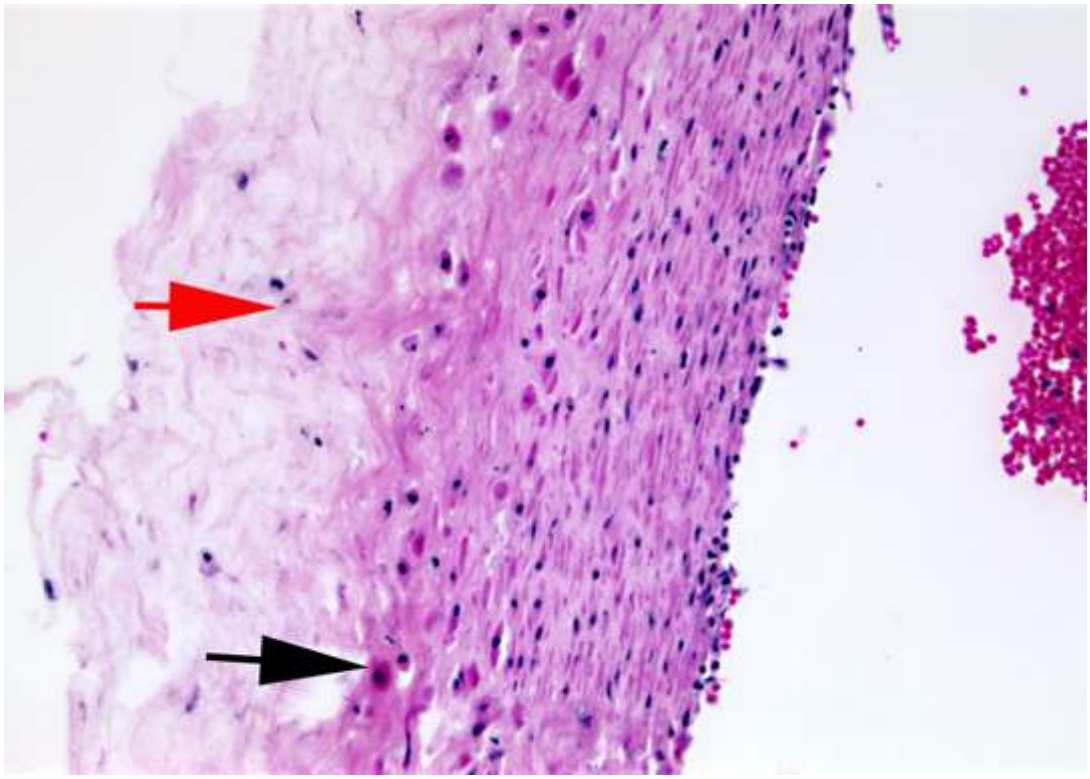


The umbilical cord is excessively long (>85 cm), hypertwisted (>5 coils/cm), and shows red discoloration due to degenerative changes accompanying fetal death.

Courtesy of Raymond W. Redline, MD.

Graphic 51778 Version 1.0

Meconium myonecrosis

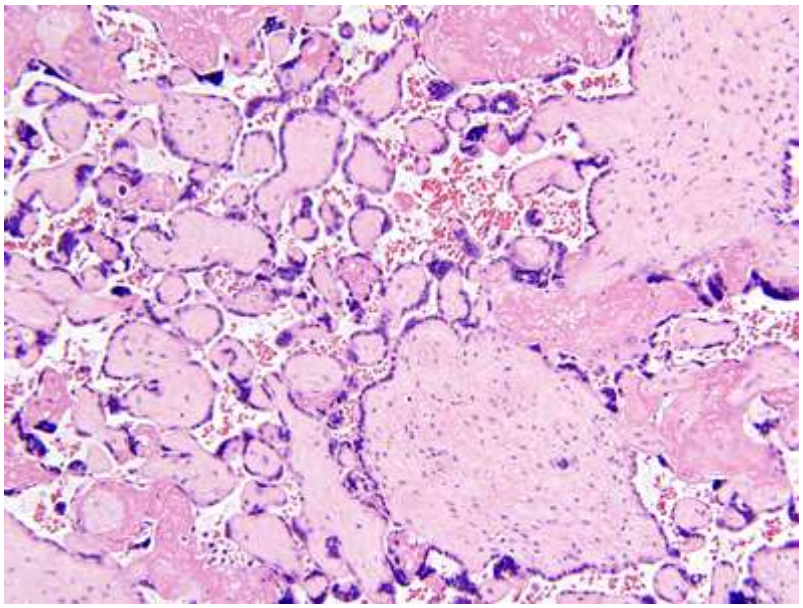


Black arrow shows orangophilic apoptotic smooth muscle cell, and red arrow shows meconium pigment.

Courtesy of Drucilla J Roberts, MD.

Graphic 67487 Version 3.0

Severe fetal vascular malperfusion (fetal thrombotic vasculopathy)

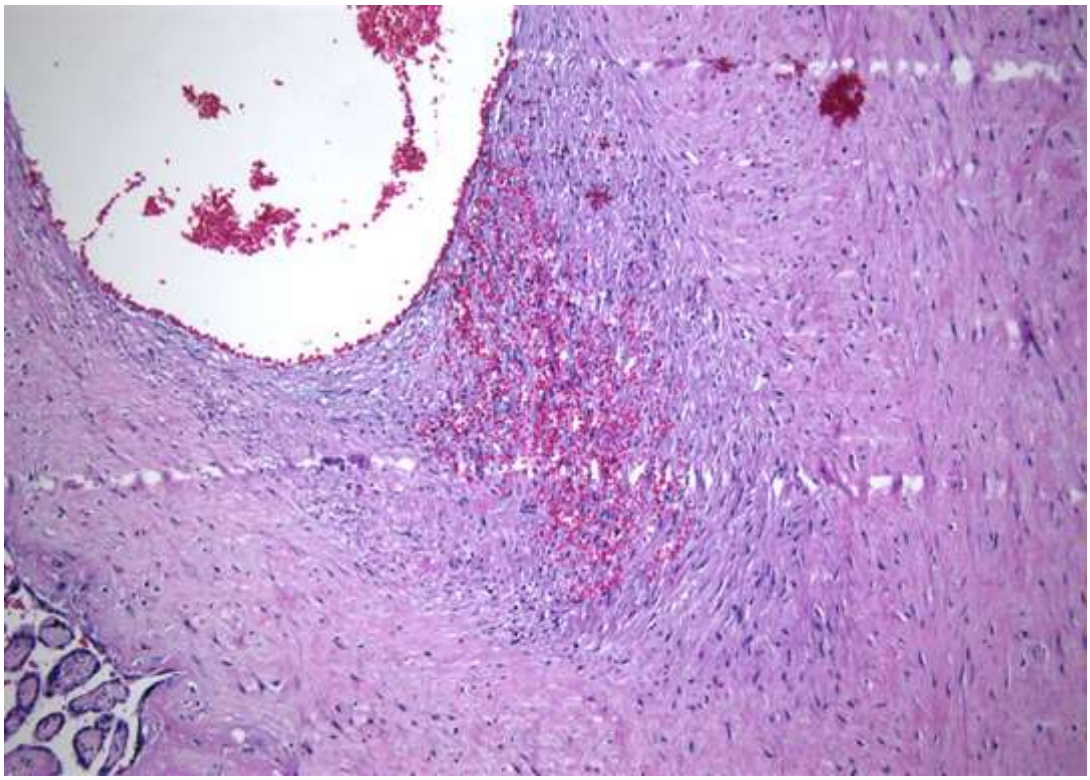


A large portion of the villous tree (>15 villi/slide) shows loss of fetal vessels and hyaline fibrosis secondary to upstream vascular occlusion.

Courtesy of Raymond W. Redline, MD.

Graphic 59894 Version 3.0

Fetal stem/chorionic vessel obliteration (fetal vascular malperfusion)

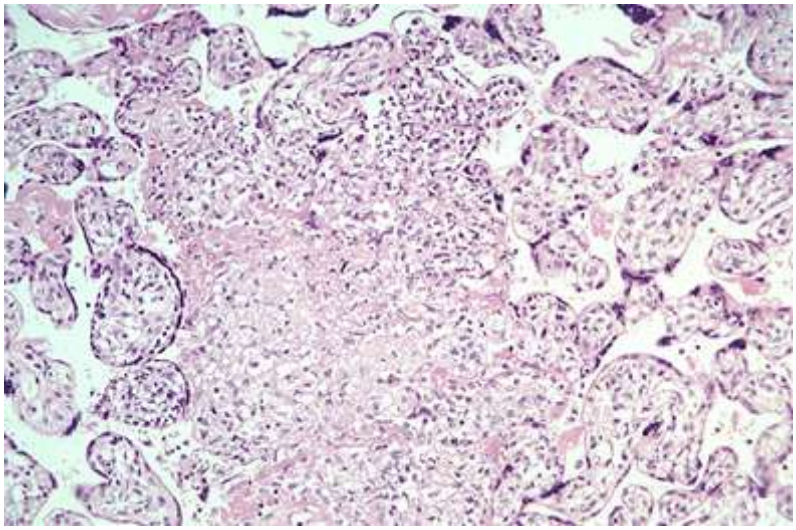


Hemorrhagic endovasculitis in the stem villus of a live born infant with cardiac failure.

Courtesy of Drucilla J Roberts, MD.

Graphic 50997 Version 4.0

Chronic villitis (VUE)

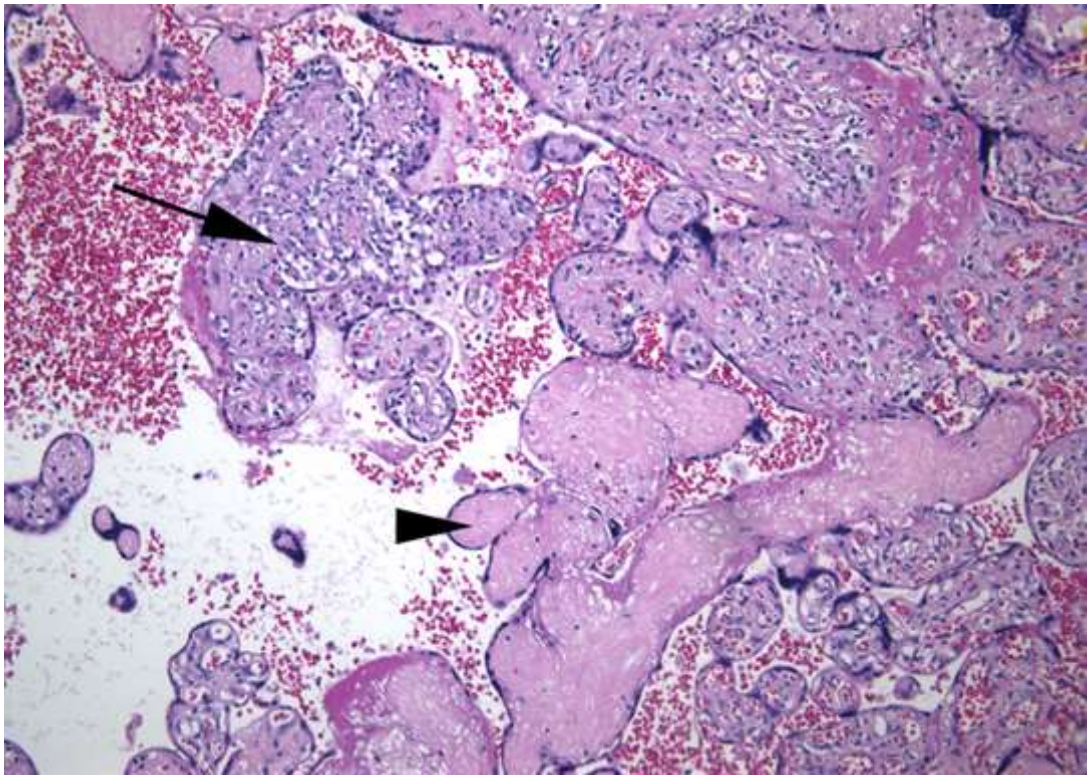


There is increased cellularity of the villi with sclerosis of the villi due to collapse of the villous vessels and clumping of the involved villi.

Courtesy of Drucilla J Roberts, MD.

Graphic 64413 Version 4.0

Lymphohistiocytic (chronic) villitis

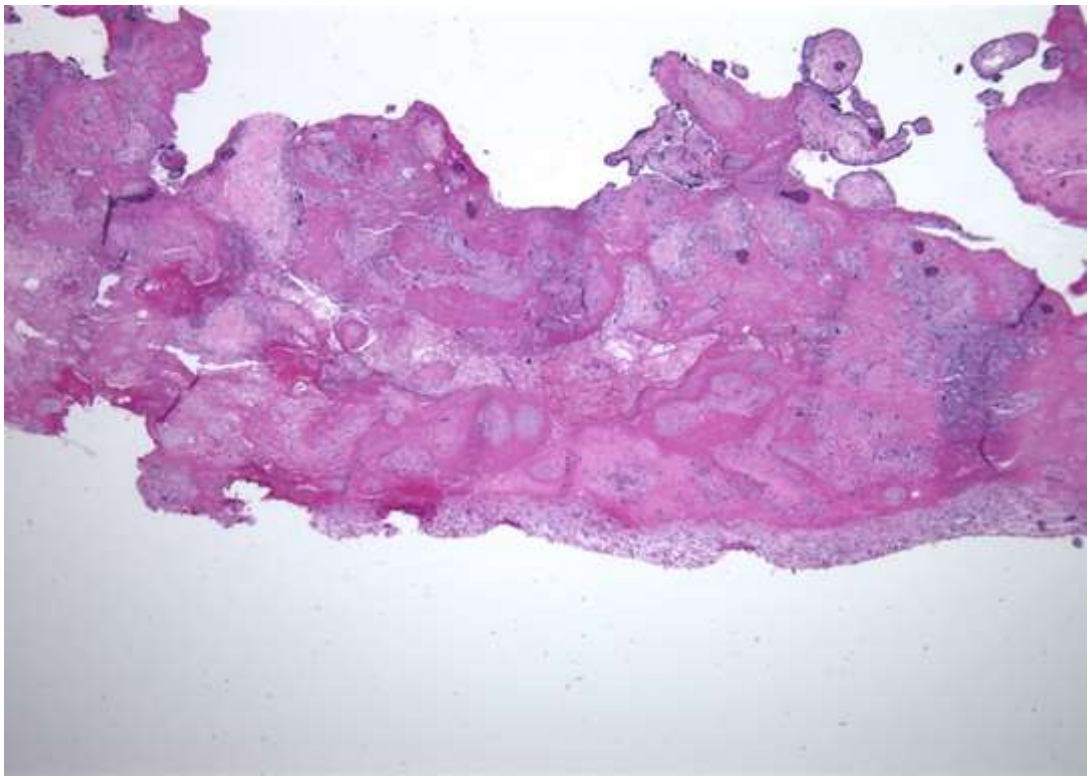


Arrow points to a mononuclear inflammatory infiltrate in a term placenta. Pregnancy was complicated by fetal growth restriction. Arrowhead shows avascular villi presumably due to the vascular damage from the lymphohistiocytic villitis "upstream."

Courtesy of Drucilla J Roberts, MD.

Graphic 77237 Version 4.0

Massive perivillous fibrin deposition (maternal floor infarction)

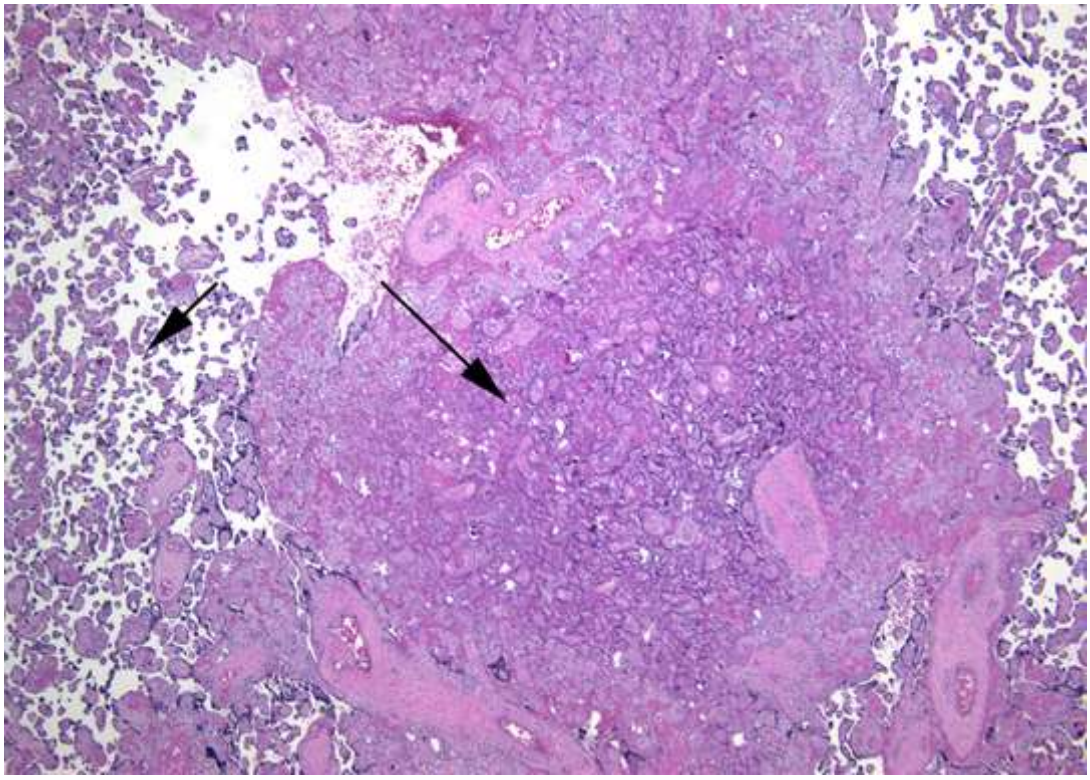


Band of fibrinoid material along maternal floor of placenta causing "strangulation" and necrosis of the villi.

Courtesy of Drucilla J Roberts, MD.

Graphic 59608 Version 6.0

Maternal vascular malperfusion

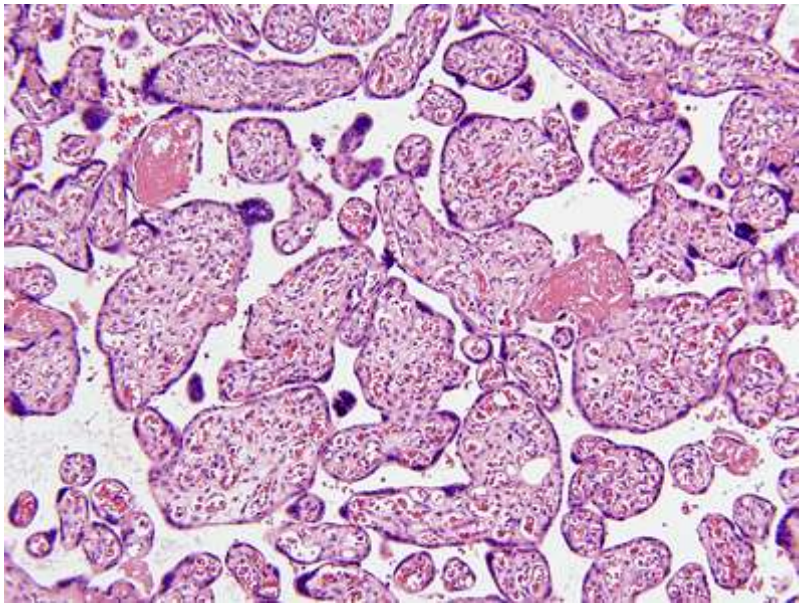


Preterm placenta from a pregnancy complicated by severe preterm preeclampsia. The arrows show areas of accelerated maturity of the villi (short arrow) and a central infarct (long arrow).

Courtesy of Drucilla J Roberts, MD.

Graphic 51550 Version 3.0

Villous chorangiosis



Terminal villi show an increase in the number of capillaries per villous cross-section (at least 10 capillaries in 10 contiguous villi in several areas of the placenta).

Courtesy of Raymond W. Redline, MD.

Graphic 80543 Version 3.0

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Raymond W Redline, MD No relevant financial relationship(s) with ineligible companies to disclose. **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.

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